Host–Guest Complexes of C-Ethyl-2-methylresorcinarene and Aromatic N,N′-Dioxides

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The C-ethyl-2-methylresorcinarene (1) forms 1:1 in-cavity complexes with aromatic N,N′-dioxides, only if each of the aromatic rings has an N–O group. The structurally different C-shaped 2,2′-bipyridine N,N′-dioxide (2,2′-BiPyNO) and the linear rod-shaped 4,4′-bipyridine N,N′-dioxide (4,4′-BiPyNO) both form 1:1 in-cavity complexes with the host resorcinarene in $C_{6v}$ crown and $C_{2v}$ conformations, respectively. In the solid state, the host–guest interactions between the 1,3-bis(4-pyridyl)propane N,N′-dioxide (BiPyPNO) and the host 1 stabilize the unfavorable anti-gauche conformation. Contrary to the N,N′-dioxide guests, the mono-N-oxide guest, 4-phenylpyridine N-oxide (4PhPyNO), does not form an in-cavity complex in the solid state. The host–guest complexation and the relative guest affinities were studied through 1H NMR competition experiments in methanol. Single-crystal X-ray crystallography of the 1:1 complexes supports the proposed solution-state structures, also revealing strong hydrogen bonds between the host and the guests, not observed in solution owing to hydrogen/deuterium (H/D) exchange processes in methanol.

1. Introduction

In host–guest chemistry, resorcinarenes[11] are a key host macrocyclic compound in the contemporary area of supramolecular chemistry with applications in biology, material science, and molecular recognition processes.[1a–c, 2, 3] The electron-rich interior cavity is the hallmark component that binds versatile guests by selective affinity by using non-covalent interactions.[1a–c] In the $C_{6v}$ conformation, host–guest chemistry leading to open inclusion, macro, and nano capsular self-assemblies with broad range of guests are well reported.[1a–c, 2] In supramolecular host–guest chemistry, for selective guest encapsulation, either host or guest molecules, and at times both, require significant chemical modifications.[3] As a result, a large number of reports on how to tailor the cavity fit, ranging from discrete molecules to ions, with resorcinarenes are studied in spontaneous processes.[3, 4] Usually, the in-cavity molecular recognition results from π–π, cation–π, and C–H–π interactions. The majority of reported cation–π interactions with resorcinarenes in the $C_{6v}$ conformation are observed with quaternary ammonium and phosphonium cations,[2, 5] although some π–π and C–H–π interactions occur with differences in electron delocalization of the aromatic planar guest molecules.[4, 6] In addition, the alkyl chains of the lower rim can also be functionalized to self-assemble either directly on metal surfaces or metal-supported ligands for potential sensing applications.[3, 7] In addition, the hydroxyl groups of the upper ring can participate in hydrogen bonding with guest molecules, leading to a variety of self-assembled structures.[5, 6]

A flexible guest with a rigid host enables size and structural complexity, and such guests manifest more conformational freedom outside the resorcinarene cavity, thus limiting their ability to form inclusion complexes. Bipyridines are an important class of biaryl compounds with C–C bond rotational properties, which usually change with the chemical environment such as electronic, substituents, and steric factors.[8] The high affinity of N–O groups in pyridine N-oxides for solvent molecules and hydrogen-bond (HB) interactions provides an opportunity for the organic parts to undergo molecular recognition with electron-deficient or -rich host molecules. In our earlier work, we studied the host–guest chemistry of C-ethyl-2-methylresorcinarene and pyridine mono-N-oxides resulting in dimeric capsular complexes.[6] This observed host–guest inclusion complexes was mainly due to π–π and C–H–π interactions between the π-rich host and the π-deficient N-oxide guests.[6] Later, these interactions prompted us to utilize C-ethyl-2-methylresorcinarene as a reaction vessel to construct a specific coordination sphere of copper(II) in the multicomponent reactions of pyridine N-oxide copper(II) complexes.[9]

In this contribution, the host–guest complexion with four aromatic N-oxides, namely, 2,2′-bipyridine N,N′-dioxide (2,2′-BiPyNO), 4,4′-bipyridine N,N′-dioxide (4,4′-BiPyNO), 1,3-bis(4-
with the MeOH solvent molecules can mask significant host–guest characteristic features. Herein, guest binding was analyzed through a series of competition experiments by ¹H NMR spectroscopy in highly competitive and protic methanol solvent. In the solid state through single-crystal X-ray diffraction studies, the inclusion complexes mainly through C–H···π and strong HB interactions were validated.

