Anion–π Interactions

DOI: 10.1002/anie.200800636

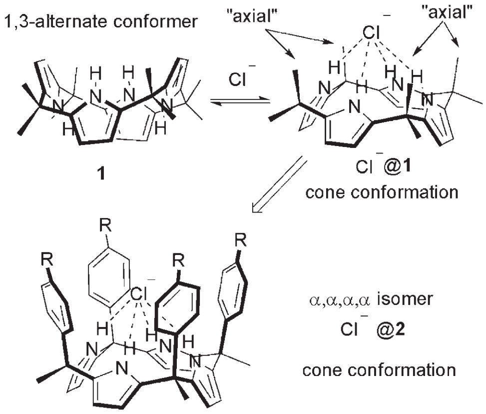
Quantitative Evaluation of Anion–π Interactions in Solution**

*Guzmán Gil-Ramírez, Eduardo C. Escudero-Adán, Jordi Benet-Buchholz, and Pablo Ballester**

Chemical intuition assigns a repulsive force to the interaction of anions with the π system of aromatic compounds. Consequently, for many years anion–π interactions have been completely neglected as noncovalent interactions suitable for the construction of efficient anion receptors.[1] In 2002 four computational studies suggested the existence, in the gas phase, of strong attractive interactions between highly π-acidic aromatic systems and anions lying above the plane of the π system.[2] These seminal studies triggered an extensive investigation of the physical nature of anion–π interactions using electronic structure methods.[3] Moreover, since 2004, the reporting of several supramolecular complexes obtained in the solid state, in which anions are nestled up next to aromatic rings, has increased interest in the subject.[4]

Models and estimates of the factors that govern the binding geometry, the binding strength, and the nature of anion–π interactions are available mainly from computational studies.[3] In solution, only the use of highly electron-deficient arenes has allowed the unambiguous quantification of the halide–π interaction in the absence of other intermolecular attractive interactions.[5] Accordingly, more experimental quantitative data on the magnitudes of the interaction of anions and π systems of aromatic rings in solution are needed, as well as further understanding of the influence of the substituents on the aromatic ring.[6]

Weak interactions may be detected as modulations of stronger binding forces by using synthetic receptors in combination with the "enforced proximity" approach.[7] Octamethyl calix[4]pyrrole (**1**; Scheme 1) is an effective receptor for anions,[8] and the binding of halide anions organizes the receptor into the cone conformation.



Scheme 1. Chloride binding promotes a change from the 1,3-alternate to cone conformation of **1**. Substitution of the "axial" methyl groups of **1** by *p*-substituted phenyl groups produces a calix[4]pyrrole receptor **2** with a deep aromatic cavity surrounding the halide ion.

As shown in Scheme 1, the conelike conformation of the α,α,α,α stereoisomer of calix[4]pyrrole **2** bearing axially substituted aryl groups on each of the four *meso* carbons contains a deep aromatic cavity capable of including anions.[9,10] The formation of four hydrogen bonds between a halide ion and the NH groups of the calix[4]pyrrole scaffold constitutes a reliable interaction which positions the anion above the planes of the π systems of the *meso* aryl substituents (enforced proximity). Previous studies have already shown that chemical modification of the substituents of the aromatic rings alters the intrinsic anion-binding selectivity and affinity of the basic calix[4]pyrrole skeleton.[11] Herein, we report a systematic study of the binding of chloride to a series of *meso*-tetraaryl calix[4]pyrrole receptors **2** displaying deep and electronically tunable aromatic cavities. The receptors are used as model systems to obtain quantitative data on the strength of the anion–π interaction in solution and also to measure the effect of the aromatic substituents.

