Exploring Molecular Interactions

Synthesis and Studies of Clip-Shaped Molecular Hosts

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**Abstract**


Molecular recognition via noncovalent interactions plays a key role in many biological processes such as antigen-antibody interactions, protein folding, the bonding and catalytic transformation of substrates by enzymes, etc. Amongst these noncovalent interactions, electrostatic interactions, hydrogen bonding, π-π interactions, and metal-to-ligand bonding are the most prominent. Exploring noncovalent interactions in host-guest systems that range from small hydrocarbon systems to more complex systems is the main motivation of this thesis. The present study involves the design, synthesis and characterization of clip-shaped molecules as host structures, and an examination of their binding properties with a variety of guests using NMR spectroscopy.

Several clips with a hydrocarbon or glycoluril backbone were synthesized. The binding of cations to small, hydrocarbon-based clips suggests that binding is enhanced by the rigidity and cooperativity between the two sidewalls of the clip. Binding is also very much dependant on the solvent properties.

Glycoluril-based clips built with aromatic sidewalls provide a deep cavity for binding guest molecules. The binding properties of these hosts were studied with several guests such as cations, Lewis acids and Lewis bases. Lewis basic binding sites in theacenaphthene-terminated clip were dominating in guest binding. Complexation-induced conformational changes in the wall-to-wall distance were observed for this clip.

In contrast, for a porphyrin-terminated clip with metal centers, very strong binding to a series of Lewis basic guests of various sizes into the clip cavity was observed. Conformational locking of guests with long alkyl chains was achieved, suggesting that, this clip could be useful as a potential molecular tool for the structural characterization of acyclic molecules with several stereogenic centers. This porphyrin clip was also shown to bind substituted fullerenes in the cavity.

**Keywords:** Glycoluril clips, host-guest systems, supramolecular chemistry, complexation induced shifts, conformational restriction, NMR spectroscopy, fullerene binding

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List of Papers included in this thesis

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:


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Paper I – “Reproduced with permission from the publisher. Copyright 2007 American Chemical Society.”
Contribution Report

The author wishes to clarify his contributions to the research presented in the present thesis.

Paper I. Performed the experimental work related to the reference compound, participated in discussion of the manuscript.

Paper II. Performed the experimental work including synthesis and NMR studies, contributed to the interpretation of the results and to the writing of the manuscript.

Paper III. Performed the syntheses, characterization, and binding studies, contributed to the interpretation of the results, provided first draft of manuscript, participated in the writing of the manuscript.

Paper IV. Performed the experimental work, the NMR studies, contributed to the interpretation of the results and to the writing of the manuscript.
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Abbreviations

aa \hspace{1cm} \textit{anti-anti}

Ar \hspace{1cm} Aryl

as \hspace{1cm} \textit{anti-syn}

CIS\hspace{1cm} \text{Complexation induced shift(s)}

conc.\hspace{1cm} \text{concentrated}

DABCO\hspace{1cm} 1,4-diazabicyclo[2.2.2.]octane

DDQ\hspace{1cm} 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMP\hspace{1cm} \text{Dess-Martin periodinane}

DMSO\hspace{1cm} \text{Dimethyl sulfoxide}

G\hspace{1cm} \text{Guest}

H\hspace{1cm} \text{Host}

h\hspace{1cm} \text{hours}

hv\hspace{1cm} \text{Ultraviolet or visible irradiation}

IR\hspace{1cm} \text{Infrared}

K\hspace{1cm} \text{Association constant}

NMR\hspace{1cm} \text{Nuclear Magnetic Resonance}

NOE\hspace{1cm} \text{Nuclear Overhauser Effect}

ppb\hspace{1cm} \text{Parts per billion}

ppm\hspace{1cm} \text{Parts per million}

ROESY\hspace{1cm} \text{Rotating-frame Overhauser Enhancement Spectroscopy}

r.t.\hspace{1cm} \text{Room temperature}

ss \hspace{1cm} \text{\textit{syn-syn}}

T_1\hspace{1cm} \text{Spin-lattice relaxation time}

TFA\hspace{1cm} \text{Trifluoroacetic acid}

THF\hspace{1cm} \text{Tetrahydrofuran}

TPP\hspace{1cm} \text{Tetraphenylporphyrin}

Trt\hspace{1cm} \text{Triphenylmethyl}

UV-vis\hspace{1cm} \text{Ultraviolet-visible}

v:v\hspace{1cm} \text{volume:volume}
1. Introduction

Exploring noncovalent interactions in clip-shaped host-guest systems that range from small hydrocarbon systems to more complex systems is the main motivation of this thesis. Multiple interactions can affect guest binding, and it is challenging to balance these interactions in order to select a particular binding site among several ones in the same molecule for the intended purpose.

The objectives of the present work are:

- Design, synthesis and characterization of host structures that have the potential to bind a large variety of guests.
- Exploration of the molecular interactions between these hosts and variety of guests and investigation of the factors influencing complexation.
- Conformational restriction of flexible molecules and subsequent structural characterization using NMR spectroscopy.
- Incorporation of switchable units in the hosts for wider applications.

The main purpose of this work is the structural characterization of small and flexible molecules in solution using NMR spectroscopy. The structural analysis of small molecules is a major difficulty in organic chemistry due to their fast conformational changes in solution. In principle, this can be achieved by restricting the conformations of a molecule by locking it in a host; this can be done using a molecular tool. A molecular tool is a host system that can bind the target molecule. The tool (referred to as ‘host’) should interact with the small molecule (‘guest’) to form a host-guest complex in which the guest has restricted conformational mobility (Figure 1).

Figure 1. Schematic representation of a host-guest complex.
Host-guest interactions provide additional information to simplify the analysis. This phenomenon was nicely illustrated in the literature by Gogoll et al. for \((\pi\text{-allyl})\)palladium complexes\(^1\), and by Hannak et al.,\(^2\) and Rebek et al.\(^3\) for alkyl long chains. This whole concept is an example of supramolecular chemistry.

### 1.1 Supramolecular chemistry: History and developments

Friedrich Wöhler is regarded as a pioneer in organic synthesis because of the first laboratory synthesis of urea in 1828. Since that time, molecular chemistry has developed a substantial number of methods for the construction of very complex molecular structures by making and breaking covalent bonds in a controlled fashion. The next step is to gain control over intermolecular interactions. A new approach to building highly complex entities beyond molecules and towards supramolecules without using covalent bonds emerged during the late 1960s. This area of chemistry is called supramolecular chemistry.

![Scheme showing the use of covalent chemistry to build the host, and non-covalent chemistry to form the host-guest complex.](image)

Figure 2. Scheme showing the use of covalent chemistry to build the host, and non-covalent chemistry to form the host-guest complex.

The term ‘supramolecular chemistry’, coined by Jean-Marie Lehn in 1969, is defined as “the chemistry of molecular assemblies and of the intermolecular bond”.\(^4\) In covalent chemistry, atoms are held together by covalent bonds to form molecules. In supramolecular chemistry, the components are held together by noncovalent intermolecular interactions to build a supramolecular system (Figure 2). This new approach to understanding Nature began in 1894,\(^5\) when Emil Fischer proposed the lock-and-key model to describe the interaction of an enzyme with its substrate, and the specificity of that interaction. According to this model, enzymes are very specific because the enzyme and substrate possess specific complementary geometrical fea-
tures that fit exactly one into another as lock and key. Molecular recognition and supramolecular function are the two main principles of this mechanism. This model fails to explain the stabilization of the transition state that enzymes used to achieve. In 1958, Daniel Koshland suggested a modification to this model, which is called the “induced fit model”. In this model, binding interactions cause an induced fit in which the binding site changes shape to accommodate the substrate (e.g. drug).

