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## Chloride-binding in organic–water mixtures: the powerful synergy of C–H donor groups within a bowl-shaped cavity†

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**For the first time, the tetrafluorobenzyl unit has been considered as a C–H···anion binding motif. In synergy with imidazolium groups within a bowl-shaped receptor, it has allowed for the effective binding of chloride in solution. Remarkable affinity was observed in organic–water mixtures.**

In the field of anion recognition,<sup>1</sup> the relevance of C–H···anion interactions<sup>2,3</sup> in the stabilization of receptor:anion complexes has been recognized only recently. This encouraged researchers to investigate in depth the nature of this type of interaction and to develop new CH hydrogen bonding motifs.<sup>4</sup>

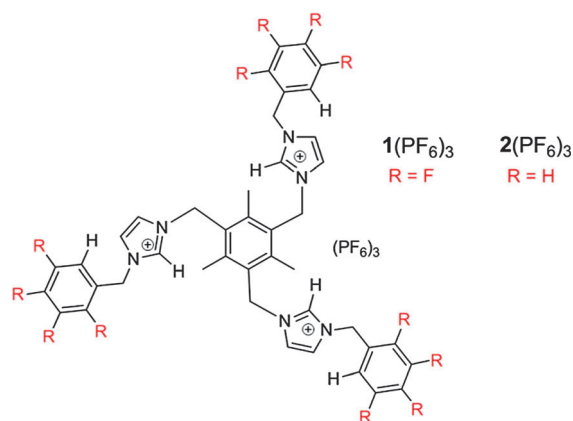
The potentialities of both neutral and cationic C–H groups as H-bond donors mainly depend on the proton's acidity, which in turn relies on the substituents' capability of stabilizing the corresponding conjugated anion. Aryl protons are known to be more acidic than the alkyl ones.<sup>5</sup> When attached to electron-withdrawing substituents, the H-bond donor tendencies of C–H groups may become comparable to those of traditional H-donors (*e.g.* NH and OH).<sup>6</sup> The literature shows many cases of neutral receptors in which a substantial contribution to the anion binding energetics is given by C–H bonds.<sup>4</sup>

Among cationic C–H donors, the imidazolium group is particularly noteworthy. Its interaction with anions involves the formation of (C–H)<sup>+</sup>···X<sup>−</sup> hydrogen bonds, characterized by a strong electrostatic contribution, due to the marked positive partial charge located between the nitrogen atoms.<sup>7</sup> In the literature, high anion affinity in competing media has been achieved by arranging a number of positively charged imidazolium groups around well-defined cavities (*e.g.* in macrocyclic or cage-like systems).<sup>4,7</sup> However, effective binding in organic–water

mixtures has been seldom obtained with imidazolium-based open-chain receptors.

The goals of this work are to (i) advance the understanding of C–H···anion interactions; (ii) evaluate the potentialities of a new CH donor; (iii) obtain high recognition in aqueous solution with an open-chain receptor. To achieve these goals, imidazolium and 2,3,4,5-tetrafluorobenzyl groups were chosen as CH bonding units. As far as the authors know, the tetrafluorobenzyl moiety had never been explored as a CH donor in anion recognition before. This is quite surprising, considering the *pK* per hydrogen of 1,2,3,4-tetrafluorobenzene compared to benzene<sup>8</sup> and therefore the potentialities of the C–H group as a H-donor. The bowl-shaped receptor **1**(PF<sub>6</sub>)<sub>3</sub> was obtained by appending three anion chelating arms (each containing the 2,3,4,5-tetrafluorobenzyl and the imidazolium units) to a mesitylene platform (see Scheme 1).

