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Anion Effects on the Recognition of Ion Pairs by Calix[4]arene-Based Heteroditopic Receptors

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Received February 26, 2002

A novel heteroditopic receptor (**5**) based on a rigid calix[4]arene cavity bearing at the upper rim four arylsulfonamido binding sites has been synthesized. The binding abilities of this new host have been investigated in apolar solvents toward a series of tetramethylammonium salts (tosylate, chloride, acetate, trifluoroacetate, and picrate) and compared with those of monotopic and heteroditopic calix[4]arene-bis(crown-3)-based receptors **1** and **2** in order to evaluate the role of the anion on ion-pair recognition. While monotopic host **1** shows an efficiency order toward the different salts that increases when the anion is less interactive (Hofmeister trend), an opposite role of the counteranion on the recognition process was observed with host **5** (anti-Hofmeister trend). A more complex behavior is experienced by host **2**, which shows a high and leveled efficiency for all the anions tested. The results obtained were explained on the basis of the different types of ion pairs present in the recognition process. Further information on the role of the anion were obtained by the "dual host" strategy utilizing the tri-*n*-butylthioureido derivative of tren **7**, which forms a stable complex with chloride anion. The very high efficiency shown by these heteroditopic hosts opens new routes in supramolecular projects and is a very interesting tool in the molecular recognition of ion-pairs and its applications.

Introduction

The comprehension of the role played by the several factors that are at the base of the selective and efficient recognition of charged species by synthetic receptors is one of the main objectives of supramolecular chemistry. When recognition processes occur in apolar solvents, the binding of cations[1] or anions[2] occurs through the formation of a complex between suitable hosts and their ion pairs, which are the actual guests present in these media.[3] The Coulombic interaction between the ions modifies the charge density present on the ionic species that should be recognized by the host[4] so that the counterion can strongly, and usually adversely, affect the efficiency of the ion under investigation.[8,9]

Quite often, to minimize these effects and enhance binding of the cations or the anions, low-coordinating counterions, e.g., picrate and tetrabutylammonium, respectively, have been employed.[1,2] Less studied and straightforward is the situation where the coordinating power of the counterion cannot be neglected. Only

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(1) (a) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Gokel, G. W., Eds.; Pergamon: London, 1996; Vol. 1. (b) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.

(2) (a) Seel, C.; de Mendoza, J. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., McNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 519−522. (b) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., Garcia-España, E., Eds.; Wiley-VCH: New York, 1997. (c) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609−1646. (d) Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443−448. (e) Gale, P. A. *Coord. Chem. Rev.* **2000**, *199*, 181−233. (f) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79−128. (g) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 487−516.

(3) See, for example: (a) Mo, H.; Wang, A.; Stone Wilkinson, P.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1997**, *119*, 11666−11673. (b) Hasselgren, C.; Fisher, K.; Jagner, S.; Dance, I. *Chem. Eur. J.* **2000**, *6*, 3671−3678.

(4) The interaction of the counterion with cations or anions in apolar organic solvents is mainly electrostatic in nature, but other contributions may not be neglected. In reference to the specific case of the tetraalkylammonium−anion interactions,[5] the relative evaluation of such interactions is possible only when spherical ions[6] are compared. With anions having different geometry, the comparison of anions such as alkyl- or aryl-sulfonate with picrate becomes problematic. To the best of our knowledge, a systematic evaluation of the interacting power of anions in ion pairing does not exist. In fact, the Hofmeister series,[7] which is largely employed in biochemistry or in ion-selective electrode (ISE) studies, although useful also in rough ion pair interaction evaluation, does not represent a relative measurement of the electrostatic interactions between the ions in the ion pair, but it is rather correlated with their hydration energy. Therefore, the measurement of the interaction energy of ion pairs having different counteranions with a host with low steric hindrance can be employed as an additional experimental method to evaluate such interactions.

(5) See, for example: Okada, T. *J. Chromatogr. A* **1997**, *758*, 19−28.

(6) Marcus, Y. *Ion Solvation*; Wiley & Sons, Ltd.: Chichester, U.K., 1985; Dekker, Inc.: New York, 1997.

(7) Hofmeister, F. *Arch. Ex. Pathol. Pharmakol.* **1888**, *24*, 247−260.

(8) For the effect of anions on cation recognition, see: (a) Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 839−846. (b) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443−12452. (c) Bartoli, S.; Roelens, S. *J. Am. Chem. Soc.* **1999**, *121*, 11908−11909. (d) Böhmer, V.; Dalla Cort, A.; Mandolini, L. *J. Org. Chem.* **2001**, *66*, 1900−1902. (e) Arduini, A.; Giorgi, G.; Pochini, A.; Secchi, A.; Ugozzoli, F. *J. Org. Chem.* **2001**, *66*, 8302−8308.

(9) For the cation effect on anion recognition see, for example: Shukla, R.; Kida, T.; Smith, D. *Org. Lett.* **2000**, *2*, 3099−3102.

10.1021/jo025655s CCC: $22.00
Published on Web 07/16/2002

recently have studies aimed at disclosing the role of counterions on these recognition processes been reported.[8,9] In this context, the methodologies adopted so far to increase the binding efficiency consist of the simultaneous use of two receptors: one for the cation and another one for the anion ("dual host strategy")[10] or, as reported by Kubik[11] and Jeong[12] in the case of organic ammonium salt recognition, by using heteroditopic receptors bearing preorganizable binding sites in which the positive allosteric effects of the anion strongly enhance binding of tetraalkylammonium cation.