The host-guest complex between silver ion (Ag⁺) and ethene is one of the earlier examples of the supramolecular systems. A series of compounds called clathrates were reported by H. M. Powell in 1948. These are formed by the inclusion of small molecules (guests) such as methanol or hydrogen sulfide enclosed in cavities formed by the host compound (for example, a hydroquinone network). The products formed with no covalent bond and little or no direct attachment between host and guest. They were originally used in crude oil refining, and later developments in similar systems led to enhanced properties.

Research by Charles Pedersen, Donald Cram and Jean-Marie Lehn during the 60s and 70s established the basis for supramolecular chemistry. They were awarded with the Nobel Prize in Chemistry in 1987 for their valuable contributions to this field. With the initial motivation of mimicking Nature, supramolecular chemistry continues its expansion to include understanding and mimicking biological processes, molecular recognition, molecular self-assembly, catalysis, materials chemistry, medicinal chemistry, dynamic covalent chemistry and many more fields. Examples of the wide variety of supramolecular systems (Figure 3) include well-pre-organized macrocycles, such as cyclodextrins, crown-ethers, cyclophanes, and supramolecular capsules; non cyclic-compounds having cavities, such as molecular tweezers and clips; shape descriptors like bowls, and scissors; dynamic switching devices such as switches, sensors, and rotaxanes, etc.

![Figure 3. Examples of supramolecular systems.](image)

a) Pederson’s 18-crown-6 complexed with potassium ion; b) Klärner’s molecular ‘clip’ complexed with 1,4-dinitrobenzene; c) Rebek’s ‘tennis ball’.
1.2 Noncovalent interactions

Noncovalent or intermolecular interactions are responsible for the formation of supramolecular systems, which are mentioned in the previous section. These interactions include electrostatic interactions (e.g., ion-ion, ion-dipole, dipole-dipole), hydrogen bonding,\textsuperscript{18} metal-to-ligand bonding,\textsuperscript{19} \(\pi\)-\(\pi\) interactions,\textsuperscript{20} cation-\(\pi\) interactions,\textsuperscript{21} van der Waals forces,\textsuperscript{22} hydrogenic effects,\textsuperscript{23} etc. These interactions are much weaker than covalent bonds (20 kJ mol\(^{-1}\) for a typical hydrogen bond versus 350 kJ mol\(^{-1}\) for a C-C single bond), but they become significant when considered in numbers. These systems are the result of not only additive but also cooperative interactions. As the interactions are weak, they are easily disrupted.

All intermolecular forces are fundamentally electrostatic in character.\textsuperscript{24} The following is an account of different interactions and their strengths, ordered by decreasing strength.

**Ionic bonds**: Ion-ion interactions between a cation and an anion. These are in similar strength to covalent bonds (100–350 kJ/mol)

**Metal-to-ligand bonds**: The bonding of metal to ligand is generally considered to be the strongest of the directional noncovalent interactions. The energies of these bonds are on the same order as those of covalent bonds. Using these directional metal-ligand dative bonds, several supramolecular coordination cage compounds with various proposed applications have been prepared.\textsuperscript{19,25}

**Ion-dipole interactions**: These are the interactions between ions and partial charges on the end of a polar molecule or dipole, and are usually 50-200 kJ/mol in strength. For example, Na\(^+\) binds to six water molecules or to six oxygens in crown ether.

**Cation-\(\pi\) interactions**: These are basically electrostatic interactions between a positively charged species and the face of a \(\pi\) system (0-80 kJ/mol) (Figure 4). The interactions of alkali and alkaline earth metals to \(\pi\) systems are weak and considered as supramolecular; however, the classification of transition-metal binding to conjugated systems as cation-\(\pi\) bonding is largely debated in the literature.\textsuperscript{21} Cation-\(\pi\) interactions are not limited to metals; it has been demonstrated that ammonium and complex organic cations are good \(\pi\) binders. This interaction is now considered to be as important as hydrogen bonding, ion pairing and hydrophobic effects in determining the structures of proteins.\textsuperscript{26}

**Dipole-dipole interactions**: Significant attraction can develop from the alignment of dipoles on adjacent molecules (5-50 kJ/mol). The strength of
these interactions decreases drastically with increases in distance. Ketones are good examples (Figure 4).

\[ \text{H} \quad \text{K} \quad \text{C} \quad \text{O} \quad \text{RR} \, \text{COR} \, \text{R} \, \text{R} \, \text{R} \, \text{R} \]

**Figure 4.** Illustrations of some of the noncovalent interactions.

**Hydrogen bonding:** One of the most important noncovalent interactions (2-50 kJ/mol), hydrogen bonding is the attraction between a hydrogen atom attached to an electronegative atom and a second species bearing a lone pair, as in D–H–A, where the hydrogen-bond donor D is O, N, F, S, or C and the acceptor A is O, N, F, S, or X. Directionality is the main advantage of the hydrogen bond. The interaction is maximized when the D–H–A bond angle is near 180° and the hydrogen aligns itself with the unshared pair of the acceptor A. Strong, conventional hydrogen bonding is observed when both D and A are quite electronegative, as in N–H–O. When either or both D and A are of moderate or weak electronegativity, the hydrogen bond is weak and non-conventional, as in C–H–O. Weak hydrogen bonds of OH, NH, and CH to double bonds and triple bonds are observed; in particular, hydrogen bonds between these groups and the double bonds in the aromatic rings are recognized as playing key roles in the stabilization of biomolecular structures.

**Aromatic interactions:** Aromatic or π-π interactions are direct interactions between the aromatic rings (0-50 kJ/mol). Substituent effects are important, as the interactions dependent on electron-rich and electron-poor aromatics. Face-to-face and edge-to-face aromatic interactions (Figure 4) are the two major types. Aromatic units attract each other when the interaction of the π system of one arene with the σ system of the other is stronger than the π-π repulsions. π-π Interactions are the major contributors to the stability of the double helical structure of DNA, intercalation of drugs into DNA, porphyrin aggregation, crystal packing of aromatic units, etc.

**van der Waals forces:** These are weak intermolecular interactions arising from the fluctuating polarization of an electron cloud by an adjacent nucleus (<5 kJ/mol). These forces are weak and nondirectional, but the overall contribution of van der Waals forces is crucial for binding.

**Hydrophobic effect:** The hydrophobic effect describes the tendency of nonpolar molecules to form intermolecular aggregates in polar solvents. Less polar guests might be directed into the nonpolar regions of the hosts in polar
solvents. This is a very important effect in biological systems, as they are mostly composed of water.

The energies of covalent and noncovalent interactions are compared in Figure 5.

Figure 5. Energies of covalent and noncovalent interactions.

1.3 Methods used for studying complexation phenomena

Complexation phenomena of host-guest systems is usually monitored and quantified by spectroscopic methods and various other techniques. The results of the complex formation are expressed as an association constant or binding constant $K$. $K$ can be measured using UV-vis spectroscopy, NMR spectroscopy, fluorescence spectroscopy, IR spectroscopy, capillary electrophoresis, etc. In a host-guest complex, all of the complex, free host and guest are in equilibrium. The reaction is represented as:

$$ H + G \Leftrightarrow H \cdot G $$

$$ K = \frac{[H \cdot G]}{[H][G]} \quad (1) $$

where $[H]$, $[G]$, $[H \cdot G]$ are concentrations of host, guest and host-guest complex respectively.

A short summary of some of the methods and techniques used for the complexation studies in this thesis are given in this section.
1.3.1 UV-vis Spectroscopy

The absorption of ultraviolet or visible radiation by a molecule leads to transitions among the energy levels of the molecule. Many organic compounds absorb UV-light. Distinct absorption bands corresponding to the free and complexed molecules are observed. Complexation is evident by a change in the wavelength of the absorption maximum or through the isosbestic points. An isosbestic point is a point where several absorption curves from different species overlap. Data can be obtained using micro molar concentrations. The main drawback of using UV-vis spectroscopy to characterize host-guest complexes is that no adequate information is obtained about the binding mode or position of the guest in the complex.