2. Results and Discussion

2.1. Solution Studies

Pyridine N-oxides (PyNO) were recently shown as suitable guests for π-rich host 1, stabilized by in-cavity π–π and C–H···π interactions, and HBs between the oxygen of N-oxides and the hydroxyl groups of the host 1. The aromatic ring of the PyNOs located deep in the cavity with the N–O group pointing upwards was the most favorable host–guest complexation, as all the possible host–guest interactions would be maximized.

For the ¹H NMR studies, the structures of the 1:1 in-cavity complexes were done by molecular modelling for all the four complexes (Spartan, MM level calculations) so that the guest N–O groups were first solvated with the methanol molecules and then the 1:1 complexes with the host were minimized. The modelled structures clearly suggest that the inclusion complexes occur through C–H···π interactions whereas N–O groups interact with methanol molecules through HBs (Figure 2, also see the Supporting Information, Figures S7–S10 with excluded solvent molecules).

A series of ¹H NMR experiments in highly competitive methanol (CD3OD, 298 K) were done between the host 1 and the guests (2,2'-BiPyNO, 4,4'-BiPyNO, 4PhPyNO, and BiPyPNO) to probe their host–guest complexes in solution. Despite the strong solvating power of methanol, it was used as the solvent owing to the limited solubility of the guest molecules in protic solvents. In addition to both solvation and competition of the bulk solvent, the hydrogen/deuterium (H/D) exchange processes will affect all exchangeable protons such as the –OH groups and therefore the potential HB interactions between the host 1 and the guests could not be observed. In the NMR experiments, equimolar mixtures (30 mm) of the host 1 and guests were prepared and the ¹H NMR spectra recorded. In the experiment with 2,2'-BiPyNO, a significant up-field shift of 0.75 ppm for the protons b–d (including the para-protons) of the guest was observed (Figure 2a–c), which was clearly larger than the up-field shift of 0.62 ppm for the para-protons of regular pyridine mono-N-oxide with host 1 under similar experimental conditions. Smaller up-field shifts of the ortho-protons a (0.23 ppm) were observed. The larger up-field shift results from the larger shielding of the para-protons of the guest upon complexation with the host 1. This indicates a tighter fit of the 2,2'-BiPyNO guest into the cavity compared with the regular PyNO and is indicative for the cis-configuration (Figure 2d,e) of 2,2'-BiPyNO. The para-protons are thus located deep in the cavity of the host and therefore heavily shielded.

The formation of cis-2,2'-BiPyNO@1 in-cavity complex is due to the rotation of the bipyridinic C–C bond. The above knowledge directed us to investigate the linear BiPyNO isomer, namely 4,4'-BiPyNO as guest, which has para-oriented N–O groups (Figure 3b). The ¹H NMR results show very small up-field shifts of 0.03–0.05 ppm for the 4,4'-BiPyNO protons (Figure 4). Taking into consideration the fast exchange process in solution, the size and linearity of the 4,4'-BiPyNO, it is difficult to conclude that these small changes result from either the formation of an in-cavity host–guest complex or an exo assembly. The modelled structure of 4,4'-BiPyNO@1 shown in Figure 4d,e, where the heavily solvated 4,4'-BiPyNO resides over the host 1 cavity, not inside as in 2,2'-BiPyNO@1, display-
ing only very weak C−H···π interactions at distances of approximately 3.66 and 3.62 Å between the host and the guest, supporting the small up-field shifts of the proton signals.

To probe the importance of the di-N−O moiety in 4,4′-BiPyNO, a mono-N−O guest, 4PhPyNO, was studied. 1H NMR studies between the host 1 and 4PhPyNO were performed to probe the effect of the lack of the second N−O group in the guest molecule. The 1H NMR experiments reveal small up-field shifts of 0.09/0.01 ppm for guest 4PhPyNO protons attributed to the weak host−guest interactions between the host 1 and the guest 4PhPyNO in a fast exchange process (Figure S1 in the Supporting Information). Again, it is difficult to confirm if the host−guest forms endo- or exo-complexation from such small shift changes. The NMR data was compared with the energy minimized structure (Figure S9 in the Supporting Information). The structure of the modelled host−guest complex and the observed weak C−H−π interactions with distances of approximately 3.55 and 3.66 Å are similar to those of 4,4′-BiPyNO@1, and are in line with the observed small up-field shifts of the proton signals.

