Synthesis and Properties of New Lipophilic Macrotricyclic Cylindrical Cryptands

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Cylindrical cryptands **2a–c**, in which two 1,7-dioxa-4,10-diazacyclododecane rings are connected by two equally substituted propylene bridges, have been obtained in appreciable yields by a "one-pot" synthesis. The assembling of the macrotricyclic structure is likely driven by the template effect of metal cations. These compounds, both as free receptors or as complexes, exist as *cis* and *trans* diastereoisomers, which do not interconvert and have been separated and characterized by X-ray analysis. The extraction constants (K_e) of cryptands **2** for alkali picrates under $CHCl_3/H_2O$ and solid/liquid two-phase conditions have been measured by UV-vis spectrophotometry. The complexation behavior of cryptands **2** has been rationalized analyzing the preorganization of binding sites in the minimum energy conformations obtained by molecular mechanics calculations. Minimum energy conformations have been calculated also for the previously reported cryptands **1** and have been compared with those of **2**. Results fit reasonably well with those of X-ray structures.

Introduction

The synthesis of receptors featuring metal cation complexes with very high stability and/or selectivity is a topic of growing interest, mostly for the wide range of applications they have found in different fields of chemistry, physics, medicine, and biology.[1] Recent examples reported in the literature demonstrate the importance of these properties when receptors have to be used for very sophisticated applications such as (i) the immobilization of radioactive rubidium for organ imaging[2] and silver-111 for cancer radioimmunotherapy;[3] (ii) the use of chromoionophores as selective optical sensors toward lithium and sodium cations;[4] (iii) the use of lipophilic carriers for the transport of sodium cations across liposome membranes,[5] and so on.

A suitable and general way aimed to impart complexation selectivity consists on tuning the topology of the binding sites of receptors whose rigidity is ensured by a policyclic structure.[6] Seeking lipophilic receptors capable of forming highly stable and selective complexes with alkali and alkaline earth metal cations, we focused our attention on macrotricyclic cylindrical cryptands.

They are easily prepared by linking two macrocycles together through two bridges, thus leading to the formation of three cavities: two lateral (those of the macrocyclic subunits) and a central one.[7] Depending on the length of the bridging chain, cylindrical cryptands can behave either as monotopic or as ditopic receptors. The monotopic character is imposed by the use of bridges short enough to build up only a small molecular cavity, forming highly stable mononuclear complexes.[8]

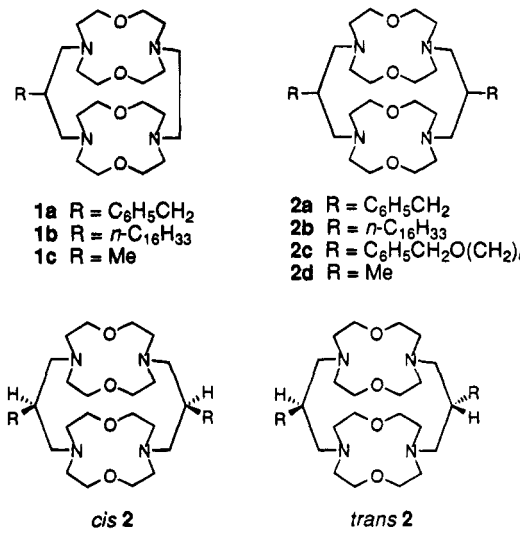

Figure 1. Macrotricyclic cylindrical cryptands **1a–c** and **2a–d**.

In previous papers we reported the synthesis of lipophilic cylindrical cryptands **1** in which two 1,7-dioxa-4,10-diazacyclododecane rings are linked together by one ethylene and one propylene bridges (Figure 1). The lipophilic character is ensured by the presence of a hydrophobic group, e.g. a long hydrocarbon chain or a benzyl group, on the central carbon atom of the propylene bridge. Cryptands **1a** and **1b** were prepared by a multistep synthesis, and the final ring closure of the macrotricycle was driven by the template effect of the sodium cation.[9] These compounds form highly stable and selective complexes with Na^+, and this property was used

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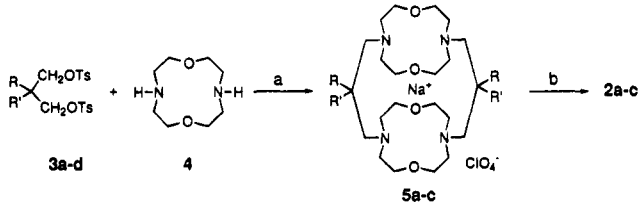
Scheme 1. Synthesis of Free Ligands 2a–c