We have prepared a series of neutral α,α,α,α-tetraaryl calix[4]pyrroles **2** containing deep aromatic cavities with fixed walls (Scheme 2). Different *para* substituents (R) are used to modify the charge distribution of the aromatic ring. Compounds **2a–e** were synthesized by the acid-catalyzed condensation of pyrrole and the corresponding methyl aryl ketone under standard reaction conditions. Careful purification (crystallization and/or chromatography techniques) allowed the isolation of the corresponding α,α,α,α isomers in yields ranging from 6 to 20%. Compounds **2f** and **2g** are simple derivatives of **2e** and were readily obtained through described methodologies.[9a,b]

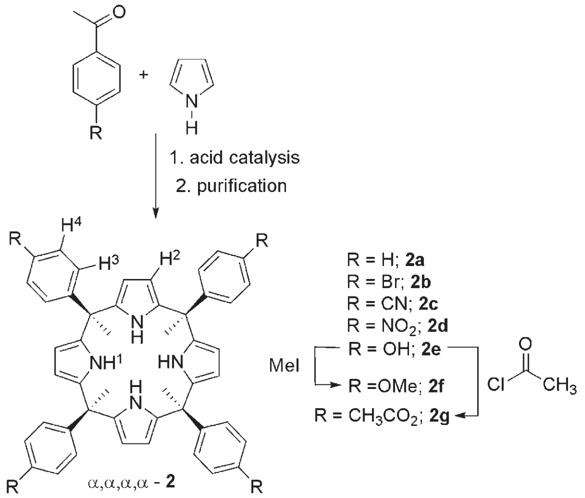
Configurational assignment was performed by a combination of ^{1}H NMR spectroscopy and single-crystal X-ray crystallographic analysis.[12] All the α,α,α,α isomers **2a–g** display only one type of β-pyrrole resonance and exhibit, in acetonitrile solution, a sharp and well-resolved proton spectrum indicative of a time-averaged C_4 symmetry. The

---

[*] G. Gil-Ramírez, E. C. Escudero-Adán, J. Benet-Buchholz, Prof. P. Ballester
Institute of Chemical Research of Catalonia (ICIQ)
Avda. Països Catalans 16, 43007 Tarragona (Spain)
Fax: (+34) 977-920-221
E-mail: pballester@iciq.es
Homepage: http://www.iciq.es/english/research/grups_eng/ballester/entrada.htm
Prof. P. Ballester
Catalan Institution for Research and Advanced Studies (ICREA)
Pg. Lluís Companys 23, 08010 Barcelona (Spain)

[**] We thank the Spanish MEC for generous grants (CTQ2005-08989-C01-C02/BQU and Consolider Ingenio 2010, Grant CSD2006-0003). We also thank ICIQ Foundation and Generalitat de Catalunya, DURSI (2005SGR00108) for financial support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Chemical structures of the *meso*-tetraaryl calix[4]pyrroles **2a–g**.

single-crystal X-ray structures of free α,α,α,α isomers grown from coordinating solvents revealed in most cases that the calixpyrrole core is in a cone conformation, with one solvent molecule included in the aromatic cavity and hydrogen bonded to the four NH groups (Figure 1).

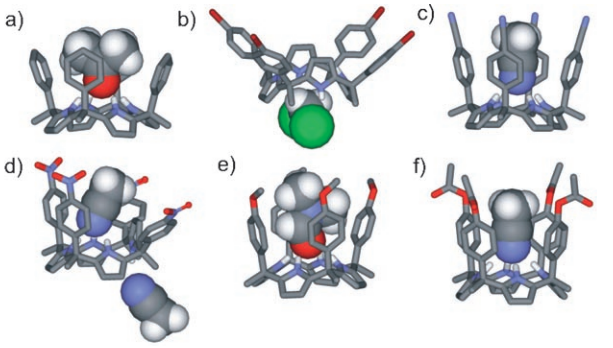


Figure 1. X-ray crystal structures of the solvates of the receptors: a) **2a** + acetone, b) **2b** + dichloromethane, c) **2c** + acetonitrile, d) **2d** + acetonitrile, e) **2f** + DMF, and f) **2g** + acetonitrile. DMF = *N*,*N*-dimethylformamide. H white, C gray, O red, N blue, Cl green.

