Modulation and binding properties of extended glycoluril molecular clips†‡

Prasad Polavarapu,[a] Helena Melander,[a] Vratislav Langer,[b] Adolf Gogoll*[a] and Helena Grennberg*[a]

Received (in Durham, UK) 3rd October 2007, Accepted 10th December 2007
First published as an Advance Article on the web 8th January 2008
DOI: 10.1039/b715208f

A glycoluril clip (**1**) provides a deep cavity for binding of guest molecules. Guest species interact preferentially *via* hydrogen bonding or ion–lone pair interactions. Complexation-induced conformational modulation of the cavity wall distance was observed. At higher guest–host ratios, inclusion compounds with organic guest molecules are obtained. The X-ray crystallographic structure of **1**·(NH_4PF_6)·3$CHCl_3$·2CH_3OH shows formation of a network of clips connected *via* polar and non-polar interactions.

1. Introduction

Host–guest systems are of considerable current interest both as mimics for biologically important receptors as well as artificial equivalents for potential new detectors, model systems for intermediates in organometallic chemistry, and tools for molecular screening and analysis. Model systems for supramolecular entities are also at the forefront of new research avenues in organic, bioorganic and biochemical research.[1] Generally, these systems rely on non-covalent intermolecular interactions. We have previously employed interactions between molecules for structure determination in solution by NMR spectroscopy. Initially, we have focused on organopalladium complexes, where the role of the metal was to enforce binding *via* metal–π-allyl complexation. However, steric interactions could be shown to modulate the assortment of organic ligands that could be accommodated by the chelating dinitrogen host.[2] In order to expand the range of possible guest structures, and to achieve a larger flexibility in the shape of the host binding sites, we have more recently turned our attention to clip-shaped bis-arene systems with the ability to bind neutral or cationic guests by π–cation or π–π interactions.[3–8] In one recent example, we have reported a clip with a rigid bis-aryl cavity (5.730 Å) showing increased binding of Ag(I) ions as compared to mono-arene or flexible bis-arene cavities.[8] Because of a wall-to-wall distance shorter than the optimal distance of 6.84 Å,[5] accommodation of organic guests bulkier than toluene[9] is less likely to be observed for such small cavities.

An attractive scaffold that might allow both modulation of the wall-to-wall distance in a preorganised binding site as well as easy synthetic access and flexibility for attachment of a variety of walls, and thus incorporation of various binding sites for non-covalent interactions, is available through glycoluril derivatives.[10] Adapting the extensive work by Nolte and co-workers,[11] the diphenylglycoluril backbone should allow the construction of clips with arene units at least 7 Å apart.[12] However, previous examples indicate that even a larger binding site may suffer from steric repulsions that counteract the binding of guests if it is situated too close to the glycoluril backbone unit. Therefore, we set out to design glycoluril based clips with a deeper binding cavity compared to the previously reported compounds.

A particular challenge is to balance several potential binding sites in the same molecule for the intended purpose.[11] The diphenylglycoluril backbone itself provides a stilbene-type bis-aryl unit at the outside of the backbone, which may bind metal ions, if not small aromatic guests. Furthermore, the heteroatoms present in the inner turn of the clip are hydrogen bond acceptors accessible to Lewis acids. Therefore, it is essential that the additional binding sites at the top of the clip have higher affinity for the intended guests than those of the backbone.

In the present paper, we present the synthesis of two novel, deep cavity arene-terminated clips **1** and **2** based on the previously reported precursor clip **3**,[13] a ^{1}H NMR survey of their interactions with neutral and cationic guests, as well as the formation and X-ray analysis of a **1**·NH_4PF_6 complex. These studies should provide a key to a deeper understanding of the host behaviour of this group of compounds.

2. Results and discussion

2.1 Preparation and characterisation of clips

The arene-terminated molecular clips **1** and **2** were prepared from the precursor glycoluril derivative **3** by nitration, reduction of the tetranitro intermediate **4** to the tetra-amine **5**, followed by immediate reaction with 1,2-diketones **6** or **7**

[a] *Department of Biochemistry and Organic Chemistry, Uppsala University, Box 576, S-751 23 Uppsala, Sweden. E-mail: Adolf Gogoll@biorg.uu.se. E-mail: Helena.Grennberg@biorg.uu.se*
[b] *Environmental Inorganic Chemistry, Department of Chemical and Biological Engineering, Chalmers University of Technology, S-412 96 Gothenburg, Sweden*

† Dedicated to Jan-E. Bäckvall on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: NMR titration spectra and CIS values, ^{1}H NMR spectrum of complex clip **1**·$PhNO_2$, AM1 data for potential energy *vs.* clip **1** wall distance, and hydrogen bond parameters from the X-ray analysis. See DOI: 10.1039/b715208f

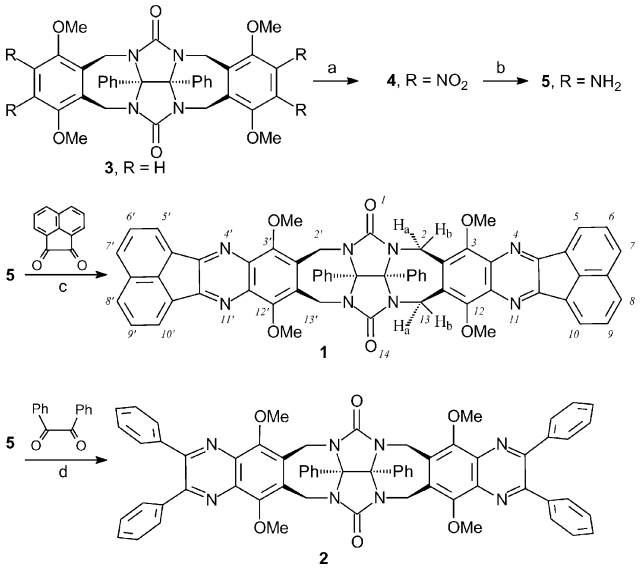


Fig. 1 Synthesis of clips **1** and **2**, a: HNO_3, Ac_2O, −78 °C, then 12 h at rt, 82%; b: Pd/C (10%), HCO_2NH_4, 4 h; c: acenaphthenequinone (**6**), THF–CH_3OH 1 : 1, reflux 48 h, Ar, 49% from **4**; d: benzil (**7**), THF–CH_3OH 1 : 1, HOAc, reflux 16 h, Ar, 47% from **4**.

(Fig. 1). It turned out to be essential that the nitration step be carried out at −78 °C.[14] In the reduction step, the extremely air-sensitive tetra-amine is not isolated, but subjected immediately to the corresponding 1,2-diketone under an argon atmosphere. Clips **1** and **2** were obtained in 49% and 47% isolated yields based on intermediate **4**.

