Conformational Behavior and Binding Properties of Naphthalene-Walled Clips

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Abstract: The conformational behavior and binding properties of various clip-shaped receptor molecules, based on the building block diphenylglycoluril, were studied by NMR, X-ray analysis, and computational techniques. The conformation and the binding properties of these clips are dependent on the number and type of side walls. Host molecules with two naphthalene side walls and with methoxy groups at the 2- and 7-position are able to bind aromatic guests and silver ions by an induced-fit mechanism.

Keywords: host–guest chemistry · molecular recognition · pi interactions · supramolecular chemistry

Introduction

Two models are frequently used to describe the binding of a substrate molecule to the site of a receptor molecule: the lock and key model and the induced fit model. Fischer used the term lock and key 100 years ago,[1] and it was Cram who combined it with the ideas of preorganization.[2] Many host–guest complexes have been designed on the basis of Fischer and Cram's principles,[3] and have very high association constants, even in chloroform.[4] The induced fit model[5a] was proposed by Koshland and is more relevant to binding processes in biological systems. According to Koshland, the substrate induces a reorganization of the receptor or the substrate molecule changes its conformation upon binding. The importance of the induced-fit mechanism is, for instance, clearly demonstrated by the binding of nicotinamide nucleotides to the enzyme oxidoreductase:[5b] here reorganization activates certain functions of the enzyme. A better understanding of the way the induced-fit type of receptors work is of great importance for the future design of synthetic receptors capable of performing certain tasks or functions.

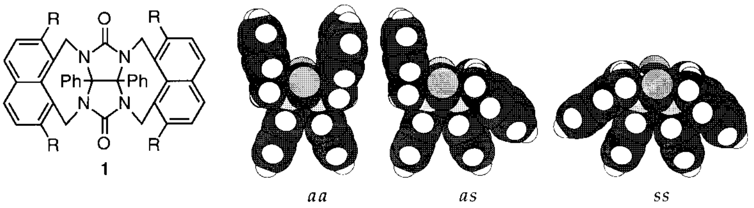

Figure 1. The different possible orientations of the 1,8-connected naphthalene side walls in clip **1**, which result in three conformations which interconvert slowly on the NMR time scale: *anti–anti* (*aa*), *anti–syn* (*as*), and *syn–syn* (*ss*).

We have previously reported on the conformational properties of clip molecules of type **1**.[6a] In solution, these compounds exist in three conformations: *aa*, *as*, and *ss* (Figure 1), of which the *as* conformation predominates (ca. 90 %). Binding of aromatic guest molecules occurs only in the minor *aa* conformer, where the guest is sandwiched between the two aromatic cavity walls and held by π–π stacking interactions. On addition of excess guest molecules, the two other conformers disappear completely. Preliminary binding studies have been carried out with this type of molecule; however, several questions still remain, the most important one being: why is the clip molecule initially present as the *as* conformer? Another question is related to the binding interactions in the host–guest complex, which are different from those known for donor–acceptor complexes, for example complexes between hexamethylbenzene and electron-poor aromatic compounds.[7] In order to answer these questions, we present here additional conformational studies and binding data as well as X-ray structures of new clip molecules, which are compared with those of **1**. A thorough understanding of the mechanism of induced-fit binding in this system is of use for the future development of enzyme mimics.

Results and Discussion

Synthesis: The syntheses of clips **1a**[6a,b] and **2–8**[6c] have been described elsewhere. The first attempt to synthesize **1b** by

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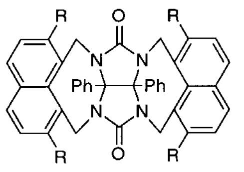
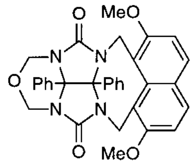


1a: R=OMe
1b: R=H



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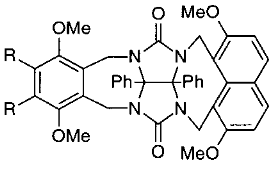
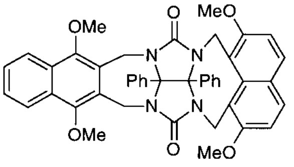


3 R=H
4 R=NO$_2$



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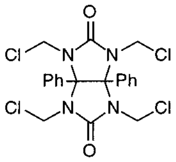

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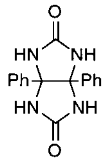

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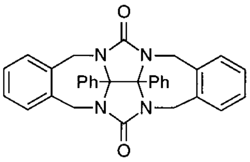

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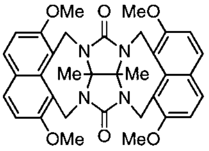

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reaction of naphthalene with the tetrachloro derivative **6** in the presence of a Lewis acid resulted in a mixture of isomers which could not be separated. Therefore, another route was developed in which 1,8-dimethylnaphthalene was brominated to yield 1,8-bis(bromomethyl)naphthalene, which was subsequently treated with diphenylglycoluril (**7**) in DMSO/KOH to yield **1b** (34%).

