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The "nitrogen effect": Complexation with macrocycles potentiates fused heterocycles to form halogen bonds in competitive solvents

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Weak intermolecular forces are typically very difficult to observe in highly competitive polar protic solvents as they are overwhelmed by the quantity of competing solvent. This is even more challenging for three-component ternary assemblies of pure organic compounds. In this work, we overcome these complications by leveraging the binding of fused aromatic N-heterocycles in an open resorcinarene cavity to template the formation of a three-component halogen-bonded ternary assembly in a protic polar solvent system.

Introduction

Calixarenes, resorcinarenes, and other macrocyclic cavitands are widely studied hosts for many guest systems.^[1-4] These hosts are known for their ability to bind molecular guests through multiple non-covalent interactions in their tailored but shallow internal cavities.^[5] Amongst many architectures reported, two-component dimeric and hexameric capsules are relatively common^[6,7] while all organic three-component assemblies are relatively rare.^[8,9] One key advantage of these host compounds is the ease of functionalization on either the upper or lower rim.[10-12] The possibility of functionalizing resorcinarene with fluorescent groups makes them potentially useful point-of-care sensors for diagnostics.^[13] However, a major limitation in the application of these macrocycles to solve biomedical challenges is that the choice of quest is restricted to small molecules, with salts preferred for the stronger potential for stable interactions. The utility of the systems would be greatly expanded by taking advantage of the emergent properties of a bound guest that can interact with a third component. We recently reported on a series of ternary complexes whereby a C-ethyl-2-methylresorcinarene binds a pyridine in its internal cavity; both components of the resulting complex can then synergistically participate in hydrogen bonds with different carboxylic acids to form tight ternary complexes.^[8] The pK_a of the carboxylic acids was critical in determining the robustness of the ternary assemblies; some were very stable in quite competitive solvent environments. Proton transfer was also observed in the ternary assembly of carboxylic acids with very low pKa values.

Aromatic nitrogen heterocyclic (N-heterocycles) motifs — e.g. pyridine, quinoline, and imidazole — are widespread in nature and quite prevalent in biological and pharmaceutical compounds.^[14-19] When protonated, they can form host-guest complexes with aromatic cavity-containing macrocycles through cation- π interactions.^[14,20,21] Their complexes with artificial receptors such as crown ethers have also been widely reported.^[22-24] There are

several reports of complexes of resorcinarenes with aromatic nitrogen heterocycles, however, in the majority of these reports, the aromatic N-heterocycles such as pyridine and 4,4'-bipyridine are mostly used as building blocks in the construction of multicomponent architectures. There are also reports of complexes between nucleosides, their derivatives and resorcinarenes.^[25] Rissanen and co-workers reported several crystal structures of *endo*-complexes of five aromatic N-heterocycles with C-_{ethyl}-resorcinarenes highlighting π - π and C-H··· π to be the key interactions.^[20]

Halogen bonding (XB) is a highly directional non-covalent interaction occurring between electron-deficient halogen atoms and a Lewis base.^[26,27] This affinity results from an electropositive region on a halogen atom that is polarized by electronwithdrawing groups.^[28,29] Due to the high polarizability of the larger halogen atoms, the strength of the XB increases as radius increases: I > Br >> Cl >>> F; the more electropositive halogens yield stronger interactions. While polarized electrostatic attractions are critical to halogen binding, it is in effect a composite of charge transfer, van der Waal's interactions, and dipole-dipole interactions.[30] Aromatic N-heterocycles such as pyridine are potent XB acceptors. Rebek and coworkers reported amplified XB between an N-containing pyridine and O-containing δ -lactone with iodoperfluorinated propane and butane inside a sealed hydrogen bonded dimeric deep cavity cavitand capsule in a non-competing, non-polar, 1,3,5- trimethylbenzene-d¹² solvent.^[31] The nature of the solvent is essential: non-polar solvents can drive the mutual interaction of polar components, stabilizing any complex. Furthermore, in their report, the guest and the XB donor were all trapped inside a sealed dimeric capsule, greatly increasing local concentration, so the components were forced to interact. We wished to see if we can similarly leverage the electron-rich internal cavity of resorcinarenes as hosts for fused aromatic Nheterocycles in a potential 3-component open assembly. Herein, we aim to investigate the following: a) can we harness the preference for N-heterocycles as suitable guest of endowith resorcinarenes? Will these complexation endocomplexations lead to open inclusion complexes or capsular assemblies? b) If open inclusion complexes, can the fused aromatic N-heterocycle, when anchored in the cavity of the resorcinarene, participate in halogen bonding as an XB acceptor in a three-component ternary assembly in a competitive solvent environment?