Glycoluril derivatives with structures similar to those of **1**–**3** may be involved in conformational equilibria between isomers having different orientations of the wall segments attached to the glycoluril core (Fig. 2).[15] Such processes may result in sets of separate ^{1}H NMR signals for individual species. For solutions of **1** and **3**, only single sets of signals were detected by ^{1}H NMR spectroscopy (500 MHz). Clips **1** and **3** were analysed in the temperature range −55 °C to +55 °C, with observation of a single conformer, as opposed to a fast equilibrium between several conformers. The conformer observed corresponds to the *aa* (*i.e.*, closed clip, Fig. 2) orientation of the "walls". This was proven for clips **1** and **3** by the observation of the NOEs involving the elbow CH_2 unit (C-2, C-2′, C-13, C-13′). As is evident from inspection of structures derived from semi empirical calculations (AM1), in the *aa* conformer, the elbow protons H_a would be expected to be closest to the phenyl groups, and H_b closest to the methoxy groups. In the *as* conformer, both elbow protons H_a and H_b on the open side would be closest to the methoxy protons. The exclusive detection of an NOE between the H_a protons and the phenyl protons, and of an NOE between the H_b protons and the CH_3O protons is consistent with the *aa* conformer and also assigns the identity of these protons (Fig. 1). The negligible shift changes observed for clip **1** on varying the temperature indicate that this clip, in contrast to **3**,[12,16] is not aggregating under the conditions of this investigation.

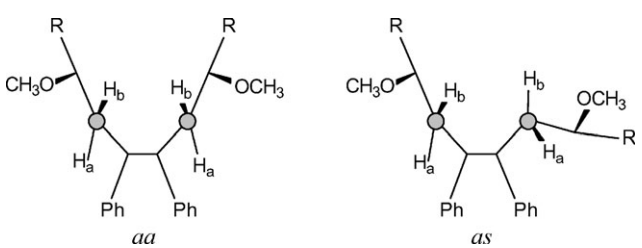


Fig. 2 Schematic presentation of the *aa* (closed) and *as* (open) conformers of glycoluril clips.

2.2 Interactions with water

Clip **1** binds water molecules, indicated by a ^{1}H NMR water peak that shifts to higher frequencies as the temperature is decreased, from δ 1.580 at +25 °C to δ 2.077 at −55 °C.[17] The relative integral of this signal decreases with temperature, approaching the equivalent of four protons at −55 °C. This indicates an equilibrium between free and clip-bound water molecules. The water signal in solutions of clip **3** behaves differently, *i.e.*, two separate signals are observed at δ = 4.73 and 4.15 (broad) at 25 °C. At −55 °C, these peaks disappeared, indicating the freezing out of loosely bound water.

Obviously, water binds differently to these clips. Most likely, water binds weakly to the glycoluril oxygens of clip **3**, but stronger to the pyrazine nitrogens of **1**, substituted pyrazines being stronger bases (pK_a 0.6–2.8)[18] than urea analogues (pK_a *ca.* 0.1–0.2),[19] and in keeping with literature data on pyrazine hydrogen bonding with water.[20]

2.3 Interactions with arenes in chloroform solution

Aromatic host systems belonging to the same general group as our clips are reported to bind electron-deficient aromatic compounds both in the solid state and in solution.[3,12,15] However, for chloroform solutions of clip **1**, no interaction with tetraquinodimethane or tetracyanobenzene could be detected by ^{1}H NMR or UV-Vis spectroscopy. Similar results were obtained for 1,3-dinitrobenzene, 4-chloronitrobenzene and 1,4-dinitrobenzene, which was surprising in view of the large distance between the methoxy substituents, which has been suggested to prevent access to the cavity in related clips,[4d] and which thus should not influence arene–arene interactions in clip **1**. We propose that for clip **1**, binding of weakly interacting aromatic guest molecules is prevented by competition with far more abundant solvent molecules (*vide infra*). In contrast, 1,3-dihydroxybenzene (resorcinol), which is a Lewis acid, was found to bind to clips **1**–**3**. Binding to **3** has previously been studied and proposed to occur by hydrogen bonding to the glycoluril oxygens.[4a,11,21] The location of resorcinol inside the clip cavity was deduced from the observed negative complexation induced shifts (CIS). The observed ^{1}H NMR chemical shift changes for clip **3** in the presence of resorcinol in the current investigation (Fig. 3) are in accordance with that proposal. For clips **1** and **2**, however, while ^{1}H NMR chemical shift changes indicate interaction with resorcinol, we conclude that the binding site for resorcinol cannot be the same as in clip **3**. In particular, the chemical shifts of the resorcinol protons change to lower frequencies, *i.e.*, CIS are negative, in the presence of clip **3**. In contrast, resorcinol proton signals are shifted to higher frequencies (positive CIS) in the presence of clip **1**. Clip **2** has a similar but smaller

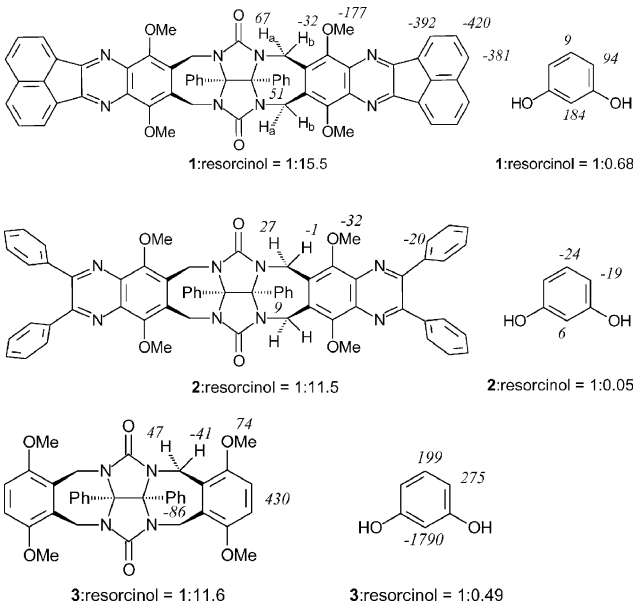


Fig. 3 ^{1}H NMR CIS, $\Delta\delta = \delta_{(1+\text{resorcinol})} - \delta_1$ (or $\delta_{\text{resorcinol}}$) in ppb observed for clips **1**–**3** upon addition of resorcinol.