^{1}H NMR spectroscopy was also used to probe the chloride binding in solution and provide structural information on the geometry of the complex (Figure 2). We used tetrabutylammonium chloride (TBACl) as the precursor of the chloride guest. In acetonitrile and in the range of concentrations used, this electrolyte is predominantly dissociated and the binding process of calix[4]pyrroles with TBACl is expected to produce simple Cl^-@**1** anionic complexes.[13] The initial addition of 0.5 equivalents of TBACl to an acetonitrile solution (1 mM) containing the aryl calix[4]pyrrole **2**[14] induced the appearance of a new set of proton signals except for **2e**.[15] When more than 0.5 equivalents of TBACl was added, the new signals grew at the expense of the signals of free **2**. Consequently, the new signals were assigned to protons of the receptor in the Cl^-@**2** complex.

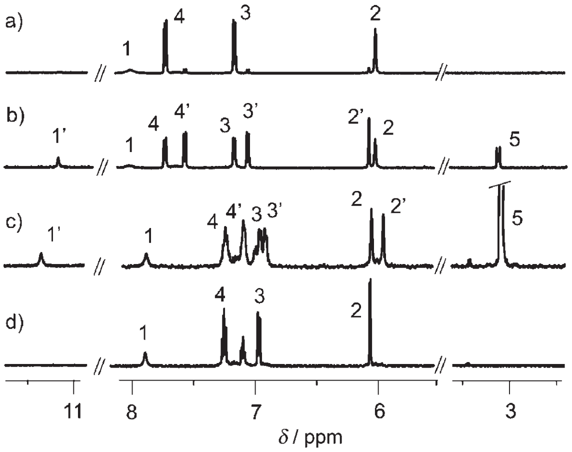


Figure 2. Regions of the ^{1}H NMR spectra of free receptors **2a** and **2c** and their chloride inclusion complexes (CD_3CN, 298 K, [**2**] = 1.3 mM, 500 MHz). See Scheme 2 for proton assignment. Numbers with primes indicate the signals of complexed **2**; "5" represents the *N*-CH_2 protons of TBA. a) **2c**; b) **2c** + 0.55 equiv TBACl; c) **2a** + 5 equiv TBACl; d) **2a**.

Upon chloride binding, the peaks of the pyrrole NH groups were consistently shifted downfield ($\Delta\delta = 3.03$ to 3.48 ppm) while the signals for the *ortho* and *meta* aromatic protons of the complex moved upfield ($\Delta\delta = -0.16$ to -0.05). The values of the downfield shift experienced by the NH groups are consistent with the formation of four hydrogen bonds with the chloride, whereas the observed upfield shifts of the aromatic protons (shielding effect) indicate that the receptors **2** do not interact with the chloride ion by means of $C{-}H\cdots Cl^-$ hydrogen bonds but instead through Cl^-–π interactions. Moreover, the existence of separate signals for free and bound calix[4]pyrrole receptor **2** indicates that the exchange of the bound chloride by a solvent molecule is slow on the NMR timescale. Most likely, the release of the included chloride ion requires the conversion of the low-energy cone conformer assigned to the anionic complex into a higher-energy half-cone or alternate conformer.

Taken together, these results constitute a clear indication that in solution the Cl^-@**2** complexes adopt a binding geometry featuring the calixpyrrole core in a cone conformation and the chloride deeply included in the aromatic cavity formed by the axially oriented phenyl groups.[16] The included chloride is hydrogen bonded to the four pyrrolic NH groups and experiences anion–π interactions with the π system of the aromatic rings.