1.3.2 NMR Spectroscopy

NMR spectroscopy is the main method used for complexation studies in this thesis. The most common effect, chemical shift change, is followed for all the complexation studies. Diffusion measurements and relaxation time ($T_1$) measurements are also used occasionally. In addition to the evidence of complexation processes, NMR gives information concerning the position of the actual interaction. The following distinct situations are to consider concerning the NMR method:

- (a) When the host-guest complexation equilibrium exchange rate is similar to the NMR time scale, the peaks in the NMR spectra are broadened.
- (b) When the exchange rate is fast on the NMR time scale, only an averaged spectrum of free and bound guest (and host) molecules is observed.
- (c) When the exchange rate is slow on the NMR time scale, individual peaks corresponding to free and bound guest (and host) molecules are observed.

An increase in the chemical shift of a proton upon complexation is due to a decrease in electron density around that proton, and vice versa. The observed variations in electron density can be attributed to the noncovalent interactions, such as hydrogen bonding or complexation of Lewis acids, that play a role in the formation of the complex. Anisotropic effects arising from aromatic ring currents (Figure 6) or other functional groups also cause major chemical shift differences.
To determine complex stoichiometry, chemical shifts are measured at different host and guest concentrations while keeping the total concentration constant. The data is then plotted as shown in Figure 7 to get the Job’s plot.28 The maximum point in the curve gives the mole ratio, i.e. the stoichiometry, of the host-guest complex.

![Schematic illustration of the chemical shift anisotropic effects generated by the aromatic ring currents of benzene ring. $B_0$ indicates the outer magnetic field.](image)

*Figure 6. Schematic illustration of the chemical shift anisotropic effects generated by the aromatic ring currents of benzene ring. $B_0$ indicates the outer magnetic field.*

![Job’s plot showing 1:1 stoichiometry, position of maximum at 0.5.](image)

*Figure 7. Job’s plot showing 1:1 stoichiometry, position of maximum at 0.5.*

Binding constants can be measured by the NMR titration method, where the chemical shifts for varying ratios of guest:host are monitored. The shift changes and the concentrations are plotted using linear data treatment methods such as the Benesi-Hildebrand method,29 the Scott method,30 or a non-linear curve fitting method31 to obtain the binding constant.

Wherever possible, variable temperature studies have been done for both the free hosts and host-guest complexes to see the changes in conformation or dynamics, in the system. Nuclear Overhauser effects and the magnitudes of coupling constants have been used to assess the conformations of guests bound to clips. Variable temperature and nuclear Overhauser effect spectra are also useful for the analysis of conformations of the clips alone.
1.3.3 X-ray Crystallography

X-ray diffraction is not a method to study dynamic processes, but is the most powerful technique to obtain the solid-state 3D structures of the molecules or supramolecules. A crystal is a supramolecular entity formed by billions of molecules in a periodic arrangement that results from a delicate balance of intermolecular interactions. To grow a crystal suitable for X-ray diffraction is quite tricky, and depends on several factors, such as choice of solvent(s), temperature, method of crystallization, etc. Furthermore, solution and solid-state structures are not necessarily identical because of solvation and dynamics in solution state.
Silver ions are known to form well-organized multilayered structures with a large variety of aromatic systems. These systems are mostly composed of conformationally flexible ligands, or of ligands having a cavity larger than the ionic radius of Ag\(^{+}\). It was of our interest to study the binding properties of a rigid clip-shaped ligand having the smallest conceivable cavity. Host structures selected for these studies are shown in Figure 8.

Aromatic interactions such as \(\pi-\pi\) and cation–\(\pi\) interactions are very important binding forces in biological and synthetic systems.\(^{20b,21}\) Noncovalent cation–\(\pi\) interactions are of fundamental importance in metal-catalyzed organic synthesis, relying upon the reactivity of coordinated organic species.\(^{33}\) Binding of alkali-metal ions to aromatics is electrostatic in nature, and is relatively weak compared to the binding of transition metals, the adducts are of which are more stable due to bonding and back bonding. Rigid bis-arene clip 2.1, with a cavity size of 5.7 Å (at the terminus), is a molecule preorganized for the selective binding of cations. As the cavity of 2.1 is small, it is not expected to bind aromatic guests. The synthesis of clip 2.1, open \(trans\)-dimer 2.2, and the reference compound di-\(tert\)-butylstilbene (2.3), as well as binding studies with these clips and with the \(trans\)-dimer (2.2) are discussed. We will also discuss the effects of solvent on the binding ability of these clips. An extended version of clip 2.1 is 6,7-benz[\(c\)]acephenanthrylene dimer (2.4), which is a chiral host that can bind guests with both \(\pi-\pi\) and cation–\(\pi\) interactions.
2.1 Clip synthesis and complexation studies

Z- and E-acenaphthylene dimers (2.1 and 2.2, respectively), and the reference compound (Z)-1,2-di-tert-butylstilbene (2.3) were prepared according to literature procedures and are described in paper 1. 6,7-benz[c]acephenanthrylene dimer (2.4) is a potential host for further developments beyond this thesis.

The binding of silver ions to 2.1, 2.2, and 2.3 was examined in various solvents, and the binding constants were determined using NMR titrations (Table 1). For the reaction of the Z isomer with AgCF$_3$SO$_3$, the binding constants ($K$) were 4.9 and 38 M$^{-1}$ in THF-d$_8$ and CDCl$_3$/CD$_3$OD (9:1); whereas for the E isomer, $K$ values of 0.4 and 4.1 M$^{-1}$, respectively were obtained. For the binding of AgCF$_3$SO$_3$ to 2.3 in CDCl$_3$, chemical shift changes of the protons were in accordance with the reported data. In THF, a $K$ value of 3 was obtained; whereas in CDCl$_3$/CD$_3$OD (9:1) mixture a reliable value could not be obtained due to the low solubility of 2.3.

The variation in the magnitude of $K$ can be attributed to the cooperativity between the two sidewalls of the cleft (cooperative effect) and solvent dependence. These values show that, in the same solvent, the cooperative effect plays an important role for the Z isomer 2.1, but obviously is not possible in case of the E isomer 2.2. For both the E and Z isomers, coordination of the solvent to the metal plays a major role in the binding strength of silver ions to the ligands. In strongly coordinating solvent, the $K$ values are lower; in comparatively week coordinating solvents, the values are higher. The larger value for 2.1 compared to 2.3 could be due to the rigidity of 2.1 and the resulting preorganization.

Table 1. Binding constants $K$ (M$^{-1}$) for Ag$^+$ with different ligands, obtained in various solvents.

<table>
<thead>
<tr>
<th>Solvent vs. ligand</th>
<th>2.1</th>
<th>2.2</th>
<th>2.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>4.9</td>
<td>0.4</td>
<td>3</td>
</tr>
<tr>
<td>CDCl$_3$+CD$_3$OD (9:1)</td>
<td>38</td>
<td>4.1</td>
<td>not obtained</td>
</tr>
</tbody>
</table>
2.2 Stoichiometry of complexation and solid state structure

A 1:1 binding of silver ions to the clip 2.1 was observed in solution. A different stoichiometry was observed in the solid state, where each ligand binds to two silver ions, and two such ligands are situated in the cluster [2.1·(AgCF$_3$SO$_3$)$_2$]$_2$. The unit cell and crystal packing of the cluster are shown in Figure 9.

Figure 9. X-ray structure of the [2.1·(AgCF$_3$SO$_3$)$_2$]$_2$ clusters and their crystal packing (hydrogen atoms are omitted for clarity).