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CH₃ Pair 1 Pair 2 XB Donor d) Phe XB1 b) ĊНа MeC2 a) Figure 1. Structures of $C_{\text{ethyl}}\text{-}2\text{-methylresorcinarene}~(\text{MeC2})$ as host, fused aromatic naphthalene and phenanthrene (Np, Phe), fused aromatic Nheterocycle quinoline and phenanthroline (Qu, Phen) as guests and XB acceptor, and 1-iodononafluorobutane (XB1) as XB donor. answer these questions, we selected a Cethyl-2-

То methylresorcinarene (MeC2) as host, fused aromatic naphthalene and phenanthrene (Np, Phe), fused aromatic N-heterocycle quinoline and phenanthroline (Qu, Phen) as guests and XB acceptor, and 1-iodononafluorobutane (XB1) as XB donor (Figure 1)

Results and Discussion

Complexation studies in pure methanol

Studying solution-phase host-guest complexation of a macrocycle using NMR spectroscopy is well established.[32-34] In our case, very limited changes were observed in chloroform between the isolated components and physical mixtures, and so we selected methanol as a solvent. In methanol, the complexes are in rapid equilibrium with the free components, therefore only one peak is observed in their NMR spectra as an average of the free and complexed species. Lower ppm values (shielding) of a guest's proton signals are characteristic of a guest predominantly in the cavity of the macrocycle. Moreover, the orientation of the guest within the cavity can be deduced by comparing the degree of shielding of the guest protons; the effect is greater for those deeper in the resorcinarene cavity.^[8,31,35] In addition, the degree of shielding can also be used as a qualitative indication of the strength of association between the host and guests.[36-39] In this study, we also use ¹H NMR to highlight the difference in hostguest complexation between the pairs of guests Np and Qu, and Phe and Phen to explore the "nitrogen effect". For example, significant shielding of Qu's proton signals compared to those of Np suggests Qu and the host predominantly exist as binary endocomplexes in solution. Furthermore, the greater degree of shielding for 1H_b and 1H_g compared to 1H_a and 1H_c shows the guest sits in the hydrophobic cavity in a way that orients the N atom to the solvent environment (Figure 2). This binary complex affords two unique properties compared to free guinoline in solution that can be leveraged for a stronger halogen bond: 1) the host's hydrophobic cavity restricts free molecular rotation of bound Qu, and 2) the orientation of the Lewis basic N atom towards the solvent orients and accommodates the directionality of a halogen bond in solution. Similarly, significant shielding of the fused Nheterocycle Phen signals were observed with very limited shift changes to the resonances in the fused Phe compound (Figure S2).



Figure 2. An expansion of the ¹H NMR (CD₃OD, 298 K, 300 MHz) of MeC2 complexes with Np and Qu. Spectra are produced from (a) 20 mM MeC2, (c) 20 mM Np, (e) 20 mM Qu, 2:1 mixture of (b) MeC2 (40mM) and Np (20mM), and 2:1 mixture of (d) MeC2 (40mM) and Qu (20mM). Dashed lines highlight the observed shift changes of the resonances, labels are in ppm.