Conformational behavior: In order to gain insight into the conformational behavior of the clip molecules, ^{1}H NMR studies were carried out in CDCl$_3$. The different sets of ^{1}H NMR signals for each conformer of a clip molecule were assigned with the aid of 2D COSY NMR. For clips **1a**,[6] **2–5** this assignment is described elsewhere.[6c] Clip **1b** displayed two sets of signals in the ^{1}H NMR spectrum, suggesting that only two of the three possible conformers were present in solution (Figure 2). The main conformer was either *ss* or *aa*, since only one set of AB signals was found for its NCH_2 protons. Comparison of the spectra of **1b** with the spectra of **1a** and **2–5** and use of Johnson–Bovey[8] tables to calculate ring current contributions made it clear that both walls of **1b** were in the *anti* position with respect to the phenyl rings on the convex side of the DPG framework. Consequently, the main conformer was the *aa* one. The minor species, displaying two sets of AB signals for the NCH_2, protons, was the *as* conformer.

The naphthalene moiety, which is in the *syn* orientation in the *as* conformer of **1b**, induces a large upfield shift in the signals of the protons in the phenyl ring, which are in its shielding zone. On heating, these and other ^{1}H NMR signals of the *as* conformer became broader, suggesting that the two conformers were interconverting faster on the NMR time scale. At 330 K the ^{1}H NMR resonances (400 MHz) of the *aa* conformer, however, were not significantly broadened, implying that coalescence was not yet reached. The rate of interconversion between the two conformations could not be determined by this technique since experiments at higher temperature could not be carried out.

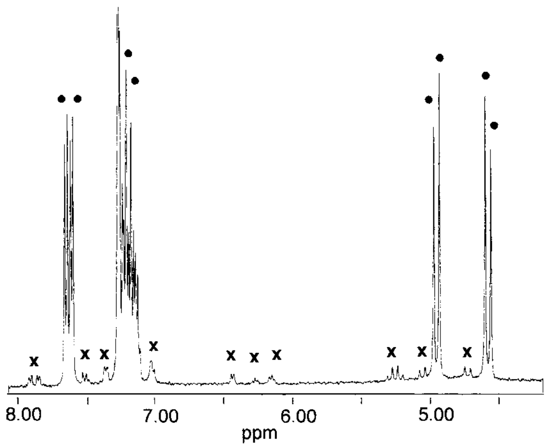


Figure 2. ^{1}H NMR spectrum of **1b**, showing two conformers: the major one is *aa* (●) and the minor one is *as* (**x**).

The ratios in which the different conformers of clips **1–5** occur in chloroform solution are presented in Table 1. They give useful information about the conformational behavior of these molecules. The large difference between the conformational ratios measured for **1a** and **1b** indicates that the methoxy groups attached at the 2- and 7-positions of the naphthalene moieties have an enormous influence on the conformation of the clip molecules. The distance between the methoxy group and the oxygen atom of the carbonyl function is 2.96 Å in the *anti* conformer and 4.09 Å in the *syn* conformer (calculated from the X-ray structure of **1a** and **2** (vide infra) and modeled structures). When the methoxy group is in the plane of the aromatic ring, which is the case in the solid state (vide infra), the lone pairs of the methoxy oxygen atoms point towards the oxygen atoms of the carbonyl functions. It is likely, therefore, that oxygen–oxygen repulsion plays a dominant role in the conformational behavior of **1a**. This was further confirmed by examination of the

Table 1. Ratio of conformers of molecular clips in chloroform solution and the energy differences between them.

Clip	Conformational ratio	$K_{(as/aa)}$[a]	ΔG (kJ mol^{-1})
1a	*aa*:*as*:*ss* = 2.7:89.6:7.7	33	−8.66
1b	*aa*:*as* = 93:7	0.075	6.41
2	*a*:*s* = 77:23	0.30	2.98
3	*a*:*s* = 15:85	5.67	−4.29
4	*a*:*s* = 35:65	1.86	−1.53
5	*a*:*s* = 24:76	3.17	−2.85

[a] Based on the equilibrium *aa* ⇌ *as* or *a* ⇌ *s*.

conformation of a clip molecule derived from **1a** in which one of the carbonyl groups was reduced to a CH_2 group.[9] This latter molecule was found to exist in a higher proportion in the *aa* conformation (ca. 20%).

