Host–Guest Chemistry

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A Calix[5]arene-Based Heterotetratopic Host for Molecular Recognition of Long-Chain, Ion-Paired α,ω-Alkanediyldiammonium Salts**

Domenico Garozzo, Giuseppe Gattuso, Anna Notti, Andrea Pappalardo, Sebastiano Pappalardo, Melchiorre F. Parisi,* Marta Perez, and Ilenia Pisagatti*

Ion-pair recognition, that is, the simultaneous complexation of cation and anion guest species by neutral hosts, is an emerging field of topical interest in supramolecular chemistry with great potential for biological, analytical, and environmental applications.[1] It is well known that the ion-binding process with neutral receptors is adversely affected by the ion-pairing of guest salts,[2] so that it is common practice to make use of salts with weakly coordinating counterions,[3] which result in enhanced host-guest associations. On the other hand, the ion-pairing interference can be circumvented either by using an appropriate combination of anion and cation receptors (binary host strategy)[4] or by designing specific heteroditopic receptors that take advantage of favorably positioned binding sites as well as induce positive cooperative and allosteric effects.[5] So far a plethora of heteroditopic receptors have been developed for inorganic ion pairs,[6] but much less has been reported for organic salts.[5c,7]

The molecular recognition of α,ω-alkanediyldiammonium salts has been actively investigated with different classes of artificial homo(poly)topic receptors. Among these, cylindrical macrotricyclic hosts,[8] cucurbiturils,[9] crown ether[10] and glycoluril derivatives,[11] bimetallic porphyrin dimers,[12] as well as *p-tert*-butylcalix[5]arenes[13] have been employed. However, none of the receptors used so far has been equipped with complementary counterion-binding sites.

[*] Prof. S. Pappalardo
Dipartimento di Scienze Chimiche
Università di Catania
Viale A. Doria 6, 95125 Catania (Italy)
Fax: (+39) 095-580-138
E-mail: spappalardo@dipchi.unict.it
Dr. G. Gattuso, Dr. A. Notti, Dr. A. Pappalardo, Prof. M. F. Parisi, Dr. I. Pisagatti
Dipartimento di Chimica Organica e Biologica
Università di Messina
Salita Sperone 31, 98166 Messina (Italy)
Fax: (+39) 090-393-895
E-mail: mparisi@unime.it
Dr. D. Garozzo, Dr. M. Perez
CNR, ICTP Catania
Viale Regina Margherita 6, 95125 Catania (Italy)

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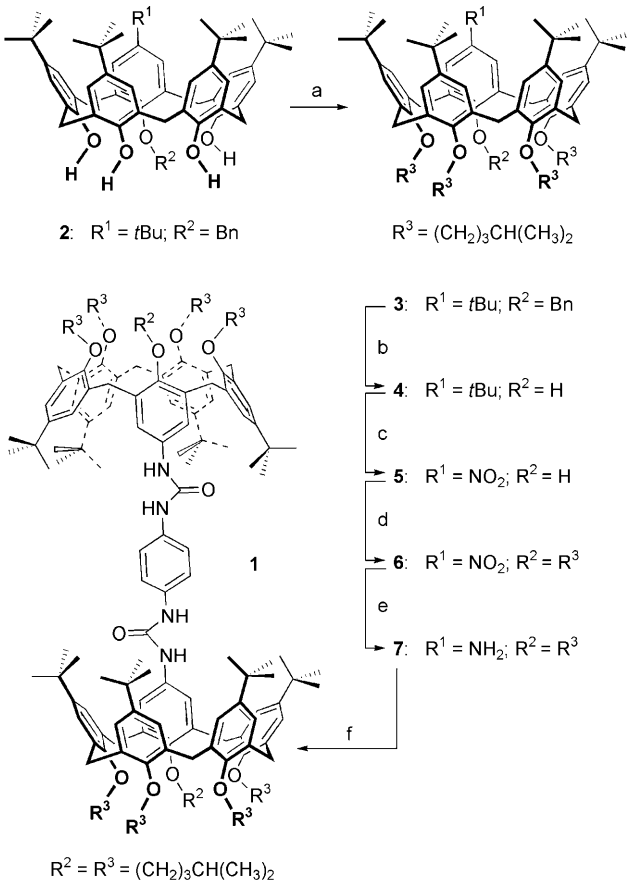
Following our specific interest in the development of neutral multisite receptors for biogenic (poly)ammonium salts,[14] we report herein the synthesis and unique molecular recognition abilities of the first heterotetratopic receptor, **1**, which consists of two convergent, conformationally fixed, cone calix[5]arene units (cation-binding sites) that are covalently linked at their upper rims by means of a 1,4-bis(ureido)phenylene spacer (anion-binding sites). Host **1** readily forms overall charge-neutral, unimolecular capsules (ligand-separated ion-pair complexes) of nanoscale dimensions by tight encapsulation[15] of linear α,ω-alkanediyldiammonium ions, which range from 1,12-dodecane- to 1,16-hexadecanediammonium, inside the inner space defined by the two converging calix[5]arene cavities by simultaneously binding each of the two counteranions to the peripheral ureido functions through hydrogen bonds.