Moving from our interest on the recognition of organic ammonium cations through the aromatic cavity of calixarenes,[1b,13] we are pursuing a systematic investigation of the parameters that can increase the efficiency of these hosts in apolar media. Initially, we tackled this problem by rigidifying and extending the calix[4]arene aromatic cavity[8a,14] and verified that, in general, both rigidity[15] and extension of the apolar calixarene binding site benefit cation binding. More recently, we studied the recognition of tetramethylammonium salts using a flexible and preorganizable heteroditopic calix[4]arene receptor bearing binding sites able to interact with both the cation and the anion and observed a positive allosteric effect on ion-pair recognition.[8e]

It thus appeared to us that although the problem of ion-pair recognition is well documented,[16,17] to the best of our knowledge, no systematic studies have been reported so far to evaluate the relative efficiency of receptors designed according to different approaches. This precludes a clear and direct understanding of the role played by the different parameters that affect ion-pair recognition. A possible approach could derive from the use of simpler heteroditopic receptors bearing binding sites able to interact cooperatively with both the cation and the anion without the requirement of appreciable rearrangement of the binding sites upon ion-pair recognition.[8e,9,10a,16,17]

In this paper we report a comparative study on the complexation properties of tetramethylammonium salts by easily accessible receptors derived from the rigid calix[4]arene platform and bearing auxiliary hydrogen bond donor binding sites at the upper rim.

Results and Discussion

Design and Synthesis of Hosts. The design of receptors was based on the analysis of molecular models, obtained by preliminary molecular modeling studies,[18] which showed that the introduction of a methylenephenylureido moiety or four arylsulfonamido moieties on the upper rim of the rigidified calix[4]arene-bis(crown-3) **1** would result in receptors having the appropriate sterical and arrangement of binding sites to interact with the tetramethylammonium ion-pair guests.

A convenient spatial arrangement of binding sites is offered by receptor **2** where the hydrogen bond donor methylenephenylureido sidearm anchored onto the upper rim of the rigid calix[4]arene-bis(crown-3) (**1**) could interact with the anion cooperatively with the rigid calixarene cavity. A complementary combination of binding sites is represented by **5**, which bears four arylsulfonamido groups. These binding sites could participate to the recognition process both as hydrogen bond donor groups and, by reorientation, favoring the intermolecular contacts with the cation. The recognition of tetramethylammonium salts should thus occur as a tight ion pair with **2** and as a looser, probably ligand-separated, ion pair with the cation embedded into the aromatic cavity and the anion hydrogen bonded at the exterior of the calixarene cavity with **5**.

Host **2**, which was previously synthesized and utilized for the recognition of amides,[19] can be easily obtained from the calix[4]arene-bis(crown-3) **1**[8a] by a Tscherniac–Einhorn amidomethylation reaction[20] using *N*-hydroxymethyl-*N*′-phenylurea[21,22] in a trifluoroacetic acid–dichloromethane mixture. To establish the role of the ureido NH, compound **3**, where two methyl groups block

(10) (a) Chrisstoffels, L. A. J.; de Jong, F.; Reinhoudt, D. N.; Sivelli, S.; Gazzola, L.; Casnati, A.; Ungaro, R. *J. Am. Chem. Soc.* **1999**, *121*, 10142−10151. (b) Murad, M. M.; Hayashita, T.; Shigemori, K.; Nishizawa, S.; Teramae, N. *Anal. Sci.* **1999**, *15*, 1185−1189. (c) Kavallieratos, K.; Sachleben, R. A.; Van Berkel, G. J.; Moyer, B. A. *Chem. Commun.* **2000**, 187−188. (d) Kavallieratos, K.; Danby, A.; Van Berkel, G. J.; Kelly, M. A.; Sachleben, R. A.; Moyer, B. A.; Bowman-James, K. *Anal. Chem.* **2000**, *72*, 5258−5264. (e) Kavallieratos, K.; Moyer, B. A. *Chem. Commun.* **2001**, 1620−1621. (f) Levitskaia, T. G.; Moyer, B. A.; Peter, V. B.; Marchand, A. P.; Krishnudu, K.; Chen, Z.; Huang, Z.; Kruger, H. G.; McKim, A. S. *J. Am. Chem. Soc.* **2001**, *123*, 12099−12100.

(11) Kubik, S. *J. Am. Chem. Soc.* **1999**, *121*, 5846−5855.

(12) Jeong, K.-S.; Hahn, K.-M.; Cho, Y. L. *Tetrahedron Lett.* **1998**, *39*, 3779−3782.

(13) For comprehensive reviews on calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745. (b) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (c) *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000.

(14) Arduini, A.; Pochini, A.; Secchi, A. *Eur. J. Org. Chem.* **2000**, 2325−2334.

(15) For a recent paper about complexation of quats by rigid calix[4]arene derivatives, see: Orda-Zgadzaj, M.; Wendel, V.; Fehlinger, M.; Ziemer, B.; Abraham, W. *Eur. J. Org. Chem.* **2001**, 1549−1561.

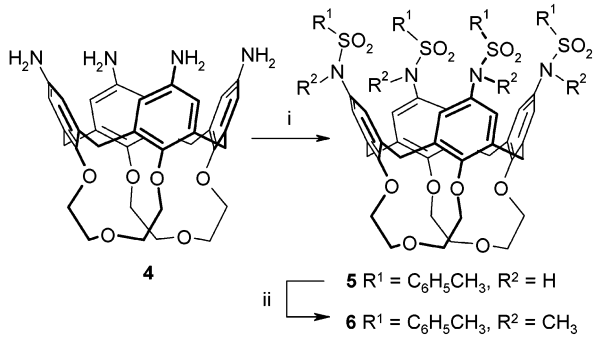
(16) Reviews that discuss heteroditopic ion-pair receptors: (a) Reetz, M. T. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Eds.; Pergamon: Oxford, 1996; Vol. 2, 553−562. (b) Stibor, I.; Hafeed, D. S. M.; Lhôtak, P.; Hodacova, J.; Koca, J.; Cajan, M. *Gazz. Chim. Ital.* **1997**, *127*, 673−685. (c) Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443−448. (d) Kimura, E.; Koike, T. *Chem. Commun.* **1998**, 1495−1500. (e) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486-516.