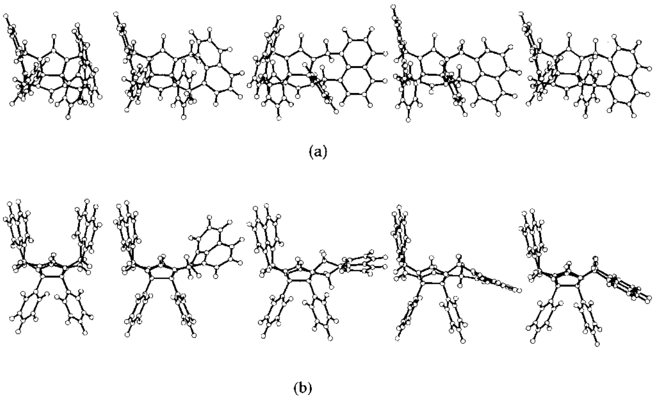
Despite the unfavorable oxygen–oxygen repulsion, compound **1a** apparently prefers to be in a conformation with one side wall *anti* and one side wall *syn*. This indicates that other factors must play a role, otherwise the *ss* form would be the dominant conformer. We believe that solvation effects are also very important. When clip **1a** is in the *aa* conformation, the cavity will be poorly solvated since chloroform solvent molecules are too large to fit in the cavity. If the molecule is in the *as* conformation, the aromatic walls will be more fully exposed to solvent molecules. The ratio of the two conformations of the mono-side-walled clip **2** is in agreement with this idea: for this compound the *anti* conformer is more favorable than the *syn* conformer (ratio 77:23). The *anti* conformer of **2** was also found in the solid state structure (vide infra). This preference for the *anti* conformation indicates that it is more favorable for the wall to be in the up position. In the case of the di-walled species **1a** the enthalpic gain is less than the loss of solvation that occurs when the cavity is formed, hence, the *as* conformer is preferred.

When the solvent was changed stepwise from chloroform to pure methanol, the percentage of the *aa* conformer of **1a** increased gradually from ca. 2 to 15%. Methanol molecules can fit more easily into the cavity of the *aa* conformer than chloroform molecules, and hence this improved solvation leads to a higher percentage of the *aa* conformer. The electrostatic repulsion between the oxygen atoms of the side wall and the carbonyl oxygen atoms will also decrease as the percentage of methanol increases; this further stabilizes the *aa* conformer.

The conformational behavior of compounds **3**, **4**, and **5** is in agreement with the results discussed above. The benzene side wall and the 1,4-dimethoxynaphthalene side wall are both observed to be in the *anti* conformation. The opposite 2,7-dimethoxynaphthalene side wall in **3**, **4**, and **5**, therefore, prefers to be in the *syn* orientation in order to produce the *as* conformation. The small energy differences between the conformations of the clips **1a**, **3**, **4**, and **5** are probably an effect of different cavity sizes and substituents on the side walls.

A computational study was carried out to support the experimental studies on the conformational behavior of the clip molecules. The heats of formation of the different conformers of **1b** and the di-benzene-walled clip **8** were calculated with a variety of force fields (CHARMm, AMBER, AM1). In all cases, the *aa* conformer of **1b** was calculated to have a lower energy than the *as* conformer, in line with experimental observations. For **8**, the *aa* conformer was also calculated to be more favorable than the *as* conformer, which is also in agreement with experiment.

The process of interconverting one clip conformer to another was also calculated with AM1 [15] and the CHARMm[16] force field. In the case of CHARMm, the flipping process involving one benzene side wall of **8** was calculated to be a one-step mechanism, with both methylene bridges rotating simultaneously. In contrast, the flipping of each of the naphthalene walls of **1b** was calculated to be a two-step mechanism by both the AM1 and the CHARMm force field. The flipping process occurred via a stable intermediate which had only one methylene group rotated (see Figure 3).


(a)

(b)

Figure 3. The calculated mechanism (AM1) of the flipping of a 1,8-connected naphthalene side wall in clip **1b**. a) View from above; b) front view.

The energy required to convert one wall from the *anti* to the *syn* form was calculated to be significantly smaller for the benzene clip **8** (35 kJ mol^{-1}) than for the naphthalene clip **1b** (62 kJ mol^{-1}). Our experimental results and theoretical calculations are in agreement with calculations carried out by Sygula and Rabideau on the ring inversion of 9,10-dihydroanthracene and 7,12-dihydropleiadene.[17] They calculated that the flipping process was a one-step mechanism in the case of the benzene compound, and a two-step mechanism in the case of the naphthalene compound.