The target biscalixarene **1** was synthesized in six steps from the known 31-benzyloxy-*p-tert*-butylcalix[5]arene (**2**)[16] according to the sequence illustrated in Scheme 1. The exhaustive *O*-alkylation of **2** with 4-methylpent-1-yl tosylate and K_2CO_3 in CH_3CN at reflux produced pentaether **3** in 77% yield which, upon Pd/C-catalyzed hydrogenolysis in EtOAc, gave monohydroxy intermediate **4** in 93% yield. The



Scheme 1. Synthesis of **1**: a) $TsO(CH_2)_3CH(CH_3)_2$, K_2CO_3, CH_3CN, reflux, 12 h, 77%; b) H_2, Pd/C, EtOAc, room temperature, 4 h, 93%; c) 68% HNO_3/AcOH, CH_2Cl_2, 0°C, 25 min, 77%; d) $TsO(CH_2)_3CH(CH_3)_2$, NaH, THF, reflux, 48 h, 70%; e) $SnCl_2 \cdot 2H_2O$, EtOAc/EtOH, reflux, 24 h, 68%; f) 1,4-C_6H_4-$(NCO)_2$, $CHCl_3$, room temperature, 6 h, 66%. Ts = *p*-toluenesulfonyl; Bn = benzyl.

subsequent selective *ipso*-nitration of **4** with 68% HNO_3 and acetic acid in CH_2Cl_2 afforded 5-nitro derivative **5** in 77% yield. Further *O*-alkylation of the residual hydroxy group with 4-methylpent-1-yl tosylate and NaH in dry THF furnished the 5-nitro pentaether **6** in 70% yield which was converted into 5-amino-calixarene **7** in 68% yield by reduction with $SnCl_2{\cdot}2H_2O$ in EtOH/EtOAc at reflux. Final coupling of two molecules of **7** with 1,4-phenylene diisocyanate in dry $CHCl_3$ led to biscalix[5]arene **1** in 66% yield.

The binding affinity of receptor **1** for linear, long-chain α,ω-alkanediyldiammonium ($\mathbf{C_8}$–$\mathbf{C_{16}}$) dichloride salts, as well as the host-guest architectures they form, were investigated by a combination of ^{1}H NMR spectroscopy and electrospray mass spectrometry (ESI-MS). The former method takes advantage of the large upfield shifts experienced by the methylene resonances of the guest upon encapsulation of the dication[4a,14] and the downfield shifts of the NH resonances of the host (in nonprotic media) which signal the simultaneous binding of the counteranions. ESI-MS exploits the remarkable tendency of the π-basic calix[5]arene cavity to include alkylammonium guests, thus providing ion labels for the detection of encapsulated complexes in the gas phase.[13,17,18]

H_3N^+—$(CH_2)_n$—$^+NH_3$

$\mathbf{C_8}$: n = 8
$\mathbf{C_{10}}$: n = 10
$\mathbf{C_{12}}$: n = 12
$\mathbf{C_{14}}$: n = 14
$\mathbf{C_{16}}$: n = 16