The linear 4,4′-BiPyNO@1 and 4PhPyNO@1 complexes indicate that the host−guest interactions will be enhanced if the guest can adopt a conformation where the guest maximizes the interactions between the electron-deficient parts of the guest with the electron-rich cavity of the host, “driving” the guest deeper into the cavity of the host. To test this hypothesis, a guest, 1,3-bis(4-pyridyl)propane N,N′-dioxide, BiPyPNO, with a very flexible central part between two pyridine N-oxide moieties was used. The ligand is well known to be stable in the anti-anti conformation[13] (Figure 5).

Figure 3. Steric effects causing a) cis- and trans-modes[12] in 2,2′-BiPyNO, and b) non-coplanar aromatic rings in 4,4′-BiPyNO.

Figure 4. 1H NMR spectra (CD3OD, 298 K) of 30 mM solution of a) 1, b) 4,4′-BiPyNO, and c) equimolar mixture of 1 and 4,4′-BiPyNO. d, e) Energy-minimized structures for 4,4′-BiPyNO@1. Representation: d) host in ball and stick; guest and methanol molecules in capped-stick models. e) Host in ball and stick; guest and methanol molecules in CPK models. Black broken lines are HB and C−H···π(centroid) interactions.

Figure 5. Possible conformations of BiPyPNO.[13]

The 1H NMR experiments in CD3OD show significant up-field shifts for all the guest protons with the aliphatic protons showing the largest shifts (Figure 6). The up-field shifts for the α,α′ and β protons were exactly the same (0.85/0.85 ppm), which supports the anti-gauche conformation. The up-field shifts of

Figure 6. 1H NMR spectra (CD3OD, 298 K) of 30 mM solution of a) 1, b) BiPyPNO, and c) equimolar mixture of 1 and BiPyPNO. d, e) Energy-minimized structures for 4,4′-BiPyNO@1. Representation: d) host in ball and stick; guest and methanol molecules in capped-stick models. e) Host in ball and stick; guest and methanol molecules in CPK models. Black broken lines are HB and C−H−π(centroid) interactions.
the methylene hydrogens of BiPyPNO were the largest observed, also indicating that these protons are deeply located in the cavity of the host 1. The changes in the host 1 protons signals support the flexibility of the host 1, which is capable of modulating its conformation to accommodate the guests. The modelled structure of the 1:1 complex (Figure 6d,e), shows that the guest undergoes significant conformational change to the anti-gauche conformation to maximize the host-guest interactions without disturbing the C4v conformation.

The NMR results confirm that all guests interact with the host, yet the possible endo-host-guest complex guests 4,4’-BiPyNO and 4PhPyNO could not be overruled owing to the small up-field shifts upon complexation. The binding priority of the host 1 towards the four used guests was studied in solution through qualitative guest displacement experiments. It is known that, for macrocyclic hosts, the shielding of the guest protons is not proportional to the binding strength. In the binding priority experiments, 1H NMR spectroscopy of a 1:1 mixture of one guest and the host is recorded. One equivalent of a second guest is then added to this mixture and the 1H NMR spectrum is recorded. The chemical shift changes of the guest protons are then compared with the chemical shift changes when the second guest is not present.

Taking the binding priority experiment between 2,2’-BiPyNO and BiPyPNO and as an example (Figure 7) revealed that 2,2’-BiPyNO@1 (75%) is three times more favored than BiPyPNO@1 (25%). Experiments were performed accordingly with different equimolar mixtures of each of the two guests and the host 1 and a clear ranking of the guest priority was observed (Figures S2–S6, Table S1 in the Supporting Information). The host affinity towards the guests decreases in the following order: 2,2’-BiPyNO > BiPyPNO > 4,4’-BiPyNO ≥ 4PhPyNO. The C–H activation by N–O groups and degree of flexibility of the guest molecules are all responsible for the guest affinity.

2.2. Solid-State Structures of the Complexes

The solid-state structures of the host–guest complexes were analyzed through single-crystal X-ray diffraction studies. All the single crystals were grown from methanol. To our surprise, three out of four solid-state complex structures bear remarkable resemblance to the modelled 1:1 in-cavity complexes reported in the solution study above (Figures 2, 4, and 6).

