ChemComm

IYC 2011
International Year of CHEMISTRY

This article is part of the

Supramolecular Chemistry web-based thematic issue

celebrating the International Year of Chemistry 2011

Guest editors: Professors Philip Gale, Jonathan Sessler and Jonathan Steed

All articles in this issue will be gathered together online at www.rsc.org/chemcomm/supra.

ChemComm

Dynamic Article Links

Cite this: *Chem. Commun.*, 2011, **47**, 5979–5981

www.rsc.org/chemcomm

COMMUNICATION

Two levels of conformational pre-organization consolidate strong CH hydrogen bonds in chloride–triazolophane complexes†‡

Yuran Hua, Raghunath O. Ramabhadran, Jonathan A. Karty, Krishnan Raghavachari and Amar H. Flood*

Received 21st January 2011, Accepted 3rd April 2011
DOI: 10.1039/c1cc10428d

Structural rigidity is verified as a pre-organizational factor that acts together with the macrocyclic effect such that synthesis helps in paying the cost of bringing together electropositive CH donors ready for H-bonding with chloride.

Pre-organization is a foundational concept in supramolecular chemistry where enhanced binding arises from optimal conformational preparation and low solvation of the host.[1] The importance of a host's conformational pre-organization was exemplified by comparing rigid spherands to less organized acyclic ether hosts for cation binding.[1] Demonstrations of increasing pre-organization in the field of anion binding are rare. On the basis of their structure, triazolophanes[2] are a class of anion-binding macrocycles that enable such an examination. While the specific enthalpy and entropy factors resist generalization,[3] they can be described for each specific system. We do this here, and in response to a recent proposal by Craig,[4] we focus on the enthalpic benefit of pre-organizing electropositive H-bond donors.

Triazolophanes display large Cl^- binding strengths from non-classical[5] CH H-bond donors: the affinity is as high as $K_a = 5 \times 10^6\ M^{-1}$ (CH_2Cl_2) with tetraphenylene triazolophane, **1** (Fig. 1). The origins of this affinity are still being verified. Chloride stabilization is provided by CH H-bonds[6,7] from the 1,2,3-triazole units[2,4,8,9] and the weaker phenylene CH donors.[8] Yet this is only half the story. Unlike most neutral receptors, these macrocycles, as well as those of Hamilton,[10] Jeong[11a] and Maeda,[12] are rigid. Consequently, these are all thought to be "highly"[1] pre-organized such that the H-bond donors are already directed into the center of the cavity. Achieving this structure, however, forces the electropositive triazole hydrogens into contact[13] with each other—an enthalpic cost that is largely paid during the synthesis of the rigid macrocycle **1**.

Based on this description, the key question emerges: Does rigidity afford additional benefits for the macrocycle? This idea has never before been tested experimentally with shape-persistent macrocycles.[2,10–12] We recognized that the idea could be investigated in a straightforward manner because it is easier to remove rigidity from **1** than to add it, which is the task undertaken in most other cases.[1,14] Triazolophane **2** (Fig. 1) was designed to make use of propylene linkers (blue) to reduce the rigidity generating a "partially"[1] pre-organized macrocycle while retaining a similar size (24-membered) and the semi-planar east–west wings as in **1**. Furthermore, replacing phenylene with methylene CH donors is believed to reduce the H-bond strength by half.[7b,15] Our estimates for the sum of the individual CH···Cl^- strengths[16,17] provide *ideal* Cl^--binding free energies in the optimal configuration for eight H-bonds in **1** and **2** of $\Delta G_{ideal} = -48$ and -44 kJ mol^{-1} (Table 1), respectively. Calculations on the conformations of **1**[8] and **2** (*vide infra*)[16] show them to have similarly-small configurational (entropy) changes[2c,4,18] upon Cl^- binding. However, these conformations are differently organized such that we expect there will be a drop in Cl^- binding for **2** in order to prepare the correct conformation when electropositive hydrogens are brought together for binding. To provide a measure of this effect, we calculate electrostatic potentials

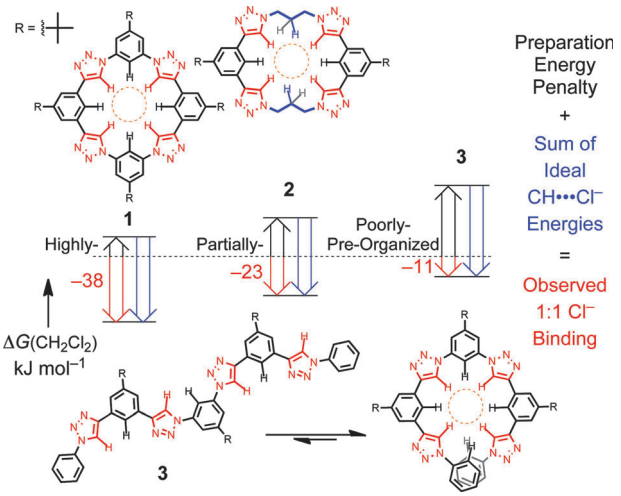

Fig. 1 Different levels of pre-organization in rigid macrocycle **1**, flexible macrocycle **2** and oligomeric receptor **3**.