The affinity of **1** for α,ω-alkanediyldiammonium dichloride salts was initially investigated by ^{1}H NMR titration experiments in $(CDCl_2)_2/CD_3OD$ (2:1 *V*/*V*). Addition of the guest salt (up to 4 equivalents) to a solution of **1** (1.0×10^{-3} M) caused the formation of very strong inclusion complexes, whose host–guest stoichiometries (1:1 and/or 2:1) and geometries depend on the length of the diammonium ion and the [host]/[guest] ratio (see Figure 1). The ^{1}H NMR spectra of the inclusion complexes of calix[5]arenes with alkylammonium guest ions normally show distinct signals for the free and complexed host and guest species in slow exchange on the ^{1}H NMR timescale.[13,14,18] Here, signals corresponding to the free host and guests could barely be seen in the spectra of equimolar host–guest mixtures of **1** with the longer alkyldiammonium ($\mathbf{C_{12}}$–$\mathbf{C_{16}}$) dichloride salts, which suggests very high association constants ($K_a > 10^6\,M^{-1}$) for the formation of the capsular (C-shaped) 1:1 host–guest complexes with C_s symmetry. Similar results were observed using other solvent systems (including neat $(CDCl_2)_2$, $CDCl_3$, and CD_2Cl_2, or mixtures thereof with up to 50% content of CD_3OD), or on changing—in the case of $\mathbf{C_{12}}$—the nature of the counteranion (diacetate, dibromide, and dipicrate salts). Notably, the spectra did not change upon further addition of salt or on tenfold dilution of the solution.

In contrast, titration experiments of **1** with the shorter alkyldiammonium ($\mathbf{C_8}$ and $\mathbf{C_{10}}$) dichloride guest salts gave rise to changes in the ^{1}H NMR spectra that are consistent with the initial formation of the S-shaped (for $\mathbf{C_8}$) or C-shaped (for $\mathbf{C_{10}}$) 1:1 host–guest complexes for equimolar host–guest solutions and which eventually evolved toward the formation of the S-shaped 1:2 host–guest complexes (C_{2h} symmetry) after further addition of salt (Figure 1). This is clearly shown by the evolution of the ^{1}H NMR spectra in the titration experiment of **1** with $\mathbf{C_{10}}{\cdot}2\,Cl^-$ (Figure 2). Addition of one

