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MECHANISMS OF FORMATION OF PSEUDOCALIXARENE SCHIFF BASE MACROCYCLES INVESTIGATED BY ESI-MS

BY

RAFAL KULMACZEWSKI

SUPERVISOR PROF. VICKIE MCKEE

A DOCTORAL THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF DOCTOR OF PHILOSOPHY OF LOUGHBOROUGH UNIVERSITY

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Abstract

Starting from 4-substituted phenols, three dialdehydes were synthesised as Schiff base pseudocalixarene macrocyclic precursors. Two of the dialdehydes, 2,2’–methylene-bis-[(6-hydroxymethyl)-4-methylphenol] and 2,2’–methylene-bis-[(6-hydroxymethyl)-4-phenylphenol] were structurally characterised. For the phenyl substituted compound condensation with 1,3-diaminopropan-2-ol, with transition metal ions as template, was investigated and a series of dinuclear complexes was synthesised and characterised by IR, FAB-MS and elemental analysis. The analytical data implied that the complexes have the same saddle shape conformation controlled by hydrogen bonds resulting from mono-deprotonation of the methylenediphenol units as was observed in previous work.

A range of TM2M trinuclear complexes [TM = Cu(II), Ni(II) and M = Li(I), Na(I), Mg(II), Ca(II)] of (2+2) macrocycles was synthesised and characterised by IR, MS (FAB, ESI) and elemental analysis. Additionally [Cu2Ca(2+2)(NO3)2](MeOH)2 was characterised by X-ray crystallography.

An ESI-MS was used to follow condensation reactions between 2,2’–methylene-bis-[(6-hydroxymethyl)-4-tert-butylphenol] and 1,3-diaminopropan-2-ol in solution with various templates. It was found that, when a transition metal is used alone, the reaction produces only the (2+2) macrocycle. Cu(II) produced equilibrium mixtures containing dicopper(II) and tricopper(II) species but Ni(II) and Zn(II) yielded only dinuclear complexes.

When transition metal ions were used in combination with group 1 or group 2 metal ions, the size of the macrocycle and nuclearity of the complex depended on the synthetic route and nature of alkali or alkaline earth metal. Among the products identified in the ESI-MS spectra were trinuclear complexes of the (2+2) macrocycle, pentanuclear sandwich complexes of two (2+2) macrocycles, tetranuclear (3+3) complexes, pentanuclear (4+4) and hexanuclear (6+6) species.

One of the routes resulted in formation of [BaCu4(4+4)]2+ ion via a [BaCu4(dialdehyde)4]2+ cluster which was established to be a double template process where both metals are necessary for formation of the macrocycle. The central Ba(II) ion holds the dialdehydes together and the Cu(II) ion orients the carbonyl groups for Schiff base condensation.
Acknowledgements

Firstly, I would like to thank my supervisor Prof. Vickie McKee for giving me opportunity to do a Ph.D. which extended my university education to ten years. Thank you Vickie for your patience, guidance and support during those four years at Loughborough. A huge thanks for sacrificing Saturdays so this thesis could be completed.

Many thanks to Pauline King for running elemental analysis, especially those batches containing dozens of samples. Thanks to Drs Martin Smith, Paul Kelly and Mark Elsegood for being there when required. Also I would like to thank Prof. Colin Creaser and Dr Jim Reynolds for use of their ms instruments and also for helpful discussions.

A special thanks to Sheena Grainger for acquiring data for over a thousand ESI-MS samples for me in such a short period of time. Also to the EPSRC NMSSC for all the FAB-MS data and for kind answers to my silly questions.

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Biggest thanks go to my Mum for making me who I am and also for mental and financial support during long years of my studies. A very, very, very special thanks to my wife Agnes for reminding me that a year it was a plenty of time! Honestly, I could have not done it without you and your love. At the end I would like to thank to my daughter Zuzanna for constant tidying up of my hard copied data. Thanks Zuzka for making each day of my life special.
Ligands and clusters referred to in the thesis

\[ \text{H}_2\text{mhtbp} \quad \text{C}_{23}\text{H}_{32}\text{O}_4 \]
\[ \text{H}_2\text{mhmp} \quad \text{C}_{17}\text{H}_{20}\text{O}_4 \]
\[ \text{H}_2\text{mhpp} \quad \text{C}_{22}\text{H}_{24}\text{O}_4 \]
\[ \text{H}_2\text{mfhp} \quad \text{C}_{23}\text{H}_{26}\text{O}_4 \]
\[ \text{H}_2\text{mfmp} \quad \text{C}_{17}\text{H}_{16}\text{O}_4 \]
\[ \text{H}_2\text{mfpp} \quad \text{C}_{27}\text{H}_{30}\text{O}_4 \]

\[ \text{2} + 2 \]
\[ \text{3} + 3 \]
\[ \text{4} + 4 \]

\( R = \text{Me} \quad \text{C}_{40}\text{H}_{40}\text{N}_2\text{O}_6 \)
\( R = \text{Ph} \quad \text{C}_{40}\text{H}_{40}\text{N}_2\text{O}_6 \)
\( R = \text{tBu} \quad \text{C}_{53}\text{H}_{60}\text{N}_2\text{O}_6 \)
\( R = \text{Me} \quad \text{C}_{58}\text{H}_{60}\text{N}_6\text{O}_9 \)
\( R = \text{tBu} \quad \text{C}_{78}\text{H}_{60}\text{N}_6\text{O}_9 \)
\( R = \text{Me} \quad \text{C}_{90}\text{H}_{80}\text{N}_6\text{O}_{12} \)
\( R = \text{Ph} \quad \text{C}_{122}\text{H}_{98}\text{N}_6\text{O}_{12} \)
\( R = \text{tBu} \quad \text{C}_{194}\text{H}_{128}\text{N}_6\text{O}_{12} \)
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<td>softness, Pearson scale</td>
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<tr>
<td>µ</td>
<td>micro $10^{-6}$</td>
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<tr>
<td>µL</td>
<td>microlitre $10^{-6}$ litre</td>
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<td>Å</td>
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Electron Impact Mass Spectrometry
equiv. equivalent
Electrospray
Electrospray Ionisation Mass Spectrometry
et al. and others
Fast Atom Bombardment
Fast Atom Bombardment Mass Spectrometry
Figure(s)
Full Width at Half Maximum
gram(s)
hour(s)
2,2’-methylene-bis[(6-formyl)-4-methylphenol]
2,2’-methylene-bis[(6-formyl)-4-phenylphenol]
2,2’-methylene-bis[(6-formyl)-4-tert-butylphenol]
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2,2’-methylene-bis[(6-hydroxymethyl)-4-phenylphenol]
2,2’-methylene-bis[(6-hydroxymethyl)-4-tert-butylphenol]
High Pressure Liquid Chromatography
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<td>T</td>
<td>Temperature</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TM</td>
<td>Transition metal</td>
</tr>
<tr>
<td>ToF</td>
<td>Time of Flight</td>
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<tr>
<td>V</td>
<td>Volt</td>
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<tr>
<td>v/v</td>
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<td>w</td>
<td>weak</td>
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</table>
Chapter 1

INTRODUCTION
1.1. What is a supramolecular chemistry?

The beginning of this young discipline of chemistry dates from late 1960s when Pedersen published his work on cyclic polyethers and their metal complexes.\textsuperscript{1-4} The term supramolecular however was first introduced by Lehn in 1978\textsuperscript{5} who shared Nobel Prize for work in this field with Cram and Pedersen. Lehn defined supramolecular chemistry as chemistry of molecular assemblies and intermolecular interactions or more colloquially as “chemistry beyond the molecule”.\textsuperscript{6} Fig. 1.1 shows the Lehn concept of supramolecular chemistry and explains how it differs from conventional molecular, covalent bond based chemistry.\textsuperscript{5,6} The molecular receptor can be synthesised by formation of covalent bonds in multistep reaction from simple components referred to as A, B, C and D.

![Fig. 1.1 Lehn concept of supramolecular chemistry.](image)

The super-molecule formation requires molecular recognition phenomena between the receptor and substrate and may result in specific functions or properties. When the receptor possesses additional reactive groups it may effect chemical transformation of the bound substrate and therefore act as a catalyst. If the receptor is lipophilic it may behave as a carrier and change the location of the bound substrate. Recognition chemistry is also viewed as host – guest chemistry, where the host compound can be defined as a chemical species which retains convergent binding sites and the guest molecule has divergent binding sites. Complementarity between these two is achieved by interactions of various natures. The supramolecular Nobel Prize laureate Cram describes the various structural relationships which take place in such a complex\textsuperscript{7}, hydrogen bonding, ion pairing, π-acid to π-base interactions, metal-to-ligand binding, van der Waals attractive forces, solvent reorganisation, and partially made or broken
covalent bonds (transition states). Examples of hosts used in supramolecular chemistry are shown in Fig. 1.2.

Crown Ether$^{1-4}$

Lariat ether$^8$

Podand$^9$

Calixarene$^{10}$

Cryptand$^{11-12}$

Spherand$^{13-14}$

Cyclodextrin$^{15}$

Schiff base macrocycle$^{16}$

Fig. 1.2 Some types of the host molecules used in supramolecular chemistry.
Supramolecular chemistry, the chemistry of designed intermolecular interaction is still expanding with its current emphasis placed on:

a) Biological interface (enzyme mimics,\textsuperscript{17-20} membrane transport processes,\textsuperscript{21-23} base pairing and DNA recognition\textsuperscript{24-25}),

b) Separation and extraction chemistry,\textsuperscript{26-29}

c) Physical and materials chemistry (supramolecular polymers,\textsuperscript{30-31} molecular machines,\textsuperscript{32-34} single molecule magnets,\textsuperscript{35-40} molecular electronic memories\textsuperscript{41}),

d) Self-assembly processes (chemistry in coordination cages,\textsuperscript{42-44} self-sorting systems of subcomponents\textsuperscript{45-47}).

Although supramolecular chemistry lies at an intersection of many science disciplines, the basic principles of coordination chemistry are important in the formation of the host guest complexes. Thus the macrocyclic effect, the coordination template effect and Pearson hard and soft acids and bases theory (HSAB) are briefly discussed in this chapter together with one particular type of host molecule, Schiff base macrocycles.
1.1.1. The chelate and macrocyclic effect

The term chelate is from Greek word chela and refers to the great claws of the lobster. It was introduced by Morgan\textsuperscript{48} for the metal – organic or inorganic systems in which calliper like groups bind the central metal to produce heterocyclic rings. The resulting complex has greater stability than metal with monodentate ligands system.\textsuperscript{49-50} The macrocyclic effect as an expansion of chelate effect is an increased thermodynamic and kinetic stability of macrocyclic complexes with metal ions in comparison to their open chain analogs. It was first reported by Cabbiness and Margerum\textsuperscript{51-52} who found that the Cu(II) complex with cyclic compound \textit{meso}-5,7,7,12,14,14-hexamethyl-1,4,8-11-tetraazacyclotetradecane (tet a) has a 10000 times higher formation constant than for the complex with non-cyclic ligand but a similar sequence of chelate rings (Fig. 1.3).

\begin{align*}
\text{Thermodynamic stability} & \quad \text{Kinetic stability} \\
[Cu(\text{tet a})]^{2+} & [Cu(2,3,2-tet)]^{2+} \\
\log K = 28 & \log K = 23.9 \\
\text{Stability constants for reaction Cu}^{2+} + L & \frac{K}{[Cu(L)]^{2+}} \\
\text{log } K = 15.34 & \text{log } K = 22.2 \\
\text{log } K = 27.2 & \\
\text{Better match between metal ion size and macrocyclic cavity} & \text{results with increased thermodynamic stability} \\
\text{Dissociation rate for } [Cu(L)]^{2+} + nH^{+} & \text{C}u^{2+} + H_{n}L^{m+} \\
 k_{a} = 3.6 \times 10^{-7} \text{[sec}^{-1}] & k_{a} = 4.1 \text{[sec}^{-1}] \\
\end{align*}

Fig. 1.3 Ligands used in the discovery of macrocyclic effect by Cabbiness and Margerum.\textsuperscript{51-54}

As later found,\textsuperscript{53-56} this increased thermodynamic stabilisation of macrocyclic complex has both, enthalpic and entropic contributions.

The enthalpic is related to number of factors (e.g. solvation effects, geometrical preferences, strength of metal-ligand bonds etc). Enthalpic contribution can be either favourable or unfavourable. The single most important factor seems to be the relative sizes of the metal ion and the macrocyclic cavity. As shown in Fig. 1.3 Cu(II) ion forms more stable complex with cyclam as a result of better fit between the cation and macrocyclic hole.
The entropic contribution arises from the fact that the macrocycle is less conformationally flexible so loses fewer degrees of freedom when makes a metal complex. In simple words, macrocyclic ligand is already preorganised for complexation and requires less energy for any conformational changes prior to bind the guest molecule.

The macrocyclic complexes are also kinetically stabilised in comparison with the linear chain ligands. This is observed mostly in the dissociation step as the rates of dissociation for macrocyclic complexes are much slower. The dissociation rate of \([\text{Cu(teta)}]^2+\) is measured to be \(3.6 \times 10^{-7} \text{ [sec}^{-1}]\) where the open chain analog \([\text{Cu(2,3,2-tet)}]^2+\) is 4.1 \text{ [sec}^{-1}]\) (Fig. 1.3). As described by Cabiness, \([\text{Cu(teta)}]^2+\) needs to fold before the first bond is broken so the process has higher activation energy than for the open chain ligand, where a terminal donor dissociates and is protonated, then the next donor in the chain and so on until the ligand is “unwrapped” from the metal ion.

The macrocyclic effect is even stronger in bicyclic ligands such as cryptands, for the same reasons as discussed above and it is often called macrobicyclic or cryptate effect.\(^{12}\) Fig. 1.4 shows summary of the chelate, macrocyclic and macrobicyclic effects.

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INCREASED STABILITY AND DEGREE OF HOST ORGANISATION

Fig. 1.4 The chelate, macrocyclic and macrobicyclic effect.
1.1.2. The coordination template effect

The coordination template effect is an effect in which a metal ion employed in the reaction allows access to certain ligands which would be hard to synthesise otherwise. The first reports of this phenomenon were published in the 1960s by Thompson and Busch. They reported a dramatic example of the role played by a metal ion in the condensation between $\alpha$-diketones and $\beta$-mercaptoethylamine. They suggested that the role of the metal ion was to bring the reactants together in the product form that is most favourable for complexation (Fig. 1.5).

Busch and Thompson also distinguished between two classes of template processes, the equilibrium displacement and the kinetic template process. The first one is known as thermodynamic template effect and is what they observed in the condensation between diketones and mercaptoethylamine. Ni(II) as a template ion picks the complementary ligand from the equilibrium mixture and shifts the equilibrium towards the chelated product.

The second class of template effect is the kinetic template effect. It involves formation of cyclic intermediate around the metal centre which promotes formation of cyclic product. In the kinetic effect the product cannot be formed without the metal centre. Fig. 1.6 shows the example of kinetic template effect studied by Thompson and Busch.
The directive influence of the Ni(II) metal centre on formation of the macrocyclic complex (compound 5) is what Busch and Thompson called the kinetic template effect. In reaction A, Ni(II) is not involved in template process. The Ni(II) complex (compound 1) reacts with a monofunctional halide in two reasonably slow steps. In the first monosubstituted thioether is produced (compound 2) which in the second step is again S-alkylated into the final product (compound 3). In contrast, in reaction B when Ni(II) complex is reacted with α,α’- dibromo-o-xylene only the first step is slow. After combining the first sulphur with the reagent the intermediate compound is produced (compound 4). Then, the remaining sulphur and bromine, oriented for cyclisation, rapidly give rise to macrocycle 5. The ring closure reaction is promoted by the central metal ion which holds both mercapto groups in cis positions. Measurable concentrations of the intermediate compound 4 were not observed which Busch and Thompson called “the essence of the kinetic coordination effect”.  

Perhaps, the synthesis of crown ethers in the presence of group 1 metals studied by Mandolini and Masci is a better illustration of the kinetic template effect. A schematic representation of this process is shown in Fig. 1.7.
The key step in the template synthesis of this benzo-15-crown-5 is the formation of an intermediate compound in which the functional groups (-O\textsuperscript{−}) and (-Br) are brought together close to each other by chelating to the metal ion. When the groups are held in close proximity they cyclise readily because the nucleophilic phenolate oxygen attacks the positive dipole on the carbon atom of the CH\textsubscript{2}-Br fragment. The intermediate pre-crown complex is found to bind the metal more strongly than the reactant or product. In general, associations between alkali metal ions and the crown ethers are dependent upon the nature of the metal and the ring size of the crown ether, which is related to the length of polyether chain. In simple terms, if a host to selectively bind an alkali metal ion is desired, then this ion should be used as template for its formation. The driving force for the association between polyether chain and central metal is the coulombic interaction between them. The metal ion by chelating the appropriate terminal atom from the side chain allows the rest of oxygen donors to wrap around, which additionally stabilises the intermediate complex. In fact, the metal is acting as kind of a catalyst which stabilises the cyclic intermediate and therefore increases the rate of formation of the crown product. This is why this phenomenon is called the kinetic template effect.

1.1.3. Hard and Soft Acid and Base Theory (HSAB)

The hard and soft acid and base theory published by Pearson and Songstad in the late 1960s was originally applied to organic chemistry as an extension to the Lewis acid-base theory.\textsuperscript{64} In general terms it states that hard acids prefer to interact with hard bases and soft acids prefer to interact with soft bases. The classification of hard acids and bases is shown in Table 1.1.
Table 1.1 Classification of hard and soft acids and bases.

<table>
<thead>
<tr>
<th>ACIDS</th>
<th>BASES</th>
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</thead>
<tbody>
<tr>
<td><strong>HARD</strong></td>
<td>H₂O, OH⁻, F⁻, AcO⁻, (PO₄)³⁻, (SO₄)³⁻, (CO₃)²⁻, NO₃⁻, ClO₄⁻, ROH, RO⁻, R₂O₅, NH₃, RNH₂, N₂H₄</td>
</tr>
<tr>
<td>H⁺, Li⁺, Na⁺, K⁺, Be³⁺, Mg²⁺, Ca²⁺, Sr²⁺, Sn²⁺, Al³⁺, Se³⁺, Ga³⁺, In³⁺, Cr³⁺, Co³⁺, Fe³⁺, As³⁺, Ir³⁺, Ti⁴⁺, Zr⁴⁺, VO²⁺, UO²⁺²⁺, (CH₃)₂Sn²⁺, BeMe₂, BF₃, BCl₃, B(OR)₃, Al(CH₃)₃, Ga(CH₃)₃, In(CH₃)₃, RPO₂⁺, ROPO₂⁺, RSO₂⁺, ROSO₂⁺, SO₃²⁻, I⁻, I⁺, I²⁺, R₂C⁺, RCO⁺, CO₂, NC²⁻</td>
<td></td>
</tr>
<tr>
<td><strong>SOFT</strong></td>
<td>R₂S, RSH, RS⁻, I⁻, SCN⁻, S₂O₅²⁻, Br⁻, R₂P, R₂As, (RO)₂P, CN⁻, RNC, CO, Benzene, H⁺, R⁺</td>
</tr>
<tr>
<td>Cu⁺, Ag⁺, Au⁺, Tl⁺, Hg⁺, Cs⁺, Pd²⁺, Cd²⁺, Pt²⁺, Hg²⁺, CH₃Hg⁺, RH₂, RS⁻, RSe⁺, RTe⁺⁺, Br⁺, HO⁺, RO⁺, I₂, Br₂, Trinitrobenzene, etc. Chloranil, Quinones, etc. Tetracyanoethylene, etc. O, Cl, Br, I, R₃C, Bulk metals M⁰</td>
<td></td>
</tr>
<tr>
<td>HX (hydrogen bonding molecules) Fe²⁺, Co²⁺, Ni²⁺, Zn²⁺, Cu²⁺, Zn²⁺, Pb²⁺, SO₂, NO⁺</td>
<td></td>
</tr>
<tr>
<td><strong>BORDERLINE</strong></td>
<td>ArNH₂, Pyridine, N₃⁻, Cl⁻, NO₂⁻, SO₃⁻²</td>
</tr>
</tbody>
</table>

Soft base donors are defined in various ways: as atoms of high polarizability or low electronegativity, which can be easily oxidised and with low lying empty orbitals. Hard base donors are of low polarizability, high electronegativity, hard to oxidise and possess high energy empty orbitals which are hard to access. Soft acid acceptors are ions of low positive charge, large size with several easily excited outer electrons. The hard acid has a large positive charge, small size and does not have easily excited outer electrons.

As established by Pearson, the electronic properties of the atoms involved in donor acceptor interaction correlate to their hardness by equations: $\chi = (I + A)/2$, $\eta = (I - A)/2$ and $\sigma = 1/\eta$. The I is the ionisation potential, A is an electron affinity, $\chi$ is the absolute electronegativity and $\eta$ is absolute hardness and $\sigma$ describes softness.

HSAB theory is very useful tool for supramolecular chemistry. It allows to predict complexation preferences of ligands bearing certain donor groups or design ligands for selective binding of metal ions.
1.2. Schiff base macrocyclic compounds

Schiff bases, compounds containing an imine bond (-C=N) can be obtained by nucleophilic addition of the primary amines to aldehydes. They are named after Hugo Schiff who discovered them. The condensation reaction in which they are prepared is reversible so high yields of Schiff base products often require removal of water. The Schiff base reaction mechanism is shown in Fig. 1.8.

![Schiff base reaction mechanism](image)

Fig. 1.8 Schiff base reaction mechanism.

The first Schiff base macrocyclic ligands (Fig. 1.9) were reported at the beginning of the 1960s and were formed in the aldol condensation between [Ni(en$_2$)]$^{2+}$ and acetone (Curtis) and in the Fe(II) templated condensation of 2,6-diacetylpyridine with a tetramine compound (Busch).

![Curtis aldol condensation of acetone and [Ni(en)$_2$]$^{2+}$](image)

Curtis aldol condensation of acetone and [Ni(en)$_2$]$^{2+}$ 1961

![Busch Fe(II) templated reaction between 2,6-diacetylpyridine and A) triethylenetetramine B) tetraethylenepentaamine](image)

Busch Fe(II) templated reaction between 2,6-diacetylpyridine and A) triethylenetetramine B) tetraethylenepentaamine 1964

Fig. 1.9 Synthesis of the first reported Schiff base macrocyclic ligands.
Imines are medium-soft donors and are of great importance in the coordination chemistry of transition metals as they readily form stable complexes. The strong interaction of a transition metal ion with an imine nitrogen is as a result of back bonding with, the \( \pi^* \) \((-\text{C=N})\) antibonding orbital. Transition metal ion templates are indispensable in the syntheses of many Schiff base cyclic compounds, especially in the case of bifunctional compounds as non-template reactions often give polymeric products. Depending on the shape of the carbonyl and amine reactants, and also on the metal salt used, different ring sizes can be formed during the cyclization process. The areas of Schiff base cyclic and acyclic ligands and the template synthesis of their complexes are well reviewed in literature.\(^{70-77}\)

A schematic representation of the possible macrocyclic products formed in the reaction between a dicarbonyl compound and a diamine moiety is shown in Fig. 1.10.

\[
\begin{align*}
&\text{(1+1) macrocycle} \\
\text{(2+2) macrocycle} \\
\text{(3+3) macrocycle} \\
\text{(4+4) macrocycle}
\end{align*}
\]

\( D \) = phenol, pyridine, thiophen, furan

Fig. 1.10 Schematic representation of the (1+1), (2+2), (3+3) and (4+4) Schiff base macrocycles yield in the reaction between bifunctional species.

If one molecule of dicarbonyl compound reacts with one molecule of diamine a (1+1) macrocycle is formed. If two molecules of each component condense together (2+2) macrocycle is formed, and so on.
Macrocyclic Schiff base systems have attracted attention of researchers for a various reasons, thanks to their potential applications (biochemistry, catalysis, material science, activation processes, transport and separation phenomena), or thanks to simplicity of preparation and availability for further modifications (i.e., reduction to polyamine compounds).

1.2.1. Schiff Base macrocycles derived from 2,6-diformyl-4-substituted phenols

1.2.1.1. Template synthesis of (2+2) homodinuclear systems

In 1970 Robson and Pilkington reported a series of transition metal dinuclear complexes with a new Schiff base macrocyclic ligand, now commonly known as the Robson macrocycle. It was the (2+2) condensate yielded in a template reaction between 2,6-diformyl-4-methylphenol and 1,3-diaminopropane in the presence of an appropriate metal salt. A schematic representation of the template synthesis and general structure of Robson macrocycles is shown in Fig. 1.11.

Fig. 1.11 Schematic representation of synthesis of Robson complexes where M = Cu(II), Ni(II), Fe(II), Zn(II), Co(II), Mn(II) and X = Cl⁻, (HSO₄)⁻, (ClO₄)⁻.

The binding sites of Robson macrocycle (grey spheres in Fig. 1.11) comprise two hard phenolate donors bridging the metal ions and two softer imine nitrogen donors. The macrocyclic complex has a flat conformation (except for the lateral chain part) and the intermetallic distance in most cases is roughly 3 Å. When the metal ion is 5- or 6-coordinate, additional solvent molecules or anions chelate axially to the metal ions. For 5-coordinate systems there are two possible geometrical arrangements of these axially coordinating ligands. They both can lie on the same side of the mean plane which is the
cis-geometry or on the opposite sides which is trans-geometry. The possible coordination spheres for the central metal ion in symmetrical (2+2) complexes are shown in Fig. 1.12.

\[ \text{a) } [M_2(2+2)]^{2+} \]
M is 4 coordinate in square planar geometry

\[ \text{b) } [M_2(2+2)X_2] \]
M is 5 coordinate in square pyramidal geometry
X are in trans position

\[ \text{c) } [M_2(2+2)X_4] \]
M is 6 coordinate in octahedral geometry
possible cis-trans isomers in the case of different axial ligands

Fig. 1.12 Schematic representations of central metal coordination spheres in dinuclear complexes with Robson macrocycle.

Example structures of a) \([\text{Pd}_2(2+2)]^{2+}\), b) \([\text{Zn}_2(2+2)(\text{H}_2\text{O})_2]^{2+}\) and c) \([\text{Co}^{II}\text{Co}^{III}(2+2)(\text{MeOH})_2\text{Br}_2]^+\) adapted from literature\textsuperscript{78-80} and rendered in POVray software\textsuperscript{81} are shown in Fig. 1.13.

Relatively inert platinum group metal ions do not template formation of the (2+2) ligand so the Pd(II) complex (a) was synthesised from the free macrocyclic ligand by insertion. The \([\text{Pd}_2(2+2)]^{2+}\) cation has a highly planar conformation, the metal centres are square planar with metals bonded to two phenolic oxygen donors and two imine nitrogen donors. The intermetallic distance is 3.15 Å.

Fig. 1.13 Crystal structures adapted from literature\textsuperscript{78-80} showing complexes of Robson’s binucleating symmetrical ligand with a) 4-coordinate metal centres  b) 5-coordinate metal centres and c) 6-coordinate coordinate.
Picture b (Fig. 1.13) shows the centrosymmetric \([\text{Zn}_2(2+2)(\text{H}_2\text{O})_2]^{2+}\) cation with a center of inversion at the middle of the \(\text{Zn}_2(\mu\text{-phenoxide})_2\) plane. The macrocycle has flat conformation and the square-pyramidal geometry of the metal center is completed by coordination with a water molecule \textit{trans} to the mean plane. The distance between two Zn(II) ions is 3.17 Å and the Zn-OH_2 distance is longer than the other Zn-O and Zn-N distances.

The picture c represents the mixed valence cation \([\text{Co}^{\text{II}}\text{Co}^{\text{III}}(2+2)(\text{MeOH})_2\text{Br}_2]^{+}\) complex synthesised by Robson et al. The macrocycle, in contrast to the two previously described cases, does not have a flat conformation. It is slightly folded with the dihedral angle between two phenoxide groups of 22°. Adjacent sets of the N_2O_2 donors are coplanar. The Co^{II}-Co^{III} distance is 3.15 Å, very similar to that described for previous structures.

Interestingly, in some cases, when acetate salts are used in the template synthesis chains can be isolated or dimeric cations may be linked by the oxygen donors (Fig. 1.14).

![Diagram](image)

Fig. 1.14 Geometry around the metal centres in a) cation chain \([\text{M}_2(2+2)(\text{AcO})]^+\) b) face to face dimer ion \({[	ext{M}_2(2+2)(\text{OAc})]_2(\text{O})_2}]^{n+}\).

Structures showing the face-to-face interactions of the dimer cation \({[	ext{Fe}_2^{\text{III}}(2+2)(\text{OAc})]_2(\text{O})_2}]^{2+}\) and an acetate linked cation chain, representing two unusual types of the possible central metal geometry in symmetrical (2+2) complexes (Fig. 1.12) are shown in Fig. 1.15.
The cation \([\text{Mn}_2(2+2)(\text{AcO})]^+\) (Fig. 1.15 a) consists of dinuclear macrocyclic units connected together by acetate ligands into a chain. In each unit the manganese environment is square pyramidal with two nitrogen and two oxygen atoms from the macrocyclic ligand and an oxygen atom from an acetate anion in the apical position. The Mn(II) cation lies above the base plane towards the acetate anion because it is too large to fit in within the macrocycle cavity. The Mn1-Mn1a separation is 3.27 Å.

The tetrairon complex (Fig. 1.15 b) was formed in the template reaction between the 2,6-diformyl-4-methylphenol and 1,3-diaminopropane in the presence of \(\text{NH}_4\text{PF}_6\). The crystal structure of the tetranuclear oxoiron(III) cation consists of two dinuclear \([\text{Fe}_2^{\text{III}}(2+2)(\text{OAc})]^{3+}\) macrocyclic units linked by the oxo ligands. Each unit has a flat
conformation except for the lateral aliphatic chains and binds two iron(III) ions in the \( \text{N}_2\text{O}_2 \) coordination sites. The metal ions are 6-coordinate and their coordination spheres are completed by oxo ligands and bridging acetate ions. The Fe1-Fe2 separation is 3.078 Å.

1.2.1.2. Stepwise template synthesis of (2+2) heterodinuclear systems

The macrocyclic complexes of symmetrical ligands discussed above, excluding the palladium complex (Fig. 1.13 a) were obtained in single step metal template condensation. However, unsymmetrical Robson type ligand systems cannot be produced in one step syntheses. The first stepwise synthesis was done by Okawa and Kida in 1972. They synthesised the mononuclear and dinuclear complexes of macrocyclic ligands similar to these reported by Robson. The family of complexes reported by Okawa and Kida is shown in Fig. 1.16.

![Complexes reported by Okawa](where \( n = 2 \) \( m = 2 \), \( n = 2 \) \( m = 3 \) and \( n = 3 \) \( m = 3 \) respectively).

The stepwise reaction is very useful in the synthesis of heterodinuclear systems or asymmetrical ligands. The heterodinuclear complexes of Schiff base macrocycles in comparison with acyclic ligands are additionally stabilised because of the macrocyclic effect. Furthermore the macrocyclic ligands can provide a well-defined environment for the bound metal ions which influence their potentially interesting physicochemical properties.

Template synthesis of the binucleating asymmetric ligand requires two steps in which two dissimilar diamine links are used. In the first step, a mononuclear open chain complex is produced in the condensation between two diformylphenol molecules and one diamine. In the second stage, the dicarbonyl complex is converted into a cyclic product.

17
by another Schiff base condensation but with a second diamine. If a heteronuclear complex is required, a different transition metal is used in the final stage.

The synthetic process adopted by Panther and Behrens, leading to the family of macrocyclic complexes featuring both dissimilar transition metals and lateral chains is shown in Fig. 1.17. An example structure of one of the complexes is also shown.

In general, structures of asymmetric ligand complexes are not much different from those for the symmetrical examples. As depicted in Fig. 1.17 the heterodinuclear \([\text{Ni}^{II}\text{Cu}^{II}(2+2)(\text{ClO}_4)_2]\) complex has a flat conformation exactly as found for the compounds with identical diamine links. Both metal ions are accommodated in the \(\text{N}_2\text{O}_2\) coordination sites. The Ni–N and Ni-O bonds are shorter than the relative Cu-N and Cu-O. The Ni(II) has a square planar geometry and Cu(II) is in the octahedral geometry with two perchlorate ions (for clarity only oxygens binding to copper are shown) binding axially. The metal-metal separation is 2.96 Å which is slightly less than in typical symmetrical Robson macrocycles.
Interestingly, when Pb(II) is used in the second cyclisation step, a sandwich complex is produced. The isolation of Cu$_2$ and Ni$_2$ sandwich complexes with Pb(II) by Okawa resulted in modification of their own stepwise metal template cyclisation procedure. The Cu$_2$Pb or Ni$_2$Pb sandwich complexes of asymmetrical ligand upon addition of M(II) sulphates undergo transmetallation reactions resulting insoluble PbSO$_4$ and CuM or NiM dinuclear complexes where M = Mn(II), Zn(II), Fe(II), Co(II), Ni(II) or Cu(II). This resulted in numerous macrocyclic ligands the with ability to coordinate various combinations of transition metals. Fig. 1.18 summarises the stepwise synthesis involving transmetallation of Cu$_2$Pb or Ni$_2$Pb sandwich complexes and shows the family of asymmetrical ligands and their complexes obtained via this method.

The structure of a Ni$^{II}$Mn$^{II}$ asymmetrical macrocyclic complex obtained via the described transmetallation route, and the structure of related sandwich Cu$_2$Pb complex are shown in Fig. 1.19.
In complex B both metals occupy the typical N₂O₂ coordination sites. Ni(II) assumes the square planar geometry and Mn(II) assumes 6-coordinate geometry with additional dmf molecules in cis-geometry to each other. Mn(II) ion is too large to fit into the macrocycle cavity so it lies above the basal plane of the macrocycle.

In the trinuclear cation A, the Pb(II) ion also is too large to fit into the macrocycle cavity. It lies above the mean plane of macrocycle and coordinates to two N₂O₂ sets of donor atoms from each macrocycle linking them into a sandwich molecule.

A heterodinuclear complex Cu^{II}Pb^{II} of a different (2+2) macrocyclic ligand was obtained also by Okawa. The incorporation of Pb(II) into the asymmetrical ligand to form dinuclear complex required a hydroxyl group in the lateral chain which coordinates to the metal ions. Incorporation of two lead(II) ions into a symmetrical dinuclear complex Pb₂(2+2) was also achieved.

The fact that the Robson macrocyclic ligand is able to accommodate the large Pb(II) cation prompted Lisowski and Starynowicz to synthesise family of heterodinuclear macrocyclic complexes containing Ni(II) and lanthanide ions of general formula [Ni^{II}Ln^{III}(2+2)]Cl₃. These were the first examples of 3d-4f complexes where the metals were bound within the macrocyclic core. The stepwise template cyclisation
leading to [Ni\textsuperscript{II}Ln\textsuperscript{III}(2+2)]Cl\textsubscript{3} complexes and molecular structure of [Ni\textsuperscript{II}La\textsuperscript{III}(2+2)]Cl\textsubscript{3} is presented in Fig. 1.20.

![Diagram of the molecular structure of [NiLa(2+2)]Cl\textsubscript{3} complex.]

Fig. 1.20 Stepwise template synthesis and molecular structure of the [NiLa(2+2)]Cl\textsubscript{3} complex.

In [Ni\textsuperscript{II}La\textsuperscript{III}(2+2)]Cl\textsubscript{3} the macrocycle retains a planar conformation with the exception of the side diamine link where alkoxo oxygen is coordinating to the lanthanum ion. La(III) ion is 8 coordinate and lies well above the macrocycle basal plane similar to the related Cu\textsuperscript{II}Pb\textsuperscript{II} complex.\textsuperscript{91}

1.2.1.3. Template synthesis of (2+2) polynuclear systems

The 2+2 condensation between 2,6-diformyl-4R-phenol (where R = tert-butyl or methyl) and various diamines (ethylene, triethylene, 1,3-diaminopropan-2-ol, or 1,3,5-triaminopropan) discussed above resulted mainly in dinuclear complexes of transition metals. In most cases, additional donor atoms introduced to the side chains were not involved in coordination to the central metal so the chelate rings about the metal centres remained essentially the same, preventing ligands from binding more than two ions. The few exceptions included the large Pb(II) and La(III) ions.\textsuperscript{87, 91-93} The first template synthesis of a tetranuclear (2+2) macrocyclic complex was reported by Robson et al.\textsuperscript{94}
Tetranickel(II) and tetracobalt(II) complexes of related acyclic Schiff base ligands were already known. The macrocyclic tetranucleating ligand was achieved by using sodium salt of 2,6-bis(aminomethyl)-4-methyl phenol as the diamine link in the condensation with the appropriate diformyl phenol. The schematic representation of the synthesis and the potential binding sites proposed by Robson are shown in Fig. 1.21.

Fig. 1.21 One pot template synthesis of the tetranucleating ligand reported by Robson.

Fig. 1.22 shows the crystal structure of the isolated tetranickel(II) complex. The four nickel ions are in an approximately square arrangement. The macrocycle provides three donors for each metal atom, the two phenolate oxygens and one imine nitrogen. The 6-coordinate geometry of the metal ions is completed by hydroxo bridge (O5), which binds equally to all four nickel ions and by bridging acetate ions and methanol molecules. The macrocycle has a bowl-like conformation with the aromatic rings inclined on the same side of the Ni₄ plane which is reminiscent of the calixarenes.

Fig. 1.22 Crystal structure of the [Ni₄(2+2)(OH)(OAc)₂(MeO·H·MeO)] complex.
Simultaneously, McKee and Tandon reported syntheses of tetracopper\(^{96}\) and the tetramanganese\(^{97}\) complexes of the (2+2) macrocycles derived from 1,5-diaminopentan-3-ol and 2,6-diformyl-4-\textit{tert}-butyl- or 2,6-diformyl-4-methylphenol respectively. A schematic representation of the synthesis and binding sites of the ligand are shown in Fig. 1.23.

As shown in Figure 1.23 the (2+2) macrocyclic ligand has a five-carbon side chain carrying an additional oxygen donor which somewhat corresponds to the tetraneucleating ligand reported by Robson. However, the lateral chain carbons are aliphatic and their oxygen donors are alcohol groups. This brings some flexibility to the system in comparison with the relatively rigid aromatic system of the diiminophenol. For this reason the molecular structure of the tetracopper(II) species has flat conformation (Fig. 1.24) in contrast to the bowl-shaped tetranickel(II) species reported by Robson.

Fig. 1.23 Template synthesis of the tetranuclear complexes reported by Tandon and McKee.\(^{96-97}\)

Fig. 1.24 The top (left) and the edge (right) view of the \([\text{Cu}_4(2+2)\text{OH}]^{3+}\) cation reported by McKee.\(^{96}\) The nitrates and water donors are removed for clarity.
In the \([\text{Cu}_4(2+2)(\text{OH})]^3+\) cation each metal ion is coordinated to an imine nitrogen, one phenoxide oxygen, one alkoxide oxygen, the central hydroxide ion and one axial donor water or nitrate. All oxygen donors are deprotonated and each bridges two adjacent Cu(II) ions.

In the non protic solvents, or with added base, the tetracopper(II) complex dimerises with loss of the proton from the central hydroxo group to give an octacopper(II) complex (Fig. 1.25).

![Diagram](image_url)

**Fig. 1.25** Dimerisation of the tetracopper(II) complex into the octacopper(II) promoted by base.

In the octacopper complex the halves of the dimer are linked by the central oxo ligand of each macrocyclic unit. The independent macrocyclic units are arranged in similar manner as in the tetracopper(II) monomer. The oxo anion (O1) is 5-coordinate binding to the four Cu(II) ions from the one macrocyclic ligand and axially to the Cu2a atom from the second macrocyclic unit. This bond and the equivalent bond between the central oxo oxygen from the second macrocycle hold the dimeric ion together. In addition there are weaker interactions between Cu1 and O4a, Cu3 and O3a, Cu1a and O4, and Cu3 and O3 which are marked by the dashed lines.

Homonuclear multi template Schiff base condensations between 2,6-diformyl-4R-phenol (R = Me or tert-butyl) and 1,5-diaminopentane-3-ol or 2,6-
bis(aminomethyl)-4-methylphenol results in macrocyclic ligands having the four metals in close proximity and essentially in the same coordination environment. The shape of the complex depends on the nature of the side link. Various tetranuclear complexes of these types can be afforded by other template reactions.\textsuperscript{100-102}

More recently McKee \textit{et al.}\textsuperscript{103-104} isolated and structurally characterised heterotetranuclear complexes of the same (2+2) macrocyclic ligand. The stepwise synthesis involved metal deficient template formation of the dicopper(II) complex with two protonated empty sites. Then this precursor was reacted with a Ni(II) salt to yield the final product. The geometrical arrangement of the metal ions in the final product was found to be determined by the geometry of the dinuclear intermediate. From the three possible arrangements of Cu(II) ions within the four potential binding sites, the copper ions adopted the side-by-side geometry binding to the alkoxo, hydroxo and two phenoxo donors (Fig. 1.26).

![Controlled synthesis of the Cu\textsubscript{2}Ni\textsubscript{2} heterotetranuclear complex of the (2+2) macrocycle.](image)

The structure of the neutral complex \{[Cu\textsubscript{2}Ni\textsubscript{2}(2+2)O(OAc)][Ni\textsubscript{2}(dfmp)(OAc)(OH)\textsubscript{3}]} \textsuperscript{104} and coordination sphere of the metal centres are shown in Fig. 1.27. The structure of macrocyclic part is essentially the same as the homotetranuclear species described
above. The metal ions are bridged by deprotonated phenoxyo and alkoxo donors together with the central oxo ligand. The Ni1 and Ni2 ions are additionally bridged by the acetate ion below the basal plane and by diformylmethylphenolate anion with hydroxo oxygen at the top. The additional hydroxide and a second acetate ion bridge the Ni3 and Ni4 ions in an assembly sitting on top of the macrocycle.

![Structure of the [[Cu2Ni2(2+2)O(OAc)]]Ni2(dfmp)(OAc)(OH)3] complex.](image)

1.2.1.4. Template synthesis of (n+n) systems

Polynuclear Schiff base complexes are of special interest because of their bonding and magnetic interactions and also because polymetallic centres in close proximity have potential value in catalysis. The condensations between 2,6-diformyl-4R-phenol (R = Me or tert-butyl) and various diamine links in the presence of transition metals described above led to di- tri- or tetranuclear species of the (2+2) macrocycle. In order to divert condensation into the larger macrocyclic products, Tandon et al.\textsuperscript{105} used the 1,3-diaminopropan-2-ol linker and additional base (NEt\textsubscript{3}) for deprotonating the hydroxyl groups promoting their coordination. This resulted in a new (3+3) cyclisation product in the form of hexanuclear complex which additionally formed a dodecanuclear dimer (Fig. 1.28).
Fig. 1.28 Template synthesis of the hexanuclear complex of the (3+3) macrocycle and structures of the [Cu₆(3+3)(OH)]³⁺ and [{Cu₆(3+3)(OH)}₂(NO₃)₂]⁺ cations.

Each macrocyclic unit has a dished conformation with six Cu(II) ions in approximately square planar geometry coordinating to the imine nitrogen and phenolate, alkoxide and hydroxide oxygens which make the bridges between the metal centres. The six and five atom chelate rings involving phenolate and alkoxide oxygen donors form a flat hexagonal arrangement of the copper centres. The central cavity of the macrocycle is occupied by three hydroxides, of which two interact axially with the Cu(II) ions from the second macrocyclic unit, holding the dimer together.

A hexanuclear complex of a (3+3) macrocycle was also reported by Robson et al.¹⁰⁶ (Fig. 1.29). The Cu(II) template synthesis between 2,6-diformyl-4-methyl-phenol and 2,6-diaminomethyl-4-methylphenol in one case (instead of the (2+2) complex) resulted in an expanded (3+3) macrocycle incorporating six metal ions. In contrast to the
complex reported by Tandon, in this relatively rigid system the six Cu(II) ions adopt a boat conformation.

Tandon also reported a slightly modified metal template condensation between 2,6-diformyl methylphenol and 1,3-diaminopropan-2-ol leading to the heptanuclear complex of the same (3+3) condensate. This complex, again forms a dimeric complex accommodating fourteen copper(II) ions in the assembly. Half of the dimer molecule together with the metal arrangement is presented in Fig. 1.30.
The macrocyclic unit adopted a similar conformation to the hexanuclear complex and the hexagonal arrangement of six Cu(II) ions remained the same. The seventh copper ion filled in the hole at the centre of the hexagon.

A (3+3) Schiff base macrocycle derived from 2,6-diformyl-4-methyl phenol can also be formed in alkali metal template synthesis. Using an excess of the group 1 metal Gao synthesised a family of free macrocyclic ligands with the chiral diamine links. Formally, transition metal complexes of the ligands (Fig. 1.31) can be generated by direct reaction of ligand with the required metal such as Ni(II), Cu(II) or Zn(II). Surprisingly, when the Ni(II) salt was used for the insertion, a ring contraction reaction leading to the dinuclear complex of the (2+2) macrocycle took place. The trinickel(II) complex was only afforded when the sodium salt of the (3+3) ligand was used in the complexation reaction.

Fig. 1.31 Gao alkali metal template synthesis of (3+3) macrocyclic ligands containing chiral side links and complexation properties of one of them.
1.2.2. Schiff base pseudocalixarene macrocycles

Calixarenes are oligocyclic compounds consisting of $p$-substituted phenol rings separated by methylene links. The history of calixarenes is as old as the history of the polymer Bakelite, which resulted in the phenol – formaldehyde condensation. The presence of tetracyclic compounds among the products of the phenol – formaldehyde reaction was presumed, but not confirmed, by Zinke and Ziegler in the 1940s.\textsuperscript{109-110} Their work was continued by Cornforth who was able to isolate two tetrameric products of similar melting points and molecular weights.\textsuperscript{111} The name “calixarene” was first introduced by Gutsche and Mathukrishnan and is derived from the Greek vase called “calix crater”\textsuperscript{10} It originated from the shape similarity between a vase and the space filling model of the cyclic tetramer. The “arene” part indicates the aromatic moieties in the system. The pioneering work in field of calixarenes was done by the same researchers\textsuperscript{112-119} and subsequently also by the Shinkai group.\textsuperscript{120-123} The more systematic name calix[n]arene is dependent on the number of aromatic rings in the cyclic compound ($n$ can be 4, 5, 6, 7 or 8), and residue in $p$-position on the phenol atoms. The $p$-tert-butyl-calix[4]arene is shown in Fig. 1.32.

![Diagram of calix[4]arenes](image)

Fig. 1.32 Conformations of calix[4]arenes.\textsuperscript{115-118}

Calix[n]arenes are conformationally mobile in solution at room temperature. However, this ability can be frozen by transforming phenolic groups into bulky esters or ethers.\textsuperscript{114} Calix[4]arenes have four conformational isomers named: cone, partial cone, 1,2-
alternate and 1,3-alternate and these are illustrated in Fig. 1.32. The larger rings are more flexible so assigning conformations is less relevant. The conformations of calix[5] and calix[7] have not been studied so intensively because of synthetic issues but it is known that 5-membered calix rings in the solid state have a cone conformation. The molecular structure of the \textit{p-}tert-butyl-calix[4]arene\textsuperscript{124} showing cone conformation is presented in Fig. 1.33.

