Not-So-Weak Hydrogen Bonds

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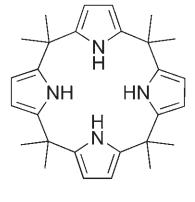
Benzene-, Pyrrole-, and Furan-Containing Diametrically Strapped Calix[4]pyrroles—An Experimental and Theoretical Study of Hydrogen-Bonding Effects in Chloride Anion Recognition[**]

Dae-Wi Yoon, Dustin E. Gross, Vincent M. Lynch, Jonathan L. Sessler, Benjamin P. Hay,* and Chang-Hee Lee**

Weak hydrogen bonds recently have arisen as a topic of interest in supramolecular chemistry.[1] Among the various interactions being studied, the C–H···anion hydrogen bonds have drawn considerable attention. Positively charged groups, such as imidazolium cations, provide strong C–H donors and have been used extensively in the design of numerous anionophore architectures.[2] There is increasing evidence, however, that even charge-neutral C–H donors may be strong enough to be exploited effectively in anion recognition chemistry. Such interactions, which involve both aliphatic and aryl C–H groups, have been inferred from gas-phase studies,[3] deduced from NMR spectroscopic studies through, for example, chemical-shift changes,[4–7] and observed in solid-state structures.[4,5,8] A recent review of anion–arene adducts notes that C–H···anion hydrogen bonding, rather than interaction with the π system, is by far the most prevalent bonding motif observed in the solid state.[9] These experimental observations are supported by theoretical analyses.[10,11] For instance, Hay and Bryantsev have calculated that benzene C–H···anion hydrogen bonds are significant,[11a] being roughly half the strength of typical neutral N–H···anion hydrogen bonds. In a subsequent theoretical report, it was noted that the aryl C–H···Cl binding energies in the gas phase can be tuned from -8 to $-16\,\mathrm{kcal\,mol^{-1}}$ by altering the *para* substitution from NH_2 to NO_2.[11b] Although there are some examples where complementary aryl C–H···anion interactions have been deliberately incorporated into the design of anion receptors,[7,12] to the best of our knowledge, no efforts have been made to date to test theoretical predictions through the synthesis and experimental study of a matched series of anion receptors. We now report efforts along these lines.

In the context of ongoing efforts to develop the chemistry of calixpyrroles (e.g., **1**), we recently reported the synthesis of the strapped calixpyrrole **2**.[13] In this case, a single-crystal X-ray diffraction study revealed the presence of a short C–H···Cl$^-$ contact in the solid state.[4] This evidence for hydrogen bonding was later confirmed in solution by NMR spectroscopic means. However, because it provided only a single datum point, it was not possible to assess the extent to which this C–H···Cl$^-$ interaction contributed to the overall chloride anion binding process. In an effort to address this issue, we have now synthesized the corresponding pyrrole- and furan-strapped congeners **3** and **4**, where **3** allows a comparison of NH vs. CH hydrogen bonding and **4**, which lacks a donor, provides a "negative control". The chloride anion binding properties of this series were then analyzed in the solid state, in acetonitrile and dimethylsulfoxide solution, and through theoretical analyses. The results obtained provide support for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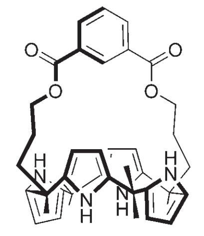
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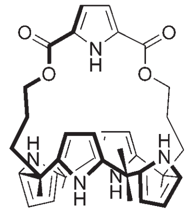
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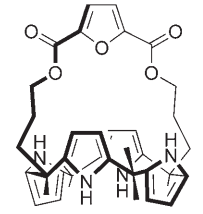
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[*] Dr. D.-W. Yoon, D. E. Gross, Dr. V. M. Lynch, Prof. J. L. Sessler
Department of Chemistry and Biochemistry
The University of Texas at Austin
Austin, TX 78712 (USA)
Fax: (+1) 512-471-7550
E-mail: sessler@mail.utexas.edu
Dr. B. P. Hay
Chemical Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830-6119 (USA)
Prof. C.-H. Lee
Department of Chemistry and Vascular System Research Center
Kangwon National University
Chun-Chon 200-701 (Korea)

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the notion that C–H···Cl^- interactions are significant, at least within the well-defined[14] anion recognition environment provided by this series of diametrically strapped calixpyrroles.