X-ray structures: We were able to crystallize compound **2** (only the *anti* conformer) by slow diffusion of diethyl ether into a chloroform solution of this compound. The X-ray structure of **2** is depicted in Figure 4. The methoxy groups are in the plane of the naphthalene ring, with the lone pairs of the oxygen atoms pointing towards the carbonyl oxygen atoms of the glycoluril unit. The distance between the two oxygens is only 3 Å. There is almost no twist in the diphenylglycoluril framework of the molecule (torsion angle C31-C1-C2-C21 is 0.4°, torsion angle N1-C1-C2-N2 is 0.7°), which contrasts with

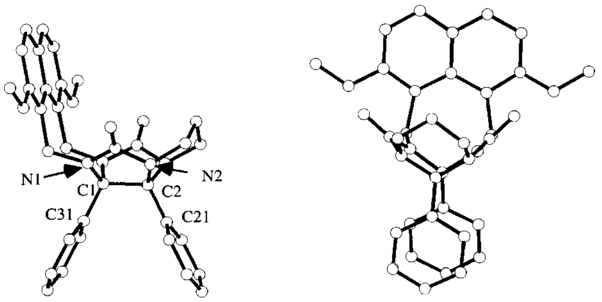


Figure 4. X-ray structure of **2**; front view (left), side view (right). Hydrogen atoms have been omitted for clarity.

the twist found for a clip with two 1,4-dimethoxybenzene side walls.[6b]

The angle between the lines through the carbonyl groups in **2** (44.5°) is somewhat larger than the same angle in the above mentioned 1,4-dimethoxybenzene clip (39°), and the distance between the two carbonyl oxygen atoms is somewhat smaller (5.34 Å compared with 5.52 Å). These small differences are a result of the larger 8-membered ring, which is formed by connecting the naphthalene moiety to the diphenylglycoluril unit, compared with the 7-membered ring which is present in the 1,4-dimethoxybenzene clip. This larger ring confers greater rigidity upon molecule **2** compared with benzene-walled clips (e.g. **8**).

Attempts to crystallize **1a** failed, probably because different conformations precipitated together so that a single crystalline product could not form. Therefore, this molecule was crystallized in the presence of a guest molecule. Several crystals of **1a** were obtained with silver perchlorate and silver tetrafluoroborate as the guest molecules. Unfortunately, these crystals were unstable under the X-ray conditions. Finally, nitrobenzene was used as a guest molecule. A single brown crystal suitable for X-ray analysis was slowly grown (three months) from a mixture of chloroform and nitrobenzene. The structure is shown in Figure 5. The nitrobenzene guest molecule is sandwiched between the two naphthalene rings in an offset manner. As expected, the nitro group of the guest is pointing out of the cleft. The guest molecule is not symmetrically bound in the cleft, but prefers to be approximately parallel to one of the aromatic surfaces. The angle between the planes of the aromatic guest and the naphthalene rings is approximately 5.39° for one side wall and 16° for the other side wall. The center-to-center distance between the aromatic side walls is 6.8 Å. The distance between the aromatic ring of the guest and the side wall of the host is 3.4 Å, which is ideal for π–π stacking interactions. As in the case of **2**, the twist in the diphenylglycoluril framework is small (torsion angle C21-C1-C1′-C21′ = 2.1°, torsion angle N1-C1-C1′-N1′ = 13.7°). The distance between the carbonyl oxygens atoms is 5.67 Å, and the angle between the lines through the carbonyl groups is 37.9°. As in the structure of **2**, the methoxy groups of the side walls are in the plane of the naphthalene rings.

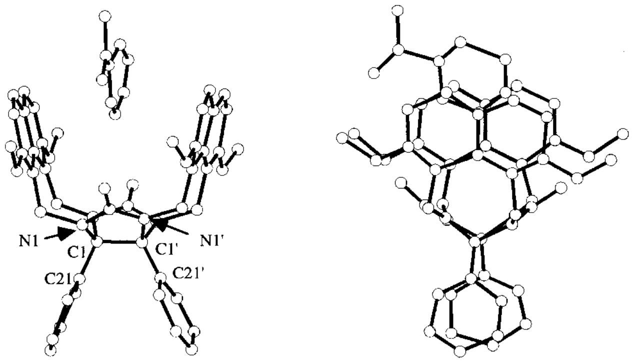


Figure 5. Front view (left) and side view (right) of the X-ray structure of the complex of nitrobenzene with clip **1a**. Hydrogen atoms have been omitted for clarity.

Binding properties:

Binding of aromatic guest molecules: Depending on the type of guest molecule, binding in our clips can be achieved by means of π–π interactions only or by a combination of π–π interactions and hydrogen bonding. In the former case, the geometry of the host–guest complex is determined completely by the optimal π–π interaction, whereas in the latter case the geometry is mainly determined by the optimal hydrogen bonding interaction.[18] In Table 2 the association constants of complexes between aromatic guest molecules and clip molecules **1a**, **1b**, and **2** are presented. Examination of Table 2 reveals that the binding of guest molecules in host molecule **1b** is much weaker than in **1a**. This implies that the presence of the methoxy groups, which make the naphthalene moieties more electron-rich, significantly enhances the binding. Unfortunately, the binding constants of clip **1b** were too low to enable a good comparison to be made with the binding constants of **1a**. The results, however, suggest that the two clips display an opposite trend in the complexation of aromatic guest molecules that are bound by π–π interactions only. Clip molecule **2**, which has only one side wall, has a negligible interaction with guest molecules that are unable to form hydrogen bonds. The presence of the second side wall, as observed for benzene-walled clip molecules, is necessary for the formation of a host–guest complex of sufficient stability.[18] The complexation of 1,3-dihydroxybenzenes to **1a** and **1b** follows the same pattern as found for the substituted benzene-walled clip molecules.[18] The complexation to **1a** is much more favorable than to either **1b** or **2** because of the absence of the methoxy groups in **1b** and because of the fact that only one side wall is present in **2**.

