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A Large Cavity Cryptand for Recognition of Dianionic Substrates in Aqueous Solution

Andrea Bencini,[a*] Antonio Bianchi,[a*] Vieri Fusi,[b] Claudia Giorgi,[a] Piero Paoletti[a*] and Barbara Valtancoli[a]

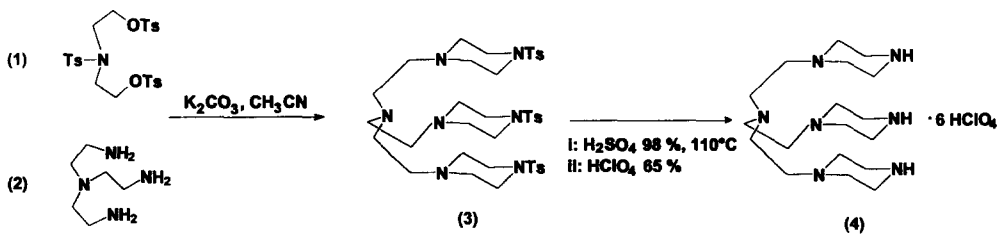
[a]Department of Chemistry, University of Florence, Via Maragliano 75/77, 50144 Florence, Italy

[b]Institute of Chemical Sciences, University of Urbino, P[za] Rinascimento 6, 61029 Urbino, Italy

Abstract. The synthesis of a new cryptophane composed by two polyamine moieties connected by aromatic units is reported. This macrobicycle behaves as a selective receptor for naphthalen disulfonate anions in aqueous solution.

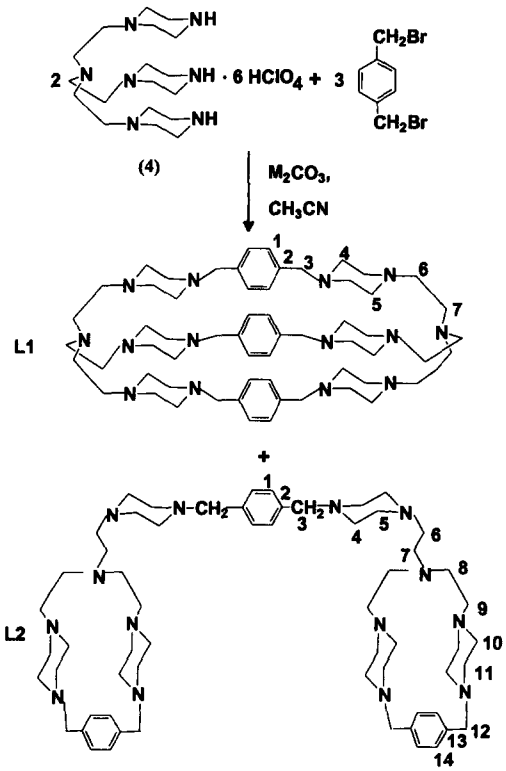
The design of polyammonium receptors containing structural features that impart high selectivity in the recognition of different guests has received much attention in the past several years.[1-5] Polyammonium macrocycles can strongly interact in aqueous media with polyanionic substrates, *via* charge-charge interactions and hydrogen bonding.[6-9] Aromatic subunits are often introduced as integral parts of these receptors. Polyammonium macrocycles containing two or more 1,4-benzo moieties have been most often used as water-soluble receptors with hydrophobic cavities that can also interact with guests by π-stacking or π-cation interactions. In particular, great effort has been devoted to design and synthesis of macrocyclic or macropolycyclic receptors containing aromatic subunits as rigid spacers to link two polyamine moieties or two polyaza-crown structures.[10-16]

Several macrobicycles containing two tripod tris(2-aminoethyl)amine units (**2** in scheme 1) connected by three aromatic spacers have been synthesised;[17-19] Schiff base condensations were commonly used, followed by reduction of the imino groups. The resulting cryptands have been successfully used for the encapsulation of binuclear metal assemblies inside the macrocyclic cavity.[20] Furthermore, protonated species of these receptors can be used for coordination of anions, which are enclosed inside the tridimensional cavity.[19,21]
The piperazine ring is a good building block to form large receptors.[22-24] The insertion of such moieties in macrocyclic frameworks may increase the rigidity and preorganization of the macrocycle, thus increasing its



Scheme 1

selectivity in substrate binding. To this purpose we have synthesised the precursor molecule **4**, which contains three piperazine rings. The procedure developed for synthesis of **4** utilises the simple starting material **1**, which can be obtained by tosylation of diethanolamine in high yields.[21] Reaction of **2** with 3 equivalents of **1** was carried out in refluxing CH_3CN (12 h) in presence of K_2CO_3 as a base (10 equiv.) (Scheme 1). After removing the solvent, the resulting yellowish oil was chromatographated on neutral alumina (activity II/III, eluent $CHCl_3$) to yield **4** as a white solid (70% yield). Removal of tosyl groups was performed in 98% H_2SO_4 (70 h, 110°C). Addition of diethyl ether to the solution gave a thick oil, which was dissolved in alkaline aqueous solution. Extraction with chloroform gave the crude product **4** (90 % yield),[25] which was purified as a perchlorate salt.