The key intermediate for the synthesis of the pyrrole-strapped calix[4]pyrrole **3**, pyrrole-2,5-dicarboxylic acid (**5a**), was prepared from the diester **6** (Scheme 1).[15] The dicarboxylic acid was then converted to the bis-acid chloride **7a** by heating at reflux in thionyl chloride, followed by simple distillation and rigorous drying under high vacuum. Reaction of **7a** with 2.0 equiv of 5-(3-hydroxypropyl)-5-methyldipyrromethane **8**[13a] in the presence of pyridine yielded the bis-dipyrromethane **9a**. Finally, acid-catalyzed condensation of **9a** in the presence of excess acetone afforded the desired pyrrole-strapped calix[4]pyrrole **3** in 15% yield.

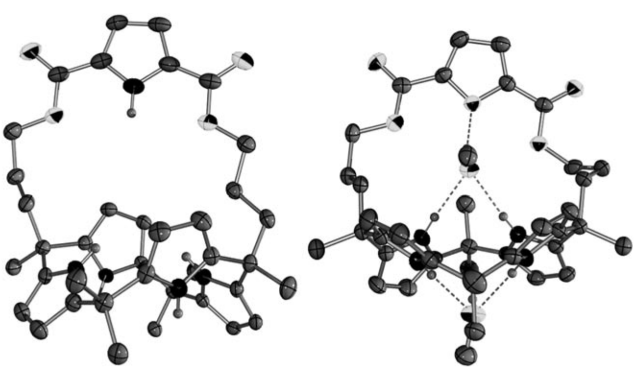
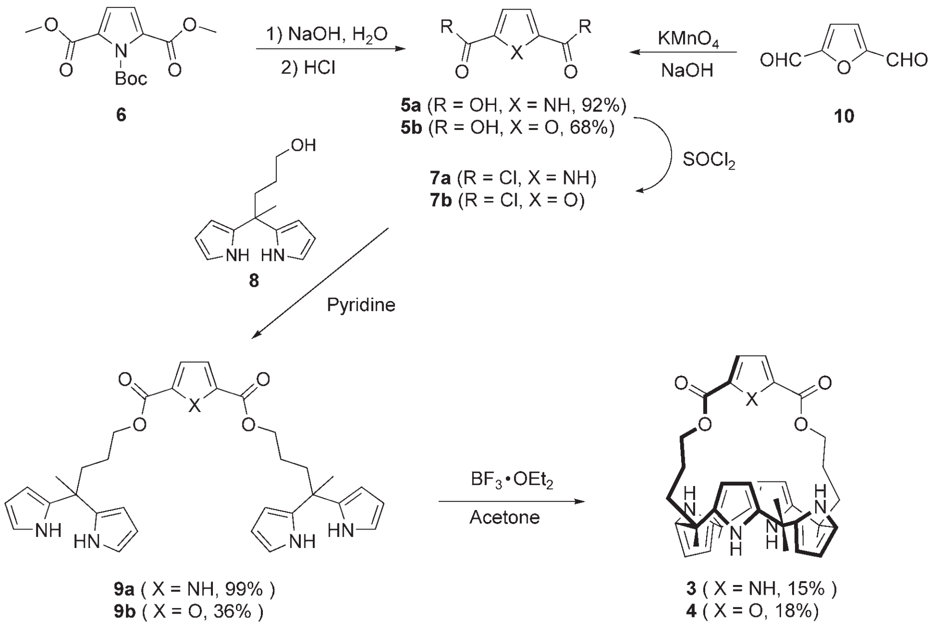


Figure 1. Single-crystal X-ray diffraction structures of the anion-free forms of receptors **3** (left) and **4**·2 MeOH (right).[16]



Scheme 1. Synthesis of the pyrrole-strapped calix[4]pyrrole **3** and analogous furan system **4**.

The analogous furan-strapped calix[4]pyrrole **4** was synthesized from furan-2,5-dicarboxylic acid (**5b**). This precursor was readily prepared— through oxidation with $KMnO_4$— from 2,5-diformyl furan **10**, which in turn was obtained by formylation of furan with *n*BuLi and DMF followed by acidic work-up. In analogy to above, the resulting dicarboxylic acid **5b** was converted to the corresponding acid chloride **7b** using thionyl chloride; reaction with **8** gave the bis-dipyrromethane **9b**, which was condensed with acetone in the presence of $BF_3 \cdot OEt_2$ to afford the desired furan-strapped calix[4]pyrrole **4** in 18% yield (Scheme 1). Both new compounds, **3** and **4**, were characterized by standard spectroscopic means, as well as by X-ray diffraction analysis (Figure 1). Interestingly, compound **3** adopts a 1,3-alternate conformation in its anion-free form, while compound **4** (containing two molecules of methanol) adopts a 1,2-alternate conformation, at least in the solid state.