From the analysis of crystallographic data, it is evident that there are considerable changes in the cavity size and angle between the two naphthalene walls upon binding of Ag$^+$ ions to 2.1 compared to 2.1 alone. The binding of Ag$^+$ to the inside rather than the outside of the cavity despite these considerable distortions indicates the importance of the cooperative effect.

2.3 Conclusions

Complexation studies of highly rigid and more flexible ligands with silver ions were accomplished. Noncovalent cation-π interactions between silver ions and small hydrocarbon clips are observed. The importance of cooperative effect and preorganization in binding the guests is nicely illustrated. Silver ions were strongly bound to the clip having rigid and preorganized binding sites, whereas binding is weaker towards flexible clips. It is evident from the magnitude of the complexation constants $K$ that silver ion complexation to the ligands is weaker in strongly coordinating solvents (e.g. THF) than in less coordinating solvents. In the solid state, isolated clusters are organized in nonpolar pleated sheets, with π-π stacking distances resembling graphite, suggesting possible applications in organometallic and material chemistry.
Smaller hydrocarbon-based clips were shown in the previous section to bind silver ions. It turned out that, other than solvent effects, rigidity and preorganization of the clips are the most important factors influencing complexation. To increase the scope of guest binding and for better synthetic access to a variety of sidewalls, the glycoluril backbone was chosen for further studies. Nolte and co-workers have done extensive research on the synthesis of glycoluril derivatives and their applications in supramolecular catalysis. They have reported several clip-shaped molecules and their binding properties with different guests, such as dihydroxy aromatics. Clips based on diphenylglycoluril derivatives are attractive scaffolds for several reasons:

- Convenient synthetic access to a range of derivatives allows the incorporation of various binding sites.
- Provides a cleft with arene units at least 7 Å apart for the accommodation of aromatic guests.
- Preorganized binding sites.
- Rigid backbone with diphenyls provides a stilbene-type bisaryl unit.

We set out to design glycoluril-based clips with deeper cavities in order to study the binding properties with different guests. The three clips used for our studies, shown in Figure 10 are an acenaphthene-terminated clip (3.1), a benzil-terminated clip (3.2), and the reference diphenylglycoluril clip (3.3).

*Figure 10. Clips used for the studies (left to right): Diphenylglycoluril reference clip (3.3), benzil-terminated clip (3.2) and acenaphthene-terminated clip (3.1). The distance between sidewalls is shown for each clip.*
There are several potential binding sites in the clips 3.1 to 3.3. Some potential guests are described below.

**Cations**: Stilbene-type bisaryl units of the glycoluril backbone present in all three clips can bind metal ions through cation-π interactions. Metal ions can also find similar bisaryl units at the top of the rim in 3.2. It is less likely that 3.1 will accommodate metal ions in the pocket, as the distance between the sidewalls is too large for cooperative binding. The pyrazine nitrogens in 3.1 and 3.2 are also potential binders of metal ions. The same holds for the other cations, like ammonium or alkylammonium ions.

**Hydrogen bonding guests**: Urea carbonyls (pK$_a$ ca. 0.1 – 0.2$^{41}$) are known to be a potential hydrogen-bond acceptors for 3.3,$^{42}$ and are present in other clips as well. Nitrogens of substituted pyrazines (pK$_a$ ca. 0.6 – 2.8$^{43}$) in 3.1 and 3.2 are stronger bases and better acceptors of hydrogen bonding. Weak hydrogen bonding to the arenes is also possible in all three clips.

**Aromatic compounds**: π-π interactions can bind aromatic guests in the cleft or outside the cleft to the aromatic sidewalls of the clips.

It is a particular challenge to balance all these potential binding sites in the same molecule, and to understand the binding phenomena. A detailed study of different guests with the clips 3.1–3.3 is given below.

### 3.1 Synthesis and characterization

The target clips 3.1 and 3.2 were synthesized starting from the glycoluril building blocks (Scheme 1). Diphenylglycoluril (3.4)$^{44}$ tetracyclic ether (3.5)$^{45}$ and dimethoxybenzene clip (3.3)$^{46}$ were synthesized following literature procedures.

The dimethoxybenzene clip 3.3 was nitrated in the presence of excess 65% aqueous nitric acid in acetic anhydride at -70 °C to give the tetranitro derivative 3.6 as pale yellow powder in 80% yield.$^{47}$ Compound 3.6 was then reduced to the air-sensitive tetraamino compound 3.7 with ammonium formate in presence of Pd/C. The acenaphthene clip 3.1 was produced by adding acenaphthenequinone to the tetraamine 3.7 in THF/methanol (1:1, v:v) under an argon atmosphere, and was collected as a pale yellow powder in 49% yield. The benzil clip 3.2 was prepared in the same way as 3.1 by adding benzil to the tetraamine 3.7. 3.2 was also a pale yellow powder and was obtained in 47% yield.
Scheme 1. Synthesis of clips 3.1, 3.2, and 3.3. Reagents and conditions: a: TFA, Benzene; b: paraformaldehyde, 1M NaOH, conc. HCl, DMSO, Argon, 100 °C, 75%; c: conc. H₂SO₄, NaOH, 99%; d: HNO₃, Ac₂O, -70 °C, then 12 h at r.t., 82%; e: Pd/C (10%), HCO₂NH₄, 4 h; f: THF/CH₃OH (1:1), reflux 48 h, Argon, 49% from 3.6; g: THF/CH₃OH 1:1, reflux 16 h, Argon, 47% from 3.6.

Conformational analysis: Clips derived from glycoluril are known to exhibit conformational equilibria between isomers having sidewalls pointing up or down, as shown in Figure 11.⁴⁸ For these isomers, separate signals for individual species can be observed in ¹H NMR spectra. However, variable temperature NMR spectra of 3.1 and 3.3, recorded between +55 and -55 °C, show only one set of signals. Observation of an NOE between the Hₐ protons and bottom phenyl protons, and another between the Hₐ protons and OCH₃ protons confirms that the clips 3.1 and 3.3 exist in aa conformer.
3.2 Binding studies

Complexation with various guests, including 1,3-dihydroxybenzene, silver ions, ammonium ions, and nitrobenzene was examined.

**Interactions with 1,3-dihydroxybenzene (resorcinol):** Clip 3.3 has been shown to bind resorcinol via hydrogen bonding to the glycoluril oxygens. The negative complexation induced shift (CIS) values for the resorcinol protons indicate that the compound was bound in the cavity of 3.3. The experimental observations in the present study with 3.3 are in accordance with the

![Chemical structures](image_url)

*Figure 12. CIS, \( \Delta \delta = \delta_{\text{complex}} - \delta_{\text{clip}} \) (or \( \delta_{\text{resorcinol}} \)) in ppb observed for clips 3.1–3.3 upon the addition of resorcinol.*
Clips 3.1 and 3.2 also bind resorcinol, as evident from the $^1$H NMR chemical shifts, but do so differently from clip 3.3. While negative CIS values are observed for resorcinol when binding to 3.3, positive CIS values are observed when binding to 3.1 (Figure 12). This is likely due to the binding of resorcinol outside the cavity, most probably through hydrogen bonding to the pyrazine nitrogens. In the case of clip 3.2, the effects are smaller suggesting that resorcinol could be bound to 3.2 in a different geometry than to 3.1.

Concerning changes in the $^1$H NMR spectra of the clip protons, as the guest is not bound inside the cavity, the negative CIS values for the protons of clip 3.1 can be attributed to electronic effects. However, as is described in the introduction, complexation of Lewis acids to the pyrazine nitrogens would be expected to reduce the electron density, and should increase the chemical shifts of the clip protons (positive CIS). Nevertheless, the opposite is observed in case of both 3.1 and 3.2 (Figure 12).