Scheme 2

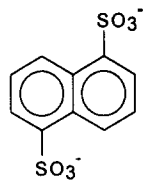
4 is a versatile precursor for synthesis of large cavity macrobicyclic receptors. Reaction of **4** with *p*-dibromoxylene in 2:3 molar ratio gives the cryptophane **L1** and the isostructural bis-macrocycle **L2**. This reaction was performed in refluxing CH_3CN (48h) in presence of M_2CO_3 (M = Li, Na, K, Cs) (Scheme 2). After evaporation of the solvent the crude product was chromatographated on alumina (activity II/III, $CHCl_3$ as eluent) giving **L1** and **L2** (28% and 10% yields, respectively).[25] Both compounds can be further purified as perchlorate salts. Addition of 65% $HClO_4$ to ethanolic solutions of **L1** and **L2** gave the H_8**L1**$(ClO_4)_8$ and H_{10}**L2**$(ClO_4)_{10}$ compounds in almost quantitative yields. The ^{13}C NMR spectrum of **L1** shows seven sharp peaks attributed to carbons 1-7, while the ^1H NMR one exhibits two singlets for the hydrogens 1 and 3, both integrating 12 protons, in accord with a ternary D_{3h} time-averaged symmetry for the molecule. A broad signal

is observed for the piperazine rings, denoting a rapid exchange process of chair-chair interconversion. The NMR spectral features of **L2** account for a reduced D_{2h} time averaged symmetry. The ^{13}C NMR spectrum shows 14 signals corresponding to the carbons 1-14. In the ^{1}H NMR spectrum, the benzylic hydrogens 3 and 12, as well as the aromatic ones 1 and 14, give two singlets, integrating 4 and 8 protons, respectively.

It is to be noted that the yield of the reaction for both **L1** and **L2** does not vary significatively by using different alkaline carbonate, suggesting the absence of any template effect in this cyclization.

The simple one pot reaction described above is a promising route to obtain different cryptophane receptors by reaction of **4** with other disubstituted aromatic or heteroaromatic moieties.

The receptor **L1** is composed by two polyamine binding units separated by *p*-phenilene spacer. Protonation of **L1** gives charged species. In particular, the octacharged H_8L1^{8+} cation is present in aqueous solution over a wide pH range (pH 3-6). In this cation the eight protons are equally shared between the two polyamine units, giving a ditopic receptor where two tetracharged moieties are spaced by three aromatic rings. Such a species may enable **L1** to form complexes with anions in aqueous solution. In order to test the coordination properties of **L1** toward anionic species, we have analysed its binding ability toward naphthalen disulfonate (NDS^{2-}) and naphthalen monosulfonate (NMS^{-}) anions. ^{1}H NMR spectra recorded on aqueous solutions containing H_8L1^{8+} and 1,5-NDS^{2-}, 2,6-NDS^{2-} or 2,7-NDS^{2-} show a marked upfield shift for both the aromatic protons of the substrate (up to 0.7 ppm) and those of the receptor. This allows one to determine the stability constants of the adducts between the octacharged H_8L1^{8+} receptor and 1,5-NDS^{2-}, 2,6-NDS^{2-} and 2,7-NDS^{2-} by means of ^{1}H NMR titrations (0.1 M NMe_4Cl aqueous solution, pD 3.8, 25°C).[26] The receptor forms stable 1:1 complexes with NDS^{2-} anions in aqueous solution with Log *K* values for the equilibrium $H_8L1^{8+} + NDS^{2-} = [H_8L1(NDS)]^{6+}$ of 5.0, 2.7 and 2.6 for 1,5-, 2,7- and 2,6-NDS^{2-}, respectively. These data point to the possibility that the NDS^{2-} dianions may be encapsulated inside the macrocyclic cavity, with each anionic group interacting with one of the polyammonium subunits of the receptor, *via* electrostatic forces and hydrogen bonds formation. Actually, a much lower stability was found in the case of the 1-naphthalen monosulfonate anion (Log $K < 1$), where only one anionic group is present. This suggests that both the anionic functions of the NDS^{2-} anions give charge-charge interactions with the polyammonium moieties of H_8L1^{8+}. Furthermore, the upfield shifts observed in the ^{1}H NMR spectra for the signals of the aromatic protons of both H_8L1^{8+} and NDS^{2-} indicate that π-stacking interactions also take place. π-Stacking interactions and solvophobic effects acting on the naphthalene moiety further contribute to the stability of the adducts.