(17) Recent examples of salt-binding receptors: (a) Scheerder, J.; van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1090−1093. (b) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307−1311. (c) Redman, J. E.; Beer, P. D.; Dent, S. W.; Drew, M. G. B. *Chem. Commun.* **1998**, 231−232. (d) Beer, P. D.; Dent, S. W. *Chem. Commun.* **1998**, 825−826. (e) Beer, P. D.; Hopkins, P. K.; McKinney, J. D. *Chem. Commun.* **1999**, 1253−1254. (f) White, D. J.; Laing, N.; Miller, H.; Parsons, S.; Coles, S.; Tasker, P. A. *Chem. Commun.* **1999**, 2077−2078. (g) Kubik, S.; Goddard, R. *J. Org. Chem.* **1999**, *64*, 9475−9486. (h) Teramae, N.; Shigemori, K.; Nishizawa, S. *Chem. Lett.* **1999**, 1185−1186. (i) Tozawa, T.; Misawa, Y.; Tokita, S.; Kubo, Y. *Tetrahedron Lett.* **2000**, *41*, 5219−5223. (j) Cooper, J. B.; Drew, M. G. B.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2000**, 2721−2728. (k) Deetz, M. J.; Shang, M.; Smith, B. D. *J. Am. Chem. Soc.* **2000**, *122*, 6201−6207. (l) Shi, X.; Fettinger, J. C.; Davis, J. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2827−2831. (m) Tuntulani, T.; Poompradub, S.; Thavornyutikarn, P.; Jaiboon, N.; Ruangpornvisuti, V.; Chaichit, N.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2001**, *42*, 5541−5544. (n) Nabeshima T.; Hanami, T.; Akine, S.; Saiki, T. *Chem. Lett.* **2001**, 560−561. (o) Mahoney, J. M.; Beatty, A. M.; Smith, B. D. *J. Am. Chem. Soc.* **2001**, *123*, 5847−5848. (p) Cooper, J. B.; Drew M. G. B.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2001**, 392−401. (q) Uppadine, L. H.; Redman, J. E.; Dent, S. W.; Drew, M. G. B.; Beer, P. D. *Inorg. Chem.* **2001**, *40*, 2860−2869.

(18) Theoretical calculations (in vacuo) based on molecular mechanics (MM+ force field) and semiempirical methods (AM1) have been carried out to optimize the geometry of the complexes formed by hosts **2** and **5** with tetramethylammonium salts (see Supporting Information).

(19) Arduini, A.; Pochini, A.; Secchi, A. *J. Org. Chem.* **2000**, *65*, 9085−9091.

SCHEME 1[a]



[a] Reagents and conditions: (i) TsCl, Et_3N, CH_2Cl_2; (ii) NaH, CH_3I, DMF.

the sidearm hydrogen bonding donor ability toward anions, was synthesized by reaction of **2** with iodomethane.

Receptor **5** was synthesized by reaction of tetraaminocalix[4]arene-biscrown-3 (**4**)[23] with tosyl chloride (see Scheme 1) in 75% yield. In DMSO-d_6, receptor **5** shows the typical ^{1}H NMR spectrum of an upper rim tetrafunctionalized biscrown-3-calix[4]arene blocked in the cone conformation in which the four axial and four equatorial methylene protons resonate as four distinct doublets at δ = 4.77, 4.22, 2.93, and 2.84 ppm, respectively (see Experimental Section).

The twelve methyl protons of the 4-methylphenylsulfonyl units resonate at δ = 2.37 ppm, while the four NH protons resonate as a singlet at δ = 9.67 ppm. The ^{1}H NMR of **5** is solvent dependent, and in less polar solvents such as $CDCl_3$ and 8:2 $CDCl_3/CD_3CN$, the four NH protons resonate at higher fields and their chemical shift is dependent on solution concentration.

To disclose the role of the four NH groups in tetramethylammonium salt binding, the tetramethylated derivative **6** was synthesized in 48% yield by reaction of **5** with CH_3I in DMF using NaH as a base (see Scheme 1).

Binding Studies and Discussion

The binding ability toward a series of tetramethylammonium (Me_4N) salts having different counterions (chloride (Cl), tosylate (TsO), acetate (Ac), trifluoroacetate (TFA), picrate (Pic)) was evaluated by ^{1}H NMR spectroscopic titrations[24] in $CDCl_3$ for hosts **2** and **3**, and in 8:2 $CDCl_3/CD_3CN$ for hosts **5** and **6**. To evaluate the role of the anion in the recognition process, the titrations of Me_4NCl were also performed in the presence of the tri-*n*-butylthioureido derivative of tren (**7**), synthesized by Jeong and co-workers, which forms a stable complex with chloride anion.[12,25]

All NMR spectra showed time-averaged signals for the free and complexed species; hence, the association constants (K_{as}) were determined using methods previously described,[8a] a 1:1 stoichiometry having been verified through "continuous variation" methods, by adding increasing amounts of the appropriate host solution (concn = 0.01 M) to a solution of the guest (concn = 0.001 M) and monitoring the upfield shift of the NCH_3 signal (see Figure 2). The results obtained are reported in Table 1.