Upon titration of resorcinol with the clip 3.1, major lowering of the chemical shifts of the clip protons, as well as signal broadening, were observed until 4 equivalents of resorcinol were added. At higher resorcinol concentrations ([resorcinol]/[3.1] > 8), the chemical shifts of the acenaphthene protons increased, indicating the presence of two counteracting effects, one with negative and other with positive CIS (Figure 13). The latter is likely due to the electronic effects. These observations suggest that complexation equilibria involving resorcinol hydrogen bonding to all four pyrazine nitrogens of the clip 3.1 are present. Binding-constant determinations and low-temperature studies of the complex were not possible due to

![Figure 13](image-url). Expansions of $^1$H NMR spectra (CDCl$_3$, 500 MHz, 25 °C) showing chemical shift changes of acenaphthene and backbone phenyl protons during the titration of clip 3.1 with resorcinol.
the precipitation of the complex at higher concentrations of resorcinol. A quantitative evaluation of the precipitate using $^1$H NMR also confirmed the 1:4 stoichiometry of 3.1-resorcinol.

The larger CIS effects for the complexation of resorcinol to 3.1 compared to 3.2 are most likely due to conjugation of the pyrazines to the acenaphthene unit in 3.1, which is absent in 3.2, and also due to the involvement of benzil protons in phenyl rotation.

**Interactions with cations:** Cations are known to bind to aromatic compounds. As the binding of resorcinol is directed to pyrazine nitrogens, it is interesting to examine cations, to see the competition between bis-arenes and pyrazine nitrogens. Upon titration of clip 3.1 with silver perchlorate in CDCl$_3$/CD$_3$OD (9:1), all the acenaphthene $^1$H NMR signals experience negative CIS values and broaden until the addition of 1 equivalent of Ag$^+$ ($\Delta\delta$ values decrease in the order H-5 > H-6 > H-7) (Figure 14). All other protons experience small shift differences. At higher temperatures (50 °C), these broad signals sharpen, giving an averaged $\delta$ value (termed as pseudocoalescence) due to increased exchange rate (Figure 15). At higher concentrations of Ag$^+$, an insoluble precipitate gradually formed, and this prevented

![Diagram](image-url)

*Figure 14.* CIS, $\Delta\delta = \delta_{\text{complex}} - \delta_{\text{clip}}$ in ppb observed for clips 3.1–3.3 upon the addition of AgClO$_4$ (left) and for clips 3.1 and 3.2 upon the addition of NH$_4$PF$_6$ (right).
low-temperature NMR studies of the complex. However, gravimetric analysis of the precipitate demonstrated the formation of 1:1 complex. In the case of 3.2, all aromatic protons experienced positive CIS except o-benzil protons, for which there was an initial decrease in chemical shift that was followed by an increase at higher concentrations. Contrary to the case of 3.1, no broadening of the signals was observed. Following the binding of Ag⁺ to clip 3.3, a rather small positive CIS was observed for all aromatic protons. Based upon these observations, it is likely that the binding of Ag⁺ ions to 3.1 and 3.2 occurs through the pyrazine nitrogens and that complexation involves dynamic equilibria between several species, as is evident from the peak broadening seen in 3.1. Small positive CIS values for the phenyl protons of the glycoluril backbone indicate weak binding to the cis-diphenyl pocket in all clips.

![Figure 15. Variable temperature ¹H NMR spectra of clip 3.1 with AgClO₄ (1:1.4) at 50 °C, at 25 °C, and of clip 3.1 without AgClO₄.](image)

Weak Lewis acids such as ammonium and alkylammonium ions are also examined for binding with these clips. ¹H NMR titration of clip 3.1 with aliquots of NH₄PF₆ in CDCl₃/CD₃OD (7:3) resulted in negative CIS values for the acenaphthene protons (Δδ values decreased in the order H-5 > H-6 > H-7) (Figure 14), similarly to the binding of Ag⁺ ions. For clip 3.2, the effects are similar but smaller; clip 3.3 shows no considerable shift changes. Clip 3.1 interacts weakly with primary alkylammonium chlorides; however, with more highly N-substituted compounds no interactions were observed. Therefore, it is likely that NH₄⁺ ions are binding to the pyrazine nitrogens with hydrogen bonding, and cooperative hydrogen bonding or interactions with other parts of the clip determine the overall binding strength. This cooperativity is less possible with more highly N-substituted ammonium ions. This description of ammonium binding to 3.1 is also supported by X-ray crystallography.
Air-sensitive crystals of a 3.1·NH₄PF₆ complex were obtained from layered solutions of clip 3.1 and NH₄PF₆. Crystallographic analysis shows the presence of pairs of clips, connected by two ammonium ions situated between the clip molecules. These dimers are arranged in rows with π-π stacking interactions between the sidewalls of adjacent clips. It is evident from the crystal structure that NH₄⁺ ions are connected to the pyrazine nitrogens, as expected. The inclusion of solvent molecules is also observed (Figure 16). Another interesting observation is that the distance between the outer-rim carbons of each clip’s sidewalls is 11.38 Å, much larger than the optimal distance (6.84 Å) for binding of aromatic guests. This indicates the presence of a sufficiently large cavity to accommodate aromatic guests.

Figure 16. X-Ray crystallographic lattice arrangement of clip 3.1·NH₄PF₆, showing the presence of disordered solvent molecules (2×CHCl₃) in the clip cavity. Additional solvent molecules are located outside the cavity. Hydrogen atoms omitted.

Cavity volume and inclusion compounds: Inclusion of solvent molecules in the molecular cavities of several hosts has been observed using crystallographic analysis. Solvent inclusion is proposed as a general feature of shape- and size-selective binding for these hosts. Inclusion complexes can be formed with weak noncovalent interactions or without any specific interaction, just filling the space of the cavity. This results when a suitable guest is present in large excess or as a solvent during the crystallization process. The crystal structure of the ammonium complex with clip 3.1 includes chloroform molecules in the cavity. Furthermore, the cavity is big enough for binding aromatic units. This prompted us to investigate the inclusion of other molecules. Clip 3.1 was dissolved in nitrobenzene, and the solution was heated under vacuum to remove the free nitrobenzene. The resulting solid was then dissolved in CDCl₃ and examined by ¹H NMR. A 1:1 mixture of free nitrobenzene and 3.1 was observed, suggesting that exactly one nitrobenzene molecule per clip had been present in the isolated solid, situated in
the cavity. This weakly bound nitrobenzene is set free when the inclusion complex is dissolved. Thus it appears that, although organic molecules can be accommodated in the cavity of clip 3.1, the interactions are very weak and competition with solvent molecules renders the detection of the guest difficult.

From the complexation studies and from X-ray crystallographic analysis of the complexes formed with clip 3.1, it is obvious that resorcinol and cations bind to the pyrazine nitrogens. However, the negative CIS values observed for clip 3.1, and to a lesser extent for clip 3.2, cannot be explained by the usual electronic effects, which should give positive CIS values. Another reasonable explanation would be complexation-induced conformational changes that reduced the distance between the sidewalls with in the closed (aa) conformer of the clips 3.1 and 3.2 (Figure 17). Computational studies of clip 3.1 with varied wall-to-wall distances indicated that the variation required for the observed CIS would be associated with only a small change in potential energy (≈24 kJ/mol). The decrease in distance between the sidewalls would at the same time cause the elbow protons H₄ to move away form the bottom phenyls, giving rise to the positive CIS that is observed experimentally.

Figure 17. Overlay of two molecules of clip 3.1 with wall-to-wall distance 11.4 Å (opened) and 4.1 Å (closed) respectively.

A summary of binding of clip 3.1 with various guests is given in Table 2.