![Crystal structure of the \textit{p-}tert-butylcalix[4]arene\textsuperscript{124}; top and side view; hydrogen bonding is marked by dashed lines.](image)

The planar conformation is sterically prohibited for calixarenes and therefore coordinated metal ions cannot take full advantage of the bridging potential of the phenol groups. Moreover, the hydrogen bond system makes the lower rim tetraphenolic site hardly accessible by the potential metal ion guest. This hydrogen bonding can be removed in two ways, one involves transformation of the calixarene into the ether or ester form which form complexes more readily. The second, less convenient, requires the use of very strong base for the formation of the mono- or dianionic form of the calixarene. The calixarenes have one additional coordination site, the \(\pi\)-electron rich cavity which allows them to form inclusion complexes with various species such as amines, solvent molecules or metal ions.\textsuperscript{125-127} Example structures of calix[4]arene complexes with Na(I)\textsuperscript{128} and Rb(I)\textsuperscript{129} are shown in Fig. 1.34.
In contrast to most calix[n]arenes, the Schiff base macrocyclic ligands discussed in previous sections make complexes using some or all of their phenolic oxygens in the bridging mode. This allows them to form polynuclear species. In order to merge properties of both calixarenes and Robson macrocycles our group developed the new class of macrocyclic compounds called pseudocalixarenes. An example of a pseudocalixarene is the Schiff base macrocycle formed by the condensation between 2,2'-methylene-bis-[(6-formyl)-4-tert-butyl]phenol (H$_2$mftbp) and diamine compound as a side link. The expansion of the Robson macrocycle by an extra phenolic unit of the dicarbonyl adds more possible binding sites within the Schiff base macrocyclic ligand relative to the Robson macrocycle. The (2+2) condensation product between H$_2$mftbp and diamine features the Robson-like N$_2$O$_2$ binding sites (A) and the hard tetraphenolic site (B), and the methylenediphenol group characteristic of calixarenes (Fig. 1.35).
The pseudocalixarene formed with 1,3-diaminopropan-2-ol as the side link possesses three binding sites. Two of them are mentioned above and the third one results from the bridging properties of the alkoxo ligand. This new macrocyclic ligand is capable of forming mono- di- tri- and tetranuclear species (Fig. 1.36).

![Figure 1.36 Schematic representation of mono- di- tri- and tetranuclear complexes of pseudocalixarene macrocycle.](image)

1.2.2.1. Metal template free synthesis of pseudocalixarenes

Independently from our group, Hisaeda and co-workers reported the synthesis of similar macrocyclic ligands derived from 2,2'-methylene-bis-6-formylmethylphenol. Under high dilution conditions the diformyl compound was reacted with 1,2-bis(2-aminoethoxy)ethane to afford a mixture of (2+2), (3+3), (4+4), (5+5), (6+6) and (7+7) cyclocondensation products of which the first three were successfully isolated.

![Figure 1.37 Pseudocalixarenes isolated by Hisaeda in non template synthesis.](image)
The (2+2) condensate was the major product obtained by the non-template method. However, when the boric acid is employed as a template a pure macrocyclic ligand can be obtained.\textsuperscript{134} The structure of the free pseudocalixarene ligand afforded in the condensation between H\textsubscript{2}mftbp and o-phenylenediamine is shown in Fig. 1.38.

![Fig. 1.38 The free pseudocalixarene macrocycle yield by Hiseada.\textsuperscript{134}](image)

### 1.2.2.2. Transition metal template synthesis of dinuclear complexes

When the condensation between H\textsubscript{2}mftbp and 1,3-diaminopropan-2-ol is carried in the presence of the transition metal salt (transition metal:dialdehyde:diamine molar ratio 1:1:1) it yields dinuclear complexes of the pseudocalixarene. Dinuclear complexes with transition metals like Cu(II), Zn(II), Co(II), Ni(II), Mn(II) were successfully synthesised and characterised by J. Barreira Fontecha in our group (Fig. 1.39).\textsuperscript{132,135}

![Fig. 1.39 Transition metal template synthesis of (2+2) pseudocalixarene Schiff base macrocycle.](image)

In general, for the dinuclear complexes investigated by J. Barreira Fontecha the macrocyclic ligand is doubly deprotonated with one proton lost from each methylenediphenol group. A saddle shape conformation results due to strong hydrogen
bonds between phenol and phenolate oxygen. Each metal is coordinated by two phenol oxygen, two imine nitrogen donors and, if there is a link between the metal ions, by the bridging group. The basal planes about each metal centres are inclined at ca. 86° to each other. The metal separation varies from 3.6 Å to 4.4 Å. A schematic representation of the metal geometry in the V-shaped complex with (2+2) macrocyclic ligand is shown in Fig. 1.40.

Fig. 1.40 Schematic representation of metal geometry within a typical saddle shaped (2+2) macrocycle.

Figure 1.41 shows examples of two saddle-shape cations [Cu$_2$H$_2$(2+2)Cl]$^{+}$ and [Ni$_2$H$_2$(2+2)(MeOH)$_2$]$^{2+}$, in which the conformation is attributed to the H-bond between monodeprotonated methylenediphenols.\textsuperscript{132,135} This is especially clear for the nickel cation, where the methanol oxygen (O2s) axially coordinating to Ni2 is too far from the second nickel ion to make a bridge but, despite this the macrocycle still has a saddle conformation. In the copper cation the shape is additionally stabilised by the chloride link between Cu1 and Cu2.

Fig. 1.41 Structures of a) [Cu$_2$H$_2$(2+2)Cl]$^{+}$ cation and b) [Ni$_2$H$_2$(2+2)(MeOH)$_2$]$^{2+}$ cation.\textsuperscript{132,135}
The saddle-shape conformation of the macrocyclic complex is lost when Mn(III) is used as a template in the (2+2) condensation. Mn(III) is a stronger Lewis acid than the divalent metal ions and causes full deprotonation of the phenols so removes the H-bonds. The metal ions are further apart than in the examples described above (ca. 7 Å) and the phenolate groups are rotated. The metal ions lie on opposite sides of the macrocycle (Fig. 1.42).

![Fig. 1.42 Structure of neutral open conformation complex [Mn$_2^{III}$(2+2)(Cl)$_2$(dmf)(dms)]](image)

A second possible method of opening the saddle-shape conformation is feasible by pH change for divalent metals. In basic solutions all the phenols are fully deprotonated so H-bonding is not possible and the saddle-shape cannot be maintained. An example structure of an “open” [Cu$_2$(2+2)] neutral macrocyclic complex is presented in Fig. 1.43. The complex is very similar to that described for trivalent manganese, the Cu(II) ions and phenolate oxygens in each methylenediphenol are well separated and macrocycle is stretched.

![Fig. 1.43 Structure of [Cu$_2$(2+2)] open conformation complex.](image)
Possible transformations between open and saddle-shape structure are schematically presented in Fig. 1.44.

Fig. 1.44. Possible switching between saddle shape and open conformation.

1.2.2.3. Transition metal template synthesis of tri- and tetra-homonuclear complexes of the (2+2) macrocycle

The condensation between H₂mftbp and 1,3-diaminopropan-2-ol in the presence of two equivalents of Cu(NO₃)₂·6H₂O (Cu:dialdehyde:diamine molar ratio 2:1:1) on short reflux (up to 1 h.) yields the tetracopper product which on recrystallisation from dmf converts into the tricopper species. Overnight reflux of the same reaction mixture produces a mixture of tri- and tetranuclear species (Fig. 1.45).¹³²

Fig. 1.45 Schematic representation of template synthesis of polynuclear complexes.
The crystal structures of both tetracopper(II) and tricopper(II) complexes of the (2+2) macrocycle are presented in Fig. 1.46.

Fig. 1.46 Structures of a) [Cu$_3$(2+2)NO$_3$]$^+$ cation b) [Cu$_4$(2+2)(OH)$_2$(H$_2$O)(EtOH)]$^+$ cation.$^{131}$

The trinuclear complex (a) has very similar conformation to the H-bonded dinuclear species. The central Cu(II) ion holds the saddle-shape of complex by binding to the four phenolate oxygens. In terms of Pearson HSAB theory this is not expected to be a preferred coordination site for Cu(II) but it is possible that charge transfer from fully deprotonated phenols stabilises the structure. The remaining copper ions reside in the typical Robson type N$_2$O$_2$ coordination sites. All three copper ions complete their coordination spheres by binding axially to nitrate oxygen donors. The tetrnuclear complex (b) is different from di- and trinuclear, the macrocycle is sharply folded down its long axis with each half close to planar. The adjacent phenols are monodeprotonated and connected by hydrogen bonds (dashed lines). The Cu(II) ions occupy the four equivalent NO$_2$ sites with three donors provided by macrocyclic ligand, the imine nitrogen, phenoxo and alkoxo oxygens. Additionally Cu1 and Cu4 are bridged by hydroxide and water oxygen donors and Cu2 and Cu3 by hydroxide and ethanol donors.$^{131}$
1.3. Aim of this work

The purpose of work described in this thesis is to study template mechanisms for formation of (2+2), (3+3) and (4+4) pseudocalixarene Schiff base macrocyclic complexes with transition metals and transition metals with group 1 or 2 metals. The roles that metal ions play during formation of these macrocycles and possible impact on the distribution of products will be examined. To investigate what happens in reaction mixtures during the syntheses an electrospray ionisation mass spectrometry (ESI-MS) is employed.
Chapter 2

SYNTHESIS OF 4-SUBSTITUTED METHYLENEDIPHENOL DIALDEHYDES
2.1. Introduction

The synthesis of methylenediphenol dialdehydes (compound 2 in Fig. 2.1) containing two salicylaldehyde units joined by a methylene link has been recently under development in the McKee group.\textsuperscript{135,136-137} The process comprises two major steps similar to the synthesis of p-substituted diformylphenols.\textsuperscript{138} A reaction scheme showing routes to the phenol related Schiff base macrocyclic compounds and calixarenes is shown in Fig. 2.1. In the first step methylenediphenol dialcohol (compound 1 in Fig. 2.1) is formed in a hydroxymethylation between phenol and formaldehyde (reaction A).

![Reaction Scheme](image)

Fig. 2.1 Schematic representation of phenol – formaldehyde reactions yielding precursors and their transformation into macrocycles.
As described in the introduction chapter, the reaction between phenol and formaldehyde has been known from the beginning of the 20th century when the polymer Bakelite was produced for the first time.\textsuperscript{109-110} Since then, the reaction has been extensively studied but despite that, it is still difficult to direct it to a specific linear oligomer. Nevertheless, a procedure for the isolation of methylenediphenol dialcohol (which is used in synthesis of asymmetric calixarenes) can be found in the literature.\textsuperscript{139} The mechanism of the phenol-formaldehyde reaction in basic solution was proposed in the last century\textsuperscript{140} but it is still not certain why particular linear oligomers or calixarenes are formed under particular conditions. The reaction probably occurs through the hydroxymethylphenol unit forming o-quinonemethides which react with the starting phenolates to produce oligomers (Fig. 2.2).

![Fig. 2.2 Formation mechanism of methylenediphenol dialcohols.](image)

The second step in the synthesis of dicarbonyls (reaction B in Fig. 2.1) requires selective oxidation of the lateral alcohol groups, leaving the phenols and methylene link unaffected.

Figure 2.3 shows the three methylenediphenol dialdehydes successfully synthesised in our group together with corresponding dialcohols. Their syntheses will be described in this chapter. Reaction C presented in Fig. 2.1, the condensation of dialdehydes with
diamine compounds leading to the related macrocyclic products, will be discussed in the following chapters.

Fig. 2.3 Methylene diphenol dialdehydes and dialcohols synthesised in the McKee group.
2.2. Organic synthesis

Synthetic procedures developed for the three dialdehydes are shown in Fig. 2.4. In general, addition of base to the solution containing 4-substituted phenol and formaldehyde initiated the reaction. Then after an appropriate time to the cooled reaction mixture acid was introduced to neutralise oligomeric phenolic species. Protonated phenols are less soluble in the aqueous solution so usually they precipitated as white solids. Separation of the desired compound was achieved by means of selective extraction or recrystallisation. In the next step isolated methylenediphenol dialcohols were oxidised to the related dialdehydes using activated manganese (IV) oxide.

Fig. 2.4 Synthetic routes for three methylenediphenol dialdehydes.
2.2.1. Synthesis of 2,2’–methylene-bis-[(6-hydroxymethyl)-4-tert-butylphenol]

(H$_2$mhtbp; 2.1)

In general, the synthesis of H$_2$mhtbp was the most inconvenient and had the lowest overall yield 16%. The H$_2$mhtbp was synthesized from 4-tert-butyphenol and formaldehyde following the literature procedure with slight modifications.$^{139}$ The 4-tert-butyphenol was ground before use and placed with formaldehyde under an atmosphere of N$_2$. Then sodium hydroxide solution was added (phenol:NaOH molar ratio 1:1) and the mixture was heated at 50 °C, in an atmosphere of N$_2$ for 8 days. The resulting resinous precipitate was filtered off and dissolved in 50 mL of acetone. At this stage another precipitate had formed which was removed by filtration. The acetone solution was then acidified using cold acetic acid. Because the expected oil separation$^{139}$ did not take place the acidic solution was diluted and extracted with diethyl ether and with ethylacetate. Both organic extracts were combined, washed with H$_2$O and dried over anhydrous Na$_2$SO$_4$, and the solvents were removed to yield over 30 g of orange oily substance. This was dissolved in toluene and product was precipitated by light petroleum ether to produce H$_2$mhtbp in 16% yield. The literature yield 20% has not been reached despite: a) the extraction was carried with various solvents (xylene, chloroform or toluene), b) different solvent mixtures were used to precipitate the H$_2$mhtbp and c) numerous solvents were employed in Soxhlet extractions.

Column chromatography of dry orange oily substance (CHCl$_3$:aceton 10:1 v/v) gave the product but with significantly reduced yield. Also 2,6-hydroxymethyl-4-tert-butyl phenol and methylenetriphenol dialcohol were identified in the orange oil after chromatographic separation.

The low literature yield of H$_2$mhtbp$^{139}$ might suggest that the methylenediphenol is not the major species among several oligomeric phenol based products in the reaction mixture. Perhaps change of the experimental conditions such as a different reaction time or a base would result in the mixture where H$_2$mhtbp will be a major compound.

The $^1$H NMR spectrum of H$_2$mhtbp shows characteristic singlets at 3.83 ppm and 4.69 ppm, for CH$_3$OH and CH$_2$ in 2:1 ratio which confirms the purity (Fig. 2.5).
**2,2'-methylene-bis-[6-hydroxymethyl]-4-tert-butylphenol H$_2$ mhtbp**

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<tr>
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<td>8.38 ppm</td>
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Fig. 2.5 $^1$H NMR spectrum and proton assignments for H$_2$mhtbp in CDCl$_3$. 
2.2.2. Synthesis of 2,2’-methylene-bis-[(6-hydroxymethyl)-4-methylphenol] (H$_2$mhmp; 2.2$^{141}$)

The methyl-substituted compound was prepared from 4-cresol and formaldehyde$^{141}$ under very mild conditions in comparison to the other phenols. The molar ratio of a weak base, K$_2$CO$_3$, used in relation to phenol was 1.5:1. The reaction time was only 24 h. The work-up procedure involved: a) neutralisation of phenolic solution with hydrochloric acid, b) filtration of the resulting yellowish solid and c) washing with ethylacetate:cyclohexane mixture (1:1 v/v). The resulting off-white solid was dried in air to 31% yield. Formation of H$_2$mhmp was confirmed by $^1$H NMR. The spectrum (Fig. 2.6) shows phenol aromatic proton peaks (singlets), methyl aliphatic protons (singlet), methylene link protons and hydroxymethyl group protons (both are singlets). To determine H$_2$mhmp purity the most important information is the ratio between the integrals for methylene and hydroxymethyl group protons {3.77 and 4.67 [ppm] respectively in d-chloroform} which should be 2:1. If it is otherwise, then the sample contains some other oligomers.

![2,2’-methylene-bis-[(6-hydroxymethyl)-4-methylphenol] H$_2$mhmp](image)

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<tr>
<td>d</td>
<td>6.95 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>e</td>
<td>6.67 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>f</td>
<td>8.38 ppm</td>
<td>2H, s</td>
</tr>
</tbody>
</table>

Fig. 2.6 $^1$H NMR spectrum and proton assignments for H$_2$mhmp in CDCl$_3$. 
2.2.3. Synthesis of 2,2’–methylene-bis-[(6-hydroxymethyl)-4-phenylphenol] (H$_2$mhpp; 2.3)

This novel ligand precursor has been synthesized for the first time in our lab. Incorporating phenyl group instead of aliphatic should strengthen the π–π in molecular level interactions, increase the rigidity of the molecule and give the possibility of fluorescence which is important in terms of sensor chemistry.

The 4-phenylphenol was treated with an excess of two equiv. of KOH and 4 days stirring at 40°C to react with formaldehyde and yield H$_2$mhpp as one of the main products. The TLC study on the reaction mixture after acidification showed two major components. The structure of the second product was determined by EI-MS and $^1$H NMR to be of 2,6-hydroxymethyl-4-phenylphenol. The separation of the two compounds was achieved by selective extraction of the single phenol dialcohol into hot chloroform. Recrystallisation from methanol gave spectroscopically pure H$_2$mhpp. The yield (49%) is the highest observed for methylenediphenol dialcohols in the phenol–formaldehyde condensation. Figure 2.7 shows the $^1$H NMR spectrum and assignments for H$_2$mhpp acquired in d$_6$-dmso.

<table>
<thead>
<tr>
<th>Protons</th>
<th>Chemical shift (d-DMSO)</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>7.2-7.5 ppm</td>
<td>2H, m</td>
</tr>
<tr>
<td>b</td>
<td>4.03 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>c</td>
<td>4.67 ppm</td>
<td>4H, s</td>
</tr>
<tr>
<td>d</td>
<td>7.2-7.5 ppm</td>
<td>2H, m</td>
</tr>
<tr>
<td>e</td>
<td>7.2-7.5 ppm</td>
<td>2H, m</td>
</tr>
<tr>
<td>f</td>
<td>8.9 ppm</td>
<td>2H, bs</td>
</tr>
<tr>
<td>g</td>
<td>7.2-7.5 ppm</td>
<td>4H, m</td>
</tr>
<tr>
<td>h</td>
<td>7.2-7.5 ppm</td>
<td>4H, m</td>
</tr>
</tbody>
</table>

Fig. 2.7 $^1$H NMR spectrum and proton assignments for H$_2$mhpp in (CD$_3$)$_2$SO.
2.2.4. Summary of methylenediphenol dialcohol synthesis

The three targeted dialcohols were successfully isolated from phenol-formaldehyde base catalysed condensations in yields ranging from 16% to 49%. The yields obtained were low but corresponded to the literature values.\textsuperscript{139, 141} As the main impurities, the 2,6-bis-hydroxymethylphenol and the triphenolic oligomer were identified by mass spectrometry.

![Chemical structures](image)

Fig. 2.8 The impurities identified during synthesis of methylenediphenol dialcohols.

As mentioned above, the phenol-formaldehyde condensation is very difficult to control in terms of diversion into one single product. A summary of the analytical characterisations is shown in Table 2.1. The methylenediphenoldialcohols melted at temperatures about 140°C. They all showed affinity for the sodium cation which was noticed by means of mass spectroscopy (EI-MS). The mass peak for [M+Na]\textsuperscript{+} was present in data collected for each compound. They behaved in the same manner on thin layer chromatography (TLC). The retention factor (R\textsubscript{f}) values measured for them in chloroform:acetone (5:1 v/v) were approx 0.3. The 2:1 hydroxymethyl to methylene proton ratio in \textsuperscript{1}H NMR was observed across all spectra which were acquired.

<table>
<thead>
<tr>
<th>Methylenediphenol dialcohol</th>
<th>Melting point [°]</th>
<th>TLC RF values in CHCl\textsubscript{3}:Acetone 5:1(v/v)</th>
<th>EI-MS peaks [M+Na]\textsuperscript{+} m/z</th>
<th>Characteristic δ [ppm] for hydroxymethyl and methylene link</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{H}_2\text{mhpp})</td>
<td>137-39</td>
<td>0.26</td>
<td>435</td>
<td>4.67 (4H, s) 4.03 (2H, s)</td>
<td>49</td>
</tr>
<tr>
<td>(\text{H}_2\text{mhmp})</td>
<td>139-141</td>
<td>0.34</td>
<td>311</td>
<td>4.67 (4H, s) 3.77 (2H, s)</td>
<td>30</td>
</tr>
<tr>
<td>(\text{H}_2\text{mhtbp})</td>
<td>145-147</td>
<td>0.3</td>
<td>395</td>
<td>4.69 (4H, s) 3.83 (2H, s)</td>
<td>16</td>
</tr>
</tbody>
</table>
2.2.5. Oxidation of methylenediphenol dialcohols to their carbonyl derivatives

Since Ball, Goodwin and Morton first reported the use of MnO$_2$ for transformation of vitamin A to retinene$^{142}$ it has been a very popular oxidising agent especially in the oxidations of primary and secondary alcohols to the corresponding carbonyl compounds.$^{143-148}$ It is a selective oxidant which can be used in various solvents, (chloroform, dichloromethane, pet ether, acetone, hexane or acetonitrile). The choice of solvent is important as water and alcohols compete with substrates in the adsorption processes occurring on the MnO$_2$ surface which causes its deactivation. The activation can be achieved by simple dehydration techniques.$^{149}$

Activated MnO$_2$ can be prepared by reduction of permanganate anion in neutral or basic aqueous solution as is described by the equation: $^{150}$

$$2\text{KMnO}_4 + 3\text{MnSO}_4 + 2\text{H}_2\text{O} \rightarrow 5\text{MnO}_2 + \text{K}_2\text{SO}_4 + 2\text{H}_2\text{SO}_4$$

The oxidation mechanism with manganese(IV) oxide is thought to involve an adsorption stage, a coordinated stage with Mn(IV) and an intermediate with a Mn(III) free radical site.$^{151}$ The typical oxidation pattern is presented in Fig. 2.9.

![Fig. 2.9 The MnO$_2$ oxidation mechanism.$^{151}$](image)

The MnO$_2$ can be used in one pot oxidation process which leads directly from primary alcohols to a range of synthetically useful functionalities.$^{152-154}$

Oxidations of the methylenediphenol dialcohols to their dialdehyde forms were carried with MnO$_2$ as an oxidising agent. For each gram of dialcohol 5 g of MnO$_2$ was used.
The reaction progress was followed by TLC and $^1$H NMR spectroscopy. When complete transformation was confirmed, the MnO$_2$ was filtered off and washed with chloroform or dry THF. Then solvent was removed under vacuum and the dialdehyde was crystallised from ethanol. Results are discussed below.

2.2.5.1. Oxidation of H$_2$mhtbp to 2,2'-methylene-bis-[(6-formyl)-4-tert-butylphenol] (H$_2$mftbp; 2.4)

Oxidation of H$_2$mhtbp was the easiest. H$_2$mhtbp was just stirred in chloroform with MnO$_2$ for 5 h. at ambient temperature and then reaction mixture was filtered. The expected dialdehyde was produced after rotary evaporation of the chloroform washings. In addition, it was purified by recrystallisation from EtOH to give H$_2$mftbp in 50% yield. Figure 2.10 shows the $^1$H NMR spectrum acquired in CDCl$_3$ with proton assignments. NMR spectroscopy confirmed formation of the dialdehyde compound as, with the progress of the reaction, the peak due to the hydroxymethyl group at 4.66 [ppm] disappeared and the aldehyde appeared at 11 [ppm].

<table>
<thead>
<tr>
<th>Proton(s)</th>
<th>Chemical shift in CDCl$_3$</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1.22 ppm</td>
<td>18H, s</td>
</tr>
<tr>
<td>b</td>
<td>3.96 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>c</td>
<td>11.12 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>d</td>
<td>7.30 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>e</td>
<td>7.58 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>f</td>
<td>9.79 ppm</td>
<td>2H, s</td>
</tr>
</tbody>
</table>

Fig. 2.10 $^1$H NMR spectrum and proton assignments for H$_2$mftbp in CDCl$_3$. 
2.2.5.2. Oxidation of H$_2$mhmp to 2,2’–methylene-bis-[(6-formyl)-4-methylphenol] (H$_2$mfmp; 2.5)

Oxidation was performed in dry THF due to poor solubility of H$_2$mhmp in chloroform. The full conversion to dialdehyde was achieved after 4 h. of reflux as established by TLC and NMR. Then the reaction mixture was filtered under reduced pressure. The dialdehyde was washed out from MnO$_2$ filter cake with THF followed by chloroform. In the most cases when the filtrate with combined washings was evaporated a brown oil appeared. The recrystallisation procedure from ethanol as well as precipitation from mixtures of solvents (toluene/pet ether, toluene/n-hexane, and chloroform/n-hexane) did not result in the separation of carbonyl compound from this oil. It seemed possible that the methylenediphenol dialdehyde might be deprotonated and still bonded to manganese species, acidic extractions were attempted to either chloroform or diethylether but these were also unsuccessful.

Column chromatography with a range of chloroform:acetone mixtures starting from 30:1 to 5:1 (v/v) yielded spectroscopically pure H$_2$mfmp but reduced the yield of the oxidation to 10%. A higher mass of oxidizing agent was tested but at the end oil was observed. The highest yield of the oxidation (20%) was achieved when the crude solid was isolated directly by evaporation of filtrate. After several experiments, conditions which have to be fulfilled together to reproduce this result were determined: a) MnO$_2$ has to be freshly made (no longer than 4 days kept in the oven), b) really dry THF has to be used for making MnO$_2$ suspension and c) reactant alcohol must be dry.

![2,2’–methylene-bis-[(6-formyl)-4-methylphenol] H$_2$mfmp](image)

<table>
<thead>
<tr>
<th>Proton(s)</th>
<th>Chemical shift in CDCl$_3$</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2.2 ppm</td>
<td>6H, s</td>
</tr>
<tr>
<td>b</td>
<td>3.92 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>c</td>
<td>11.1 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>d</td>
<td>7.14 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>e</td>
<td>7.22 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>f</td>
<td>9.77 ppm</td>
<td>2H, s</td>
</tr>
</tbody>
</table>

Fig. 2.11 $^1$H NMR spectrum and proton assignments for H$_2$mfmp in CDCl$_3$.\n
The product was easily identified by IR and $^1$H NMR spectroscopy. The IR spectrum showed characteristic C=O stretching vibration at $1649 \text{ cm}^{-1}$ and phenolic OH bending vibrations at $1268 \text{ cm}^{-1}$ and in NMR a similar characteristic peak disappearance and appearance of aldehyde peaks at $11 \text{ [ppm]}$ as for $\text{H}_2\text{mfbp}$ were observed (Fig. 2.11).

2.2.5.3. Oxidation of $\text{H}_2\text{mhpp}$ to 2,2'–methylene-bis-[(6-formyl)-4-phenylphenol] ($\text{H}_2\text{mfpp}; 2.6$)

For the same reason as for the oxidation of $\text{H}_2\text{mhmp}$, dry THF was employed as solvent, using the same mass ratio of reagents and the same reaction time. After rotary evaporation to dryness of the filtrate and MnO$_2$ washings, a yellow solid was obtained. The crude substance was recrystallised from EtOH to afford $\text{H}_2\text{mfpp}$ in 70% yield. $\text{H}_2\text{mfpp}$ was unambiguously identified by $^1$H NMR (Fig. 2.12). It was also characterised by IR, EIms and elemental analysis as this macrocyclic precursor was synthesised for the first time. The IR spectrum showed the characteristic C=O vibration at $1657 \text{ cm}^{-1}$. The EI spectrum recorded showed [M$^+$] peak at m/z 408.

![Image: 1H NMR spectrum and proton assignments for H2mfpp in (d6-dmso).](image_url)

<table>
<thead>
<tr>
<th>Protons</th>
<th>Chemical shift (d-DMSO)</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>a, g, h, d, e</td>
<td>7.2-7.5 ppm</td>
<td>14H, $\beta$</td>
</tr>
<tr>
<td>b</td>
<td>4.1 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>c</td>
<td>11.3 ppm</td>
<td>2H, s</td>
</tr>
<tr>
<td>f</td>
<td>9.9 ppm</td>
<td>2H, s</td>
</tr>
</tbody>
</table>

Fig. 2.12 $^1$H NMR spectrum and proton assignments for $\text{H}_2\text{mfpp}$ in (d$_6$-dmso).
2.2.5.4. Summary of the oxidations

The three targeted dialdehydes were successfully synthesised. Both H$_2$mfpp and H$_2$mftbp were obtained in reasonably good yields. The isolation and purification steps for H$_2$mfmp could still be improved as the oxidation was not reproducible. The oxidation products were easily identified by $^1$H NMR and their formation was confirmed by disappearance of the hydroxymethyl CH$_2$ singlet at 4.7 [ppm] and the emergence of C=O carbonyl protons at 11.2 [ppm]. Analytical data are summarised in Table 2.2.

Table 2.2 Summary of methylenediphenol dialdehydes characterisations.

<table>
<thead>
<tr>
<th>Methylenediphenol Dialdehyde</th>
<th>Melting point [°]</th>
<th>TLC R$_f$ in CHCl$_3$</th>
<th>Oxidation yield [%]</th>
<th>δ [ppm] characteristic protons</th>
<th>IR characteristic vibrations [cm$^{-1}$]</th>
<th>EIms peaks found [m/z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$mfpp</td>
<td>213</td>
<td>0.74</td>
<td>70</td>
<td>11.29 (2H, s) 4.1 (2H, s)</td>
<td>1663</td>
<td>[M+H]$^+$ 368</td>
</tr>
<tr>
<td>H$_2$mfmp</td>
<td>182-184</td>
<td>0.74</td>
<td>26</td>
<td>11.09 (2H, s) 3.99 (2H, s)</td>
<td>1649</td>
<td>[M+Na]$^+$ 307</td>
</tr>
<tr>
<td>H$_2$mftbp</td>
<td>168-70</td>
<td>0.74</td>
<td>50</td>
<td>11.69 (4H, s) 3.96 (2H, s)</td>
<td>1657</td>
<td>[M -e]$^+$ 408</td>
</tr>
</tbody>
</table>

The low yields of the oxidation reactions and the poor materials balances suggest that resulting dialdehyde is still bound to the MnO$_2$ surface despite washing the filtercake with various solvents. Alternative oxidation methods, including potassium dichromate and barium manganate as oxidising agents were also tested in the oxidations of methylenediphenol dialcohols. Both produced oily mixtures similar to those observed for oxidation of H$_2$mhmp to H$_2$mfmp. This combined with the results of extensive study carried by X. Ma$^{137}$ for transformations of H$_2$mhmp into H$_2$mfmp suggests that MnO$_2$ oxidation method is the most efficient.
2.3. Single crystal X-ray study of the methylenediphenol dialdehydes

Single crystals of H$_2$mfmp and H$_2$mfpp suitable for single crystal X-ray diffraction study were successfully obtained by slow evaporation from chloroform solutions and their structures were determined. All the X-ray collection data are summarised in Tables 1 and 2 respectively of the Appendix 1 along with the refinement details. The cif files are included in the DVD Appendix 3.

2.3.1. Structure of H$_2$mfmp

H$_2$mfmp crystallises in the monoclinic space group P2$_1$. The molecule and unit cell packing down the c axis are shown in Fig. 2.13. The position of atoms, bond lengths and angles are similar to that found for the related H$_2$mftbp structure.$^{136}$ The molecule is non-planar, with the two aryl rings inclined at 78.84 (9) ° with respect to one another and the tert-butyl groups lying on opposite sides of the molecule.

Fig. 2.13 Single crystal structure of H$_2$mfmp and unit cell.

The apparent folding of the molecule is actually due to rotation about the C9-C8 and C7-C8 bonds. There is an intramolecular hydrogen bond between the phenol hydrogen atoms and the adjacent carbonyl oxygens which is shown as black dotted lines (Table 2.3).

Table 2.3 Hydrogen bond details for H$_2$mfmp [Å and °].

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H-A)</th>
<th>D...A</th>
<th>≤(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1-H1...O4</td>
<td>0.94</td>
<td>1.75</td>
<td>2.627(2)</td>
<td>153.7</td>
</tr>
<tr>
<td>O2-H2...O3</td>
<td>0.92</td>
<td>1.81</td>
<td>2.6277(19)</td>
<td>146.9</td>
</tr>
</tbody>
</table>
The $\text{H}_2\text{mfmp}$ molecules are packed into a zigzag chains probably as a consequence of the $\pi$-$\pi$ interactions between the carbonyl groups and phenyl rings from the parallel chains. This is schematically shown by the blue dotted lines. The distance between carbonyl group and centroid of phenol ring participating in the stack is 3.294 Å.

### 2.3.2. Structure of $\text{H}_2\text{mfpp}$

$\text{H}_2\text{mfpp}$ crystallises in the triclinic space group $P\overline{1}$ with an unusual packing arrangement having seven dialdehyde molecules in the asymmetric unit and cell volume of over 7000 Å$^3$. The crystal structure and the view of asymmetric unit where each dialdehyde is coloured by symmetry equivalence are shown in Fig. 2.14. Similar to the structure of $\text{H}_2\text{mfmp}$, there is an intramolecular hydrogen bond between the phenol hydrogen atoms and adjacent carbonyl oxygens which is marked by black dotted lines (Table 2.5).

**Fig. 2.14** Crystal structure and diagram with each dialdehyde coloured by symmetry equivalence.
The 4-substituted phenyl rings lying on the opposite side of the methylene links are “twisted” relative one to another. Table 2.4 summarises angles between phenyl rings in each dialdehyde molecule.

Table 2.4 Angles [°] between phenyl rings in the seven independent dialdehyde molecules; For numbering scheme see Fig 2.14.

<table>
<thead>
<tr>
<th>molecule</th>
<th>rings 1 and 2</th>
<th>rings 2 and 3</th>
<th>rings 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>31.77(7)</td>
<td>80.07(5)</td>
<td>39.99(6)</td>
</tr>
<tr>
<td>B</td>
<td>38.86(6)</td>
<td>80.65(5)</td>
<td>37.59(7)</td>
</tr>
<tr>
<td>C</td>
<td>35.25(7)</td>
<td>79.74(5)</td>
<td>37.05(7)</td>
</tr>
<tr>
<td>D</td>
<td>38.73(6)</td>
<td>77.35(5)</td>
<td>24.33(8)</td>
</tr>
<tr>
<td>E</td>
<td>23.30(7)</td>
<td>78.70(5)</td>
<td>30.99(7)</td>
</tr>
<tr>
<td>F</td>
<td>33.76(7)</td>
<td>79.86(5)</td>
<td>31.94(7)</td>
</tr>
<tr>
<td>G</td>
<td>36.89(6)</td>
<td>78.66(5)</td>
<td>32.97(7)</td>
</tr>
</tbody>
</table>

The dialdehyde molecules are packed as shown in Fig. 2.15 probably due to π-π interactions. The most direct overlap identified is between phenyl rings 1 of molecules D and E (Fig. 2.14). The centroid-centroid distance between these overlapping rings is 3.833 Å.

Fig. 2.15 Packing diagram for H₄mfpp dialdehyde.
Table 2.5 Hydrogen bonds for H$_2$mfpp [Å and °].

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1A)-H(01A)...O(4A)</td>
<td>0.84</td>
<td>1.87</td>
<td>2.6133(18)</td>
<td>146.3</td>
</tr>
<tr>
<td>O(2A)-HO2A...O(3A)</td>
<td>0.84</td>
<td>1.87</td>
<td>2.6171(19)</td>
<td>146.6</td>
</tr>
<tr>
<td>O(1B)-HO1B...O(4B)</td>
<td>0.84</td>
<td>1.89</td>
<td>2.6267(19)</td>
<td>146.5</td>
</tr>
<tr>
<td>O(1B)-HO1B...O(4B)</td>
<td>0.84</td>
<td>1.87</td>
<td>2.6051(19)</td>
<td>146.2</td>
</tr>
<tr>
<td>O(1C)-HO1C...O(4C)</td>
<td>0.84</td>
<td>1.87</td>
<td>2.607(2)</td>
<td>145.8</td>
</tr>
<tr>
<td>O(2C)-HO2C...O(3C)</td>
<td>0.84</td>
<td>1.89</td>
<td>2.6305(19)</td>
<td>146.1</td>
</tr>
<tr>
<td>O(1D)-HO1D...O(4D)</td>
<td>0.84</td>
<td>1.90</td>
<td>2.6402(19)</td>
<td>145.9</td>
</tr>
<tr>
<td>O(2D)-HO2D...O(3D)</td>
<td>0.84</td>
<td>1.86</td>
<td>2.596(2)</td>
<td>145.8</td>
</tr>
<tr>
<td>O(1E)-HO1E...O(4E)</td>
<td>0.84</td>
<td>1.88</td>
<td>2.6145(19)</td>
<td>146.0</td>
</tr>
<tr>
<td>O(2E)-HO2E...O(3E)</td>
<td>0.84</td>
<td>1.89</td>
<td>2.632(2)</td>
<td>146.0</td>
</tr>
<tr>
<td>O(1F)-H(221)...O(4F)</td>
<td>0.84</td>
<td>1.88</td>
<td>2.620(2)</td>
<td>145.5</td>
</tr>
<tr>
<td>O(2F)-HO2F...O(3F)</td>
<td>0.84</td>
<td>1.90</td>
<td>2.634(2)</td>
<td>145.7</td>
</tr>
<tr>
<td>O(1G)-HO1G...O(4G)</td>
<td>0.84</td>
<td>1.88</td>
<td>2.6224(19)</td>
<td>146.3</td>
</tr>
<tr>
<td>O(2G)-HO2G...O(3G)</td>
<td>0.84</td>
<td>1.88</td>
<td>2.617(2)</td>
<td>146.2</td>
</tr>
</tbody>
</table>
Chapter 3

FORMATION OF HOMO AND HETERONUCLEAR COMPLEXES OF (2+2) PSEUDOCALIXARENE SCHIFF BASE MACROCYCLES - AN ESI-MS STUDY
3.1. Synthesis and characterisation of dinuclear complexes of a (2+2) Schiff base macrocycle based on H$_2$mfpp dialdehyde

Pseudocalixarene Schiff base macrocyclic complexes based on the tert-butyl-substituted phenol (H$_2$mfbp) were described in the introduction. The methyl substituted (H$_2$mfmp), first synthesised in our group by X. Ma, was also used in template synthesis of related complexes. This resulted in successful isolation of the dicopper(II) and dinickel(II) complexes of the (2+2) macrocycle (Fig. 3.1). The structures of both H$_2$mfmp based cations are shown in Fig. 1.40 and are very similar to the related H$_2$mfbp [Cu$_2$(2+2)Cl]$^+$ ion.

Fig. 3.1 Crystal structures of a)[Cu$_2$(2+2)Cl(THF)$_2]^+$ and b) [Ni$_2$(2+2)Cl(THF)$_2]^+$ studied by X. Ma. The THF carbons are omitted for clarity.

Similarly, the novel phenyl substituted methylenediphenol dialdehyde, H$_2$mfpp was condensed with 1,3-diaminopropan-2-ol in the presence of transition metal salts to produce dinuclear complexes some of which are discussed in this Chapter. A schematic representation of a typical synthesis is shown in Fig. 3.2.

Fig. 3.2 Schematic representation of transition metal template synthesis of dinuclear complexes of the (2+2) macrocycle based on H$_2$mfpp.
Successful formation of Schiff base macrocyclic complexes was initially confirmed by means of IR spectroscopy. The characteristic dialdehyde (C=O vibration at 1655 cm\(^{-1}\)) and diamine stretches were replaced by an imine (C=N) bands appearing at lower frequency ca. 1620 cm\(^{-1}\), this is shown in Fig. 3.3 for dicopper(II) complexes.

![IR spectra of Cu(II) complexes](image)

Fig. 3.3 The IR spectra of two Cu(II) complexes expanded in range 1750-1500 cm\(^{-1}\) showing characteristic imine bands appearing instead of carbonyl.

Characteristic IR stretches and formulae assigned for the four synthesised complexes derived from novel phenyl substituted methylene-diphenoldialdehyde H\(_2\)mfpp are listed in Table 3.1.

Table 3.1 Selected data for the dinuclear complexes of (2+2) macrocycle derived from H\(_2\)mfpp.

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Formula</th>
<th>Colour</th>
<th>IR spectra [cm(^{-1})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td><a href="MeCN">Cu(_2)H(_2)(2+2)(ClO(_4)))(EtO)</a>(_2)(H(_2)O)(_6)</td>
<td>Green</td>
<td>3387(s, OH); 1620(s, C=N); 1119, 1073, 1042 (s, ClO(_4))</td>
</tr>
<tr>
<td>3.2</td>
<td>[Cu(_2)H(_2)(2+2)(Cl)])(Cl)(EtOH)(_2)(Et(_2)O)</td>
<td>Green</td>
<td>3387(s, OH), 1627(s, C=N), 1064(s, Cl)</td>
</tr>
<tr>
<td>3.3</td>
<td><a href="OAc">Mn(_2)H(_2)(2+2)</a>(_2)(H(_2)O)(_2)</td>
<td>Brown</td>
<td>3434 (s, OH); 1618(s, C=N); 1443 (s, COO)</td>
</tr>
<tr>
<td>3.4</td>
<td><a href="OAc">Zn(_2)H(_2)(2+2)</a>(_2)(H(_2)O)(_4)</td>
<td>Orange</td>
<td>3438(b, m, OH); 1630(s, C=N); 1459(s, COO)</td>
</tr>
</tbody>
</table>
Further indication of the dinuclear nature of the complexes was obtained from mass spectral data. Fast Atom Bombardment (FAB) mass spectrometry (more accurately known as Liquid Secondary Ion Mass Spectrometry) provided by National Mass Spectrometry Service at Swansea was used for the characterisation of solid samples. In this technique the samples are dissolved in liquid matrix (3-nitrobenzyl alcohol) and ionised using a beam of caesium ions.155

The mass to charge (m/z) value taken for FAB-MS data tables is that of the most intense peak belonging to a set of peaks in the experimental spectrum. The theoretical isotope profile was provided by NMSSC for most of the samples and showed a good match with the \([M_2^{II}H_2(2+2) - H]^+\) peaks which were positively identified for all of the dinuclear complexes. All spectra also showed relatively intense peaks due to the matrix compound (e.g. m/z = 289, m/z = 307) due to the poor solubility of the pseudocalixarene complexes.

The dicopper(II) complexes were afforded by standard template reaction but with an additional base NEt$_3$ introduced to the system to promote deprotonation of methylenediphenoldialdehydes. Fig. 3.4 shows spectra of the dicopper(II) complexes. Spectrum a was acquired for compound 3.1 and spectrum b for compound 3.2. The inset spectrum shows the assignment for peaks at m/z 1049.

Fig. 3.4 FAB-MS Spectra of a) [Cu$_2$H$_2$(2+2)(ClO$_4$)(EtO)](MeCN)$_2$(H$_2$O)$_6$ (compound 3.1) and b) [Cu$_2$H$_2$(2+2)(Cl)](Cl)(EtOH)$_2$(Et$_2$O) (compound 3.2).
Apart from the \([\text{Cu}_2\text{H}_2(2+2)-\text{H}]^+\) peaks observed at m/z 1049, higher mass peaks can be assigned to acetonitrile (MeCN) and chloride ion adducts, the major peak attributions are listed in Table 3.2.

Table 3.2 Major peak attributions for 3.1 and 3.2.

<table>
<thead>
<tr>
<th>m/z</th>
<th>Relative Abundance (%)</th>
<th>Fragments</th>
<th>Calculated mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>289</td>
<td>50</td>
<td>NOBA matrix</td>
<td>n/a</td>
</tr>
<tr>
<td>307</td>
<td>100</td>
<td>NOBA matrix</td>
<td>n/a</td>
</tr>
<tr>
<td>1049</td>
<td>25</td>
<td>([\text{Cu}_2\text{H}_2(2+2)-\text{H}]^+)</td>
<td>1049</td>
</tr>
<tr>
<td>1085</td>
<td>10</td>
<td>([\text{Cu}_2\text{H}_2(2+2)\text{Cl}]^+)</td>
<td>1085</td>
</tr>
<tr>
<td>1111</td>
<td>10</td>
<td>([\text{Cu}_2\text{Na}(2+2)(\text{MeCN})]^+)</td>
<td>1111</td>
</tr>
</tbody>
</table>

The FAB-MS spectrum of \([\text{Mn}_2\text{H}_2(2+2)](\text{OAc})_2(\text{H}_2\text{O})_2\) (Fig. 3.5, Table 3.3) confirmed formation of the dinuclear complex (compound 3.3). The inset spectrum in Fig. 3.5 shows the peak assignment for \([\text{Mn}_2\text{H}_2(2+2)(\text{OAc})]^+\) at m/z 1091.

![Fig. 3.5 FAB-MS spectrum of \([\text{Mn}_2\text{H}_2(2+2)](\text{OAc})_2(\text{H}_2\text{O})_2\) complex.](image)

It is hard to predict on the basis of the mass spectral data whether the acetate ion coordinates to the metals in the complex but the observed acetate adduct agrees with the IR data where \((\text{OAc})^-\) was positively identified. Nevertheless the singly charged monoisotopic set of peaks at m/z 1031 can be attributed to \([\text{Mn}_2\text{H}_2(2+2)-\text{H}]^+\) species. All major peak attributions for compound 3.3 are gathered in Table 3.3.
Table 3.3 Major peak attributions for compound 3.3.

<table>
<thead>
<tr>
<th>m/z</th>
<th>Relative Abundance (%)</th>
<th>Fragments</th>
<th>Calculated mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>289</td>
<td>60</td>
<td>NOBA matrix</td>
<td>n/a</td>
</tr>
<tr>
<td>307</td>
<td>100</td>
<td>NOBA matrix</td>
<td>n/a</td>
</tr>
<tr>
<td>1031</td>
<td>20</td>
<td>[Mn₂H₂(2+2)-H]⁺</td>
<td>1031</td>
</tr>
<tr>
<td>1091</td>
<td>10</td>
<td>[Mn₂H₂(2+2)OAc]⁺</td>
<td>1091</td>
</tr>
</tbody>
</table>

Figure 3.6 shows FAB-MS spectrum of the dizinc(II) (2+2) complex together with the isotope match calculated by NMSS Centre at Swansea.

![FAB-MS spectrum of dizinc(II) (2+2) complex](image)

The spectrum of the dizinc complex exhibits several low mass fragments which most likely result from the fragmentation of the macrocycle. The most intense peaks, related to macrocyclic fragment [Zn₂H₂(2+2)-H]⁺ found at m/z 1051, correspond to those described for Cu(II) and Mn(II). The higher mass peaks are assigned for Na(I), NaOH and (OAc)⁻ adducts of the basic [Zn₂(2+2)] unit (Table 3.4).

Table 3.4 Major peak attributions for compound 3.4.

<table>
<thead>
<tr>
<th>m/z</th>
<th>Relative Abundance (%)</th>
<th>Fragments</th>
<th>Calculated mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>207</td>
<td>100</td>
<td>Fragmented molecule or NOBA matrix</td>
<td>n/a</td>
</tr>
<tr>
<td>1051</td>
<td>65</td>
<td>[Zn₂H₂(2+2)-H]⁺</td>
<td>1051</td>
</tr>
<tr>
<td>1073</td>
<td>20</td>
<td>[Zn₂Na(2+2)]⁺</td>
<td>1073</td>
</tr>
<tr>
<td>1091</td>
<td>15</td>
<td>[Zn₂Na(2+2)OH-e⁻]⁺</td>
<td>1091</td>
</tr>
<tr>
<td>1109</td>
<td>&lt; 10</td>
<td>[Zn₂H₂(2+2)(OAc)]⁺</td>
<td>1109</td>
</tr>
</tbody>
</table>
No crystals of these complexes have been obtained but comparison of the colour and ms spectra with those of the structurally characterised H$_2$mftbp, H$_2$mfmp derivaties suggest the same saddle-shaped structure with each methylenediphenol group monodeprotonated.