Resorcinarenes form capsular assemblies in solution.[40-46] Our group and others have reported dimeric capsular assemblies of unfunctionalized resorcinarenes in methanol with suitable guests such as ammonium or phosphonium cations. [47-50] To determine if these N-heterocycles template capsular assemblies in methanol solution, we turned to 2D diffusion ordered NMR spectroscopy (DOSY). DOSY is a suitable technique to determine intermolecular interactions in solution because the diffusion coefficient of a molecular species under specific conditions (e.g. concentration, solvent, temperature etc) depends on its molecular weight, size, and shape. First, we used 2D DOSY to measure the diffusion coefficient of the guests (Qu and Phen), and MeC2 in pure methanol (Table 1). The diffusion coefficients ($D \times 10^{-9}$ in m²s⁻¹) of MeC2, Qu, and Phen were calculated in the selfassembly of host-guest solutions. Larger molecules have smaller diffusion coefficients compared to small molecules. From the DOSY results, we determined that MeC2 forms open 1:1 inclusion complexes with Qu (Table 1) which makes the Qu available to engage with a third species via halogen bonding. No reliable diffusion coefficient was observed for Np which is likely due to its very weak interactions with MeC2. Interestingly, MeC2 forms a 2:1 dimeric capsular assembly with the N-heterocycle Phen in pure methanol and an open 1:1 inclusion complex with the fused aromatic Phe (Table 1, Figure 3, Figure S7).



Figure 3. The ¹H NMR (CD₃OD, 298 K, 300 MHz) of MeC2 complex with Phen. Spectra are produced from (a) 20 mM MeC2, (b) 20 mM Phen, (c) 2:1 mixture of MeC2 (40 mM) and Phen (20 mM), (d) 2D DOSY NMR spectra (CD₃OD, 298 K, 300 MHz) of a 2:1 mixture of MeC2:Phen, showing the chemical species present in the sample. Chemical shifts [ppm] are shown on the x-axis and the diffusion coefficients [log m²s⁻¹] on the y-axis of the 2D plot. Dashed lines

represent the residual solvent

Sample in CD₃OD^a

MeC2

Np

Qu

Phe

Phen

MeC2 + Np (2:1)

MeC2 + Qu (2:1)

MeC2 + Phe (2:1)

MeC2 + Phen (2:1)

MeC2

Qu

MeC2 + Qu

MeC2 + Qu + XB1 (1:1:1)

Phen

MeC2 + Phen (1:1)

MeC2 + Phen + XB1 (1:1:2)

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RESEARCH ARTICLE highlight the observed shift changes of the resonances, labels are in ppm. Star Table 1. Average Diffusion Coefficients $D(\times 10^{-9} \text{ m}^2 \text{s}^{-1})$ of the host, the guests, and the host-guest mixtures at 298 K. D, Guest D, Host 1.020±0.110 2.490±0.200 2.260 ± 0.070 2.440±0.010 1.360±0.040 _c 1.190± 0.210 1.930±0.350 1.010±0.240 2.020±0.230 1.050±0.200 0.820±0.010 0.950±0.010 Samples in 50/50 CD₃Cl: CD₃OD^t 0.569±0.040 1.520±0.118 1.331 ± 0.027 0.489±0.004 1.325 ± 0.021 0.490±0.002 1.148 ± 0.090 1.049±0.001 0.489±0.008

 $^{a,b}\text{Diffusion}$ coefficients of CD_3OD ranges between 1.840–2.090×10^-9 m^2s^{-1} °Poor relaxation. No reliable diffusion coefficient for Np probably because of a relatively weak binding process.

1.036±0.001

0.479±0.009

X-Ray crystallography

Although the nature of a species in the solid state may not reflect its interactions in solution, and care must be taken in interpretation, X-ray crystal structures provide unambiguous information about possible interactions. Co-crystallization of Phen with MeC2 in MeOH resulted in a water-mediated dimeric capsule, Phen@(MeC2)2·9H2O, consistent with the dimeric capsule in solution observed by DOSY NMR. All attempts at crystallization of the MeC2 with the other guests from MeOH resulted only in homocrystals of either host or guest molecules. In the capsule Phen@(MeC2)₂, two molecules of MeC2 are joined together by $_{host}(H-O)\cdots H_2O\cdots (H-O)_{host}$ hydrogen bond interactions and take on an eclipsed conformation, which is most likely related to the involvement of the endo-guest and water molecules in mediating the capsule. The centroids of the planes, defined by the hosts' methine carbons, are separated by a distance of 11.64 Å. which is longer than the distances reported for dimeric capsules encapsulating tetraalkylammonium salts.^[51] This can be attributed to the larger size of the Phen. The Phen is situated inside the cavity, and the C-H interactions between its C-H groups and the MeC2 aromatic rings range from 2.71 to 3.0 A.