Previously, we reported the X-ray crystal structure of **2**·Cl^-.[4] Evaluation of this structure revealed three types of anion–receptor contacts in the solid state, namely to the four pyrrolic NH protons, to a proton of the benzene strap, and to two aliphatic protons (Figure 2, left). In the present study, diffraction-grade crystals of **3**·Cl^- were obtained by slow diffusion of methanol into a dichloromethane solution of **3** containing an excess of tetrabutylammonium chloride (TBACl). The resulting X-ray diffraction structure revealed that the calix[4]pyrrole subunit exists in the expected cone conformation and that the chloride anion exhibits hydrogen bonding contacts analogous to those observed in **2**·Cl^-. The average calixpyrrole N–H···Cl^- distances are comparable in both complexes, being 2.407 Å and 2.425 Å for **3** and **2**, respectively. Similarly, the average aliphatic C–H···Cl^- distances are comparable in both complexes: methylene 2.578 Å and 2.467 Å and methyl 2.945 Å and 2.979 Å for **3** and **2**,

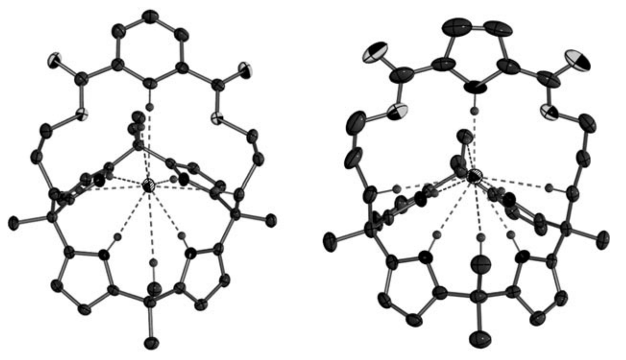


Figure 2. Single-crystal X-ray diffraction structures of the chloride anion complexes of the strapped calix[4]pyrroles **2** and **3**.[16] In both cases, N–H···anion and C–H···anion contacts of ≤ 3 Å are shown. The structure of **2**·Cl^- was originally published in reference [4].

respectively. However, there is a large difference in the distance involving the apical strap-derived contact, with the pyrrole strap providing a closer N−H···Cl$^-$ contact by 0.63 Å than the corresponding benzene CH interaction. The dihedral angles around the 2,5-substituted pyrrole and the 1,5-substituted benzene moieties in the straps also differ, that is, the benzene subunit is tilted more than the pyrrole subunit, presumably to compensate the shorter net linker distance. At present, no experimental structural information is available for the corresponding chloride anion complex of the congeneric furan-based system **4**.

Electronic structure calculations were performed to assess the relative strengths of the three types of hydrogen bonding interactions in the absence of complicating effects arising from steric constraints imposed by the ligand architecture and environmental factors. As seen in Table 1, electronic binding energies, ΔE, for complexes of Cl$^-$ with the simple donors pyrrole, benzene, and methane are fully consistent with measured gas-phase ΔH values. The expected trend in hydrogen-bond strengths is obtained with pyrrole > benzene > methane.[11a] Moreover, these results confirm that the C−H···Cl contacts observed in the crystal structures of **2**·Cl$^-$ and **3**·Cl$^-$ are attractive in nature and make a significant contribution to the overall binding. In all cases geometries for these 1:1 complexes (Figure 3) reveal closer contacts than those observed in the strapped calixpyrrole macrocycles. This effect is predominantly due to the fact that a single anion–molecule interaction polarizes and redistributes the anion charge differently than multiple anion–molecule interactions, leading to stronger interactions and shorter distances.

Table 1: Comparison of calculated electronic binding energies, ΔE [kcal mol^{-1}],[a] with experimental gas-phase values for ΔH [kcal mol^{-1}] for Cl$^-$ complexes with simple hydrogen-bond donors.