As a proof of concept, we investigated the binding tendencies of **1**<sup>3+</sup> towards the chloride anion by NMR titrations in pure acetonitrile and in CD<sub>3</sub>CN/d<sub>6</sub>-DMSO 9 : 1 and CD<sub>3</sub>CN/D<sub>2</sub>O 4 : 1 (v/v) mixtures. Chloride was chosen as the target anionic guest as it has a spherical shape, which adapts properly to the bowl-shaped



**Scheme 1** Tripodal imidazolium-based anion receptors studied in this work.

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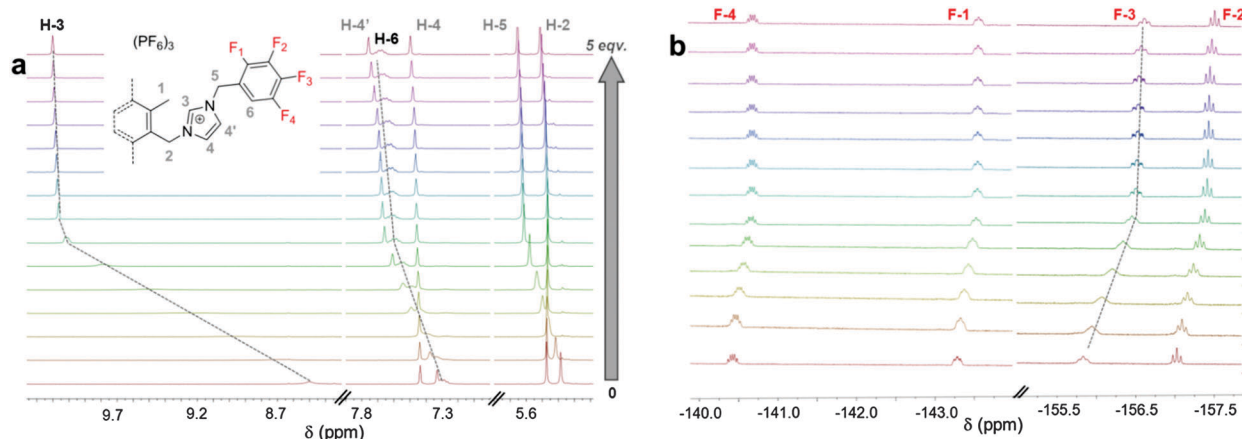


Fig. 1 Families of (a)  $^1\text{H}$ - and (b)  $^{19}\text{F}$ -NMR spectra recorded upon addition of TBACl (0  $\rightarrow$  5 eq.) to a solution of  $\mathbf{1}(\text{PF}_6)_3$  in pure  $\text{CD}_3\text{CN}$  (25  $^\circ\text{C}$ ).

cavity<sup>9</sup> of our tripodal system. Moreover, among spherical anions, it is known to form stable complexes with imidazolium-based receptors in competing media.<sup>7</sup>

In order to prove the contribution of the tetrafluorobenzyl groups to chloride binding, we performed NMR measurements under the same conditions on the non-fluorinated analogue receptor  $\mathbf{2}^{3+}$  [see  $\mathbf{2}(\text{PF}_6)_3$  in Scheme 1].

In Fig. 1, the results obtained in pure  $\text{CD}_3\text{CN}$  upon  $^1\text{H}$ - and  $^{19}\text{F}$ -NMR titrations of  $\mathbf{1}^{3+}$  with  $\text{Cl}^-$  (as the TBA salt) are reported. As expected from the formation of H-bonding interactions with the anion, most protons belonging to the upper-rim of the receptor's cavity undergo a down-field shift upon chloride addition. Protons H-3, in particular, are strongly de-shielded, due to the participation of the imidazolium  $(\text{C-H})^+$  groups in the binding ( $\Delta\delta = +1.6$  ppm, see the profile in Fig. S1, ESI<sup>†</sup>). A significant down-field shift was also observed for the multiplet $\ddagger$  signal of H-6 ( $\Delta\delta = +0.38$  ppm, see Table 1). This result confirms that the protons of the tetrafluorobenzyl rings are involved in the interaction. The experimental profiles as well as the Job plots indicate the formation of a 1 : 1  $\mathbf{1}^{3+}/\text{Cl}^-$  complex. However, the curvature was too steep to allow a reliable determination of the binding constant. The formation of the 1 : 1  $\mathbf{1}^{3+}/\text{Cl}^-$  complex was also demonstrated by  $^{19}\text{F}$ -NMR titration in pure acetonitrile (see the family of spectra in Fig. 1b). Notably, upon the addition of TBACl to the receptor, all the fluorine signals underwent an up-field shift, due to the shielding effect exerted by chloride. In fact, anion inclusion induces the polarization of the C–H groups involved in the binding, with a consequent increase of the electron density felt by the fluorine atoms. The shift of the  $\text{PF}_6^-$  signal, on the other