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, IN 47405, USA. E-mail: aflood@indiana.edu; Fax: +1 (812)855-8300; Tel: +1 (812)856-3642

† This article is part of a ChemComm 'Supramolecular Chemistry' web-based themed issue marking the International Year of Chemistry 2011.

‡ Electronic supplementary information (ESI) available: Syntheses, spectra, titration data, and data modeling. See DOI: 10.1039/c1cc10428d

Table 1 Observed, ideal[17] and computed[25] energy values (kJ mol^{-1})[a]

R =	**1**	**2**	**3**
ΔG_a **R** + Cl^- = **R**·Cl^-	−38 ± 2	−23 ± 2	−11 ± 1
ΔG_{ideal} $\mathbf{R}^*$ + Cl^- = **R**·Cl^-	−48	−44	−52
ΔE_{prep} $\mathbf{R}^{\#}$ = $\mathbf{R}^{\#*}$	+10	+24	+33

[a] * = prepared structure, # = model of receptor.

(ESP, HF/3-21G, SPARTAN)[16] as a function of different conformations and correlate higher positive ESP values to the build-up of repulsion.

The idea of pre-organization has been visited with other shape-persistent receptors[10,11b,12] as the macrocyclic effect.[19] Triazolophanes are no exception, as was shown using the "poorly" pre-organized oligomer **3** (Fig. 1), which folds around Cl^- with much reduced affinity[2b] even though its ideal[16] binding energy using nine H-bond donors[17] is ΔG_{ideal} = −52 kJ mol^{-1}. Consequently, we expect its low-energy conformations to have smaller ESPs than **2**, which would generate a larger electrostatic penalty upon preparation of the folded form, explaining some of the drop in Cl^- binding. Additional entropy adjustments will also arise from freezing out the conformations[18] and rotations.

Solvation is also known to play a role.[4] Small differences in solvation upon Cl^- binding across the complexes is expected.[20] There will also be a small favorable effect of pre-organization in **1** for excluding some but not all solvent, however, this effect is assumed to be small for the uncharged receptors.

By examining differences between oligomeric **3** and flexible **2**, we will focus on identifying any benefit arising from directing the electropositive triazole hydrogens toward the center region of the cavity (macrocyclic effect) and when comparing **2** with **1**, to identify the benefit of rigidly forcing them close together (conformational pre-organization).

The synthesis of **2** is described in the supporting information. Titration of tetrabutylammonium chloride (TBA^+·Cl^-) into a solution of **2** (CH_2Cl_2) generated signals for the anion-complex (**2**·Cl^-) using electrospray ionization mass spectrometry[2c,16] and for the complexed ion-pair (**2**·Cl^-·TBA^+) using diffusion NMR.[2c] The following three equilibria co-exist together in solution:

$$\mathbf{2} + Cl^- = \mathbf{2}\cdot Cl^- \quad \Delta G_a \qquad (1)$$

$$TBA^+ + Cl^- = TBA^+\cdot Cl^- \quad \Delta G_{ip} \qquad (2)$$

$$TBA^+ + \mathbf{2}\cdot Cl^- = \mathbf{2}\cdot Cl^-\cdot TBA^+ \quad \Delta G_{ipc} \qquad (3)$$

NMR titration of **2** with TBA^+·Cl^- (Fig. 2) suggests weak binding on account of the poor saturation after 20 equivalents. All the inward facing protons shift downfield with large peak migrations from the triazole H^a ($\Delta\delta$ = 2.3 ppm) and phenylene H^b ($\Delta\delta$ = 1.0 ppm). The peak position of propylene H^d was barely affected. These shifts indicate the dominance of C–H···Cl^- H-bonds on the peak positions.[21] The positions of protons a–c, and the α-CH_2 proton on TBA^+ were included in the estimation of the binding constants.[16]

Using the complete set of binding equilibria, the 1 : 1 binding energy for **2**·Cl^- was determined[16] to be ΔG_a = −23 ± 2 kJ mol^{-1}. This value is smaller than the ion pairing between Cl^- and TBA^+ (ΔG_{ip} = −28 kJ mol^{-1}),[22] indicating