Donor	ΔE (DFT)[b]	ΔE (MP2)[c]	ΔH
pyrrole	−23.09	−22.50	−18.8[3b]
benzene	−8.32	−8.42	−8.6 to −10.5[3b, 10a, 17]
methane	−3.06	−3.36	−3.6[18]

[a] $\Delta E = E(\text{complex}) - E(\text{chloride}) - E(\text{donor})$. Electronic structure calculations were performed with NWChem.[19] [b] B3LYP/DZVP2. [c] MP2/aug-cc-pVDZ.

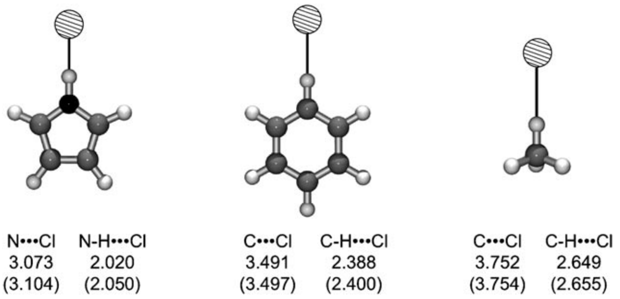


Figure 3. Optimized geometries for Cl$^-$ complexes with pyrrole, benzene, and methane. Distances are given below each structure at the MP2/aug-cc-pVDZ and B3LYP/DZVP2 (in parentheses) levels of theory. Cartesian coordinates and absolute energies for all optimizations are included in the Supporting Information.

To gain further insight into the contribution of the C−H···Cl and N−H···Cl contacts provided by the straps in **2** and **3**, the less expensive B3LYP/DZVP2 level of theory was used to optimize the geometry of the chloride-bonded structures for strapped calixpyrroles **2** and **3**, as well as for the furan analogue **4** (Figure 4). Starting from the crystallographic coordinates, **2** and **3** were optimized under gas-phase conditions. This yielded geometries that were little changed from the solid state and had comparable average calixpyrrole N−H···Cl$^-$ distances (2.398 Å and 2.311 Å for **3** and **2**, respectively). Similarly, the average aliphatic C−H···Cl distances are comparable in both complexes (i.e., methylene 2.640 Å and 2.563 Å and methyl 2.933 Å and 3.019 Å for **3** and **2**, respectively). Optimization using starting coordinates derived by replacing the benzene unit in **3** with a furan unit yielded a putative geometry for **4**·Cl$^-$. This complex shows the same hydrogen-bonding motifs and distances as seen in **2** and **3**, with the exception that the furan moiety fails to provide an additional hydrogen-bond donor. To obtain a measure of the chloride affinity offered by each of the host configurations, single-point energies were calculated after removal of the chloride anion. Subtracting the energy of Cl$^-$ and the host binding configuration from that of the complex yields the following ΔE values: −67.64 (**3**) < −63.46 (**2**) < −58.25 kcal mol^{-1} (**4**). Consistent with the calculations on the simple prototype donors, these binding energies predict that the pyrrole-strapped system **3** should prove to be a better receptor than the corresponding benzene species **2**, and that the latter system should prove to be a better receptor than the furan-strapped calix[4]pyrrole **4**.[20]

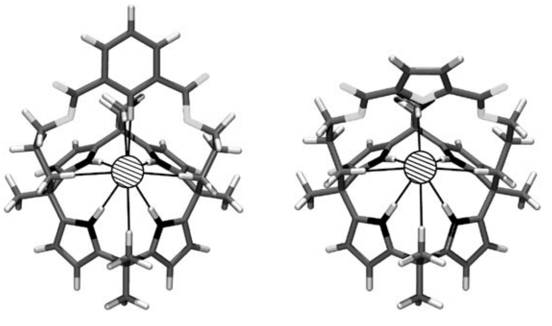

2 **4**

Figure 4. Optimized B3LYP/DZVP2 geometries of the chloride anion complex of the benzene-strapped calix[4]pyrrole **2** and the furan-strapped calix[4]pyrrole **4**. A corresponding view for the pyrrole-strapped system **3**, as well as Cartesian coordinates and absolute energies for all three species, is included in the Supporting Information.