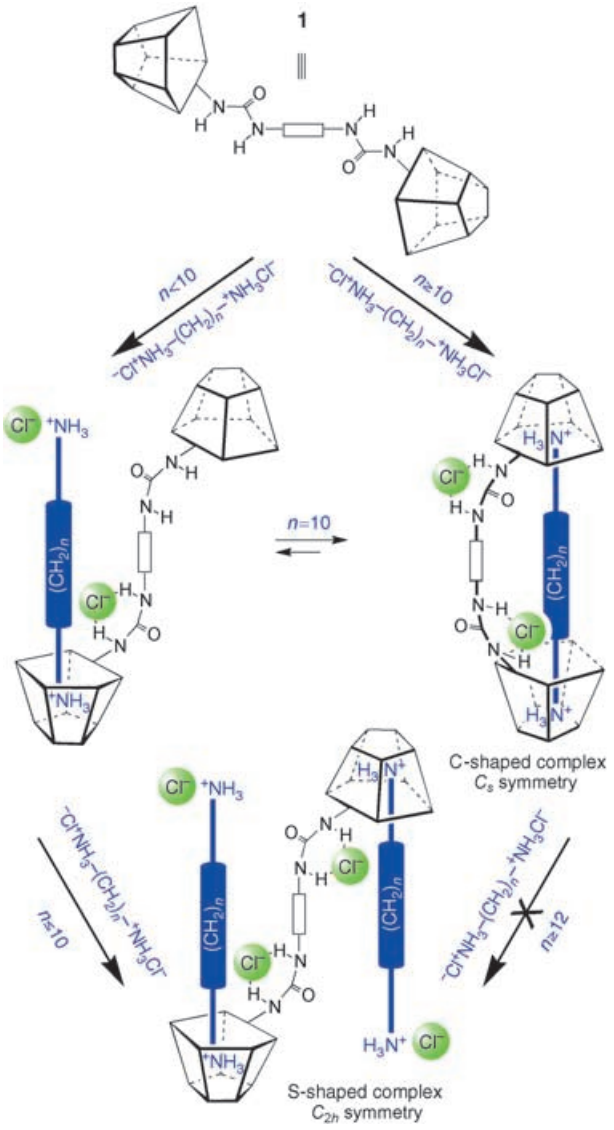


Figure 1. Schematic representation of the influence of the spanning of the guest α,ω-alkanediyldiammonium ions on the complexation pathways leading to C-shaped and/or S-shaped inclusion complexes with host **1**.

equivalent of salt caused the almost exclusive formation of the C-shaped 1:1 complex, as revealed by the presence of a set of five upfield methylene resonances for the included dication (Figure 2b).[19] Upon further addition of salt, a second more-spread set of signals for the included guest became evident in the highfield region of the spectra ($\delta = -1.9$ to 0.7 ppm) as a result of the incipient formation of the S-shaped 1:2 host–guest complex (Figure 2c and d). This conclusion is validated by the triplet detected at $\delta = 2.55$ ppm which is assigned to the α′-CH_2 protons of the guest and is judged of diagnostic value for the S-shaped complexes.[18] The latter architecture was the only host–guest species present in solution when a total of four equivalents of $\mathbf{C_{10}}{\cdot}2\,Cl^-$ had been added to **1** (Figure 2e).

The use of nonprotic solvents revealed the beneficial effect of the ureido functions of **1** which facilitate the loosening of the ion-paired salt and the association of the

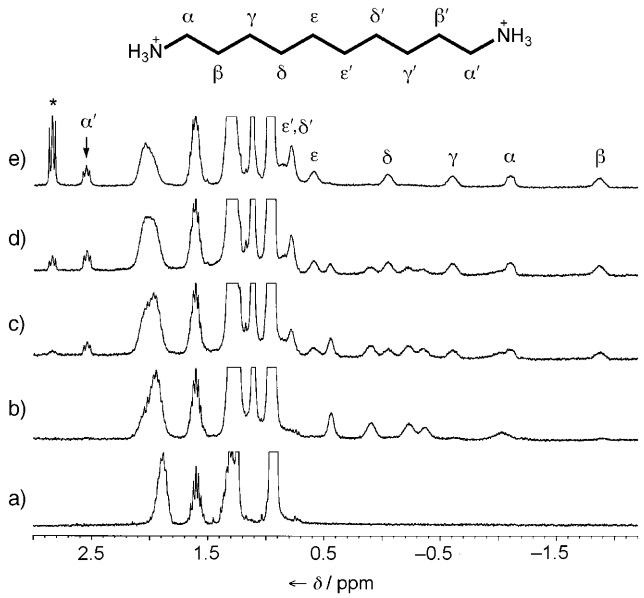


Figure 2. Highfield regions of the ^{1}H NMR spectra (300 MHz; 22 ± 1 °C; 2:1 $(CDCl_2)_2/CD_3OD$) recorded during the titration experiment of **1** (1.0×10^{-3} M) with $\mathbf{C_{10}}\cdot2Cl^-$: a) **1**; b) $\mathbf{1}/\mathbf{C_{10}}\cdot2Cl^-$ (1:1); c) $\mathbf{1}/\mathbf{C_{10}}\cdot2Cl^-$ (1:1.5); d) $\mathbf{1}/\mathbf{C_{10}}\cdot2Cl^-$ (1:2); e) $\mathbf{1}/\mathbf{C_{10}}\cdot2Cl^-$ (1:4). The triplet labeled with an asterisk refers to the α- and α′-CH_2 of uncomplexed $\mathbf{C_{10}}\cdot2Cl^-$, which is present in excess.

anion by formation of six-membered chelate rings with halide or picrate anions and eight-membered chelate rings with carboxylate anions.[20]