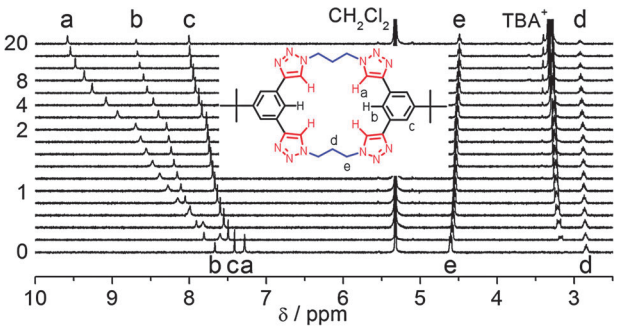

Fig. 2 ^{1}H NMR titration of **2** (500 μM) upon addition of 0–20 eq. of TBA^+·Cl^- in CD_2Cl_2 (298 K).

the strong competition between semi-rigid triazolophane **2** and the TBA^+ cation for Cl^-. Consistent with Fuoss' Law,[23] the ion-pairing of **2**·Cl^- with the TBA^+ countercation (eqn (3), ΔG_{ipc} = −21 ± 3 kJ mol^{-1}) was weaker than between Cl^- and TBA^+ (−28 kJ mol^{-1}).

The prior titration data on oligomer **3**[2b] was re-evaluated to accommodate ion pairing. A reliable simulation of the NMR peak positions[16] was generated when considering the direct formation of ion-pair complex **3**·Cl^-·TBA^+ (eqn (4)). Based on reasonable assumptions,[16] the binding affinity for **3**·Cl^- was estimated as ΔG_a = 11 ± 1 kJ mol^{-1}.

$$\mathbf{3} + TBA^+ + Cl^- = \mathbf{3}\cdot Cl^-\cdot TBA^+ \quad \beta_{ipc} = K_a \times K_{ipc} \qquad (4)$$

This datum completes the series (Table 1). Differences between ΔG_a and ΔG_{ideal}[17] define the preparation *free* energies.[24]

Calculations on **1–3** and their complexes provide insights into the nature of the pre-organization by considering their conformations, *computed* preparation energies (ΔE_{prep}, Table 1)[25] and electropositive character. The results on an analog of **1** ($\mathbf{1}^{\#}$, Fig. 3)[8] can be compared to the computational results on an analog of **2** ($\mathbf{2}^{\#}$, Fig. 3) and of **3** ($\mathbf{3}^{\#}$),[16] where all *t*-butyls are replaced with hydrogens. In $\mathbf{1}^{\#}$, the empty triazolophane shows[8] (Fig. 3) the electropositive hydrogens (blue) barely directed out of the receptor's plane with average nonbonded H···H distances of 2.30 Å and an ESP maximum situated on the triazole hydrogens of 287 kJ mol^{-1} (= 287 ev for "ESP value"). Upon Cl^- binding, the structure planarizes with $d_{H\cdots H}$ decreasing by 0.14 Å to 2.16 Å. By examining the structure with the Cl^- removed, $\mathbf{1}^{\#*}$, an increase in the ESP to 327 ev (more blue) was observed. Presumably this increase is reflected in the computed energy penalty to prepare the perfectly planar structure $\mathbf{1}^{\#*}$ of ΔE_{prep} = 10 kJ mol^{-1}.[25]

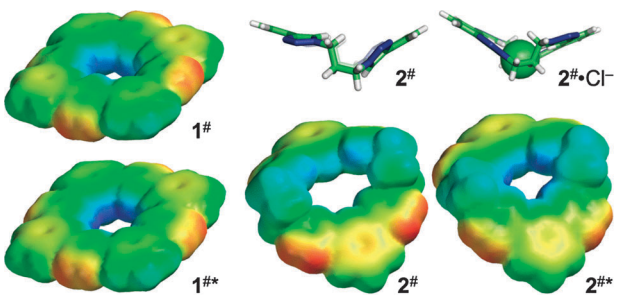

Fig. 3 Optimized structures (B3LYP/6-31 + G(d,p)) of $\mathbf{1}^{\#}$, $\mathbf{2}^{\#}$ and $\mathbf{2}^{\#}$·Cl^- and the prepared structures $\mathbf{1}^{\#*}$ and $\mathbf{2}^{\#*}$; ESP (isovalence = 0.002: −230 (red) to 330 (blue) ev.