effect. Most likely, resorcinol is interacting with the pyrazine units in **1** and **2** by hydrogen bond formation, with the resorcinol located outside of the cavity, subjecting it to electronic effects but not anisotropy effects from the clip walls. Likewise, for the clip protons of **3**, CIS are negative in its complex with resorcinol, and have been explained by the exposure to the aromatic ring current anisotropy effect of the resorcinol guest.[11] Surprisingly, also clip **1** shows lower chemical shifts, *i.e.*, negative CIS, for most of its protons when exposed to resorcinol. However, in this case this cannot be an anisotropy effect from the aromatic ligand as for clip **3** (*vide supra*). The larger effect on the acenaphthene protons of clip **1** (H-5, H-6, H-7 and symmetry related positions, see Fig. 1, $\Delta\delta = -381$ to -420 ppb) as compared to the rim phenyl protons of clip **2** ($\Delta\delta = -20$ ppb) is most likely due to the involvement of these protons in phenyl rotation. Lack of conjugation between the pyrazine unit and the tilted phenyl rings (clip **2**), as opposed to the conjugated acenaphthene unit (clip **1**) also might result in such quantitatively different chemical shift effects. However, since hydrogen bonding or complexation of Lewis acids to the pyrazine nitrogens should result in reduced electron density, thus positive CIS, which is the opposite of what is observed for **1** and **2**, this explanation can be discarded (*vide infra*). Incidentally, upon protonation of clip **1** with trifluoroacetic acid (TFA), such positive CIS are observed, with $\Delta\delta_{\text{H-5}} \approx \Delta\delta_{\text{H-7}} > \Delta\delta_{\text{H-6}}$, as would be expected from resonance formulae for protonation of the pyrazine nitrogens.

On titration of clip **1** with resorcinol, CIS to lower frequencies as well as signal broadening are observed until four equivalents of resorcinol have been added (Fig. 3 and Fig. 4). At higher resorcinol ratios (**1** : resorcinol beyond 1 : >8), the chemical shifts of protons H-5, H-6, and H-7 increased again (Fig. 4), which indicates the presence of two counteracting effects, one with negative, and the other with positive CIS. The latter is likely to be an electronic effect, *i.e.*,

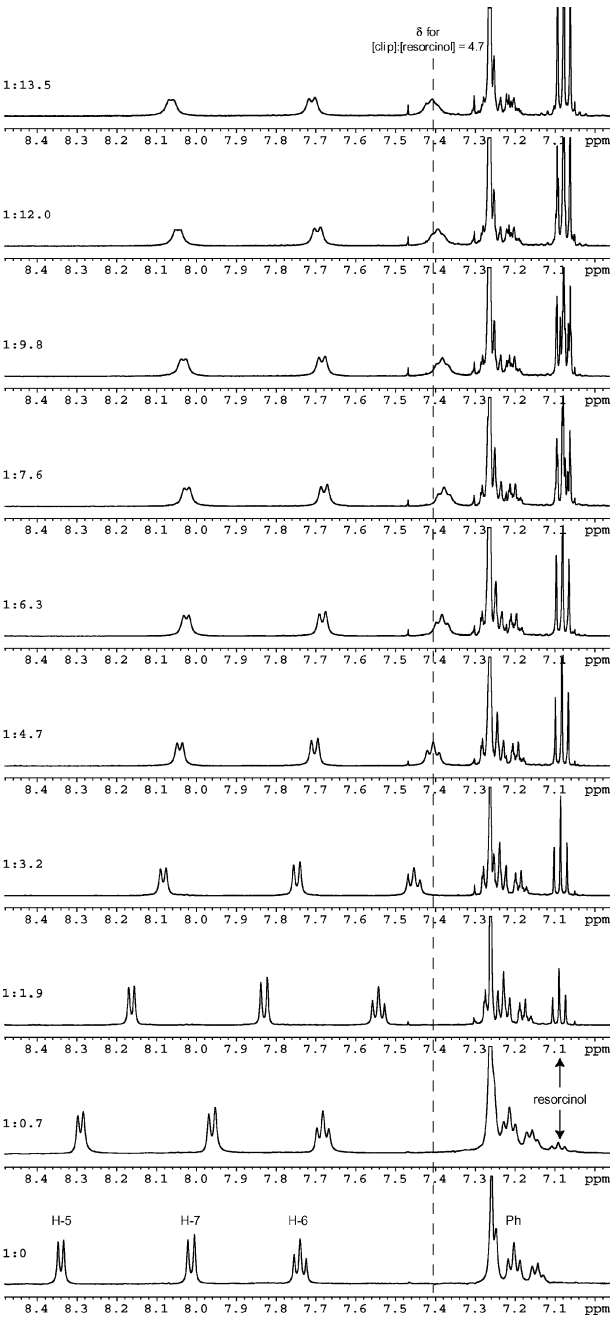


Fig. 4 Expansions of ^{1}H NMR spectra showing chemical shift alterations of rim (H-5, H-6, H-7) and backbone phenyl protons during titration of a solution of clip **1** with resorcinol ($CDCl_3$ solution, 500 MHz, 25 °C). Molecular ratios of clip **1** : resorcinol are indicated.

reducing the electron density of the pyrazine nitrogens due to hydrogen bonding. Furthermore, at higher resorcinol concentrations, a yellow solid gradually precipitated from the solution. This prevented quantitative evaluation in terms of linear or non-linear fitting procedures as well as low temperature NMR studies of the interaction. The precipitate was collected and re-dissolved in $CDCl_3$, with ^{1}H NMR analysis showing the presence of clip **1** and resorcinol in a 1 : 4 stoichiometric ratio. In summary, these observations clearly indicate complexation equilibria involving resorcinol hydrogen bonding to

the four pyrazine nitrogens of clip **1** (Fig. 5), followed by aggregation of the resulting complex.

2.4 Interactions with Ag^+ and other cations in solution

Clips **1**–**3** have several potential binding sites for different non-covalent interactions. Therefore, we also investigated interactions with cationic guests. Silver ions and other cationic guests may bind to bis-arene cavities,[6,7] but also to Lewis-basic heteroatoms. In addition, all clips have a stilbene-like (*i.e.*, *cis*-diphenyl) site for cooperative binding in the backbone segment. Clip **2** possesses two further such sites at the rims of the walls, whereas the acenaphthene units at the rims of **1** likely constitute a less cooperative bis-arene binding site due to the larger distance between these arene units. Furthermore, the pyrazine nitrogens of **1** and **2** likely accept not only hydrogen bond donor guests but also Lewis acids.