The shifts of the N-H resonances of **1** upon ligand-separated ion-pair complexation of the various $\mathbf{C_{12}}$ salts in $(CDCl_2)_2$ provide a qualitative picture of the strength of the anion-binding site (Table 1). Entries 3–6 suggest an anti-Hofmeister[21] trend in the complexation of the counteranion by heterotetratopic **1**, with the largest $\Delta\delta$ values being observed for the more densely charged Cl^- and $CH_3CO_2^-$ anions (in $(CDCl_2)_2$: $CH_3CO_2^- \approx Cl^- > Br^- > Pic^-$). A comparison between entries 2 and 4 shows also that the encapsulation of the dication enhances the acidity of the urea NH groups through an electron-withdrawing effect to result in a better uptake of chloride anions (positive allosteric effect).[5]

Table 1: Variation of the chemical shift of urea NH resonances of **1** (300 MHz, 1.0×10^{-3} M in $(CDCl_2)_2$) after the addition of one equivalent of guest salt.

Entry	Guest	δ [ppm]		Δδ [ppm]	
		NH_a[a]	NH_b[a]	NH_a[a]	NH_b[a]
1	none	6.44	5.88		
2	nBu$_4$N$^+$Cl$^-$	7.21[b]	6.63[b]	0.77	0.75
3	$\mathbf{C_{12}}\cdot2CH_3CO_2^-$	8.91	8.60	2.47	2.72
4	$\mathbf{C_{12}}\cdot2Cl^-$	8.81	8.51	2.37	2.63
5	$\mathbf{C_{12}}\cdot2Br^-$	8.28	8.08	1.84	2.20
6	$\mathbf{C_{12}}\cdot2Pic^-$	7.40[c]		1.24	

[a] NH_a and NH_b refer to the two groups close to the calixarene unit and the 1,4-phenylene moiety, respectively. [b] Fast complexation equilibrium on the NMR timescale; data refer to the addition of two equivalents of salt. [c] Broad signal, partly buried under the aromatic protons of the calixarene units. Pic = picrate.

The slow exchange in the capsular complexes of **1** with diammonium salts allowed TROESY (transverse rotating-frame Overhauser effect spectroscopy) NMR spectroscopy to be carried out at room temperature, and the spectra obtained were fully consistent with the expected structure and symmetry of the complexes. Most importantly, the TROESY spectra (Figure 3b) showed clear intermolecular NOE cross

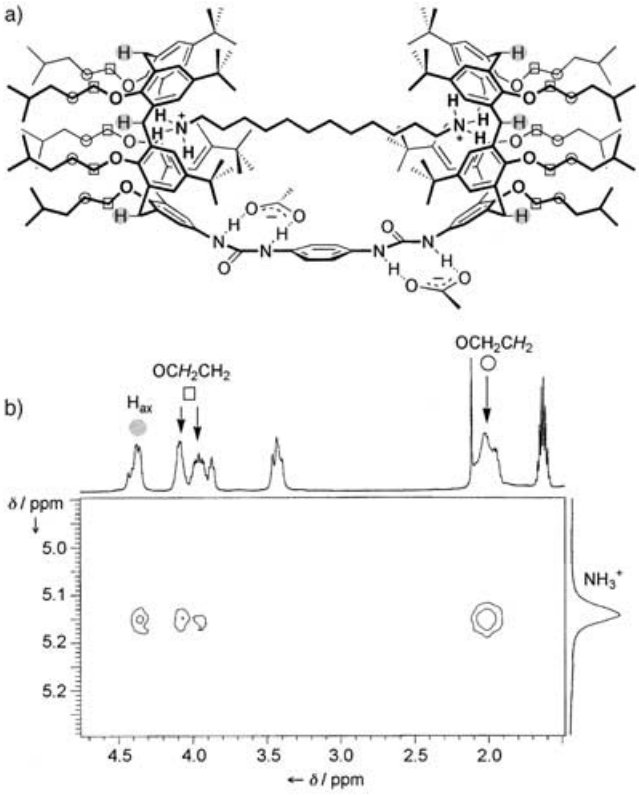


Figure 3. a) Structure of the C-shaped capsular $\mathbf{1}\cdot\mathbf{C_{12}}\cdot2CH_3CO_2^-$ complex with labeling of the relevant hydrogen atoms showing NOE interactions between the host and guest. b) Selected region of the TROESY NMR spectrum (500 MHz) of $\mathbf{1}\cdot\mathbf{C_{12}}\cdot2\ CH_3CO_2^-$ (5.0×10^{-3} M in $(CDCl_2)_2$). ax = axial.