3.2. Synthesis and characterisation of heteronuclear TM$_2$M complexes (TM = transition metal M = group 1 or 2 metal ion) of (2+2) Schiff base macrocycles

Polynuclear macrocyclic complexes containing both transition metals and group 1 or group 2 metals are quite rare. Examples include complexes reported by Reedijk$^{156-157}$ for ligands with two different cavities, one salen-like for binding the transition metals and a polyether site for binding hard metal ions (Fig 3.7 a). The other example type of ligand featuring both relatively “soft” N$_2$O$_2$ sites and a hard six oxygen centre was recently synthesised by Nabeshima et al. (Fig. 3.7 b).$^{77, 158-159}$

![Macrocycle Ligands](image)

Fig. 3.7 Macro cyclic ligands comprising two types of compartment for binding two different types of metal ions in polyheteronuclear complexes.

As discussed in the introduction, the pseudocalixarene Schiff base macrocycles resulting from (2+2) condensation between methylenediphenoldialdehyde and 1,3-diaminopropan-2-ol possess different coordination sites with the potential to bind transition metals together with alkali or alkaline earth metals. The synthesis and characterisation of heterotrinuclear complexes with group 1 and group 2 metals is discussed below.
3.2.1. Trinuclear TM$_2$M complexes (TM = transition metal and M = group 1 metal ions) of (2+2) pseudocalixarene macrocycles

Preliminary work on formation of heterotrinuclear complexes with group 1 metals and H$_2$mfbp as dialdehyde was conducted by J. Barreira Fontecha$^{135}$ and led to isolation of [Cu$_2$Na(2+2)(H$_2$O)](OAc) and [Zn$_2$Na(2+2)(OAc)(EtOH)](AcOH) complexes (Fig. 3.8).

![Crystal structures](image)

**Fig. 3.8** Crystal structures of a) [Cu$_2$Na(2+2)(H$_2$O)]$^+$; b) [Zn$_2$Na(2+2)(OAc)(EtOH)](AcOH) and c) the dimer molecule of b.

The trinuclear complex with Cu(II) and Na(I) was initially obtained accidentally by using solvent contaminated with NaOH. From then on formation of heteronuclear complexes was performed in presence of base as this deprotonates the phenols which makes them better ligands for binding hard metals.
The structure of complex a (Fig. 3.8) is slightly different from the saddle shape discussed in the introduction for tricopper(II) complex (Fig. 1.45). The methylenediphenol groups are fully deprotonated, binding Na(I) in central position. However, the Na(I) ion has a larger ionic radius than Cu(II) therefore the phenolate oxygen donors are further apart than in the tricopper complex, the saddle shape is stretched and the Na(I) ion lies above the mean plane of the phenolate donors. Two Cu(II) ions occupy the typical Robson site of the macrocyclic ligand. Similar dilation of the V shape geometry is observed in the trinuclear complex with Zn(II) and Na(I) (Fig. 3.8 b). The Na(I) ion again binds in the tetraphenolate site lying somewhat above the mean plane. Interestingly this complex was isolated as a dimer (Fig. 3.8 c) where one of the pendant alcohol groups from another macrocyclic unit is involved in the coordination sphere of Zn(II) ions.

A further investigation which is presented in this chapter resulted in isolation of dicopper complexes with Li(I), Na(I), Mg(II) and Ca(II). The complexes were afforded by using two methylenediphenol dialdehydes: the tert-butyl H₃mftbp (compounds 3.7 and 3.8) and phenyl H₂mfpp dialdehyde (3.5; 3.6; 3.9 and 3.10). They were prepared by template condensation reactions with 1,3-diaminopropan-2-ol in the presence of appropriate metal salts. Formation of the complexes was initially confirmed by IR spectroscopy as described above. The spectrum shown in Fig. 3.9 for the [Cu₂Na(2+2)(OH)](H₂O) complex derived from the H₃mftbp dialdehyde (compound 3.8).

![Fig. 3.9 The IR indicated formation of Schiff base pseudocalixarene (C=N bond).](image-url)
The synthesised trinuclear complexes of small pseudocalixarenes with alkaline metals are listed in Table 3.2 together with some characteristic IR bands.

Table 3.2 Selected data for the complexes investigated.

<table>
<thead>
<tr>
<th>Compound number</th>
<th>dialdehyde</th>
<th>Formula</th>
<th>Colour</th>
<th>IR spectra [cm⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>H₂mfpp</td>
<td>[Cu₂Li(2+2)(Cl)(EtOH)₂]</td>
<td>green</td>
<td>3387(s, OH); 1620(s, C=N); 1049 (m, Cl⁻)</td>
</tr>
<tr>
<td>3.6</td>
<td>H₂mfpp</td>
<td>[Cu₂Li(2+2)][OH(H₂O)₂]</td>
<td>dark green</td>
<td>3476(s, OH); 1634(s, C=N);</td>
</tr>
<tr>
<td>3.7</td>
<td>H₂mftbp</td>
<td>[Cu₂Li(2+2)][OH(H₂O)]</td>
<td>dark green</td>
<td>3468 (s, OH); 2966(s, CH₃); 1629(s, C=N);</td>
</tr>
<tr>
<td>3.8</td>
<td>H₂mftbp</td>
<td>[Cu₂Na(2+2)][OH(H₂O)]</td>
<td>dark green</td>
<td>3426(b, m, OH); 2961(s, CH₃); 1626(s, C=N);</td>
</tr>
<tr>
<td>3.9</td>
<td>H₂mfpp</td>
<td>[Cu₂Na(2+2)][ClO₄]</td>
<td>green</td>
<td>3486(s, OH); 1629(s, C=N); 1122(s, ClO₄);</td>
</tr>
<tr>
<td>3.10</td>
<td>H₂mfpp</td>
<td>[Ni₂Na(2+2)][(OAc)]</td>
<td>brown yellowish</td>
<td>3426(s, OH); 1620(s, C=N); 1449(s, COO');</td>
</tr>
</tbody>
</table>

Successful formation of complexes was also confirmed by FAB-MS or electrospray mass spectrometry (ESI-MS) and elemental analysis. Crystallisation attempts were unsuccessful despite using various combinations of solvents. When crystals were obtained they had very weak diffracting abilities so data were not collected. A single crystal suitable for X-ray analysis was achieved only for the trinuclear complex with Cu(II) and Ca(II). This structure will be described later in this chapter (section 3.2.2.2).
3.2.1.1. Cu$_2$Li complexes of (2+2) pseudocalixarene macrocycles

Three trinuclear complexes with Cu(II) and Li(I) were obtained. Two were produced in template reactions where both metal salts were refluxed with the dialdehyde for some time and then 1,3-diaminopropan-2-ol was added followed by base (compounds 3.5 and 3.7). The third complex (3.6) was formed in a reaction where the hard metal ion was refluxed overnight with H$_2$mftbp and diamine in the presence of base. Then the copper salt was introduced to the reaction mixture and refluxed for additional 5 h. (Fig. 3.10).

![Synthesis of complexes](attachment:image)

Formation of the trinuclear species was confirmed by FAB mass spectrometry. The spectra of the complexes showed [Cu$_2$Li(2+2)]$^+$ fragments at m/z 973 for the H$_2$mftbp based ligand (3.7) and at m/z 1055 for the H$_2$mfpp one (3.5 and 3.6).

![FAB-MS spectra](attachment:image)

Fig. 3.10 Synthesis of Cu$_2$Li(I) complexes of the (2+2) Schiff base pseudocalixarene macrocycle.

Fig. 3.11 FAB-MS spectra of Li(I) complexes  a) H$_2$mftbp based [Cu$_2$Li(2+2)](OH)(H$_2$O) compound 3.7 with isotope match performed at Swansea (inset) b) H$_2$mfpp based[Cu$_2$Li(2+2)](OH)(H$_2$O)$_2$ compound 3.6.
It seems that the order in which metal salts are introduced to the reaction mixture does not have an impact on the products isolated. This agrees with suggestions from the preliminary study on these complexes carried out by J. Barreira Fontecha.\textsuperscript{135}

### 3.2.1.2. TM$_2$Na complexes of (2+2) pseudocalixarene macrocycles

Two pseudocalixarene Schiff base macrocyclic complexes based on dialdehydes H$_2$mftpb and H$_2$mfpp with Cu(II) and Na(I) were synthesised (3.8 and 3.9). They were produced via different pathways as shown in Fig. 3.12. A trinuclear complex with Ni(II) and Na(I) was also formed in a similar metal template condensation between H$_2$mfpp and 1,3-diaminopropan-2-ol (3.10).

![Synthesis of complex 3.8](image)

![Synthesis of complex 3.9](image)

![Synthesis of complex 3.10](image)

Fig. 3.12 Schematic representation of syntheses leading to 3.8, 3.9 and 3.10.

The trinuclear character of the complexes was confirmed by mass spectrometry techniques (FAB, ESI). All complexes showed [TM$_2$Na(2+2)]$^+$ peaks (Fig. 3.13). The FAB data were collected for H$_2$mfpp macrocycles. Again, due to the poor solubility of these complexes the NOBA matrix peaks at m/z 289 and m/z 307 were found with the highest relative abundance. The ESI-MS spectrum of complex 3.8 showed additional high mass peaks at m/z 1954. These could be related to a dimer of [Cu$_2$Na(2+2)]$_2$ similar to that described for the complex with Zn(II) and Na(I) in Figure 3.8.
Successful formation of trinuclear complexes with Na(I) was further confirmed by elemental analysis. The general formulae of the compounds formed can be written as [T₂Na(2+2)]X where T represents Cu(II) or Ni(II) and X is a counter ion, only complex 3.8 exhibited one H₂O solvate molecule. The calculated and experimental values of CHN analysis are listed in Table 3.3.

Table 3.3 CHN data for the trinuclear complexes with Na(I).

<table>
<thead>
<tr>
<th>Compound</th>
<th>CHN calculated</th>
<th>CHN experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="OH">Cu₂Na(2+2)</a>(H₂O)</td>
<td>C 60.84%</td>
<td>C 60.63%</td>
</tr>
<tr>
<td></td>
<td>H 6.58%</td>
<td>H 6.58%</td>
</tr>
<tr>
<td></td>
<td>N 5.46%</td>
<td>N 5.58%</td>
</tr>
<tr>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="ClO%E2%82%84">Cu₂Na(2+2)</a></td>
<td>C 61.55%</td>
<td>C 61.30%</td>
</tr>
<tr>
<td></td>
<td>H 4.14%</td>
<td>H 4.33%</td>
</tr>
<tr>
<td></td>
<td>N 4.79%</td>
<td>N 4.76%</td>
</tr>
<tr>
<td>3.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="OAc">Ni₂Na(2+2)</a></td>
<td>C 66.44%</td>
<td>C 66.89%</td>
</tr>
<tr>
<td></td>
<td>H 4.59%</td>
<td>H 4.80%</td>
</tr>
<tr>
<td></td>
<td>N 5.00%</td>
<td>N 5.32%</td>
</tr>
</tbody>
</table>
As for the complexes with Li(I), the order in which the metal salts were added to the reaction mixture did not affect the formation of trinuclear complexes.

3.2.2. Trinuclear Cu2M complexes (where M = group 2 metal ions) of a (2+2) pseudocalixarene macrocycle

Template synthesis of (2+2) pseudocalixarene Schiff base macrocycles with Cu(II) and either Mg(II) or Ca(II) also resulted in formation of trinuclear species. The three complexes afforded with H2mftbp dialdehyde are listed in Table 3.7. As for the previously discussed complexes, formation of the pseudocalixarene macrocycles was confirmed by appearance of new imine stretches instead of carbonyl bands in the IR spectra (Table 3.7). Complexes with Ba(II) are omitted here and will be discussed individually in chapter 4.

Table 3.7 Selected data for Cu2M trinuclear complexes with group 2 metal ions.

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Formula</th>
<th>Colour</th>
<th>IR spectra [cm⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.11</td>
<td><a href="NO%E2%82%83">Cu₂Mg(2+2)</a>(ClO₄)(EtOH)(H₂O)₄</td>
<td>green</td>
<td>3379(s, OH); 2955(s, CH₃); 1627(s, C=N); 1087(s, ClO₄⁻);</td>
</tr>
<tr>
<td>3.12</td>
<td><a href="ClO%E2%82%84">Cu₂Ca(2+2)</a>(OH)(EtOH)(H₂O)₄</td>
<td>dark green</td>
<td>3447(b,m, OH), 2961(s, CH₃); 1634(s, C=N), 1150,1117,1064(s, ClO₄⁻)</td>
</tr>
<tr>
<td>3.13</td>
<td><a href="NO%E2%82%83">Cu₂Ca(2+2)</a>₂(H₂O)₂</td>
<td>dark green</td>
<td>3441(s, OH), 1627(s, C=N),</td>
</tr>
</tbody>
</table>

3.2.2.1. Cu₂Mg complex of a (2+2) pseudocalixarene macrocycle

The synthesis of trinuclear complex with Cu(II) and Mg(II) involved overnight reflux of H2mftbp dialdehyde, Mg(NO₃)₂·6H₂O and 1,3-diaminopropan-2-ol in the presence of base. Then Cu(ClO₄)₂·6H₂O was added to the reaction mixture and reflux was continued (Fig. 3.14).
Successful formation of a trinuclear complex with Mg(II) was confirmed by mass spectrometry. Both FAB-MS and ESI-MS showed \( \{\text{Cu}_2\text{Mg}(2+2)+e^-\}^+ \) species related to peaks at m/z 990. The electrospray spectrum (Fig. 3.15 b) additionally contained high mass peaks most likely related to dimer formation \( \{[\text{Cu}_2(2+2)]_2\text{Mg} +e^-\}^+ \) at m/z 1954. Peaks centered at m/z 1474 can be assigned to the \([\text{Cu}_3\text{Mg}(3+3) +e^-]_3^+ \) complex. The low mass peaks in FAB-MS spectrum (Fig. 3.15 a) were not assigned but most likely they result from fragmentation of larger molecules.

Fig. 3.15 a) FAB-MS spectrum of the trinuclear complex with Mg(II) b) ESI-MS spectrum of Cu$_2$Mg complex 3.11.
The trinuclear character of the complex was supported by elemental analysis which was consistent with the formulation of \([\text{Cu}_2\text{Mg}(2+2)](\text{NO}_3)(\text{ClO}_4)(\text{EtOH})(\text{H}_2\text{O})_4\) compound (Table 3.8).

Table 3.8 The elemental analysis data for \([\text{Cu}_2\text{Mg}(2+2)](\text{NO}_3)(\text{ClO}_4)(\text{EtOH})(\text{H}_2\text{O})_4\).

<table>
<thead>
<tr>
<th>Compound</th>
<th>CHN calculated</th>
<th>CHN experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.11</td>
<td>C 50.98%</td>
<td>C 50.98%</td>
</tr>
<tr>
<td>(<a href="%5Ctext%7BNO%7D_3">\text{Cu}_2\text{Mg}(2+2)</a>(\text{ClO}_4)(\text{EtOH})(\text{H}_2\text{O})_4)</td>
<td>H 6.18%</td>
<td>H 6.44%</td>
</tr>
<tr>
<td></td>
<td>N 5.51%</td>
<td>N 5.84%</td>
</tr>
</tbody>
</table>

3.2.2.2. \(\text{Cu}_2\text{Ca}\) complexes of a (2+2) pseudocalixarene macrocycle

Two \(\text{Cu}_2\text{Ca}\) complexes were obtained using the same synthetic procedure as described for Mg(II) (Fig. 3.14): \([\text{Cu}_2\text{Ca}(2+2)](\text{ClO}_4)(\text{OH})(\text{EtOH})(\text{H}_2\text{O})_4\) (complex 3.12) and \([\text{Cu}_2\text{Ca}(2+2)(\text{NO}_3)_2](\text{H}_2\text{O})_2\) (complex 3.13) which resulted from an ESI-MS experiment reaction mixture solution (section 5.3.1).

The FAB spectrum of 3.12, the ESI-MS spectrum of the reaction mixture from which 3.13 was isolated and the ESI-MS spectrum of powdery solid from which it was crystallised are presented in Fig. 3.16 a, b and c respectively.

The FAB-MS spectrum (Fig. 3.16 a) shows peaks at m/z 1107 corresponding to a trinuclear fragment \([\text{Cu}_2\text{Ca}(2+2)(\text{ClO}_4)]^+\). The peaks at m/z 969 can be assigned to the dinuclear species \([\text{Cu}_2\text{H}(2+2)]^+\). The low mass peaks are most likely due to fragmentation of higher mass fragments.
The ESI-MS spectrum of the reaction mixture from which complex 3.13 was produced (Fig. 3.16 b) is discussed in detail in section 5.3.1. but it can be clearly seen than the peaks at m/z 1067 related to the [Cu$_2$Ca(2+2)(NO$_3$)$_2$]$^+$ fragment are of very low intensity and higher mass species predominate. Spectrum (c) (ESI-MS) represents the crystalline solid obtained from reaction mixture presented in figure (b) by slow evaporation. Peaks at m/z 322 and 706 are not assigned and may be due to fragmentation of higher mass species. The peaks at m/z 1068 and m/z 1953 are attributed to fragments [Cu$_2$Ca(2+2)(NO$_3$)]$^+$ and a [{Cu$_2$(2+2)Na}]$^+$ dimer with Na(I) ion, respectively. The elemental analysis data (Table 3.9) support the trinuclear character of synthesised complexes.
Table 3.9 The elemental analysis data for trinuclear complexes with Ca(II).

<table>
<thead>
<tr>
<th>Compound</th>
<th>CHN calculated</th>
<th>CHN resulted</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.12 <a href="ClO%E2%82%84">Cu₂Ca(2+2)</a>(OH)(EtOH)(H₂O)₄</td>
<td>C 52.17%</td>
<td>C 52.30%</td>
</tr>
<tr>
<td></td>
<td>H 6.41%</td>
<td>H 6.42%</td>
</tr>
<tr>
<td></td>
<td>N 4.51%</td>
<td>N 4.76%</td>
</tr>
<tr>
<td>3.13 <a href="H%E2%82%82O">Cu₂Ca(2+2)(NO₃)₂</a>₂</td>
<td>C 53.44%</td>
<td>C 53.40%</td>
</tr>
<tr>
<td></td>
<td>H 5.87%</td>
<td>H 6.10%</td>
</tr>
<tr>
<td></td>
<td>N 7.20%</td>
<td>N 7.26%</td>
</tr>
</tbody>
</table>

Recrystallisation of 3.13 from MeOH by slow evaporation led to green crystals of [Cu₂Ca(2+2)(NO₃)₂](MeOH)₂ where H₂O molecules were replaced by MeOH solvate molecules. The complex crystallises in space group C2/c with Ca(II) lying on a 2-fold axis. The asymmetric unit and the molecular structure are shown in Fig. 3.17, crystallographic data are summarised in Table 3 of Appendix 1 and the cif file is included in DVD Appendix 3.

This neutral complex has a similar saddle shape to the dinuclear and homotrinuclear complexes discussed in the Introduction. However, here the fold is not as sharp since the fully deprotonated methylenediphenols are further apart than in related complexes because they are coordinated to the larger Ca(II) ion. The distance between adjacent methylenediphenol oxygens is ca. 3.696 Å where for the corresponding tricopper(II) [Cu₃(2+2)]⁺ it is 2.919 Å. Selected bond lengths and angles are summarised in Table 3.10.
Table 3.10 Selected bond lengths and angles for [Cu$_2$Ca(2+2)(NO$_3$)$_3$](MeOH)$_2$.

<table>
<thead>
<tr>
<th></th>
<th>Bond Length (Å)</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(1)–O(2A)</td>
<td>1.959(3)</td>
<td>3.1463(6)</td>
</tr>
<tr>
<td>Cu(1)–N(5)</td>
<td>1.962(4)</td>
<td>2.497(3)</td>
</tr>
<tr>
<td>Cu(1)–N(1)</td>
<td>1.967(4)</td>
<td>2.497(3)</td>
</tr>
<tr>
<td>Cu(1)–O(4a)</td>
<td>2.440(3)</td>
<td>3.1463(6)</td>
</tr>
<tr>
<td>Cu(1)–Ca</td>
<td>3.1462(6)</td>
<td>2.497(3)</td>
</tr>
<tr>
<td>Ca–O(2A)</td>
<td>2.400(3)</td>
<td>2.405(3)</td>
</tr>
<tr>
<td>Ca–O(2Aa)</td>
<td>2.400(3)</td>
<td>2.405(3)</td>
</tr>
<tr>
<td>Ca–O(1)</td>
<td>2.405(3)</td>
<td>2.405(3)</td>
</tr>
<tr>
<td>Ca–O(1a)</td>
<td>2.405(3)</td>
<td>2.405(3)</td>
</tr>
<tr>
<td>Ca–O(5a)</td>
<td>2.400(3)</td>
<td>2.405(3)</td>
</tr>
<tr>
<td>Ca–Cu(1a)</td>
<td>3.1463(6)</td>
<td>2.497(3)</td>
</tr>
</tbody>
</table>

Symmetry operations for equivalent atoms: a $-x+1$, $y$, $-z+1/2$
The Ca(II) ion is eight-coordinate, binding to four phenolate oxygen donors from deprotonated methylenediphenol units and to two oxygen donors from each nitrate anion. The central alkaline earth metal lies above the mean plane described by the four phenolate donors as it is too large to fit into the macrocyclic cavity. The calcium ion is in approximately rectangular antiprismatic geometry. The two copper ions occupy the typical N₂O₂ Robson sites of the macrocyclic ligand, binding to two imine nitrogen and two phenolate oxygen donors. Their coordination sphere is completed by nitrate oxygen donors weakly coordinating in the axial position.

3.3. Summary of the syntheses of dinuclear and heterotrinuclear complexes of (2+2) pseudocalixarene Schiff base macrocycles

The novel H₂mfpp dialdehyde used in transition metal template condensation with 1,3-diaminopropan-2-ol yielded similar complexes to those already known with H₂mftbp and H₂mfmp dialdehydes. The very poor solubility of the products and weak diffraction of crystals obtained disallowed use of X-ray crystallography as tool for an unambiguous confirmation of their structures but other analytical techniques confirmed their dinuclear character. The probable saddle-shape of the Cu(II) complexes was deduced from the observation that the fully deprotonated open dicopper(II) complexes are dark brown whereas the complexes obtained were green. The detailed study of transition metal template formation of the dicopper(II) complexes carried out by J. Barreira Fontecha showed that clean samples of the dicopper(II) complexes could be afforded only for copper chloride. In most cases the reaction with 1 equiv. of Cu(II) salt produced mixtures of dicopper(II) and tricopper(II) complexes.

Trinuclear complexes of (2+2) macrocycles derived from H₂mftbp and H₂mfpp dialdehydes, combining transition metal with the alkaline or alkaline earth metals were successfully synthesised. FAB-MS data confirmed their formation showing characteristic ions [TM₂M(2+2)]⁺ for complexes with group 1 metals where TM is transition metal and M is Na(I) or Li(I) and [TM₂M(2+2)X]⁺ for the group 2 metals where M is Mg(II) or Ca(II) and X is anion. The data collected from elemental analysis were also consistent with the proposed trinuclear character. For all the syntheses an additional base was required to deprotonate the methylenediphenols. For some of these complexes the FAB-MS data also suggested formation of larger macrocyclic cations.
like the \([\text{Cu}_3\text{Mg}(3+3)+\text{e}^-]\) or \([\text{Cu}_3\text{Na}(3+3)]^+\). The crystal structure of \([\text{Cu}_2\text{Ca}(2+2)(\text{NO}_3)_2]\) complex revealed a stretched saddle-shape for the macrocycle, with the Ca(II) ion occupying the hard tetraphenolate site. The possible involvement of central metal in template mechanisms still remains obscure.

Collected data for the solid samples were consistent with the suggestion that formation of these heterotrinitrinuclear complexes does not depend on order in which central metal is introduced to the reaction mixture. Moreover, as mentioned in the introduction, transition metal only template formation of \((2+2)\) macrocycle initiated by S. Goetz\textsuperscript{130} and continued by J. Barreira Fontecha\textsuperscript{135} can also produce tri- and tetra-nuclear macrocyclic complexes. The nuclearity of these products was attributed the amount of transition metal used, time of the reaction and type of metal salt.

In order to gain more detailed information about the processes occurring during these reactions, not having detailed answers from analysis of solid samples we turned to electrospray ionisation mass spectrometry (ESI-MS) to investigate what actually happens in the reaction mixture solution.
3.4. Introduction to electrospray mass spectrometry (ESI-MS)

The central phenomenon of electrospray was well known as early as the end of the 19th century. In 1882 Lord Rayleigh calculated the limit of charge which can be carried by a droplet of liquid without it breaking up into smaller droplets. His theoretical study was confirmed experimentally in 1917 by Zeleny who photographed this process. He also measured the potential at which droplets can be held at the end of capillary tube before disintegrating to a narrow jet. His study of electric field impact on droplets was extended by Taylor. He showed that, when soap or oil/water samples are placed in electric field they form a conical meniscus presently known as a Taylor Cone.

Pioneering work for today’s electrospray ionisation mass spectrometry (ESI-MS) technique was carried out by Doyle. He demonstrated that by using electrospray it is possible to obtain intact gaseous phase molecular ions of given mass/charge (m/z) values separated by velocities throughout the beam. Over 20 years later, the first paper on electrospray ionisation mass spectrometry was published by Fenn, who was awarded a Nobel Prize for his work in 2003. A Schematic representation of Fenn’s electrospray ion source is shown in Fig. 3.18.

Fig. 3.18 Schematic representation of Fenn’s electrospray ion source.
Despite many modifications, the basic arrangement for ESI sources remains essentially the same. Liquid sample enters the electrospray (ES) chamber, usually at flow rates of several µL/min, through a stainless steel hypodermic needle which is at high potential (2-5 kV) with respect to the conical electrode. The electric field at the tip of the needle charges the liquid surface, disperses it into a fine spray of charged droplets and the droplets move by Coulombic forces to the transfer capillary at the end wall of the ES chamber. Formation of charged species is supported by counter-flow drying gas which washes solvent vapours away from evaporating droplets. In addition the drying gas can entrain some of the molecular ions formed in the ES chamber before they enter the transfer capillary and exit as a free jet to the vacuum chambers but the vast majority of molecular ions passes the skimmer and arrives at the mass analyser. The analyser separates species transferred from the ion source according to their mass to charge (m/z) ratio. There are several types of mass analysers but separation is based on electromagnetism. The time-of-flight (TOF) mass analyser classifies ions according to the time difference between a start signal and the pulse generated when the ion reaches the detector. The quadrupole mass filter comprises of four cylindrical rods arranged symmetrically with opposite rods connected electrically in pairs. It uses direct current (DC) and radio frequency (RF) to establish ions trajectories through the rods. Only ions with a narrow range of m/z values will present stable trajectories and will travel to the detector. Ions without stable trajectories do not get to the detector.

Generation of gas phase molecular ions from charged droplets in the ES chamber is explained by the two models shown in Fig. 3.19. The Ion Evaporation Model (IEM) proposed by Iribane and Thompson postulates that, before droplets with only one solute molecule are formed, the electrostatic repulsion is strong enough to desorb free ions from its surface.
The Charge Residue Model (CRM) argues that, during evaporation of solvent, charged droplets shrink until surface tension can no longer sustain the charge (Rayleigh limit). The resulting instability rips the droplets apart forming offspring droplets that also evaporate. This sequence is repeated until droplets containing only one solute molecule are produced. When the last solvent molecule is evaporated a free gas phase ion is left.

Because ESI is a very soft method of ionisation it permits the study large and fragile molecules. This is why Fenn’s publication began a real revolution in the study of large biological molecules. This is also why we employed this technique as a powerful tool to investigate metal template mechanisms in the formation of large macrocyclic systems. Nowadays there are thousands of publications based on ESI-MS. However there are not many examples in the literature where ESI-MS is utilised to follow reactions in solution.170-178

**3.4.1. Instrumentation and data interpretation**

Several experiments were conducted where the Schiff base condensations were followed by ESI mass spectrometry. Three different spectrometers were used during this study. Preliminary work was conducted on a Waters LCT ToF spectrometer, a Waters Synapt HDMS system was employed for tandem ms/ms experiments and majority of work was carried out on a ThermoFisher Exactive Orbitrap coupled to an Advion Triversa NanoMate injection system.
Sample preparation protocol, sampling times and synthetic details are described in the Experimental chapter. However at this stage it has to be emphasised that all the samples analysed were reaction mixture solutions. They were taken out from the refluxing ethanol solutions, diluted with methanol to quench the reaction and data were acquired on the ms instruments without any purification. Timings given in this study represent the reflux times to the moment when samples were extracted from the solution. The only exception is the reaction presented in section 4.5.2 where the reaction time was measured not as a reflux time but as a total time required for the data acquisition. There was a delay time between extraction and acquisition due to the physical actions required for the collection of ms data (transport, set up of instrument, syringe the solution). However, an experiment described in section 4.5.2 showed that the reaction is effectively quenched when sample is taken out from the reaction mixture and diluted with methanol.

A few points about the interpretation of the mass spectra have to be discussed here. When chemical species give a signal in the mass spectrum this is convincing evidence that their precursors exist in the solution. If the expected mass fragments are not found in the spectrum this does not demonstrate unambiguously that they are not present in the solution. It could be only that they are not reaching the detector under the particular conditions set on the ms instrument. Very often molecular ions appear in the spectra associated with solvent molecules or as Na(I) adduct ions. These effects are common in ESI-MS.

The major peaks found in the spectra have been assigned and these data are presented in full in the Appendix DVD. Assignment of mass peaks to the chemical species is explained in detail for one example in this chapter (section 3.5.1), all other assignments were performed in the same manner.
3.5. Electrospray mass spectrometry investigation of template formation of (2+2) pseudocalixarene Schiff base macrocyclic complexes

Of the three synthesised methylenediphenol dialdehydes, the tert-butyl dialdehyde (H$_2$mftbp) was selected for detailed ESI-MS study because preliminary experiments showed it behaved best on the spectrometer. Moreover it appeared to have the best solubility and readiness for crystallisations reported in the chapter 2.

3.5.1. Cu(II) template formation of the (2+2) pseudocalixarene Schiff base macrocycle

The Cu(II) template formation of the dinuclear complex was initially studied. Figure 3.20 shows schematically a typical ESI-MS experiment which was used throughout this work. How to read it is explained below.

![Diagram showing Cu(II) template formation](image)

Fig. 3.20 Schematic representation of Cu(II) template formation of small pseudocalixarene.

The H$_2$mftbp dialdehyde and Cu(ClO$_4$)$_2$·6H$_2$O were dissolved in EtOH and brought to reflux. The first and second samples for the ESI-MS analysis were extracted after 10 min. and 55 min. of reflux respectively. After 1 h. of reflux 1,3-diaminopropan-2-ol was introduced to the reaction mixture and reflux was continued overnight. The third sample for the ESI-MS was taken out from the refluxing solution 10 min. after addition of the diamine and the fourth 40 min. later. The final sample was extracted after overnight reflux.
Figure 3.21 shows spectra of the five samples analysed for the formation of the (2+2) macrocycle. The top two spectra are those of the reaction mixture containing Cu(ClO\textsubscript{4})\textsubscript{2}·6H\textsubscript{2}O and H\textsubscript{2}mftbp in EtOH after 10 and 55 min. of reflux. As can be seen there is not much difference between them and the spectra look almost identical. Most of the peaks were assigned to Cu\textsubscript{x}(dialdehyde)\textsubscript{y} species of different x:y ratios. Details of the assignments can be found in the Appendix DVD.

Addition of diamine changes the relative intensities between peaks representing Cu\textsubscript{x}(dialdehyde)\textsubscript{y} adducts and results in new [Cu(Hmftbp)(diamine)]\textsuperscript{+} peaks at m/z 520 (middle spectrum in Fig. 3.21). Species giving peaks at m/z 544 and at m/z 1136 are gone.

At this stage of reaction all components required for the (2+2) macrocycle formation were in solution but after 35 min. of reflux from diamine addition there was little evidence of progress in the reaction, Cu\textsubscript{x}(dialdehyde)\textsubscript{y} compounds remained as the major components.
Reflux was continued overnight (bottom spectrum in Fig. 3.21) and this resulted in a much cleaner spectrum showing peaks from two major species, dicopper(II) \([\text{Cu}_2\text{H}_2(2+2)(\text{ClO}_4)_2]^+\) at m/z 1069 and tricopper(II), singly charged \([\text{Cu}_3(2+2)(\text{ClO}_4)_3]^+\) at m/z 1130 and doubly charged \([\text{Cu}_3(2+2)]^{2+}\) at m/z 515. Those peaks are highlighted in blue boxes and their assignment will be explained in detail as an example of how all assignments in the course of this work were conducted.

Three spectra are shown in Fig. 3.22. The bottom spectrum shows the experimental data in an expansion of the region above 1000 m/z (marked by a blue box in the previous figure). The middle and top spectra are calculated using the isotope model tool provided with the MS software. There is a reasonably good match in m/z values calculated for those macrocyclic complexes and, which is also important in the case of compounds including polyisotopic elements, the calculated and experimental isotope distribution patterns match.

Fig. 3.22 Peak assignments for tricopper(II) and dicopper(II) (2+2) macrocyclic species conducted on Waters instrument using MassLynx software.

Of the three instruments used in the course of this work, the most accurate and precise data were collected on Thermo Fisher Exactive Orbitrap mass spectrometer. Figure 3.23 shows calculated isotope distribution pattern using the Xcalibur Qual Browser for \([\text{Cu}_3(2+2)(\text{ClO}_4)_3]^+\) fragment (top spectrum) and the experimental data from experiment conducted on the Thermo Fisher instrument. Because the instrument gave very high
resolution data the isotope patterns were calculated as Gaussian profiles for 40 samples/peak with resolving power 100 000 measured at full width at half maximum (FWHM).

The mass accuracy can be defined as an Error = \frac{|M_c - M_r|}{M_c}; where M_c is calculated mass and M_r is experimentally measured mass. The error values are calculated for the most intense peak from the pattern at m/z 1130 for both instruments are shown in Table 3.11.

Table 3.11 Example calculation of mass accuracy defined as an error.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Selected peak [m/z]</th>
<th>Mass calculated by instrument software [m/z]</th>
<th>Mass measured [m/z]</th>
<th>Error [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synapt</td>
<td>1130</td>
<td>1130.2188</td>
<td>1130.2454</td>
<td>23.53</td>
</tr>
<tr>
<td>ThermoFisher</td>
<td>1130</td>
<td>1130.2182</td>
<td>1130.2155</td>
<td>2.39</td>
</tr>
</tbody>
</table>

The data collected on the Orbitrap instrument is at least ten times more accurate than these for the Synapt or LCT mass spectrometers. Despite the 20 ppm difference between calculated and measured mass for [Cu_3(2+2)(ClO_4)]^+ ion on the Waters instruments there is good match between isotope patterns and it is very unlikely that
these peaks correspond to some other fragment as the number of possibilities is limited by the reagents used. Therefore in the course of this work we do not focus on the precision of measured data but on the characteristic isotope distribution pattern fit which allows unambiguous assignment of the peak clusters.

Figure 3.24 also shows a comparison of experimental data with calculated values but this time it is calculated for the doubly charged species \([\text{Cu}_3(2+2)]^{2+}\) giving a peak at m/z 515. The doubly charged species can be recognised because the adjacent peaks in the pattern are exactly half a mass unit apart.

![Figure 3.24 peak assignments for the doubly charged tricopper(II) (2+2) macrocyclic complex fragment.](image)

As mentioned above, after overnight reflux the reaction mixture contains the expected (2+2) dicopper(II) macrocycle but there is also a substantial amount of the tricopper(II) complex present. Because a stoichiometric amount of Cu(II) for the formation of dinuclear compound has been used, there will be some dialdehyde left over in the solution which is indicated by peaks [(H$_2$mftbp) + H]$^+$ at m/z 367 (bottom spectrum Fig. 3.21). An additional 2 h. of reflux did not generate any changes to the system which still comprised both macrocyclic complexes and dialdehyde species. It appears that the reaction reached an equilibrium and formation of the (2+2) product cannot be completed. As established by J. Barreira Fontecha$^{135}$ from similar reaction mixtures the dicopper(II) (2+2) complex can be isolated by recrystallisation procedure. Most likely it is a product of preferential crystallisation which disturbs the equilibrium.
3.5.2. Synthesis of (2+2) Schiff base pseudocalixarene in the presence of Cu(ClO$_4$)$_2$.6H$_2$O in various stoichiometries

Studies of Cu(II) template formation of the (2+2) macrocycle described above demonstrated that overnight reflux of Cu(ClO$_4$)$_2$.6H$_2$O, H$_2$mftbp dialdehyde and 1,3-diaminopropan-2-ol in ethanol produces an equilibrium mixture of dicopper(II) \([\{\text{Cu}_2\text{H}_2(2+2)\}^{2+}, \text{Cu}_2\text{H}_2(2+2)(\text{ClO}_4)\}^+]\) and tricopper(II) macrocyclic species \([\{\text{Cu}_3(2+2))^{2+}, \text{Cu}_3(2+2)(\text{ClO}_4)\}^+]\). In contrast J. Barreira Fontecha’s study$^{135}$ of the solids isolated from Cu(ClO$_4$)$_2$.6H$_2$O template condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol indicated formation of only tetracopper(II) complex. Additionally, analysis of solids isolated from Cu(II) templated reaction mixtures and crystal samples, led J. Barreira Fontecha to the conclusions that a) dicopper(II) complex can be reached on a short reflux with certain counterions like Cl$^-$, BF$_4^-$ b) the tetracopper(II) macrocycle might be a kinetic product and the tricopper(II) the thermodynamic product of condensation. Therefore factors controlling nuclearity of the (2+2) macrocyclic complexes were tested in ESI-MS experiments. Cu(ClO$_4$)$_2$.6H$_2$O was used in three stoichiometries relative to the H$_2$mftbp dialdehyde. Cu:dialdehyde ratios were as follows 1:1 using the LCT ToF mass spectrometer, 1.5:1 and 2:1 the Orbitrap mass spectrometer. The molar ratios of reagents and reaction conditions used were proposed by J. Barreira Fontecha for the synthesis of di-, tri- and tetra-copper(II) products.$^{135}$

In all experiments Cu(ClO$_4$)$_2$.6H$_2$O was refluxed with H$_2$mftbp for 30 min. and then 1,3-diaminopropan-2-ol was added. Reflux was continued overnight with samples taken for ESI-MS analysis (Fig. 3.25).
Spectra acquired for reaction A are shown in Fig. 3.26. This experiment is almost identical to that described in the previous section, differing only in the reflux times for samples extracted for ESI-MS analysis. Most of the observed peaks have already been discussed and assigned. Here we are concentrating on peaks related to macrocyclic complexes which are marked as follows. Peak related to the dinuclear complex are marked by green circles, the trinuclear species are indicated by black circles and the tetranuclear by blue squares.

The top spectrum in Fig. 3.26 shows reaction mixture after 30 min. reflux from addition of 1,3-diaminopropan-2-ol. The tetracopper(II) complex is indicated by singly charged peaks \([\text{Cu}_4(2+2)(\text{OH})_3]^+\) at m/z 1148 and doubly charged peaks \([\text{Cu}_4(2+2)(\text{OH})_2]^{2+}\) at m/z 565. The tricopper(II) product is marked by doubly charged peaks \([\text{Cu}_3(2+2)(\text{OH})_2]^{2+}\) at m/z 524. The tricopper(II) macrocycle pattern overlaps with singly charged peaks from \([\text{Cu}({\text{Hmftbp}})(\text{diamine})]^+\) species at m/z 520. Major peak attributions for macrocyclic complexes from this experiment are summarised in Table 3.12.
Fig. 3.26 Spectra of reaction mixtures from experiment A with 1 equiv. of Cu(ClO$_4$)$_2$·6H$_2$O; dinuclear complex species are marked by green circle; trinuclear complex related peaks are marked by black circles and tetranuclear complex peaks are marked by blue square.

After 30 min. of reflux acyclic imine fragments also can be identified in the spectrum which confirms ongoing Schiff base condensations. The dialdehyde condensed with one diamine is related to a peak [CuH(mftbp)(diamine) - (H$_2$O)] at m/z 502 and the condensation of two molecules of dialdehyde with one diamine is attributed to a peak [Cu$_2$H(mftbp)$_2$(diamine) - (H$_2$O)] at m/z 933.

The second spectrum, acquired after 1 h. reflux, shows only changes in the relative intensities between peaks. The tetracopper(II) (2+2) complex is identified in the reaction mixture but it is not a major species spectrum although the reaction time corresponds to that used for its synthesis. The isolation procedure for the tetranuclear complex reported by J. Barreira Fontecha$^{135}$ was based on analysis of solid samples which resulted from reaction mixtures after specific work-up methods. Here, reaction mixture solution was investigated without any further purification so it is hard to determine whether tetracopper(II) complex is the main macrocyclic product accessible via short reflux method. As noted for the dicopper(II) complex isolated from the equilibrium mixture described in the previous section, it could be a product of preferential crystallisation.
The spectrum from the reaction mixture after 5 h. reflux is much cleaner. The tetracopper(II) peaks are gone. The new peaks appearing in the spectrum, doubly charged at m/z 515 and singly charged at m/z 1130 correspond to the tricopper(II) complex (Table 3.12).

Table 3.12 Major peak assignments for experiments A, B and C.

<table>
<thead>
<tr>
<th>Peak [m/z]</th>
<th>Peak [m/z] Experiments B &amp; C</th>
<th>Fragments</th>
<th>Calculated [m/z] MassLynx</th>
<th>Calculated [m/z] Xcalibur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>485.0013</td>
<td>485.1762</td>
<td>[Cu$_3$H$_4$(2+2)]$^{2+}$</td>
<td>485.1785</td>
<td>485.1780</td>
</tr>
<tr>
<td>502.2102</td>
<td>502.1893</td>
<td>[CuH(mftbp)(diamine) -(H$_2$O)]$^+$</td>
<td>502.1893</td>
<td>502.1887</td>
</tr>
<tr>
<td>515.4970</td>
<td>515.6353</td>
<td>[Cu$_3$(2+2)]$^{2+}$</td>
<td>515.6353</td>
<td>515.6344</td>
</tr>
<tr>
<td>524.6604</td>
<td>524.6400</td>
<td>[Cu$_3$(2+2)(OH)$_2$]$^{2+}$</td>
<td>524.6400</td>
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</tr>
<tr>
<td>565.1346</td>
<td>565.1024</td>
<td>[Cu$_4$(2+2)(OH)$_2$]$^{2+}$</td>
<td>565.1024</td>
<td>564.1022</td>
</tr>
<tr>
<td>571.1448</td>
<td>571.1106</td>
<td>[Cu$_4$(2+2)(MeO)(OH)]$^{2+}$</td>
<td>571.1106</td>
<td>571.1100</td>
</tr>
<tr>
<td>1130.2513</td>
<td>1130.2188</td>
<td>[Cu$_4$(2+2)(ClO$_4$)]$^{2+}$</td>
<td>1130.2188</td>
<td>1130.2182</td>
</tr>
<tr>
<td>1148.2574</td>
<td>1148.2306</td>
<td>[Cu$_4$(2+2)(OH)$_2$]$^{2+}$</td>
<td>1148.2306</td>
<td>1148.2306</td>
</tr>
<tr>
<td>not observed</td>
<td>1241.1688</td>
<td>[Cu$_4$(2+2)(MeO)(OH)(ClO$_4$)]$^{2+}$</td>
<td>1241.1688</td>
<td>1241.1688</td>
</tr>
<tr>
<td>(2+2)$^2$ = C$<em>{32}$H$</em>{64}$N$_4$O$_6$</td>
<td>(mftbp)$^2$ = C$<em>{23}$H$</em>{26}$O$_4$</td>
<td>(diamine)$^3$ = C$<em>3$H$</em>{10}$N$_2$O</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Finally, after 20 h. of reflux from addition of 1,3-diaminopropan-2-ol (Fig. 3.26) the reaction reaches equilibrium as subsequent samples showed no further changes. The (2+2) macrocycle is in the form of dinuclear and trinuclear complexes. There is also some H$_2$mftbp dialdehyde in the reaction mixture because tricopper(II) macrocyclic complex requires less dialdehyde for the formation.

In summary, before the condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol in the presence of 1 equiv. of Cu(ClO$_4$)$_2$·6H$_2$O reached equilibrium, trinuclear and tetranuclear complexes of (2+2) macrocycle were identified in the reaction mixture solution. The tetracopper(II) complex appeared early in the process in form of [Cu$_4$(2+2)(OH)$_2$]$^{2+}$, [Cu$_4$(2+2)(MeO)(OH)]$^{2+}$ and [Cu$_4$(2+2)(OH)$_3$]$^+$ (Table 3.12) then disappeared which is consistent with the suggestion that this is a kinetic product of condensation but not the thermodynamic. The tricopper(II) complex related to peaks [Cu$_3$(2+2)(OH)$_2$]$^{2+}$ was also present in the reaction mixture after 30 min. of reflux and then also disappeared. The new tricopper(II) complex related peaks [Cu$_3$(2+2)]$^{2+}$ and [Cu$_3$(2+2)(ClO$_4$)]$^+$ arose after 5 h. of reflux and the same ions were identified for the
final sample of equilibrium mixture. Despite the fact that the relative intensities of dicopper(II) signals increased after overnight reflux there is no direct evidence that they resulted from the disappearing trinuclear species.

Spectra from the experiments with 1.5 equiv. of Cu(ClO$_4$)$_2$·6H$_2$O (experiment B) and 2 equiv. (experiment C) are shown in Fig. 3.27 on the left and right side respectively. The spectra are much cleaner than in experiment A, showing similar peaks from [CuH(mftbp)]$^+$ at m/z 430, [CuH(mftbp)(diamine)]$^+$ at m/z 520 and [CuH$_3$(mftbp)$_2$] at m/z 798 for experiment B and only Cu(mftbp) adducts for the reaction with 2 equiv.

Surprisingly, although the stoichiometry used was expected to promote formation tricopper(II) and tetracopper(II) products, these are not observed after 30 min. of reflux in contrast to reaction A. The tri- and tetracopper macrocyclic species can be identified after 4 h. of reflux in reaction B and after 20 h. of reflux in experiment C (Fig. 3.27). Fragments due to tetracopper(II) complex are marked by blue squares and tricopper(II) complex peaks are marked by black circles. The tetracopper(II) (2+2) complex is assigned to the doubly charged peaks [Cu$_4$(2+2)(OH)$_2$]$_2$$^{2+}$ at m/z 564, [Cu$_4$(2+2)(MeO)(OH)]$_2$$^{2+}$ at m/z 571 and singly charged [Cu$_4$(2+2)(MeO)(OH)(ClO$_4$)]$^+$ at m/z 1241. The tricopper(II) (2+2) macrocyclic complex is assigned to the doubly charged peaks [Cu$_3$(2+2)]$_2$$^{2+}$ at m/z 515, [Cu$_3$(2+2)(OH)$_2$]$_2$$^{2+}$ at m/z 525 and singly charged [Cu$_3$(2+2)(ClO$_4$)]$^+$ at m/z 1130.