In the presence of silver ions, pronounced changes in the ^{1}H NMR chemical shifts of clip **1** were observed (Fig. 6). For clip

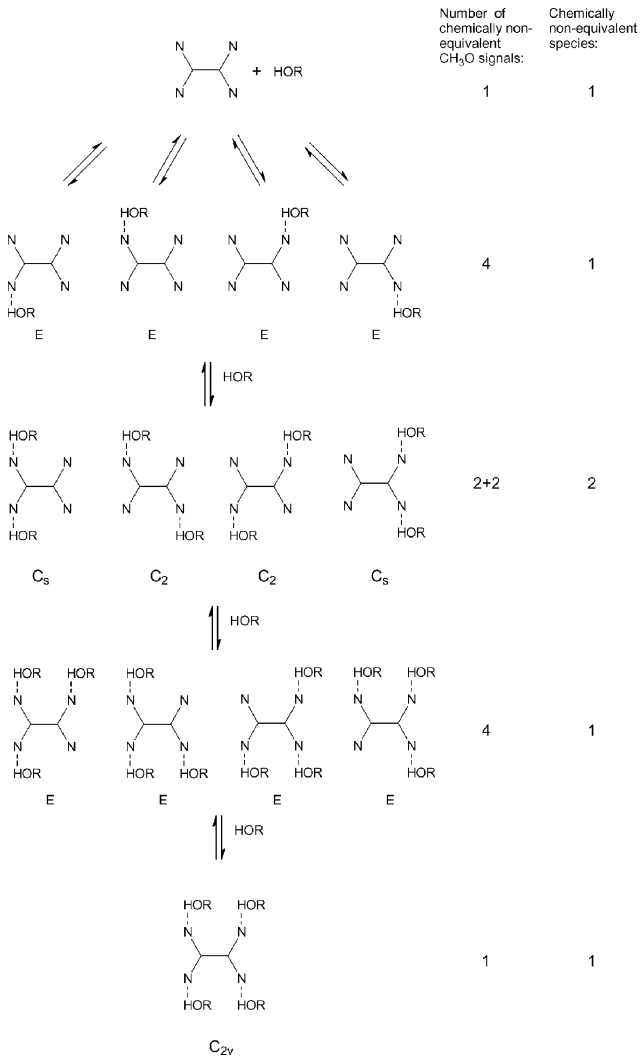


Fig. 5 Schematic presentation of possible complexes formed between clip **1** and resorcinol binding to the four pyrazine nitrogens. The symmetry is indicated for each species. For the classifications of the symmetry groups, the resorcinol is assumed to reorientate rapidly (R = *m*-C_6H_4OH).

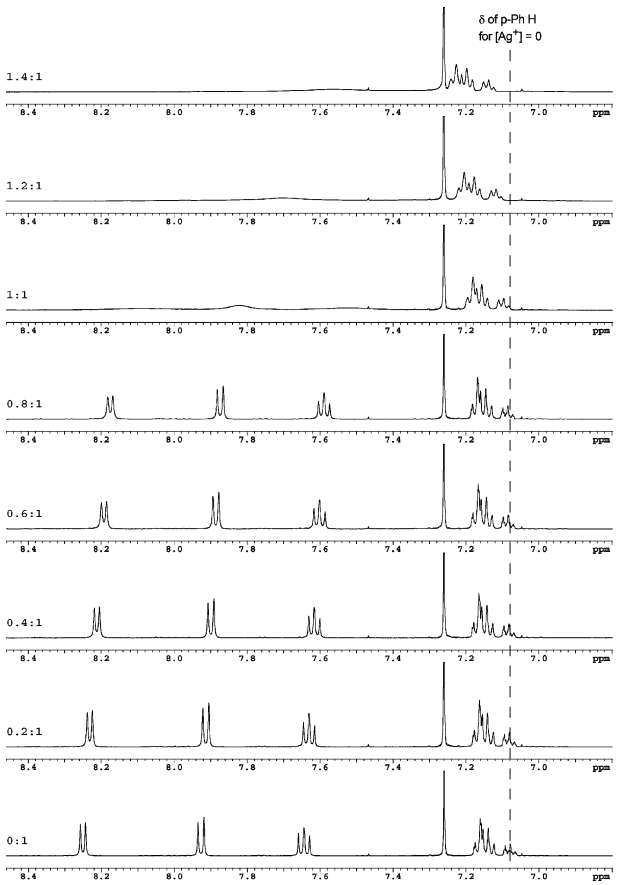


Fig. 6 Expansion of the aromatic region of ^{1}H NMR spectra of clip **1** with various Ag^+ : **1** ratios, indicated on the left hand side of the spectra (500 MHz, solvent $CDCl_3$–MeOH-d_4 9 : 1). The dashed line indicates δ for the *para*-Ph protons of backbone Ph groups in the absence of Ag^+.

1 : Ag^+ ratios 1 : <1, the acenaphthene signals (H-5, H-6, H-7 and symmetry related positions) are broader than in the absence of Ag^+ and have negative CIS, with a $|\Delta\delta|$ order of H-5 > H-6 > H-7. This broadening holds also for the methoxy protons and the H-2_a signals of the elbow CH_2 unit, although the latter have a positive CIS. The signal of H_b remains largely unaffected. Silver ion addition to clip **2** produced an initial decrease of chemical shifts, followed by an increase at higher silver ratios. Signal broadening of protons at the outer rim, *i.e.*, the terminal phenyl rings, was not observed. All clips, including **3**, exhibit small and similar chemical shift effects (to higher frequencies) for phenyl protons of the glycoluril core when exposed to silver ions. These effects are likely to indicate weak binding of Ag^+ to the backbone *cis*-diphenyl pocket.[6,8]

These observations suggest that the pyrazine nitrogens of **1** and **2** provide the most efficient binding site for Ag^+.[22,23] The complexation results in a dynamic equilibrium between several species, obvious from the spectrum of the acenaphthene protons of clip **1**. These signals exhibit a pseudo-coalescence, *i.e.*, a sharp signal appears at an average δ value due to increased exchange rate when increasing the temperature for a mixture with a Ag^+/clip **1** ratio > 1 (Fig. 7).

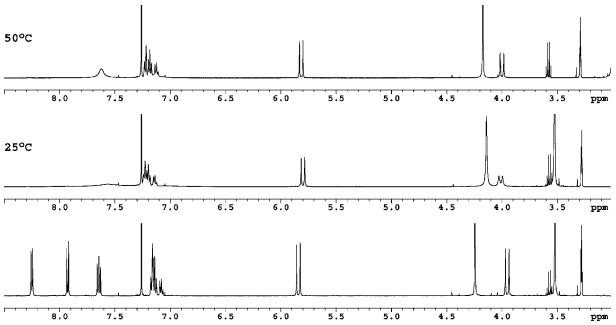


Fig. 7 Variable temperature ^{1}H NMR spectra of clip **1** with $AgClO_4$ (ratio 1 : 1.4) at 50 °C and 25 °C, respectively. Bottom: Spectrum for $[Ag^+] = 0$.