In light of the above prediction, attempts were made to study the anion binding properties of the pyrrole-strapped calix[4]pyrrole **3** using proton NMR spectroscopy. Unfortunately, even in [D$_6$]DMSO, which was expected to favor a rapid equilibrium, sets of peaks consistent with slow association/dissociation kinetics (i.e., slow exchange) were observed. Nonetheless, these spectroscopic studies provided insights into the mode of binding and the stoichiometry. For instance, in the absence of anions two singlets were observed for the pyrrolic NH's, namely one at $\delta = 11.58$ ppm (pyrrole on the strap) and another at $\delta = 9.43$ ppm (calix[4]pyrrole). However, upon addition of less than 1.0 equiv TBACl two singlets appeared at $\delta = 12.87$ and 10.92 ppm. The β-pyrrolic protons were also shifted upfield upon chloride anion binding as expected (see the Supporting Information). Complete appearance of these new signals, with a corresponding disappearance of the original signals, was observed after the addition of 1.0 equiv Cl^-. These observations are consistent with a strong 1:1 binding motif and the inclusion of chloride in the cavity of the pyrrole-strapped calix[4]pyrrole **3**. With the furan-strapped calix[4]pyrrole **4**, slow association/dissociation kinetics were also observed in the case of TBACl. The NMR signals of the pyrrolic NH's were shifted downfield from $\delta =$ 9.40 to 11.47 ppm. Additionally, the signals of the β protons on the furan subunit were shifted upfield, along with the calix[4]pyrrole β-pyrrolic protons, as in the case of **2** and **3**.

Given that the system was undergoing slow exchange relative to the NMR time scale, we chose the isothermal titration calorimetry (ITC) as the method to quantify the interaction of chloride (as the TBA salt) with calixpyrroles **1**–**4** (Table 2). Although we have already reported the chloride anion binding affinity for the benzene-strapped calixpyrrole **2**, measured in acetonitrile at 30 °C,[13a] the titrations have been repeated at 25 °C to allow for a direct comparison between calixpyrroles **1**–**4** under identical conditions. The lowering of the temperature by 5 K afforded a slightly higher affinity constant for the interaction of **2** with TBACl ($K_a = 2.2\times10^6$ vs. $1.4\times10^6\,\text{M}^{-1}$; estimated errors <10 %). As expected, the introduction of an additional NH hydrogen-bond donor into the strap enhanced the chloride affinity by an order of magnitude relative to **2** ($K_a = 2.2\times10^6$ and $1.8\times10^7\,\text{M}^{-1}$, for **2** and **3**, respectively; see Table 2). The interaction of **3** with chloride has both a more favorable enthalpy and entropy, explaining the higher affinity observed for this system than for **2**. Conversely, when compared to **2**, the enthalpy of the furan analogue **4** drops by 15 %, and the observed $K_a = 1.9\times10^5\,\text{M}^{-1}$ represents an order-of-magnitude decrease.

Table 2: Thermodynamic data for the interaction of calixpyrroles **1**–**4** with chloride.[a]

Host	$T\Delta S$	ΔH	ΔG	K_a [M^{-1}]	K_a/K_4[b]
1[c]	−2.91	−10.16	−7.29	2.2×10^5	1.2
2	−1.90	−10.54	−8.64	2.2×10^6	12
3	−1.44	−11.34	−9.90	1.8×10^7	95
4	−1.67	−8.87	−7.20	1.9×10^5	1

[a] Units of $T\Delta S$, ΔH, and ΔG are kcal mol^{-1}; titrations were run at 25 °C in acetonitrile, and chloride was used in the form of its tetrabutylammonium salt. [b] K_a/K_4 is the affinity enhancement ratio relative to the furan-strapped system **4**. [c] From reference [14b].

Previously we had shown an order-of-magnitude increase in the chloride affinity of calix[4]pyrrole **1** by adding a CH donor to the calixpyrrole scaffold (receptor **2**). Now, by tuning the substituent on the strap we have been able to span a wider range of binding affinities. Specifically, we have found that replacing the CH hydrogen-bond donor of the benzene-strapped system by a pyrrolic NH donor increases the chloride anion affinity by an additional order of magnitude. Conversely, the furan equivalent **4**, a "negative control", displayed a lower chloride anion affinity relative to the benzene- and pyrrole-strapped receptors **2** and **3** by ca. one and two orders of magnitude, respectively. As with the theoretical analysis,[20] other factors obscure/prevent/preclude the quantitative assignment of the aryl C−H⋯anion bond strength from these solution data. Nevertheless, it is important to stress that the present experimental findings are fully consistent with theory. They thus provide support for the proposal that C−H⋯anion interactions can be exploited to good effect in the design of anion receptors and that such not-so-weak hydrogen bonds may have a role to play in terms of explaining biological anion recognition processes.