Table 2. Association constants (K_a) of complexes between aromatic guest molecules and the *aa* conformers of different host molecules in $CDCl_3$ at 298 K.

Guest	K_a (M^{-1}) **1a**[a]	K_a (M^{-1}) **1b**[b]	K_a (M^{-1}) **2**
1,3-dinitrobenzene	115[c]	20	< 2
1,4-dicyanobenzene	178[c]	5	< 2
1,3-dihydroxy-5-pentylbenzene	1400	45	20[a]
hexyl 3,5-dihydroxybenzoate	9000	300	–

[a] Calculated from the change in ratio of the conformers as a function of the guest concentration (estimated errors 10–15%); see ref. [6]. [b] Calculated by fitting the ^1H NMR chemical shifts of the naphthalene protons as a function of the guest concentration. The calculated CIS value for proton H_4 of the naphthalene side wall ($\delta = -0.36$) is comparable to the CIS value calculated for clip **8** (see ref. [6b]). [c] Values taken from ref. [6].

In an earlier paper we proposed that aromatic guest molecules are bound between the walls of clip **1a** in an offset geometry.[6a] The crystal structure of the complex between nitrobenzene and **1a** shows that this proposal is correct (Figure 5).[19] The nitro group of the guest points out of the cleft. The distance between the aromatic ring of the guest and the side wall is 3.4 Å, which is ideal for π-stacking interactions.

Binding of silver ions:[20] It is known in the literature that silver ions can form complexes with C=C bonds and with aromatic surfaces.[21] X-ray structures of silver ions complexed to benzene molecules show that the binding is towards one of the double bonds of the aromatic ring, with an Ag–benzene distance of approximately 2.5 Å.[22] When the sparingly soluble salt $AgClO_4$ was added to a solution of **1a** in $CDCl_3$ a decrease in the *sa* and an increase in the *aa* conformer was observed by ^1H NMR. Subsequent titrations of this host with various silver salts in $CD_3OD/CDCl_3$ (1:9 v/v, to increase the solubility of the salts) revealed that the proportion of the *ss* conformer also increased. This indicates that the latter is also capable of binding a silver ion more strongly than the *sa* conformer (Figure 6). Relative binding constants for silver ions to the various conformers were calculated from the changes in the conformational ratios (Table 3). The *aa* conformer appeared to give the strongest complexes with the silver salts. This conformer can form a sandwich complex with the silver ion interacting with both of the aromatic side walls. Shifts in the ^1H NMR signals of the aromatic protons of the *aa* and *ss* conformers were also observed, but these shifts could not be used to calculate the geometries of the complexes. The equilibria in these systems are too complex to be interpreted because the silver ions are bound to different conformations, whose ratios change upon increasing the silver concentration. As can be seen in Table 3, the values of K_{aa} and K_{ss} strongly depend upon the type of silver salt. The stronger the interaction is between the anion and the silver ion, the weaker the complex is between the silver salt and the clip molecule. A similar observation was made by Crookes et al. in their studies on the complexation of various silver salts to ethene.[23] They explained the observed anion dependencies as a result of competition between the anion and the ethene for the Ag^+ cation.

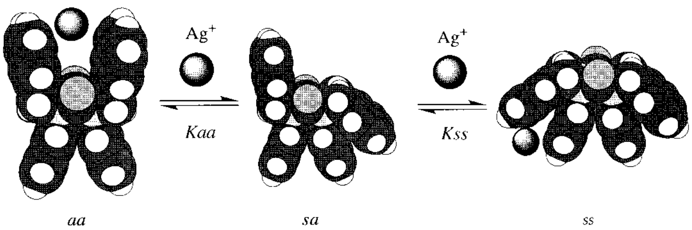


Figure 6. Binding of Ag^+ ions by the *aa* and the *ss* conformers of clip **1a**. Methoxy groups have been omitted.

Table 3. Relative association constants (M^{-1}) for the complexation of silver salts to the *aa* and *ss* conformers of **1a**.[a,b]

Silver salt	K_{aa}	K_{ss}
$AgClO_4$	149	53
$AgBF_4$	98	37
CF_3SO_3Ag	50	25
$AgPF_6$	10	10

[a] Estimated error 15%. [b] No binding was observed for the following silver salts: CH_3SO_2Ag, Ag_2SO_4, Ag_2CO_3, $C_6H_5CO_2Ag$, CH_3CO_2Ag.