At Ag^+ : clip ratios >1 : 1, an insoluble precipitate is formed. As was the case for studies with resorcinol, the limited solubility of the complex prevents both low temperature NMR studies and quantitative evaluations of the complexation process. However, gravimetric analysis of the precipitate obtained from a solution of clip **1** indicated formation of a 1 : 1 complex, *i.e.*, [clip **1**]·$AgClO_4$.

Also, ammonium ions might bind *via* π–cation interactions or *via* hydrogen bonding to the pyrazine segments.[24–26] Addition of ammonium hexafluorophosphate to clips **1** and **2** resulted in ^{1}H chemical shift changes similar to those observed in the presence of silver ions, *i.e.*, negative CIS, with $\Delta\delta$ in the order H-5 > H-6 > H-7. With clip **3**, on the other hand, effects were very weak. Weak interactions with clip **1** were also detected for a series of primary alkylammonium hydrochlorides, whereas more highly N-substituted compounds did not show interactions. It thus appears likely that RNH_3^+ ions form hydrogen bonds to the pyrazine units, and interact weakly or not at all with other regions of the clips. This is also supported by the X-ray crystallographic analysis (*vide infra*).

The negative CIS observed for clips **1** and, to a lesser extent, clip **2**, upon binding of resorcinol, Ag^+ ions, or NH_4^+, cannot be explained by charge effects (*cf.* the positive CIS for protonation with TFA). Nor can they be explained by ligand anisotropy effects, as was possible for the interaction between resorcinol and clip **3**, or by aggregation of glycoluril clips with arene walls, which was applicable to previously reported clips with smaller cavities.[3,11] Since no paramagnetic species are involved either, the only reasonable explanation is a complexation induced conformational change of clips **1** and **2**, resulting in a closer distance between the opposing arene walls within the closed (*aa*) conformer of a clip (Fig. 8). The observed effects of up to *ca.* −0.4 ppm would require a distance between the acenaphthene units of clip **1** of around 4 Å according to the Johnson–Bovey model.[27] Due to the phenyl rotation of the rim phenyls of clip **2**, a considerably smaller effect is expected for this clip, and is also observed. According to computations (AM1), the energy difference between the lowest energy conformation of clip **1** and a conformation with the distance required to produce the observed CIS is only *ca.* 24 kJ mol^{-1} (Fig. 8). At the same time, such a clip cavity contraction would move the elbow protons H-2_a away from the backbone phenyl ring, which is in agreement with the observed positive CIS for these protons. A possible driving force responsible for the closing of the clip cavity might be a dynamic process where a binding species, *i.e.*, resorcinol, Ag^+ or NH_4^+ ions, is involved in a fast equilibrium, alternately binding to two pyrazine nitrogens of opposed clip walls.

2.5 X-Ray crystallographic characterisation of an ammonium–clip 1 complex

Air-sensitive crystals suitable for X-ray crystallographic characterisation were obtained from layered solutions of clip **1** and ammonium hexafluorophosphate. The arrangement of individual units of clip **1**·NH_4PF_6 in the crystal lattice appears to be governed by ionic interactions with the ammonium ions and their counterions, resulting in pairs of clips (Fig. 9). As expected, all ammonium ions are located close to pyrazine units,[26] with two ammonium ions situated between two clip molecules (a and b), with a N–N ($NH_4^+\cdots$clip-N) distance of 3.091(2) Å (clip a), 3.359(3) Å (clip b), and a N–O ($NH_4^+\cdots OCH_3$) distance of 2.887(2) Å (clip b). Dimers are arranged in rows with non-polar interactions between them. Interestingly, the single methoxy group of each clip that is not oriented towards the cavity is instead directed towards the clip molecule of the adjacent pair, suggesting dipole–dipole interactions. The distance between the contacting walls of these dimers is 3.431(3) Å, which is similar to the intermolecular distance in crystals of acenaphtho[1,2-*b*]pyrazine (3.417(2) Å),[28] and not far from that in graphite (3.354 Å),[29] indicating

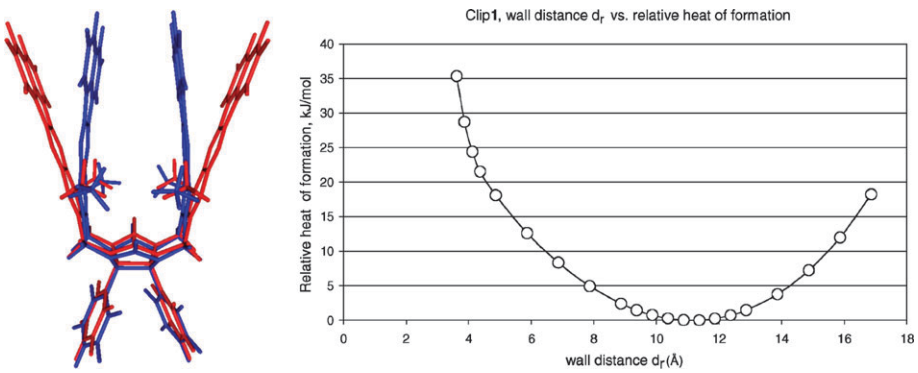


Fig. 8 Overlay of two molecules of clip **1** with d_r = 11.4 Å (red) and 4.1 Å (blue), respectively, and potential energy profile of wall distance *vs.* relative heat of formation.

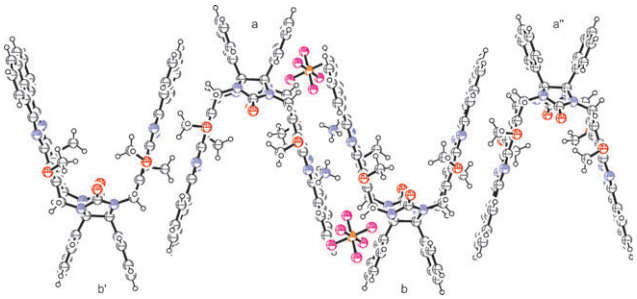


Fig. 9 Lattice arrangement of clip **1**·NH_4PF_6: pair of molecules (a + b) held together *via* ammonium ions, adjacent molecules (a″ and b′) with π–π stacking and dipole–dipole interactions. Solvent molecules are omitted for clarity. Non-hydrogen atoms are shown at the 50% probability level (isotropic spheres).