At present, we are working to generalize these findings by extending the studies to other receptor systems and by investigating the extent to which the choice of strapping entity can affect the binding of other anionic guests. The results of these efforts will be reported in due course.

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[1] M. Nishio in *Encyclopedia of Supramolecular Chemistry* (Ed.: J. L. Atwood, W. Jonathan), Marcel Dekker, New York, **2004**, pp. 1576–1585.

[2] a) K. Sato, S. Arai, T. Yamagishi, *Tetrahedron Lett.* **1999**, *40*, 5219–5222; b) E. Alcalde, C. Alvarez-Rua, S. Garcia-Granda, E. Garcia-Rodriguez, N. Mesquida, L. Perez-Garcia, *Chem. Commun.* **1999**, 295–296; c) H. Ihm, S. Yun, H. G. Kim, J. K. Kim, K. S. Kim, *Org. Lett.* **2002**, *4*, 2897–2900; d) S. K. Kim, B. G. Kang, H. S. Koh, Y. J. Yoon, S. J. Jung, B. Jeong, K.-D. Lee, J. Yoon, *Org. Lett.* **2004**, *6*, 4655–4658; e) K. Chellappan, N. J. Singh, I.-C. Hwang, J. W. Lee, K. S. Kim, *Angew. Chem.* **2005**, *117*, 2959–2963; *Angew. Chem. Int. Ed.* **2005**, *44*, 2899–2903; f) W. W. H. Wong, M. S. Vickers, A. R. Cowley, R. L. Paul, P. D. Beer, *Org. Biomol. Chem.* **2005**, *3*, 4201–4208; g) S. In, S. J. Cho, J. Kang, *Supramol. Chem.* **2005**, *17*, 443–446; h) J. Yoon, S. K. Kim, N. J. Singh, K. W. Kim, *Chem. Soc. Rev.* **2006**, *35*, 355–360; i) V. Amendola, M. Boiocchi, B. Colasson, L. Fabbrizzi, M.-J. Rodriguez Douton, F. Ugozzoli, *Angew. Chem.* **2006**, *118*, 7074–7078; *Angew. Chem. Int. Ed.* **2006**, *45*, 6920–6924; j) T. Fahlbusch, M. Frank, J. Schatz, H. Schmaderer, *Eur. J. Org. Chem.* **2006**, 1899–1903; k) W. J. Belcher, M. Fabre, T. Farhan, J. W. Steed, *Org. Biomol. Chem.* **2006**, *4*, 781–786; l) K. Sato, Y. Sadamitsu, S. Arai, T. Yamagishi, *Tetrahedron Lett.* **2007**, *48*, 1493–1496.

[3] a) M. A. French, S. Ikuta, P. Kebarle, *Can. J. Chem.* **1982**, *60*, 1907–1918; b) J. W. Larson, T. B. McMahon, *J. Am. Chem. Soc.* **1984**, *106*, 517–521; c) M. Albertí, A. Castro, A. Lagana, M. Moix, F. Pirani, D. Cappelletti, *Eur. Phys. J. D* **2006**, *38*, 185–191; d) H. Schneider, K. M. Vogelhuber, F. Schinte, J. M. Weber, *J. Am. Chem. Soc.* **2007**, *129*, 13022–13026; e) S. S. Zhu, H. Staats, K. Brandhorst, J. Grunnenberg, F. Gruppi, E. Dalcanale, A. Lutzen, K. Rissanen, C. A. Schalley, *Angew. Chem.* **2008**, *120*, 800–804; *Angew. Chem. Int. Ed.* **2008**, *47*, 788–792.

[4] C.-H. Lee, H.-K. Na, D.-W. Yoon, D.-H. Won, W.-S. Cho, V. M. Lynch, S. V. Shevchuk, J. L. Sessler, *J. Am. Chem. Soc.* **2003**, *125*, 7301 – 7306.

[5] a) S. O. Kang, D. VanderVelde, D. Powell, K. Bowman-James, *J. Am. Chem. Soc.* **2004**, *126*, 12272 – 12273; b) I. E. D. Vega, P. A. Gale, M. E. Light, S. J. Loeb, *Chem. Commun.* **2005**, 4913 – 4915; c) H. Maeda, Y. Kusunose, *Chem. Eur. J.* **2005**, *11*, 5661 – 5666; d) T. Zielinski, M. Kedziorek, J. Jurczak, *Chem. Eur. J.* **2008**, *14*, 838 – 846.