Fig. 3.27 Spectra from the reactions B) with 1.5 equiv of Cu(ClO$_4$)$_2$·6H$_2$O and C) with 2 equiv. of Cu(ClO$_4$)$_2$·6H$_2$O; trinuclear complex related peaks are marked by black circle and tetrannuclear complex peaks are marked by blue squares.
In reaction B after 20 h. of reflux from the addition of 1,3-diaminopropan-2-ol, the reaction reaches an equilibrium as the next samples analysed by ESI-MS showed no further changes. Two macrocyclic species are found in solution, tricopper(II) and tetracopper(II) (2+2) complexes. For reaction C with 2 equiv. Cu(ClO$_4$)$_2$∙6H$_2$O the whole process is slower as peaks from [CuH(mftbp)]$^+$ at m/z 430 are still present after 20 h. It takes 25 h. of reflux before the reaction reaches equilibrium (no changes by ESI-MS) and, as for experiment B, tetracopper(II) and tricopper(II) (2+2) macrocyclic species are produced. The spectrum of the reaction mixture with 2 equiv. of Cu(II) salt (experiment C) after 25 h. of reflux is shown in Fig. 3.28.

Fig. 3.28 Spectrum of an equilibrium mixture of tetracopper(II) and tricopper(II) (2+2) macrocyclic species acquired for the reaction with 2 equiv. Cu(ClO$_4$)$_2$∙6H$_2$O after 25 h. reflux; dicopper(II) complex marked by green circles; tricopper(II) complex by black circles and tetracopper(II) complex by blue squares.

In conclusion, condensations between H$_2$mftbp and 1,3-diaminopropan-2-ol with 1.5 and 2 equiv. of Cu(ClO$_4$)$_2$∙6H$_2$O are much slower than described for 1 equiv. of Cu(II) salt. They both produce similar equilibrium mixtures of trinuclear and tetranuclear species although stoichiometries of reactants were used to promote formation of one particular macrocyclic complex. An excess of Cu(II) ions evidently slows formation of (2+2) macrocycle. The copper binds to all free components present in solution before it forms the intermediate species with the right configuration of ligands for formation of the macrocycle.
3.5.3. Synthesis of (2+2) Schiff base pseudocalixarene in the presence of CuCl₂ and Cu(NO₃)₂·3H₂O

The formation of equilibrium mixtures between di- and tri-copper(II) complexes was also investigated using anhydrous CuCl₂ (experiment A) and Cu(NO₃)₂·3H₂O (experiment B). J. Barreira Fontecha’s study showed that copper chloride used in the condensation between H₂mftbp and 1,3-diaminopropan-2-ol leads to isolation of only the dicopper(II) complex but copper(II) nitrate yields both tricopper(II) and teracopper(II) complexes.135

In two parallel experiments, H₂mftbp dialdehyde was refluxed with the Cu(II) salts (1 equiv.) for 30 min. and then 1,3-diaminopropan-2-ol was added. Reflux was continued for 20 h. and then reaction mixture solutions were examined by ESI-MS (Fig. 3.29).

![Schematic representation of ESI-MS experiments with CuCl₂ and Cu(NO₃)₂·3H₂O.](image)

The spectra of reaction mixtures after 20 h. of reflux from addition of 1,3-diaminopropan-2-ol are shown in Fig. 3.30 and major peak assignments are presented in Table 3.13.

Spectrum A represents reaction mixture from the experiment with chloride anions. The major compound found is the free (2+2) macrocycle, condensate of two diamines and two dialdehydes, assigned to the doubly charged peaks [H₆(2+2)]²⁺ at m/z 423 and singly charged [H₅(2+2)]⁺ at m/z 845 which are marked by circles. The dicopper(II) complex can be assigned to the [Cu₂H₂(2+2)(Cl)]⁺ peaks at m/z 1005 and additionally...
to very small intensity peaks \([\text{Cu}_2\text{H}_2(2+2)]^+\) at \(m/z\) 967 highlighted by green circles. The other macrocyclic species are related to monocopper(II) fragments \([\text{CuH}(2+2)]^{2+}\) at \(m/z\) 453 and \([\text{CuH}_2(2+2)]^+\) at \(m/z\) 906 which are marked by the green half circles. The tricopper(II) (2+2) macrocyclic species are not observed in the spectrum which is consistent with the green colour of reaction mixture solution.

Fig. 3.30 Spectra of reaction mixtures after 20 h. of reflux A) \text{CuCl}_2, \text{H}_2\text{mfbp}, 1,3-diaminopropan-2-ol B) \text{Cu(NO}_3)_2\cdot3\text{H}_2\text{O}, \text{H}_2\text{mfbp}, 1,3-diaminopropan-2-ol; dicopper(II) complex marked by green circles; tricopper(II) complex by black circles; (2+2) free macrocyclic ligand by circles and monocopper(II) complex by green half circles.

In contrast, spectrum B for the nitrate reaction mixture is a clean spectrum of the equilibrium mixture of the dicopper(II) (2+2) and the tricopper(II) (2+2) macrocyclic species as was found in the experiments with perchlorate anions. The dicopper(II) species are assigned to the doubly charged species \([\text{Cu}_2\text{H}_2(2+2)]^{2+}\) at \(m/z\) 484 and singly charged due to \([\text{Cu}_2\text{H}(2+2)]^+\) at \(m/z\) 967. The tricopper(II) complex gives rise to doubly
charged peaks \([\text{Cu}_3(2+2)]^{2+}\) at \(m/z\) 515 and singly charged \([\text{Cu}_3(2+2)(\text{NO}_3)]^+\) at \(m/z\) 1093.

Table 3.13 Major peak attributions for experiments A and B.

<table>
<thead>
<tr>
<th>Peak ([m/z])</th>
<th>Fragments</th>
<th>Calculated ([m/z])</th>
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</thead>
<tbody>
<tr>
<td><strong>Experiment A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>423.2634</td>
<td>([\text{H}_6(2+2)]^{2+})</td>
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<td>453.7203</td>
<td>([\text{CuH}_4(2+2)]^{2+})</td>
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<td>478</td>
<td>grease related</td>
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<tr>
<td>845.5195</td>
<td>([\text{H}_5(2+2)]^+)</td>
<td>845.5212</td>
</tr>
<tr>
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<td>([\text{CuH}_3(2+2)]^+)</td>
<td>906.4351</td>
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<tr>
<td>967.3471</td>
<td>([\text{Cu}_2\text{H}(2+2)]^+)</td>
<td>967.3491</td>
</tr>
<tr>
<td>1005.3216</td>
<td>([\text{Cu}_2\text{H}_2(2+2)(\text{Cl})]^+)</td>
<td>1005.3247</td>
</tr>
<tr>
<td><strong>Experiment B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>484.1774</td>
<td>([\text{Cu}_3\text{H}_3(2+2)]^{2+})</td>
<td>484.1782</td>
</tr>
<tr>
<td>515.6332</td>
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</tr>
<tr>
<td>1030.3428</td>
<td>([\text{Cu}_3\text{H}_2(2+2)(\text{NO}_3)]^+)</td>
<td>1030.3447</td>
</tr>
<tr>
<td>1093.2545</td>
<td>([\text{Cu}_3(2+2)(\text{NO}_3)]^+)</td>
<td>1093.2578</td>
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</table>

In conclusion, it appears that the counterion of Cu(II) salt used as template in condensation between \(\text{H}_2\text{mftbp}\) and 1,3-diaminopropan-2-ol does have an impact on the nuclearity of complexes formed. As suggested by J. Barreira Fontecha,\(^{135}\) a good coordinating anion with suitable radius such as \(\text{Cl}^-\) bridges two coppers accommodating the \(\text{N}_2\text{O}_2\) coordination sites and yields only the dinuclear complex \([\text{Cu}_2\text{H}_2(2+2)(\text{Cl})]^+\) which was confirmed by the ESI-MS. Perhaps the chloride link between transition metals in saddle-shape dinuclear macrocycle stops possible conversion of this dicopper(II) complex into the tricopper(II) species. The perchlorate and nitrate salts used in the same condensation result in equilibrium mixtures of dicopper(II) and tricopper(II) (2+2) complexes (when 1 equiv. of Cu(II) salt is used). Probably lack of a good bridging ion makes the centre position of macrocycle more accessible for the third copper ion.

The nuclearity of complexes is also controlled by the Cu(II):aldehyde ratio. As found, condensations with 1.5 equiv. and 2 equiv. of Cu(II) perchlorate yield equilibrium mixture of tricopper(II) and tetracopper(II) (2+2) macrocyclic complexes.
Another factor which has an impact on the nuclearity is the reaction time. Although short refluxes do not produce clean macrocyclic products, they can be isolated by recrystallisations with various solvent combinations from short refluxed reaction mixtures. For the Cu:aldehyde ratio of 1:1, on short reflux, surprisingly tricopper(II) and tetracopper(II) (2+2) species are observed in the spectra. When higher ratios of Cu:dialdehyde are used no macrocyclic species are observed up to 4 h. of reflux.

It seems that trinuclear (2+2) complex is a thermodynamic product of condensations between H₂mftbp and 1,3–diaminopropan-2-ol in various stoichiometries. In solution it has a dark brown colour which might be explained by charge transfer between fully deprotonated macrocyclic ligand and Cu(II) ion. The reasons why Cu(II) so readily occupies the hard tetraphenolate oxygen binding site remain obscure however the unsaturated bond system of macrocyclic ligand might suggest its noninnocent redox behaviour. If this is the case, the charge of the [Cu₃(2+2)]²⁺ cation could be delocalized over the double bond system of macrocyclic ligand.

3.5.4. Synthesis of a (2+2) pseducalixarene Schiff base macrocycle in presence of Ni(ClO₄)₂·6H₂O or Zn(NO₃)₂·6H₂O

Formation of equilibrium mixtures was investigated for Ni(ClO₄)₂·6H₂O and Zn(NO₃)₂·6H₂O templates in short ESI-MS experiments. Reaction mixtures were examined after 20 h. of reflux which corresponds to reaction times proposed by J. Barreira Fontecha for synthesis of polynuclear complexes.

In the experiments, H₂mftbp dialdehyde and the metal salt, Ni(ClO₄)₂·6H₂O (either 1 equiv. or 1.5 equiv.) or Zn(NO₃)₂·6H₂O (1 equiv.) were refluxed for 30 min. then 1,3-diaminopropan-2-ol was added and reflux was continued overnight (Fig. 3.31). In the experiment using Zn(II), samples for ESI-MS analysis were extracted after 30 min. of reflux, before addition of diamine, and 20 h. after addition. In experiments A and B, with Ni(II), they were examined only after 20 h. of reflux from addition of diamine.
Fig. 3.31 Schematic representation of ESI-MS experiments with A) 1 equiv. of Ni(ClO\textsubscript{4})\textsubscript{2} \cdot 6H\textsubscript{2}O, B) 1.5 equiv. of Ni(ClO\textsubscript{4})\textsubscript{2} \cdot 6H\textsubscript{2}O and C) 1 equiv. of Zn(NO\textsubscript{3})\textsubscript{2} \cdot 6H\textsubscript{2}O.

Spectra acquired in the experiments with Ni(ClO\textsubscript{4})\textsubscript{2} \cdot 6H\textsubscript{2}O are shown in Fig. 3.32 The top spectrum represents reaction A, where 1 equiv. of Ni(II) salt was used and the bottom spectrum reaction B with 1.5 equiv. of Ni(II) salt.

Fig. 3.32 Spectra of Ni(ClO\textsubscript{4})\textsubscript{2} \cdot 6H\textsubscript{2}O/H\textsubscript{2}mftbp/diamine reaction mixtures examined after 20 h. of reflux from addition of diamine.

In both experiments A and B, the major species found in the reaction mixtures after 20 h. of reflux are attributed to the dinickel(II) (2+2) macrocycle. It is indicated by peaks corresponding to \([\text{Ni}_2\text{H}_2(2+2)]^{2+}\) at m/z 479, \([\text{Ni}_2\text{H}(2+2)]^+\) at m/z 957 and \([\text{Ni}_2\text{H}_2(2+2)(\text{ClO}_4)]^+\) at m/z 1057 (experiment B) and m/z 1059 (experiment A).
two different values observed for the same peak at m/z 1057 is due to a slight change in the relative intensity between the highest peaks in the patterns, ms software labels the highest peak from the pattern.

The trinuclear complex, which for corresponding Cu(ClO$_4$)$_2$·6H$_2$O experiments was present with both stoichiometries, is not observed in either of the spectra. The tetranickel(II) complex is a minor product of reaction B, it can be identified by very weak relative intensity peaks for [Ni$_4$(2+2)(MeO)(OH) -H]$^+$ at m/z 1121. It appears that condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol in the presence of Ni(ClO$_4$)$_2$·6H$_2$O does not produce an equivalent equilibrium mixture to that found for the Cu(II). Ni(II) as a template yields only the dinuclear complex of the (2+2) macrocycle for Ni(II):dialdehyde ratio 1:1 and dinuclear complex with the tetranickel species as minor product for ratio 1.5:1.

Spectra from experiment C, using Zn(NO$_3$)$_2$·6H$_2$O are shown in Fig. 3.33. The reaction mixture before addition of 1,3-diaminopropan-2-ol consists mainly of species related to the dialdehyde, [H$_3$(mftbp)]$^+$ at m/z 369 and [ZnH$_3$(mftbp)$_2$]+ at m/z 799. At this point the mixture is similar to that with Cu(ClO$_4$)$_2$·6H$_2$O where Cu(mftbp) and Cu(mftbp)$_2$ adducts were the major compounds identified.

Fig. 3.33 Spectra acquired in experiment C with Zn(NO$_3$)$_2$·6H$_2$O.
An overnight reflux results in the dizinc(II) (2+2) macrocyclic complex, indicated by peaks for \([\text{Zn}_2\text{H}_2(2+2)]^{2+}\) at m/z 489 and \([\text{Zn}_2\text{H}_2(2+2)(\text{OH})]^+\) at m/z 989, this is the major product of the condensation. Peaks at m/z 1034 were attributed to a mixture of the related dinuclear fragments, \([\text{Zn}_2\text{H}_2(2+2)(\text{NO}_3)]^+\) at m/z 1034 and \([\text{Zn}_2\text{H}_2\text{Na}(2+2)(\text{OH}_2)_2+2e^-]^+\) at m/z 1031 (Fig. 3.34).

In summary, Zn(II) or Ni(II) template ions produce only dinuclear complexes when metal:dialdehyde ratio is set to 1:1. They were identified by ESI-MS as doubly charged \([\text{M}_2\text{H}_2(2+2)]^{2+}\) and singly charged \([\text{M}_2\text{H}_2(2+2)X]^+\) fragments where \(\text{M} = \text{Zn(II)}\) or Ni(II) and \(X = \text{ClO}_4^-\) or \(\text{NO}_3^-\). Neither Ni(II) or Zn(II), despite their similar ionic size to Cu(II), from trinuclear complexes with the (2+2) pseudocalixarene. This could be related to the redox properties of the transition metal and the ability of the macrocycle to act as noninnocent ligand.

Tetranuclear Zn(II) or Ni(II) complexes with of the (2+2) macrocycle can be isolated in solid form as was established by J. Barreira Fontecha but their synthesis was promoted by addition of base which deprotonates the alcohol groups of the side chains as well as generating bridging OH\(^-\) ions. When base is not used isolation of tetranuclear complexes is most likely a result of preferential crystallisation.
A summary of the condensations between H$_2$mftbp and 1,3-diaminopropan-2-ol in the presence of Ni(II), Zn(II) and Cu(II), salts is shown in Fig. 3.35.

Fig. 3.35 Diagram showing accessibility of pseudocalixarene homonuclear complexes.

### 3.5.5. ESI-MS study of heteronuclear complexes of (2+2) pseudocalixarenes

Analysis of solid products described in the synthetic part of this chapter led to the conclusion that the sequence in which metal salts are introduced to the reaction mixture does not have an impact on the distribution of macrocyclic products in heteronuclear complexes. To confirm this, syntheses of TM$_2$M complexes (TM = transition metal and M = group 1 or 2 metal) of a (2+2) macrocycle derived from H$_2$mftbp via three major routes was followed by ESI-MS. The routes differ mainly in the order in which reactants were introduced to the reaction mixture.

**Route 1:** This was a two stage process, first the transition metal ion (TM) was used as a template in condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol in an overnight reflux. Then the group 1 or 2 metal ion was added followed by NEt$_3$ and reflux was continued until the ESI-MS showed no further changes.
**Route 2:** In the second type of ESI-MS experiment typically the $\text{H}_2\text{mftbp}$, transition metal salt and central metal salt were refluxed in ethanol for 30 min. and after that time 1,3-diaminopropan-2-ol was added followed by base. The reaction mixture was allowed to reflux until the ESI-MS showed no further changes.

**Route 3:** $\text{H}_2\text{mftbp}$ was refluxed overnight in EtOH with the group 1 or 2 metal salt and 1,3-diaminopropan-2-ol in the presence of base. The transition metal salt was then introduced to the system and reflux was continued until there was no further change indicated by ESI-MS.

**Route 4:** Similar to Route 2, differing in the order in which 1,3-diaminopropan-2-ol and NEt$_3$ (base) were introduced to the reaction mixture.

Formation of macrocyclic species *via* Route 1 was monitored by ESI-MS for Li(I), Na(I), Mg(II) and Ca(II) as central metals and Cu(II) as transition metal. In one experiment Ni(II) was used as transition metal and Cu(II) as potential central metal. Also by this route Cu(II) chloride was used in combination with Na(ClO$_4$). The Route 2 was investigated by ESI-MS for Cu(II) with Na(I) and Cu(II) with Mg(II) metal combinations. Finally experiment with Zn(II) and Na(I) salts was conducted by route 3. The route 4 was not used in the experiments described in this chapter. The summary of synthetic routes studied for the heteronuclear complexes of (2+2) Schiff base pseudocalixarene is shown in Table 3.14 and Fig. 3.37.

Table 3.14 Summary of metal ion combinations employed for template formation of (2+2) Schiff base pseudocalixarene complexes.
Fig. 3.36 Proposed synthetic patterns leading to the heteronuclear complexes of pseudocalixarene macrocycles investigated in the ESI-MS experiments; Each 1dialdehyde:1diamine condensate is represented by a different colour.

3.5.5.1. Formation of Cu$_2$M [M = Na(I), Li(I), Ca(II) and Mg(II)] complexes of (2+2) macrocycle by Route 1

Formation of heterotrinuclear complexes with Cu(II) and four different central metals, alkali metals Na(I) (experiment A) and Li(I) (experiment B) and alkaline earth metals Ca(II) (experiment D) and Mg(II) (experiment C) was investigated by ESI-MS (Fig. 3.37). Possible formation of larger macrocyclic assemblies such as a sandwich compound was also examined.
The spectrum of the equilibrium mixture of dicopper(II) (2+2) and tricopper(II) (2+2) macrocyclic complexes reached as described earlier in this chapter (section 3.5.1) is shown again in Fig. 3.38 for reference.

When group 1 or 2 metal ions were introduced to this reaction mixture, followed by base it is most likely to induce the following changes: First, the NEt$_3$ would cause full deprotonation of the dinuclear complexes indicated by peaks [Cu$_2$H$_2$(2+2)]$^{2+}$ and [Cu$_2$H$_2$(2+2)(ClO$_4$)]$^+$. The group 1 or 2 ion can then bind to the tetraphenolate site.
resulting in formation of \([\text{Cu}_2\text{M}(2+2)]^+\) species for \(\text{M} = \text{Li(I)}\) and \(\text{Na(I)}\) or \([\text{Cu}_2\text{M}(2+2)]^{2+}\) for \(\text{M} = \text{Mg(II)}\) and \(\text{Ca(II)}\). The trinuclear complex \([\text{Cu}_3(2+2)]^{2+}\) with the relatively soft Cu(II) ion occupying the central site of the (2+2) macrocycle should also undergo the transmetallation reaction with harder group 1 or 2 metal ions resulting the same trinuclear \(\text{Cu}_2\text{M}\) species in solution. For larger metal ions sandwich complexes are anticipated as one of the products of this reaction, as their ionic size might prevent them fitting into the macrocycle hole but it will be large enough to bind two (2+2) macrocyclic units together.

Figure 3.39 shows spectra of the reaction mixtures from experiments A, B, C and D analysed 2 h. after addition of \(\text{NEt}_3\). The expected peaks related to \([\text{Cu}_2\text{M}(2+2)]^+\) fragments for \(\text{Li(I)}\) and \(\text{Na(I)}\) and \([\text{Cu}_2\text{M}(2+2)\text{X}]^+\) fragments for \(\text{Mg(II)}\) and \(\text{Ca(II)}\) where \(\text{X} = \text{ClO}_4^-\) are observed in all experiments and are indicated by corresponding cartoons. Major peak attributions are presented in Table 3.15.

![Fig. 3.39 Spectra acquired in the reactions with Cu(ClO4)2·6H2O and A) with Na(ClO4) B) with Li(NO3) C) Mg(ClO4)2·6H2O D) Ca(ClO4)2·4H2O. Each 1dialdehyde:1diamine condensate and each metal is shown in different colour.

Peaks \([\text{Cu}(\text{diamine})(\text{NEt}_3)(\text{MeOH})]^+\) at m/z 303 with the highest relative intensity are also found in the spectra of each reaction mixture. Moreover, in the reactions A, B and C the tetracopper(II) (2+2) macrocyclic complex gives rise to peaks for
[Cu$_4$(2+2)(ClO$_4$)(MeO)(OH)]$^+$ at m/z 1241. Formation of this tetranuclear compound is probably favoured by the added base. Additionally, the Na(I) adduct of the [Cu$_2$(2+2)] species is found in the experiments with Mg(II) and Ca(II). As mentioned earlier in this chapter, the ESI-MS is not the most decisive method for identifying the sodium species because the Na$^+$ adduct appears at low intensity very often in the spectra even when sodium was not used intentionally.

Table 3.15 Major peak assignments for the Cu$_2$M ESI-MS experiments where M = Na (experiment A), Li(I) (experiment B), Mg(II) (experiment C) and Ca(II) (experiment D).

<table>
<thead>
<tr>
<th>Peak [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
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<td><strong>Experiment A</strong></td>
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</tr>
<tr>
<td>303.2044</td>
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<td>989.3307</td>
<td>[Cu$_2$Na(2+2)]$^+$</td>
<td>989.3310</td>
</tr>
<tr>
<td>1241.1675</td>
<td>[Cu$_4$(2+2)(MeO)(OH)(ClO$_4$)]$^+$</td>
<td>1241.1683</td>
</tr>
<tr>
<td><strong>Experiment B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>303.2044</td>
<td>[Cu(diamine)(NEt$_3$)(MeOH)]$^+$</td>
<td>303.1578</td>
</tr>
<tr>
<td>973.3567</td>
<td>[Cu$_3$Li(2+2)]$^+$</td>
<td>973.3572</td>
</tr>
<tr>
<td><strong>Experiment C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>303.2045</td>
<td>[Cu(diamine)(NEt$_3$)(MeOH)]$^+$</td>
<td>303.1578</td>
</tr>
<tr>
<td>1091.2728</td>
<td>[Cu$_3$Mg(2+2)(ClO$_4$)]$^+$</td>
<td>1091.2730</td>
</tr>
<tr>
<td>1241.1682</td>
<td>[Cu$_4$(2+2)(ClO$_4$)(MeO)(OH)]$^+$</td>
<td>1241.1683</td>
</tr>
<tr>
<td><strong>Experiment D</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>503.1514</td>
<td>[Cu$_2$Ca(2+2)]$^{2+}$</td>
<td>503.1516</td>
</tr>
<tr>
<td>744.1373</td>
<td>[Cu$_3$(mftbp)(EtO)$_2$(ClO$_4$)]$^+$</td>
<td>743.9705</td>
</tr>
<tr>
<td>1107.2495</td>
<td>[Cu$_2$Ca(2+2)(ClO$_4$)]$^+$</td>
<td>1107.2505</td>
</tr>
</tbody>
</table>

$^{(2+2)^+} = C_{35}H_{64}N_4O_6$  
$^{(diamine)^{11+}} = C_3H_{16}N_2O$  
$^{(mftbp)^+} = C_{23}H_{26}O_4$

The doubly charged peaks at m/z 1042 and triply charged at m/z 1097 appearing in the spectrum B are not assigned. The limited number of chemical compounds which might form from the (2+2) macrocycle with Cu(II) and Li(I) ions in the presence of base suggest contamination of acquired samples, especially because the above peaks were related to di- and trivalent species not used in this experiment. Possibly contaminants are picked up in the ms instrument as in the course of this work the phenomena of unwanted ions carrying over from a previous sample was observed several times.

Formation of the Cu$_2$Na complex of (2+2) macrocycle via Route 1 was also performed with anhydrous CuCl$_2$ and sodium perchlorate (experiment E). As established in section 3.5.3 of this chapter, when the copper(II) chloride salt is used in the condensation between H$_2$mftbp and 1,3- diaminopropan-2-ol, the dinuclear complex of the small
pseudocalixarene and free ligand are identified in the reaction mixture solution. Fig. 3.40 shows schematic representation of the experiment and spectrum of reaction mixture analysed 2 h. after addition of NEt₃.

Fig. 3.40 Spectrum of CuCl₂/dialdehyde/diamine/Na(ClO₄)/NEt₃ reaction mixture with the schematic representation of an experiment.

The major compound found is the (2+2) free macrocyclic ligand represented by doubly charged peaks for [H₆(2+2)]²⁺ at m/z 423 and singly charged [H₅(2+2)]⁺ at m/z 845. The expected heteronuclear complex is also found and it can be identified by peaks for [Cu₂Na(2+2)]⁺ at m/z 989. This experiment shows once more that CuCl₂ results different reaction mixtures than these produced by the perchlorate salt. The peaks from this experiment were previously assigned and can be found in Tables 3.12 and 3.13.

Despite the use of additional base, which should promote formation of polynuclear species (Cu₃ or Cu₄), one of the main macrocyclic complexes in solution corresponds to [Cu₂H₂(2+2)Cl]⁺ at m/z 1005. This again is consistent with the suggestion that a chloride ion bridging two copper ions together stabilises the saddle shape maintained by hydrogen bonds between monodeprotonated methylenediphenols. It reduces accessibility of the hard tetraphenolate for the potential binding metal ions and stops the [Cu₂H₂(2+2)Cl]⁺ ion from further conversions to polynuclear species.
These ESI-MS experiments suggest that the Cu$_2$Na complex isolated by J.Barreira Fontecha$^{135}$ from a corresponding reaction mixture is rather a product of preferential crystallisation as the free macrocyclic ligand and the dinuclear complex are the major species existing in reaction mixture solution.

In the experiment carried out with Ni(II) and Cu(II) perchlorates (experiment F), by the same reaction route, accessibility of the central site of the dinickel(II) (2+2) complex to Cu(II) ion was investigated. As described in section 3.5.3, Ni(II) used as a template in the condensation between H$_2$mtftp dialdehyde and 1,3-diaminopropan-2-ol yields the dinuclear complex only. Cu(II) used in the same condensation produces mixture of dinuclear with the tricopper(II) form of the macrocycle, where the central copper ion binds to the four hard oxygen donors from fully deprotonated methylenediphenol units. Therefore, the free central site of the dinickel(II) complex should be able to bind a Cu(II) ion and result in heteronuclear Ni$_2$Cu complex of (2+2) macrocycle.

In this experiment dinickel(II) (2+2) complex was synthesised first and then Cu(ClO$_4$)$_2$ $\cdot$6H$_2$O was added to the reaction mixture with reflux maintained for 2 h. A schematic representation of an experiment and the acquired spectra are shown in Fig. 3.41. The major peak assignments are listed in Table 3.16.

![Fig. 3.41 The Ni(II) and Cu(II) experiment conducted via Route 1.](image)

The top spectrum is a clean spectrum of the dinickel(II) (2+2) complex which is represented by doubly charged peaks for [Ni$_2$H$_2$(2+2)]$^{2+}$ at m/z 479, singly charged peaks for [Ni$_2$H(2+2)]$^+$ at m/z 957 and [Ni$_2$(2+2)(ClO$_4$)]$^+$ at m/z 1059. The bottom
spectrum shows the reaction mixture of the dinickel(II) complex 2 h. after addition of Cu(ClO$_4$)$_2$-6H$_2$O. The dinickel (II) complex is still present in the reaction mixture and new peaks appear at m/z 510 and m/z 1120. These peaks are assigned to the [Ni$_2$Cu(2+2)]$^{2+}$ and [Ni$_2$Cu(2+2)(ClO$_4$)]$^+$ species respectively, so the nickel(II) ion is not replaced by copper(II) ion in the dinuclear macrocycle. The Cu(II) ion is bound only in the tetraphenolate central site of the ligand. As for the experiment with only Cu(ClO$_4$)$_2$-6H$_2$O (section 3.5.1), an equilibrium mixture of dinuclear and trinuclear species is formed. Here however the trinuclear species are Ni$_2$Cu mixed transition metals complex.

Table 3.16 Peak attributions for experiment with Ni(ClO$_4$)$_2$-6H$_2$O and Cu(ClO$_4$)$_2$-6H$_2$O.

<table>
<thead>
<tr>
<th>Peak [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>479.1832</td>
<td>[Ni$_2$H$_2$(2+2)]$^{2+}$</td>
<td>479.1839</td>
</tr>
<tr>
<td>957.3590</td>
<td>[Ni$_2$H(2+2)]$^+$</td>
<td>957.3606</td>
</tr>
<tr>
<td>1059.3102</td>
<td>[Ni$_3$H$_2$(2+2)(ClO$_4$)]$^+$</td>
<td>1059.3123</td>
</tr>
<tr>
<td>2nd sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>510.6381</td>
<td>[Ni$_3$Cu(2+2)]$^{2+}$</td>
<td>510.6386</td>
</tr>
<tr>
<td>1120.2253</td>
<td>[Ni$_3$Cu(2+2)(ClO$_4$)]$^+$</td>
<td>1120.2263</td>
</tr>
</tbody>
</table>

Undoubtedly, formation of this heterotrinuclear [Ni$_3$Cu(2+2)]$^{2+}$ complex cation in solution implies that the Cu(II) ion can access the central site of the dinuclear (2+2) macrocyclic complex regardless of the metal which is coordinated by the N$_2$O$_2$ site.

In summary:

1) Trinuclear TM$_2$M complexes of (2+2) pseudocalixarene with Cu(II) and group 1 or 2 metals are accessible by Route 1. Here the group 1 or 2 ion is not involved in template formation of macrocycle, the trinuclear complexes form by complexation and transmetallation of the dicopper and tricopper complexes respectively.

2) The ESI-MS may not be definitive in the case of Na(I) complexes. Adducts are often produced even when sodium is not added to the reaction. Therefore the relative intensity of Na(I) clusters corresponding peaks should be significant.

3) CuCl$_2$ produces different reaction mixture from these observed for copper perchlorate. The major species identified for the copper(II) chloride experiment are the
(2+2) free macrocyclic ligand and the $[\text{Cu}_2\text{H}_2(2+2)\text{Cl}]^+$ complex cation similar to that described in section 3.5.3.

4) The (2+2) macrocyclic ligand is versatile and possesses an ability to bind various metals in the central tetraphenolate position which leads to either homo- or heterotrinuclear complexes. It can contract to accommodate metal ions with short ionic radii such as Li(I) and Mg(II) or stretch for complexes with larger ionic radii metals such as Na(I) and Ca(II), as found in the synthetic part of this chapter. Furthermore, calixarene-type tetraphenolate site of the macrocyclic ligand can be occupied by the relatively soft metal Cu(II) in heteronuclear Ni$_2$Cu system with Ni(II) accommodated in the N$_2$O$_2$ site.

3.5.5.2. Formation of Cu$_2$M [$M = \text{Na(I) and Mg(II)}$] complexes of (2+2) macrocycle by Route 2

Formation of Cu$_2$Na (experiment A) and Cu$_2$Mg (experiment B) complexes of the (2+2) macrocycle in solution were examined via Route 2. In experiment A H$_2$mf, Cu(ClO$_4$)$_2$·6H$_2$O and NaClO$_4$ were refluxed for 30 min. and after that time 1,3-diaminopropan-2-ol and NEt$_3$ were introduced 30 min. apart and reflux was continued for 2 h. after which the reaction mixture was analysed by ESI-MS. Experiment B was carried out similarly but Mg(NO$_3$)$_2$·6H$_2$O was used instead of the Na(I) salt (Fig. 3.42).

![Fig. 3.42 Schematic representation of ESI-MS experiments with Cu(II) and: A) Na(I) B) Mg(II), conducted via Route 2.](image)

Figure 3.43 shows spectra acquired for the reaction mixtures 2 h. after addition of NEt$_3$. In reaction A, expected $[\text{Cu}_2\text{Na}(2+2)]^+$ ion is the major species identified (at m/z 989).
Additionally, the (3+3) macrocyclic product represented by peaks \([\text{Cu}_3\text{Na}(3+3)]^{+}\) at m/z 1474 can be found, together with the \([\text{Cu}(\text{NEt}_3)(\text{amine})(\text{MeOH})]^+\) fragment at m/z 303, as described in previous section. The inset diagram shows m/z 989 peak assignments.

![Fig. 3.43 Spectra acquired 2 h. after addition of base to the reaction mixtures A) Cu(ClO_4)_2·6H_2O, NaClO_4/H_2mftbp/diamine B) Cu(ClO_4)_2·6H_2O, Mg(NO_3)_2·6H_2O/H_2mftbp/diamine.](image)

Surprisingly, the major macrocyclic product of the condensation between H_2mftbp and 1,3-diaminopropan-2-ol in the presence of Cu(II) and Mg(II) is not the trinuclear complex of (2+2) macrocycle but the larger (3+3) macrocyclic complex \([\text{Cu}_3\text{Mg}(3+3)]^{2+}\) (at m/z 737) and singly charged \([\text{Cu}_3\text{Mg}(3+3)(\text{ClO}_4)]^+\) at m/z 1574 (Table 3.17). The only trinuclear Cu_2Mg related species is \([\text{Cu}_2\text{Mg}(2+2)(\text{ClO}_4)]^+\) found at m/z 1091. Also among products the (4+4) condensate or (2+2) sandwich species can be found. The doubly charged peaks at m/z 979 and at m/z 989 are more likely
related to the (4+4) macrocyclic species, $[\text{Cu}_4\text{Mg}(4+4)]^{2+}$ and $[\text{Cu}_4\text{Mg}(4+4)(\text{OH}_2)]^{2+}$ respectively, because the synthetic pattern of this route favours formation of (4+4) condensate over a sandwich molecule (see chapter 4).

Table 3.17 Major Peak assignments for experiment B.

<table>
<thead>
<tr>
<th>Peak [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>737.7475</td>
<td>$[\text{Cu}_3\text{Mg}(3+3)]^{1+}$</td>
<td>737.7474</td>
</tr>
<tr>
<td>979.8342</td>
<td>$[\text{Cu}_4\text{Mg}(4+4)]^{2+}$</td>
<td>979.8345</td>
</tr>
<tr>
<td>988.8394</td>
<td>$[\text{Cu}_4\text{Mg}(4+4)(\text{OH}_2)]^{2+}$</td>
<td>988.8398</td>
</tr>
<tr>
<td>1091.2721</td>
<td>$[\text{Cu}_3\text{Mg}(2+2)(\text{ClO}_4)]^{1+}$</td>
<td>1091.2730</td>
</tr>
<tr>
<td>1474.5002</td>
<td>$[\text{Cu}_3\text{Mg}(3+3)+e^-]^{1+}$</td>
<td>1474.4875</td>
</tr>
<tr>
<td>1574.440</td>
<td>$[\text{Cu}_3\text{Mg}(3+3)(\text{ClO}_4)]^{1+}$</td>
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<tr>
<td>1957.6701</td>
<td>$[\text{Cu}_4\text{Mg}(4+4)+e^-]^{1+}$</td>
<td>1957.6714</td>
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</table>

In conclusion, ESI-MS studied formation of Cu$_2$M complexes of (2+2) macrocycle by route where both metals are refluxed with H$_2$mftbp, before diamine and base are introduced showed that larger macrocyclic products than the (2+2) complex can be produced. This requires the alkaline or alkaline earth metal involvement in the template processes as Cu(II) ions were found to yield only the small pseudocalixarene macrocycle. Unexpectedly, in the reaction with Cu(II) and Mg(II) the main macrocyclic product found was the (3+3) condensate but in mixture with (probably) the (4+4) molecule. The ionic radius of the Mg(II) ion is smaller than Na(I) but it produced the larger macrocycles. This may be because magnesium is a harder metal so binds better to the hard phenolate donors of dialdehyde than to other species present in solution so is more involved in template process. For the Cu(II) with Na(I) reaction, a trinuclear complex of the (2+2) macrocycle was the major product identified by ESI-MS but there was also a significant amount of the (3+3) macrocycle.

Route 2 does not lead to clean macrocyclic products. When all reactants are used together and base is introduced to the system there seems to be a competition between metals, Cu(II) template formation of (2+2) macrocycle and group 1 or 2 metal template formation of larger macrocyclic species.
3.5.5.3. Formation of Zn$_2$Na complex of (2+2) macrocycle via Route 3

The synthetic procedure for isolation of the [Zn$_2$Na(2+2)(OAc)]$_2$ complex proposed by J.B. Fontecha$^{135}$ was investigated by ESI-MS. The Na(I) salt, H$_2$mftbp dialdehyde and diamine were refluxed overnight in the presence of base and, after that time the reaction mixture was examined by ESI-MS. Then the Zn(II) salt was introduced and the reaction mixture refluxed for 2 h. when it was again examined by ESI-MS (Fig. 3.44).

Fig. 3.44 Schematic representation of Na(I) and Zn(II) ESI-MS experiment.

The top spectrum in Fig. 3.45 represents Na(I), dialdehyde, diamine and base reaction mixture after an overnight reflux. At this stage the mixture contains free macrocyclic ligands (2+2), (3+3) and the (4+4) and their sodium adducts with the (2+2) condensate as predominant species. The peak assignments are presented in Table 3.18. The observed products correspond to the non-template Schiff base condensation between H$_2$mfmp and 1,2-bis(2-aminoethoxy)ethane reported by Hisaeda$^{133}$ where a similar mixture of macrocyclic compounds (2+2), (3+3) and (4+4) was formed.
Fig. 3.45 Spectra acquired in the Na(I) and Zn(II) experiment; Cartoons represent macrocyclic species.

The second spectrum was acquired in the range m/z 200-4000 after 2 h. of reflux from addition of Zn(II) to the reaction mixture. It shows mainly peaks {Na[Zn$_2$(2+2)]$_2$}$^+$ which can be assigned to the sandwich or (4+4) cations. More likely they are related to the sandwich complex because the (2+2) macrocycle and its sodium adduct were the main macrocyclic species in reaction mixture before addition of Zn(II). The dimer molecule of Zn$_2$Na complex [Zn$_2$Na(2+2)(OAc)(EtOH)$_2$]$_2$∙2EtOH isolated by J. Barreira Fontecha$^{135}$ from similar reaction mixture discussed in section 3.2.1 of this chapter may be the product of preferential crystallisation as FAB-MS spectrum of this dimer complex did not show any high mass related peaks but only the Zn$_2$Na trinuclear complex fragments.

Table 3.18 Major peak attributions for Zn(II) and Na(I) experiment.

<table>
<thead>
<tr>
<th>Peak [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
</tr>
</thead>
<tbody>
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<td>1$^{st}$ sample</td>
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<td>845.5212</td>
</tr>
<tr>
<td></td>
<td>867.5011 [H$_5$Na(2+2)]$^+$</td>
<td>867.5031</td>
</tr>
<tr>
<td></td>
<td>1289.7578 [H$_5$Na(3+3)]$^+$</td>
<td>1289.7600</td>
</tr>
<tr>
<td></td>
<td>1713.0158 [H$_5$Na(4+4)]$^+$</td>
<td>1713.0203</td>
</tr>
<tr>
<td>2$^{nd}$ sample</td>
<td>1965.6574 {Na[Zn$_2$(2+2)]$_2$}$^+$</td>
<td>1965.6677</td>
</tr>
</tbody>
</table>
3.6. Conclusions

Transition metal template condensation between novel \( p \)-phenyl methylenediphenol dialdehyde \((H_2mfpp)\) and 1,3-diaminopropan-2-ol resulted dinuclear complexes of the \((2+2)\) macrocyclic ligand similar to those found for the related dialdehydes \( H_2mfmp \) and \( H_2mftbp \). No crystallographic data were obtained for these complexes due to their poor solubility and/or weak diffracting properties of the grown crystals. However, the other analytical data collected successfully confirmed their formation.

Trinuclear complexes of the \((2+2)\) macrocycles derived from \( H_2mftbp \) and \( H_2mfpp \) of general formula \( TM_2M \) \([TM = Cu(II), Ni(II) \) and \( M = Li(I), Na(I), Mg(II) \) and \( Ca(II))\] were synthesised in good yields. Their formation was found to be independent of the order in which metal salts were introduced to the reaction mixtures. More detailed investigation by ESI-MS for the \( H_2mftbp \) dialdehyde reactions gave valuable insight about the species present in solution during the formation of homo- and heteronuclear complexes of the \((2+2)\) macrocycle. By monitoring the condensation reaction between \( H_2mftbp \) and 1,3-diaminopropan-2-ol under various conditions, it was found that:

1) Cu(II) : dialdehyde ratio of 1:1 produces an equilibrium mixture of dinuclear and trinuclear complexes of \((2+2)\) macrocycle when perchlorate or nitrate salts are used. The same condensation conducted with the chloride salt yields only a dinuclear complex with a chloride bridge between metals which probably prevents further transformation into polynuclear species. Therefore, character of the afforded macrocyclic complex depends on the counterion employed in the template processes.

2) Changing the Cu:dialdehyde ratio from 1:1 to 1:1.5 or 1:2 results in equilibrium mixtures containing the tricopper(II) and tetracopper(II) species.

3) Formation of the \((2+2)\) macrocycle in the presence of Cu(II) perchlorate does not go cleanly through an intermediate assembly of two copper(II) ions holding two dialdehyde ligands ready for the Schiff base cyclisation. The process is more complicated and the refluxed reaction mixture before equilibrium contains other macrocyclic species. The first appearance of the tetracopper(II) complex is found after 30 min. of reflux where all components required for formation of \((2+2)\) are present in solution. This tetranuclear assembly disappears with the progress of reaction, this is consistent with the suggestion that this complex is an initial kinetic product of that
condensation. Also 30 min. after addition of diamine some signals due to trinuclear complex are observed. The assigned formula \([\text{Cu}_3(2+2)(\text{OH}_2)]^{2+}\) contains a water molecule which might alternatively be related to a non-cyclic assembly where one of the two amine groups has still not reacted with the carbonyl. This species, after 5 h. of reflux, is transformed into the tricopper(II) complex which seems to be the thermodynamic product of that condensation. Signals due to dicopper(II) (2+2) species grow after overnight reflux. There is no direct evidence that they form from the tricopper(II) or tetracopper(II) complexes.

4) Formation of the trinuclear species was not observed using Ni(II) or Zn(II) templates so appears to be specific to Cu(II). The brown colour of the tricopper(II) complex solutions and solids (isolated by J. Barreira Fontecha\(^{135}\)) suggest possible charge transfer between fully deprotonated methylenediphenol ligand and Cu(II) ions. Also the methylenediphenolate groups might act as noninnocent ligands where some charge is delocalised over the unsaturated bond system.\(^{182-187}\)

5) A trinuclear Ni\(_2\)Cu complex of (2+2) macrocycle was successfully identified in the reaction mixture solution when Cu(II) salt was introduced to the dinickel(II) (2+2) complex. This leads to a conclusion that Cu(II) can be accommodated in the central position in combination with the other transition metals which template formation of the (2+2) macrocycle.

6) The trinuclear Cu\(_2\)M complexes where M is group 1 or 2 metal obtained by Route 1 are result of both transmetallation of tricopper(II) complex and complexation of the dicopper(II) complex. The alkaline and alkaline earth metals are not involved in template processes. The central metals are probably too small to sandwich two (2+2) condensate molecules therefore they yield only trinuclear species.

7) The experiments with both metals present from the start of the condensation (Route 2) give a different distribution of macrocyclic products to Route 1 experiments. Because Cu(II) as template yields only (2+2) condensate, the hard metal ion has to be involved in the template processes directing condensation into larger condensates. This was evident especially for Mg(II) where the (3+3) macrocycle was the main species identified by ESI-MS in the reaction mixture solution. One of the reaction mixtures from this route upon slow evaporation yielded crystals of \([\text{Cu}_2\text{Ca(NO}_3)_2](\text{MeOH})_2\) suitable for X-ray single crystal experiment so the structure of Cu\(_2\) with a group 2 metal
was revealed. As expected, the Ca(II) ion is found in the central binding site above the mean plane of four methylenediphenolate oxygen donors. This shows the flexibility of (2+2) macrocyclic ligand central site. What happens when the larger ion Ba(II) is used in the condensation is discussed in the next chapter.

8) Route 3 experiment with Zn(II) and Na(I) resulted a range of free macrocyclic products [the (2+2), (3+3) and (4+4)] after overnight reflux. Therefore, it can be assumed that Na(I) was not involved in the template processes. When a Zn(II) salt is introduced to the above reaction mixture it results probably a sandwich complex with zinc and sodium as an effect of complexation.

Further work in this area might include a closer investigation of the first 30 min. from addition of 1,3-diaminopropan-2-ol to observe probable formation of the tetracopper(II) and tricopper(II) macrocyclic complexes. Also, for Cu(II) chloride various stoichiometries promoting formation of polynuclear complexes could be examined to test the suggestion that a chloride bridge prevents dinuclear complex from further reactions. The ability of Cu(II) to bind to the central position could be studied with other transition metal TM₂Cu complexes and the properties of these heterotrinuclear species could be examined.
Chapter 4

FORMATION OF Ba(II) AND Cu(II) HETERONUCLEAR COMPLEXES OF PSEUDOACALIXARENES MACROCYCLE INVESTIGATED BY ESI-MS
4.1. Ba(II) and Cu(II) heteropolynuclear complexes of large pseudocalixarenes

Previous work on polyheteronuclear complexes of pseudocalixarene macrocycles carried out by J. Barriera Fontecha\textsuperscript{135} showed that, in the reaction between \( \text{H}_2\text{mftbp} \) dialdehyde and 1,3-diaminopropan-2-ol in the presence of \( \text{Cu(ClO}_4\text{)}_2\cdot6\text{H}_2\text{O} \) and \( \text{Ba(ClO}_4\text{)}_2\cdot3\text{H}_2\text{O} \) with triethylamine as base, three macrocyclic products can be isolated. The sandwich macrocyclic complex, made of the two \((2+2)\) macrocycles with Ba(II) ion sitting between them \{Ba\[Cu_2(2+2)\]_2\}(ClO_4)_2\cdotEtOH\cdot4H_2O, the [BaCu_4(4+4)](ClO_4)_2\cdot4H_2O complex and the [BaCu_3(3+3)](ClO_4)_2\cdot2H_2O complex. The related complexes were previously characterised by X-ray crystallography and the cations are shown in Fig. 4.1.

