ChemComm

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

Journal Name

ARTICLE TYPE

Halogen Bonded Analogues of Deep Cavity Cavitands

N. Kodiah Beyeh,*[a] Mario Cetina[a,b] and Kari Rissanen*[a]

The first examples of halogen bonded analogues of deep cavity cavitands with guest binding properties, formed between *N*-alkyl ammonium resorcinarene halides as acceptor and bromotrichloromethane as donor, are reported in the solid state and in solution.

Resorcinarene cavitands[1] with pre-organized cavities are suitable hosts for a variety of guests.[2] The cavity in these host compounds can be extended further through the formation of a second cavitand seam leading to the formation of deep cavity cavitands.[3] Deep cavity cavitands possess a more elongated deeper cavity and can bind a variety of larger and/or elongated guests through several weak interactions.[4]

The mimicking of covalent systems using a variety of weak interactions is a constant challenge in contemporary supramolecular chemistry. Predicting and designing supramolecular architectures based on the utilization of multiple weak interactions is always a challenging task and the final assemblies are in most cases a compromise between the competing weak interactions and the geometrical constraints of the building blocks.[5] Hydrogen bonds (HB) are by far the most frequently used weak interactions in the design of organic supramolecular architectures.[5b,c] Recently, the "long lost brother" of hydrogen bond, *viz.* the halogen bond (XB) has been defined[6] and been extensively used especially in crystal engineering[7] and recently also in materials chemistry.[8] The XB results from the charge transfer interaction between polarized halogen atoms and Lewis bases.[6] It is analogous to hydrogen bond in terms of strength and directionality.

Anions are general very good Lewis bases and hence suitable XB acceptors. The spherical, symmetrical and electronic nature of halides makes them excellent both as HB and XB acceptors.[9] Receptors composed of both halogen and hydrogen bond donor groups working cooperatively are uncommon. Taylor *et al.*[10] have demonstrated the selective recognition of anions by a host showing both halogen and hydrogen bonds as a result of a "compromise" between the distinct preferences of the two interactions. Supramolecular host systems utilizing both HB and XB with defined functions are a challenging prospect. Herein, HB and XB work in tandem in the presence of halide anions to form a host system analogous to deep cavity cavitands[3] both in shape and cavity size.

In the presence of excess formaldehyde, Mannich condensation reaction,[11] between primary amines and resorcinarenes results to tetrabenzoxazines. The ring opening of tetrabenzoxazines by mineral acids under refluxing conditions leads to the formation of *N*-alkyl ammonium resorcinarene halides.[12] A very strong circular intramolecular hydrogen bonded anion seam is formed between the halide anions and the $-NH_2^+$-R moieties leading to extended cavitand-like structures defined as hydrogen bond analogues of cavitands.[12] The size, electronic and hydrogen bond acceptor affinity makes the chlorides and bromides optimum anions for this process.[12a,b] The ability of these halides to also act as XB acceptors opens the door for further extension of the cavity via halogen bonding, if a proper XB donor is available.
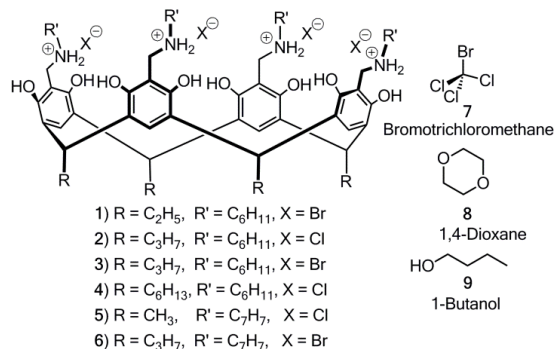

Fig. 1 *N*-Alkyl ammonium resorcinarene halides **1-6**, bromotri-chloromethane (XB donor) **7** and guests 1,4-dioxane **8** and 1-butanol **9**.

A set of *N*-alkyl ammonium resorcinarene chloride and bromide salts (**1-6**) of varying upper rim substituents, with either a rigid cyclohexyl group or a flexible benzyl group (flexibility originating from the $-CH_2-$ group) were synthesized (Fig. 1). A very interesting and cheap XB donor molecule, namely bromotrichloromethane (CCl_3Br) **7**, was used since the bromine atom is substantially polarized by the three chlorine atoms. The CCl_3Br (**7**) is liquid at room temperature thus making it both a suitable solvent and building block for the construction of halogen bonded architectures.