[6] a) Q.-Y. Chen, C.-F. Chen, *Tetrahedron Lett.* **2004**, *45*, 6493; b) J. Y. Kwon, Y. J. Jang, S. K. Kim, K. H. Lee, J. S. Kim, J. Yoon, *J. Org. Chem.* **2004**, *69*, 5155 – 5157; c) C. Fujimoto, Y. Kusunose, H. Maeda, *J. Org. Chem.* **2006**, *71*, 2389 – 2394; d) R. Nishiyabu, M. A. Palacios, W. Dehaen, P. Anzenbacher, Jr., *J. Am. Chem. Soc.* **2006**, *128*, 11496 – 11504.

[7] Y. Li, A. H. Flood, *Angew. Chem.* **2008**, *120*, 2689 – 2692; *Angew. Chem. Int. Ed.* **2008**, *47*, 2649 – 2652.

[8] a) C. A. Ilioudis, D. A. Tocher, J. W. Steed, *J. Am. Chem. Soc.* **2004**, *126*, 12395 – 12402; b) M. J. Chmielewski, M. Charon, J. Jurczak, *Org. Lett.* **2004**, *6*, 3501 – 3504.

[9] B. P. Hay, V. S. Bryantsev, *Chem. Commun.* **2008**, DOI: 10.1039/b800055g.

[10] a) K. Hiraoka, S. Mizuse, S. Yamabe, *Chem. Phys. Lett.* **1988**, *147*, 174 – 178; b) Z. M. Loh, R. L. Wilson, D. A. Wild, E. J. Bieske, A. Zehnacker, *J. Chem. Phys.* **2003**, *119*, 9559 – 9567; c) J. A. Ortuno, R. Exposito, C. Sanchez-Pedreno, M. I. Albero, A. Espinosa, *Anal. Chim. Acta* **2004**, *525*, 231 – 237; d) P. Botschwina, R. Oswald, V. Dyczmons, *Int. J. Mass Spectrom.* **2007**, *267*, 308 – 314.

[11] a) V. S. Bryantsev, B. P. Hay, *J. Am. Chem. Soc.* **2005**, *127*, 8282 – 8283; b) V. S. Bryantsev, B. P. Hay, *Org. Lett.* **2005**, *7*, 5031 – 5034; c) O. B. Berryman, V. S. Bryantsev, D. P. Stay, D. W. Johnson, B. P. Hay, *J. Am. Chem. Soc.* **2007**, *129*, 48 – 58.

[12] C.-S. Zuo, J.-M. Quan, Y.-D. Wu, *Org. Lett.* **2007**, *9*, 4219 – 4222.

[13] a) D.-W. Yoon, H. Hwang, C.-H. Lee, *Angew. Chem.* **2002**, *114*, 1835 – 1837; *Angew. Chem. Int. Ed.* **2002**, *41*, 1757 – 1759; b) C.-H. Lee, H. Miyaji, D.-W. Yoon, J. L. Sessler, *Chem. Commun.* **2008**, 24 – 34.

[14] a) P. A. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140 – 5141; b) 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.

[15] T. J. Donohoe, C. E. Headley, R. P. C. Cousins, A. Cowley, *Org. Lett.* **2003**, *5*, 999 – 1002.

[16] The crystal data and experimental details for the structural refinement of **3**, **3**·Cl, and **4**·2MeOH are provided in the Supporting Information. CCDC-682547 (**3**), CCDC-682548 (**3**·Cl), and CCDC-682549 (**4**·2MeOH) 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.

[17] a) J. Sunner, K. Nishizawa, P. Kebarle, *J. Phys. Chem.* **1981**, *85*, 1814 – 1820; b) G. J. C. Paul, P. Kebarle, *J. Am. Chem. Soc.* **1991**, *113*, 1148 – 1154.

[18] K. Hiraoka, T. Mizuno, T. Iino, D. Eguchi, S. Yamabe, *J. Phys. Chem. A* **2001**, *105*, 4887 – 4893.

[19] E. J. Bylaska et al., "NWChem, A Computational Chemistry Package for Parallel Computers, Version 5.0" (**2006**), Pacific Northwest National Laboratory, Richland, Washington 99352-0999, USA. See the Supporting Information for the full citation.

[20] Whereas this analysis provides a quantitative measure of the chloride affinity offered by each binding configuration, we recognize that it does not account for other contributions to the overall binding affinity, such as conformational reorganization that may occur prior to binding or the influence of solvation.