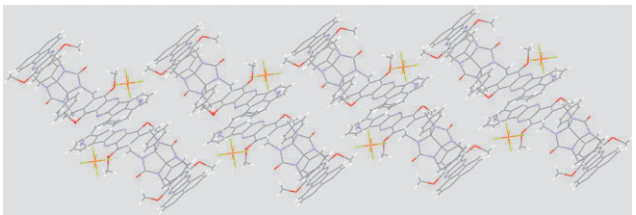


Fig. 10 Lattice arrangement of clip **1**·NH_4PF_6, showing alignment of dimers along the *a* axis *via* polar interactions. Solvent molecules are omitted for clarity.

π–π stacking interactions between the sidewalls of the clips. The dimer rows are aligned parallel to the crystallographic *a* axis by polar contacts (Fig. 10).

2.6 Cavity volume and solvatisation

The cavity angle (Table 1) for clip **1** is smaller than that for most previously reported clips, *e.g.*, **3**,[13] and **8**,[30] whereas the distance d_r between outer rim carbons is far larger for clip **1** than for the others, and also larger than the suggested optimal distance for binding aromatic guests of 6.84 Å.[5] Furthermore, clip **1** also has a considerably deeper cavity than these previously reported clips. In this context, a particularly appealing finding is that the cavity of the clip is filled by chloroform molecules (Fig. 11), further chloroform and methanol molecules are present in the crystal lattice but outside of the clip cavity. This obviously reflects the solvent mixture used for crystallisation, and is also reflected in the elemental analysis of clip **1**. Incorporation of solvent molecules into the crystal lattice is not uncommon. In particular, inclusion of solvent molecules into molecular cavities has been observed in crystallographic analysis of related clips,[12,31,32] and this has been proposed as being a general feature for shape selective binding for this type of host molecule.[31b] Since obviously more than one solvent molecule can be accommodated inside the cavity of **1**, it appears unlikely that cavity size and effects from substituents close to the backbone[4] should block incorporation of small arene guests inside the cavity of clip **1** in titration experiments. A more likely explanation is competition between the solvent and the intended guests, where high concentration of solvent molecules and fast exchange render detection of both solvent and arene complexation difficult.

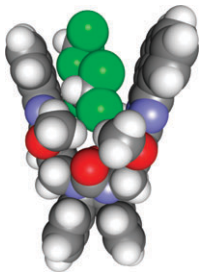
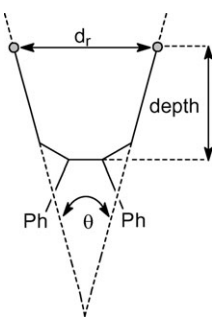
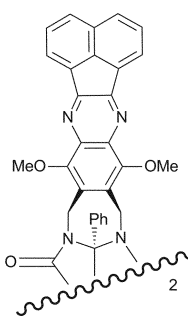
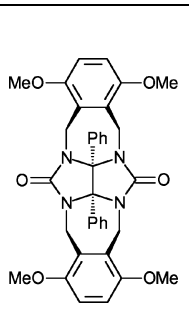
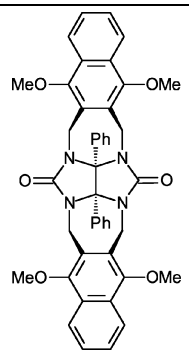
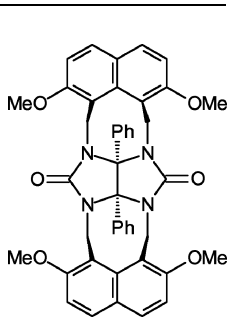


Fig. 11 Lattice arrangement of clip **1**·NH_4PF_6: clip cavity filled with disordered solvent molecules (*i.e.*, 2 × $CHCl_3$). Additional chloroform and methanol molecules are located outside of the clip cavity.

Thus, although clip **1** can accommodate organic molecules in its cavity, binding appears to be not sufficiently strong to generate appreciable populations of such host–guest complexes in solution. One problem is the accessibility of hydrogen bonding donor sites for species situated outside of the cavity

Table 1 Key geometrical features for **1**·NH_4PF_6 and related clips

	1·NH_4PF_6	**3**[a]	**8**[b]	**9**[c]
					
Cavity angle (θ)/°	33.2	48.5	54.1	26.8
Outer rim distance (d_r)/Å[d]	11.38	7.91	10.37	7.01
Depth/Å	10.88	4.55	6.73	5.26

[a] Ref. 13. [b] Ref. 30. [c] Ref. 12, inclusion complex with nitrobenzene. [d] Between rim carbons.

(*cf.* binding of NH_4^+ ions as well as formation of a 1 : 4 complex with resorcinol). In addition, solubility properties of **1** prevent the use of, *e.g.*, a polar solvent that otherwise might direct less polar guests into the cavity. A tempting question is whether it might be possible to force guest molecules into the cavity by choice of solvent used for recrystallisation. We believe this to be the case for the chloroform molecules found inside the cavity in the crystal lattice of clip **1**·NH_4PF_6 (volume of $CHCl_3$: 93.28 Å^3). Recrystallisation conditions might thus lead to incorporation of an arene guest without the requirement of specific binding interactions, if competition with less strongly binding but more abundant solvent molecules (*e.g.*, chloroform) can be avoided. Thus, when clip **1** was dissolved in hot nitrobenzene, followed by evaporation of excess nitrobenzene, a solid compound of composition clip **1**·$PhNO_2$ (volume of $PhNO_2$: 137.03 Å^3) was obtained. This appears to be a nice illustration of the recently proposed importance of molecular volume for the formation of molecular inclusion compounds.[32]

3. Conclusions

We have devised a molecular clip with a deep cavity as well as several binding sites for hydrogen bonding, metal–lone pair, metal–π and π–π interactions. As expected, the strongest of these interactions, *i.e.*, hydrogen bonding and metal–lone pair binding, in competition with π–π interactions, dominated the overall performance of this host. Formation of sufficiently stable inclusion complexes in solution requires a host with the ability to provide a cavity environment sufficiently different from the surrounding solvent, or binding sites directed towards the inside of its molecular cavity. The deep cavity of clip **1** allows for considerable conformational flexibility to modulate the wall-to-wall distance upon complexation. Studies are in progress to utilise this flexibility for more specific binding, as well as to provide a more selective primary binding site at the outer rim of a clip for specific host–guest interactions.