Single crystals of halogen-bonded complexes suitable for X-ray analysis were grown by slow evaporation from a mixture of **1**, **5** and **6** and a slight excess of **7** in chloroform. In the structure $\mathbf{1(7)_4}$ the hydrogen bonds between the ammonium moieties and bromides form the strong circular hydrogen bond seam $(\cdots NR'R''H_2^+\cdots Br^-\cdots NR'R''H_2^+\cdots Br^-\cdots)_2$ leading to a cavitand-like structure.[12] Four CCl_3Br molecules are halogen bonded to the bromide anions thereby extending the cavity height by *ca.* 2 Å. resulting in an analogue of a deep cavity cavitand[3b] (Fig. 2a - c).
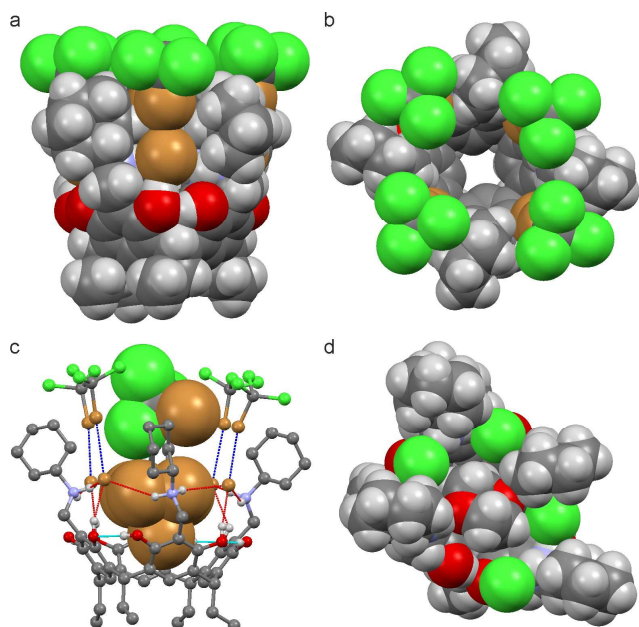
Fig. 2 CPK representation of the deep cavity cavitand $1(7)_4$, showing positions of CCl$_3$Br molecules which fill up the spaces between the cyclohexyl moieties (side view, a) and cavity (top view, b). Ball and stick representation (c) of $1(7)_4$ showing HBs, XBs and in CPK style the included CCl$_3$Br molecules (the upper with occupancy 0.5 and the lower with 0.75 disordered over five orientations). The hydrogen atoms that do not participate in the intracomplex interactions are omitted for clarity. CPK representation (d) of **8@4** showing the guest molecule situated in the center of the cavity and snugly hydrogen bonded to the host.

The CCl$_3$Br molecules bind to the open space between cyclohexyl rings of the resorcinarene tetracation with both CCl$_3$Br···Br$^-$ halogen bonds and van der Waals CCl$_3$Br···cyclohexyl interactions. The four CCl$_3$Br bonds to the four bromide anions through moderate XBs, the XB ratio[13] R_{XB} for the four XB's observed in $1(7)_4$ varies between 0.85 and 0.90 (Fig. 2a and 2c). The halogen bonded CCl$_3$Br molecules form a wall together with the cyclohexyl rings resulting in a deep cavity (Fig. 2b). The height of the cavity is *ca.* 12 Å and thus *ca.* 2 Å larger than those observed in two X-ray structures of covalent deep cavity cavitands reported by Gibb *et al.*[3b] The effective diameter of the cavity in $1(7)_4$ defined by the closest van der Waals surfaces between the opposite chlorine atoms of CCl$_3$Br molecules is *ca.* 7 Å, large enough for the CCl$_3$Br to pass into the cavity (Fig. 2c). The solvent accessible cavity void volume was calculated to be *ca.* 550 Å^3 (see ESI).

Further evidence that CCl$_3$Br is a good XB donor was obtained from two additional complexes between **5** and **7**, and **6** and **7**. These complexes are not analogues of the deep-cavity cavitands due to the conformational twisting by the methylene spacers between the ammonium moieties and phenyl rings. However, these complexes exhibit similar CCl$_3$Br···Cl$^-$/Br$^-$ halogen bonds as in $1(7)_4$ (see ESI).