Figure 4. X-ray structure of the host-guest dimeric 2:1 capsule Phen@(MeC2)2. Ball and stick representation with the guest in CPK mode. Disordered guest and water molecules are not shown for viewing clarity.

Complexation studies in methanol-chloroform mixture

The high dielectric constant makes methanol a highly competitive solvent and thus non-ideal for the formation of halogen bonds in solution. Chloroform is a much better solvent for halogen bonding; however, host-guest complexes were not observed in pure chloroform. In order to investigate the possibility of a halogen bonded ternary assembly, we turned to a 50/50 v/v methanol/chloroform solvent mixture. Even at 50%, methanol is still, of course, strongly able to interfere in the formation of any but the strongest XBs. To obtain an indication of a potential hostguest system that could form XBs, we prepared equimolar mixtures of MeC2 and either Qu or Phen. The nitrogen effect is still observed, resulting in shifts to lower ppm of the guest signals, indicating endo-complexation in this mixed solvent system (Figure 5). As expected, when comparing these systems to the same ones in pure methanol, the degree of shielding is less pronounced (Figures 2, 5).



Figure 5. An expansion of the ¹H NMR (CD₃OD/CDCI₃, v/v, 298 K, 300 MHz) of MeC2 complexes with Qu (20 mM) and XB1 (20 mM). Spectra are produced from (a) MeC2, (e) Qu, equimolar mixtures of (b) MeC2+Qu, (d) Qu+XB1, and (c) MeC2+Qu+XB1 (20 mM each). Dashed lines highlight the observed shift changes of the resonances, labels are in ppm.

XB1 is known to form potent halogen bonds with pyridine and other nitrogen-containing aromatic compounds.^[26] However, these studies have been done in non-competing solvents such as pure chloroform. This is because protic and highly polar solvents will provide strong competition as halogen bond acceptors and will inhibit the stability of XBs in solution. To identify halogen les of use; OA articles are governed by the applicable Creative Commons

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bonding we first monitored the ¹H NMR signals of **Qu** for indication of potential halogen bonding in an equimolar mixture with XB1. Of particular significance is the Ha closest to the nitrogen acceptor since this is most sensitive to changes in the chemical environment on the nitrogen. No signal changes were observed (Figure 5). The ¹⁹F NMR of the fluorine attached to the same carbon as the iodine reveals very small changes of only -0.01 ppm (Figure 6). We then turned to ¹³C NMR by monitoring the carbon closest to the nitrogen (carbons "a" and "i", Figure 7). Small shifts of 0.15 and 0.14 ppm lower were observed. The ¹H, ¹⁹F and ¹³C NMRs all reveal very weak to no XB between **Qu** and XB1 in this mixed and highly competing methanol-chloroform solvent system. However, we know that MeC2 forms endocomplexes with either Qu or Phen in this mixed solvent system. We hypothesized that this complex, holding the guest in a defined conformation and increasing the electron density on the guest, might be sufficient to make Qu a suitable XB partner for XB1. The ternary assembly might be able to do what a binary system cannot accomplish. For example, the halogen bond interaction can be enhanced in the ternary assembly compared to binary system. Consequently, we titrated one equivalent of XB1 into a 1:1 mixture of MeC2 and either Qu or Phen. First, we compared the ¹H NMR of the two-component (pre-titration) and three-component mixtures. In the two-component mixture, the Qu Ha protons move 0.27 ppm lower, signifying complexation in the hydrophobic cavity. In the same solvent mixture, 1 equivalent of XB1 causes H_a to be shielded by 0.23 ppm to accommodate the halogen bond while in-cavity. Next, we conducted ¹⁹F NMR experiments to monitor the fluorine signals of XB1 in similar three-component self-assembly. Similarly, we monitored the fluorine signals on the same carbon as the iodine as they are most sensitive to halogen bond formation. For comparison, in a 1:1 mixture of Qu and XB1, the fluorine signals of interest only moved by -0.01 ppm. In the ternary mixtures, this signal moves by -0.06 ppm (Figure 6). This can be interpreted as an increase in the number of halogen bonded species due to the macrocycle but could also be due to an unintended interaction of the macrocycle. To provide additional evidence, we conducted ¹³C and 2D DOSY NMR of the MeC2, Qu and XB1 in the mixed solvent system (Table 1).