hand, may be attributed to the displacement of the counterion from the receptor's cavity upon chloride inclusion. The plateau is reached at 1 eq. of the added anion (see Fig. S1–S3, ESI<sup>†</sup>). Interestingly, among the aromatic fluorine atoms, the strongest up-field shifts are observed with F-3 and F-2 ( $\Delta\delta = -0.78$  and  $-0.49$  ppm, respectively, at 4.5 eq. TBACl), even if they are the farthest away from the bound chloride (see the structure). In an aromatic moiety, the contribution to the chemical shift of fluorine residues is mostly due to the mesomeric effect exerted in the *ortho* and *para* positions. It is worth noting that F-3 and F-2, being in *para* to the residues involved in the interaction with chloride, are strongly affected by the increase in electronic density on carbons 5 and 6, consequent to the polarisation of the C–H bonds in the adduct.

NMR titration experiments with TBACl were also performed in more competing media, *i.e.* in  $\text{CD}_3\text{CN}/d_6\text{-DMSO}$  9 : 1 and  $\text{CD}_3\text{CN}/D_2O$  4 : 1 (v/v) mixtures (see spectra in Fig. S4–S11, ESI<sup>†</sup>). In  $\text{CD}_3\text{CN}/d_6\text{-DMSO}$  9 : 1, the affinity of  $\mathbf{1}^{3+}$  towards chloride is still very high ( $\geq 6$  log units) as shown by the steep curvature of the profile in Fig. 2 [blue symbols:  $\Delta\delta(\text{H-3})$  vs. eq. of TBACl]. As in pure acetonitrile, chloride binding mostly involves the protons of the cavity's upper-rim (see Table 1).

In the same medium, the  $^1\text{H}$ -NMR titration of  $\mathbf{2}^{3+}$  with TBACl gave a binding constant of 5.11(7) log units (see Fig. S5–S7, ESI<sup>†</sup>). The lower chloride affinity of  $\mathbf{2}^{3+}$  compared to  $\mathbf{1}^{3+}$  confirms, for

Table 1  $^1\text{H}$ -NMR titrations of  $\mathbf{1}(\text{PF}_6)_3$  and  $\mathbf{2}(\text{PF}_6)_3$  with TBACl

	$\Delta\delta$ (ppm)/ $\mathbf{1}(\text{PF}_6)_3$	$\Delta\delta$ (ppm)/ $\mathbf{2}(\text{PF}_6)_3$
H-3	+1.60 <sup>a</sup> ; +0.89 <sup>b</sup> ; n.a. <sup>c</sup>	+1.16 <sup>b</sup> ; n.a. <sup>c</sup>
H-4'	+0.43 <sup>a</sup> ; +0.28 <sup>b</sup> ; +0.20 <sup>c</sup>	+0.30 <sup>b</sup> ; +0.11 <sup>c</sup>
H-5	+0.27 <sup>a</sup> ; +0.16 <sup>b</sup> ; +0.08 <sup>c</sup>	+0.15 <sup>b</sup> ; +0.03 <sup>c</sup>
H-6, H-o	+0.38 <sup>a</sup> ; +0.19 <sup>b</sup> ; +0.10 <sup>c</sup>	$\leq 0.01^b$ ; $-0.02^c$

<sup>a</sup> Pure  $\text{CD}_3\text{CN}$ . <sup>b</sup>  $\text{CD}_3\text{CN}/d_6\text{-DMSO}$  9 : 1 and <sup>c</sup>  $\text{CD}_3\text{CN}/D_2O$  4 : 1 (v/v) mixtures.  $\Delta\delta$  ( $\pm 0.01$  ppm) of the selected protons in the presence of 12 eq. of TBACl. The corresponding spectra are shown in the ESI. n.a.: not available.