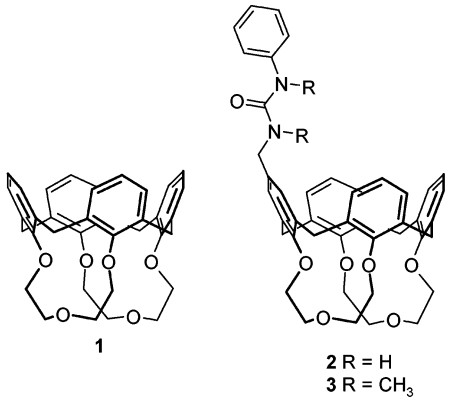


FIGURE 1. Monotopic (**1**) and heteroditopic (**2** and **3**) calix[4]arene hosts.

The model monotopic calix[4]arene-bis(crown-3) **1** was chosen as a reference host for this study, and its binding properties toward tetramethylammonium salts were studied previously in $CDCl_3$; however, data taken from the literature[8a,e] have also been inserted in Table 1 for comparison.

From the data reported in Table 1, it emerges that the monotopic host **1**, which possesses a rigid cone structure, because of the absence of additional binding sites, recognizes the Me_4N cation as a tight ion pair, thus experiencing a lower binding ability with the highly interacting anions. This is reflected by the values of the K_{as} measured for the different salts, which increases when the anion is less interactive (Hofmeister trend)[7] and follows the order Cl ⊂ **7** > TFA ≅ Pic > Ac > Cl > TsO. On the contrary, the efficiency order experienced by host **5** is TsO > Pic > Cl > Ac > TFA > Cl ⊂ **7** that, excluding the picrate anion, evidences an opposite role of the counteranion on the recognition processes (anti-Hofmeister trend).[7]

More complex is the order observed with host **2** in $CDCl_3$: Pic ≅ TFA > Cl > Cl ⊂ **7** ≅ Ac > TsO. In particular, excluding tosylate anion, generally strong binding with no discernible trend is observed with all the anions tested.

The complexation of chloride by ligand **7** causes different effects on Me_4N^+ binding by the calixarene hosts **1**, **2**, and **5**. In particular, with **1**, the loosening of the $Me_4N^+Cl^-$ ion pair results in an increase in K_{as} from 80 to 428 M^{-1}; with host **5**, K_{as} strongly decreases from 180

(20) (a) Zaugg, H. E.; Martin, W. B. In *Organic Reactions*; Cope, A. C., Ed.; Wiley: New York, 1965; Vol. 14, pp 52−269. (b) Zaugg, H. E. *Synthesis* **1970**, 49−73. (c) Zaugg, H. E. *Synthesis* **1984**, 85−110.

(21) Zigeneur, G.; Voglar, K.; Pitter, R. *Montash. Chem.* **1954**, *85*, 1196−1207.

(22) For the synthesis of calix[4]arene derivatives using the Tschernіac−Einhorn amidomethylation reaction, see: van Bommel, K. J. C.; Westerhof, F.; Verboom, W.; Reinhoudt, D. N.; Hulst, R. *J. Prakt. Chem.* **1999**, *341*, 284−290.

(23) (a) Arduini, A.; Mirone, L.; Paganuzzi, D.; Pinalli, A.; Pochini, A.; Secchi, A.; Ungaro, R. *Tetrahedron* **1996**, *52*, 6011−6018. (b) Arduini, A.; Böhmer, V.; Delmau, L.; Desreux, J.-F.; Dozol, J.-F.; Carrera, M. A. G.; Lambert, B.; Musigmann, C.; Pochini, A.; Shivanyuk, A.; Ugozzoli, F. *Chem. Eur. J.* **2000**, 2135−2144.

(24) For a recent review on determination of association constants using NMR data, see: Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170 and references therein.

(25) Werner, F.; Schneider, H.-J. *Helv. Chim. Acta* **2000**, *83*, 465−478.

TABLE 1. Association Constants K_{as} (M^{-1}) of 1:1 Complexes of Tetramethylammonium Salts Me_4N^+ X^- with Hosts 1 and 2 in $CDCl_3$ and with Host 5 in a $CDCl_3/CD_3CN$ Mixture[a]

host/X^-	TsO	Cl	Ac	Pic	TFA	Cl ⊂ **7**
1	33(10)[b]	80(25)[b]	247(30)[b]	328(14)[c]	362(75)[c]	428(88)[c]
2	700(200)	8800(800)	5000(1000)	d	13 000(4000)	3800(600)
5	570(120)	180(12)	120(10)	250(10)	70(12)	27(7)

[a] Measured at $T = 300$ K by ^1H NMR titration; all values are the result of at least duplicate experiments, and standard deviations are in brackets. [b] See ref 8a. [c] See ref 8e. [d] No good fitting of the experimental data points has been obtained for any titration experiments performed due to the extensive guest complexation observed even using highly diluted guest and host solutions ($<10^{-4}$ M). An association constant of ca. 20 000 M^{-1} has been estimated, but for this value range, as reported by other authors,[24] the accuracy of the determination is very poor.