To have additional data about the host-guest properties and to compare the cavity size of the XB complex $1(7)_4$, the compound **4** was recrystallized from 1,4-dioxane resulting in a 1:1 host-guest complex. The included 1,4-dioxane molecule in **8@4** fills up the cavity of resorcinarene tetracation and sits deep in the center of the cavity of **4**, slightly below the plane of the cation-anion belt and in a position which enables N−H···O hydrogen

bonding between the host and the guest (Fig. 2d).

Demonstrating XB in solution is a tedious and elusive process due to the solvent effects, yet recent reports show NMR spectroscopy to be the most powerful and reliable tool to study XB in solution.[14] Most of the solution studies have been performed by using perfluorinated hydrocarbons and ^{19}F NMR to study the XB.[14] However, comparative monitoring[14b] of ^{1}H NMR chemical shift changes was utilized for the detection of halogen bond formation first by Bertrán and Rodríguez.[14a]

Due to the lack of fluorine atoms on the XB donor CCl$_3$Br, a series of ^{1}H and ^{13}C NMR measurements were performed in CDCl$_3$ to investigate the existence of XB of CCl$_3$Br in solution and to probe the host-guest properties of the deep cavity cavitand $1(7)_4$. Several samples containing the resorcinarene hosts **2 - 3**, the XB donor **7** in 1:4 ratio and/or with slight excess of the guest molecules **8 - 9** were prepared [*viz.* $2(7)_4$, $8@2(7)_4$, $9@2(7)_4$, $3(7)_4$, $8@3(7)_4$, $9@3(7)_4$] and their ^{1}H and ^{13}C NMR recorded at 303 K. The absence of hydrogen atoms in CCl$_3$Br makes direct observation of the influence of halogen bonding in solution via ^{1}H NMR studies very difficult. However the X-ray structure shows the halides to be halogen bonded to the bromine of the CCl$_3$Br (Fig. 2). Therefore if XB does exist in solution, there should be a slight influence on the ^{1}H NMR chemical shifts of the –OH and –NH$_2$ groups synergistically. Indeed, XB was observed by slight shifting of the –OH and –NH$_2$ signals [for example in $2(7)_4$, +7.87 Hz for –OH and -7.14 Hz for –NH$_2$] (Fig. 3, and ESI).
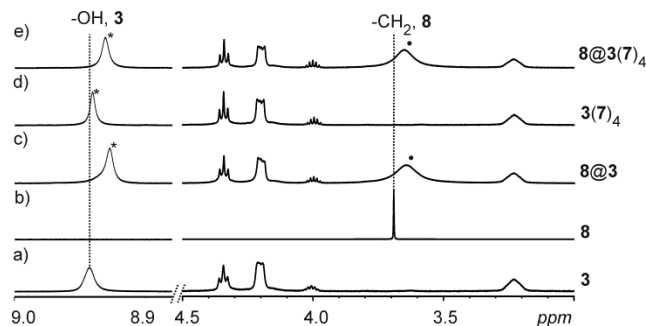

Fig. 3 Partial ^{1}H NMR spectra of several combinations of host **3**, the XB donor CCl$_3$Br (**7**) and 1,4-dioxane (**8**) as guest. The asterisk indicates the signal shifts of the hydroxyl groups of the host **3** and black dot indicates the signal shift of the guest **8**. Dotted lines are references of the position of the free host **3** and free guest **8** and indicate the shifts resulting from interaction between the compounds.

In the presence of guests **8** and **9**, significant complexation-induced up field shifts in the ^{1}H NMR resonances of the guest protons were observed from samples **8@2**, **9@2**, **8@3** and **9@3**. Similar complexation-induced ^{1}H NMR shifts of the guest protons, the hosts' –OH and the –NH$_2$ protons [for example in $8@3(7)_4$, –CH$_2$ of **8**, 19.90 Hz, –OH, -6.08 Hz and –NH$_2$, +7.64 Hz] were observed from the samples containing the host, XB donor CCl$_3$Br and the guests, (Fig. 3, ESI) and hence support the existence of HB and XB in solution, *viz.* the deep cavity cavitand analogue $2(7)_4$ and $3(7)_4$ are also retained in solution.