![Diagram of complexes](image)

Fig. 4.1 Products of the reaction between \( \text{H}_2\text{mftbp} \) dialdehyde and 1,3-diaminopropan-2-ol with Cu(II), Ba(II) and triethylamine. Colour key: in the sandwich complex each half of the molecule is given by different colour, where for the other complexes each colour indicates 1 diamine : 1 dialdehyde condensate. Copper ions are shown as a green spheres and the Ba(II) cation is produced as a violet sphere.

The left column in Fig. 4.1 shows the single crystal X-ray structures of the cations, the middle column represents connectivity diagrams and in the right column are
cartoons that will be used to represent this macrocyclic species further in this chapter. On the basis of structural and ESI-MS data collected for Cu(II) template synthesis of the (2+2) macrocycle, a reaction scheme can be proposed that shows the reaction pathways expected to lead to each of these products.

As shown in Fig. 4.2 a sandwich complex was produced when Ba(II) and triethylamine were added to reaction mixture obtained by Cu(II) templated dialdehyde-diamine condensation (Route 1). As discussed in the previous chapter, when Cu(II) perchlorate is used in the reaction between H₂mftbp and 1,3-diaminopropan-2-ol it yields the (2+2) macrocycle as dicopper(II) Cu₂(2+2) and tricopper(II) Cu₃(2+2) complexes. If a Ba(II) salt is added to the solution of this complex, Ba(II) ion is too large to fit within the tetraphenolic site of a single macrocycle, so it would link the two ions together by coordinating to their phenolate donors. This only happened when an additional base (NEt₃) is added to fully deprotonate the methylenediphenols as monodeprotonated methylenediphenols have a H-bond between the two adjacent oxygen atoms of each unit, which disables them from coordinating to hard barium ion.

The (4+4) macrocycle was reached when the dialdehyde was reacted with diamine in the presence of both metal salts and triethylamine (Route 2). If Ba(II) ions were not in the solution before addition of diamine compound, a sandwich complex would be
expected as a product, as described above. So the Ba(II) ions must be introduced to the reaction mixture before the diamine compound.

Finally, as established by J. Barreira Fontecha, the (3+3) macrocycle was isolated from the reaction mixture when, in the first step, dialdehde is refluxed with diamine in the presence of Ba(II) and triethylamine and then, in the second stage Cu(II) is introduced to the system (Route 3).

The three synthetic routes described above were investigated by ESI-MS to see what actually happens in the reaction mixture solutions.

### 4.2. Towards the sandwich complex

In this experiment, when formation of (2+2) macrocycle in the form of dicopper(II) and tricopper(II) complexes was completed, Ba(ClO$_4$)$_2$·3H$_2$O was introduced followed by NEt$_3$. After each addition changes in the reaction mixture solution were investigated by ESI-MS. A schematic representation of the experiment illustrating the sampling sequence is shown in Fig. 4.3. The first part of experiment, formation of (2+2) macrocycle in presence of Cu(ClO$_4$)$_2$·6H$_2$O was discussed in sections 3.5.1 and 3.5.2 and is shown in grey colour.

![Schematic representation of Route 1 ESI-MS experiment with Cu(II) and Ba(II).](image)

Once formation of the (2+2) macrocycle was confirmed by ESI-MS, Ba(ClO$_4$)$_2$·3H$_2$O (0.25 equivalents relative to dialdehyde) in ethanol was introduced to the system. The
reaction mixture was then investigated to see whether, upon addition of Ba(II) ions, a sandwich macrocycle is formed. Figure 4.4 shows spectra before and 30 min. after addition of Ba(II). There is no sign of progress in the reaction as the spectra are very similar apart from a peak at m/z 236 which is assigned to $[\text{Ba(ClO}_4\text{)}]^\text{+}$.

![Figure 4.4 Spectra of the reaction mixture of Cu/dialdehyde/diamine/ after overnight reflux, before and 30 min. after addition of Ba(ClO$_4$)$_2$$\cdot$3H$_2$O.](image)

Dropwise addition of NEt$_3$ to the solution with (2+2) macrocyclic species and unreacted Ba(II) resulted an immediate formation of the sandwich complex. A sample for the analysis was extracted 1 min. after addition of base, then as quickly as possible, transported to the ESI-MS instrument. The top spectrum in Fig. 4.5 represents that first sample which was acquired after addition of base and exhibits doubly charged peak $\{\text{Ba[Cu}_2(2+2)\text{]}_2\}^{2\text{+}}$ at m/z 1036 and singly charged $\{\text{Ba[Cu}_2(2+2)\text{]}_2(\text{ClO}_4\text{)}\}^\text{+}$ at m/z 2174. They are both related to the sandwich macrocycle. Reflux was continued for another 40 min. (bottom spectrum of Fig. 4.5) but this did not cause any significant further changes to the reaction mixture solution. It was concluded that a sandwich macrocyclic cation is formed rapidly as triethylamine deprotonates the methylenediphenol groups and makes them available for Ba(II) ions.
This ESI-MS experiment supported the proposals made on the basis of structural data and gave us more detailed view of the process. In summary when Ba(II) is added to the equilibrium mixture of Cu(II) complexes it does not affect the equilibrium. Ba(II) ions remain inactive in terms of coordination by the methylenediphenol groups until an extra base is introduced to the reaction mixture. When this happens they immediately coordinate methylenediphenolate units forming sandwich macrocyclic cations.
4.3. Towards the (4+4) macrocycle

Based on structural data it was proposed that the \([\text{BaCu}(4+4)]^{2+}\) macrocyclic cation is formed when the Ba(II) ions are added to the reaction mixture before the diamine. Based on this knowledge an experiment was conducted where \(\text{H}_3\text{mftbp}\) (1 equiv.), \(\text{Cu(ClO}_4\text{)}_2\cdot6\text{H}_2\text{O}\) (1 equiv.) and \(\text{Ba(ClO}_4\text{)}_2\cdot6\text{H}_2\text{O}\) (0.25 equiv.) were refluxed in ethanol for 5 h. and then 1 equivalent of 1,3-diaminopropan-2-ol was added dropwise. Reflux was maintained for 30 min. and after that time triethylamine was introduced to the reaction mixture with reflux continued for further 4 hours. Reaction progress was followed by ESI-MS (Fig. 4.6).

![Chemical Structure](image)

\(\text{Cu(ClO}_4\text{)}_2\cdot6\text{H}_2\text{O}\)
1 equiv.

\(\text{Ba(ClO}_4\text{)}_2\cdot3\text{H}_2\text{O}\)
0.25 equiv.

\(\text{EtOH}\)

**Fig. 4.6** Schematic illustration of the Route 2 ESI-MS experiment with Cu(II) and Ba(II).

Spectra of the Cu(II), Ba(II) and dialdehyde reaction mixture before and after addition of 1,3-diaminopropan-2-ol are shown in Fig. 4.7. The top spectrum represents the first sample analysed in this experiment, when the reaction mixture consists of dialdehyde with both inorganic salts. All observed peaks correspond to the various \(\text{Cu}_x(\text{aldehyde})_y\) adducts also seen in the Cu(II) template formation of (2+2) macrocycle described in section 3.5.1. At this point in the reaction Ba(II) ions are not coordinated by methylenediphenols as the only observed species is assigned to Ba(II) is \([\text{Ba(ClO}_4\text{)}])^+\) at m/z 236. Considering the ms data collected from both experiments, it seems that the presence of Ba(II) ions in the reaction mixture does not have any impact on the reaction between \(\text{H}_3\text{mftbp}\) dialdehyde and Cu(II) ions, as the nature of the solution is very similar to that observed in the previous Route 1 experiment.
The bottom spectrum was recorded 30 min. after addition of 1,3-diaminopropan-2-ol. Introduction of diamine causes alterations in peak intensities and results in new peaks, \( \text{e.g.} \ [\text{Cu(Hmftbp)(diamine)} - (\text{H}_2\text{O})]^+ \) at m/z 502 and \([\text{Cu(Hmftbp)(diamine)}]^+ \) at m/z 520\) as was observed in experiment described in section 3.5.1.

Fig. 4.7 Spectra of Cu/Ba/dialdehyde reaction mixture (top) and Cu/Ba/dialdehyde/diamine reaction mixture (bottom).

The 1,3-diaminopropan-2-ol is a weak base and does not deprotonate methylenediphenols so they do not coordinate Ba(II) ions which only appear in the spectra in the form of perchlorate cation \([\text{Ba(ClO}_4]^+ \) giving peaks at m/z 236. Also 30 min. reflux does not bring any important changes to the reaction mixture. In spite of the fact that both metal templating agents are in solution there is no evidence of macrocyclic products. Next 1 mL of NEt\(_3\) is added to the solution. Spectra of the reaction mixture before addition of base, 1 min. after, 5 min. after and 4 h. after are represented in Fig. 4.8. The response from the system is immediate, the base deprotonates the methylenediphenol units which coordinate to the Ba(II) ions and the \((4+4)\) macrocycle represented by peaks, doubly charged \([\text{BaCu}_4(4+4)]^{2+} \) at m/z 1036 and singly charged \([\text{BaCu}_4(4+4)(\text{ClO}_4)]^+ \) at m/z 2174, is assembled within 5 min. After 4 h. the reaction is over as there is no further significant change in the reaction mixture solution indicated by ESI-MS.
Fig. 4.8 Spectra of Cu/Ba/dialdehyde/diamine reaction mixture before and 1, 5 min. and 4 h. after addition of base (NEt$_3$).

Figure 4.9 shows the ESI-MS of the reaction mixture solution of the [BaCu$_4$(4+4)]$^{2+}$ macrocyclic cation after 4 h. of reflux from addition of base. Surprisingly the (3+3) macrocycle was identified as a minor product by this reaction route. It is represented by family of singly charged peaks, [BaCu$_3$(3+3)(ClO$_4$)]$^+$ at m/z 1688, [BaCu$_3$(3+3)(EtOH)(ClO$_4$)]$^+$ at m/z 1737, [BaCu$_3$(3+3)(EtOH)$_2$(ClO$_4$)]$^+$ at m/z 1781 and related doubly charged peaks, [BaCu$_3$(3+3)]$^{2+}$, [BaCu$_3$(3+3)(EtOH)]$^{2+}$, [BaCu$_3$(3+3)(EtOH)$_2$]$_2^{2+}$ at m/z 794, 818 and 840 respectively.

In summary, the pathway proposed on the basis of structural data for the (4+4) compound appears correct. As suggested, both metals have to be in the solution before diamine is introduced, in other words, the Ba(II) salt must be added to the system before the (2+2) macrocycle has formed. Ba(II) ions do not coordinate until addition of an extra base to the system deprotonates the methylenediphenol groups. However formation of the (4+4) macrocycle is not a clean process as (3+3) macrocyclic species were found in the reaction mixture solution as a minor product. This contrasts with J. Barreira Fontecha’s study where the [BaCu$_3$(3+3)](ClO$_4$)$_2$·2H$_2$O complex was isolated from a reaction mixture where the sandwich complex appeared to be the main product. It seems that each macrocyclic product forms independently and the Ba(II) ion is a limiting reagent for both processes. There is no indication that the (2+2) macrocycle can be rearranged to form the (4+4) analogue.
4.4. Which macrocycle is it?

The (4+4) macrocyclic species gives two ESI-MS peaks corresponding to \([\text{BaCu}_4(4+4)]^{2+}\) at \(m/z\) 1036 and \([\text{BaCu}_4(4+4)(\text{ClO}_4)]^+\) at \(m/z\) 2174 which were described above. These are exactly the same masses as assigned for the sandwich complex, peaks for \([\text{Ba}[\text{Cu}_2(2+2)]_2]^{2+}\) at \(m/z\) 1036 and \([\text{Ba}[\text{Cu}_2(2+2)]_2(\text{ClO}_4)]^+\) at \(m/z\) 2174. Since both complexes have the same molecular formula and give the same results by elemental analysis a question arises as to how they may be distinguished. This was achieved by means of a tandem (ms/ms) experiment. Tandem ms/ms is a technique where the specification of the ms instrument, equipped with more than one mass analyster and an ion trap cell (also known as collision cell) permits one chemical species to be selected from an analyte sample and its fragmentation pattern to be studied.

Ions giving rise to doubly charged peaks at \(m/z\) 1036 from each experiment previously discussed were separately trapped inside the instrument and were exposed to 60 V collision energy. For the sandwich complex it is expected that it will break into the two halves of which is made relatively easily. The \([\text{BaCu}_4(4+4)]^{2+}\) macrocyclic cation does not have such an obvious fragmentation route.

Figure 4.10 shows the resulting ESI-MS spectra of the Route 1 sandwich complex reaction mixture. The main spectrum shows that the species giving rise to the doubly charged peak at \(m/z\) 1036 has been physically isolated in the instrument. The inset
spectrum (ms/ms spectrum) shows the fragmentation of the trapped ion. The initial doubly charged peak $[C_{104}H_{126}N_8O_{12}Cu_4Ba]^2^+\text{ at m/z 1036}$ has almost gone from the spectrum and new peaks assigned to doubly charged $[BaCu_2(2+2)]^2^+$ at m/z 552 and two singly charged peaks $[Cu_2(2+2)]^+$ at m/z 968 and $[BaCu_2(2+2)]^+$ at m/z 1104 are observed. These peaks represent the (2+2) dicopper(II) macrocycle and (2+2) dicopper(II) complex with Ba(II). This is consistent with the suggestion that the reaction mixture solution contained mainly the sandwich complex which, as predicted breaks up into the two macrocyclic parts. The remaining part of the signal at m/z 1036, which was not fragmented by 60 V collision energy, could be related to the (4+4) macrocycle or maybe the fragmentation was not 100% efficient so it represents the sandwich complex left over.

Fig. 4.10 Fragmentation of the isolated m/z 1036 peak related species from sandwich complex reaction mixture. The inset picture shows the resulted ms/ms spectrum.

Figure 4.11 shows the results of the same experiment for the isolated species from the (4+4) complex reaction mixture related to peak $[C_{104}H_{127}N_8O_{12}Cu_4Ba]^2^+$ at m/z 1036 and assigned for $[BaCu_4(4+4)]^2^+$. As can be seen, in contrast to the sandwich complex, a collision energy of 60 V does not result in much fragmentation as the doubly charged peak $[C_{104}H_{127}N_8O_{12}Cu_4Ba]^2^+$ remains intact. The low intensity peaks in the inset spectrum at m/z 553, m/z 968 and m/z 1107, are similar to these discussed above and they most likely represent the halves of the sandwich complex. Therefore there appears
to be a small amount of sandwich complex in the reaction mixture containing primarily (4+4) condensate.

Fig. 4.11 Fragmentation of trapped species related to peaks at m/z 1036 and assigned to (4+4) macrocycle. Inset picture shows the ms/ms spectrum.

In summary, the doubly charged peaks at m/z 1036 from both reaction routes may not be related to completely clean products. For the Route 1 reaction path, peaks \([C_{104}H_{126}N_8O_{12}Cu_4Ba]^{2+}\) at m/z 1036 were mostly from the sandwich complex \([Ba(Cu_2(2+2))_2]^{2+}\), but as established in the above experiments, the sandwich reaction mixture could also contain some of the (4+4) condensate \([BaCu_4(4+4)]^{2+}\). In the reaction mixture obtained by Route 2, the major species giving rise to the doubly charged peaks \([C_{104}H_{127}N_8O_{12}Cu_4Ba]^{2+}\) at m/z 1036 was the (4+4) macrocyclic complex \([BaCu_4(4+4)]^{2+}\) but the presence of the sandwich product \([Ba(Cu_2(2+2))_2]^{2+}\) was also indicated.
4.5. Ba(II) and Cu(II) cluster with mftbp dianion [BaCu$_4$(mftbp)$_4$]$^{2+}$

During synthetic work on the formation of the [BaCu$_4$(4+4)]$^{2+}$ with H$_2$mfmp as dialdehyde X. Ma$^{137}$ found that, when 1,3-diaminopropan-2-ol is not used in the reaction and NEt$_3$ is added to the dialdehyde solution containing both metal salts, a new compound can be isolated from the reaction mixture. It is an assembly of four fully deprotonated mfmp dialdehyde ligands held together by Cu(II) and Ba(II) ions. The [Cu$_4$Ba(mfmp)$_4$(EtOH)$_4$](ClO$_4$)$_2$·4EtOH complex was isolated and structurally characterised for the first time by X. Ma.$^{137}$ Brown crystals of a corresponding cluster [BaCu$_4$(mftbp)$_4$(EtOH)(MeOH)$_3$](ClO$_4$)$_2$ derived from H$_2$mftbp were grown from methanolic solution by slow evaporation.

The connectivity diagrams, X-ray single crystal structures and cartoon which will represent the [BaCu$_4$(dialdehyde)$_4$]$^{2+}$ cluster further in this chapter are shown in Fig. 4.12.

![Fig. 4.12 X-ray single crystal structure, connectivity diagram and cartoon for the [BaCu$_4$(mftbp)$_4$]$^{2+}$ and [BaCu$_4$(mfmp)$_4$]$^{2+}$ cations. Cu(II) ions are shown by green spheres and the Ba(II) ion is represented by violet spheres.](image-url)
The X-ray data collection parameters are summarised in Table 4 of Appendix 1 along with the details concerning the refinement and disorders and the cif file is included in DVD Appendix. The structure of cation \([\text{BaCu}_4(\text{mftbp})_4(\text{EtOH})(\text{MeOH})_3]^{2+}\) and geometry around the metal ions is shown in Fig. 4.13. The Ba(II) ion is 8-coordinate and has rectangular antiprism geometry, coordinating the four phenolato oxygen donors of each dialdehyde. The methylenediphenol dianions (mftbp)\(^{2-}\) are folded with the phenol rings approximately orthogonal to each other so they can provide all eight oxygen donors and wrap around the central barium atom. There are two sets of Ba-O bond lengths, one in the range 2.70-2.74 Å and the other between 2.87-2.97 Å (Selected bond lengths and angles relevant to the metal ion coordination are given in Table 4.1). Cu(II) ions are 5-coordinate and have square pyramidal geometry. Each of them coordinates two carbonyl and two phenolate oxygens making a square base with methanol or ethanol ligand as an apical donor. Overall, the \([\text{BaCu}_4(\text{mftbp})_4(\text{EtOH})(\text{MeOH})_3]^{2+}\) cation could be regarded as a copper/(mftbp)\(^{2-}\) metallacycle assembled about a Ba(II) template.

![Fig. 4.13 Right: Structure of \([\text{BaCu}_4(\text{mftbp})_4(\text{EtOH})(\text{MeOH})_3]^{2+}\) cation, Left: coordination spheres around the metal centres; Colour key: Ba(II) violet, Cu(II) green, oxygen red, carbon brass.](image-url)
Table 4.1 Selected bond lengths [Å] and angles [°] for [BaCu$_4$(mftbp)$_2$(EtOH)(MeOH)$_3$]$^{2+}$.

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<tr>
<td>O(3)-Ba(1)-O(14)</td>
<td>62.70(10)</td>
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<td>91.56(16)</td>
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<td>83.61(18)</td>
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<tr>
<td>O(11)-Ba(1)-O(14)</td>
<td>136.81(11)</td>
<td>O(11)-Cu(4)-O(16)</td>
<td>103.77(19)</td>
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<tr>
<td>O(2)-Cu(1)-O(5)</td>
<td>174.5(2)</td>
<td>O(15)-Cu(4)-O(16)</td>
<td>103.77(19)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>O(2)-Cu(1)-O(6)</td>
<td>87.50(16)</td>
<td>O(12)-Cu(4)-O(16)</td>
<td>96.46(19)</td>
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<td>O(5)-Cu(1)-O(6)</td>
<td>95.35(19)</td>
<td>O(11)-Cu(4)-O(400)</td>
<td>88.5(2)</td>
<td>1</td>
<td></td>
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<tr>
<td>O(2)-Cu(1)-O(1)</td>
<td>91.89(17)</td>
<td>O(15)-Cu(4)-O(400)</td>
<td>89.9(2)</td>
<td>1</td>
<td></td>
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<tr>
<td>O(5)-Cu(1)-O(1)</td>
<td>84.20(19)</td>
<td>O(12)-Cu(4)-O(400)</td>
<td></td>
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<td></td>
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<tr>
<td>O(6)-Cu(1)-O(1)</td>
<td>165.9(2)</td>
<td>O(16)-Cu(4)-O(400)</td>
<td></td>
<td>1</td>
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</table>
Comparison of this $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ assembly with the structure of the macrocyclic $[\text{BaCu}_4(4+4)]^{2+}$ cation, suggests that this could be an intermediate on the way to the macrocyclic product. For comparison the structures of both compounds are shown again in Fig. 4.14, the bond lengths and angles in both are quite similar. In the macrocycle (2) the Ba(II) ion is also 8-coordinate and binds to all eight phenolate oxygen donors, bond lengths about the Ba(II) cation again fall in two sets: four Ba-O bonds range from 2.65-2.70 and the other four are approx. 0.3 Å longer (2.96 – 3.16 Å). This may be because the phenolate oxygens participating in those bonds are also weakly coordinating as apical donors to the opposite copper ions and hence weakening the bond to the barium ion. The Cu(II) ions are five coordinate and occupy the Robson sites of the macrocycle with N$_2$O$_2$ donors in the mean plane. Two copper ions are coordinated to methanol as the axial ligand and the other two to the phenolate axial ligands.

Verifying the suggestion that the $[\text{BaCu}_4(\text{mftbp})_4(\text{EtOH})_2(\text{MeOH})_2]^{2+}$ cluster is an intermediate compound in the synthesis of the $[\text{BaCu}_4(4+4)(\text{MeOH})_2]^{2+}$ macrocyclic cation would provide more information about the cyclisation process and help to clarify the role of each metal in the macrocycle formation. It seems likely that simple addition of 1,3-diaminopropan-2-ol to the $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ assembly should result in amine condensation with the carbonyl groups which will lead to the closure of macrocyclic ring (Fig. 4.14). The synthesis of $[\text{BaCu}_4(\text{mftbp})_4(\text{EtOH})(\text{MeOH})_3]^{2+}$ requires refluxing of H$_2$mfbp dialdehyde with both Ba(II) and Cu(II) salts before base is introduced. Then, in order to transform this assembly into a macrocycle, diamine must be added. The reaction (which corresponds to Route 4 as described in the previous chapter) examined by ESI-MS.
4.5.1. Formation of $[\text{BaCu}_4(4+4)]^{2+}$ complex via the $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ assembly with ideal stoichiometries under reflux conditions

In this experiment dialdehyde $\text{H}_2\text{mftbp}$, $\text{Cu(ClO}_4)_2\cdot 6\text{H}_2\text{O}$ (1 equiv) and $\text{Ba(ClO}_4)_2\cdot 3\text{H}_2\text{O}$ (0.25 equiv.) were refluxed for 30 min. and after that time NEt$_3$ was added. When formation of the $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ was completed an ethanol solution of 1,3-diaminopropan-2-ol was introduced to the reaction mixture and reflux was continued. Samples were taken for ESI-MS analysis at intervals to investigate the transformation (Fig. 4.15).

![Diagram showing the reaction steps](image)

Fig. 4.15 Schematic representation of Ba(II) and Cu(II) Route 4 experiment.

The top spectrum in Fig. 4.16 shows the first sample of Cu(II), Ba(II) and dialdehyde reaction mixture analysed after 30 min. of reflux. It exhibits $\text{Cu}_x(\text{aldehyde})_y$ peaks with different $x:y$ ratios as was observed in Cu(II) template formation of the (2+2) macrocycle described in section 3.5.1. After 30 min. of reflux, NEt$_3$ was added dropwise to the reaction mixture. The very clean spectrum of the sample taken out from the reaction mixture after 1 min. of reflux is shown in the middle of Fig. 4.16. Addition of base resulted in immediate assembly of $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ cation which is indicated by doubly charged peaks $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ at m/z 928 and singly charged $[\text{BaCu}_4(\text{mftbp})_4(\text{ClO}_4)]^+$ at m/z 1955.
Fig. 4.16 Spectra of Cu/Ba/dialdehyde reaction mixture solution before and after addition of base (NEt$_3$).

The bottom spectrum in Figure 4.16 shows the same reaction mixture but after 21 min. of reflux. There is no change in the spectrum suggesting that the formation of this compound is completed 1 min. after addition of base.

The [BaCu$_4$(mftbp)$_4$]$^{2+}$ aggregate requires eight Schiff base condensations for conversion into [BaCu$_4$(4+4)]$^{2+}$ macrocyclic cation. In order to see if this transformation occurs 1,3-diaminopropan-2-ol was introduced to the reaction mixture. Figure 4.17 shows three spectra, the top one that of the reaction mixture containing the [BaCu$_4$(mftbp)$_4$]$^{2+}$ assembly before addition of diamine, the middle represents reaction mixture 40 min. after addition of diamine and the bottom one after 2 h. of reflux from addition of diamine.
Fig. 4.17 Spectra of the reaction mixture containing \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cluster cation before and after addition of 1,3-diaminopropan-2-ol.

By 40 min. after addition of diamine the doubly charged peaks \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) at m/z 928 representing the cluster are almost gone from the spectrum. Instead a set of three doubly charged peaks at m/z 982, 1009, 1036 appears in the spectrum together with several peaks in the mass range between m/z 200-500. The peaks at m/z 1036 are the expected (4+4) macrocycle peaks for \([\text{BaCu}_4(4+4)]^{2+}\), where all four diamines have reacted with dicarbonyl groups. The peaks \([\text{BaCu}_4(\text{mftbp})_2(2:2)]^{2+}\) at m/z 982 and \([\text{BaCu}_4(\text{mftbp})(3:3)]^{2+}\) at m/z 1009 indicate formation of a cluster with two and three diamine links, respectively (Fig. 4.18).

Fig. 4.18 Schematic representation of the \([\text{BaCu}_4(\text{mftbp})]^{2+}\) cluster with two and three diamine links, \([\text{BaCu}_4(\text{mftbp})_2(2:2)]^{2+}\) and \([\text{BaCu}_4(\text{mftbp})(3:3)]^{2+}\) respectively.
Peaks in the range m/z 200-500 were not assigned as their isotope pattern indicated that they were related to the organic fragments not bearing any metals. After 2 h. of reflux the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cluster is completely gone as peaks at m/z 928 are no longer found in the spectrum. The reaction mixture comprises the three major species described above giving doubly charged peaks at m/z 982, 1009 and 1036 with slight change in the relative intensities between them (Fig. 4.19).

![Diagram showing species assigned to doubly charged peaks at m/z 982, 1009 and 1036.](image)

**Fig. 4.19** Schematic representation of species assigned to doubly charged peaks at m/z 982, 1009 and 1036.

Peaks at m/z 995, 1023 and m/z 1046 were not assigned but most likely they correspond to clusters present in Figure 4.19 as they show similar pattern of m/z difference 27 which indicates formation of two imine bonds (loss of two water molecules) for 1,3-diaminopropan-2-ol in condensation with H_2mftbp cluster.

Figure 4.20 shows all the data acquired for longer reflux periods after addition of diamine to \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cluster. Only the mass range around m/z 700-1000 is shown since all significant changes in this process are indicated by peaks appearing in
this region. Following the spectra from the top, which displays the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\)
peaks at \(m/z\) 928, to the bottom, which contains the \([\text{BaCu}_4(4+4)]^{2+}\) peaks at \(m/z\) 1036, we see conversion of the cluster cation into macrocyclic cation. In contrast to the formation of \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) this is a slow process, it takes over 8 h. for cyclisation to be completed, whereas it takes only 1 min. to form the cluster assembly with mftbp dianion.

![Spectra showing \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) reaction mixture from addition of 1,3-diaminopropan-2-ol to completion of the conversion into \([\text{BaCu}_4(4+4)]^{2+}\).](image)

It is seems likely that diamine groups react with the BaCu₄ cluster sequentially and form assemblies with from one to four diamine links. The compound with just one diamine condensed is not observed. However, in the second spectrum there is peak pattern at the \(m/z\) 955 which corresponds to the calculated value for this complex \({\{[\text{BaCu}_4(\text{mftbp})_3(1:1)]^{2+} = m/z\ 955\}}\) but the data are very weak so the isotope patterns cannot be matched. Evidently, the condensation of the first two diamines is considerably faster than addition of the third and fourth. The signal due to the initial \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cluster at \(m/z\) 928 is lost within 2 h. and the assembly with two diamines condensed \([\text{BaCu}_4(\text{mftbp})_2(2:2)]^{2+}\) at \(m/z\) 982 has disappeared by 3.5 h. After 6 h. only the product of 6 condensations \({\{[\text{BaCu}_4(\text{mftbp})(3:3)]^{2+} at m/z\ 1009\}}\) and the
final product \([\text{BaCu}_4(4+4)]^{2+}\) are left in solution. It appears that the final stage of the process has some steric barrier.

Despite the similarities between \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) and \([\text{BaCu}_4(4+4)]^{2+}\) their structures are different. The geometry at the Cu(II) ions is much more planar for CuO\(_4\) than CuN\(_2\)O\(_4\) (Fig. 4.14) and there is the unsymmetrical reduction in the Cu...Cu distances. The copper ions not axially coordinated to phenolate donors (Cu2 and Cu4 structure 2 in Fig. 4.14) are further apart (4.241Å) than the other two (3.464Å). Therefore the full conversion requires geometric adjustments, so it takes over 8 h. for the transformation to be completed as reaction mixture investigated after 8.5 h. does not show any further significant changes.

### 4.5.2. Formation of \([\text{BaCu}_4(4+4)]^{2+}\) complex via the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) assembly with ideal stoichiometries at room temperature

The experiment above was repeated at room temperature, to investigate whether the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) will form in mild conditions and to examine what time is needed for that formation. In the previous study, the reaction was quenched when the extracted samples were cooled and diluted with MeOH and allowed to stand. For this experiment an accurate time was measured from the moment of addition of triethylamine to the moment when the data were acquired. A schematic representation of this study is shown in Fig. 4.21.

![Fig. 4.21 Schematic representation of Ba(II) and Cu(II) cluster route (Route 4) to (4+4) macrocycle carried out at RT.](image-url)
The top spectrum in Fig. 4.22 shows the reaction mixture acquired 3 min. 43 sec after addition of triethylamine. It is a very clean spectrum of the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cation which is exhibited by doubly charged peak at m/z 928. Surprisingly, the cluster assembles very quickly even at room temperature, its formation is complete within the time needed for data acquisition.

The next spectra shown in Fig. 4.22 represent the reaction mixture after addition of 1,3-diaminopropan-2-ol to the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) at various reaction times running top to bottom. In contrast to the situation where the reaction mixture is under reflux conditions, addition of diamine results in the formation of either the (3+3) macrocycle or the open chain product comprising three dialdehydes condensed with four diamines. They both have identical formula weights and give rise to peaks at m/z 839 for \{[\text{BaCu}_3(3+3)(\text{diamine})]^{2+}\} or \([\text{BaCu}_3(3:4)]^{2+}\) and at m/z 1778 for \{[\text{BaCu}_3(3+3)(\text{ClO}_4)(\text{diamine})]\}^{+} or \([\text{BaCu}_3(3:4)(\text{ClO}_4)]^{+}\). The major peak assignments from this experiment are shown in Table 4.2.
Table 4.2 Major peak attributions for the RT experiment.

<table>
<thead>
<tr>
<th>Peak [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
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<tbody>
<tr>
<td>Room Temperature Conversion Of [BaCu₄(mftbp)₄]²⁺</td>
<td></td>
<td></td>
</tr>
<tr>
<td>928.1771</td>
<td>[BaCu₁₄(mftbp)₁]²⁺</td>
<td>928.1766</td>
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<tr>
<td>839.7463</td>
<td>[BaCu₃(3+3)(diamine)]²⁺ or [BaCu₃(3:4)]²⁺</td>
<td>839.7472</td>
</tr>
<tr>
<td>989.3293</td>
<td>[Cu₂Na(2+2)]⁺</td>
<td>989.3310</td>
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<tr>
<td>1036.2947</td>
<td>[BaCu₄(4+4)]²⁺</td>
<td>1036.2930</td>
</tr>
<tr>
<td>1081.3317</td>
<td>[BaCu₄(4+4)(diamine)-H]⁺</td>
<td>1081.3326</td>
</tr>
<tr>
<td>1778.4452</td>
<td>[BaCu₃(3+3)(ClO₄)(diamine)]⁺ or [BaCu₃(3:4)(ClO₄)]⁺</td>
<td>1778.4434</td>
</tr>
<tr>
<td>(2+2)⁺ = C₅₂H₆₄N₄O₆</td>
<td>(3+3)⁻ = C₇₈H₉₆N₄O₂₁</td>
<td>(4+4)⁺ = C₁₀₄H₁₂₈N₄O₁₂</td>
</tr>
<tr>
<td>(diamine)⁻ = C₃H₁₀N₂O</td>
<td>(mftbp)⁺ = C₂₃H₂₆O₄</td>
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</tr>
</tbody>
</table>

The cluster cations with two and three diamines condensed, which were indicated in the previous experiment by peaks at m/z 982 and 1009 respectively, are not observed. This suggests different conversion mechanism of the [BaCu₄(mftbp)₄]²⁺ into the macroyclic product [BaCu₄(4+4)]²⁺. The [BaCu₄(4+4)]²⁺ cation exists in solution just after 30 min. of stirring (middle spectrum in Fig. 4.22) and is related to doubly charged peaks at m/z 1036. After 17 h. of stirring reaction mixture comprises the (4+4) product with a substantial amount of either the (3+3) macrocycle or the open chain (3:4) condensate. The low relative intensity peaks [Cu₂Na(2+2)]⁺ at m/z 989 related to the (2+2) macrocycle suggest that there might be some sandwich compound {Ba[Cu₂(2+2)]₂}²⁺ present in the reaction mixture which also contributes to the peak pattern at m/z 1036.

After 20 h. of stirring the reaction mixture did not show any significant changes. It appears that the [BaCu₄(mftbp)₄]²⁺ is converted into either [BaCu₃(3+3)(diamine)]²⁺ or [BaCu₃(3:4)]²⁺ species and the [BaCu₄(4+4)]²⁺ macrocyclic product. This transformation can be achieved in two ways: the first involves breaking up the cluster and formation of Schiff base condensation products from simple building blocks. The second is more complicated and is shown schematically in Fig. 4.23.
Fig. 4.23 Proposed transformation patterns of [BaCu₄(mftbp)]²⁺ into the [BaCu₄(4+4)]²⁺ and either [BaCu₃(3+3)]²⁺ or [BaCu₃(3:4)]²⁺.

The route marked by black arrows shows the transformation of [BaCu₄(mftbp)]²⁺ into the (4+4) and (3+3) macrocycles. The first stage after addition of 1,3-diaminopropan-2-ol requires one (mftbp)²⁻ dianion to leave the [BaCu₄(mftbp)]²⁺ species. Then each of the exposed carbonyl ends reacts with diamine to give compound with two diamines on. In the next stage, another two diamines condense with the remaining carbonyl groups to link together the three methylenediphenol units and precursor drops off one of the Cu(II) ions in the form Cu(amine) compound. Then intramolecular Schiff base condensation closes the ring up into the [BaCu₃(3+3)]²⁺ macrocyclic cation.
The route marked by red arrows shows the proposed transformation pattern of \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) into the \([\text{BaCu}_3(3:4)]^{2+}\) species and then possibly into macrocyclic products. Because sequential Schiff base condensation found under reflux conditions was not observed in this experiment it is possible that four diamines condense at the same time but making only six Schiff base condensate assembly. Subsequently one Cu(mftbp) fragment is dropped by this cluster to result in the \([\text{BaCu}_3(3:4)]^{2+}\) open chain cation. This cation could be converted into either the (3+3) or (4+4) macrocycles but there is no direct evidence of these processes.

The sample of the reaction mixture solution which was analysed after 5 min. from addition of diamine was left aside for 30 min. and then re-examined by ESI-MS (Fig. 4.24). There is no significant change in the resulted spectrum. In contrast, spectrum of reaction mixture acquired after 30 min. stir from addition of diamine presented in Fig. 4.22 is much cleaner and shows the \([\text{BaCu}_4(4+4)]^{2+}\) species at m/z 1036. Therefore, when the extracted sample is diluted with MeOH and allowed to stand at ambient temperature the reaction is effectively quenched.

Fig. 4.24 Top: Spectrum of reaction mixture solution analysed after 5 min. stir. Bottom: the same sample analysed again after 30 min. at room temperature.
4.5.3. Formation of $[\text{BaCu}_4(4+4)]^{2+}$ complex via $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ assembly with varied stoichiometries under reflux conditions

All previous work on the (4+4) macrocyclic species carried by J. Barreira Fontecha was done with a $\text{Ba(II)}:\text{H}_2\text{mftbp}$ ratio of 0.5:1. This is 0.25 equiv. excess of the central ion as for the formation of $[\text{BaCu}_4(4+4)]^{2+}$ only 0.25 equiv. of $\text{Ba(II)}$ is required. The influence of this extra $\text{Ba(II)}$ ions was examined in separate experiment under reflux conditions, where $\text{H}_2\text{mftbp}$, $\text{Cu(ClO}_4)_2\cdot6\text{H}_2\text{O}$ (1 equivalent) and $\text{Ba(ClO}_4)_2\cdot3\text{H}_2\text{O}$ (0.5 equivalent) were refluxed for 30 min. and then triethylamine was added. After addition, reflux was continued for 30 min. and, when formation of intermediate cluster was completed and confirmed by ESI-MS, 1,3-diaminopropan-2-ol was introduced to the system (1equiv.). The ratio of reagents used was therefore as follows, $\text{Ba(II)}:\text{Cu(II)}:\text{H}_2\text{mftbp}:\text{diamine} = 0.5:1:1:1$. Reflux was maintained for further 4 h. with ESI-MS monitoring. An analogous experiment was set up with 0.25 equiv. of $\text{Ba(II)}$ ions to investigate an impact of these extra ions in solution but also to examine what happens during the first 40 min. of reflux after addition of diamine as, in the previous experiment under reflux conditions, the first sample was studied after that time. A schematic representation of this experiment is shown in Fig. 4.25.

Fig. 4.25 Conversion of $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ into $[\text{BaCu}_4(4+4)]^{2+}$ experiments with (A) 0.5 equiv. and (B) 0.25 equiv. of $\text{Ba(II)}$ ions.
Figure 4.26 shows two sets of data, on the left are spectra from experiment A and on the right are spectra with the stoichiometric amount of Ba(II) ions for the formation of \([\text{BaCu}_{4}(4+4)]^{2+}\). 

The top spectra represent Cu(II), Ba(II), dialdehyde and base reaction mixture after 30 min. reflux. Surprisingly, peaks \([\text{BaCu}_{4}(\text{mftbp})_{4}]^{2+}\) at m/z 928 are present in both cases hence excess of Ba(II) ions does not have an influence on the formation of this cluster. The excess of Ba(II) ions present in solution is not indicated in the spectrum so the barium must be present as species which do not fly on the instrument. The next spectra were acquired after addition of diamine to both reaction mixtures. For experiment A, after 1 min. the (4+4) macrocyclic ion is major species in the reaction mixture, represented by peaks \([\text{BaCu}_{4}(4+4)]^{2+}\) at m/z 1036. For the 0.25 equiv. of Ba(II) ions, after 3 min. of reflux, the (4+4) cation is not evident, instead cluster with two diamines is seen at m/z 982. Peaks \([\text{Cu}({\text{Hmftbp}})({\text{diamine}})]^{+}\) at m/z 520 are also present in this spectrum 3 min. after addition of diamine. The transformation is much faster with an excess of Ba(II) ions and is finished after 1 h. of reflux as reaction mixture does not show any further changes after 3.5 h. reflux. Additionally, when an excess of Ba(II)
ions is used the (3+3) product can be identified as peaks due to $[\text{BaCu}_3(3+3)(\text{EtO})_2]^{2+}$ at m/z 840 also appear in the spectra from experiment A. This suggests that there is a different mechanism involved in the transformation. Formation rates of cluster with three diamines and the final (4+4) macrocyclic product are significantly higher so it seems that the additional Ba(II) species present in solution remove somehow the steric barrier which prevents the final cyclisation stages but in exchange they lead to assembly of the (3+3) macrocycle.

In experiment B, spectra up to 40 min. after introduction of diamine to the system (which were not investigated in section 4.5.1), show a mixture of three Schiff base condensates marked by peaks at m/z 982, 1009 and 1036. With time, the intensity of peaks at m/z 982 decrease and the intensities of peaks at m/z 1009 and 1036 increase exactly as described in section 4.5.1. As established, the full conversion of the $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ into $[\text{BaCu}_4(4+4)]^{2+}$ under these conditions requires over 8 h. reflux.

Next, conversion of $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ into $[\text{BaCu}_4(4+4)]^{2+}$ was performed with a reduced amount of diamine compound to see whether it will slow the process enough to identify the cluster condensed with just one diamine molecule. For comparison, the corresponding reaction with the excess of 1,3-diaminopropan-2-ol was also investigated by ESI-MS (Fig. 4.27).

![Fig. 4.27 Schematic representation of $[\text{BaCu}_4(4+4)]^{2+}$ formation via $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ cluster with A) 1.25 equiv. of 1,3-diaminopropan-2-ol and B) 0.75 equiv. of 1,3-diaminopropan-2-ol.](image-url)
Spectra from both experiments are shown in Fig. 4.28 where, the left data set represents the study with an excess of diamine and on the right, the experiment with diamine as limiting reagent is displayed.

As expected, the reaction with a reduced amount of diamine (B) goes in “slow motion” as, 1 h. of reflux results in four Schiff base condensations which is indicated by peaks [BaCu₄(mftbp)₂(2:2)]⁺ at m/z 982 assigned to the cluster with two diamines condensed. There is no 3 or 4 condensate product after 1 h. of reflux. Interestingly, 3 min. after addition of diamine, a Cu(dialdehyde)(diamine) assembly can be found which is related to peaks [Cu₂(mftbp)(diamine)-H]⁺ at m/z 581. This, together with dialdehyde related peaks [Na(H₃mftbp)]⁺ at m/z 391, suggests partial decomposition of the [BaCu₄(mftbp)₄]²⁺ cluster assigned to peaks at m/z 928.

Fig. 4.28 A: Conversion experiment conducted with molar ratio Ba:Cu:H₃mftbp:diamine =1:4:4:5;
B: Conversion experiment conducted with molar ratio Ba:Cu:H₃mftbp:diamine =1:4:4:3.

In the presence of excess diamine (A), the conversion is completed after 30 min. of reflux. This is similar to the experiment with excess of Ba(II) ions, where formation of the (4+4) macrocyclic cation is much quicker than in the reaction where all reactants are used in the stoichiometric ratio for the (4+4) product. Also, as found for transformation of [BaCu₄(mftbp)₄]²⁺ carried out at room temperature, the (3+3) macrocycle or the 3:4 condensate is observed at m/z 839. In contrast to the ambient temperature conversion,
relative intensity of these peaks decrease as the peaks for $[\text{BaCu}_4(4+4)]^{2+}$ at m/z 1036 grow with time. This fits better to the explanation that peaks at m/z 839 are due to $[\text{BaCu}_3(3:4)]^{2+}$ open chain species which transform into the (4+4) macrocycle (red arrow route in Fig. 4.23).

Figure 4.29 shows expanded spectrum of the reaction mixture from experiment B after 30 min. reflux from addition of 1,3-diaminopropan-2-ol. The doubly charged peaks $[\text{BaCu}_4(\text{mftbp})(3:1)]^{2+}$ at m/z 955 represent the cluster condensed with only one diamine molecule which were not previously seen in any of these conversion experiments.

A lower concentration of diamine in reaction mixture results in slower formation rates for the products of sequential Schiff base condensations. Thanks to that, the product of only two condensations (1 diamine) can be observed and the product of condensation with 3 diamines {related to peaks $[\text{BaCu}_4(\text{mftbp})(3:3)]^{2+}$ at m/z 1009} is not seen in this experiment.
4.5.4. Summary of \([\text{BaCu}_4(4+4)]^{2+}\) syntheses through the \([\text{BaCu}(\text{mftbp})_4]^{2+}\) cluster route

In summary, \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) forms when triethylamine is added to the solution containing \(\text{H}_2\text{mftbp}\) dialdehyde with \(\text{Cu(II)}\) and \(\text{Ba(II)}\) ions. This assembly occurs at room temperature and is fast, possibly over immediately after base is introduced to the system but it was complete when spectra were recorded 3 min. 43 sec after addition. Moreover, the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) complex is an intermediate in the formation of \([\text{BaCu}_4(4+4)]^{2+}\) and can be transformed into the macrocycle by simple addition of diamine. The \([\text{BaCu}_4(4+4)]^{2+}\) macrocyclic cation can be accessed by two routes (Fig. 4.30) but only Route 4 via intermediate assembly of \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) produces clean solution of macrocyclic complex.

Fig. 4.30 Schematic representation of two synthetic routes leading to the (4+4) macrocycle.
The transformation of \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) requires eight Schiff base condensations at the diacarbonyl groups and under reflux this process is sequential because diamines react one by one which is schematically shown in Fig. 4.31. The condensation with the first and second diamines is fast and the \([\text{BaCu}_4(\text{mftbp})_3(1:1)]^{2+}\) species, the intermediate cluster with one diamine link, can only be identified when the reaction has insufficient diamine. The third and fourth diamines condense more slowly as it takes over 2 h. of reflux to reach the \([\text{BaCu}_4(\text{mftbp})(3:3)]^{2+}\) cation. Full conversion of the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) into \([\text{BaCu}_4(4+4)]^{2+}\) is slow, it requires over 8 h. reflux which suggests some steric barrier in the final cyclisation stages.

The transformation can be speeded up by using an excess of Ba(II) ions or diamine but in these cases reaction also yields the (3+3) product or the (3:4) open chain condensate. This suggests involvement of a different mechanism. Perhaps, the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) assembly breaks up and then macrocyclic species form from simpler components or one of the patterns illustrated in Fig. 4.23 is employed.

The transformation of the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) intermediate assembly can also be achieved at room temperature. Although it appears to occur via different mechanism to that found for stoichiometric amounts of reagents under reflux conditions. It is more similar to the reaction with an excess of diamine. There is also a significant amount of \([\text{BaCu}_3(3+3)\text{(diamine)})^{2+}\) or \([\text{BaCu}_3(3:4)]^{2+}\) product in the reaction mixture but its conversion into the (4+4) is not observed. This might be because \([\text{BaCu}_3(3:4)]^{2+}\) conversion into \([\text{BaCu}_4(4+4)]^{2+}\) requires reflux conditions as in experiment with excess of diamine. A schematic representation of \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) conversion into macrocycle under reflux conditions, proposed on the basis of ESI-MS data, is presented in Fig. 4.31.
In intermediate cluster experiments with an excess amounts of reagents, not all of the components can be assembled into $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$. This opens the possibilities of alternative reaction routes which results in a higher formation rates for the $(4+4)$ macrocycle but also in formation of the $(3+3)$ macrocycle. This is somewhat similar to the subcomponent self assembly observed by Nitschke.\textsuperscript{45-47} In his Cu(I) imine aqueous systems, coordination preferences of ligands and metal were as well acting together towards certain structure out of several possible structures. In general terms, system usually tries to satisfy as much as possible coordination requirements of ligands and metals heading for the lowest total energy.