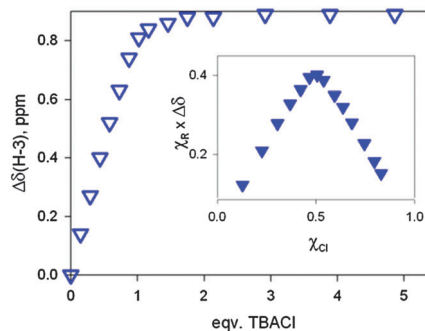


Fig. 2  $^1\text{H}$ -NMR titration of  $\mathbf{1}^{3+}$  (0.2 mM) with TBACl in  $\text{CD}_3\text{CN}/d_6\text{-DMSO}$  9 : 1. Inset: Job plot ( $\chi_R$ ,  $\chi_{\text{Cl}}$  = molar fractions of  $\mathbf{1}^{3+}$  and TBACl).



the latter, the contribution of the tetrafluorobenzyl units to the anion binding. In the case of  $2^{3+}$ , the interaction with chloride mainly involves the imidazolium protons H-3 ( $\Delta\delta = +1.16$ , see Table 1). The benzyl fragment is less affected; in particular, no shifts are observed for the *ortho* protons, H-o (*i.e.* the analogues of H-6). The upfield shift observed for most aryl signals is instead attributable to an effect of the anionic guest. The higher chloride affinity of  $1^{3+}$  compared to  $2^{3+}$  was confirmed in the  $\text{CD}_3\text{CN}/\text{D}_2\text{O}$  4 : 1 (v/v) mixture (Fig. 3). In this medium, the signals of the acidic protons H-3 could not be observed due to fast exchange with  $\text{D}_2\text{O}$ .<sup>2,10</sup> Nevertheless, thanks to the shifts of other protons, a binding constant of 3.37(7) log units could be determined for the  $1^{3+}/\text{Cl}^-$  couple. [Moreover, titration studies with TBABr and TBAI allowed us to determine the constants for the  $1^{3+}/\text{Br}^-$  and  $1^{3+}/\text{I}^-$  couples, which resulted in 2.66(3) and 2.34(3) log units, respectively (see the ESI†).] Notably, the  $1^{3+}/\text{Cl}^-$  binding constant is among the highest obtained with open-chain organic receptors in aqueous solution.<sup>1–4</sup> In the case of  $2^{3+}$ , the chloride induced shifts were significantly smaller. The corresponding binding constant was found to be 2.17(4) log units. [Unfortunately, in titrations with  $\text{Br}^-$  and  $\text{I}^-$ , small variations were observed in the NMR spectrum and precipitation occurred at high concentrations of TBA salts, thus preventing the determination of the affinity constants for these anions.]