Figure 6. An expansion of the ¹⁹F NMR (CD₃OD/CDCl₃, v/v, 298 K, 300 MHz) of XB complexes with Qu and MeC2. Spectra are produced from (a) XB1 (20 mM) and equimolar mixtures (20 mM) of (b) MeC2+Qu, (d) Qu+XB1, and (c) MeC2+Qu+XB1. Dashed lines highlight the observed shift changes of the resonances, labels are in ppm.

The ¹³C NMR of the ternary mixture shows a significant shift in the resonances compared to any of the binary systems (**MeC2+Qu** and **Qu+XB1**). Taking carbon "a", closest to the nitrogen of **Qu**, the ternary mixtures show a lower ppm shift of 1.03 with only 0.50 ppm for **MeC2+Qu** and 0.15 ppm for **Qu+XB1** mixtures. Even bigger shift changes are observed for carbon "i": 1.44 ppm in the ternary mixture as compared to 0.47 ppm and 0.14 ppm for the **MeC2+Qu** and **Qu+XB1** mixtures respectively (Figure 7). These results thus support the presence of a ternary system held together by XB and C-H… π interactions as well as size complementarity.



Figure 7. An expansion of the ¹³C NMR (CD₃OD/CDCl₃, v/v, 298 K, 400 MHz) of MeC₂ complexes with Qu (20 mM) and XB1 (20 mM). Spectra are produced from (a) MeC₂, (b) Qu, equimolar mixture of (c) Qu+XB1 (20 mM each), (d) MeC2+Qu (20 mM each), and (e) MeC2+Qu+XB1 (20 mM each). Dashed lines highlight the observed shift changes of the resonances, labels are in ppm.

To get further insights into these assemblies in the mixed solvent systems, we used 2D DOSY NMR. Unfortunately, the diffusion coefficients of XB1 cannot be measured directly due to the absence of hydrogen atoms. Looking at the different mixtures of MeC2, Qu and XB1 as an example, the results show diffusion coefficients of 0.569±0.040×10⁻⁹ m²s⁻¹ and 1.520±0.118×10⁻⁹ m²s⁻¹ for the pure MeC2 and Qu respectively. The binary mixture reveals diffusion coefficients of 0.489±0.004×10⁻⁹ m²s⁻¹ and $1.331\pm0.027\times10^{-9}$ m²s⁻¹ for MeC2 and Qu respectively. In the three-component mixture, diffusion coefficients 0.490±0.002×10⁻⁹ m²s⁻¹ and 1.325±0.021×10⁻⁹ m²s⁻¹ for MeC2 and Qu respectively. The diffusion coefficients give 0.489±0.008×10⁻⁹ m²s⁻¹ and 1.049±0.001×10⁻⁹ m²s⁻¹ as well as 0.479±0.009×10⁻⁹ m²s⁻¹ and $1.036\pm0.001\times10^{-9}$ m²s⁻¹ for MeC2 and Qu in the binary and ternary mixtures respectively. In a capsular construct, the diffusion coefficients should be the same as all components move together. However, in an open inclusion complex, we expect a dynamic equilibrium between the complex and the monomeric species, and as the monomeric species are different sizes, and as the on-off rates are fast, we get a single value for each species where decreases in the diffusion constants suggest interaction. In these two components and three-component mixtures, the decrease in the diffusion coefficients of both MeC2 and Qu and Phen show they all are more likely to participate in a larger assembly in both the binary and ternary mixtures.

Quantification of binding

Lastly, we employed isothermal titration calorimetry (ITC) to quantify some of the binding processes and get an insight into the thermodynamics of the binding. The thermodynamics of hostguest complexation were assessed using a series of ITC experiments in 50:50 methanol and chloroform (Figure S15-17, Table 2). The parameters K_a , ΔH , ΔS , and ΔG were determined by fitting the ITC curves to a one-site binding model. Given the competitive nature of the solvent environment for XB formation, the thermodynamics of the ternary system formation cannot be reliably determined without large errors. The effect of the nitrogen on the fused aromatic is also observed in the self-assembly of the guests with the host MeC2. Complex formation between MeC2 and the Qu was spontaneous (AG<0) at 298 K. This selfassembly is enforced by the methanol that drops the hydrophobicity of the solvent to favor endo-complexation in the cavity of the resorcinarene. The negative ΔH and positive T ΔS values indicate the complexation is favored by both enthalpy and entropy. However, this self-assembly does not occur between MeC2 and Np (Figure S15). Moreover, the ITC titration of the Qu with XB1 establishes the halogen bond formation between the two components in the mixed solvent system. It is noteworthy that the