Table 2. Summary of various guests studied with clip 3.1.

<table>
<thead>
<tr>
<th>Guest</th>
<th>Interaction</th>
<th>Techniques used (stoichiometry observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resorcinol</td>
<td>Hydrogen bonding to pyrazine nitrogens</td>
<td>NMR and quantitative analysis of the precipitate ([Resorcinol]/[clip] = 4)</td>
</tr>
<tr>
<td>Ag⁺</td>
<td>Metal-to-ligand bonding to pyrazine nitrogens</td>
<td>NMR and gravimetric analysis of the precipitate ([Ag⁺]/[clip] = 1)</td>
</tr>
<tr>
<td>NH₄⁺</td>
<td>Hydrogen bonding to pyrazine nitrogens</td>
<td>NMR and X-ray crystallography</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>Inclusion compounds</td>
<td>NMR ([Nitrobenzene]/[clip] = 1)</td>
</tr>
</tbody>
</table>
3.3 Conclusions

In summary, we have synthesized new molecular clips with a deep cavity and several binding sites for hydrogen bonding, metal-lone pair, cation-π and π-π interactions. Complexation studies with various guests show that, as expected, metal-lone pair and hydrogen bonding interactions dominated, and these studies are supported by X-ray crystallographic analysis of the complex 3.1·NH₄PF₆. However, specific binding of guests inside the cavity was not achieved because of the dominant binding sites positioned outside the cavity and due to solvation effects. The negative CIS observed for the ace-naphthene protons of clips 3.1 and 3.2 was proposed to be due to the modulation of the wall-to-wall distance of these clips upon complexation with the guest. This was supported by a computational treatment of the structure suggesting a small energy difference between the closed and opened structure of 3.1. This conformational flexibility in these systems is very interesting for further developments.
4 *Bis*-porphyrin-terminated glycoluril-based clips [Paper III, IV]

The presence of strong binding sites (pyrazine nitrogens) on acenaphthene clip 3.1 causes the guests to bind outside the cavity. Specific binding of the guests inside the cavity could be achieved by:

- Providing more selective primary binding sites at the outer rim of the clip.
- Blocking the accessibility to the pyrazine nitrogens.

In principle, this could be achieved by constructing a glycoluril backbone with *meso*-tetraarylporphyrin sidewalls. An energy-minimized model of this type of clip shows that the *meso*-phenyls of the porphyrins block the pyrazine nitrogens (Figure 18). At the same time, metals, such as zinc, that can be coordinated in the porphyrin could provide strong and cooperative binding sites for guests with Lewis base functionalities.

*Figure 18.* Pyrazine nitrogens are accessible in clip 3.1, but masked by the phenyl units in clip 4.1. Two different views of each clip are shown, with arrows indicating the pyrazine nitrogens.

Clip 4.1 has several potential binding sites, as does clip 3.1, but clip 4.1 has the additional advantage of zinc in the porphyrins that can bind Lewis bases.
4.1 Synthetic strategies for porphyrin-terminated clips

The retrosynthesis of porphyrin clips is shown in Scheme 2. The target porphyrin clips (4.1 or 4.2) can be obtained by condensing the tetraamino glycoluril derivative with porphyrin dione. The latter might be obtained by the direct dihydroxylation of porphyrin, followed by oxidation. Alternatively, it can be constructed stepwise by nitration, reduction, oxidation and finally hydrolysis. The synthesis of the tetraamine was described in the previous section. Synthesis of porphyrin dione was achieved as described in the next section.

Scheme 2. Retrosynthesis of the porphyrin clips.

4.1.1 Synthesis of porphyrin building blocks

Porphyrin diones (4.3 and 4.4, Scheme 3) were obtained by starting with the synthesis of free-base porphyrins. The free-base meso-tetraphenylporphyrin (TPP) 4.5,51 the metalloporphyrins Cu(II)TPP52 and Zn(II)TPP53 were obtained according to the literature procedures. We attempted the direct dihydroxylation of metallated porphyrin using OsO₄ according to the literature procedures,54 but were unsuccessful. The same dihydroxylation using RuO₄ (produced in situ from RuCl₃ and NaIO₄) did not yield the desired product.55 This could be due to over-oxidation or to the cleavage of double bonds resulting in the formation of fission products.56 Thus, the alternative stepwise route shown in Scheme 3 was adopted.
This multistep route begins with the nitration of metalloporphyrins. The β-nitroporphyrins Cu(II)TPPNO$_2$ (4.6) and TPPNO$_2$ (4.7) were prepared according to literature procedures. Reduction of the nitro compound (4.7) to β-aminoporphyrin (4.8) was achieved with tin chloride dihydrate and conc. HCl. As the aminoporphyrin was sensitive to light and air, it was oxidized immediately after basic work-up. Oxidation was accomplished with Dess-Martin periodinane, followed by hydrolysis with 1 M HCl to get the dioxo compound (4.3) in 48% yield from 4.7. Metallation of 4.3 with zinc acetate dihydrate produced 4.4 in quantitative yield.

The different methods attempted for the synthesis of dioxo porphyrin are shown in the Scheme 3. Phenyl groups were used as the meso-substituents; low solubility rendered work with tolyl and $p$-tert-butylphenyl substituents difficult. Very little product was obtained from the hydroxylation of 4.6 using the sodium salt of benzaldoxime. In summary, the stepwise synthesis of porphyrin dione worked well compared to the direct method, despite the tedious work-up and purification procedures.

\[ \begin{array}{ccc}
\begin{array}{c}
\text{H} \quad \text{N} \\
\end{array}
& \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \qu
4.1.2 Assembly and characterization of clips

Porphyrrin clips were synthesized by the condensation of air-sensitive tetraamine (3.7) with the dioxo porphyrin compound (4.3 or 4.4) to get the corresponding free-base (4.2) or zinc-containing porphyrin clip (4.1) in low yields (Scheme 4). Purification of both clips was quite difficult. We were unable to obtain pure sample of compound 4.2, likely due to the presence of tautomers (several 1H NMR signals were observed for the porphyrin NH protons in the negative region of the spectrum). This was confirmed when the free-base (4.2) was metallated with zinc, producing mainly compound 4.1. Clip 4.1 was subjected to several flash chromatographic columns using various eluents (CHCl₃, mixtures of CH₂Cl₂ and MeOH and of toluene and MeOH at different ratios) to purify it sufficiently. The inclusion of solvent molecules or solvation of the clip also rendered the purification difficult. Traces of toluene were very difficult to remove from the clip, likely due to the formation of inclusion compounds.

Scheme 4. Reagents and conditions: a: THF/MeOH 1:1, reflux, 16 h, N₂; b: Zn(OAc)₂·2H₂O, MeOH/CHCl₃, reflux, 3 h.

The appearance of four meso-0-Ph proton peaks in the ¹H NMR spectrum of 4.1 in toluene-d₈ (Figure 19) indicates that the phenyl rotation is restricted, causing the inner and outer o-Ph protons to experience different environments. Broadening of the methoxy and elbow CH₂ signals in ¹H NMR spectrum of 4.1 is likely due to aggregation as these peaks sharpen at very low concentrations (0.1 μmol). Variable-temperature NMR studies show much broader signals at low temperatures (-50 °C), indicating more aggregation. No evidence for the presence of different clip backbone conformations was found.
4.2 Complexation studies

The zinc-containing clip 4.1, which has Lewis acid binding sites, is more interesting for complexation studies than is 4.2. Coordination of nitrogen and oxygen ligands to Zn-porphyrins is well known in the literature.59 The interactions of clip 4.1 with Lewis bases such as diamines and diols, and with nonpolar guests (substituted fullerenes), were tested (Figure 20). A series of flexible and rigid N-substituted compounds and terminal diols were chosen for this purpose. Diamines are strongly bound in the clip cavity, whereas very weak binding was observed with 1,6-hexanediol using ¹H NMR spectroscopy.