To further probe the existence of $2(7)_4$ and $3(7)_4$ and confirming the halogen bonding in solution, a series of ^{13}C NMR (despite its low sensitivity) measurements were carried out aiming to observe the direct signal shifts of the carbon atom in **7** while it is directly bonded to the bromine atom by XB (Fig. 4 and

ESI). In the analyses, the signals of CCl₃Br, the –CH₂ of **8**, the –OCH₂– and –CH₃– of **9**, were monitored. Small up field shifts of the CCl₃Br were observed (1.37 Hz in **2(7)₄**, and 1.56 Hz in **3(7)₄**, Fig. 4, ESI). The host guest complexes showed complexation-induced up field shifts of the guest carbons (for example, **8@2**, -5.95 Hz, Fig. 4 and ESI).
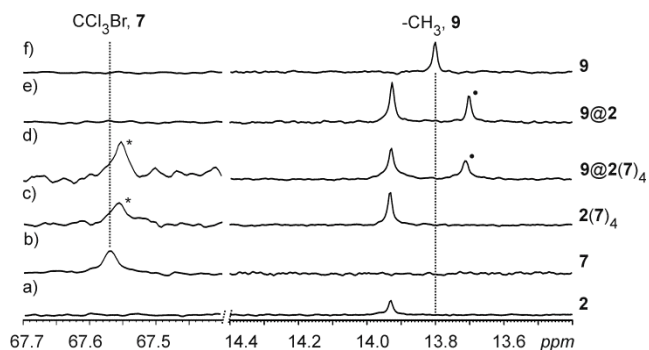

Fig. 4 Partial ^{13}C NMR spectra of several combinations of host **2**, XB donor CCl₃Br (**7**) and 1-butanol (**9**) as guest. The asterisk indicates the signal shifts of the CCl₃Br carbon and black dot indicates the signal shifts of the -CH₃ carbon of the 1-butanol guest. Dotted lines are references of the position of the free host **2** and free guest **9** indicating the shifts resulting from interactions within **2(7)₄** and **9@2(7)₄**.

Interestingly, the complexation-induced up field shifts of the carbons of the XB donor **7** and the guests **8** and **9** were also observed when samples containing the hosts, XB donor **7** and the guest in a 1:4:slight excess of the guests, respectively, were measured [for example in **9@2(7)₄**, 1.70 Hz of **7**, 2.67 Hz of –OCH₂– of **9**, Fig. 4, ESI]. These results show direct changes of the signals of the carbon atoms of the CCl₃Br **7** and the guests. This further supports the existence of the HB and XB assemblies with guest complexation in solution.

In conclusion, we presented the first example of a combined HB and XB analogues of deep cavity cavitands with host-guest properties. The ability of NMR spectroscopy to reliably observe nucleus specific information and thermodynamic information[12b] was used to probe the existence of XB in solution via a series of ^{1}H and ^{13}C NMR analyses. X-ray crystallography confirms moderately strong XBs between the CCl₃Br donor and the bromide acceptors in the resorcinarene host **1**. These results show the formation of an analogue of a deep cavity cavitand, with the cavity size even bigger than those reported in some covalent deep cavity cavitands.[3a] Most interestingly, the presence of guest molecules containing both HB donating and accepting groups did not dissociate the assemblies and even showed clear host-guest complexation into the cavity of the assemblies. The CCl₃Br molecules proved out to be highly versatile XB donors. The fact that CCl₃Br is very cheap and liquid at room temperature opens the door for its application as both solvent and/or building block in the construction of even more sophisticated XB architectures.

Notes and references

ᵃ Department of Chemistry, NanoScience Centrer, University of Jyväskylä, P. O: Box 35, 40014 Jyväskylä, Finland. Tel: +358 50 562 3721; E-mail: ngong.k.beyeh@jyu.fi, kari.t.rissanen@jyu.fi
ᵇ Present address: Department of Applied Chemistry, Faculty of Textile Technology, University of Zagreb, Prilaz baruna Filipovića 28a, 10000 Zagreb, Croatia. E-mail: mario.cetina@ttf.hr