Fig. 4.31 Conversion pattern of the $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ into the $[\text{BaCu}_4(4+4)]^{2+}$ under reflux conditions.
4.6. Towards $[\text{BaCu}_3(3+3)]^{2+}$ cation via Route 3

According to data reported in J. Barriera Fontecha’s PhD thesis, $[\text{BaCu}_3(3+3)]^{2+}$ was formed in the condensation between $\text{H}_2\text{mftbp}$ and 1,3-diaminopropan-2-ol. In the first step, dialdehyde was refluxed with diamine in the presence of Ba(II) ions and triethylamine and then in the second stage, Cu(II) ions were introduced to the system which, corresponds to the Route 3 described in previous chapter. This was re-examined in an ESI-MS experiment (Fig. 4.32).

Spectra from this experiment are shown in Fig. 4.33. The top two spectra represent $\text{H}_2\text{mftbp}$, Ba(II), diamine and base reaction mixture after an overnight reflux. At this stage it contains primarily the (2+2) condensate with other free macrocyclic ligands ranging from up to the (4+4) macrocycle. The (2+2) product is related to peaks $[\text{H}_5(2+2)]^+$ at m/z 845 and $[\text{NaH}_4(2+2)]^+$ at m/z 867. The (3+3) condensate is indicated by peaks $[\text{H}_7(3+3)]^+$ at m/z 1267 and (4+4) is giving rise to peaks $[\text{H}_9(4+4)]^+$ at m/z 1691.
The reaction mixture after overnight reflux is similar to the experiment where Na(I) ions were refluxed overnight with dialdehyde and diamine in the presence of base (section 3.5.5.3). The Ba(II) ion is not involved in template processes as distribution of products identified in the reaction mixture is similar to that for non-template condensation in a related ligand system.\textsuperscript{133}

The bottom two spectra in Fig. 4.33 represent the reaction mixture after addition of Cu(II) ions. Once Cu(II) is introduced to the system both metals form complexes with the free macrocyclic ligands already existing in solution. The (2+2) assembles a sandwich species with Cu(II) and Ba(II), the (3+3) and (4+4) form $[\text{BaCu}_3(3+3)]^{2+}$ and $[\text{BaCu}_4(4+4)]^{2+}$ respectively. Both the sandwich $\{\text{Ba[Cu}_2(2+2)\}_2\}^{2+}$ and $[\text{BaCu}_4(4+4)]^{2+}$ assemblies give rise to doubly charged peaks at m/z 1036. The $[\text{BaCu}_3(3+3)]^{2+}$ cation is indicated by lower relative intensity peaks at m/z 795.

The higher mass doubly charged peaks at m/z 1287 and at m/z 1520 can be assigned to larger pseudocalixarene complexes, for the $[\text{BaCu}_5(5+5)]^{2+}$ and for $[\text{BaCu}_6(6+6)]^{2+}$ respectively. A spectrum of the reaction mixture after addition of Cu(ClO$_4$)$_2$·6H$_2$O expanded in range m/z 1200-1700 is shown in Fig. 4.34.
In conclusion, the synthetic route proposed for the \([\text{BaCu}_3(3+3)]^{2+}\) macrocyclic complex proposed on the basis of structural data is shown to be incorrect. Although \([\text{BaCu}_3(3+3)]^{2+}\) can be obtained as minor product in the formation of \([\text{BaCu}_4(4+4)]^{2+}\). Also it may be a minor product of intermediate cluster \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) conversion into the \((4+4)\) species conducted at room temperature or with excess of \(\text{Ba}^{2+}\) ions or 1,3-diaminopropan-2-ol. Possible conversion mechanisms of the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cluster into the \([\text{BaCu}_3(3+3)]^{2+}\) macrocycle were discussed in the previous section (Fig. 4.23).
4.7. Conclusions – double template effects

Our ESI-MS study of condensations between H₂mftbp and 1,3-diaminopropan-2-ol with Cu(II) and Ba(II) ions showed the following:

1) Formation of the \( \text{Ba}[[\text{Cu}_2(2+2)]_2]^{2+} \) sandwich requires addition of base as well as Ba(II) to a solution containing the (2+2) complex. Once triethylamine is added, the sandwich assembles within 1 min. (Route 1).

2) \([\text{BaCu}_4(4+4)]^{2+}\) is formed when Ba(II) ions are added before the diamine (Route 2), \([\text{BaCu}_3(3+3)]^{2+}\) is also present in this reaction mixture.

3) When a Ba(II) salt is refluxed with H₂mftbp and diamine in the presence of base, free macrocyclic ligands [primarily (2+2)] but no barium complexes were observed in the ESI-MS (Route 3).

4) Reaction of Cu(II), Ba(II) and H₂mftbp in the presence of base forms the cluster \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) which is an intermediate in the formation of \([\text{BaCu}_4(4+4)]^{2+}\) (Route 4).

5) The \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) intermediate can be transformed by sequence of eight Schiff base condensations into the clean (4+4) macrocyclic complex (Route 4). This reaction takes over 8 h. reflux to complete. The reaction is not clean at room temperature.

6) The above reaction is faster with an excess of Ba(II) ions or diamine, but the product contains some (3+3) macrocycle and (3:4) open chain condensate respectively.

The ESI-MS observations provide information on the reaction chemistry which was not available previously and permit more detailed reaction mechanisms to be proposed.

The process by which \([\text{BaCu}_4(4+4)]^{2+}\) is assembled is a double template reaction, both Ba(II) and Cu(II) ions must be present. The function of the Ba(II) ions is to bind the deprotonated methylenediphenols together, while the Cu(II) ions preorganise the intermediate assembly for Schiff-base condensation by controlling the orientation of the carbonyl groups. This process is schematically shown in Fig. 4.35.
Fig. 4.35 Double template effect in formation of \([\text{BaCu}_{4}(4+4)]^{2+}\).

An extended reaction scheme summarising the Ba(II) and Cu(II) heteronuclear complexes afforded by the four reaction routes studied is shown in Fig. 4.36.

Fig. 4.36 Revised reaction scheme for the large polyheteronuclear pseudocalixarene complexes.
Chapter 5

ESI-MS STUDY OF DIFFERENT TEMPLATE COMBINATIONS IN FORMATION OF HETEROPOLYNUCLEAR COMPLEXES OF PSEUDOCALIXARENE MACROCYCLES
5.1. Introduction

The double template effect described in previous chapter is related to the core/shell metal template effect recently reported by Nabeshima and co-workers (Fig. 5.1).\textsuperscript{188} Their study of Schiff base condensations between 2,3-dihydroxybenzene-1,4-dicarbaldehyde and 1,2-bis-(aminooxy)ethane with Zn(II) and La(III) led to similar conclusions about the role of each metal in the formation of 36-membered macrocyclic hexaoxime complex. The La(III) ion brings the three dialdehyde anions together by binding to their phenolate oxygens and the Zn(II) orients the carbonyl groups for Schiff base condensation. However, in their system core or shell metal ions can be used independently to assemble the same macrocyclic product. In case of the double template effect both metal ions have to be present simultaneously for the formation of (3+3) or (4+4) macrocyclic complexes.

![Fig. 5.1 Nabeshima core/shell template effect.\textsuperscript{188}](image)

Previous work on polyheteronuclear complexes carried out by J. Barreira Fontecha\textsuperscript{135} indicated that the choice of transition metal does not affect the size of macrocyclic product which is dependent on the central metal ion. Varying the size of central metal ion could also program the size of the macrocyclic product. The double template formation of pseudocalixarenes might operate using any transition metal ion used with a hard Lewis acid such as group 2 or lanthanide metal ions. The transition metals Ni(II), Zn(II), Mn(II) and Co(II) are like Cu(II), effective as templates in the Schiff base condensation yielding the (2+2) macrocyclic system\textsuperscript{132} so in principle, they should also template formation of larger macrocyclic systems. The similar ionic size of copper, nickel and zinc ions suggest that Cu(II) can be easily replaced in the systems discussed in previous chapter. However, different geometrical preferences might prevent them from forming all the compounds observed for Ba/Cu combination.
To test these ideas, condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol, with different combinations of metal ions was examined by ESI-MS. How the choice of the metal system affects the macrocyclic products is discussed in this chapter.

5.2. Ba(II) with Ni(II) and Ba(II) with Zn(II) template formation of pseudocalixarene Schiff base macrocycles

Condensations between H$_2$mftbp and 1,3-diaminopropan-2-ol with Ba(II) and Zn(II) or Ni(II) as metal templates were investigated by ESI-MS to examine the influence of the transition metal on the distribution of the large pseudocalixarene products. The three macrocyclic complexes, the sandwich, (4+4) and (3+3) are expected to be accessible via the same reaction routes as for the Ba(II) and Cu(II) system. As discussed in the previous chapter the sandwich complex might be produced by two routes: Route 1, when Ba(II) is added to the reaction mixture containing dizinc or dinickel (2+2) macrocyclic species, followed by an extra base; Route 3, where Ba(II) is used on long reflux with dialdehyde, diame and base solution before the transition metal salt is introduced. By this method the free macrocyclic ligands are produced in the first instance and then upon addition of the second metal the complexation occurs.

Route 2 should yield the (4+4) macrocycle, with the (3+3) as a minor product and in Route 4, when base is used before diamine, intermediate clusters [BaZn$_4$(mftbp)$_4$]$^{2+}$ and [BaNi$_4$(mftbp)$_4$]$^{2+}$ could be formed first and then transformed into the clean (4+4) macrocyclic products. The reaction routes and metal systems used in the ESI-MS study are summarised in Table 5.1.

<table>
<thead>
<tr>
<th>Route number</th>
<th>Metal system</th>
<th>Dialdehyde</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route 1</td>
<td>Ba(II) and Ni(II)</td>
<td>H$_2$mftbp</td>
<td>5.2.1</td>
</tr>
<tr>
<td>Route 2</td>
<td>Ba(II) and Ni(II)</td>
<td>H$_2$mfmp</td>
<td>5.2.2.1</td>
</tr>
<tr>
<td></td>
<td>Ba(II) and Zn(II)</td>
<td>H$_2$mftbp</td>
<td>5.2.2.2</td>
</tr>
<tr>
<td>Route 3</td>
<td>Ba(II) and Zn(II)</td>
<td>H$_2$mftbp</td>
<td>5.2.3</td>
</tr>
<tr>
<td>Route 4</td>
<td>Ba(II) and Ni(II)</td>
<td>H$_2$mftbp</td>
<td>5.2.4.1</td>
</tr>
<tr>
<td></td>
<td>Ba(II) and Zn(II)</td>
<td>H$_2$mftbp</td>
<td>5.2.4.2</td>
</tr>
</tbody>
</table>
5.2.1. Route 1 experiment with Ba(II) and Ni(II)

In this experiment Ni(II) was used as a template in condensation between H$_2$mfhtbp and 1,3-diaminopropan-2-ol. Then Ba(II) was added followed by base. This might be expected to yield the \{Ba[Ni$_2$(2+2)$_2$]$^2^+$\} complex. A schematic representation of the experiment with extraction times for ESI-MS analysis is presented in Fig. 5.2 and the spectra are shown in Fig. 5.3.

![Schematic diagram of the experimental process](image-url)

**Fig. 5.2 Route 1 ESI-MS experiment with Ba(II) and Ni(II).**

The top spectrum in Fig. 5.3 shows Ni(II), H$_2$mfhtbp and diamine reaction mixture after overnight reflux. This is a clean sample of the dinickel (2+2) complex represented by doubly charged peaks [Ni$_2$H$_2$(2+2)]$^{2^+}$ at m/z 478 and singly charged peaks [Ni$_2$H(2+2)]$^+$ at m/z 957 and [Ni$_2$H$_2$(2+2)(ClO$_4$)]$^+$ at m/z 1057. As discussed in Chapter 3 Ni(II) does not form a trinickel complex of (2+2) macrocycle, unlike the corresponding experiment with Cu(II) ions.
The next three spectra show the reaction mixture after addition of Ba(II) ions and triethylamine which should prompt the formation of \{Ba[\text{Ni}_2(2+2)]\}_2^{2+} \text{ sandwich species. Unexpectedly, after 30 min. of reaction from addition of NEt}_3 \text{ the anticipated compound is found at m/z 1026 with very low relative intensity (below 10%). Instead peaks from non-macrocyclic fragments Ni}_x(\text{di-aldehyde})_y(\text{di-amine})_z \text{ appear on the spectra at m/z 515, 589, 715, 791 and m/z 813 (Table 5.2). Also the (2+2) macrocycle is not the major compound in solution as it was before the addition of base. It can be identified mainly as the sodium adduct due to peaks [Ni}_2\text{Na}(2+2)]^+ \text{ at m/z 979. The presence of Ni(aldehyde)(amine) fragments suggest hydrolysis of imine bonds prior to formation of the larger pseudocalixarene systems. Further 1.5 h. of reflux does not bring any significant changes to the reaction mixture. After overnight reflux the reaction mixture exhibits peaks at m/z 1026 assigned to the sandwich ion \{Ba[\text{Ni}_4(2+2)]\}_2^{2+}. The pattern at m/z 1026 could also be attributed to the (4+4) macrocycle (peaks [BaNi}_4(4+4)]^{4+}) as the observed Ni(dialdehyde)(di-amine) fragments imply that assembly processes started from the beginning.}
Table 5.2 Major peak attributions for Ba(II) and Ni(II) Route 1 ESI-MS experiment.

<table>
<thead>
<tr>
<th>Peaks [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
</tr>
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<tbody>
<tr>
<td>479.1832</td>
<td>[Ni₂H₃(2+2)]²⁺</td>
<td>479.1839</td>
</tr>
<tr>
<td>497.1942</td>
<td>[NiH(mftbp)(diamine·H₂O)]⁺</td>
<td>497.1945</td>
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<tr>
<td>515.2048</td>
<td>[NiH(mftbp)(diamine)]⁺</td>
<td>515.2050</td>
</tr>
<tr>
<td>587.2734</td>
<td>[NiH(mftbp)(diamine·H₂O)(diamine)]⁺</td>
<td>587.2738</td>
</tr>
<tr>
<td>715.2620</td>
<td>[Ni₂(mftbp)(diamine·H₂O)(diamine-H)]²⁺</td>
<td>715.2622</td>
</tr>
<tr>
<td>775.2831</td>
<td>[Ni₂Na(mftbp)(diamine)⁺+2e]⁻</td>
<td>775.2810</td>
</tr>
<tr>
<td>796.2538</td>
<td>[Ni₃(3+3)(EtOH)(H₂O)(OH)₂-2e]²⁺</td>
<td>796.2600</td>
</tr>
<tr>
<td>813.2663</td>
<td>[Ni₂(mftbp)(diamine)₃(EtOH)(OH)]⁺</td>
<td>813.3201</td>
</tr>
<tr>
<td>832.2546</td>
<td>[BaNi₃(3+3)(diamine)]²⁺ or [BaNi₃(3:4)]²⁺</td>
<td>832.2599</td>
</tr>
<tr>
<td>877.2948</td>
<td>[BaNi₃(3+3)(diamine)₂]²⁺</td>
<td>877.2950</td>
</tr>
<tr>
<td>957.3589</td>
<td>[Ni₂H(2+2)]²⁺</td>
<td>957.3606</td>
</tr>
<tr>
<td>979.3422</td>
<td>[Ni₂Na(2+2)]⁺</td>
<td>979.3425</td>
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<tr>
<td>1026.8046</td>
<td>[BaNi₄(4+4)]²⁺ or [Ba[Ni₃(2+2)]]²⁺</td>
<td>1026.8050</td>
</tr>
<tr>
<td>1058.4810</td>
<td>[Ni₃(2+2)(HNEt₃)]⁺</td>
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<td>1059.3102</td>
<td>[BaNi₃(3+3)(diamine)₂]²⁺</td>
<td>1059.3123</td>
</tr>
<tr>
<td>1139.5230</td>
<td>[Ni₃(2+2)(MeOH)₃(H₂O)₃+H]⁺</td>
<td>1139.4971</td>
</tr>
<tr>
<td>1485.5947</td>
<td>[NiH₃(3+3)(EtOH)+2e]²⁺</td>
<td>1485.5947</td>
</tr>
<tr>
<td>1691.4562</td>
<td>[Ni₃(3+3)(EtOH)(ClO₄)(H₂O)(OH)₂-3e]⁻</td>
<td>1691.4676</td>
</tr>
<tr>
<td>(mftbp)²⁻ = C₂₃H₂₆O₄</td>
<td>(2+2)⁰ = C₅₂H₆₄N₄O₆</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3+3)⁶⁺ = C₇₆H₅₆N₄O₉</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4+4)⁶⁻ = C₁₀₄H₁₂₈N₄O₁₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(diamine)⁰ = C₃H₁₀N₂O</td>
<td></td>
</tr>
</tbody>
</table>

In contrast to the Ba/Cu experiment, where the sandwich molecule was the main product formed immediately after addition of base, the Ba/Ni system requires an overnight reflux to produce the {Ba[Ni₂(2+2)]₁}²⁺ species. The (3+3) macrocycle is also produced as byproduct, however peaks for [BaNi₃(3+3)(amine)₂]²⁺ at m/z 877 and for [BaNi₃(3+3)(amine)]²⁺ or [BaNi₃(3:4)]²⁺ at m/z 832 might imply that the transformation processes are not completed, although the reaction mixture does not show any significant changes by ESI-MS after overnight reflux.

In summary, the sandwich complex can be synthesised when Cu(II) ions are replaced by Ni(II) ions. However, by this route for Ni(II) and Ba(II) ions there is also a significant amount of the (3+3) macrocycle in the reaction mixture. Its formation requires rearrangement of the already formed (2+2) macrocycle. This can be achieved by hydrolysis of imine bonds which makes this system dynamic in contrast to the Ba(II) and Cu(II) template combination.
5.2.2. Route 2 experiments with Ba(II) and Ni(II) and Ba(II) with Zn(II)

Formation of heteropolynuclear complexes of [BaZn₄(4+4)]²⁺ and [BaNi₄(4+4)]²⁺ were studied in the same manner as described for the Route 2 experiment with Ba(II) and Cu(II) (section 4.3) but samples for ESI-MS analysis were extracted only after addition of base which is the turning point in these processes.

5.2.2.1. Ba(II) and Ni(II)

The experiment investigating formation of the (4+4) macrocycle with Ba(II) and Ni(II) ions was conducted on the LCT ToF instrument with H₂mfmp. The synthetic procedure remained the same, namely H₂mfmp, Ba(ClO₄)₂·3H₂O (0.5 equiv.) and Ni(ClO₄)₂·6H₂O (1 equiv.) were brought to reflux and then 1,3-diaminopropan-2-ol was added followed by triethylamine. After 5 h. of reflux the reaction mixture was investigated by ESI-MS (Fig. 5.4).

Fig. 5.4 Spectrum of Ba(II)/Ni(II)/H₂mfmpdialdehyde/diamine/ base reaction mixture 5 h. after addition of base and schematic representation of Ba(II) and Ni(II) Route 2 experiment ; inset spectrum shows the expanded range between m/z 600-900.

All major peaks observed in the spectrum can be assigned to Ba(II) species, Ba(MeO)⁺ at m/z 168, [Ba(MeO)₂]⁺ at m/z 196 and [Ba(ClO₄)]⁺ at m/z 236. The inset spectrum shows the expanded m/z 600-900 range. The anticipated [BaNi₄(4+4)]²⁺ macrocyclic...
complex is represented by doubly charged peaks at m/z 859 with very low overall relative intensity. The major macrocyclic species found is the [BaNi$_3$(3+3)(diamine)$_2$]$^{2+}$ complex giving rise to doubly charged peaks at m/z 751. As for Route 1, the (3+3) macrocyclic product seems to be preferred by Ba(II) and Ni(II) template system. However here, it appears mainly in form of diamine adduct which might suggest that some rearrangement is still ongoing in the system.

5.2.2.2. Ba(II) and Zn(II)

In a Route 2 experiment with Ba(II) and Zn(II) both metal salts were refluxed with H$_2$mtfbp for 30 min. and after that time 1,3-diaminopropan-2-ol was added followed by base. Reflux was continued for 30 min. and reaction mixture was studied by ESI-MS.

![Fig. 5.5 Spectrum acquired in Route 2 experiment with Ba(II) and Zn(II) together with schematic representation of this experiment.](image)

Figure 5.5 shows spectrum of the reaction mixture 30 min. after addition of base. The anticipated [BaZn$_4$(4+4)]$^{2+}$ complex is indicated by doubly charged peaks at m/z 1040. The strong relative intensity peaks at m/z 1965 can be attributed to [NaZn$_4$(4+4)]$^+$ species. This sodium adduct has probably formed inside the instrument and it has to be preceded by loss of central Ba(II) ion as Na(I) compound was not used intentionally in this experiment. The intensity of peaks at m/z 1965 might be due to the acquisition mode of the data. The spectrum was acquired in range up to m/z 4000 and these conditions promote species with high m/z ratios reaching to the detector.
The peaks at m/z 1965 were previously described in section 3.5.5.3 where they were attributed to the \( \{\text{Na}[\text{Zn}_2(2+2)]_2\}^+ \) sandwich species. However, as found for Ba/Cu experiments, reaction route employed in this experiment is expected to promote formation of the (4+4) macrocyclic complex over a sandwich complex, which was favoured by Route 3 for Ba/Cu system.

Ba(II) with Zn(II) template combination in Route 2 appears to act more similarly to the Ba(II) and Cu(II), as in both the (4+4) macrocycle is the main product found in the reaction mixture. In contrast, the same route examined for Ba(II) and Ni(II) metal ions seems to be favouring formation of the (3+3) system.

### 5.2.3. Route 3 experiment with Ba(II) and Zn(II)

J. Barriera Fontecha\(^1\) proposed that \( \{\text{Ba}[\text{Zn}_2(2+2)]_2\}^{2+} \) sandwich complex is formed when a Ba(II) salt is refluxed overnight with an dialdehyde, diamine and base and then a Zn(II) salt is introduced. Therefore H\(_2\)mftbp dialdehyde and Ba(ClO\(_4\))\(_2\) 6H\(_2\)O (0.5 equiv.) were refluxed for 30 min. and then 1,3-diaminopropan-2-ol was added followed by NEt\(_3\). Reflux was continued overnight and after that time ZnCl\(_2\) (1 equiv.) was introduced to the system. The reaction mixture was allowed to reflux for further 5 h. and the progress of the reaction was monitored by ESI-MS. A schematic representation of the ESI-MS experiment is shown in Fig. 5.6.

![Fig. 5.6 Route 3 ESI-MS experiment with Ba(II) and Zn(II).](image-url)
As established in Chapter 4 (section 4.6), overnight reflux of Ba(II), dialdehyde, diamine and base solution leads to the formation of free macrocyclic products where the (2+2) condensate is the majority and Ba(II) does not coordinate to the macrocycles until the transition metal is added. Figure 5.7 shows all spectra acquired in the Route 3 experiment with Ba(II) and Zn(II) metal ions.

Fig. 5.7 Spectra acquired in the Ba(II) and Zn(II) sandwich ESI-MS experiment.

The top spectrum in Fig. 5.7 represents Ba(II), H₂mftbp, diamine and base reaction mixture acquired after overnight reflux shows the expected products. The next spectra represent the reaction mixture after addition of Zn(II) salt. Analogous to the Ba(II) and Cu(II) experiment, straight after introduction of the transition metal ions the sandwich complex is formed giving rise for doubly charged peaks \( \{\text{Ba}[\text{Zn}_2(2+2)]_2\}^{2+} \) at m/z 1040. As described in the previous section, peaks at m/z 1965 can be assigned to \( \{\text{Na}[\text{Zn}_2(2+2)]_2\}^+ \) sandwich complex. Additional 5 h. of reflux does not bring any significant changes to the reaction mixture so the formation of complexes is over immediately after addition of ZnCl₂.

In this route neither metal is involved in template formation of macrocycles. The condensation between H₂mftbp and 1,3-diaminopropan-2-ol is similar to that for a non-template conditions and results primarily in free (2+2) macrocyclic ligand. This then
forms complexes with the metal ions present in solution. The Route 3 experiment with Ba(II) and Zn(II), similar to the Ba(II) and Cu(II) experiment, yields mainly the \(\{\text{Ba}[\text{Zn}_2(2+2)]_2\}^{2+}\) sandwich complex.

### 5.2.4. The intermediate cluster experiments (Route 4)

As discussed in section 2.1.3 and shown in Fig. 4.39, when base is added before diamine to the solution containing mftbp with Ba(II) and Cu(II), the \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cluster is formed. Possibly replacement of Cu(II) with Ni(II) or Zn(II) ions will lead to the formation of analogous \([\text{BaNi}_4(\text{mftbp})_4]^{2+}\) or \([\text{BaZn}_4(\text{mftbp})_4]^{2+}\) species. Attempted formation of these assemblies was examined by ESI-MS and is described below.

#### 5.2.4.1. Ba(II) and Ni(II)

In order to obtain the \([\text{BaNi}_4(\text{mftbp})_4]^{2+}\) cluster, Ba(ClO\(_4\))\(_2\)·3H\(_2\)O and Ni(ClO\(_4\))\(_2\)·6H\(_2\)O were refluxed together with H\(_2\)mftbp and after 30 min. triethylamine was added. Then after another 30 min. 1,3-diaminopropan-2-ol was introduced to the reaction mixture to convert the possible assembly into the macrocycle. Reflux was maintained overnight and the reaction progress was monitored by ESI-MS. A schematic representation of this experiment is shown in Fig. 5.8.

![Schematic of Route 4 experiment with Ba(II) and Ni(II)](image)

**Fig. 5.8 Route 4 experiment with Ba(II) and Ni(II).**

The first two spectra in Fig. 5.9 show the reaction mixture 1 min. and 30 min. after addition of triethylamine. In the analogous Ba/Cu experiment, introduction of base resulted in immediate formation of \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) cation. Here the predicted cluster...
is not observed in the spectra, instead after 1 min. of reflux the assembly of three dialdehydes with three nickel ions and one barium ion can be identified giving rise to peaks for [BaNi₃(mftbp)₃(MeO)(EtOH)₂-H₂O]⁺ at m/z 1517. After 30 min. the reaction also contains Ni(dialdehyde) adducts identified by peaks for [Ni(mftbp)(H₂O)]⁺ at m/z 443, [Ni(mftbp)(EtOH)₂]⁺ at m/z 471 and [Ni(mftbp)(EtOH)₂]⁺ at m/z 517. The doubly charged peaks appearing at m/z 493 are assigned to [BaNi₂(mftbp)]²⁺ fragments.

The bottom three spectra represent reaction mixture after addition of diamine to the solution described above. After 5 min. of reflux the previously observed peaks are gone resulting new peaks, which represent Niₓ(dialdehyde)ₙ(diamine)ᵢ species of different x:y:z ratio, at m/z 497, 515, 587, 715 and 791 (Table 5.3). Peaks at m/z 497 and m/z 715 are assigned to fragments with dialdehyde and diamine less a water molecule, which might indicate ongoing Schiff base condensation.

Fig. 5.9 ESI-MS data collected in Route 4 experiment with Ba(II) and Ni(II).
Table 5.3 Major peaks attribution for Route 4 experiment with Ba(II) and Ni(II).

<table>
<thead>
<tr>
<th>Peaks [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>425.1255</td>
<td>[NiH(mftbp)]+</td>
<td>425.1257</td>
</tr>
<tr>
<td>443.1361</td>
<td>[NiH(mftbp)(H2O)]+</td>
<td>443.1363</td>
</tr>
<tr>
<td>471.1674</td>
<td>[NiH(mftbp)(EtOH)]+</td>
<td>471.1676</td>
</tr>
<tr>
<td>493.0703</td>
<td>[BaNi2(mftbp)2]+</td>
<td>493.0705</td>
</tr>
<tr>
<td>497.1944</td>
<td>[NiH(mftbp)(diamine-H2O)]+</td>
<td>497.1945</td>
</tr>
<tr>
<td>499.2102</td>
<td>[NiH2(mftbp)(diamine)-OH]+</td>
<td>499.2101</td>
</tr>
<tr>
<td>515.2050</td>
<td>[NiH(mftbp)(diamine)]+</td>
<td>515.2050</td>
</tr>
<tr>
<td>517.2093</td>
<td>[NiH(mftbp)(EtOH)]+</td>
<td>517.2095</td>
</tr>
<tr>
<td>587.2736</td>
<td>[NiH(mftbp)(diamine)=H2O]+</td>
<td>587.2738</td>
</tr>
<tr>
<td>715.2621</td>
<td>[NiH(mftbp)(diamine-H2O)2(diamine-H)]+</td>
<td>715.2622</td>
</tr>
<tr>
<td>832.2555</td>
<td>[BaNi3(3+3)(diamine)]2+ or [BaNi3(3:4)]2+</td>
<td>832.2552</td>
</tr>
<tr>
<td>848.3671</td>
<td>[Ni2(mftbp)2-e]+</td>
<td>848.2364</td>
</tr>
<tr>
<td>877.2950</td>
<td>[BaNi3(3:3)(diamine)=C23H26NO4]2+</td>
<td>877.2954</td>
</tr>
<tr>
<td>1026.8051</td>
<td>[BaNi4(4+4)]2+ or [Ba[Ni2(2+2)]2]+</td>
<td>1026.8050</td>
</tr>
<tr>
<td>1067.4674</td>
<td>[Ni3(2+2)(OH)=C10bH128N6O12]2+</td>
<td>1067.2933</td>
</tr>
<tr>
<td>1517.3465</td>
<td>[BaNi3(mftbp)2(MeO)=C84H68N6O2]2+</td>
<td>1517.3497</td>
</tr>
<tr>
<td>1609.4462</td>
<td>[BaNi3(3+3)(OH)=C32H28N6O4]2+</td>
<td>1609.4447</td>
</tr>
</tbody>
</table>

\[
(mftbp)_2 = (2+2)^2 = C_{32}H_{30}N_{6}O_{6} \\
(3+3)^6 = C_{76}H_{68}N_{6}O_{6} \\
(4+4)^8 = C_{10b}H_{128}N_{6}O_{12}
\]

There is no direct evidence of sequential condensation between diamine and carbonyl groups of the [BaNi3(mftbp)3(MeO)(EtOH)=H2O]2+ species as found for the corresponding [BaCu4(mftbp)4]2+ cation. It is most likely that this cluster is broken up and the assembly processes start from the basic subcomponents. However, after 5 h. of reflux doubly charged peaks [BaNi3(3+3)(amine)=C23H26NO4]2+ at m/z 877 representing the (3+3) macrocycle start to appear and after 24 h. of reflux it becomes one of the major compounds in the reaction mixture. The second macrocyclic product identified in the reaction mixture after 24 h. of reflux is either the sandwich [Ba[Ni2(2+2)]2]+ complex or [BaNi4(4+4)]2+ complex giving rise to doubly charged peaks at m/z 1026.

In contrast to the Ba/Cu experiment, the Route 4 experiment with Ba(II) and Ni(II) is not a clean process, addition of base does not result in formation of only one assembly. Several fragments are found in solution with [BaNi2(mftbp)2]2+ and [BaNi3(mftbp)3(MeO)(EtOH)=H2O]2+ as majority. Addition of diamine also leads to more than one macrocyclic product which is probably not reached via sequential transformation of the BaNi3 assembly. Several Ni(dialdehyde)(diamine) fragments appearing shortly after the diamine is introduced to the system, and disappearance of
BaNi$_3$ cluster peaks suggest decomposition of this cluster. The assembly processes start from the beginning and result a mixture of products similar to that observed in Route 1 experiment with Ba(II) and Ni(II). As previously discussed despite the fact the reaction mixture does not show any significant changes by ESI-MS peaks [BaNi$_3$(3+3)(diamine)$_2$]$^{2+}$ and [BaNi$_3$(3+3)]$^{2+}$ suggest that the assembly processes might not be completed.

As yet, the difference between Ba/Ni and Ba/Cu template combination remains obscure. Perhaps the geometrical preferences of the transition metals have to be taken onto account here, as the nickel(II) ion is more rigid than copper(II) so is not always adopting the Cu(II) geometries. This might be why the distribution of macrocyclic products is different in Ba/Ni template system.

5.2.4.2 Ba(II) and Zn(II)

Analogous to Ba/Cu and Ba/Ni Route 4 experiments, a possible assembly of [BaZn$_4$(mftbp)$_4$]$^{2+}$ cluster was examined by ESI-MS. Ba(NO$_3$)$_2$ (0.5 equiv) and Zn(NO$_3$)$_2$·6H$_2$O (1equiv.) were reflux with H$_2$mftbp for 30 min. and after that time triethylamine was introduced with reflux continued for another 30 min. Then reaction mixture was extracted for an ESI-MS analysis and diamine was added to investigate possible conversion of the anticipated cluster into Schiff base macrocycle. Reflux was maintained for 90 min. with samples taken at intervals for an ESI-MS analysis. A schematic representation of this experiment is shown in Fig. 5.10.

![Diagram](image-url)
The top two spectra in Fig. 5.11 represent Ba(II), Zn(II) and H₂mftbp reaction mixture 1 and 30 min. after addition of triethylamine respectively. Surprisingly, no barium or zinc related peaks can be found in the spectra as the observed peaks do not have their characteristic isotope patterns. Whatever Ba(II) and Zn(II) species are formed in solution do not flight through the ms instrument under these conditions. All peaks were attributed to Na(dialdehyde) adducts and are listed in Table 5.4.

At this stage in similar experiments, Ba(II) and Cu(II) template system produced [BaCu₄(mftbp)₄]²⁺ cation and for Ba(II) with Ni(II) a [BaNi₃(mftbp)]²⁺ complex was indentified in solution. Perhaps the Ba(II) with Zn(II) ions form some cluster with H₂mftbp in solution but it is unstable under conditions of experiment and does not get to the ms detector.

Fig. 5.11 Spectra of Ba/Zn/dialdehyde/base reaction mixture before and after addition of diamine.

The third spectrum in Fig. 5.11 represents reaction mixture 5 min. after addition of diamine. Unexpectedly, at this stage, macrocyclic species are present in solution. As established in chapter 3 formation of dinuclear (2+2) complex is a slow process and requires an overnight reflux. Here, the (2+2) macrocycle is found just 5 min. after introduction of diamine. It is represented by peaks [Zn₂H₂(2+2)(OH)]⁺ at m/z 989 and doubly charged [Zn₄(2+2)(diamine-H)₂]²⁺ at m/z 639 (Table 5.4). Peaks at m/z 1965 can be attributed to the (4+4) or the sandwich complexes, [NaZn₄(4+4)]²⁺ or
{Na[Zn\textsubscript{2}(2+2)]\textsubscript{2}}^{2+}$ respectively. The reaction route should promote formation of the (4+4) macrocycle but because the (2+2) is identified in the reaction mixture, it is possible that a mixture of both species give rise to pattern at m/z 1965. Similarly, low relative intensity peaks at m/z 1040 can be attributed to the [BaZn\textsubscript{4}(4+4)]^{2+} or {Ba[Zn\textsubscript{2}(2+2)]\textsubscript{2}}^{2+} or to a mixture of both. As discussed in chapter 4 a ms/ms experiment needs to be conducted to distinguish which macrocyclic product is formed.

The major species indentified in solution 5 min. after addition of diamine are dialdehyde with diamine condensates, giving rise to peaks at m/z 469 and m/z 513. Peaks at m/z 667 and m/z 729 can be attributed to the Zn(dialdehyde)(diamine) fragments (Table 5.4). The loss of water in those species confirms ongoing Schiff base condensation. An organic fragment at m/z 307 is not assigned but it might be a result of the dialdehyde fragmentation which was not previously observed under the experimental conditions.

<table>
<thead>
<tr>
<th>Peaks [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>391.1875</td>
<td>[Na\textsubscript{2}(mftbp)]\textsuperscript{+}</td>
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</tr>
<tr>
<td>465.2607</td>
<td>[Na\textsubscript{2}(mftbp)(EtOH)\textsubscript{2}H\textsubscript{2}O]\textsuperscript{+}</td>
<td>465.2611</td>
</tr>
<tr>
<td>469.3059</td>
<td>[H\textsubscript{2}(mftbp)(diamine-H\textsubscript{2}O)(EtOH)-H\textsubscript{2}O]\textsuperscript{+}</td>
<td>469.3061</td>
</tr>
<tr>
<td>513.3434</td>
<td>[H\textsubscript{2}(mftbp)(diamine-H\textsubscript{2}O)\textsubscript{2}]\textsuperscript{+}</td>
<td>513.3435</td>
</tr>
<tr>
<td>639.1673</td>
<td>[Zn\textsubscript{2}(2+2)(diamine-H)]\textsuperscript{2+}</td>
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<tr>
<td>667.3403</td>
<td>[ZnH(mftbp)(diamine-H\textsubscript{2}O)\textsubscript{2}(EtOH)\textsubscript{2}]\textsuperscript{+}</td>
<td>667.3408</td>
</tr>
<tr>
<td>729.2463</td>
<td>[Zn\textsubscript{2}(mftbp)(diamine-H\textsubscript{2}O)\textsubscript{2}(diamine-H)]\textsuperscript{+}</td>
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</tr>
<tr>
<td>759.3860</td>
<td>[Na\textsubscript{2}(mftbp)\textsubscript{2}]\textsuperscript{+}</td>
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</tr>
<tr>
<td>833.4591</td>
<td>[Na\textsubscript{2}(mftbp)\textsubscript{2}(EtOH)\textsubscript{2}H\textsubscript{2}O]\textsuperscript{+}</td>
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</tr>
<tr>
<td>907.5322</td>
<td>[Na\textsubscript{2}(mftbp)\textsubscript{2}(EtOH)\textsubscript{2}2H\textsubscript{2}O]\textsuperscript{+}</td>
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</tr>
<tr>
<td>989.3545</td>
<td>[Zn\textsubscript{2}H\textsubscript{2}(2+2)(OH)]\textsuperscript{+}</td>
<td>989.3557</td>
</tr>
<tr>
<td>1040.2905</td>
<td>[BaZn\textsubscript{4}(4+4)]\textsuperscript{2+} or [Ba[Zn\textsubscript{2}(2+2)]\textsubscript{2}]\textsuperscript{2+}</td>
<td>1040.2912</td>
</tr>
<tr>
<td>1965.6648</td>
<td>[Na\textsubscript{2}Zn\textsubscript{4}(4+4)]\textsuperscript{2+} or [Na[Zn\textsubscript{2}(2+2)]\textsubscript{2}]\textsuperscript{2+}</td>
<td>1965.6677</td>
</tr>
</tbody>
</table>

\[
\text{mftbp}^\textsuperscript{2+} = \text{C}_{23}\text{H}_{26}\text{O}_{4} \\
(2+2)\textsuperscript{2+} = \text{C}_{52}\text{H}_{66}\text{N}_{6}\text{O}_{6} \\
(4+4)\textsuperscript{8+} = \text{C}_{104}\text{H}_{128}\text{N}_{12}\text{O}_{12} \\
\text{diamine} = \text{C}_{3}\text{H}_{18}\text{N}_{2}\text{O}_{2} \\
\text{Na}^{+} = \text{C}_{23}\text{H}_{30}\text{O}_{3} \\
\text{Zn}^{2+} = \text{C}_{104}\text{H}_{128}\text{N}_{12}\text{O}_{12} \\
\text{Ba}^{2+} = \text{C}_{3}\text{H}_{18}\text{N}_{2}\text{O}_{2} \\
\text{Ba}^{2+} = \text{C}_{23}\text{H}_{30}\text{O}_{3} \\
\text{Ba}^{2+} = \text{C}_{52}\text{H}_{66}\text{N}_{6}\text{O}_{6} \\
\text{Ba}^{2+} = \text{C}_{104}\text{H}_{128}\text{N}_{12}\text{O}_{12} \\
\text{Ba}^{2+} = \text{C}_{23}\text{H}_{30}\text{O}_{3}
\]

The last two spectra in Fig. 5.11 show the reaction mixture 40 min. and 90 min. after addition of diamine and do not exhibit any significant changes. The anticipated BaZn cluster with H\textsubscript{2}mftbp and its consequent conversion into the macrocycle are not observed in this experiment. Similar to the Route 2 experiment with Ba(II) and Zn(II), the (4+4) or sandwich complex is the main macrocyclic product present in solution. It also appears with Na(I) as the central metal ion, despite the fact that sodium was not used intentionally in this experiment.
5.2.4. Summary of Ba(II) with Ni(II) and Ba(II) with Zn(II) template formation of pseudocalixarene macrocycles

In general, we confirmed that both Ni(II) and Zn(II) can function in double template processes where Ba(II) is used as the central metal. The Ba/Zn system is more like Ba/Cu as it results in similar distribution of macrocyclic products. Fairly clean sandwich \{Ba[Zn₂(2+2)]₂\}²⁺ and [BaZn₄(4+4)]²⁺ were reached through analogous routes to those described for Ba/Cu complexes. However, Ba(II) and Zn(II) template combination did not yield the [BaZn₄(mftbp)]²⁺ cluster. Moreover Ba(II) is easily replaced by Na(I) ion as all Ba/Zn experiments produced the same [NaZn₄(4+4)]⁺ or {Na[Zn₂(2+2)]₂}⁺ species. A reaction scheme summarising Ba(II) and Zn(II) template synthesis of pseudocalixarenes, analogous to proposed for Ba/Cu processes, is shown in Fig. 5.12.

Fig. 5.12 Accessibility of macrocyclic products in condensation between H₂mftbp and 1,3-diaminopropan-2-ol with Ba(II) and Zn(II) as templates.
Condensations between H$_2$mfmbp and 1,3-diaminopropan-2-ol with Ba(II) and Ni(II) as templates do not lead to clean reaction mixtures. The (3+3) macrocycle seems to be the favoured product with this metal combination because all reaction routes produced [BaNi$_3$(3+3)(amine)$_2$]$^{2+}$ species. Route 1, in contrast to the Ba/Cu system, showed decomposition of the (2+2) macrocycle prior to formation of the (3+3) species. So far this is the only example of rearrangement observed in formation of pseudocalixarene macrocycles. The Route 2 Ba/Ni experiment conducted for H$_2$mfmp dialdehyde also produced the (3+3) complex despite the fact that the stoichiometry should promote formation of the (4+4) species. Finally in Route 4 [BaNi$_3$(mfmbp)$_3$(MeO)(EtOH)$_2$-H$_2$O]$^+$ cluster is formed but breaks up after addition of diamine. Although the (3+3) macrocycle is produced by this route it is most likely assembled from the basic subcomponents. A summary of experiments with Ba(II) and Ni(II) is shown in Fig. 5.13.

Fig. 5.13 Accessibility of macrocyclic products in condensation between H$_2$mfmbp and 1,3-diaminopropan-2-ol with Ba(II) and Ni(II) as templates.
5.3. Route 3 experiments with Ca(II) and Cu(II) or Ca(II) with Zn(II)

The size of macrocycle formed in the condensation between H₂mftbp and 1,3-diaminopropan-2-ol depends, as was suggested previously, on the central metal ion radius. When Cu(II) is used as template only the (2+2) macrocyclic products are formed. When Ba(II) is used together with Cu(II) condensation is directed mainly into the (4+4) product with the (3+3) as minor product. Therefore the Ba(II) ions are required for expansion of the macrocycle. In principle, the group 2 or lanthanide metal ions with ionic radii smaller than Ba(II) might direct the reaction into the (3+3) products as the cavity of the (4+4) species would be too large for them be accommodated. Preliminary work on Ca(II) template syntheses carried by J. Barreira Fontecha led to the isolation of heteronuclear \([\text{CaCu}_3(3+3)(\text{NO}_3)_2]\cdot2\text{EtOH}\cdot2\text{H}_2\text{O} \) and \([\text{CaZn}_3(3+3)(\text{NO}_3)_2]\cdot2\text{EtOH}\cdot2\text{H}_2\text{O}\) complexes identified mainly by FAB-MS. However the synthetic route involved a long reflux step of Ca(II) salt with H₂mftbp dialdehyde, diamine and base, which for Ba(II) ions resulted a mixture of free macrocyclic ligands proving that Ba(II) was not acting as a template. If the Ca(II) behaved in the same manner, the (2+2) sandwich product should be isolated. An ESI-MS study of Ca(II) with Cu(II) and Zn(II) synthesis of pseudocalixarene is discussed below.

5.3.1. Ca(II) with Cu(II) template synthesis

The Route 1 experiment with Ca(II) and Cu(II) described in section 3.5.5.1 yielded mainly the trinuclear CaCu₂(2+2) complex by ESI-MS. However, in this reaction the Ca(II) was not involved in template processes as it was introduced to the reaction mixture containing already formed (2+2) macrocyclic species. As found by J. Barreira-Fontecha, the \([\text{CaCu}_3(3+3)(\text{NO}_3)_2]\cdot2\text{EtOH}\cdot2\text{H}_2\text{O}\) complex can be obtained when H₂mftbp dialdehyde with Ca(II) and diamine in presence of base are refluxed overnight and then a Cu(II) salt is introduced. This synthetic pattern, corresponding to Route 3, experiment was investigated by ESI-MS. A Schematic representation of ESI-MS experiment is shown in Fig. 5.14.
Figure 5.15 shows spectra acquired in the Ca(II) and Cu(II) experiment. The top spectrum represents the reaction mixture after overnight reflux, before the addition of Cu(II). As for the corresponding Ba/Cu reaction the spectrum shows (2+2) and (3+3) free macrocyclic ligands, related to peaks [H₅(2+2)]⁺ and [H₇(3+3)]⁺ at m/z 845 and m/z 1267 respectively. The major species in solution is related to the doubly charged peak at m/z 1413. This can be assigned to the formula [C₁₅₆H₁₉₅H₁₃O₂₁Ca₆]²⁺ which could represent three macrocyclic cations: the product of condensation between six dialdehydes and six diamines [Ca₆H₃(6+6)(NO₃)]²⁺, a sandwich complex made from two (3+3) macrocycles each bonding three Ca(II) ions {H₃[Ca₃(3+3)]₂(NO₃)}²⁺ or the double sandwich complex made of three (2+2) dinuclear Ca(II) units stacked on each other {H₃[Ca₃(2+2)]₃(NO₃)}²⁺. To distinguish between them a tandem ms/ms experiment was conducted which is described in detail further in this section.
The second spectrum was recorded 1 h. after introduction of Cu(II) ions and shows a family of doubly charged peaks at m/z 1413, 1444, 1476 and 1507. The difference in m/z values of 32 units and change of the isotope patterns between these doubly charged peaks suggests that one, two, and three Cu(II) ions were accommodated by the species assigned to peaks at m/z 1413, so Ca₆Cu assembly is represented by peaks at m/z 1444, Ca₆Cu₂ at m/z 1476 and finally Ca₆Cu₃ give rise to peaks at m/z 1507. As mentioned above this could be any of the three macrocyclic cations, the (6+6), sandwich or double sandwich related to these peaks. Also after addition of Cu(II) ions to the reaction mixture the free (2+2) macrocyclic ligand forms the dicopper complex giving rise to peaks for [Cu₂H(2+2)]⁺ at m/z 967 and for [Cu₂Na(2+2)]⁺ at m/z 989.

The bottom three spectra show reaction mixture after 2, 5 and 24 h. reflux from addition of Cu(II) salt. The reaction progresses towards the Ca₆Cu₃ adduct marked by peaks [C₁₅₆H₁₉₀O₂₂N₁₂Ca₆Cu₃]²⁺ at m/z 1507 which is the major compound found in the spectrum after overnight reflux.