Quantitative assessments of the binding constants with chloride and most receptors **2** were made by simple integration of the ^{1}H NMR spectra and/or by means of isothermal titration calorimetry (ITC) experiments. As a result of the low solubility of **2b** in acetonitrile, we used the solubility technique in this particular instance.[17] In all cases we used acetonitrile containing about 200 ppm of water as solvent. The calculated association constants for the 1:1 complexes are summarized in Table 1. The inclusion complexes Cl^-@**2** can

Table 1: Association constants K_a [$\times 10^3\,\mathrm{M}^{-1}$] measured in acetonitrile or CD_3CN at 298 K for the *endo* 1:1 complexes of **2** and chloride. Statistically corrected free energy values $\Delta\Delta G$ [kcal mol^{-1}] calculated for the chloride–π interactions. ^{1}H chemical shift values δ_{NH} [ppm] of the pyrrole NH groups and their complexation-induced change in chemical shift $\Delta\delta$ [ppm].

	2f	**2a**	**2g**	**2b**	**2c**	**2d**	**1**
R	MeO	H	$MeCO_2$	Br	CN	NO_2	–
K_a	0.13[a]	0.25[a]	1.10[a,b]	3.80[c]	33.0[b]	180[b]	108[b]
	±0.03	±0.02	±0.20	±0.40	±3.50	±20.0	±11.0
$-\Delta G$	2.9	3.1	4.1	4.8	6.2	7.2	6.9
$\Delta\Delta G$[d]	1.0	0.9	0.7	0.5	0.1	−0.1	–
δ_{NH}	7.9	7.9	8.0	–	7.9	8.1	7.4
$\Delta\delta$	3.5	3.5	3.2	–	3.1	3.0	3.6

[a] K_a value determined by ^{1}H NMR spectroscopy. [b] K_a value determined by ITC. [c] K_a value determined using solubility titration. [d] $\Delta\Delta G = (\Delta G_{Cl^-@2} - \Delta G_{Cl^-@1})/4$.

also be readily detected by negative-ion mass spectrometry (MS). The relative binding affinities of chloride towards calix[4]pyrrole receptors established by ESI-MS competitive binding experiments are in line with the results obtained in solution (see the Supporting Information).

In general, the association constant values for the Cl^-@**2** complexes increase with the electron-withdrawing character of the R substituent. The chemical shift data presented in Table 1 show that the strength of the primary interaction, that is, the hydrogen bonding between the pyrrolic NH groups and the chloride anion, is not significantly perturbed by the introduction of the *meso* phenyl groups and by the modification of their *para* substituent. Thus, the change in chemical shift experienced by the NH proton signal upon chloride binding is quite similar in the entire receptor series.[18]

The differences in the stability constants calculated for the Cl^-@**2** complexes can provide a direct measurement of the relative interaction energy of chloride with different aromatic π systems.[19] The maximum contribution of the chloride–π interactions to the overall free energy of binding in the receptor series **2** can be estimated as +4.4 kcal mol^{-1} (about 1.1 kcal mol^{-1} per aromatic ring). This value represents the difference in free binding energy between **2f** and **2d**. Due to the fact that repulsive chloride–π interactions are surely operative in the complex Cl^-@**2f**, the value of 1 kcal mol^{-1} represents an overestimation of the stabilization energy for the attractive interaction between the chloride ion and the π system of *p*-nitrophenyl in acetonitrile. The chloride complex (Cl^-@**1**) of octamethyl calix[4]pyrrole (**1**) supplies an ideal reference to better quantify the free energy values for chloride–π interactions in solution.[20] The statistically corrected chloride–π free energy values ($\Delta\Delta G$) for various substituted aromatics are reported in Table 1.

The obtained data indicate that in all cases, except for R = NO_2, the free energy for the chloride–π interaction is repulsive. The magnitude of the repulsion, however, is clearly sensitive to the nature of the aromatic substituent R. The calculated $\Delta\Delta G$ data correlate well with the corresponding Hammett constants for the *para* and *meta* substituents[21] (σ_p $R^2 = 0.95$ and σ_m $R^2 = 0.92$, Figure 3), thus providing some insight into the origin of the variation. A likely explanation of the observed trend is consistent with the existence and variation of an electrostatic interaction involving the anion (chloride) and the electrostatic potential surface of the aromatic ring.[22]

The maximum free energy value measured for the chloride–π interaction with this model system is clearly repulsive and can be estimated as approximately 1.0 kcal mol^{-1} (R = OMe). An increase in the electron-withdrawing character of the R substituent induces a less repulsive anion–π interaction. This result could be simply caused by the depletion of the electron density of the π clouds of the aromatic rings owing to the influence of the substituent. Nevertheless, this simple model also suggests that eventually, when R = NO_2, the interaction between the anion and the aromatic surfaces could become slightly attractive (ca. −0.1 kcal mol^{-1}).