Geometry optimization (B3LYP/6-31+G(d,p)) shows that the lowest energy conformation of the empty macrocycle $\mathbf{2}^{\#}$ (Fig. 3) is different from the one minimized for the complex $\mathbf{2}^{\#}\cdot Cl^-$. The key difference is the two semi-planar east–west wings in $\mathbf{2}^{\#}$ are arranged in a divergent manner (average $d_{H\cdots H}$ = 2.53 Å, ESP = 253 ev), whereas in $\mathbf{2}^{\#}\cdot Cl^-$, they re-arrange to converge the CH H-bonds onto the Cl^- ion. The average $d_{H\cdots H}$ = 2.27 Å reduces by 0.26 Å, twice as much as $\mathbf{1}^{\#*}$, indicative of differences in rigidity. When the Cl^- is removed from the structure of the complex, the ESP (296 ev) has increased and the preparation energy of $\mathbf{2}^{\#*}$ (ΔE_{prep} = 24 kJ mol^{-1}) comes close to the difference between ΔG_a and ΔG_{ideal} (Table 1) of 21 kJ mol^{-1}. Consistent with predictions, the ESP of $\mathbf{2}^{\#}$ starts out smaller than $\mathbf{1}^{\#}$—the empty flexible macrocycle relaxes its structure to diverge the electropositive hydrogens. However, once $\mathbf{2}^{\#*}$ is prepared, its ESP increases (more blue than $\mathbf{2}^{\#}$) because the penalty of bringing its electropositive hydrogens together is paid by Cl^- binding.

In the case of oligomer $\mathbf{3}^{\#}$, 44 conformations were found within a span of 18 kJ mol^{-1} (AM1).[16] In the six lowest-energy ones ($<1.5\ kT$), and just as for $\mathbf{1}^{\#}$ and $\mathbf{2}^{\#}$, the triazole protons are directed away from each other. The average ESP for the six conformations of $\mathbf{3}^{\#}$ (236 ev) is even smaller than $\mathbf{2}^{\#}$ (253 ev), which is consistent with expectations. However, the ESP of the prepared receptor $\mathbf{3}^{\#*}$ (302 ev) is very close to $\mathbf{2}^{\#*}$ (296 ev). Correspondingly, the computed preparation energy[16] ΔE_{prep} = 33 kJ mol^{-1} is larger than that of $\mathbf{2}^{\#*}$ (24 kJ mol^{-1}). However, it falls short of the amount needed ($\Delta G_a - \Delta G_{ideal}$ = 41 kJ mol^{-1}) to take full advantage of the H-bond donors,[17] suggesting that factors (solvation and entropy) other than pre-organization of the electropositive hydrogens are playing a role in weakening the stability of $\mathbf{3}\cdot Cl^-$.

The structures of $\mathbf{1}^{\#}$, $\mathbf{2}^{\#}$ and $\mathbf{3}^{\#}$ show that the receptors try to achieve relaxed conformations by diverging the electropositive hydrogens, as suggested by Craig.[4] Forming a macrocycle confers a benefit[24] of ~20 kJ mol^{-1} for which some of this will arise from bringing the hydrogens together. The rigid constraints in $\mathbf{1}^{\#}$ prevent it from relaxing as much electropositive character as $\mathbf{2}^{\#}$ resulting in a benefit of ~11 kJ mol^{-1} to the preparation energy.[25] This line of reasoning suggests that rigidity can allow a jump in the stability of the Cl^- complexes that a partially pre-organized macrocycle alone cannot furnish. It is also the feature that confers the halide selectivity for Cl^- and Br^- over F^- and I^-.[2b]

Rigidity is identified as a pre-organizational factor in tetraphenylene triazolophanes that acts with the macrocyclic effect to prevent the relaxation of electropositive hydrogens such that they remain pre-organized in a complementary manner for forming CH$\cdots Cl^-$ H-bonds. While the analysis presented here gives credence to electrostatics, a full deconvolution will require evaluations of solvation and an estimate of the relative weights of each contributing factor.

We thank the NSF (CHE-0844441 and CHE-0911454) for funding and the referees for input.