The relative binding constant of the *ss* conformers (K_{ss}) of **1a** is approximately half that of the *aa* conformer (Table 3). When clip **9**, in which the phenyl groups of the glycoluril unit are replaced by methyl groups, was titrated with $AgClO_4$, only a small change in the amount of *aa* conformer was observed. This implies that the phenyl groups of clip **1a** are involved in the binding of Ag^+ to the *ss* conformer. The association constant of the complex between $AgClO_4$ and the *aa* conformer of **9** ($K_{aa} = 44\,M^{-1}$) was smaller than that observed for the complex of this salt with the *aa* conformer of **1a** ($K_{aa} = 149\,M^{-1}$, Table 3). This is the result of a larger energy difference between the *aa* and the *as* conformers of clip **9**. When no guest was present, the amount of *aa* conformer of **9** was almost zero.

The binding site of the silver ion was located by means of ^{13}C NMR experiments; ^{13}C DEPT and 2D HETCOR (heteronuclear correlation, heteronuclear multiple-quantum coherence (HMQC)) spectra were recorded so that the ^{13}C NMR signals of clip **1a** could be assigned. However, only the signals of the *as* conformer could be completely assigned. The signals of the other conformers had intensities too low to give cross-peaks in the 2D spectra. When $AgClO_4$ was added to a solution of **1a** in $CD_3OD/CDCl_3$ (1:9 v/v), the aromatic region of the ^{13}C spectrum became extremely complex. This suggests that the aromatic rings of **1a** are involved in the process of complexation. This is in agreement with the observed shifts of the aromatic protons in the ^1H NMR spectrum upon addition of silver salts. No large shifts were seen for the carbonyl or for the methoxy groups, indicating that these groups are not involved in the binding of the silver ions. If this is indeed the case, clip **1b** should be able to bind Ag^+ cations as well. A titration experiment with $AgBF_4$ revealed that binding to **1b** does take place, but that the complex was significantly weaker ($K_{aa} = 20\,M^{-1}$) than that found for **1a**. This is probably due to the lower electron density on the aromatic side walls of **1b**.

The most favorable binding site for the silver ion was determined by AM1 calculations. The sites with the highest π-electron density can be expected to bind the silver ion. The calculated electron distribution in the naphthalene rings of **1a** and the most likely position of the silver ion is shown in Figure 7.

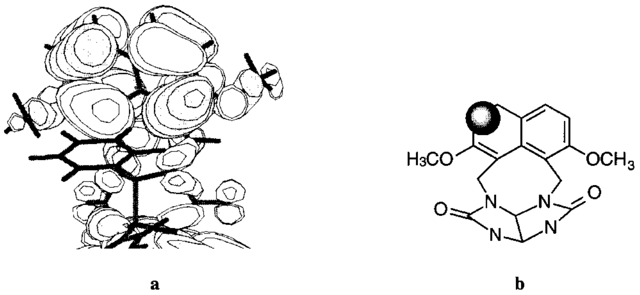


Figure 7. a) The highest occupied π orbitals of **1a** according to AM1 calculations; b) the predicted binding geometry of the silver ion with the *aa* conformer of clip **1a**.

The binding of a silver ion to the *ss* conformer of clip **1a** can occur at three possible sites: i) between the two phenyl rings, ii) between a phenyl and a naphthalene ring, and iii) on the top of one of the naphthalene walls (Figure 8). Although naphthalene is known to bind silver ions in the solid state,[22] binding studies with 2,7-dimethoxynaphthalene revealed that this compound does not form a complex with Ag^+ in methanol/chloroform solution at concentrations between 2

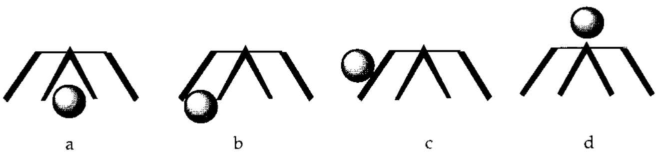


Figure 8. Schematic representation of the four possible binding sites of the silver ion in the *ss* conformer of **1a**. The second mode of complexation (b) is the proposed complex geometry.

and 20 mmol. As the *as* conformer of **9** does not bind silver either, the binding of Ag^+ to the top of a naphthalene ring (Figure 8c) can be rejected. From separate binding experiments with a diphenylglycoluril molecule without any side walls, we concluded that the silver ion is not bound between the phenyl groups of the diphenylglycoluril unit, hence the binding mode of Figure 8a can also be rejected. The most likely place for the silver ion, therefore, is between a naphthalene and a phenyl ring (Figure 8b). Again, the most electron-rich sites of the naphthalene moiety will be involved. Another possibility is that the silver ion is not complexed to the aromatic part of the *ss* conformation of **1a**, but to the concave side of the diphenylglycoluril part of the molecule, as depicted in Figure 8d. The inner pocket of a glycoluril molecule was recently calculated to be negatively charged,[24] which would make it favorable for the silver ion to be bound at this position. No experimental evidence, however, was found for this particular binding geometry.