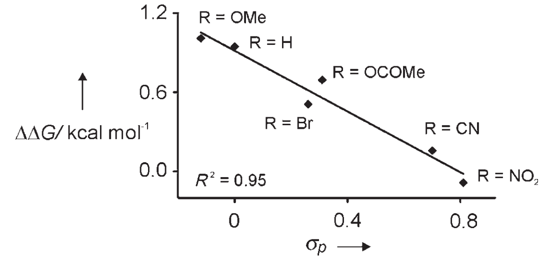


Figure 3. Experimental chloride–π interaction energies ($\Delta\Delta G$) correlate with the Hammett constant σ_p values for the substituent R.

The binding geometry proposed in solution is also supported by the formation of *endo* cavity complexes Cl^-@**2** in the solid state (Figure 4).

In conclusion, we have shown that a series of *meso*-tetraaryl calix[4]pyrrole receptors can be used as a model system to quantify chloride–π interactions in solution. By means of ^{1}H NMR spectroscopy and X-ray crystallographic studies we have demonstrated that the chloride–arene interactions observed in these complexes are established exclusively with the π-aromatic system. The quantitative Hammett free-energy relationship derived demonstrates that the detected chloride–π interactions are dominated by electrostatic effects. The observation, in the solid state and in solution, of chloride ions placed next to aromatic surfaces does not relate directly to the existence of attractive interactions between them. The values of the free energies estimated for the interaction of chloride with the π-aromatic systems are probably not transferable to other model systems. We believe, however, that the observed trend and order of magnitude should be of general applicability. Our study clearly demonstrates that, in acetonitrile solution, equipping the calix[4]pyrrole core with four additional chloride–*p*-nitrophenyl interactions does not produce a chloride receptor with much higher affinity than the simple octamethyl calix[4]pyrrole (**1**).

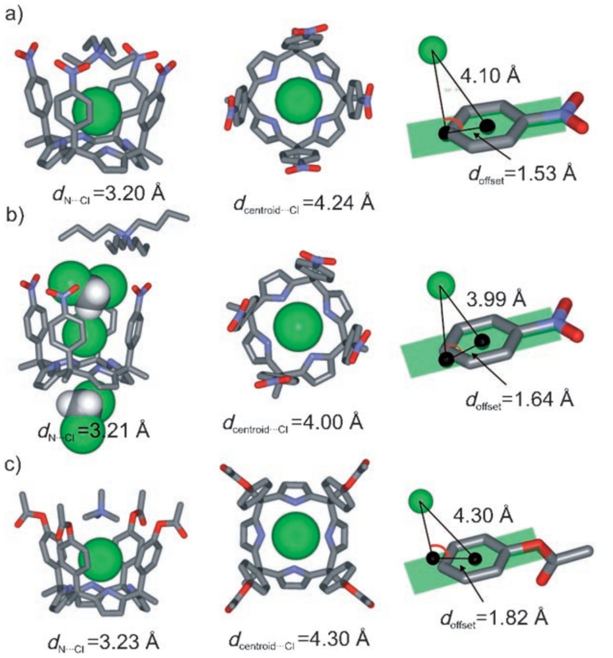


Figure 4. Side and top views (left and center, respectively) of the X-ray structures of the chloride complexes with receptors **2**: a) TEA·Cl^-@**2d**, b) TBA·Cl^-@**2d**, and c) TMA·Cl^-@**2g**. Solvent molecules and the organic cation are omitted in the top views. The right-hand column illustrates the binding motif of the anion–π interaction with the shorter distance to the ring centroid of the π system. The degree of displacement of the chloride from the center of the arene (d_{offset}) is also indicated. TEA = tetraethylammonium, TMA = tetramethylammonium. H white, C gray, O red, N blue, Cl,Cl^- green.