![Figure 20. Some of the guests used for the binding studies.](image)

4.2.1 Binding of cyclic diamines to the clip

Rigid tertiary diamines such as 4,4'-bipyridine (d_{N,N} = 7.151 Å) and 1,4-diazabicyclo[2.2.2.]octane (DABCO d_{N,N} = 2.601 Å) were chosen to monitor the flexibility of the distance between the sidewalls of the clip.

When aliquots of 4,4'-bipyridine were added to clip 4.1, the broad ¹H NMR signals assigned to the CH₃O and elbow protons became sharper, indicating that no aggregation of the complex occurred (cf. free 4.1). Pronounced
chemical shift changes were observed for the guest protons (Δδ -6.35 and -2.67 ppm) (Figure 21).

Figure 21. ¹H NMR spectra of clip 4.1 with 4,4′-bipyridine (500 MHz, CDCl₃ solution, 25 °C). a: Clip 4.1; b: [guest]/[clip]<1; c: [guest]/[clip]≈1; d: guest.

Anisotropic effects of porphyrin ring currents are expected to produce these huge changes of the chemical shifts, and bipyridine is most likely bound inside the cleft, to the two zinc ions of the porphyrins (Figure 22). At higher bipyridine concentrations, separate broad peaks for both the bound and free bipyridine protons were observed due to exchange phenomena.

Figure 22. Complex structures of clip 4.1 with 4,4′-bipyridine (left) and with DABCO (right), calculated using semi empirical methods (PM3). The distance between the two zinc ions (d_{Zn-Zn}) is indicated.

DABCO is much smaller than 4,4′-bipyridine. To accommodate this guest in the cavity, bound to the Zn(II) ions, the sidewalls of 4.1 are expected to move closer together. This was in fact observed when DABCO was added to the clip (Figure 22). The guest protons experienced major shift changes (Δδ ≈ -7.2 ppm) due to the anisotropy effects. Interestingly, when the clip
4.1/DABCO ratio was <1, two separate sets of signals for each of the clip protons were observed in $^1$H NMR. This is likely due to very strong binding and very slow exchange on the NMR time scale.

### 4.2.2 Binding of long-chain diamines to the clip

Long, acyclic alkyl chains are flexible and exist in several interchangeable conformations in solution, rendering their conformational analysis very difficult. Conformational restriction can be achieved by binding long alkyl chains having Lewis basic functionality to the metal centers in the porphyrins.

1,6-Hexyldiamine ($d_{N-N} = 8.829 \text{ Å}$) is one such flexible guest with a long alkyl chain. Very strong binding, with no aggregation, was observed for the equimolar 4.1:1,6-hexyldiamine mixture. 1,6-Hexyldiamine is bound inside the cleft (Figure 23), as evidenced from the symmetry of the guest peaks and the pronounced negative CIS values (Figure 24). Nuclear Overhauser effects are observed only between the $i^{th}$ and $(i+2)^{th}$ (a, b) protons (Figure 24). Thus, the bound 1,6-hexyldiamine exists preferentially in a single, stretched (all-trans) conformation. Therefore, the highly desired conformational restriction of the guest was achieved.

![Complex structures of clip 4.1 with 1,6-hexyldiamine (left) and with 1,8-octyldiamine (right), calculated using semi empirical methods (PM3). The distance between the two zinc ions ($d_{Zn-Zn}$) is indicated.](image)

Figure 23. Complex structures of clip 4.1 with 1,6-hexyldiamine (left) and with 1,8-octyldiamine (right), calculated using semi empirical methods (PM3). The distance between the two zinc ions ($d_{Zn-Zn}$) is indicated.
Figure 24. NMR spectra of clip 4.1 with 1,6-hexyldiamine (500 MHz, CDCl₃ solution, 25 °C). Top: a: Clip 4.1; b: [guest]/[clip]<1; c: [guest]/[clip] ≈1; d: guest; Bottom: Expansion of ROESY spectrum of [guest]/[4.1] ≈1.

As the binding of 1,6-hexyldiamine is ditopic and stretching of the alkyl chain was observed, it is interesting to study even longer diamines. Very strong binding of 1,8-octyldiamine (dₙ₋ₙ = 11.335 Å) to the clip 4.1 with the guest being bound in the pocket with ditopic interactions, was observed by NMR.
Guest protons experienced major negative CIS, as expected (Figure 25). Based on the NOEs observed between \(i^{th}\) and \((i+2)^{th}\) (a, b), between \(i^{th}\) and \((i+1)^{th}\) (c), and between \(i^{th}\) and \((i+3)^{th}\) (d), it is clear that the chain is elongated (Figure 25), but that gauche bonds must be present, \(i.e.,\) this guest is not restricted to a single conformer. This shows that the clip cavity is not large enough to accommodate a fully stretched octyldiamine molecule.

Addition of octylamine to a mono-porphyrin (Zn(II)TPP) resulted in broad peaks for the alkyl protons with partial separation. The binding was not strong, and the broadness observed could be due to the exchange phenomenon and due to conformational changes. The peaks are sharpened at low
temperatures, indicating slower dynamics. With Co(III)TPPCl, the alkyl proton peaks are sharp, and the very negative CIS effects suggest that binding is very strong. However, from the NOEs and coupling constants, it is obvious that the bound octylamine is undergoing conformational changes, so the obtained data is a weighted average of all the conformations. Thus Co(III)TPPCl acted as a chemical shift reagent, but was not useful for restricting the conformations of octylamine. This shows the cooperativity and usefulness of clip 4.1 as a molecular tool. The ability of clip 4.1 to induce conformational locking means that it could be used for the analysis of relative stereochemistry between several stereogenic centers.

4.2.3 Porphyrin clip – fulleropyrrolidine complex

The design and synthesis of porphyrin-fullerene architectures\(^{60}\) and host structures for binding fullerenes\(^{61,62}\) has been growing because of their potential applications in photosynthetic reaction center mimicry,\(^{63}\) artificial photosynthesis, molecular-level optoelectronics,\(^{64}\) etc. The clip 4.1 was shown to accommodate diamines of varying lengths in the cavity, as discussed in the previous section. As the size of fullerene is within the range of suitable guests, it appeared to be interesting to investigate the binding properties of fullerenes in view of possible applications as mentioned above. Triphenylmethylfulleropyrrolidine (4.9) was chosen for the complexation studies based on solubility reasons (Figure 26).

![Schematic representation of 4.1·4.9 complex formation.](image)

Figure 26. Schematic representation of 4.1·4.9 complex formation.

4.2.3.1 Complexation and competition experiments

Upon the addition of fullerene 4.9 to clip 4.1 in toluene-\(d_8\) in an NMR tube, no considerable shift changes were observed. However, in CDCl\(_3\), binding (4.9/4.1 \(\approx 1.5\)) was indicated by chemical shift changes and a broadening of all of the clip’s aromatic \(^1\)H NMR signals. The \(o\)-Ph protons of 4.9 were the only ones affected, and they experienced only slight chemical shift changes. This suggests that the Trt-group is positioned outside of the cavity.
and therefore is not experiencing any chemical shift effects (Figure 27). When the sample was heated to 50 °C, the peak broadening disappeared and 1H NMR shifts similar to those of the free clip were observed, indicating that binding is weaker at high temperatures. Similar effects were observed for the aliphatic protons of both clip and guest. From these experiments it is clear that the binding is not strong, and does not involve the nitrogen-centered lone pair of 4.9.

To ascertain whether the complexation occurs inside the cleft or outside, competition experiments were performed. Competition between various diamines, which are known to bind in the cavity of clip 4.1 (see above), and fullerenes can give reliable information about the binding position.