4. Experimental

4.1 General experimental details

UV-Vis spectra were recorded on a Varian Cary 3 Bio spectrophotometer using 1 mm quartz cuvettes. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury plus (^{1}H at 300.03 MHz, ^{13}C at 75.45 MHz), or on a Varian Unity 400 (^{1}H at 399.98 MHz, ^{13}C at 100.58 MHz), or on a Varian Unity Inova 500 (^{1}H at 499.94 MHz, ^{13}C at 125.7 MHz) spectrometer. Chemical shifts are reported in ppm referenced to tetramethylsilane *via* the residual solvent signal ($CDCl_3$, ^{1}H at 7.26 and ^{13}C at 77 ppm). Coupling constants are given in Hz. NMR signals were assigned from PE-COSY,[33] gHSQC,[34] gHMBC,[35] gNOESY,[36] and TOCSY[37] spectra. IR spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer. Melting points were determined using a Stuart Scientific melting point apparatus SMP10 and are uncorrected. Analytical TLC was performed using Merck pre-coated silica gel 60 F_{254} or Merck neutral aluminium oxide 60 F_{254} plates. For column chromatography Matrex silica gel (60 Å, 35–70 μm) or neutral activated or basic activated alumina (60 mesh) from Strem chemicals were used. All commercially available chemicals were purchased from suppliers and used without purification. Dry solvents were obtained by distillation from sodium and benzophenone (diethyl ether, THF) or CaH_2 (CH_2Cl_2). Geometry optimisations were done by semiempirical methods (AM1).

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]-benz[*f*]azulene-6,13-dione 3. 3 was prepared following literature procedures.[13]

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethoxy-2,3,9,10-tetranitro-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz-[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (4). 4 was prepared as previously reported.[14]. Compound **3** (2 g, 3.23 mmol) was dissolved in 10 mL acetic anhydride and cooled to −78 °C in an acetone–dry ice bath. HNO_3 (3.5 mL 65%) was slowly mixed with acetic anhydride (8.8 mL) at 0 °C and then dropwise added to the reaction mixture under stirring at −78 °C. After 30 min, the bath was removed, the reaction mixture was stirred for an additional 12 h at room temperature. Cold (0 °C) methanol (19 mL) was then added to the reaction flask. Upon further cooling, a yellow precipitate appeared. This was collected by filtration, washed with cold methanol and dried under vacuum to yield **4** (2.12 g, 82%) as yellow powder; mp: 285 °C (dec.). ^{1}H NMR data are in accordance with those reported in the literature.[14] ^{1}H NMR ($CDCl_3$): δ 7.08–7.23 (m, 10H, Ph), 5.56 (d, J = 16.5, 4H, CH_2), 4.10 (s, 12H, OCH_3), 3.93 (d, J = 16.5, 4H, CH_2).

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethoxy-2,3,9,10-tetramino-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz-[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (5).[14]. This transformation was carried out using a setup consisting of two reaction flasks connected by a glass filter adapter, with inlet for argon and mineral oil bubbler. Argon was bubbled through a mixture of dry tetrahydrofuran (50 mL), dry methanol (50 mL), and molecular sieves in one of the flasks for 30 min. With care to maintain the argon atmosphere, **4** (1 g, 1.25 mmol) and 10% Pd/C (250 mg) were added and the mixture was stirred for 10 min. Ammonium formate (1.82 g, 28.8 mmol) was added and the stirring was continued for 4 h at room temperature. Solids were removed by filtration through the glass frit by rotating the setup by 180°; transfer of the solution was aided by applying a slight argon overpressure. Due to the air sensitivity of tetra-amino compound **5**, it was used directly in the syntheses of clips **1** and **2**.

An analytical sample of **5** was obtained by evaporation of solvents to give **5** as a pale yellow oil. ^{1}H NMR data were in good agreement with those reported in the literature.[14] ^{1}H NMR ($CDCl_3$, Ar atmosphere): δ 7.08 (m, 10H, Ph), 5.38 (d, J = 16.5, 4H, CH_2), 3.84 (s, 12H, OCH_3), 3.80 (d, J = 16.5, 4H, CH_2), 1.30 (br s, 8H, NH_2).

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraaza(7′,10′-diazafluoranth-eno[8′,9′-*d*])benz[5,6]azuleno[2,1,8-*ija*](7′,10′-diazafluoranthe-no-[8′,9′-*d*])benz[*f*]azulene-6,13-dione, clip 1. With care to maintain an argon atmosphere, molecular sieves, a bar magnet,

degassed THF–methanol (1 : 1, 50 mL) and acenaphthenequinone **6** (450 mg, 2.5 mmol) were added to freshly prepared **5** (from 1.25 mmol of **4**). The mixture was heated at reflux for 36 h, after which time the contents were cooled down to rt, filtered, and the precipitate was washed with dichloromethane (5 × 50 mL). The combined filtrate was evaporated to dryness and the residue was re-dissolved in refluxing dichloromethane (200 mL) and filtered; the filtrate was concentrated and purified by column chromatography using dichloromethane as an eluent, and gradually increasing the polarity up to CH_2Cl_2–MeOH (8 : 2). Clip **1** was obtained as a yellow powder (594 mg, 0.612 mmol, 49% yield from **4**), mp >350 °C. ^{1}H NMR ($CDCl_3$): δ 8.33 (dd, J = 7.1, 0.7 Hz, 4H, H-5), 8.00 (dd, J = 8.3, 0.7 Hz, 4H, H-7), 7.73 (dd, J = 7.1, 8.3 Hz, 4H, H-6), 7.14–7.27 (m, 10H, Ph), 5.96 (d, J = 16.2 Hz, 4H, CH_{2b}), 4.38 (s, 12H, OCH_3), 4.01 (d, J = 16.2 Hz, 4H, CH_{2a}). ^{13}C NMR ($CDCl_3$): δ 157.7 (2C, C = O-1), 153.0 (4C, C-4a), 150.3 (4C, C-3), 136.6 (2C, C-7b), 136.2 (4C, C-3a), 134.0 (2C, C-*i*-Ph), 131.9 (2C, C-7a), 130.3 (4C, C-2a), 130.0 (4C, C-4b), 129.6 (4C, C-7), 129.1 (2C, C-*p*-Ph), 129.0 (4C, C-6), 128.6 (4C, C-*m*-Ph), 128.5 (4C, C-*o*-Ph), 122.3 (4C, C-5), 85.3 (2C, C-1b), 63.9 (4C, OCH_3, C-OCH_3), 38.3 (4C, CH_2, C-2). Elemental analysis was obtained for an analytical sample further purified by recrystallisation from a chloroform–methanol mixture. $C_{60}H_{42}N_8O_6$, calculated C, 74.22; H, 4.36; N, 11.54%. Found: C, 67.31; H, 4.42; N, 9.94%; calculated for $[100C_{60}H_{24}N_8O_6]\cdot[9CHCl_3]\cdot[6CH_3OH]$: C, 67.29; H, 4.48; N, 10.04%.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraaza(3,6-diaza-4,5-diphenylbenz[1,2-*d*])benz[5,6]azuleno[2,1,8-*ija*](3,6-diaza-4,5-diphenylbenz-[1,2-*d*])benz[*f*]azulene-6,13-dione, clip 2. With care to maintain an argon atmosphere, molecular sieves, a bar magnet, degassed THF–methanol (1 : 1, 30 mL), benzil (270 mg, 0.65 mmol) and acetic acid (1 mL) was added to recently obtained **5** (prepared from 0.309 mmol of **4**). The reaction mixture was refluxed for 16 h, and allowed to cool to ambient temperature. The precipitates were removed by filtration, and washed with dichloromethane (5 × 50 mL). The combined filtrates were evaporated to dryness and the residue was dissolved in refluxing dichloromethane (200 mL) under reflux and filtered; the filtrate was washed with sodium bicarbonate, water and brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and purified by column chromatography using 5% methanol in dichloromethane as eluent for the first column and 2% methanol in dichloromethane for the second. Clip **2** was obtained as a yellow solid (148 mg, 0.144 mmol, 47% yield from **4**), mp >310 °C. ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 8H, H-*o*-rim-Ph), 7.31 (m, 4H, H-*p*-rim-Ph), 7.25 (m, 8H, H-*m*-rim-Ph), 7.24 (m, 4H, H-*o*-Ph), 7.20 (m, 4H, H-*m*-Ph), 7.16 (m, 2H, H-*p*-Ph), 5.91 (d, J = 16 Hz, 4H, CH_{2b}), 4.33 (s, 12H, OCH_3), 3.94 (d, J = 16 Hz, 4H, CH_{2a}). ^{13}C NMR ($CDCl_3$): δ 157.6 (2C, C-1), 151.7 (4C, C-5), 149.5 (4C, C-3), 139.1 (4C, C-*i*-rim-Ph), 135.9 (4C, C-3a), 134.1 (2C, C-*i*-Ph), 130.4 (4C, C-2a), 130.0 (8C, C-*o*-rim-Ph), 129.1 (2C, C-*p*-Ph), 129.0 (4C, C-*m*-Ph), 128.9 (4C, C-*p*-rim-Ph), 128.5 (4C, C-*o*-Ph), 128.2 (8C, C-*m*-rim-Ph), 85.2 (2C, C-1b), 63.5 (4C, C-OCH_3), 38.2 (4C, CH_2, C-2).