Conclusions

It is clear from the results presented above that various factors influence the conformational behavior and the binding properties of clip molecules with naphthalene walls. These studies have shown that the methoxy groups on the side wall of clip **1a** play an important role, both in determining the conformation of the host and in promoting the complexation of guest molecules. Clip molecule **1b**, which does not have methoxy groups, mainly exists in the *aa* conformation, in contrast to **1a**, which exists mainly in the *as* conformation. The former compound shows a significantly lower affinity for aromatic guest molecules and silver ions. The lower complexation ability of **1b** compared with **1a** is due to weaker $\pi-\pi$ interactions with the guest molecules. Solvation effects also play a role in the conformational behavior of the clip molecules. A molecule with two 2,7-dimethoxynaphthalene side walls (**1a**) adopts the *anti–syn* conformation, while a molecule with only one such side wall (**2**) prefers to be in the *anti* conformation rather than in the *syn* conformation due to these solvation effects. The fact that weaker complexes are formed between aromatic guests and **2** compared with **1a** is a result of the fact that this host molecule has only one side wall, and is in agreement with the results observed for benzene-walled clip molecules.[18] The X-ray structure of a complex between nitrobenzene and **1a** clearly shows that the guest molecule is bound in an offset geometry, which is in agreement with the calculated geometry. A computational study of the conversion of the side walls of clip molecules from *anti* to *syn*, with respect to the phenyl groups of the diphenylglycoluril framework, revealed that the naphthalene walls flip according to a two-step mechanism, while the benzene walls flip according to a one-step mechanism. The latter process is much faster than the former, which leads to the conclusion that benzene-walled molecules are much more flexible. The *aa* conformer of benzene-walled clips is much more favored than the *as* and *ss* conformers, and therefore this is the only conformation observed in solution and in the solid state.

Experimental Section

General techniques: DMSO was distilled and stored over molecular sieves 3 Å before use. All other chemicals were commercial samples and used without further purification. Merck silica gel (60H) was used for column chromatography. Melting points were determined on a Jeneval polarization microscope THMS600 hot stage and are reported uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM400 MHz instrument. Chemical shifts are reported downfield from internal TMS ($\delta = 0.0$). Abbreviations used: d = doublet, dd = doublet of doublets, and m = multiplet. FAB mass spectra were recorded on a VG7070E instrument. IR spectra were recorded on a BioRad FTS-25 spectrometer. Elemental analyses were determined with a Carbo Erba Ea1108 instrument. Diphenylglycoluril (**7**) was synthesized from urea and benzil according to a literature procedure[6] and 1,8-bis(bromomethyl)naphthalene was synthesized by bromination of 1,8-dimethylnaphthalene with *N*-bromosuccinimide according to a standard procedure.[25]

17b,17c-Dihydro-17b,17c-diphenyl-7H,8H,9H,16H,17H,18H-7a,8a,16a,17-a-tetraazapentaleno[1″,6″:5,6,7;3″,4″:5′,6′,7′]dicycloocta[1,2,3-d-e:1′,2′,3′d′e′]dinaphthalene-8,17-dione (**1b**): A suspension of powdered KOH (110 mg, 1.96 mmol) in degassed DMSO (2 mL) was stirred under nitrogen for 30 min. Compound **7** (142 mg, 0.483 mmol) and 1,8-bis(bromomethyl)naphthalene (307 mg, 0.977 mmol) were added and the mixture was cooled with stirring. After 3 h, the mixture was poured into water (50 mL) and the product extracted twice with CH_2Cl_2. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (1% EtOH in CH_2Cl_2) gave 98 mg (34%) of **1b** as a white solid. A sample was recrystallized from $CHCl_3$/diethylether for analysis. M.p. > 400 °C (decomp.); IR (KBr): $\tilde{\nu}$ 1719, 1699 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): *aa* conformer: $\delta = 7.66$ (d, 4H, Napht H-4, $J = 8.0$ Hz), 7.61 (d, 4H, Napht H-2, $J = 7.0$ Hz), 7.24 (dd, 4H, Napht H3, $J = 8.0$ Hz, $J = 7.0$ Hz), 7.35–7.10 (m, 10H, ArH), 4.98 (d, 4H, NCH_2Napht, $J = 16.2$ Hz), 4.56 (d, 4H, NCH_2Napht, $J = 16.1$ Hz); *as* conformer: $\delta = 7.91$ (d, 2H, Napht H-4 a, $J = 8.2$ Hz), 7.85 (d, 2H, Napht H-2 a, $J = 6.7$ Hz), 7.50 (m, 2H, Napht H3 a,), 7.38–6.98 (m, 11H, ArH a Napht-H s), 6.43 (d, 2H, Ar-H s, $J = 7.7$ Hz), 6.30 (d, 1H, Ar-H s, $J = 7$ Hz), 6.14 (dd, 2H, Ar-H s, $J = 7$ Hz $J = 7.7$ Hz), 5.27 (d, 2H, NCH_2Napht s, $J = 14.6$ Hz), 5.20 (d, 2H, NCH_2Napht s, $J = 14.7$ Hz), 5.07 (d, 2H, NCH_2Napht a, $J = 16.2$ Hz), 4.71 (d, 2H, NCH_2Napht a, $J = 16.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 157.23$ (urea C=O), 135.79, 135.28, 133.49, 131.06, 130.62, 130.16, 128.85, 128.60, 124.82 (Napht-C and Ph-C), 84.00 (PhCN), 47.60 (NaphtCH_2N); FAB-MS (*m*-nitrobenzyl alcohol): $m/z = 599$ $[M+H]^+$; Anal. calcd for $C_{40}H_{30}N_4O_2 \cdot CHCl_3$: C 68.58, H 4.35, N 7.80; found: C 68.65, H 4.42, N 7.66.