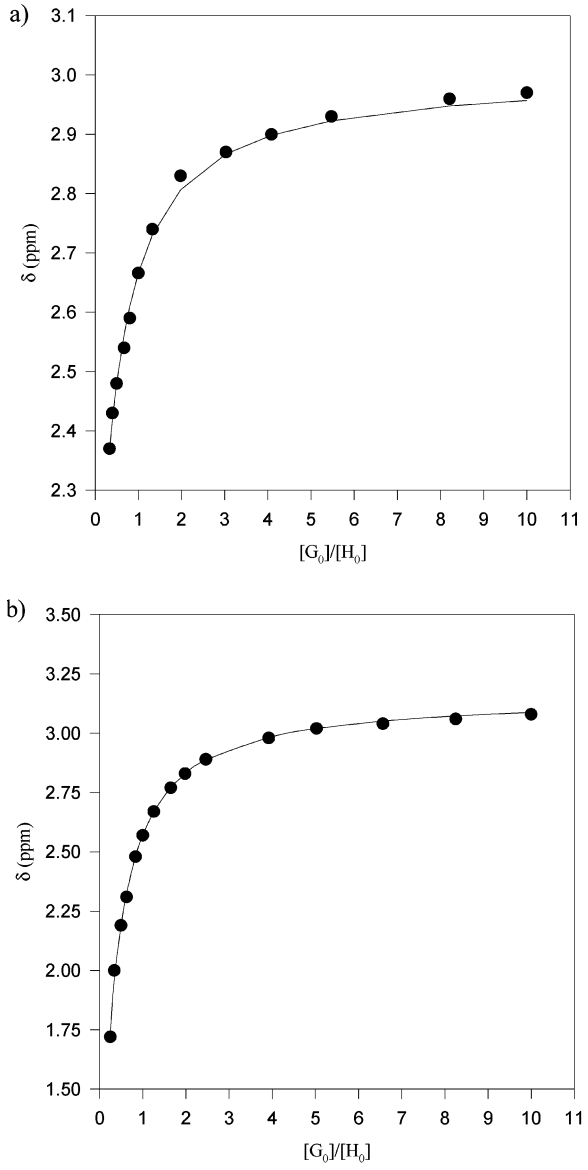


FIGURE 2. Representative isotherms of binding for host **5** with (a) tetramethylammonium tosylate ($K_{as} = 600 \pm 110$ M^{-1}) and with (b) tetramethylammonium picrate ($K_{as} = 270 \pm 20$ M^{-1}) in 8:2 $CDCl_3/CD_3CN$ ($T = 300$ K; initial concentration $[G_0] = 1.0 \times 10^{-3}$ M, $[\mathbf{5}_0] = 1.0 \times 10^{-2}$ M). The association constants were determined by monitoring the upfield shift of the NCH_3 signal.

to 27 M^{-1}; and with receptor **2**, a less extensive variation is observed.

Further insight into the determining role of the anion hydrogen bonding in these recognition processes was

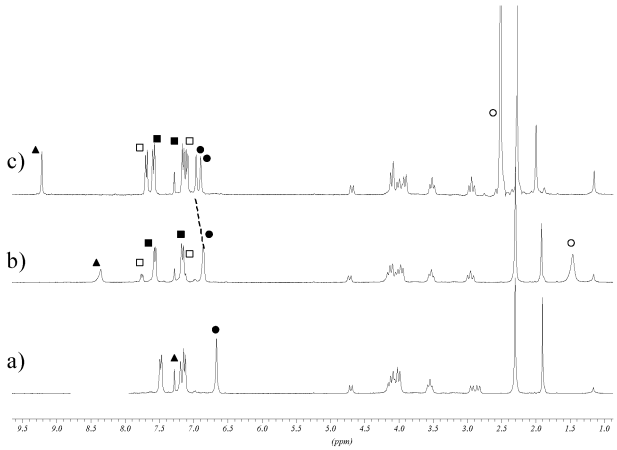


FIGURE 3. ^1H NMR spectra in 8:2 $CDCl_3/CD_3CN$ (300 MHz, 300 K): (a) free host **5**, (b) 1:1.2 complex **5** ⊃ Me_4N^+ TsO^-, and (c) 1:4 complex **5** ⊃ Me_4N^+ TsO^-. The calixarene aromatic skeleton signals are designated as ● and those belonging to arylsulfonamide groups as ▲ (NH) and ■ (Ar). The guest signals are indicated as ○ (N*Me*) and □ (Ts).

obtained with receptors **3** and **6**, in which hydrogen bonding interaction with the anion cannot take place, because of the lack of hydrogen bond donor groups, and only the cavity of the calixarene could participate in Me_4N^+ binding. Hosts **3** and **6** do not show, probably for steric reasons,[6a,15] any detectable binding ability toward the set of tetramethylammonium salts employed for hosts **2** and **5**, thus indicating that the hydrogen bond interaction of the anion with the NH groups pivots the whole recognition process.[11,12]

From the NMR study of the complexes formed by **2** and **5** with the different tetramethylammonium salts, useful information on the binding mode can be obtained. The common features of the NMR spectra of both hosts is that, in all instances, the protons of tetramethylammonium cation are shifted significantly upfield as consequence of its inclusion into the host aromatic cavity, while the NH protons of the additional binding sites experience a large downfield shift, indicating their involvement in hydrogen bonding with the anion. However, in the case of the complex of **5** with Me_4N^+ TsO^- (1:4 host−guest ratio), for example, besides a large downfield shift of NH signals, the splitting of the aromatic protons of the calix was observed (see Figure 3c). This suggests that the cation is embedded into the aromatic cavity and the anion interacts, outside of the molecular cage, with the NH groups.