4.2 Binding studies

For NMR titrations, aliquots of a guest solution were added to a solution of clip in an NMR tube using an Eppendorf pipette and recording the ^{1}H NMR spectrum after each addition. When applicable, accurate clip–guest ratios were also determined from integrals of the two species.

4.3 Gravimetric analysis of clip 1·$AgClO_4$

A solution of clip **1** (4.05 mg, 4.1708 μmol) in $CHCl_3$–CH_3OH (8:2, 2 mL) was treated with a solution of $AgClO_4$ (CH_3OH, 1 mL). The yellow precipitate was collected in a Vortex vial filter and dried, yielding 4.92 mg (4.18 μmol calculated as **1**·$AgClO_4$, Δ = +0.1%). A second, identically treated sample of clip **1** (4.89 mg, 5.04 μmol) yielded 5.88 mg (4.99 μmol calculated as **1**·$AgClO_4$, Δ = −0.9%), mp of complex >230 °C (dec.).

4.4 Inclusion compound 1·[$PhNO_2$]

Clip **1** (2.6 mg) was dissolved in freshly distilled nitrobenzene (0.3 mL) upon heating. The clear solution was cooled to room temperature. Excess nitrobenzene was removed by vacuum evaporation for 3 h. The residual yellow solid was dissolved in $CDCl_3$ and subjected to ^{1}H NMR (500 MHz, relaxation delay 30 s), showing a molecular ratio **1** : $PhNO_2$ of 1 : 1. A second sample (3.9 mg **1**, 11.5 h evaporation) rendered the same result.

4.5 X-Ray crystallography

Preparation of clip **1***–ammonium complex*. Using a screw cap vial, a saturated solution of NH_4PF_6 in $CHCl_3$–CH_3OH (7 : 3) (1 mL) was layered on top of a solution of clip **1** (5 mg) in the same solvent mixture (3 mL). After 4 h, the vial was closed and stored at room temperature. Rectangular crystals were observed within a week. These crystals were stable while covered with mother liquor, but disintegrate immediately into a fine powder upon removal. For analysis, a small droplet containing one crystal was quickly covered by a paraffin oil to protect it from contact with air and mounted on the tip of a broken capillary using the adhesion of the oil. It was then quickly mounted on the X-ray diffractometer and shock-freezed to 153 K by a flow of cold gaseous nitrogen.

Diffraction data were collected using a Siemens SMART CCD diffractometer with Mo-Kα radiation (=0.71073 Å, graphite monochromator). The crystals were cooled to 153(2) K by a flow of nitrogen gas using the LT-2A device. A half sphere of reciprocal space was scanned by 0.3 steps in ω with a crystal-to-detector distance of 3.97 cm.

Crystal data for **1**·NH_4PF_6·3$CHCl_3$·2CH_3OH, $C_{65}H_{57}Cl_9F_6N_9O_8P$, M_r = 1556.22, yellow crystals, 0.62 × 0.38 × 0.18 mm^3, triclinic, space group $P\bar{1}$, a = 13.8819(8) Å, b = 15.8365(9) Å, c = 16.0976(9) Å, α = 95.400(1)°, β = 97.683(1)°, γ = 91.180(1)°, V = 3489.6(3) Å^3, Z = 2, ρ_{calcd} = 1.481 Mg m^{-3}, $2\theta_{max}$ = 51°, Mo-Kα (λ = 0.71073 Å), omega scans, multi-scan, absorption coefficient = 0.461 mm^{-1}, min/max transmission = 0.573/0.922, θ = 1.48° to 25.50°, F(000) = 1592, T = 153(2) K, R_1 = 0.0675, wR_2 = 0.1671, refined against $|F^2|$, residual electron density = 0.325 and −0.268 e Å^{-3}. Independent reflections = 27 665, R(int) = 0.0236,

reflections included in the refinement = 27 665, σ limits = 2σ, Lorentzian polarisation with absorption corrections, restraints = 10, parameters = 757. Structure solution was achieved by direct methods, least squares using SHELXTL (Bruker, 2003). H atoms were constrained to ideal geometry. CCDC reference number 652426. For crystallographic data in CIF format see DOI: 10.1039/b715208f

Acknowledgements

The Swedish Research Council (Vetenskapsrådet) is acknowledged for financial support.

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