In CDCl₃ the complex between clip 4.1 and fullerene 4.9 (1:1.5) was mixed with 4,4′-bipyridine, resulting in a 1H NMR spectrum similar to that of the 4.1·bipyridine complex (Figure 27). This signaled the expulsion of fullerene from the clip. In the reverse experiment, the 4.1·bipyridine complex was not affected by the addition of fullerene 4.9. Thus Trt-fulleropyrrolidine, when complexed to 4.1, sits inside the pocket.

Figure 27. 1H NMR spectra of competition experiments (500 MHz, CDCl₃ solution, 25 °C). a: 4,4′-bipyridine; b: clip 4.1; c: 4.1+4,4′-bipyridine (≈1:1); d: [4.1+4,4′-bipyridine]+4.9 (≈1:1:<1); e: [4.1+4.9]+4,4′-bipyridine (≈1:1.5:1); f: 4.1+4.9 (≈1:1.5); g: clip 4.1; h: 4.9.
4.3 Conclusions

Porphyrin-terminated clip 4.1, which has a deep cavity and two opposed Lewis acid metal centers as binding sites that can force a guest into the cavity, was synthesized. Several Lewis basic guests and a fullerene derivative were bound to this clip. The cavity of 4.1 is rather flexible, binding smaller ditopic molecules (e.g. DABCO) and much longer alkyl chains (e.g. 1,8-octylidamines), and even a bulky fullerene can be accommodated. Small and flexible molecules were conformationally restricted when they were locked in the cleft of clip 4.1. Clip 4.1 functions both as a molecular tool for restricting the conformation of long alkyl chains, and as a chemical shift reagent. The importance of cooperative effect is nicely illustrated by comparing the complexation of small molecules to this clip with complexation to mono-porphyrins. Competition experiments showed that complexation of nonpolar fullerenes occurred inside the cavity of 4.1. Clip 4.1 could be used as a tool for the determination of relative stereochemistry of small and flexible compounds with several stereocenters. Clip 4.1 might even be used to determine the relative or absolute stereochemistry of chiral compounds.65
5 Outlook: Switchable clips

The clips discussed so far in this thesis were constructed based on rigid spacers, and were pre-organized in their shape. To expand the scope of guests even further, clips with switchable units in their backbone would be of interest. The spacer (switchable unit) could be any moiety that can be reversibly transformed to another isomer (e.g. cis/trans) upon irradiation with light or by thermal heating (Figure 28). The cis isomer of the clip accommodating flexible guests in a bidentate-manner can be converted to the trans isomer with selective irradiation. This can be used to restrict the conformations of the guest, and therefore to simplify its structural characterization. These systems can also be used as dynamic switching devices between on and off states. Guests bound to the cis form (switch on) could be released in the trans form (switch off) because the distance between the two binding sites is larger in the trans form. This can then be converted back to the cis form, then to the trans form again, and the cycle goes on. These systems could also be used for molecular recognition of a series of guests, and as purification devices. Synthesis of clips with different spacers and sidewalls is in progress.

Figure 28. Schematic representation of the switchable clips.
6 Conclusions

The conclusions from this work are:

- The utility of the cooperative effect in binding guests is nicely illustrated with small hydrocarbon and porphyrin clips. Silver-ion binding to small hydrocarbon-based clips is enhanced by the cooperative effect and by the rigidity in clip-shaped bis-arenes. The binding strength is highly dependent on the solvent properties.
- The synthesis and characterization of various clip-shaped molecules based on glycoluril backbones and with different sidewalls was accomplished.
- Binding studies of an acenaphthene-terminated clip with various guests showed that pyrazine nitrogens are the primary binding sites for guest binding. A complexation-induced conformational change that reduces the distance between the sidewalls is proposed to explain the experimental observations of acenaphthene-terminated clip.
- Ditopic ligands of various lengths bind strongly in the cavities of porphyrin-terminated clips, indicating that the distance between the sidewalls is being modulated. Conformational restriction of long alkyl chains is achieved with this bisporphyrin clip, thus simplifying their characterization.
- Binding of Trt-fulleropyrrolidine in the cavity of porphyrin clip 4.1 was confirmed with competition experiments.

Future developments include:

- Studies on further applications of porphyrin clips, such as the determination of relative stereochemistry between several stereogenic centers, fluorescence studies, applications in catalysis, etc.
- The synthesis of switchable clips and complexation studies of guests to these clips.
Intermolekylär växelverkan i pincettformade molekylära värdsystem:


En användning av vård-gäst-växelverkan, och ett av målen för de delarbeten som presenteras i avhandlingen, är för att underlätta strukturbestämning av små och flexibla molekyler med NMR-spektroskopi. Sådana molekyler ändrar sin konformation mycket snabbt, och förekommer därför i många konformerer som inte enkelt kan särskiljas med NMR-spektroskopi. Detaljerad strukturanalys underlättas om flexibiliteten minskas, t.ex. genom att molekylen binds till en annan molekyl (Bild 1). Om detta sker genom ickekovalent växelverkan talar man om vård-gästinteraktioner, och om det leder till minskad flexibilitet hos gästen kallar vi vårdmolekylen för ett molekylärt verktyg. Växelverkan mellan värd och gäst kan ge tillgång till ytterligare information om gästens struktur.

Bild 1. En liten molekyl växelverkar med en större, pincettlik värdmolekyl på ett sådant sätt att flexibiliteten hos gästen minskas (vänster), och ett av de vård-gästsystem som studerats under avhandlingsarbetet (höger).

Begreppet supramolekylär kemi introducerades av Jean-Marie Lehn 1969. Det definieras som “kemin hos samverkande molekyler och intermolekylär bindning”. Bindning mellan atomer i molekyler är kovalent, medan den mellan molekyler är ickekovalent (Bild 2). Alla intramolekylära (mellanmolekylära) bindingar är av elektrostatisk natur. De är svagare än kovalenta bin-
dingar och bryts därför lättare. I supramolekylära system hålls de enskilda komponenterna samman av sådana bindingar. Supramolekylära system användes initialt för att härma naturen. Idag har området expanderat, och inkluderar bl.a. studier av biologiska processer, molekylär igenkänning, molekylär självorganisation, katalys och medicinsk kemi.


I den här avhandlingen beskrivs tillverkning och studier av ett antal värd-system med pincettlik form, från aromatiska kolväten till en serie mer komplexa föreningar med glykoluril som gemensamt strukturelement. Till detta har arener och tetraarylporfyrin bundits med kovalenta pyrazinbryggor. NMR-spektroskopi har varit den dominerande metoden för detektion och kvantifiering av värd-gästinteraktioner. Komplexering detekteras på flera sätt, det vanligaste är genom de ändringar av kemiskt shift för vätekärnor som uppkommer i och med komplexeringen.

För glycolurilvärdar med exponerade pyrazinenheter skedde all interaktion med Lewissyror vid pyrazinkvävena och på utsidan av klämman. För värdsystemet med porfyriner, där pyrazinkvävena är dolda binds gästerna inuti klämman. Diaminer binds mellan de två väggarna. För några alifatiska diaminer observerades att kolkedjan bands i en enda utsträckt konformer (Bild 4), vilket visar på denna värd potential som molekylärt verktyg för att t.ex. bestämma relativ stereokemi för diaminer med mer än ett stereocenter. Andra tänkbara användningsområden är konstruktion av fotoaktiva supramolekylära system och katalys.

Bild 3. En diamin bunden i utsträckt form mellan två zink(II)porfyrinväggar i en värdmolekyl. Rotationen i kolkedjans bindingar är låst vilket förenklar detaljerad strukturbestämning med NMR-spektroskopi.
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