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strength and directionality of the halogen bond is dependent on the magnitude and size of the sigma hole.^[52] The association constant between Qu and XB1 was measured at 345±28.4 mol⁻¹. The complexation is enthalpically favorable, releasing heat to the solvent environment. However, entropy contributions in the halogen bonding with XB1 require a low reaction temperature to maintain spontaneous self-assembly.

Table 2. Thermodynamic binding parameters of formed complexes between the host (10 mM) and the guests (50 mM) by ITCa

| Complex | Ka | <i>∆H</i> kcal/mol | T∆S kcal/mol | ∆G kcal/mol |
|---------|----------|-----------------------|-----------------|----------------|
| Qu@MeC2 | 699±122 | -0.96 ± 0.085 | 2.92 | -3.88 |
| Np@MeC2 | _a | _a | _a | _a |
| Qu@XB1 | 345±28.4 | -5.02±0.092 | -1.56 | -3.46 |

^[a] ITC titration curve could not be fitted without large errors.

Conclusions

we show in a highly competitive solvent, In summary resorcinarenes prefer fused aromatic N-heterocycles. While quinoline form 1:1 open inclusion complex, the corresponding phenanthroline templates a dimeric capsule in pure methanol. The dimeric capsule was confirmed through 2D DOSY analysis and X-ray crystallography. In a mixed methanol-chloroform mixture (50/50 v/v), both N-heterocycles form 1:1 open inclusion complexes. The addition of a halogen bond donor, 1iodononafluorobutane, revealed halogen bond formation with the anchored N-heterocycle inside the resorcinarene in a threecomponent ternary assembly. The reported N-heterocycle mediation of a resorcinarene-XB1 interaction is a clear example of ternary architecture in a highly competitive solvent environment. The formation of the binary and ternary systems is investigated in solution through ¹H, ¹³C, ¹⁹F and DOSY NMR analysis as well. The electron-rich resorcinarene cavity makes the pyridine N-atom more basic through the host-guest C-H···π interactions. The ITC-derived thermodynamic parameters (negative ΔH and positive T ΔS values) for the Qu-XB1 binary system indicate that complexation is enthalpy driven and compensated by entropy, while it is both enthalpically and entropically favored in the case of MeC2-Qu. The X-ray structure permits direct observation of the weak interactions between the Phen and the MeC2 in pure methanol. The N-heterocycle quest in the cavity of the host can achieve positions for halogen bonding in a very competitive solvent environment which was far less obvious in the binary system.

Experimental Section

phenanthrene, quinoline, and phenanthroline, and the XB donor 1iodononafluorobutane, and solvents used for syntheses, NMR and ITC experiments, and crystallizations were purchased from Sigma Aldrich or Oakwood Chemicals (Estill SC, USA). The ¹H, ¹³C, ¹⁹F-NMR, and DOSY NMR experiments were carried out in either CD₃OD or CD₃OD/CDCl₃ 50/50, v/v at 298 K on either Bruker Avance 300 or 400 MHz spectrometers. ITC measurements were performed using VP-ITC VP-ITC instrument made by MicroCal.

Solid-state X-ray crystallography: The data was measured using a dualsource Rigaku SuperNova diffractometer equipped with an Atlas detector and an Oxford Cryostream cooling system using mirror-monochromated Cu-Ka radiation (λ = 1.54184 Å). Data collection and reduction for all complexes were performed using the program CrysAlisPro^[54] and Gaussian face-index absorption correction method was applied. The structure is solved with intrinsic phasing (SHELXT)^[54] and refined by full10.1002/asia.202201308