Further support for the embedding of the tetramethylammonium cation into the cavity of receptors **2** and **5** was obtained through 2D ROESY experiments that, in

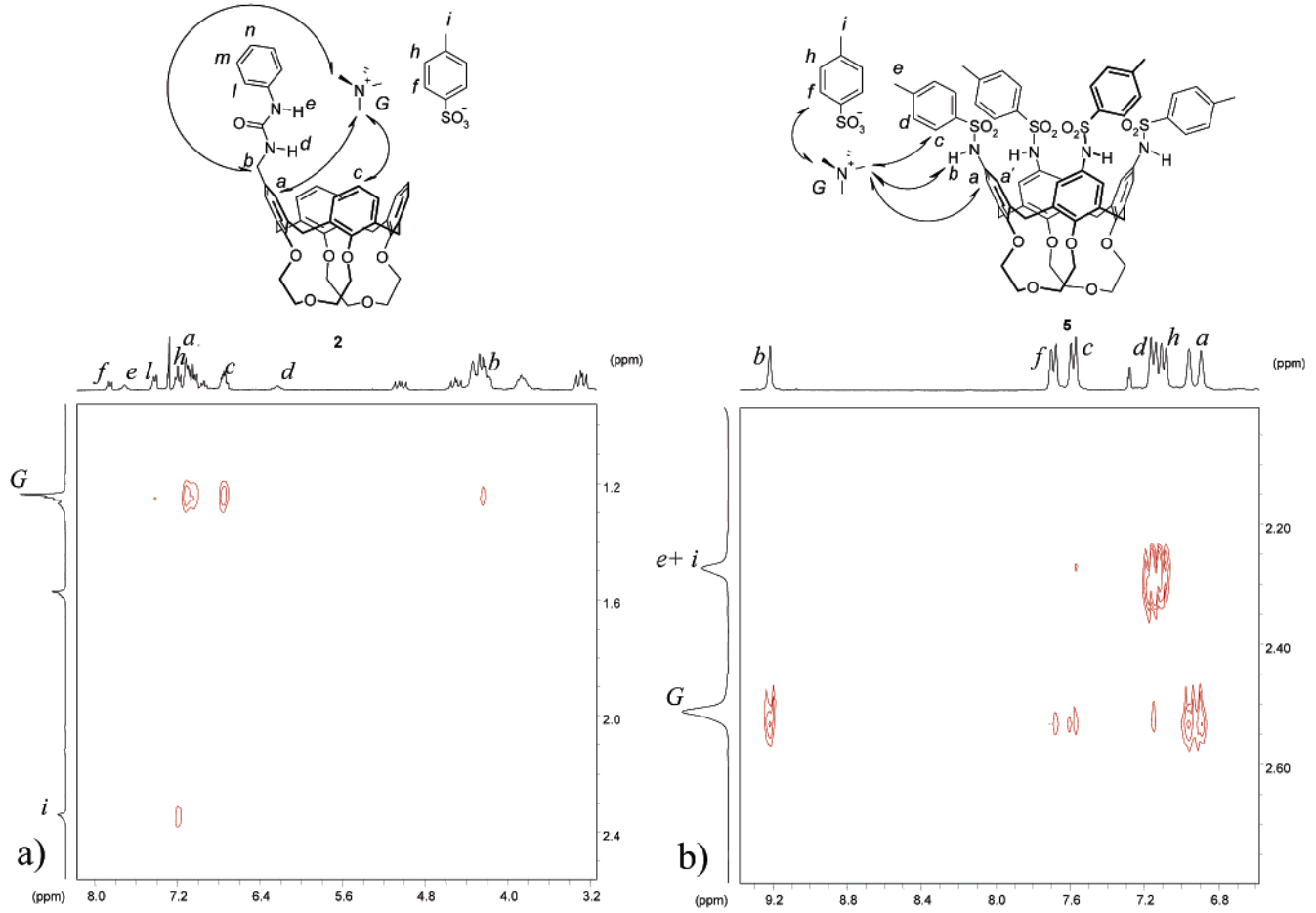


FIGURE 4. Partial 2D ^{1}H NMR ROESY spectra showing NOE intermolecular cross-peaks of (a) 1:4 complex **5** ⊃ Me_4N^+ TsO^- in 8:2 $CDCl_3/CD_3CN$ (300 MHz, 300 K) and (b) 1:0.5 complex **2** ⊃ Me_4N^+ TsO^- in $CDCl_3$ (300 MHz, 300 K).

the case of the tosylate (see Figure 4a) and acetate salts with **2**, showed intermolecular NOEs between the aromatic protons of the calixarene (*a* and *c*) and of the sidearm (*b* and *l*) with the methyl protons (*G*) of the Me_4N^+ cation. Similar results were obtained with the complex formed by Me_4N^+ TsO^- with **5** (see Figure 4b) where intermolecular NOEs between the aromatic protons belonging to the calixarene (*a*) and to the toluensulfonamido sidearm (*b* and *c*) of the host and the methyl protons of the Me_4N^+ (*G*) were observed.

These data, together with the chemical shift variations observed in the 1D spectra (see Figure 3), are in agreement with a situation in which the tetramethylammonium cation is inside the cavity created by the calixarene and the aromatic rings of the sulfonamido groups. From these experiments, however, no indications on the relative position of the counteranion could be deduced, and suitable crystals for X-ray analysis could not be obtained. Nevertheless, by looking at the chemical shift variation of the protons of the tosylate anion upon Me_4N^+ TsO^- complexation with the different receptors **1**, **2**, and **5**, further information on the structure of the ion-pairs can be obtained[8a] (see Table 2).