Experimental Section

Crystal data, a general X-ray diffraction experimental section, ESI-MS experiments, ITC titrations, ^{1}H NMR titrations, and the single-crystal X-ray structure of the complex of Cl^- with **2e** are available in the Supporting Information. CCDC-677137, -677138, -677139, -677140, -677141, -677142, -677143, -677144, and -677145 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: February 8, 2008

Keywords: anions · calixarenes · hydrogen bonds · Pi interactions · receptors

---

[1] For the first report on anion–π interactions, see: a) H. J. Schneider, F. Werner, T. Blatter, *J. Phys. Org. Chem.* **1993**, *6*, 590–594. The CH···X^- hydrogen bonding established between the CH groups of electron-deficient arenes and anions is not a result of the interaction of the anion with the π-aromatic system: b) H. Schneider, K. M. Vogelhuber, F. Schinle, J. M. Weber, *J. Am. Chem. Soc.* **2007**, *129*, 13022–13026, and reference [3g].

[2] a) D. Quiñonero, C. Garau, C. Rotger, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Angew. Chem.* **2002**, *114*, 3539–3542; *Angew. Chem. Int. Ed.* **2002**, *41*, 3389–3392; b) M. Mascal, A. Armstrong, M. D. Bartberger, *J. Am. Chem. Soc.* **2002**, *124*, 6274–6276; c) I. Alkorta, I. Rozas, J. Elguero, *J. Am. Chem. Soc.* **2002**, *124*, 8593–8598; d) D. Quiñonero, C. Garau, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Chem. Phys. Lett.* **2002**, *359*, 486–492.

[3] a) C. Garau, A. Frontera, D. Quiñonero, P. Ballester, A. Costa, P. M. Deyà, *ChemPhysChem* **2003**, *4*, 1344–1348; b) D. Kim, P. Tarakeshwar, K. S. Kim, *J. Phys. Chem. A* **2004**, *108*, 1250–1258; c) A. Clements, M. Lewis, *J. Phys. Chem. A* **2006**, *110*, 12705–12710; d) B. L. Schottel, H. T. Chifotides, M. Shatruk, A. Chouai, L. M. Perez, J. Bacsa, K. R. Dunbar, *J. Am. Chem. Soc.* **2006**, *128*, 5895–5912; e) P. U. Maheswari, B. Modec, A. Pevec, B. Kozlevcar, C. Massera, P. Gamez, J. Reedijk, *Inorg. Chem.* **2006**, *45*, 6637–6645; f) M. Mascal, *Angew. Chem.* **2006**, *118*, 2956–2959; *Angew. Chem. Int. Ed.* **2006**, *45*, 2890–2893; g) O. B. Berryman, V. S. Bryantsev, D. P. Stay, D. W. Johnson, B. P. Hay, *J. Am. Chem. Soc.* **2007**, *129*, 48–58.

[4] For recent reviews of computational and experimental work related to anion interactions with aromatic rings, see: a) P. Gamez, T. Mooibroek, S. Teat, J. Reedijk, *Acc. Chem. Res.* **2007**, *40*, 435–444; b) B. L. Schottel, H. T. Chifotides, K. R. Dunbar, *Chem. Soc. Rev.* **2008**, *37*, 68–83.

[5] Y. S. Rosokha, S. V. Lindeman, S. V. Rosokha, J. K. Kochi, *Angew. Chem.* **2004**, *116*, 4750–4752; *Angew. Chem. Int. Ed.* **2004**, *43*, 4650–4652.