By slow diffusion of diethyl ether into solutions containing  $1(\text{PF}_6)_3$  and either TBACl or TBABr, single crystals of  $[\text{1}(\text{Cl})](\text{PF}_6)_2$  MeCN (Fig. 4) and  $[\text{1}(\text{Br})](\text{PF}_6)_2$  MeCN (ESI†) suitable for X-ray diffraction analysis were obtained. Notably, the crystals of the two compounds are isomorphous. Due to the steric constraint of the tripodal receptors, anions are placed into the open part of the cavity at quite a long distance [ $\text{Cl}^-$ , 4.063(4) Å;  $\text{Br}^-$ , 4.126(2) Å] from the best plane of the mesitylene group. The anions are only slightly displaced from the top of the mesitylene's centroid and the anion-centroid-plane angles are not significantly different for the two compounds [ $\text{Cl}^-$ , 83.1(14)°;  $\text{Br}^-$ , 82.9(8)°]. The molecular symmetries of the bowl-shaped receptors in the two crystals are the same and rather distorted from the  $C_3$  symmetry promoted by the mesitylene scaffold. Anions are trapped within the cavity, where they form: (i) three short  $\text{C}-\text{H}\cdots\text{X}^-$  interactions [ $2.56(1) < \text{H}\cdots\text{Cl}^- < 2.66(1)$  Å,  $2.68(1) < \text{H}\cdots\text{Br}^- < 2.75(1)$  Å] with the H-3 protons of the imidazolium groups; and (ii) five long  $\text{C}-\text{H}\cdots\text{X}^-$  interactions [ $2.82(1) < \text{H}\cdots\text{Cl}^- < 3.09(1)$  Å,  $2.94(1) < \text{H}\cdots\text{Br}^- < 3.15(1)$  Å], three of which with the methylene H-5 protons and the other two involving the C-H groups of tetrafluorobenzyl rings (*i.e.* H-6 protons).

These results somehow confirm what is observed in solution, *i.e.* the cage arranges the peripheral groups in a way to point the H-5 and H-6 protons towards the anion, allowing the participation of both  $\text{C}_{\text{sp}^3}-\text{H}$  and  $\text{C}_{\text{sp}^2}-\text{H}$  bonds in the binding.

Both  $1^{3+}/\text{Cl}^-$  and  $2^{3+}/\text{Cl}^-$  complexes have been modelled in the gas phase through optimization at the B3LYP/6-311+G(2df,p) and 6-311+G(d,p)<sup>11</sup> levels for chloride and the other atoms, respectively (Gaussian09 program package).<sup>12</sup> Charge distribution and electrostatic molecular surface (MEP) have also been determined. According to our calculations, the most stable conformations of the complexes have a  $C_3$  symmetry, with the axis

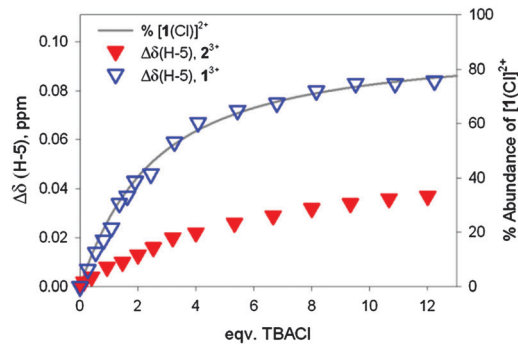


Fig. 3 Experimental profiles for the  $^1\text{H}$ -NMR titrations of  $1(\text{PF}_6)_3$  and  $2(\text{PF}_6)_3$  with TBACl in a  $\text{CD}_3\text{CN}/\text{D}_2\text{O}$  4 : 1 (v/v) mixture. The grey line corresponds to the distribution of  $[\text{1}(\text{Cl})]^{2+}$  species, obtained for a  $1^{3+}/\text{Cl}^-$  binding constant of 3.37(7) log units. See the ESI† for more details.