In fact, the observation that the complexation-induced shift follows the order **5** > **2** > **1** for the 1:1 complexes formed by these hosts with Me_4N^+ TsO^- is consistent with the assumption that, while **1** recognizes the guest as a tight ion pair, **2** binds the cation and the anion as a loose ion pair, and in **5** the two guest components are recognized as a looser, probably ligand-separated, ion pair.[26]

TABLE 2. CIS (Δδ, ppm)[a] of Proton Tosylate Anions Measured during the Titration with Hosts 1, 2, and 5

Host	Δδ (Ar*H-f*)	Δδ (Ar*H-h*)
1	-0.005	0.002
2	0.04	0.02
5	0.08	0.06

[a] Positive and negative signs reflect up- and downfield shifts, respectively.

A tentative explanation for the anion effect on the hosts **2** and **5** could derive from the hypothesis that for heteroditopic receptors, the interaction energy with the ion pair is governed by two main factors: the binding energy of the cation with the complementary binding site of the host and that of the anion with the acid centers of the host.[27] It is therefore reasonable to assume that, in general, any factor that increases the interacting capacity of a given ion with its complementary binding site produces a positive cooperative effect on the binding of its counterion.

(26) Similar chemical shift variation (ca. 0.08 ppm) of the aromatic tosylate protons was observed by us in a ligand-separated ion pair (see ref 8a).

When the cation is maintained constant as in the present study, anion variation produces opposite effects on the energy of these interactions. In fact, the binding of the cation with the calixarene cavity increases when the interacting power of the anion is low (Hofmeister trend).[8e] On the contrary, the interaction energy of the anion with the acid centers increases with the interacting power of the anion (anti-Hofmeister trend).[28]

On the basis of this hypothesis, the anti-Hofmeister trend observed with host **5** could be rationalized considering the formation of a ligand-separated ion pair where the interactions between the anion and cation are leveled and strongly decreased, while the strong hydrogen bond interaction of the anion with the NH groups of the sidearms becomes the determining factor. On the contrary, with host **2**, which binds ion pairs, these two factors operate to the same extent and both determine the binding process; consequently, a leveled and more complex trend is observed.

These considerations could explain also some data reported in the literature, although no systematic studies on the effects of anions in the complexing properties of ion pairs with heteroditopic hosts have been reported so far in the literature. Nevertheless, there are some studies where, by using receptors able to recognize salts as ligand-separated ion pairs, an anti-Hofmeister trend for the anions was observed.[29] Unfortunately, very few examples of hosts working as heteroditopic receptors of ion pairs, containing only very few examples of anion variations, are reported in the literature.[30]

Also in the field of "dual host" recognition, using a 1,3-alternate-crown-6-calix[4]arene and a disulfonamide as an anion ligand, a synergism following an anti-Hofmeister order is reported.[10e] This trend could be explained with the presence of a ligand-separated ion pair.

Conclusion

The present study shows that, in apolar media, the efficiency of synthetic heteroditopic receptors toward tetramethylammonium salt binding is strongly dependent on the nature of the anion. Comparison of this heteroditopic approach with others like extension of the aromatic cavity,[14] the dual host approach,[8e] and use of preorganizable binding sites[8e] shows that this is the most efficient one.

On this basis, the possibility of obtaining very high efficiency with very simple and easily synthesizable hosts, using the cooperative effects of simple hydrogen bonds, is a very promising tool for the recognition of ion pairs and its applications[31] and can be seen as complementary to the other possible approaches, which for example could solve the problem of the separation of specific ion pairs.[10f]

Experimental Section

All reactions were carried out under nitrogen; all solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use. All other reagents were of reagent-grade quality as obtained from commercial suppliers and used without further purification. NMR spectra (300 MHz) were recorded in $CDCl_3$ unless otherwise indicated. Mass spectra were determined in the CI mode (CH_4). Melting points are uncorrected. Compounds **1**,[8a] **2**,[19] **4**,[23] and **7**[12] were synthesized according to literature procedures.

5-[*N*,*N*-Methyl-phenyl-*N*′-methyl(ureido)]methyl-24,25,26,27-biscrown-3-calix[4]arene (3). To a solution of **2** (0.2 mmol, 0.14 g) in THF (10 mL) was added NaH (0.79 mmol, 0.02 g). The resulting heterogeneous mixture was refluxed for 30 min, and then CH_3I (2.0 mmol, 0.28 g) was added. After stirring overnight, the reaction mixture was cooled at room temperature and the reaction quenched by adding a small portion of methanol (CAUTION). The solvent was evaporated to dryness under vacuum and the solid residue taken up with water and with CH_2Cl_2. The separated organic phase was washed twice with brine, dried (Na_2SO_4), and then completely evaporated under vacuum. Purification of the solid residue by chromatography plates (eluent = 40:60 hexane/ethyl acetate) afforded 0.095 g of pure **3** (65%); mp = 108−110 °C. ^{1}H NMR (300 MHz) δ: 2.42 (s, 3H), 3.05 (s, 3H), 3.0−3.3 (m, 4H), 3.8−4.0 (m, 4H), 4.10 (s, 2H), 4.2−4.4 (m, 12H), 4.50 and 4.54 (2d, 2H, $J^1 = J^2 = 11.7$ Hz), 5.06 and 5.09 (2d, 2H, $J^1 = J^2 = 11.7$ Hz), 6.60 (bt, 1H), 6.7−6.8 (m, 9H), 7.0−7.1 (m, 6H). ^{13}C NMR (75 MHz) δ: 29.7, 29.8, 30.7, 36.3, 39.5, 53.3, 74.5, 74.6, 74.7, 76.2, 76.3, 123.5, 123.6, 123.7, 124.2, 127.2, 128.0, 128.1, 128.2, 128.9, 129.1, 132.2, 135.2, 135.3, 135.4, 135.6, 146.2, 154.2, 155.1, 155.2, 161.8. CI(+) MS *m*/*e*: 741 [MH^+]. Anal. Calcd for $C_{46}H_{48}N_2O_7$: C, 74.57; H, 6.53; N, 3.78. Found: C, 74.10; H, 6.39; N, 3.72.