To distinguish between the sandwich, the double sandwich or the (6+6) macrocycle reaction mixture was under reflux condition for 72 h. and after that time was
investigated on the Synapt instrument in the tandem ms/ms experiment. Fragmentation of the sandwich ions should generate the half ions as was discussed in section 4.4 for the \( \{ \text{Ba} \{ \text{Cu}_2(2+2) \}_2 \}^{2+} \) cation. Consequently, the \((3+3)\) macrocyclic ion would be observed for the sandwich complex ions \( \{ \text{Cu}_3[\text{Ca}_3(3+3)]_2(\text{NO}_3)+3e^- \}^{2+} \) or the \((2+2)\) macrocycle in case of the double sandwich \( \{ \text{Cu}_3[\text{Ca}_2(2+2)]_3(\text{NO}_3)+3e^- \}^{2+} \). In contrast, the \([\text{Cu}_3\text{Ca}_6(6+6)(\text{NO}_3)+3e^-]^{2+}\) species should be stable under conditions at which molecules mentioned above fragment or, in the case of fragmentation, its pattern would be more complex.

Fig. 5.16 Spectra from tandem ms/ms experiment; inset shows fragmentation of the isolated ion giving signal at \( m/z \ 1507 \).

Fig. 5.16 shows the spectrum of the species giving the peak at \( m/z \ 1507 \) with its ms/ms spectrum (inset). Fragmentation was measured at collision energy of 100 V ( \( \{ \text{Ba} \{ \text{Cu}_2(2+2) \}_2 \}^{2+} \) ion fragments at 55 V). Surprisingly the \([\text{C}_{156}\text{H}_{195}\text{H}_{13}\text{O}_{21}\text{Ca}_6]^{2+}\) ion is very stable even at 100 V collision energy and remains the major species in the ms/ms spectrum. This suggests formation of the \([\text{Cu}_3\text{Ca}_6(6+6)+3e^-]^{2+}\) macrocyclic complex. Unfortunately, no more analytical data for this \( \text{Ca}_6\text{Cu}_3 \) species were collected. The microanalyses of solid samples from this experiment indicate formation of the dinuclear species. Moreover a green crystal of \([\text{CaCu}_2(2+2)(\text{NO}_3)_2](\text{MeOH})_2\) complex described in chapter 3 (section 3.2.2.2) was isolated from this reaction mixture. Since
these high mass peaks were predominant in this experiment the trinuclear complex 
[Cu₂Ca(2+2)(NO₃)₂](MeOH)₂ appears to be a product of preferential crystallisation.

5.3.2. Ca(II) with Zn(II) template synthesis

The synthetic route proposed by J. Barreira-Fontecha¹³⁵ leading to 
[Zn₃Ca(3+3)(NO₃)]·2EtOH·2H₂O was followed by ESI-MS. This Route 3 experiment 
with Ca(II) and Zn(II) is schematically shown in Fig. 5.17.

![Fig. 5.17 Sampling pattern in Route 3 ESI-MS experiment with Ca(II) and Zn(II).](image)

As for the Ca/Cu experiment overnight reflux of Ca(II) ion with H₂mftbp dialdehyde 
and diamine in the presence of base results in formation [H₃Ca₆(6+6)(NO₃)]²⁺ species. 
This species was able to accommodate three Cu(II) ions so replacement of Cu(II) with 
Zn(II) ion might produce the corresponding Zn₃Ca₆ assembly.

The first sample of the reaction mixture containing Ca(II), H₂mftbp dialdehyde, diamine 
and base was analysed after overnight reflux. As expected the top spectrum shown in 
Fig. 5.18 exhibits the same doubly charged peaks [H₃Ca₆(6+6)(NO₃)]²⁺ at m/z 1413 
assigned to hexacalcium complex above.
When formation of Ca₆ species was completed, Zn(NO₃)₂·6H₂O was introduced to the reaction mixture. Spectra of the reaction mixture acquired 1 h., 2 h., 5 h. and 22 h. after addition are shown in Fig. 5.18. There is no indication of interaction between the Zn(II) ions and the Ca₆ complex as peaks at m/z 1413 remain unchanged in the spectra. It seems that the binding sites of this high mass cation are suitable for Cu(II) ions but not Zn(II). The only observed Zn(II) species are related to sandwich molecules giving rise to peaks for \([\text{Ca}[\text{Zn}_2(2+2)]_2]^{2+}\) at m/z 991 and \([\text{Na}[\text{Zn}_2(2+2)]_2]^{+}\) at m/z 1965.

Reaction mixture after 72 h. of reflux was also investigated on the Synapt instrument in the tandem ms/ms experiment to examine the fragmentation pattern of the compound giving the signal at m/z 1413 assigned to \([\text{H}_3\text{Ca}_6(6+6)(\text{NO}_3)]^{2+}\). The spectra of isolated cation giving rise to peak at m/z 1413 and the ms/ms spectrum acquired with over 100 V collision energy are shown in Fig. 5.19.

Fig. 5.18 Spectra acquired in Ca(II) and Zn(II) ESI-MS experiment.
The compound due to doubly charged peaks at m/z 1413 is very stable under the fragmentation conditions. It remains the major species in inset spectrum which agrees with the proposed assignment to the (6+6) macrocycle rather than the (3+3) sandwich or the double sandwich complex made from the three (2+2) macrocyclic units. Fragmentation of $[\text{H}_3\text{Ca}_6(6+6)(\text{NO}_3)]^{2+}$ produces a wide range of molecular fragments, represented by peaks observed in the range between m/z 900 and 1400.

5.3.3. Summary of ESI-MS experiments with Ca(II) as a central metal

Ca(II) in the contrast to Ba(II), acts as a template in condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol without an additional transition metal. It yields a high mass assembly in solution identified as $[\text{H}_3\text{Ca}_6(6+6)(\text{NO}_3)]^{2+}$. This assignment was supported by a ms/ms fragmentation study in which this ion was found to relatively stable with 100 V collision energy. Moreover this complex was able to bind three Cu(II) ions to form $[\text{Cu}_3\text{Ca}_6(6+6)(\text{NO}_3)+3\text{e}^-]^{2+}$ species but did not bind Zn(II) ions. The fact that it coordinates Cu(II) and does not interact with Zn(II) ion might be explained by geometrical preferences of the transition metals and by their redox properties.
It has to be emphasized that there is no supporting analytical or spectroscopic evidence confirming formation of this large macrocyclic complex for the reason that compound related to m/z 1413 was not isolated in solid form. The structure of this $[\text{H}_3\text{Ca}_6(6+6)(\text{NO}_3)]^{2+}$ ion also remains unclear. The (6+6) macrocyclic ligand can provide only twelve hard phenolate oxygen donors and (if deprotonated) six alkoxo oxygen donors. Assuming that each Ca(II) ion requires six to eight hard donors in the coordination sphere the macrocyclic system does not possess enough donor atoms to satisfy all the Ca(II) ions. Also obscure is how this assembly is able to accommodate three Cu(II) ions. Attempts to isolate this Cu$_3$Ca$_6$ species were unsuccessful as from the reaction mixture solution the [CaCu$_2$(2+2)(NO$_3$)$_2$](H$_2$O)$_2$ complex was isolated and recrystallised from methanol by slow evaporation to give single crystal of [CaCu$_2$(2+2)(NO$_3$)$_2$](MeOH)$_2$ described in section 3.2.2.2.

So far the reason why Ca(II), with smaller ionic size than Ba(II), template condensation into (6+6) product is not clear, neither is the atom connectivity in these $[\text{H}_3\text{Ca}_6(6+6)(\text{NO}_3)]^{2+}$ and $[\text{Cu}_3\text{Ca}_6(6+6)(\text{NO}_3)+3\text{e}^-]^{2+}$ species.
5.4. La(III) template synthesis

The macrocyclic complexes of lanthanides have drawn the attention of researchers due to the magnetic and spectroscopic properties which render their applications as MRI (Magnetic Resonance Imaging) agents, luminescent materials, biological markers, single molecule magnets or biocatalysts.\textsuperscript{35-36,189-198} The possibility of forming (3+3) tetra- or (4+4) pentanuclear pseudocalixarene systems with the lanthanide ions prompted us to investigate La(III) as a central metal template in the condensation between H\textsubscript{2}mftbp and 1,3-diaminopropan-2-ol. Since both (3+3) and (4+4) macrocyclic ligands can offer hard methylenediphenolate oxygen donors supported by the pendant alcohol groups oxygens, hard La(III) should act as a central metal template in the double metal template reactions. However, since the radius of La(III) is similar to that of Ca(II)\textsuperscript{199} formation of the large (6+6) macrocycle as found for Ca(II) ion is possible. All routes described in chapter 3 (section 3.5.5) were examined for La(III) ion and are summarised in Table 5.5.

Table 5.5 ESI-MS experiments with La(III).

<table>
<thead>
<tr>
<th>Route number</th>
<th>Metal Salts used</th>
<th>Section number</th>
<th>Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route 1</td>
<td>La(NO\textsubscript{3})\textsubscript{3}∙6H2O; Cu(NO\textsubscript{3})\textsubscript{2}∙3H2O</td>
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<td>A</td>
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<td></td>
<td>La(NO\textsubscript{3})\textsubscript{3}∙6H2O; Zn(NO\textsubscript{3})\textsubscript{2}∙3H2O</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>La(NO\textsubscript{3})\textsubscript{3}∙6H2O; Ni(OAc)\textsubscript{2}∙4H2O</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Route 2</td>
<td>LaCl\textsubscript{3}; Cu(ClO\textsubscript{4})\textsubscript{2}∙6H2O</td>
<td>5.4.2</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>La(OAc)\textsubscript{3}∙1.5H2O; Cu(OAc)\textsubscript{2}∙4H2O</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>La(NO\textsubscript{3})\textsubscript{3}∙6H2O; Cu(NO\textsubscript{3})\textsubscript{2}∙3H2O</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Route 3</td>
<td>La(NO\textsubscript{3})\textsubscript{3}∙6H2O; Cu(NO\textsubscript{3})\textsubscript{2}∙3H2O</td>
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<td>Route 4</td>
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<td>A</td>
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<td>La(NO\textsubscript{3})\textsubscript{3}∙6H2O; Zn(NO\textsubscript{3})\textsubscript{2}∙3H2O</td>
<td></td>
<td>B</td>
</tr>
</tbody>
</table>
5.4.1. Route 1 experiments with La(III)

The three different transition metals, Cu(II), Ni(II) and Zn(II) were used along with La(III). First, the transition metal salt was refluxed overnight with H$_2$mftbp and 1,3-diaminopropan-2-ol. Then after formation of (2+2) macrocycles were completed and confirmed by ESI-MS, the La(III) was introduced to the reaction mixture followed by base. Reflux was continued for 5 h. with samples extracted for ESI-MS analysis. Extraction pattern for ESI-MS analysis is shown in Fig. 5.20.

![Fig. 5.20 Schematic representation of Route 1 experiments with La(NO$_3$)$_3$·6H$_2$O and A) Cu(NO$_3$)$_2$·3H$_2$O B) Zn(NO$_3$)$_2$·6H$_2$O and C) Ni(OAc)$_2$·4H$_2$O.](image)

Spectra of the reaction mixtures analysed after overnight reflux are shown in Fig. 5.21. As discussed in detail in chapter 3, transition metals template formation of (2+2) macrocycle and (2+2) complexes were successfully identified in each experiment. In experiment A, dicopper(II) and tricopper(II) species were produced and in experiments B and C, dizinc(II) and dinickel(II) (2+2) macrocyclic ions were found (Table 5.6).
When formation of the (2+2) macrocycles were confirmed, La(NO₃)₃·6H₂O was added to the reaction mixtures. As with Ba(II), addition of La(III) did not bring any significant changes to the refluxed solutions (Fig. 5.22). The middle spectra in Figure 5.22 show reaction mixtures 5 min. after addition of triethylamine. As established in section 4.2 addition of base was the key step in formation of \{Ba[Cu₂(2+2)]\}_2^{2+} and 5 min. of reflux should be enough time for the formation of potential La[(TM)_2(2+2)]_2^{0+} species, where TM is the transition metal used along with lanthanum. In experiment A, the anticipated sandwich complexes with La(III) were not identified in the spectra 5 min. after introduction of triethylamine. Instead sodium adducts of the dicopper(II) complex were found giving rise to peaks \([Cu_2Na(2+2)]^+\) at m/z 989. In experiment B addition of base resulted in formation the LaZn₃ species of (2+2) macrocycle due to peaks at m/z 692 and singly charged at m/z 1414 (Table 5.6). Also, as in all experiments with Zn(II) where base was used, the peak pattern at m/z 1965 assigned to \([Na[Zn_2(2+2)]_2]^+\) cation was found.

Finally, in experiment C, the spectrum of reaction mixture, 5 min. reflux after addition of base showed some low relative intensity doubly charged peaks at m/z 1125 and m/z 1179 which were assigned to the Ni₆La sandwich species, \{La[Ni₂(2+2)]_2(OH)(diamine)_2\}_2^{2+} and \La[Ni₂(2+2)]_2(OH)(diamine)_3(H₂O)\}_2^{2+} respectively. The strongest signal was observed from the (2+2) macrocycle at m/z 957. Peaks appearing in range m/z 500 – 700 were attributed to Ni(dialdehyde)(diamine) adducts, presence of which might suggest some rearrangements in the system, e.g. hydrolysis of an imine bond of the macrocycle, as overnight reflux resulted in a clean solution of dinickel(II) (2+2) macrocycle.
Fig. 5.22 Spectra from Route 1 La(III) experiments; Left: reaction mixtures from experiment A; Middle: reaction mixtures from experiment B; Right: reaction mixtures from experiment C.

The bottom spectra represent reaction mixtures which were refluxed for an additional 5 h. and then were re-examined by ESI-MS. In experiments A and C extended reflux did not cause any changes to reaction mixtures as the spectra were identical with those previously acquired. In experiment B species giving rise to peaks at m/z 692 are gone and the \([\text{Na}[\text{Zn}(2+)]_2]^\dagger\) is the major compound identified, related to peaks at m/z 1965.

Table 5.6 Major peak attributions for Route 1 experiments with La(III).

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Peaks [m/z]</th>
<th>Fragments</th>
<th>Calculated [m/z]</th>
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<tr>
<td>A</td>
<td>484.1774</td>
<td>([\text{Cu}_2\text{H}_2(2+)]^{2+})</td>
<td>484.1782</td>
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<tr>
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<td>515.6332</td>
<td>([\text{Cu}_2(2+)]^{2+})</td>
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<td>967.3472</td>
<td>([\text{Cu}_2\text{H}(2+)]^{+})</td>
<td>967.3491</td>
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<td></td>
<td>989.3324</td>
<td>([\text{Cu}_2\text{Na}(2+)]^{+})</td>
<td>989.3310</td>
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<tr>
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<td>991.3327</td>
<td>([\text{Cu}_2\text{Na}(2+)]^{2+})</td>
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<td></td>
<td>1030.3428</td>
<td>([\text{Cu}_2\text{H}_2(2+)(\text{NO}_2)]^{+})</td>
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<tr>
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<td>1093.2544</td>
<td>([\text{Cu}_2(2+)(\text{NO}_3)]^{+})</td>
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<td>B</td>
<td>486.1753</td>
<td>([\text{Zn}_2\text{H}_2(2+)]^{2+})</td>
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<td>692.1665</td>
<td>([\text{LaZn}_2(2+)(\text{NO}_3)(\text{MeOH})_2(\text{EtOH})(\text{H}_2\text{O})_2+2e]^{2+})</td>
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<td>989.3534</td>
<td>([\text{Zn}_2\text{H}(2+)(\text{OH})]^{+})</td>
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<td>([\text{Zn}_2\text{H}_2(2+)(\text{NO}_3)]^{2+})</td>
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<td>1414.2956</td>
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<td>1965.6673</td>
<td>([\text{Na}[\text{Zn}_2(2+)]_2]^\dagger)</td>
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<td>C</td>
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<td>([\text{Ni}_2\text{H}_2(2+)]^{2+})</td>
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<td>713.1997</td>
<td>([\text{Ni}_2(\text{mftbp})(\text{diamine-H}_2\text{O})(\text{diamine-H})(\text{H}_2\text{O})_4]+)</td>
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<td>1180.2672</td>
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<td>1180.4305</td>
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<td>1213.2889</td>
<td>([\text{Ni}_2(2+)(\text{EtOH})(\text{MeOH})_2]+)</td>
<td>1213.5703</td>
</tr>
</tbody>
</table>

\[(\text{diamine})^{2+} = \text{C}_3\text{H}_{10}\text{N}_2\text{O}\]

\[(\text{mftbp})^{2+} = \text{C}_2\text{H}_5\text{H}_4\text{O}_4\]

\[(2+2)^{2+} = \text{C}_{52}\text{H}_{66}\text{N}_6\text{O}_6\]

\[(3+3)^{2+} = \text{C}_{76}\text{H}_{60}\text{N}_6\text{O}_9\]

\[(4+4)^{2+} = \text{C}_{108}\text{H}_{148}\text{N}_8\text{O}_{12}\]
Reaction mixtures analysed after 5 h. of reflux were also examined in the range up to m/z 4000 to see a possible higher mass ions present in solution. Unfortunately no signals were observed above range of m/z 2000 (Fig. 5.23) and all observed peaks were discussed above.

![Graph A: Cu/dialdehyde/diamine/La/base 5 h. reflux up to m/z 4000](image)

![Graph B: Zn/dialdehyde/diamine/La/base 5 h. reflux up to m/z 4000](image)

![Graph C: Ni/dialdehyde/diamine/La/base 5 h. reflux up to m/z 4000](image)

Fig. 5.23 ESI-MS spectra acquired 5 h. after addition of base in the Route 1 experiments with La(III).

In all three experiments, TMNa(2+2) species were identified in the spectra as the major products. Na(I) was not used purposely and it is most likely that these adducts formed in the ESI-MS instrument. Consequently, it cannot be determined unambiguously that La(III) sandwich complexes were not in reaction mixture solution. As in experiment B, perhaps La(III) ion formed sandwich complex in which was replaced by sodium ion in the instrument as the signal related to this species is surprisingly very strong. In experiment with La(III) and Ni(II) as for Ba(II) and Ni(II), addition of hard metal and base resulted in some rearrangements in the system which supports the earlier observation that dinickel (2+2) macrocyclic systems are dynamic.
5.4.2. Route 2 experiments with La(III) and Cu(II)

Route 2 experiments were conducted with three different set of Cu(II) and La(III) salts and also with different dialdehyde:Cu:La ratios as shown in Fig. 5.24. Reaction mixtures were investigated only after addition of triethylamine since this is the key stage in formation of heteropolynuclear macrocyclic complexes.

Fig. 5.24 Route 2 experiments with La(III) and Cu(II).

The top spectra in Fig. 5.25 represent the reaction mixtures investigated 5 min. after addition of base. The expected peaks from the (4+4) or (3+3) La(III) complexes were not observed in all three experiments. As in the Route 1 experiments with La(III) a Na(I) adduct of the dicopper (2+2) complex, represented by peaks [Cu₂Na(2+2)]⁺ at m/z 989, was found to be the major macrocyclic species in the spectra. Additionally, in experiment C very low relative intensity peaks at m/z 1474 were found and assigned to the (3+3) macrocycle as [Cu₃Na(3+3)]⁺ and in experiment B only the organic fragments without isotope patterns for the Cu(II) ions are seen.
Relative Abundance

Fig. 5.25 Spectra acquired in the La(III) Route 2 experiments, 5 min. and 5 h. after addition of base to:
A) Cu(ClO$_4$)$_2$·6H$_2$O/LaCl$_3$/amine  
B) Cu(OAc)$_2$·4H$_2$O/La(OAc)$_3$·1.5H$_2$O/amine  
C) Cu(NO$_3$)$_2$·4H$_2$O/La(NO$_3$)$_3$·6H$_2$O/amine.

Reaction mixtures were examined after an additional 2 h. of reflux. They did not show any significant changes except for experiment A. The copper(II) perchlorate and lanthanum(III) chloride reaction mixture (bottom spectrum in A) showed triply charged peaks at m/z 1352. The charge and the mass of the ion suggests formation of large complex including La(III) ion. In order to investigate probable formation of species resulting with mass fragments above m/z 2000 this reaction mixture was acquired in mass range up to m/z 4000. The spectrum, together with expanded ranges showing doubly and triply charged peaks, is shown in Fig. 5.26.

Fig. 5.26 Spectrum of the Cu(ClO$_4$)$_2$·6H$_2$O, LaCl$_3$, diamine and base reaction mixture after 2 h. of reflux acquired up to m/z 4000 together with the expanded ranges showing doubly and triply charged peaks.
The triply charged peaks at m/z 1353 and doubly charged peaks at m/z 2079 can be assigned to either a dimer molecule made of two (4+4) tetracopper macrocyclic species, or an (8+8) condensate coordinating eight Cu(II) and one La(III) ions, peaks \([\text{LaCu}_8(8+8)(\text{MeOH})(\text{H}_2\text{O})]^3^+\) and \([\text{LaCu}_8(8+8)(\text{ClO}_4)(\text{MeOH})(\text{H}_2\text{O})]^2^+\). These cannot be assigned unambiguously because there is no more supportive analytical data confirming their existence in solution and the m/z match between the experimental and calculated data is not as good as observed in the other systems. However, the singly charged peaks at m/z 2299 are undoubtedly related to the \([\text{LaCu}_4(4+4)(\text{ClO}_4)(\text{diamine})(\text{H}_2\text{O})+\text{e}^-]^+\) species which implies possible formation of a dimer ion made from two \([\text{LaCu}_4(4+4)]^3^+\) ions.

In summary in Route 2 experiments with La(III), with one exception, the anticipated \([\text{LaCu}_3(3+3)]^3^+\) or \([\text{LaCu}_4(4+4)]^3^+\) complexes were not observed. As in Route 1 experiments, the major species identified in reaction mixtures were assigned to the \([\text{Cu}_2\text{Na}(2+2)]^+\) fragments appearing at m/z 989. Also weak signals representing the \([\text{Cu}_3\text{Na}(3+3)]^+\) at m/z 1474 were found. It seems that ESI-MS is not suitable for investigation of these methanolic/ethanolic solutions with La(III) template system as the La(III) species do not fly on the instrument. This was evidently observed in experiment B where only low mass organic fragments appeared on the spectra. La(III) does however act as template in this reaction route, as was established by X. Ma\textsuperscript{137} using MALDI to analyse solid products.

High mass multiply charged peaks were identified for only one combination. Triply charged peaks \([\text{LaCu}_8(8+8)(\text{MeOH})(\text{H}_2\text{O})]^3^+\) at m/z 1353 and doubly charged \([\text{LaCu}_8(8+8)(\text{ClO}_4)(\text{MeOH})(\text{H}_2\text{O})]^2^+\) at m/z 2079 revealed possible formation of a LaCu\textsubscript{8} complex, as the (8+8) condensate or dimer of two (4+4) ions. Most likely they are related to the dimer because peaks at m/z 2299 were also observed for \([\text{LaCu}_4(4+4)(\text{ClO}_4)(\text{diamine})(\text{H}_2\text{O})_2+\text{e}^-]^-\).
5.4.3. Route 3 experiment with La(III) and Cu(II)

Following the Route 3 procedure described in previous chapters, La(III) was refluxed overnight with H$_2$mtfbp, 1,3-diaminopropan-2-ol and triethylamine before the Cu(II) salt was introduced. A schematic representation of this experiment is shown in Fig. 5.27.

![Schematic diagram of Route 3 experiment with La(III) and Cu(II)](image)

Fig. 5.27 Route 3 experiment with La(III) and Cu(II).

Two metal ions studied in earlier Route 3 experiments produced different results. Ba(II) ion led to a mixture of free macrocyclic ligands with the (2+2) as the major product, then after addition of Cu(II) it yielded the sandwich complex {Ba[Cu$_2$(2+2)]$_2$}$^{2+}$. Ca(II) ion produced both, the (2+2) condensate and a [H$_3$Ca$_6$(6+6)(NO$_3$)]$^{2+}$ species which was able to coordinate three Cu(II) ions. Therefore, if La(III) acts similarly to Ba(II), a mixture of free macrocycles should be observed. If it behaves alike Ca(II), large pseudocalixarene complexes together with the (2+2) free macrocyclic ligand should result.

The top spectrum in Fig. 5.28 shows the La(III), H$_2$mtfbp, diamine and base reaction mixture after overnight reflux. Peaks at m/z 845 and m/z 867 are assigned to the (2+2) free macrocyclic ligand with and without Na(I) ion. The doubly charged peaks at m/z 1136, 1172, and 1683 are assigned to La(III) related pseudocalixarene species. [La$_4$(4+4)(H$_2$O)$_2$+2e$^-$]$^{2+}$, [La(4+4)(H$_2$O)$_6$+2e$^-$] and [La$_3$H$_7$(7+7)]$^{2+}$ respectively.
Fig. 5.28 Spectra acquired in the “3+3” experiment with La(III) and Cu(II).

The middle spectrum in Fig. 5.28 was recorded after addition of Cu(NO$_3$)$_2$·3H$_2$O. Introduction of the transition metal results in immediate formation of the dicopper(II) (2+2) complex represented by peaks [Cu$_2$Na(2+2)]$^+$ at m/z 989 and the tetracopper(II) (2+2) [Cu$_4$(2+2)(MeOH)(OH)-2H]$^+$ shown by peaks at m/z 1141. Formation of tetranuclear complex can be explained by the fact that base fully deprotonates phenols and alcohols of macrocycle which promotes formation of the tetracopper(II) species. The doubly charged peaks assigned to La(III) adducts are no longer observed. This implies that any larger species are either broken up or not flying as Cu adducts.

Finally, the bottom spectrum in Fig. 5.28 recorded after 5 h. shows that additional reflux does not cause any significant changes, except that low relative intensity peaks appear at m/z 1626 which can be attributed to the pentacopper complex of (3+3) species [Cu$_5$(3+3)(MeOH)(OH)-2H]$^+$.

La(III) like Ca(II) acts as a template without transition metal in the condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol. Although, on long reflux, La(III) template produces different reaction mixture. Among the products a mixture of tri- and tetralanthanide species of the (7+7) and (4+4) Schiff base condensates can be identified. Formation of pentacopper compound after addition of Cu(II) and fact that La(III) related species are not present anymore in the spectra of reaction mixtures might suggest that Cu(II) products form from the La(III) species by transmetallation reactions.
5.4.4. Route 4 experiments with La(III)

Formation of La(III) metal cluster with H$_2$mftbp dialdehyde was investigated in ESI-MS experiments with Cu(NO$_3$)$_2$·3H$_2$O (A) and Zn(NO$_3$)$_2$·6H$_2$O (B). In both experiments H$_2$mftbp, La(NO$_3$)$_3$·6H$_2$O and transition metal salt were reflux for 30 min. before introduction of triethylamine and 30 min. before 1,3-diaminopropan-2-ol was introduced. After each addition samples were extracted for ESI-MS analysis. A schematic representation is shown in Fig. 5.29.

![Schematic representation of Route 4 experiments with La(III)](image)

In the Ba/Cu and Ba/Ni Route 4 experiments addition of triethylamine caused full deprotonation of methylenediphenols which led to the fast formation of [BaCu$_4$(mftbp)$_4$]$_2^{2+}$ and [BaNi$_3$(mftbp)$_3$(MeOH)(EtOH)$_2$·H$_2$O]$^+$ assemblies. The La/Cu reaction mixtures, presented on the left side in Fig. 5.30, showed no evidence of such [LaCu$_n$(mftbp)$_n$]$_3^{3+}$ formation. The highest mass fragments observed (after addition of base) at m/z 1091 were assigned to [NaH(mftbp)(base)$_3$(MeOH)]$^+$ species. The Cu(II) related peaks were found at m/z 577 and were attributed to [CuH(mftbp)(base)(EtOH)]$^+$ ion. Also there is no indication in ESI-MS of reaction between the possible cluster and diamine. The major peak in the spectrum after addition of diamine is due to a low mass ion and does not show characteristic metal ion isotope distribution pattern. Surprisingly, under the conditions of this experiment, in contrast to the other experiments with Cu(II) where several Cu(mftbp)(diamine) fragments were observed, the only Cu(II) related species peaks are observed at m/z 577.
The spectra of La/Zn reaction mixtures are shown on the right side in Fig. 5.30. In contrast to La/Cu experiment, addition of base to La(III), Zn(II) and dialdehyde reaction mixture resulted in formation La(dialdehyde) adducts. The \([\text{LaH}_7\text{(mftbp)}_4]^{2+}\) cation is represented by doubly charged peaks at m/z 621 and the \([\text{LaH}_5\text{(mftbp)}_3]^{2+}\) species is represented by doubly charged peaks at m/z 805. Addition of diamine to this solution resulted in a spectrum where major compound is represented by peaks at m/z 266. La(III) related peaks are gone, possibly the lanthanum assemblies break up and formation of imine bonds starts from the basic subcomponents. After 26 h. of reflux, the (2+2) macrocyclic species can be identified, the \([\text{Zn}_3(2+2)(\text{OH})]^+\) complex due to peaks at m/z 989 and trizinc give rise to doubly charged peaks \([\text{Zn}_3(2+2)(\text{EtOH})_3(\text{MeOH})]^{2+}\) at m/z 603. The doubly charged peaks at m/z 692 were assigned to trizinc and lanthanum fragments \([\text{Zn}_3\text{La}(2+2)(\text{NO}_3)(\text{MeOH})_2(\text{EtOH})(\text{H}_2\text{O})_2+2e^\cdash]^2+.\]

It appears that zinc is not acting as a template together with La(III) as there is no evidence of formation of (3+3) or (4+4) products. La(III) ion holds the dialdehyhdes together as Ba(II) in formation of \([\text{BaCu}_4(4+4)]^{2+}\) complex, but zinc does not play its role predicted by double template formation mechanism. La(III) alone probably is not templating formation of (3+3) or (4+4) macrocycle so La(dialdehyde) species cannot be transformed into a macrocycles and they disassemble. Then Zn(II) templates formation of the of (2+2) macrocycle which is found in spectrum after 26 h. of reflux.
5.4.5. Summary of La(III) experiments

In Route 1 experiments with La(III) and transition metals sodium adducts of the TM_2(2+2) macrocycle were identified as the major macrocyclic specie in ESI-MS. It is not clear why these peaks were so strong as sodium was not used intentionally in any of these experiments. Perhaps samples were contaminated with Na(I) compound before they were introduced on the instrument. Only La/Ni template system produced high mass doubly charged signals assigned to \{La[Ni_2(2+2)]_2(OH)(diamine)_2\}^{2+} and \{La[Ni_2(2+2)]_2(OH)(diamine)_3(H_2O)\}^{2+} sandwich species.

In Route 2 experiments, three combinations of Cu(II) and La(III) salts were used and in one case [Cu(ClO_4)_2·6H_2O and LaCl_3] high mass triply and doubly charged peaks were observed. They were assigned to either [LaCu_8(8+8)(MeOH)(H_2O)]^{3+} or \{La[Cu_4(4+4)]_2(MeOH)(H_2O)\}^{3+} ions which suggests that La(III) is involved in template processes as Cu(II) ion can produce only a (2+2) macrocycle. Again [Cu_2Na(2+2)]^{+} related species were the major components identified in the spectra.

In a Route 3 experiment, La(III) like to Ca(II) acted alone as a template in condensation between H_2mftbp and 1,3-diaminopropan-2-ol. This resulted in formation of [La_3H_7(7+7)]^{2+} also probably [La_4(4+4)(H_2O)_2+2e^{-}]^{2+} and, [La(4+4)(H_2O)_6+2e^{-}] macrocyclic complexes.

The ability of La(III) to function as a central metal in double template processes was confirmed in La(III) and Zn(II) Route 4 experiment where clean spectrum of La/Zn/dialdehyde/base reaction mixture showed [LaH_5(mftbp)_3]^{2+} and [LaH_7(mftbp)_4]^{2+} assemblies. However these were not transformed into macrocycles after addition of diamine. This and the fact that additional reflux resulted in formation of (2+2) macrocycle, implies that Zn(II) does not work together with La(III) as a template system.

The anticipated [LaTM_3(3+3)]^{2+} and [LaTM_4(4+4)]^{2+} or \{La[TM_2(2+2)]_2\}^{2+} were not identified in most of ESI-MS experiments. This could be because they were not stable under conditions in which samples were acquired and they do not reach the ms detector. Also, because the samples were diluted with MeOH, there is a possibility of a solvent effect and perhaps a softer solvent such as acetonitrile needs to be used for data.
acquisition. A diagram summarising distribution of products observed in ESI-MS via four described routes for La(III) ion is shown in Fig. 5.31.

Fig. 5.31 La(III) template synthesis of large pseudocalixarenes.
5.5. Other ESI-MS experiments

5.5.1. Does the choice of diamine or Ba(II) and Cu(II) salts affect formation of the (4+4) macrocycle based on $H_2\text{mftbp}$?

Formation of $[\text{BaCu}_4(4+4)]^{2+}$ with 1,3-diaminopropane and diethylamine as base (this selection was made mainly due to availability reasons) was examined in Route 2 experiment (A) where $H_2\text{mftbp}$, $\text{Cu(ClO}_4)_2\cdot 6\text{H}_2\text{O}$ (1 equiv.) and $\text{Ba(ClO}_4)_2\cdot 3\text{H}_2\text{O}$ (0.25 equiv.) were refluxed for 30 min. and then the diamine was added to the reaction mixture followed by base. After 1 h. of reflux reaction mixture was investigated by ESI-MS. Acquired spectrum is shown in Fig. 5.32 A. At this stage, $[\text{BaCu}_4(\text{mftbp})_4]^{2+}$ clusters with two and three diamines condensed, giving rise to doubly charged peaks for $[\text{BaCu}_4(2:2)(\text{mftbp})_2]^{2+}$ at $m/z$ 966 and $[\text{BaCu}_4(3:3)(\text{mftbp})]^{2+}$ at $m/z$ 985 respectively, is the majority in solution. Reaction mixture also contains some of $[\text{BaCu}_3(3+3)]^{2+}$ species, giving rise to doubly charged peaks at $m/z$ 816. Doubly charged peaks with small relative intensity at $m/z$ 1004 represent the (4+4) condensation product for 1,3-diaminopropane. Similarity with the earlier Route 2 experiments confirms that minor change of diamine and base does not change the mechanism of macrocycle formation.

Fig. 5.32 Spectra of reaction mixtures A) $\text{Ba/Cu/1,3-diaminopropene/diethylamine}$ and B) $\text{BaCl}_2/\text{CuCl}_2$/base, with schematic representation of experiments.
In experiment B formation of the intermediate cluster \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) was investigated for Ba(II) and Cu(II) chlorides. As described in Chapter 3 chloride as a good coordinating ligand might be expected to affect formation of this intermediate species. In experiment conducted via Route 4, both metals salts with dialdehyde were refluxed for 30 min. and then base was introduced. Reflux was continued for 30 min. when reaction mixture was investigated by ESI-MS. The spectrum of reaction mixture investigated after 30 min. of reflux from addition of triethylamine to the H\text{2mftbp}, CuCl\text{2}, BaCl\text{2} solution (Fig. 5.32 B) shows the expected peaks \([\text{BaCu}_4(\text{mftbp})_4]^{2+}\) at m/z 928 which demonstrates that the counter ion does not have an effect on the processes undergoing in the reaction mixture.

### 5.5.2. Route 2 experiments with H\text{2mfmp} and H\text{2mfpp} dialdehydes and Ba/Cu metal system

The other two synthesised methylenediphenoldialdehydes described in chapter 2 were also examined in Route 2 experiments with Ba(II) and Cu(II). In experiment A conducted on LCT ToF instrument, H\text{2mfmp} dialdehyde was refluxed with Ba(ClO\text{4})\text{2}∙3H\text{2}O and Cu(ClO\text{4})\text{2}∙6H\text{2}O and then 1,3-diaminopropan-2-ol was added followed by triethylamine. Reflux was continued overnight when reaction mixture solution was investigated by ESI-MS (Fig. 5.33 A). In experiment B, both metal salts were refluxed together with H\text{2mfpp} dialdehyde and then 1,3-diaminopropan-2-ol was added followed by base. A schematic representation of this experiment with spectrum and peak assignments is shown in Fig. 5.33 B.
In experiment A, overnight reflux produced a mixture of macrocyclic species identical to that observed for H$_2$mftbp dialdehyde. Both [BaCu$_3$(3+3)]$^{2+}$ and [BaCu$_4$(4+4)]$^{2+}$ based on H$_2$mfmp can be indentified in spectrum giving rise to doubly charged peaks at m/z 668 and m/z 867 respectively.

Reaction mixture from experiment B analysed 5 min. after addition of base showed expected peaks from [BaCu$_4$(4+4)]$^{2+}$ based on H$_2$mfpp at m/z 1116. This proved that Ba(II) and Cu(II) also double template condensation between H$_2$mfpp and 1,3-diaminopropan-2-ol as found for the other methylenediphenoldialdehydes. The weak signal from this species in comparison to H$_2$mfmp could be explained by the poor solubility of macrocyclic compounds derived from H$_2$mfpp in MeOH.

In summary, for all three dialdehydes (H$_2$mftbp, H$_2$mfmp and H$_2$mfpp) the Ba/Cu system was found to undergo double template condensation with 1,3-diaminopropan-2-ol leading to [BaCu$_4$(4+4)]$^{2+}$ which was identified by ESI-MS. For H$_2$mftbp precursor it was established that change of metal salt from perchlorate to chloride, diamine from 1,3-diaminopropan-2-ol to 1,3-diaminopropane and base from triethylamine to diethylamine does not to affect the double template processes as [BaCu$_4$(mftbp)$_4$]$^{2+}$ and [BaCu$_4$(4+4)]$^{2+}$ products were observed in ESI-MS spectra.
5.6. Conclusions

1) The Ba/Zn template condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol gives similar products to Ba/Cu system described in Chapter 4. [BaZn$_4$(4+4)]$^{2+}$ and [BaZn$_2$(2+2)]$_2$$^{2+}$ were successfully identified by ESI-MS however they were not the major species found in the spectra. In all experiments with this system {Na[Zn$_2$(2+2)]}$^+$ or [NaZn$_4$(4+4)]$^+$ gave the strongest signals and so far it is not clear why Ba(II) ion is being replaced by Na(I) and how this significant amount of Na(I) is introduced to the solution.

2) The Ba/Ni combination also template formation of [BaNi$_4$(4+4)]$^{2+}$ and {Ba[Ni$_2$(2+2)]$_2$$^{2+}$. In contrast to the Ba/Cu system, [BaNi$_3$(3+3)(diamine)$_2$]$^{2+}$ is found as a byproduct of the condensation. The two diamines included in the assigned formula suggest that the formation of pseudocalixarene macrocycle might not be completed. Moreover this system appears to be dynamic as the dinickel (2+2) complex after addition of Ba(II) and base appears to be rearranging into the larger macrocyclic species. This was indicated by Ni(dialdehyde)(diamine) fragments observed in ESI-MS spectra. Route 4 experiment produced the [BaNi$_3$(mftbp)$_3$(MeO)(EtOH)$_2$H$_2$O]$^+$ cluster but there was no evidence of its transformation into the (3+3) macrocyclic species.

3) Ca(II) alone templates condensation between H$_2$mftbp and 1,3-diaminopropan-2-ol into a high mass species which was assigned as [H$_3$Ca$_6$(6+6)(NO$_3$)]$^{2+}$. This assignment was supported by results of ms/ms experiment in which this ion was very stable and resulted complicated fragmentation pattern. [H$_3$Ca$_6$(6+6)(NO$_3$)]$^{2+}$ is able to accommodate three Cu(II) ions but does not interact with Zn(II) possibly due to the geometrical preferences of the transition metal ions.

4) Experiments with La(III) ions did not unambiguously answer the question of whether La(III) is involved in double template formation of pseudocalixarene macrocycles. The distribution of products also remains obscure as all employed routes resulted in observation of the [TM$_2$Na(2+2)]$^+$ ion in the ESI-MS spectra. The macrocyclic species from La/Ni and La/Cu experiments were not assigned ambiguously.
5) Double template effects in the condensation between H₂mftbp and 1,3-diaminopropan-2-ol with Ba(II) and Cu(II) was found to be not affected by change of: dialdehyde, metal counter ion, base and diamine.

For all the metal combinations investigated in this chapter ms/ms experiments are need to distinguish between (4+4) and sandwich (2+2) species. For La(III) experiments a softer solvent such as acetonitrile could be examined as well as different set of conditions on the ms instrument. Ba/Ni system also could be investigated over an extended reflux to characterise thermodynamic products of the possible rearrangements ongoing in the reaction mixture.
Suggestions for further work

Achieving good quality crystals of \([\text{Cu}_3(2+2)]^{2+}\) complex would allow examination of bond lengths to investigate possible delocalization of electrons in the macrocyclic ligand which might be redox non-innocent. Also, electrochemical methods could be employed to investigate the oxidation state of Cu(II) ions and ligand in the complex. Furthermore, a possible formation and isolation of \(\text{TM}_2\text{Cu}(2+2)\) complexes could be investigated as well as their magnetic properties, as the Cu(II) readily occupies the central position of the macrocycle. However, in case of good coordinating ligand such as chloride, it produces only dinuclear complex so CuCl\(_2\) should be investigated in the condensation between H\(_2\)mftbp and 1,3-diaminopropan-2-ol in stoichiometries promoting formation of the tri- and tetracopper(II) complexes to see if the chloride ion will prevent their formation.

A minor change of diamine showed that a \([\text{BaCu}_4(4+4)]^{2+}\) complex still could be achieved \(\text{via} \, [\text{BaCu}_4(\text{mftbp})]^{2+}\) in the double template process. However, experiments with the Ba/Cu system and diamines of different lengths should be investigated (e.g. 1,5-diaminopentan-3-ol or \(o\)-phenylenediamine). This could result in a wider range of heteropolynuclear complexes and also would establish the broader application of the mechanism.

The Ba/Zn and Ba/Ni reaction mixtures need to be examined in the ms/ms experiments to distinguish between the macrocyclic products. Perhaps different diamines might produce cleaner reaction mixtures which would allow structural characterisation of species observed by ESI-MS in those reaction mixture solutions.

For the La/TM system, the ESI-MS data acquisition could be run in the manual mode and in solvents softer than methanol to find optimum conditions for investigation of lanthanum ion template processes. Possible isolation of the La/TM heteronuclear complexes would allow studying their potential application as the single molecular magnets.

Finally, reasonably clean reaction mixture (by ESI-MS) of Ca, H\(_2\)mftbp, 1,3-diaminopropan-2-ol and base might result in crystals suitable for X-ray single crystals experiments which would unambiguously establish the structure giving rise to doubly charged peak at m/z 1413 tentatively assigned to \([\text{H}_3\text{Ca}_6(6+6)(\text{NO}_3)]^{2+}\) species.
Chapter 6

EXPERIMENTAL
E.1. General conditions

E.1.1. Solvents and reagents

Solvents for preparative chemistry were chemically pure grade or HPLC grade and were used without further purification. An absolute ethanol was used in syntheses of macrocycles and in the reactions monitored by ESI-MS unless otherwise stated. Chemicals that were not synthesised in this work were Analar or reagent grade and were used without further purification.

E.1.2. Instrumentation

$^1$H NMR spectra (400MHz) were recorded on Bruker AC250FT or DPX-400MHz spectrometer in CDCl$_3$ unless otherwise stated. Chemical shifts [δ] in ppm are relative to SiMe$_4$.

Infrared Spectra were recorded as KBr discs in the range 4000-500 cm$^{-1}$ on Perkin Elmer Paragon 1000 PC Fourier Transform Spectrometer or a Perkin Elmer Spectrum 100 Spectrometer.

Elemental Analyses were performed by Mrs Pauline King or Mr Alistair Daley within the Chemistry Department on an EAI Exeter analytical CE-440 elemental analyzer.

Low resolution Fast Atom Bombardment (FAB) spectra were recorded by the EPSRC National Mass Spectrometry Service Centre unless otherwise stated and low resolution EI spectra were recorded within the Chemistry Department Mass Service.

Single crystal X-ray diffraction data were collected at 150K on Bruker Apex II CCD diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at Loughborough University. The structures were solved by direct methods and refined by full-matrix squares on F$^2$. The Bruker SHELXTL$^{200}$ software was used for structure solution and refinement. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were inserted at calculated positions using a riding model, unless otherwise stated. The crystallography graphics were done using Mercury 2.4$^{201}$ and Ortep 3 for Windows$^{202}$ and were rendered in POV-Ray$^{81}$ software.
E.1.3. Electrospray ionisation mass spectrometry

Electrospray ionisation mass spectrometry experiments were performed on three instruments. Initial work was carried on a LCT ToF mass spectrometer equipped with the time of flight microchannel plate detector (supplied by Waters Corp. Manchester, UK) in the Centre for Analytical Science at Loughborough University. The data were processed with isotope pattern simulation using Waters MassLynx V4.1SCN639 software. A sodium formate solution was used for the instrument calibration in the range 100-2500 m/z. All data were acquired in positive ion mode with ESI capillary voltage set to 1.5 kV and the cone voltage to 35V. The nitrogen desolvation and cone gas flow rates were 20 and 290 L·h⁻¹ respectively with source and desolvation temperatures set to 120 °C. Samples were introduced to the ESI source using a syringe pump system at constant flow rate of 10 µL·min⁻¹. The voltages at RF lenses and MCP detector were RF1 5 V, RF2 2 V and MCP detector 2500 V.

The Route 1 and Route 2 experiments with Ba(II) and Cu(II) and all the MS/MS experiments were performed on Waters Synapt HDMS system (Waters, Manchester, UK) by the Experimental officer Dr Jim Reynolds in the Centre for Analytical Science at Loughborough University. The spectrometer operated in positive ion mode with an ESI voltage set to 3 kV and the cone voltage to 20 V. The nitrogen desolvation and cone gas flow rates were set to 900 L·h⁻¹ and 30 L·h⁻¹ respectively with a source temperature of 120 °C and desolvation gas temperature set to 300 °C. Samples were prepared according to the same procedure as for the LCT ToF instrument and were infused directly into ESI source at flow rate of 10 µL·min⁻¹. The instrument was calibrated prior use with sodium formate solution in the range 200-2500 m/z. The acquired data were processed using Waters MassLynx V4.1SCN639 software. The tandem MSMS experiments were carried out with various collision energies ranging from 50 V up to 120 V.

The majority of data were recorded on the Thermo Fisher Exactive Orbitrap mass spectrometer coupled to an Advion TriVersa Nanomate injection system by Mrs Sheena Grainger and Dr Mark Edgar at the departmental mass spectrometry service at Loughborough University. The instrument was used in positive ion mode and samples were delivered to the ESI source using the nanomate chip base system. The spray voltage was set to 1478 V and the capillary voltage to 92.5 V. The temperatures were
set as follows, 191 °C at capillary, 27 °C at analyser and 46 °C at the ESI source. No nebulizer or sheet gas flows were employed. The data were processed using Thermo Xcalibur software version 2.1.0.1139 provided by Thermo Scientific. The isotope pattern calculations were carried on the Thermo Xcalibur Qual Browser. The full sets of parameters are included in the ESI-MS peak assignments (Appendix 3).

E.1.3.1. ESI-MS sample preparation protocol

Samples acquired on the Waters LCT TOF and Synapt HDMS spectrometers were prepared according to the same procedure. Approximately 0.5 mL of the reaction mixture solution was taken out from the refluxing reaction mixture and placed into a sample vial. Then 25 µL was taken out and diluted with 175 µL of HPLC grade MeOH to make 200 µL solution (approx. 10^-4 M) in a screw top sample vial. Upon dilution and cooling the reaction was found to be effectively quenched. Next samples were transported to the Centre for Analytical Science and acquired on the appropriate instrument within approx 1 min. from the extraction.