[6] For other solution studies that highlight the existence of attractive anion–π interactions, see: a) O. B. Berryman, F. Hof, M. J. Hynes, D. W. Johnson, *Chem. Commun.* **2006**, 506–508; b) M. Mascal, I. Yakovlev, E. B. Nikitin, J. C. Fettinger, *Angew. Chem.* **2007**, *119*, 8938–8940; *Angew. Chem. Int. Ed.* **2007**, *46*, 8782–8784.

[7] J. Rebek, B. Askew, P. Ballester, C. Buhr, S. Jones, D. Nemeth, K. Williams, *J. Am. Chem. Soc.* **1987**, *109*, 5033–5035.

[8] a) J. L. Sessler, D. E. Gross, W.-S. Cho, V. M. Lynch, F. P. Schmidtchen, G. W. Bates, M. E. Light, P. A. Gale, *J. Am. Chem. Soc.* **2006**, *128*, 12281–12288; b) P. A. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141.

[9] a) C. J. Woods, S. Camiolo, M. E. Light, S. J. Coles, M. B. Hursthouse, M. A. King, P. A. Gale, J. W. Essex, *J. Am. Chem. Soc.* **2002**, *124*, 8644–8652; b) P. Anzenbacher, Jr., K. Jursikova, V. M. Lynch, P. A. Gale, J. L. Sessler, *J. Am. Chem. Soc.* **1999**, *121*, 11020–11021; c) L. Bonomo, E. Solari, G. Toraman, R. Scopelliti, C. Floriani, M. Latronico, *Chem. Commun.* **1999**, 2413–2414.

[10] G. Gil-Ramirez, J. Benet-Buchholz, E. C. Escudero-Adan, P. Ballester, *J. Am. Chem. Soc.* **2007**, *129*, 3820–3821.

[11] a) S. Camiolo, P. A. Gale, *Chem. Commun.* **2000**, 1129–1130; b) G. Bruno, G. Cafeo, F. H. Kohnke, F. Nicolo, *Tetrahedron* **2007**, *63*, 10003–10010.

[12] The configurations of **2a–d**, **2f**, and **2g** were confirmed unambiguously by X-ray crystallographic analysis.

[13] A. F. Danil De Namor, M. Shehab, *J. Phys. Chem. B* **2003**, *107*, 6462–6468.

[14] Free receptor **2b** has a very low solubility in acetonitrile; however, it is readily extracted in acetonitrile solutions containing TBACl.

[15] Incremental addition of TBACl to an acetonitrile solution containing **2e** produced significant downfield shifts of the proton signal assigned to the hydroxyl groups, while the pyrrole NH signals remained at a constant chemical shift. X-ray structure determination of crystals grown from acetonitrile revealed *exo* complexation of the halide with two adjacent OH groups in the Cl^-·**2e** complex. A related *exo* geometry was also reported in reference [9b] for the complex F^-·**2e**.

[16] The proposed binding geometry in solution has been shown in the solid state for several Cl^-@**2** complexes with TBA, TEA, and TMA as counterions.

[17] K. A. Connors, *Binding Constants: The Measurement of Molecular Complex Stability*, Wiley, New York, **1987**, p. 261.

[18] The average distance values for the N–Cl^- interaction measured in the X-ray structures of the Cl^-@**2** complexes of **2d**, **2f** (preliminary data), and **2g** are 3.26, 3.23, and 3.26 Å, respectively. A similar distance of 3.28 Å is observed in the Cl^-@**1** complex, see reference [9a].

[19] This difference intrinsically includes additional contributions from desolvation.

[20] $K_a = 2.5 \times 10^5\,\text{M}^{-1}$ ($\Delta G = -7.3\,\text{kcal mol}^{-1}$) has been reported in reference [8] for the Cl^-@**1** complex in anhydrous acetonitrile (< 50 ppm H_2O).

[21] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, *Vol. A*, 5th ed., Kluwer Academic/Plenum Publishers, New York, **2001**.

[22] The energies and geometries observed are indicative of an interaction mainly controlled by electrostatics. No significant color changes were observed upon anion binding.