5,11,17,23-Tetrakis-[(4-methylbenzensulfonamide)]-24,25,26,27-biscrown-3-calix[4]arene (5). A mixture of tetraaminocalix[4]arene (**4**) (0.96 mmol, 0.6 g) and triethylamine (4.8 mmol, 0.49 g) in CH_2Cl_2 (15 mL) was stirred in a 100 mL three-necked round-bottomed flask equipped with a nitrogen inlet and cooled at $T = 0$ °C in an ice bath. After the addition of *p*-toluenesulfonil chloride (4.3 mmol, 0.8 g), the resulting mixture was stirred for 1 h at room temperature, quenched with H_2O, and extracted twice with methylene chloride. The separated organic layer was washed twice with brine and dried (Na_2SO_4), and the solvent was completely evaporated under vacuum to give a pale yellow solid. Purification of the residue by column chromatography (eluent = 80:20 methylene chloride/acetone) afforded 0.9 g of pure **5** (75%); mp = 175−178 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.37 (s, 12H), 2.84 (d, 2H, $J = 12$ Hz), 2.93 (d, 2H, $J = 12$ Hz), 3.4−3.5 (m, 4H), 4.0−4.2 (m, 12 H), 4.22 (d, 2H, $J = 12$ Hz), 4.77 (d, 2H, $J = 12$ Hz), 6.67 (s, 8H), 7.36 (d, 4H, $J = 8.1$ Hz), 7.61 (d, 4H, $J = 8.1$ Hz), 9.67 (s, var. 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.5, 29.4, 30.1, 75.0, 76.3, 122.3, 123.4, 127.9, 129.0, 131.9, 135.3, 135.6, 143.2, 152.8. CI(+) MS *m*/*e*: 1241 [MH^+]. Anal. Calcd for $C_{64}H_{64}N_4O_{14}S_4$: C, 61.92; H, 5.20; N, 4.51; S, 10.33. Found: C, 61.10; H, 5.30; N, 4.45; S, 10.20.

5,11,17,23-Tetrakis-[(4-methylbenzen-*N*-methyl-sulfonamide)]-24,25,26,27-biscrown-3-calix[4]arene (6). To a solution of **5** (0.7 mmol, 0.8 g) in dry DMF (50 mL) was added NaH (3.6 mmol, 0.08 g). The resulting heterogeneous mixture was heated at 80 °C for 1 h; after the mixture was cooled to room temperature, CH_3I (7.0 mmol, 1.0 g) was added. After the mixture was stirred at room temperature overnight, the reaction was quenched by adding a small portion of methanol (CAUTION). The solvent was completely removed under vacuum and the residue taken up with CH_2Cl_2 and water. The separated organic layer was then washed twice with a satu-

(27) Other factors can determine the binding energy: the stereoelectronic matching between the anion and the acid hydrogen atoms of the sidearm and the presence of steric hindrance or of specific interactions such as the $\pi-\pi$ aromatic ones. For the "picrate effect", see: Talanova, G. G.; Elkarim, N. S. A.; Talanov, V. S.; Hanes, R. E.; Hwang, H. S.; Bartsch, R. A.; Rogers, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 11281−11290.

(28) See, for example: Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675−1683 and ref 10e.

(29) See, for example, refs 17j, 17k, 17n, 17p.

(30) See, for example, refs 9, 17o, 17q.

(31) This approach, for example, afforded the first reported preparation, using calixarenes as wheel, of a very stable pseudorotaxane with paraquat ion pairs: Arduini, A.; Ferdani, R.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3453−3456.

rated solution of Na_2SO_3, dried (Na_2SO_4), and completely evaporated to dryness. Purification of the residue by crystallization from MeOH gave 0.43 g (48%) of **6**; mp = 270 dec. ^{1}H NMR (300 MHz) δ: 2.48 (s, 12H), 2.78 (s, 12H), 3.00 (d, 4H, J = 12.6 Hz), 3.8−3.9 (m, 4H), 4.1−4.2 (m, 8H), 4.33 (d, 4H, J = 10.5 Hz), 4.40 (d, 2H, J = 12.6 Hz), 5.01 (d, 2H, J = 12.3 Hz), 6.51 (d, 4H, J = 2.4 Hz), 6.58 (d, 4H, J = 2.4 Hz), 7.2−7.4 (m, 16H). ^{13}C (75 MHz) δ: 21.5, 29.8, 30.7, 37.8, 73.5, 75.9, 126.4, 126.7, 127.7, 129.4, 133.2, 134.9, 135.3, 136.5, 144.1, 153.4. CI(+) MS *m/e*: 1297 [MH^+]. Anal. Calcd for $C_{68}H_{72}N_4O_{14}S_4$: C, 62.94; H, 5.59; N, 4.32; S, 9.88. Found: C, 62.35; H, 5.40; N, 4.17; S, 9.48.

Acknowledgment. We thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) "Supramolecular Devices" project for financial support and C.I.M. (Centro Interdipartimentale di Misure "G. Casnati") of the University of Parma for NMR and mass measurements.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of new compounds **3**, **5**, and **6** and copies of 2D NMR ROESY of **2** ⊃ Me_4N^+ Ac^-, **2** ⊃ Me_4N^+ TsO^-, and **5** ⊃ Me_4N^+ TsO^- complexes and their graphical representations as deduced by molecular mechanics and semiempirical methods. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025655S