17b,17c-Dihydro-1,6,10,15-tetramethoxy-17b,17c-dimethyl-7H,8H,9H,16-H,17H,18H-7a,8a,16a,17a-tetraazapentaleno[1″,6″:5,6,7;3″,4″:5′,6′,7′]dicycloocta[1,2,3-de:1′,2′,3′d′e′]dinaphthalene-8,17-dione (**9**): This compound was synthesized as described elsewere.[26]

Determination of association constants by ^{1}H NMR: Two general methods were used to measure the binding constants. When possible, a signal in the ^{1}H NMR spectrum of the host was followed as a function of the guest concentration (or vice versa). The curve fitting was performed with the procedure described in ref. [6b]. In the case of clips displaying more that one conformation, the ratio between the different conformers was measured as a function of the guest concentration by integration of the appropriate signals in the ^{1}H NMR spectra. More accurate results were obtained if the peak areas were determined by fitting the peaks with

Lorentz curves (WIN-NMR). When only the *aa* conformer was able to bind a guest molecule, the K_a was calculated with the Equations (1) – (5).[6a]

$$K_a = \frac{[aa \times G]}{[aa] \times [G]} \tag{1}$$

$$[aa] = \frac{[sa]}{K_{sa/aa}} \tag{2}$$

$$K_{sa/aa} = \frac{[sa]}{[aa]} \tag{3}$$

$$[aa \times G] = [aa]_{tot} - [aa] \tag{4}$$

$$[G] = [G]_{tot} - [aa \times G] \tag{5}$$

In the case of the silver ions, which also bind to the *ss* conformer, different equations were used [Eqs. (6) – (10)].

$$K_{aa} = \frac{[aa \times G]}{[aa] \times [G]} \qquad K_{ss} = \frac{[ss \times G]}{[ss] \times [G]} \tag{6}$$

$$[aa] = \frac{[sa]}{K_{sa/aa}} \qquad [ss] = \frac{[sa]}{K_{sa/aa}} \tag{7}$$

$$K_{sa/aa} = \frac{[sa]}{[aa]} \qquad K_{sa/ss} = \frac{[sa]}{[ss]} \tag{8}$$

$$[aa \times G] = [aa]_{tot} - [aa] \qquad [ss \times G] = [ss]_{tot} - [ss] \tag{9}$$

$$[G] = [G]_{tot} - [aa \times G] - [ss \times G] \tag{10}$$

Binding to the *sa* conformer was neglected. Typical concentrations for **1a** and for the silver salts were 2 mM and 1 – 20 mM, respectively.

Crystal structure analysis of the 1a – nitrobenzene complex*:* $C_{50}H_{43}N_5O_8$, $M_r = 842.9$, $T = 293$ K, triclinic, space group: *P*1, $a = 12.188(9)$, $b = 12.161(12)$, $c = 17.756(13)$ Å, $\alpha = 103.33(13)$, $\beta = 104.74(2)$, $\gamma = 107.70(2)°$, $V = 2285$ Å^3, $Z = 2$, $\rho = 1.224$ g cm^{-3}, $Mo_{K\alpha}$ radiation, $\mu = 0.78$ cm^{-1}.

Crystal structure analysis of 2: $C_{32}H_{28}N_4O_5$, $M_r = 548.6$, $T = 208$ K, orthorhombic, space group: *Pbca*, $a = 12.3332(16)$, $b = 27.874(2)$, $c = 15.1246(15)$ Å, $V = 5199$ Å^3, $Z = 8$, $\rho = 1.402$ g cm^{-3}, $Mo_{K\alpha}$ radiation, $\mu = 0.90$ cm^{-1}.

More detailed crystallographic data will be published in a separate paper.[27]

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