1,5-NDS

It is of interest that the adduct with 1,5-NDS^{2-} is much more stable than those with 2,6 and 2,7 NDS^{2-} (K = 10.000 for 1,5-NDS^{2-} *vs* K = 500 for 2,7-NDS^{2-}). The selective recognition of 1,5-NDS^{2-} over 2,7- and 2.6-NDS^{2-} may be tentatively related to a better complementarity between the polyammonium moieties of H_8L1^{8+} and the sulfonate groups of the guest in the $[H_8L1(NDS)]^{6+}$ complex, resulting in an optimal charge-charge matching. Further studies on the coordination behaviour of H_8L1^{8+} are in progress.

In conclusion, attachment of piperazine rings on the tripod amine tris(2-aminoethyl)amine leads to a versatile building block (**4**) for assembly of polyammonium receptors with large tridimensional cavities where polyanionic guests can be lodged. Furthermore, the insertion of the piperazine rings within the macrocyclic frameworks leads to an increased rigidity of the backbone, and, as a consequence, to an enhanced selectivity in anion binding.

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25. **4**: ^{1}H NMR δ ($CDCl_3$, 25°C): 2.39 (b, 12H), 2.60 (t, 6H), 2.71 (t, 6H), 2.85 (b, 12H) ppm. ^{13}C NMR ($CDCl_3$, 25°C): 44.8, 50.6, 52.0, 53.8 ppm. MS (FAB): 354 ($M + H^+$). Anal. Calcd for $C_{18}H_{39}N_7$: C, 61.13; H, 11.12; N, 27.74. Found: C, 61.3; H, 11.0; N, 27.8. **L1**: ^{1}H NMR δ ($CDCl_3$, 25°C): 2.42 (b, 72H, H4, H5, H6, H7), 3.48 (s, 12H, H3), 7.25(s, 12H, H1) ^{13}C NMR ($CDCl_3$, 25°C): 50.1 (C6), 50.7 (C4), 51.0 (C5), 51.9 (C7), 60.5 (C3), 131.0 (C2), 133.7 (C1) ppm. MS (FAB): 1014 ($M + H^+$). Anal. Calcd for $C_{60}H_{96}N_{14}$: C, 71.09; H, 9.55; N, 19.36. Found: C, 71.0; H, 9.6; N, 19.2. **L2**: ^{1}H NMR δ ($CDCl_3$, 25°C): 2.40 (b, 72H, H4-H11), 3.46 (s, 4H, H3), 3.90 (s, 8H, H12), 7.12 (s, 8H, H14), 7.24 (s, 4H, H1) ppm; ^{13}C NMR ($CDCl_3$, 25°C): 46.1 (C7), 49.7 (C6), 50.1 (C5), 50.3 (C4), 50.6 (C11), 50.9 (C10), 52.4 (C9), 52.8 (C8), 60.0 (C12), 60.9 (C3), 130.0 (C13), 131.7 (C2), 133.2 (C1), 134.3 (C14) ppm. MS (FAB): 1014 ($M + H^+$). Anal. Calcd for $C_{60}H_{96}N_{14}$: C, 71.09; H, 9.55; N, 19.36. Found: C, 71.4; H, 9.5; N, 19.5.
26. The stability constants for the equilibria $H_8L1^{8+} + NDS^{2-} = [H_8L1(NDS)]^{6+}$ were measured by means of ^{1}H NMR titrations at 25°C in 0.1 NMe_4Cl D_2O solution. In a tipical experiment increasing amounts of NDS^{2-} were added to a $1{\cdot}10^{-3}$ M aqueous solution of H_8L1^{8+} at pD 3.8, up to a NDS^{2-} : **L1** 10 :1 molar ratio. The NMR data were elaborated with the program HYPNMR (Frassineti, C.; Gelli, S.; Gans, P.; Sabatini, A.; Moruzzi, M. S.; Vacca, A. *Anal. Biochem.*, **1995**, *231*, 374-380.)

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