1   (a) J. R. Moran, S. Karbach and D. J. Cram, *J. Am. Chem. Soc.* 1982, **104**, 5826; (b) D. J. Cram, *Science* 1983, **219**, 1177; (c) D. J. Cram and J. M. Cram, *Royal Society of Chemistry: Cambridge* 1994, **4**, P009.
2   (a) S. Xiao, D. Ajami and R. Julius Jr, *Chem. Commun.* 2010, **46**, 2459; (b) R. J. Hooley, S. M. Biros and R. Julius Jr, *Chem. Commun.* 2006, 509; (c) B. W. Purse, A. Gissot and J. Rebek. Jr, *J. Am. Chem. Soc.* 2005, **127**, 11222; d) L. R. MacGillivray and J. L. Atwood, *J. Am. Chem. Soc.* 1997, **119**, 6931.
3   (a) C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.* 2004, **126**, 11408; (b) K. Srinivasan and B. C. Gibb, *Org. Lett.* 2007, **9**, 745.
4   (a) C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.* 2006, **128**, 16498; (b) H. Gan and B. C. Gibb, *Chem. Commun.* 2013, **49**, 1395.
5   (a) J-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives* 1995, p. 271; (b) G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.* 1995, **34**, 2311; c) M. M. Conn and J. Rebek Jr., *Chem. Rev.* 1997, **97**, 1647.
6   G. R. Desiraju, P. S. Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati and K. Rissanen, *Pure Appl. Chem.* 2013, **85**, 1711.
7   (a) R. W. Troff, T. Mäkelä, F. Topić, A. Valkonen, K. Raatikainen and K. Rissanen, *Eur. J. Org. Chem.* 2013, 1617. (b) M. Fourmigue, *Curr. Opin. Solid State & Mat. Sci.* 2009, **13**, 36. (c) P. Metrangolo, F. Meyer, T. Pilati, G. Resnati and G. Terraneo, *Angew. Chem., Int. Ed.* 2008, **47**, 6114. (d) L. Brammer, G. Mínguez Espallargas and S. Libri, *CrystEngComm*, 2008, **10**, 1712. (e) K. Rissanen, *CrystEngComm* 2008, **10**, 1107. (f) K. Raatikainen, K. Rissanen, *CrystEngComm* 2011, **13**, 6972. (g) M. Tuikka, P. Hirva, K. Rissanen, J. Korppi-Tommola, M. Haukka, *Chem. Commun.* 2011, **47**, 4499. (h) K. Raatikainen and K. Rissanen, *Chem. Sci.* 2012, **3**, 1235.
8   (a) A. Priimagi, G. Cavallo, A. Forni, M. Gorynsztejn-Leben, M. Kaivola, P. Metrangolo, R. Milani, A. Shishido, T. Pilati, G. Resnati and G. Terraneo, *Adv. Funct. Mater.* 2012, **22**, 2572; (b) P. Metrangolo, Y. Carcenac, M. Lahtinen, T. Pilati, K. Rissanen, A. Vij and G. Resnati, *Science* 2009, **323**, 1461.
9   P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.* 2001, **40**, 486.
10   M. G. Chudzinski, C. A. McClary and M. S. Taylor, *J. Am. Chem. Soc.* 2011, **133**, 10559.
11   K. Airola, V. Böhmer, E. F. Paulus, K. Rissanen, C. Schmidt, I. Thondorf, W. Vogt, *Tetrahedron* 1997, **53**, 10709. (b) C. Schmidt, I. Thondorf, E. Kolehmainen, V. Böhmer, W. Vogt, K. Rissanen, *Tetrahedron Lett.* 1998, **39**, 8833.
12   (a) A. Shivanyuk, T. Spaniol, K. Rissanen, E. Kolehmainen and V. Böhmer, *Angew. Chem., Int. Ed.* 2000, **39**, 3497; (b) N. K. Beyeh, M. Cetina, M. Lofman, M. Luostarinen, A. Shivanyuk and K. Rissanen, *Supramol. Chem.* 2010, **22**, 737. (c) N. Kodiah Beyeh, M. Cetina and K. Rissanen, *Cryst. Growth Des.* 2012, **12**, 4919.
13   (a) P. M. Lommerse, A. J. Stone, R. Taylor and F. H. Allen, *J. Am. Chem. Soc.,* 1996, **118**, 3108. (b) L. Brammer, E. A. Bruton and P. Sherwood, *Cryst. Growth Des.*, 2001, **1**, 277. (c) F. Zordan, L. Brammer and P. Sherwood, *J. Am. Chem. Soc.* 2005, **127**, 5979. Br$_{vdw}$ = 1.85 Å, Cl$^-_{vdw}$ =1.81, Br$^-_{vdw}$ = 1.96 Å.
14   (a) J. F. Bertrán and M. Rodríguez, *Org. Magn. Reson.* 1980, **14**, 244. (b) M. Erdelyi, *Chem. Soc. Rev.* 2012, **41**, 3547; (c) M. G. Sarwar, D. Ajami, G. Theodorakopoulos, I. D. Petsalakis and J. Rebek Jr., *J. Am. Chem. Soc.* 2013, **135**, 13672.