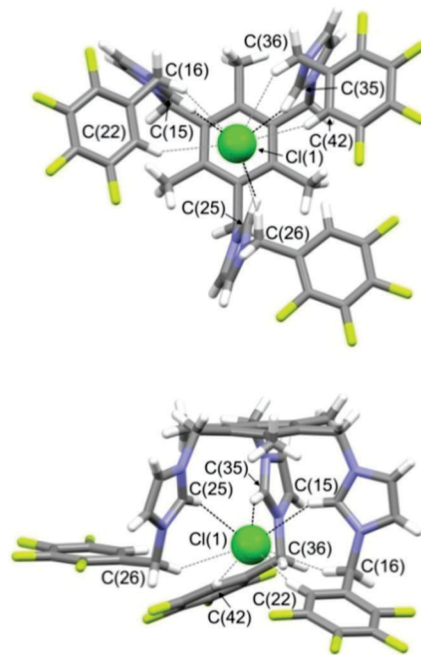


Fig. 4 Crystal structure of  $[\text{1}(\text{Cl})](\text{PF}_6)_2\cdot\text{MeCN}$ . Top (top) and lateral (bottom) views of the molecular cation  $1^{3+}$  interacting with chloride ( $\text{PF}_6^-$  counterions and MeCN have been omitted for clarity). Atom names are only reported for atoms involved in  $\text{C}-\text{H}\cdots\text{Cl}^-$  hydrogen bonds, drawn with black [ $2.56(1) < \text{H}\cdots\text{Cl}^- < 2.66(1)$  Å] and grey [ $2.82(1) < \text{H}\cdots\text{Cl}^- < 3.09(1)$  Å] dashed lines.

passing through the mesitylene's centroid and the included anion (Fig. S17, ESI†). The three arms look like a three-bladed propeller with the benzyl groups, corresponding to the blades, organized either in a clockwise or in a counter-clockwise arrangement. In the case of  $1^{3+}/\text{Cl}^-$ , the fluorine substituents strengthen the interaction between the H-6 protons and chloride. A much more closed structure is obtained compared to  $2^{3+}$ , with the chloride anion coordinated mostly by H-3 ( $\text{C}3\cdots\text{Cl}^-$ , 3.415 Å) and H-6 ( $\text{C}6\cdots\text{Cl}^-$ , 3.703 Å). Conversely, in the case of  $2^{3+}/\text{Cl}^-$ , the cavity looks more accessible; the chloride anion is coordinated by H-3 ( $\text{C}3\cdots\text{Cl}^-$ , 3.347 Å) and H-5 ( $\text{C}5\cdots\text{Cl}^-$ , 3.946 Å), but not by H-o ( $\text{C}o\cdots\text{Cl}^-$ , 5.230 Å). According to the NPA charges (Table S3, ESI†), the



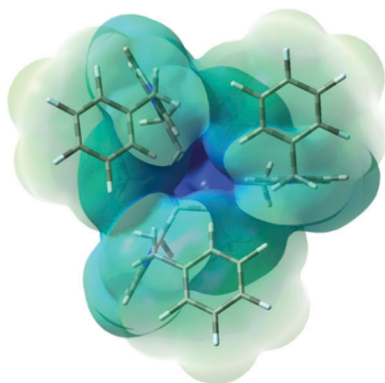
0.000e0  0.367e0

Fig. 5 Molecular electrostatic potential (MEP) surface of the receptor in the complex  $1^{3+}/\text{Cl}^-$  (transparent representation, top view). The anion is omitted for clarity.

highest positive charge is on H-3 atoms. The corresponding value is similar in the two complexes, suggesting that the  $(\text{C-H})^{\delta+} \cdots \text{Cl}^-$  interaction is the dominant one. Analogously, the MEP map shows that the highest positive values are close to H-3 (Fig. 5 and Fig. S18, ESI $^{\dagger}$ ). In the case of  $1^{3+}$ , a high positive potential is also obtained in the proximity of H-6, in agreement with the coordination tendencies of the receptor (Table S3, ESI $^{\dagger}$ ).

In conclusion, (i) the 2,3,4,5-tetrafluorobenzyl moiety was proved to be an effective CH bond donor; (ii) due to the cooperation of neutral and cationic CH donor groups, a significant increase in the chloride binding constant was obtained; (iii) compared to other tripodal imidazolium-based systems reported in the literature (e.g. the nitro-system reported in 2002 by Kim *et al.*),<sup>7</sup> the binding of chloride was also obtained in aqueous solution. These results should prove useful for both better understanding the  $\text{C-H} \cdots$  anion interactions and developing new strategies in the field of anion recognition in water.

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## Notes and references

$\ddagger$  The H-6 signal is a multiplet due to coupling with the fluorine nuclei in the *ortho* and *meta* positions.

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