peaks between the host and the guest. In particular, the NH_3^+ protons of the salt showed NOE peaks to the axial bridging methylene protons as well as to α- and β-oxymethylene protons of the lower rim substituents of the calix[5]arene moieties (Figure 3a), which provides evidence that the ammonium end group is held in position by hydrogen-bonding interactions with the ethereal oxygens. Moreover, the encapsulated ε-methylene protons of the $\mathbf{C_{12}}$ guest and the aromatic protons of the host gave rise to a cross peak.

The formation of capsular complexes between **1** and long-chain α,ω-alkanediyldiammmonium dichloride salts is further corroborated by the positive ESI mass spectra of equimolar host–guest mixtures which show prominent doubly-charged ions that correspond to $[\mathbf{1}\cdot\mathbf{C}_n]^{2+}$ (base peak) and low-intensity ion peaks for $[\mathbf{1}\cdot\mathbf{C}_n\mathrm{Cl}]^+$.[22]

The binding selectivity of **1** for the guest salts studied here was eventually determined by decreasing in highly coordinating solvents the cooperativity factors that arise from the

anion-binding sites. Addition of dimethyl sulfoxide (DMSO) to a solution of **1** in chloroform led to a strong solvation of the hydrogen-bond donor sites of the ureido functions.[23,24] This solvation caused a weakening of the binding ability of **1** toward ion-paired salts[25] and allowed the determination of the association constants by ^{1}H NMR spectroscopy. Table 2 shows that among the substrates investigated the longer $\mathbf{C_{12}}$ and $\mathbf{C_{16}}$ guest salts are more tightly bound than $\mathbf{C_8}$ and $\mathbf{C_{10}}$ by **1** as the result of capsular complexation.

Table 2: Association constants (K_a) of α,ω-alkanediyldiammonium dichloride salts with receptor **1** in $CDCl_3$/[D_6]DMSO (3:2).[a]

$H_3N^+(CH_2)_n{}^+NH_3\cdot 2Cl^-$	K_a [M^{-1}]
$n=8$	212[b]
$n=10$	163[b]
$n=12$	2.4×10^3
$n=14$	–[c]
$n=16$	2.6×10^3

[a] Determined by ^{1}H NMR spectroscopy at 22 ± 1 °C using equimolar (1×10^{-3} M) host–guest mixtures. Values are derived from the average of at least three independent measurements (standard error ≤ 15%). [b] K_a values refer to the S-shaped 1:1 complex. [c] Measurements of K_a were precluded by the limited solubility of the salt.

The binding selectivity order of **1** toward $\mathbf{C_{12}}$, $\mathbf{C_{14}}$, and $\mathbf{C_{16}}$ as chloride salts was estimated from the ESI-MS distribution percentages[26] of the relevant capsular complexes ($[\mathbf{1}\cdot\mathbf{C}_n]^{2+}$ ions). A competitive complexation experiment of **1** with a mixture of the three salts ($\mathbf{1}/\mathbf{C_{12}}\cdot 2Cl^-/\mathbf{C_{14}}\cdot 2Cl^-/\mathbf{C_{16}}\cdot 2Cl^- = 1:1:1:1$; $c=1.0\times10^{-4}$ M in $CHCl_3/CH_3OH$ (1:1)) gave the order $\mathbf{C_{14}} > \mathbf{C_{16}} > \mathbf{C_{12}}$ (60.5, 24.6, and 14.9%, respectively).[27,28]

In conclusion, we have synthesized a novel heterotetratopic receptor, **1**, that efficiently and selectively forms ligand-separated ion-pair complexes with long-chain α,ω-alkanediyldiammonium dichloride salts by combining the cooperative action of two converging calix[5]arene cavities in the encapsulation of the dication with the ability of the two ureido functions to bind the relevant counteranions. Future work will be directed toward the design of new heteropolytopic systems with specific recognition patterns.

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