matrix least squares on F² using the OLEX2 software^[55], which utilizes the SHELXL-2015 module.^[56] Non-hydrogen atoms were assigned anisotropic displacement parameters unless stated otherwise. Hydrogen atoms were placed in idealized positions and included as riding. Isotropic displacement parameters for all H atoms were constrained to multiples of the equivalent displacement parameters of their parent atoms either with $U_{iso}(H) = 1.2$ or 1.5 Ueq (parent atom). Several reflections with large discrepancies between the calculated and observed structure factors have been omitted from the least-squares refinement as outliers. Distance restraints (DFIX) and constraints (AFIX) were applied. Positional disorders were refined to two split positions, with the sum of the site occupancies of both alternative positions constrained to either half or unity (see the cif file). The X-ray crystal data and experimental details and CCDC number are given below. Data for Phen@(MeC2)₂: CCDC Number: 2231744. C₉₂H₁₂₂N₂O₂₅, M = Data for Pnen@(MeC2): CCDC Number: 2231744. $C_{92}n_{122}V_{025}$, M = 1655.91 g·mol⁻¹, brown block, 0.13 × 0.09 × 0.05 mm³, triclinic, space group P-1 (No. 2), a = 11.3550(4) Å, b = 11.5120(4) Å, c = 17.7648(6) Å, a = 95.134(3)°, β = 104.049(3)°, γ = 107.726(3)°, V = 2111.97(13) Å³, Z = 1, D_{calc} = 1.302 g·cm⁻³, F(000) = 888, μ = 0.772 mm⁻¹, T = 123(2) K, θ_{max} = 66.749°, 11973 total reflections, 5587 with lo > 20(lo), Rint = 0.0446, 200 km⁻¹ = 0.0444 km⁻¹ 7359 data, 610 parameters, 0 restraints, GooF = 1.019, $R_1 = 0.0644$ and $wR_2 = 0.1710 [lo > 2\sigma(lo)], R_2 = 0.0842 and wR_2 = 0.1860 (all reflections),$

 $0.611 < d\Delta \rho < -0.355 eA^{-3}$. Synthesis of Phen@(MeC2)₂: MeC2 (5 mg 0.0076 mmol, 1 equiv.), Phen (1.5 mg, 0.0082 mmol, 1.1 equiv.), and MeOH (1 mL) are added to a 5 mL vial at room temperature. Using a vortex mixer, the components were stirred roughly for 15 seconds. Slow evaporation of the resultant brown solution at ambient temperature gave single crystals suitable for X-ray diffraction analysis after one week

NMR solution experiments: ¹H, ¹³C, ¹⁹F, and DOSY NMR spectra were recorded on a Bruker Avance 300 MHz and 400 MHz spectrometers. All signals are given as δ values in ppm relative to TMS using residual solvent signals as the internal standard. For sample preparation, stock solutions of the receptor MeC2 (60 mM), the guests (Qu, Phen, Np, and Phe, 60 mM), and all the XB donor XB1 (60 mM) were prepared in either CD₃OD or CD₃OD/CDCl₃ v/v. For the pure samples, 200 µL of the stock solution was transferred to an NMR tube and diluted with 400 µL of pure solvent providing a 20 mM sample concentration. For a 1:1 mixture, as an example, 200 µL of MeC2, 200 µL of Qu and 200 µL of pure solvent provided a 20 mM sample concentration of each component in the mixture. For a 1:1:1 mixture, as an example, 200 µL of MeC2, 200 µL of Qu, and 200 µL of each XB1 were mixed to give a 20 mM sample concentration of each component in the mixture.

ITC solution experiments: A VP-ITC instrument by MicroCal was used to determine the molar enthalpy (ΔH) of complexation. Subsequent fitting of the data to a 1:1 binding model using Origin software provides association constant (K), change in enthalpy (ΔH) and entropy (ΔS). The ITC experiment was carried out by filling the sample cell with one sample (0.25 mM), filling the syringe with the second sample (5.0 mM), and titrating via computer-automated injector at 298 K. Blank titrations into plain solvent were also performed, and subtracted from the corresponding titration to remove any effect from the heats of dilution from the titrant.

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Keywords: Halogen bond • Resorcinarenes • Ternary assemblies • Dimeric capsules • N-Heterocycles

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Fused aromatic N-heterocycles quinoline templates a halogen-bonded ternary assembly with resorcinarene and 1iodonoonafluorobutane in a highly competitive solvent environment, while phenanthroline templates a dimeric capsule in pure methanol.

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