The X-ray analysis of host 1 with 2,2’-BiPyNO reveals a 1:1 inclusion complex, 2,2’-BiPyNO@1. The asymmetric unit contains an in-cavity 2,2’-BiPyNO and an exo-cavity methanol molecule, as shown in Figure 8a. Owing to C–C bond rotation, the pyridine rings of 2,2’-BiPyNO have a twist angle of 67.3(8)° between the pyridine rings. As a result of this twisting, and despite the fact that the N–O groups show very strong HBs to the adjacent host and methanol hydroxyl groups (Figure 8b), one of the pyridine N-oxide ring resides deep in the cavity at a position of approximately 2.65 Å from the centroid of the lower rim carbon atoms (Figure S11b, see the Supporting Information for detailed HB interactions). The deeply embedded guest aromatic para- and meta-hydrogen atoms show
C–H···π(centroid) interactions with host 1 at distances of approximately 2.44, 2.65, and 2.81 Å (Figure 8a and Figure S11 in the Supporting Information). These distances are shorter compared with the reported 1:1 host–guest complex, pyridine N-oxide@1.34 The deep inclusion of the guest into the cavity of 1 with short C–H···π(centroid) distances supports the large upfield chemical shifts observed for 2,2'-BiPyNO protons in solution by 1H NMR spectroscopy.

In 4,4'-BiPyNO@1, the host 1 adopts a C2v conformation with aromatic rings at centroid-to-centroid distances of approximately 7.90/5.56 Å, deviating from the ideal crown C2v conformation where these distances are approximately 6.96 Å.[14,15] The host 1 in C2v conformation is eventually able to accommodate the “rod-shaped” 4,4'-BiPyNO at a position of approximately 3.94 Å from the centroid of the lower rim carbon atoms (see Figure S13 in the Supporting Information). As a result, the two of the acidic ortho-hydrogen atoms (to the N–O groups) in 4,4'-BiPyNO and host 1 aromatic rings have C–H···π(centroid) contacts at distances of 2.47 Å and 2.48 Å, as shown in Figure 9a. In crystal engineering, the 4,4'-BiPyNO guest is well known to act as a HB acceptor for up to six HB donors and to exhibit various twist angle values depending on the chemical environment.[16] In the X-ray crystal structure of 4,4'-BiPyNO@1, the complexity of the HB interactions between the N–O groups and the adjacent host hydroxy groups and methanol molecules (Figure 9b), that is, N–O–(H–O)host–(H–O)host and N–O–(H–O)host–(H–O)host and N–O–O(OH)OH and N–O–O(OH)OH supports the better host–guest fit in C2v, rather than in C1v conformation. Furthermore, the twist angle of 21.5° observed in the solid state for 4,4'-BiPyNO positioned deep in the cavity shows that the guest adopts a near planar conformation to maximize the interactions with the electron-rich C2v host. If directly transferred into the solution state, this host–guest complex should result in large chemical shift changes in the NMR spectrum. However, the small chemical shift changes observed by 1H NMR spectroscopy rather supports the modelled 1:1 host–guest complex between the host 1 in C1v conformation and 4,4'-BiPyNO with a twist angle of 63.7° positioned at approximately 5.23 Å from the centroid of the lower rim carbon atoms (Figure 4d,e and Figure S8c in the Supporting Information).

The C–C bond rotation in 2,2'-BiPyNO and 4,4'-BiPyNO seems crucial for the in-cavity complexation with host 1 by maximizing the C–H···π interactions based on the following observations:

1) The cis-orientation of the N–O groups in 2,2'-BiPyNO favors in-cavity complexes with C1v conformational host 1.
2) The 4,4'-BiPyNO minimizes the C–C twist angle bond to afford a nearly planar “rod-shape” structure to maximize C–H···π interactions with C2v host 1.
3) In both 2,2'-BiPyNO@1 and 4,4'-BiPyNO@1, the guests contain symmetrically positioned N–O groups in both aromatic rings making the ortho-hydrogen atoms more acidic.