Notes and references

1 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1039–1057.
2 (*a*) Y. Li and A. H. Flood, *Angew. Chem., Int. Ed.*, 2008, **47**, 2649–2652; (*b*) Y. Li and A. H. Flood, *J. Am. Chem. Soc.*, 2008, **130**, 12111–12122; (*c*) Y. Hua, R. O. Ramabhadran, E. O. Uduehi, J. A. Karty, K. Raghavachari and A. H. Flood, *Chem.–Eur. J.*, 2011, **17**, 312–321.
3 R. M. Izatt, J. S. Bradshaw, S. A. Neilsen, J. D. Lamb and J. J. Christensen, *Chem. Rev.*, 1985, **85**, 271–339.
4 H. Juwarker, J. M. Lenhardt, J. C. Castillo, E. Zhao, S. Krishnamurthy, R. Jamiolkowski, K.-H. Kim and S. L. Craig, *J. Org. Chem.*, 2009, **74**, 8924–8934.
5 G. R. Desiraju and T. Steiner, *The weak hydrogen bond in structural chemistry and biology*, Oxford University Press, Oxford, 1999.
6 (*a*) D. W. Yoon, D. E. Gross, V. M. Lynch, J. L. Sessler, B. P. Hay and C. H. Lee, *Angew. Chem., Int. Ed.*, 2008, **47**, 5038–5042; (*b*) O. B. Berryman, A. C. Sather, B. P. Hay, J. S. Meisner and D. W. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 10895–10897.
7 (*a*) V. S. Bryantsev and B. P. Hay, *J. Am. Chem. Soc.*, 2005, **127**, 8282–8283; (*b*) L. Pedzisa and B. P. Hay, *J. Org. Chem.*, 2009, **74**, 2554–2560.
8 I. Bandyopadhyay, K. Raghavachari and A. H. Flood, *ChemPhysChem*, 2009, **10**, 2535–2540.
9 (*a*) H. Juwarker, J. M. Lenhardt, D. M. Pham and S. L. Craig, *Angew. Chem., Int. Ed.*, 2008, **47**, 3740–3743; (*b*) S. Hecht and R. M. Meudtner, *Angew. Chem., Int. Ed.*, 2008, **47**, 4926–4930; (*c*) Y. Wang, F. Li, Y. M. Han, F. Y. Wang and H. Jiang, *Chem.–Eur. J.*, 2009, **37**, 9424–9433.
10 K. Choi and A. D. Hamilton, *J. Am. Chem. Soc.*, 2003, **125**, 10241–10249.
11 (*a*) K.-J. Chang, D. Moon, M. S. Lah and K.-S. Jeong, *Angew. Chem., Int. Ed.*, 2005, **44**, 7926–7929; (*b*) K.-J. Chang, B.-N. Kang, M.-H. Lee and K.-S. Jeong, *J. Am. Chem. Soc.*, 2005, **127**, 12214–12215.
12 Y. Haketa and H. Maeda, *Chem.–Eur. J.*, 2011, **17**, 1485–1492.
13 The steric repulsions between hydrogens in all the structures and complexes considered here are believed to be negligible.
14 E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A. Abu El-Fadl and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1990, **112**, 6979–6985.
15 A similar macrocycle to **1** with one propylene replaced by a phenylene was used[2c] to study this difference in H-bonding.
16 See Supporting Information.
17 Triazole, N-linked phenylene, C-linked phenylene and propylene CH$\cdots Cl^-$ H-bonds strengths (~8.9, 3.6, 2.6 and 1.3 kJ mol^{-1}, respectively)[16] as estimated from within the structure of $\mathbf{1}^{\#}$ (Fig. 3).
18 Limits to the entropy adjustment; *e.g.*, 2 and 20 degenerate conformations freezing into one cost between 2 and 8 kJ mol^{-1}.
19 D. K. Cabbines and D. W. Margerum, *J. Am. Chem. Soc.*, 1969, **91**, 6540–6541.
20 Assuming Cl^- has a coordination number of six, the enthalpic penalty of removing ~four solvent molecules prior to binding is paid by greater translational entropy. This model assumes ~two solvents will bind with the Cl^- above and below the complex. The largest benefit from solvation is expected from **1**. Structures of the complexes[16] suggest there are small increases in solvent-accessibility going from **1** to **3**: opening solvent-accessibility on one side of $\mathbf{2}\cdot Cl^-$ is offset by reduction on the other; in $\mathbf{3}\cdot Cl^-$, receptor wrapping has a similar opening–closing compensation.
21 Any peak shifts reflect changes in conformations as well as the Cl^-.
22 S. Alunni, A. Pero and G. Reichenbach, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1747–1750.
23 R. M. Fuoss, *J. Am. Chem. Soc.*, 1958, **80**, 5059–5061.
24 Differences between preparation free energies[16] indicate that the benefit of the macrocyclic effect when generating partially pre-organized **2** from **3** is 20 kJ mol^{-1}, and rigidifying the macrocycle to be highly pre-organized in **1** provides another 11 kJ mol^{-1}.
25 ΔE_{prep} is defined as the computed energy difference between the structure of the complex with the Cl^- removed and the optimized structure of the free receptor.