Samples acquired on the Thermo Fisher Exactive Orbitrap instrument within the departmental mass spectrometry were prepared as follows. 100 µL of the reaction mixture was taken out from the 0.5 mL removed from the refluxing reaction mixture, and diluted up to 500 µL with methanol (quenched upon dilution). Next samples were carried to the departmental mass spectrometry service. Then 1 drop of that prepared solution (approx. 25 µL) was diluted with 1 mL of MeOH giving an approximate final concentration of 10^-6 mol·dm^-3. This was placed on the well plate from which the sample was injected. Data were acquired at various times (calculated from the moment of extraction).
PART A: Synthetic experiments

E.2. Chapter 2: Synthesis of 4-substituted methylenediphenol dialdehydes

E.2.1. Synthesis of 2,2′–methylene-bis-[(6-hydroxymethyl)-4-tert-butylphenol]

(H₂mhtbp; 2.1)

Freshly ground 4-tert-butylphenol (45 g, 0.30 mol) and 60 mL of 37% formaldehyde (0.8 mol) were placed in a three neck flask under an atmosphere of N₂. NaOH solution (0.35 mol; 140 mL) was added and mixture was heated for 8 days at 50 °C under a nitrogen atmosphere. The resulting yellowish resinous precipitate was filtered off and dissolved in 50 mL of acetone. The white solid precipitating from acetone solution was removed by filtration. The acetone solution was acidified by addition of 200 mL of 50% acetic acid, then it was diluted with 100 mL of water and extracted several times by ca. 300 mL of Et₂O and ca. 300 mL of ethylacetate. The organic extracts were combined, washed with 200 mL of water and dried over anhydrous Na₂SO₄. The solvents were rotary evaporated to afford 30 g of oil which was redissolved in toluene and precipitated by addition of light PET ether. The turbid solution was left in a fridge overnight. 9 g of 4-tert-butyl phenol dimer (H₂mhtbp) in 16% yield was collected by filtration under vacuum.

Melting point 145 – 147 °C

TLC Rᵢ = 0.30 in chloroform:acetone 5:1 (v/v)

¹H NMR (d-CHCl₃), δ [ppm]: 8.29 (2H, ArOH, s); 6.67 (2H, ArH, s); 6.95(2H, ArH, s); 4.67(4H, CH₂OH, s); 3.77(2H, CH₂, s); 2.16(18H, C(CH₃)₃, s)

EI - MS [m/z] (relative intensity) and (peak assignment calc.) 395 (100%), {[H₃mhtbp+Na]⁺, 395}

CHN Calc.: C 74.16%, H 8.66% for [C₂₃H₃₂O₄]

Found: C 74.2%, H 8.9%

IR(KBr), ν [cm⁻¹]: 3420 (s, OH); 1208 (s, ArOH); 875 (m, 1,2,3,5 tetrasubstituted ArH)
E.2.2. Synthesis 2,2’–methylene-bis-[(6-hydroxymethyl)-4-methylphenol] 
\((H_2mhmp; \text{2.2})\)

\[
\begin{align*}
\text{OH} + 2 \text{HCHO} & \quad \xrightarrow{1. \text{K}_2\text{CO}_3, \ 6 \text{ h}, \ 60 ^\circ \text{C}} \quad \text{OH} \quad \xrightarrow{2. \text{stirring overnight}} \quad \text{OH} \\
\text{OH} & \quad \xrightarrow{3. \text{HCl (35\%)}} \quad \text{OH}
\end{align*}
\]

\(\text{K}_2\text{CO}_3\) (107 g, 0.78 mol) of was dissolved in 1 L of distilled water and added to a mixture of 52.7 mL (0.5 mol) of 4-cresol and 157 mL of 37% formaldehyde (2.1 mol). The solution was heated at 60 °C for 6 h. and stirred at ambient temperature overnight. A yellow solid was obtained by addition of 180 mL of 12M HCl followed by vacuum filtration. A mixture of ethylacetate:cyclohexane 1:1 (v/v) was prepared and used to wash all impurities from yellow solid which finally was dried in air to result 21.74 g of off-white solid. (Yield 31%)

**Melting point** 139 – 141 °C

**TLC** \(R_f = 0.34\) in chloroform:acetone 5:1 (v/v)

**\(^1\text{H NMR}(d\text{-CHCl}_3), \delta [ppm]:** 8.33 (2H, ArOH, s); 6.91 (2H, ArH, s); 6.67 (2H, ArH, s); 4.69 (4H, CH\(_2\)OH, s); 3.77 (2H, CH\(_2\), s); 2.11 (6H, CH\(_3\), s)

**EI - MS [m/z] (relative intensity) and (peak assignment calc.)**

270 (95\%), \([H_2mhmp - H_2O]^+\); 289 (33\%), \([H_2mhmp + H]^+\);

311 (100\%), \([H_2mhmp + Na]^+\)

**CHN Calc.:** C 65.6\%, H 6.4\% for \([C_{17}H_{20}O_4]\)

**Found:** C 65.5\%, H 6.4\%

**IR\((KBr), \nu [cm^{-1}]:** 3310 (s, OH); 3006 (w, =CH\(_2\) ); 1481 (s, C-O); 1231 (s, Ar-OH)
E.2.3. Synthesis of 2,2’-methylene-bis-[{(6-hydroxymethyl)-4-phenylphenol} (H$_2$mhpp; 2.3)

A mixture of 15.3 g (0.09 mol) of 4-phenylphenol and 75 mL of 37% formaldehyde (1 mol) was cooled in an ice bath. KOH (10.2 g; 0.18 mol) was added within 15 minutes and stirred for 4 days at 40 °C. The resulting yellow paste was diluted in a ice-cold water and acidified with 80 mL of 10% HCl. Addition of acid changed the colour of solution into white. The precipitate was collected by filtration. The crude product showed two major components by TLC in chloroform:acetone 10:1 (v/v). Separation was achieved by heating with 100 mL of boiling chloroform. The insoluble fraction was collected by filtration and washed twice with 20 mL of chloroform and 50 mL of n-hexane. Two crystallizations from methanol gave 9.0 g of H$_2$mhpp in 49% yield.

**Melting point** 137 – 139 °C, decomposition to white melt

**TLC** R$_f$ = 0.26 in chloroform:acetone 5:1 (v/v)

**CHN** Calc.: C 71.5%, H 5.7 % for [C$_{27}$H$_{24}$O$_4$K]

Found: C 71.6%, H 5.4%

**$^1$H NMR** (d-DMSO), δ [ppm]: 7.5-7.3 (14H, ArH, m); 4.66 (4H, CH$_2$OH, s); 4.03 (2H, CH$_2$, s)

**IR** (KBr), ν [cm$^{-1}$]: 3321 (s, OH); 1601 (s, Ar C=C); 1474 (m, C-O); 1254 (s, Ar-OH); 879 (m, 1,2,3,5 tetrasubstituted ArH)

**EI - MS** [m/z] (relative intensity) and (peak assignment calc.)

394 (95%), {[H$_2$mhpp - H$_2$O]$^+$, 394}; 412 (70%) { [H$_2$mhpp - e$^-$]$^+$, 412}; 435 (20%) {[H$_2$mhpp + Na]$^+$, 435}
E.2.4. Preparation of activated MnO₂
A 100 g of MnSO₄ was dissolved in 125 mL of boiling distilled water and stirred at 70-80 °C. To the stirred solution a solution of 90 g of KMnO₄ in 2.5 L water was added dropwise over 5 h. When the addition was ended, the MnO₂ was filtered off, washed with 3 litres of boiling water to remove all remaining KMnO₄ and dried in the oven over a few days (140°C) to yield 90 g of active MnO₂. (Yield 94%)

E.2.5. Oxidation of H₂mhtbp to 2,2'-methylene-bis[(6-formyl)-4-tert-butylphenol] (H₂mftbp; 2.4)

MnO₂ (10 g) was suspended in 700 mL of chloroform. To the suspension 2 g of H₂mhtbp was added and the mixture was stirred for 5 h. at room temperature. The MnO₂ was filtered off and the filtercake was washed with 300 mL of chloroform followed by 100 mL of acetone. The filtrates were evaporated to dryness and washed with hot EtOH to yield 1 g of yellow H₂mftbp upon cooling. Yield 50%.

Melting point 182-185 °C

TLC R₅ = 0.74 in chloroform

¹H NMR (d-CHCl₃), δ [ppm]: 11.20 (2H, CHO, s); 9.79 (2H, ArOH, s); 7.53 (2H, ArH, s); 7.30 (2H, ArH, s); 3.83 (2H, CH₂, s); 1.21 (18H, C(CH₃)₃, s)

EI - MS [m/z] (relative intensity) and (peak assignment calc.)

368 (100%), [{H₂mftbp - e⁻}⁺, 368}; 391 (50%) { [H₂mftbp+Na]⁺, 391}

IR(KBr), ν [cm⁻¹]: 3466 (s, OH), 1657 (s, C=O), 1262 (m, ArOH).

CHN Calc.: C 74.97%, H 7.66 % for [C₂₃H₂₈O₄]

Found: C 74.56%, H 7.88%
**E.2.6. Oxidation of H₄mhmtp to 2,2’-methylene-bis[(6-formyl)-4-methylphenol] (H₂mfmp; 2.5)**

MnO₂ (16 g) was suspended in 200 cm³ of dry THF and refluxed for 30 min. after which time 2.40 g of H₄mhmp was added. Reflux was continued for 4.5 h. Next manganese dioxide was filtered off and washed with 100 mL of hot dry THF, chloroform and finally with acetone. All the filtrates were evaporated to dryness. The resulting crude solid was dissolved in EtOH with heating, and left in a fridge overnight to afford 0.48 g of H₂mfmp after trituration and filtration. Yield 20%. Yellow crystals suitable for X-ray single crystal study were obtained by slow evaporation of a chloroform solution.

**Melting Point** 168-170°C decomposition, brown melt

**TLC** Rₜ = 0.74 in chloroform

**¹H NMR (d-CHCl₃), δ [ppm]:** 11.1 (2H, CHO, s); 9.81 (2H, ArOH, s); 7.34 (2H, ArH, s); 7.23 (2H, ArH, s); 3.94 (2H, CH₂, s); 2.21 (6H, CH₃, s)

**IR(KBr), ν [cm⁻¹]:** 3466 (s, OH), 1649 (s, C=O), 1262 (m, ArOH), 3070 (w, C=O)

**CHN Calc.:** C 71.82%, H 5.67% for [C₁₇H₂₀O₄]

**Found:** C 71.59%, H 5.97%

**EI-MS [m/z] (relative intensity) and (peak assignment calc.)**

307 (100%), {[H₂mfmp+Na]⁺, 307}
E.2.7. Oxidation of H$_2$mhpp to 2,2'-methylene-bis[(6-formyl)-4-phenylphenol] (H$_2$mfpp; 2.6)

11.2 g of dry MnO$_2$ was placed in a round bottom flask and 130 mL of dry THF was added in two portions: 90 mL and 40 mL to make a suspension. The suspension was refluxed for 30 min. and after that time 2.1 g of H$_2$mhpp was added with reflux maintained for another 3 h. After formation of dialdehyde was confirmed by TLC the reaction mixture was filtered off and the manganese dioxide filtercake was washed with 50 mL of dry THF followed by 100 mL of CHCl$_3$, 100 mL of acetone and 50 mL of Et$_2$O. All the filtrates were combined and evaporated to dryness. The resulting crude solid was recrystallised from absolute ethanol to produce 1.47 g of H$_2$mfpp with 70% yield. Yellow crystals suitable for X-ray single crystal study were obtained by slow evaporation of a chloroform solution.

**Melting point** 213-214°C

**TLC** $R_f = 0.74$ in chloroform

$^1$H NMR (d-CHCl$_3$), $\delta$ [ppm]: 11.29 (2H, CHO, s); 9.88 (2H, ArOH, s); 7.5-7.3 (14H, ArH, m); 4.1(2H, CH$_2$, s)

**IR(KBr), $v$ [cm$^{-1}$]:** 3447 (broad s, OH); 1663 (s, C=O); 1271 (s, ArOH)

**CHN Calc.:** C 79.4% H 4.9% for [C$_{27}$H$_{20}$O$_4$]

**Found:** C 79.0 % H 4.9%

**EI - MS [m/z] (relative intensity) and (peak assignment calc.)**

408 (100%), {[H$_2$mfpp-e$^-$]$^+$, 408}
E.3. Chapter 3 Formation of homo and heteronuclear complexes of (2+2) pseudocalixarene Schiff base macrocycles – an ESI-MS study


E.3.1.1. [Cu₂H₂(2+2)(ClO₄)(EtO)](H₂O)₆(MeCN)₂ (3.1)

H₂mfpp (0.200 g, 0.49 mmol) was refluxed in 80 mL of EtOH in the presence of NEt₃ (1 mL) for 15 min. and after that time Cu(ClO₄)₂·6H₂O (0.180 g, 0.49 mmol) in 10 mL of EtOH was added dropwise to the refluxed solution. Caution: perchlorate salts are potentially explosive and should be used in small quantities. The brown reaction mixture was refluxed for further 30 min. and then 1,3-diaminopropan-2-ol (0.044 g, 0.49 mmol) in 10 mL of EtOH was introduced dropwise. Reflux was maintained for 4 h. The resulting green solution was concentrated by half and left aside for slow evaporation. This afforded 0.144 g of green solid, which was analysed as [Cu₂(2+2)(ClO₄)(HNEt₃) (3.1a) was washed with EtOH and H₂O and set again for crystallisation from MeCN by slow evaporation. This produced 0.098 g (Yield 28%) of dark green powdery material for which analysis suggested a formation of a Cu(II) complex of overall formula [Cu₂H₂(2+2)(ClO₄)(EtO)](H₂O)₆(MeCN)₂ (3.1b).

3.1a:

CHN Calc.: C 63.41%, H 5.16%, N 5.61% for [Cu₂(2+2)(ClO₄)(Et₃NH)

Found: C 63.51%, H 4.56%, N 5.42%

3.1b:

IR(KBr), ν [cm⁻¹]: 3387 (s, OH); 1620 (s, C=N); 1543 (m); 1442 (s); 1273 (m, ArOH); 1041 (m, Cl); 763 (m) for [Cu₂H₂(2+2)(ClO₄)(EtO)](H₂O)₆(MeCN)₂

CHN Calc.: C 57.22%, H 5.32%, N 6.07% for

[Cu₂H₂(2+2)(ClO₄)(EtO)](H₂O)₆(MeCN)₂

Found: C 56.94%, H 5.63%, N 5.93%

FAB - MS [m/z] (relative intensity) and (peak assignment calc.)

307 (100%) (NOBA matrix peaks); 1049 (10%) {[Cu₂(2+2) + H]+, 1049}; 1071 (10%) {[Cu₂Na(2+2)]+, 1071}; 1111 (10%) {[Cu₂Na(2+2)(MeCN)]+, 1111}.
E.3.1.2. [Cu$_2$H$_2$(2+2)(Cl)](Cl)(EtOH)$_2$(Et$_2$O) (3.2)

H$_2$mfpp (0.150 g, 0.37 mmol) of and 0.050 g (0.37 mmol) of CuCl$_2$ were refluxed in 60 mL of EtOH for 30 min. and after that time 0.033 g of 1,3-diaminopropan-2-ol (0.37 mmol) in 10 mL of EtOH was added dropwise to the refluxed solution. Reflux was continued for 3 h. Then reaction mixture was evaporated to dryness, washed with EtOH and H$_2$O and set for crystallisation from a CH$_2$Cl$_2$ : EtOH mixture. The resulting pale green powdery precipitate was recrystallised from DCM by slow diffusion of Et$_2$O to yield 0.036 g of Cu(II) complex which was identified as [Cu$_2$H$_2$(2+2)(Cl)](Cl)(EtOH)$_2$(Et$_2$O).

IR(KBr), $\nu$ [cm$^{-1}$]: 3387 (s, OH); 1627 (s, C=N); 1543 (m); 1405 (s); 1273 (w, ArOH); 1203 (m); 1064 (s, Cl); 763 (m)

CHN Calc.: C 63.43%, H 5.64%, N 4.35% for [Cu$_2$H$_2$(2+2)(Cl)](Cl)(EtOH)$_2$(Et$_2$O)

Found: C 63.78%, H 5.26%, N 3.74%

FAB - MS [m/z] (relative intensity) and (peak assignment calc.)

289 (60%) (NOBA matrix peaks); 307 (100%) (NOBA matrix peaks); 1049 (20%)

{[Cu$_2$(2+2) + H]$^+$, 1053}; 1085 (10%) {[Cu$_2$H$_2$(2+2)(Cl)]$^+$, 1085}.

E.3.1.3 [Mn$_2$H$_2$(2+2)](OAc)$_2$(H$_2$O)$_2$ (3.3)

H$_2$mfpp (0.200 g, 0.49 mmol) and Mn(OAc)$_2$.4H$_2$O (0.120 g, 0.49 mmol) were dissolved in 100 mL of EtOH and brought to reflux. After 30 min. of reflux 1,3-diaminopropan-2-ol (0.044 g, 0.49 mmol) in 20 mL of EtOH was added dropwise to the solution and reflux was continued for 3 h. After that time the reaction mixture was evaporated to dryness to gave brown solid which was washed with EtOH and H$_2$O to produce 0.214 g of manganese complex in 72% yield.

IR(KBr), $\nu$ [cm$^{-1}$]: 3434 (s, OH); 1618 (s, C=N); 1443 (s, COO$^-$); 1264 (m, ArOH); 1030 (m); 763 (w)
**CHN** Calc.: C 64.74%, H 5.10%, N 4.72% for [Mn₂H₂(2+2)](OAc)₂(H₂O)₂

  Found: C 64.40%, H 4.66%, N 4.85%

**FAB - MS [m/z] (relative intensity) and (peak assignment calc.)**

289 (60%) (NOBA matrix peaks); 307 (100%) (NOBA matrix peaks);
1031 (20%) {[Mn₂(2+2) + H]⁺, 1031}; 1091 (10%) {[Mn₂H₂(2+2)(OAc)]⁺, 1091}.

**E.3.1.4[Zn₂H₂(2+2)](OAc)₂(H₂O)₄ (3.4)**

H₂mfpp (0.200 g, 0.49 mmol) and Zn(OAc)₂·2H₂O (0.112 g, 0.49 mmol) were dissolved in 80 mL of EtOH and brought to reflux for 15 min. After that time 1,3-diaminopropan-2-ol (0.044 g, 0.49 mmol) in 10 mL of EtOH was added dropwise to the refluxed solution and reflux was continued for 3 h. Then the reaction mixture was evaporated to dryness to give an orange solid which was washed with EtOH and H₂O to produce 0.194 g of Zn(II) complex in 64% yield.

**IR(KBr), v [cm⁻¹]:** 3438 (b,m, OH); 1630 (s, C=N); 1459 (s, COO⁻); 1280 (m, ArOH); 886(m); 763 (w)

**CHN** Calc.: C 61.77%, H 5.19%, N 4.51% for [Zn₂H₂(2+2)](OAc)₂(H₂O)₄

  Found: C 61.69%, H 5.36%, N 4.44%

**FAB - MS [m/z] (relative intensity) and (peak assignment calc.)**

207 (100%) (NOBA matrix peaks); 281 (95%) (NOBA matrix);
1051 (65%) {[Zn₂(2+2) + H]⁺, 1051}; 1073 (20%) {[Zn₂Na(2+2)]⁺, 1073};
1091 (15%) {[Zn₂Na(2+2)(H₂O)]⁺, 1091}. 
E.3.2. Synthesis and characterisation of heteronuclear TM₂M complexes (TM = transition metal M = group 1 or 2 metal ion) of (2+2) Schiff base macrocycles.

E.3.2.1. Trinuclear TM₂M complexes with group 1 metal ions (TM = transition metal M = group 1 metal ion)

E.3.2.1.1. [Cu₂Li(2+2)](Cl)(EtOH)₂ with H₂mfpp (3.5)

H₂mfpp (0.150 g, 0.36 mmol), CuCl₂ anhydrous (0.050 g, 0.36 mmol) and LiCl (0.010 g, 0.24 mmol) were dissolved in 60 mL of EtOH and brought to reflux. After 30 min. 1,3-diaminopropan-2-ol (0.033 g, 0.36 mmol) was added dropwise over 3 min. followed by 1 mL of NEt₃. The dark green reaction mixture solution was refluxed overnight and then was evaporated to dryness. The resulting green solid was washed with H₂O and allowed to dry in the air to yield 0.100 g of [Cu₂Li(2+2)]Cl(EtOH)₂ Yield 50%.

IR(KBr), ν [cm⁻¹]: 3387 (s, OH); 1620 (s, C=N); 1442 (s); 1273 (m, ArOH); 1049 (m, Cl); 763 (w)

CHN Calc.: C 64.97%, H 5.12%, N 4.74% for [Cu₂Li(2+2)](Cl)(EtOH)₂
Found: C 65.13%, H 5.03%, N 4.26%

FAB - MS [m/z] (relative intensity) and (peak assignment calc.)
307 (100%) (NOBA matrix peaks);
1053 (10%) {[Cu₂Li(2+2)]⁺, 1053}.

E.3.2.1.2. [Cu₂Li(2+2)](OH)(H₂O)₂ with H₂mfpp (3.6)

H₂mfpp (0.200 g, 0.49 mmol) was dissolved in 60 mL of EtOH, mixed with a solution of Li(NO₃) (0.035 g, 0.49 mmol) in 10 mL of EtOH and brought to reflux. After 30 min. 0.044 g (0.49 mmol) of 1,3-diaminopropan-2-ol in 10 mL was added dropwise followed by 1 mL of NEt₃. The reaction mixture was allowed to reflux for 18 h. and then Cu(ClO₄)₂·6H₂O (0.180 g, 0.49 mmol) was introduced. Reflux was maintained for
further 5 h. The dark green solid precipitating upon cooling was collected by filtration and identified as [Cu$_2$Li(2+2)]OH(H$_2$O)$_2$. (0.222 g, Yield 82%)

IR(KBr), $\nu$ [cm$^{-1}$]: 3476 (b, m, OH); 1634 (s, C=N); 1455 (s); 1278 (m, ArOH); 1083 (w); 768 (w)

CHN Calc.: C 65.01%, H 4.82%, N 5.06% for [Cu$_2$Li(2+2)](OH)(H$_2$O)$_2$

Found: C 65.24%, H 4.81%, N 5.49%

FAB - MS [m/z] (relative intensity) and (peak assignment calc.)

207 (100%) (3-nitrobenzyl alcohol NOBA matrix peaks); 1055 (10%) {[Cu$_2$Li(2+2)]$^+$, 1055}; 1071 (5%) {[Cu$_2$Li(2+2)OH - e]$^+$, 1071}.

E.3.2.1.3. [Cu$_2$Li(2+2)](OH)(H$_2$O) with H$_2$mfbp (3.7)

H$_2$mfbp (0.100 g, 2.7 mmol), CuCl$_2$ anhydrous (0.040 g, 2.9 mmol) and LiCl (0.006 g, 14 mmol) were dissolved in 80 mL of EtOH and refluxed for 30 min. After that time 1,3-diaminopropan-2-ol was added dropwise (0.024 g, 2.7 mmol) over 3 min. followed by 1 mL of NEt$_3$. The dark brown reaction mixture was allowed to reflux for 3 h. then was concentrated to 20 mL and left aside for slow evaporation. The resulting dark green crystalline solid was washed with EtOH and H$_2$O and dried in the air to produce 0.088 g of [Cu$_2$Li(2+2)](OH)(H$_2$O) in 64% yield.

IR(KBr), $\nu$ [cm$^{-1}$]: 3468 (b, m, OH); 2966 (s, CH$_3$); 1629 (s, C=N); 1554 (m); 1461 (s); 1280 (m, ArOH); 1098 (m); 768 (w)

CHN Calc.: C 61.78%, H 6.69%, N 5.55% for [Cu$_2$Li(2+2)](OH)(H$_2$O)

Found: C 61.97%, H 7.22%, N 5.70%

FAB - MS [m/z] (relative intensity) and (peak assignment calc.)

208 (100%) (NOBA matrix peaks);
973 (50%) {[Cu$_2$Li(2+2)]$^+$, 973}.
E.3.2.1.4. [Cu$_2$Na(2+2)](OH)(H$_2$O) with H$_2$mfbp (3.8)

H$_2$mfbp (0.165 g, 4.4 mmol), CuCl$_2$ anhydrous (0.060 g, 4.4 mmol) and NaOH (0.015 g, 3.75 mmol) were added to 80 mL of hot EtOH and refluxed for 30 min. Next 1,3-diaminopropan-2-ol (0.040 g, 4.4 mmol) in 10 mL of EtOH was introduced dropwise to the refluxing solution and reflux was continued overnight. The resulting dark brown solution was evaporated to dryness, washed with H$_2$O and dried in the air to produce dark green solid identified as [[Cu$_2$Na(2+2)](OH)(H$_2$O)]. Yield 78% calc. for 0.178 g of product.

IR(KBr), $\nu$ [cm$^{-1}$]: 3426 (b, m, OH); 2961 (s, CH$_3$); 1626 (s, C=N); 1451 (s); 1270 (m, ArOH); 1079 (m); 838 (w); 774 (w)

CHN Calc.: C 60.84%, H 6.58%, N 5.46% for [Cu$_2$Na(2+2)](OH)(H$_2$O)

Found: C 60.63%, H 6.80%, N 5.58%

ESI - MS [m/z] (relative intensity) and (peak assignment calc.)

989 (90%) {[Cu$_2$Na(2+2)]$^+$, 989}; 1955 (85%) {[Cu$_2$(2+2)]$_2$Na, 1955}.

E.3.2.1.5. [Cu$_2$Na(2+2)](ClO$_4$) with H$_2$mfpp (3.9)

H$_2$mfpp dialdehyde (0.408 g, 1 mmol) of was refluxed in 100 mL of EtOH for 30 min. and after that time 0.025 g (6.2 mmol) of NaOH in 10 mL of EtOH was added to the refluxed solution. The colour changed from bright yellow to dark orange and reflux was continued for another 30 min. Then 0.089 g (1 mmol) of 1,3-diaminopropan-2-ol in 10 mL of EtOH was added dropwise over 3 min, upon addition the colour turned brown.

Next a solution of Cu(ClO$_4$)$_2$·6H$_2$O 0.370 g (1 mmol) in 10 mL of EtOH was prepared and introduced to the reaction mixture. Reflux was continued overnight. After that time, reaction mixture was concentrated under vacuum. The green precipitating solid was filtered off, washed with H$_2$O and dried in the air to afford 0.327 g of [Cu$_2$Na(2+2)]ClO$_4$ in 57% yield.

IR(KBr), $\nu$ [cm$^{-1}$]: 3486 (b, m, OH); 2962 (s, CH$_3$); 1629 (s, C=N); 1451 (s); 1280 (m, ArOH); 1122 (m, ClO$_4$); 768 (w)
CHN Calc.: C 61.55%, H 4.14%, N 4.79% for [Cu$_2$Na(2+2)](ClO$_4$)

Found: C 61.30%, H 4.33%, N 4.76%

FAB - MS [m/z] (relative intensity) and (peak assignment calc.)

307 (100%) (3-nitrobenzyl alcohol NOBA matrix peaks);
1071 (85%) \{[[Cu$_2$Na(2+2)]]^+, 1071\}.

E.3.2.1.6. [Ni$_2$Na(2+2)](OAc) with H$_2$mfpp (3.10)

H$_2$mfpp (0.200 g, 0.49 mmol) and Ni(OAc)$_2$·4H$_2$O (0.122 g, 0.49 mmol) were refluxed in 60 mL of EtOH for 30 min. After that time 1,3-diaminopropan-2-ol was added (0.044 g, 0.49 mmol) in 10 mL of EtOH followed by NaOH (0.010g, 0.25 mmol). The reaction mixture was allowed to reflux overnight. The solution was concentrated under vacuum and the precipitated brown product was collected by filtration to produce 0.163 g of [Ni$_2$Na(2+2)](OAc). Yield 59%

IR(KBr), v [cm$^{-1}$]: 3426 (m, OH); 1620 (s, C=N); 1449 (s, COO$^-$); 1284 (w, ArOH); 767 (w)

CHN Calc.: C 66.44%, H 4.59%, N 5.00% for [Ni$_2$Na(2+2)](OAc)

Found: C 66.89%, H 4.80%, N 5.32%

FAB - MS [m/z] (relative intensity) and (peak assignment calc.)

307 (100%) (NOBA matrix peaks); 1039 (25%) \{[Ni$_2$H(2+2)]^+, 1039\};
1059 (10%) \{[Ni$_2$Na(2+2)]^+, 1059\}.

E.3.2.2. Trinuclear Cu$_2$M (M = group 2 metal ions) complexes of a (2+2) pseudocalixarene Schiff base macrocycle derived from H$_2$mftpb

E.3.2.2.1. [Cu$_2$Mg(2+2)](NO$_3$)(ClO$_4$)(EtOH)(H$_2$O)$_4$ (3.11)

H$_2$mftpb (0.100 g, 0.27 mmol) was refluxed overnight in 80 mL of EtOH with Mg(NO$_3$)$_2$·6H$_2$O (0.035 g, 0.135 mmol) and 1,3-diaminopropan-2-ol (0.024 g, 0.27 mmol) in the presence of NEt$_3$ (1 mL). After that time Cu(ClO$_4$)$_2$·6H$_2$O (0.100 g, 0.27
mmol) was introduced in 10 mL of EtOH and reflux was continued for 5 h. Then dark green reaction mixture was then concentrated by half and left aside for slow evaporation. The resulting green solid was washed with EtOH, MeOH and H$_2$O and dried in the air. The analysis indicated formation of [Cu$_2$Mg(2+2)](NO$_3$)(ClO$_4$)(EtOH)(H$_2$O)$_4$ complex. (0.053 g Yield 28%).

**IR(KBr), v [cm$^{-1}$]:** 3379 (b, m, OH); 2955 (s, CH$_3$); 1627 (s, C=N); 1550 (m); 1442(s); 1265 (m, ArOH); 1087 (b, s, ClO$_4$); 802 (w)

**CHN Calc.:** C 50.98%, H 6.18%, N 5.51% for [Cu$_2$Mg(2+2)](NO$_3$)(ClO$_4$)(EtOH)(H$_2$O)$_4$

**Found:** C 50.98%, H 6.44%, N 5.84%

**FAB - MS [m/z] (relative intensity) and (peak assignment calc.)**

207 (100%) (NOBA matrix peaks); 281 (95%) (NOBA matrix peaks); 990 (5%) \{[Cu$_2$Mg(2+2) + e$^-$_]$, 990\}; 1475 (< 5%) \{[Cu$_3$Mg(3+3) + e$^-_]{, 1475}\}.

**E.3.2.2.2 [Cu$_2$Ca(2+2)](ClO$_4$)(OH)(EtOH)(H$_2$O)$_4$ (3.12)**

Ca(ClO$_4$)$_2$·4H$_2$O (0.045 g, 0.135 mmol) and 0.100 g (0.27 mmol) of H$_2$mfmbp were dissolved in hot EtOH and refluxed for 30 min. After that time 1,3-diaminopropan-2-ol (0.024 g, 0.27 mmol) was added in 10 mL of EtOH. Reflux was continued for 30 min. and then 1 mL of NEt$_3$ was introduced to the reaction mixture. Reflux was maintained for 5 h. when Cu(ClO$_4$)$_2$·6H$_2$O (0.100 g, 0.27 mmol) in 10 mL was added. The reaction mixture was allowed to reflux for further 3 h. The resulting dark green solution was evaporated to dryness, washed with H$_2$O and dried in the air to afford 0.063 g of green solid which was set to crystallise by slow diffusion of Et$_2$O into the EtOH solution. The precipitate which resulted from that crystallisation was characterised as [Cu$_2$Ca(2+2)](ClO$_4$)(OH)(EtOH)(H$_2$O)$_4$ (0.042 g, Yield 23%).

**IR(KBr), v [cm$^{-1}$]:** 3447 (b, m, OH); 2961 (s, CH$_3$); 1634 (s, C=N); 1548 (m); 1477 (s); 1272 (m, ArOH); 1150 (s, ClO$_4$); 1117 (s, ClO$_4$); 1094(s, ClO$_4$); 768 (w)

**CHN Calc.:** C 52.17%, H 6.41%, N 4.51% for [Cu$_2$Ca(2+2)](ClO$_4$)(OH)(EtOH)(H$_2$O)$_4$

**Found:** C 52.30%, H 6.42%, N 4.76%
FAB - MS [m/z] (relative intensity) and (peak assignment calc.)

190 (80%); 270 (85%); 293 (75%); 396 (65%); 399 (60%) - low m/z peaks were not assigned as most likely they resulted in the fragmentation of larger molecules

969 (65%) \{[\text{Cu}_2\text{H}(2+2)]^+, 969\}; 1107 (100%) \{[\text{Cu}_2\text{Ca}(2+2)(\text{ClO}_4)]^+, 1107\}; 1474 (30%) \{[\text{Cu}_3\text{Na}(3+3)]^+, 1474\}; 1842 (35%).

E.3.2.2.3 [\text{Cu}_2\text{Ca}(2+2)(\text{NO}_3)_2] (\text{H}_2\text{O})_2 (3.13)

For the relevant ESI-MS experiment see section E.5.3.1 and for discussion section 5.3.1. This complex was isolated from the ESIms experiment where Ca(II) ion was tested as the central metal template in the double template formation of (3+3) macrocycle. The spectrum of the reaction mixture showed the doubly charged peaks at m/z 1506 which were assigned to [\text{Cu}_3\text{Ca}_6(6+6)]^{2+} cation. There was no evidence of formation of (2+2) trinuclear macrocyclic complex with Ca(II) in reaction mixture solution.

\text{H}_2\text{mftbp} (0.100 \text{ g}, 0.27 \text{ mmol}) and \text{Ca(NO}_3)_2\cdot4\text{H}_2\text{O} (0.032g, 0.135 \text{ mmol}) were refluxed in the industrial methylated spirit (IMS) for 30 min. and after that time 1,3-diaminopropan-2-ol (0.024 g, 0.27 mmol) in 10 mL of EtOH was added dropwise followed by 1 mL of NEt$_3$. Reflux was continued for 13 h. when \text{Cu(NO}_3)_2\cdot3\text{H}_2\text{O} (0.066g, 0.27 mmol) was introduced. Then reaction mixture was allowed to reflux for 8 h. and was left aside for undisturbed evaporation. The resulting crystalline solid was analysed by IR and CHN and the results were consistent with formula [\text{Cu}_2\text{Ca}(2+2)(\text{NO}_3)_2] (\text{H}_2\text{O})_2 (0.073 \text{ g}, \text{Yield 46%}).

Recrystallisation from MeOH produced green crystals of [\text{Cu}_2\text{Ca}(2+2)(\text{NO}_3)_2] (\text{MeOH})_2 suitable for single crystal X-ray analysis.

**IR(KBr), v [\text{cm}^{-1}]:** 3441 (b, m, OH); 2946 (m, CH$_3$); 1627 (s, C=N); 1562 (m); 1384(s); 1269 (m, ArOH); 1037 (w); 837(w)

**CHN Calc.:** C 53.44%, H 5.87%, N 7.20% for [\text{Cu}_2\text{Ca}(2+2)](\text{NO}_3)_2(\text{H}_2\text{O})_2

**Found:** C 53.40%, H 6.10%, N 7.26%
PART B: Electrospray ionisation mass spectrometry experiments

The ESI-MS study comprised four types of experiments referred to as: Route 1, Route 2, Route 3 and Route 4 which are in fact related to the order in which reactants were introduced to the reaction mixture (Figure 1).

**Route 1** was a two stage process, first the (2+2) macrocycle was produced with transition metal (TM) as a template as follows. 0.100 g (0.27 mmol) of H$_2$mftbp and 1 equiv. of TM salt were reflux in 60 mL of EtOH for 30 min. and after that time 1 equiv. of 1,3-diaminopropan-2-ol (0.024 g, 0.27 mmol) in 10 mL of EtOH was added dropwise. Reflux was continued overnight. After an overnight reflux, when formation of (2+2) macrocycle was completed and confirmed by ESI-MS, in the second stage 0.25 equiv. of the central metal salt in 10 mL of EtOH was introduced. The H$_2$mftbp dialdehyde:TM:diamine:central metal molar ratio was 4:4:4:1. Reflux was maintained for 30 min. and after that time 1 mL of NEt$_3$ was added. The reaction mixture was allowed to reflux until ESIm showed no further changes in the acquired data.

**Route 2** was an experiment where H$_2$mftbp (0.1 g, 0.27 mmol) was dissolved in 60 mL of EtOH with 1 equiv. of TM salt and 0.25 equiv. of central metal salt and brought to reflux. After 30 min. 1 equiv. of 1,3-diaminopropan-2-ol (0.024 g, 0.27 mmol) in 10 mL of EtOH was introduced to the refluxed solution (the molar ratios H$_2$mftbp:TM:diamine:central metal 1:1:1:0.25 equiv.). After another 30 min. 1 mL of NEt$_3$ was added to the system and reflux was continued until the reaction mixture solution showed no further changes by ESI-MS.

In **Route 3**, H$_2$mftbp (0.1 g, 0.27 mmol) was refluxed overnight in 60 mL of EtOH with 0.5 equiv. of central metal salt and 1 equiv. of 1,3-diaminopropan-2-ol in the presence of NEt$_3$ (1 mL). The 1 equiv. of TM salt in 10 mL of EtOH was introduced to the refluxing solution and reflux was continued until there was no further change indicated by ESI-MS.
Figure 1.

*Timings given in ESI-MS study represent the reflux times to the moment when samples were extracted from the solution.

*For LCT TOF and Synapt instruments: 25 μL was taken out from 0.5 mL removed from the refluxing reaction mixture and diluted up to 200 μL with MeOH (10^-5 M).

*For Orbitrap instrument: 100 μL was taken out from 0.5 mL removed from the refluxing reaction mixture and diluted up to 500 μL with MeOH, then 1 drop of that solution was diluted with 1 mL of MeOH (final 10^-5 M).
**Route 4** was similar to **Route 2**, included 30 min. reflux of H$_2$mtfbp (0.1 g, 0.27 mmol), TM salt (1 equiv.) and central metal salt (0.25 equiv.) mixture in 60 mL of EtOH. Then, in contrast to **Route 2**, 1 mL of NEt$_3$ was added and reflux was continued for 30 min. After that time 1 equiv. of 1,3-diaminopropan-2-ol (0.024 g, 0.27 mmol) in 10 mL of EtOH was introduced to the system (ratio H$_2$mtfbp:TM:diamine:central metal 1:1:1:0.25 equiv.). The reaction mixture was allowed to reflux until it showed no further changes by ESI-MS.

For an ESI-MS experiment described in section E.3.3.1 the exact amounts of reactants used together with samples extraction pattern and timing for ESI-MS analysis is shown in the diagram, and is also explained how to read it. The other ESI-MS experiments were conducted with identical or similar amount of the dialdehyde and the related diagrams with equivalent amounts of reactants are included in the discussion chapters.

**E.3.3. Chapter 3 Formation of homo and heteronuclear complexes of (2+2) pseudocalixarene Schiff base macrocycles – an ESI-MS study**

**E.3.3.1 Cu(II) template formation of the (2+2) pseudocalixarene Schiff base macrocycle.**

![Diagram showing the formation of Cu(II) template formation of the (2+2) pseudocalixarene Schiff base macrocycle.](image-url)

- H$_2$mtfbp dialdehyde and 1 equiv. of Cu(II) salt were dissolved in 60 mL of absolute ethanol and brought to reflux. The first and the second samples for the ESI-MS were extracted after 10 min. and 55 min. of reflux respectively. After 1 h. of reflux 1 equiv. of 1,3-diaminopropan-2-ol was introduced and reflux was continued. The third sample for ESI-MS was taken out from the refluxing solution 10 min. after addition of the diamine and the fourth 40 min. later. The final sample was extracted after overnight reflux.
References


85 E. C. Constable, Coordination Chemistry of Macrocyclic Compounds, Oxford University Press, New York, 1999


161  J. Zeleny, *Phys Rev.*, **3**, 69 (1914)


163  J. Zeleny, *Phys Rev.*, Letters to the editor, 2293 (1931)


179 MassLynx V4.1 SCN639, Waters Inc. 2008

180 Qual Browser, Thermo Xcalibur 2.1.0.1139, Thermo Fisher Scientific 2009


APPENDIX 1

CRYSTAL STRUCTURE DATA
### Table 1. Crystal data and structure refinement for H$_2$mfp

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>MFMP</td>
</tr>
<tr>
<td>Chemical formula</td>
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</tr>
<tr>
<td>Formula weight</td>
<td>284.30</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoK$\alpha$, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2$_1$</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>$a = 4.6052(3)$ Å, $\alpha = 90^\circ$</td>
</tr>
<tr>
<td>Cell volume</td>
<td>704.64(9) Å$^3$</td>
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<tr>
<td>Z</td>
<td>2</td>
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<tr>
<td>Calculated density</td>
<td>1.340 g/cm$^3$</td>
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<tr>
<td>Absorption coefficient $\mu$</td>
<td>0.095 mm$^{-1}$</td>
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<tr>
<td>F(000)</td>
<td>300</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>yellow, 0.35 × 0.08 × 0.04 mm$^3$</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker APEX 2 CCD diffractometer</td>
</tr>
<tr>
<td>$\theta$ range for data collection</td>
<td>2.13 to 25.99°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>h $-$5 to 5, k $-$23 to 23, l $-$9 to 9</td>
</tr>
<tr>
<td>Completeness to $\theta$ = 25.99°</td>
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</tr>
<tr>
<td>Intensity decay</td>
<td>0%</td>
</tr>
<tr>
<td>Reflections collected</td>
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<td>Independent reflections</td>
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<tr>
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<tr>
<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
</tr>
<tr>
<td>Min. and max. transmission</td>
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<td>Structure solution</td>
<td>direct methods</td>
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<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F$^2$</td>
</tr>
<tr>
<td>Weighting parameters a, b</td>
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</tr>
<tr>
<td>Data / restraints / parameters</td>
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<tr>
<td>Absolute structure parameter</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.170 and $-$0.143 e Å$^{-3}$</td>
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</table>

**Refinement for H$_2$mfp**

The structure was solved by direct methods and refined on F$^2$ using all the reflections. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to the alcohol oxygen atoms were not included.
Table 2. Crystal data and structure refinement for \( \text{H}_2\text{mfpp} \)

The X-ray data were collected at 150K on a Bruker Apex 2CCD diffractometer using graphite monochromated Mo-K\( \alpha \) radiation (\( \lambda = 0.71073 \) Å) at Loughborough University

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<tr>
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<th>raf5</th>
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</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>( P-1 )</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>( a = 17.0257(9) ) Å, ( b = 20.2645(10) ) Å, ( c = 24.1755(18) ) Å, ( \alpha = 105.9310(10)° ), ( \beta = 100.2520(10)° ), ( \gamma = 112.6250(10)° )</td>
</tr>
<tr>
<td>Volume</td>
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</tr>
<tr>
<td>( Z )</td>
<td>14</td>
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<td>Density (calculated)</td>
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<tr>
<td>( F(000) )</td>
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<td>Crystal description</td>
<td>yellow block</td>
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<td>Theta range for data collection</td>
<td>0.92 to 26.00°</td>
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<tr>
<td>Index ranges</td>
<td>-20( \leq h \leq 20 ), -24( \leq k \leq 24 ), -29( \leq l \leq 29 )</td>
</tr>
<tr>
<td>Reflections collected</td>
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<td>Independent reflections</td>
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<td>Absorption correction</td>
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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<td>R indices (all data)</td>
<td>R1 = 0.0910, wR2 = 0.1478</td>
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<td>Largest diff. peak and hole</td>
<td>0.390 and -0.229 e.Å(^{-3})</td>
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Refinement for \( \text{H}_2\text{mfpp} \)

The structure was solved by direct methods and refined on \( F^2 \) using all the reflections. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to the alcohol oxygen atoms were not included.
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<td>Formula weight</td>
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<tr>
<td>Temperature</td>
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<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, C2/c</td>
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<tr>
<td>Unit cell parameters</td>
<td>a = 28.832(4) Å, α = 90°</td>
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<tr>
<td></td>
<td>b = 11.6610(18) Å, β = 101.054(3)°</td>
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<tr>
<td></td>
<td>c = 18.121(3) Å, γ = 90°</td>
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<tr>
<td>α rotation with narrow frames</td>
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<td>Index ranges</td>
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<td>Absorption correction</td>
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<td>Min. and max. transmission</td>
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<tr>
<td>Largest diff. peak and hole</td>
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</table>

**Refinement and disorders for [CaCu₂(2+2)(NO₃)₂](MeOH)₂**

The structure was solved by direct methods and refined on F² using all the reflections. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Oxygen atoms of one of the methanol molecules are disordered and were modelled with 70:30 occupancy of two related positions (O40 and O40’).
Table 4. Crystal data and structure refinement for [BaCu₄(mftbp)₄(MeOH)(EtOH)₃](ClO₄)₂(EtOH)₄(H₂O)₃.

The X-ray data were collected at 150K on a Bruker Apex II CCD diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at Loughborough University.

<table>
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<td>a</td>
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<td>α</td>
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<tr>
<td>b</td>
<td>25.3525(12) Å</td>
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<tr>
<td>β</td>
<td>101.8360(10)°</td>
</tr>
<tr>
<td>c</td>
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</tr>
<tr>
<td>γ</td>
<td>90°</td>
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<tr>
<td>Z</td>
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<td>F(000)</td>
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<td>Crystal size</td>
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<td>Crystal description</td>
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<td>1.48 to 25.00°.</td>
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<td>1.893 and -0.892 e.Å⁻³</td>
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</table>

Refinement and disorders for [BaCu₄(mftbp)₄(MeOH)(EtOH)₃](ClO₄)₂(EtOH)₄(H₂O)₃

The structure was solved by direct methods and refined on F² using all the reflections. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to the alcohol oxygen atoms were not included. Two of the coordinated alcohol molecules were disordered and refined as 50% methanol/ethanol. Disordered, non-coordinated solvent molecules were treated using the SQUEEZE procedure of PLATON. This was modelled as 4EtOH and 3H₂O per formula unit (134 electrons) but other combinations of EtOH/MeOH and H₂O are also possible.
APPENDIX 2
CONFERENCES AND PUBLICATIONS
CONFERENCES

December 2007
RSC Supramolecular Chemistry Meeting, Manchester, Poster “Conformational Switching Driven by H-Bond Formation” presented

March 2008
Dalton Meeting, Warwick, Poster “Template effect in 4+4 pseudocalixarene Ba$^{+2}$ Cu$^{+2}$ heteropolynuclear complexes” presented

April 2008
27th British Crystallographic Association Annual Spring Meeting, Loughborough, Poster “Double Template Effect in Polynuclear Pseudocalixarenes Complexes” presented

June 2009
Coordination Chemistry Discussion Group Meeting, Leeds, Poster ”Double Template Effect in the Formation of BaCu$_4$ Pseudocalixarene Complexes” presented

December 2009
RSC Supramolecular and Macrocycles Meeting, Cambridge, Poster “Mechanism of the Formation of Pseudocalixarene Polyheteronuclear Complexes” presented

July 2010
Coordination Chemistry Group Meeting, Bath, Oral Presentation “Double Template Effect Mechanism in the Formation of Polyheteronuclear Schiff Base Complexes”

Publications