In the case of the mono-N–O group containing 4PhPyNO, the methanol molecules reside in the cavity of 1 forming the complex, (MeOH@1)-4PhPyNO, as shown in Figure 10. The X-ray crystal structure (Figure 10) is markedly different to the modelled structure for 4PhPyNO@1 (Figure S9 in the Supporting Information), except for supporting the N–O group to act as a HB acceptor for three methanol molecules. Although, the conformation of the host 1 is C2v, in both 4,4'-BiPyNO@1 (see above) and (MeOH@1)-4PhPyNO with similar centroid-to-centroid interactions.
roid distances (Figures S13a and S15a in the Supporting Information), the less acidic ortho-protons to the N–O group in 4PhPyNO disfavors the in-cavity complex with host 1. Therefore, the self-inclusion of the methyl group in the 2-position and the methanol molecule fill in the cavity, leaving the 4PhPyNO to interact through HB interactions with the exocavity methanol molecules and adjacent hosts. The 4PhPyNO is thus situated between the host 1 molecules with closest C–C guest–host contact distance of approximately 3.42 Å (Figure 10 and Figure S16 in the Supporting Information).

As shown in Figure 11a,b, the BiPyPNO guest forms an in-cavity 1:1 complex, BiPyPNO@1, where it is in anti-gauche conformation. In BiPyPNO@1, the host 1 is in a distorted Ceq crown atom of the in-cavity guest molecule appear in the order 2,2'-BiPyPNO (2.65 Å) > BiPyPNO (3.15 Å) > 4,4'-BiPyPNO (3.94 Å). Remarkably, a very similar trend, yet with longer interaction distances, is observed from the simple MM-level molecular modeling for the structures of the 1:1 host–guest complexes: 2,2'-BiPyPNO (3.15 Å) > BiPyPNO (3.84 Å) > 4,4'-BiPyPNO (5.23 Å). Although, the above in-cavity position of the guest follows the same order, it is important to note that the solid-state packing will enhance the host–guest interactions in a highly HB competitive environment. Therefore, for example, in 4,4'-BiPyPNO@1, the disagreement of X-ray structure with $^1$H NMR solution data is evident, whereas the gas-phase modelled structures support the chemical shift changes obtained from $^1$H NMR experiments.

3. Conclusions
The four aromatic N-oxides (2,2'-bipyridine N,N'-dioxide, 4,4'-bipyridine N,N'-dioxide, 1,3-bis(4-pyridyl)propane N,N'-dioxide, and 4-phenylpyridine N-oxide) show definite host–guest complexation with the C-ethyl-2-methylresorcinarene host. The host–guest complexation in solution was investigated in the highly competitive solvent methanol by $^1$H NMR spectroscopy. Large chemical shift changes for the protons of 2,2'-bipyridine N,N'-dioxide and 1,3-bis(4-pyridyl)propane N,N'-dioxide clearly indicate that the guests reside deep in the cavity of the host 1 in solution. A series of competition experiments in solution resulted in a clear order in the binding preferences of the guests, supported by molecular modelling in the gas phase and X-ray crystal structure in the solid state. Although only C–H–π interactions can be observed in solution owing to H/D exchange processes in CD$_3$OD, both C–H–π and hydrogen-bond interactions were observed in the solid state. In the solid state, the in-cavity complexes are observed only if the N–O group is present in both aromatic rings. The C–C twist angle in 2,2'-bipyridine N,N'-dioxide and 4,4'-bipyridine N,N'-dioxide Ceq and Ceq conformational changes were found critical for the complexation. The 4-phenylpyridine N-oxide, which is structurally similar to 4,4'-bipyridine N,N'-dioxide, however, it lacks a N–O group in one of the aromatic rings and does not form an in-cavity 1:1 complex. On the other hand, the 1,3-bis(4-pyridyl)propane N,N'-dioxide is capable of showing multiple conformations, adopts an anti-gauche conformation instead of the more stable anti-anti conformation when complexed inside the cavity of the host.

Experimental Section
The C-ethyl-2-methylresorcinarene 1 and 1,3-bis(4-pyridyl)propane N,N'-dioxide (BiPyPNO) were synthesized according to reported procedures. The guests 2,2'-bipyridine N,N'-dioxide (2,2'-BiPyPNO), 4,4'-bipyridine N,N'-dioxide (4,4'-BiPyPNO), and 4-phenylpyridine N-oxide (4PhPyNO) were purchased from Sigma–Aldrich. The $^1$H NMR spectra were recorded with a Bruker Avance DRX 400 MHz spectrometer. Formation of the host–guest complexes, X-ray crystal structure experiments and refinement details, and $^1$H NMR measurements are presented in the Supporting Information. The CCDC CCDC 1529901–1529904 contains the supplementary crystal-
lographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Conflict of Interest

The authors declare no conflict of interest.

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