	R	R'	% isolated 5
a	$C_6H_5CH_2$	H	31.0
b	n-$C_{16}H_{33}$	H	29.0
c	$C_6H_5CH_2O(CH_2)_6$	H	30.6
d	n-C_4H_9	n-C_4H_9	0.0

a) Na_2CO_3, CH_3CN; then $NaClO_4$; b) *cfr* ref. 9b

for the preparation of many sodium complexes by simple anion exchange.[9b] Complexes were mainly characterized by NMR spectroscopy,[10] and in the case of the sodium perchlorate complex of the benzyl derivative **1a** a crystallographic characterization by a single crystal X-ray analysis was obtained.[9b]

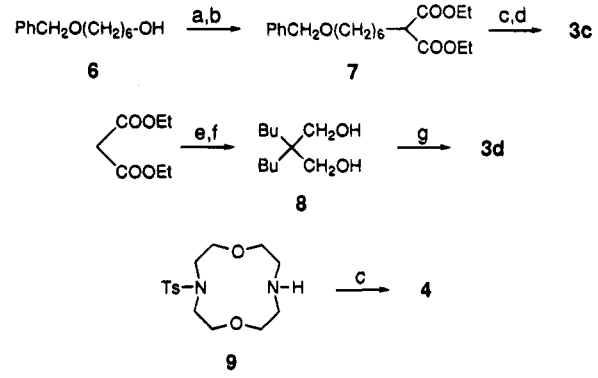
A number of receptors of this class was previously synthesized, but their complexing properties have not been examined in detail yet.[11] In the present paper we report synthesis, characterization, complexation behavior, and X-ray studies of new lipophilic cryptands **2a–c**, in which the two 1,7-dioxa-4,10-diazacyclododecane rings are connected by two propylene bridges equally substituted at the central carbon atom (Figure 1). Cryptands **2a–c** feature the following properties: (i) synthesized in appreciable yields by a one-step procedure in which the assembling of the macrotricyclic structure is likely governed by the template effect of the metal cation; (ii) characterized by an increased lipophilicity since they have two lateral hydrophobic groups; (iii) the lateral groups can bear suitable reactive functionalities open to further synthetic transformations, e.g. preparation of more organized polyreceptors, new polymeric materials, and so on; (iv) these compounds, either as metal complexes or as free receptors, can exist as two diastereoisomers, *cis* and *trans*, which can be separated by column chromatography.

Results and Discussion

Synthetic Procedure. The synthesis of lipophilic macrotricyclic cryptands **2a–c** was carried out as reported in Scheme 1 by using previously published procedures.[9b] Condensation of the bis-*p*-toluenesulfonate derivatives **3a–c** with the diaza crown ether **4** was carried out with solid Na_2CO_3 as base in refluxing acetonitrile for 4 days. After anionic exchange of *p*-toluenesulfonate with ClO_4^-, compounds **5a–c** were isolated by column chromatography in about 30% yield as a mixture of *trans* and *cis* isomers (Scheme 1).

These isomers are formed in a 2:1 *cis*/*trans* ratio and can be easily isolated in a pure form and fully characterized. In order to avoid this isomerism, the same condensation was carried out using the bis-butyl derivative **3d**, but we quantitatively recovered the starting materials. This is probably due to the poor reactivity of the neopentyl-like bis-*p*-toluenesulfonate **3d**. Free ligands **2a–c** were quantitatively obtained by continuous extraction with *n*-hexane of a solution of the corresponding sodium methoxide complexes in methanol:10% aqueous KOH:benzene in a 3:3:1 ratio for 24 h.[9b] Compound **3c** was prepared following a sequence of reactions reported in Scheme 2 by using synthetic procedures already reported for **3a,b**.[9b] Yields and characterization of **6**, **7**, and **3c** are given in the Experimental Section. Diazacoronand **4** was obtained in quantitative yield by reductive detosylation of monotosyl diazacoronand **9**[9b] with $LiAlH_4$ in THF (Scheme 2).

Scheme 2



a) MsCl, Py; b) diethyl malonate, K_2CO_3, Bu_4NBr, CH_3CN; c) $LiAlH_4$, THF; d) TsCl, Et_3N, CH_2Cl_2; e) *n*-BuBr, K_2CO_3, Bu_4NBr, CH_3CN; f) $LiAlH_4$, Et_2O; g) TsCl, Py.

In order to check the role of the metal cation in driving the macrotricyclic ring closure, the condensation reaction leading to metal complexes of **2b** was repeated under the same conditions used for the synthesis of **5b** with different alkali carbonates as bases. The templating capability of different cations, evaluated on the yields of the different complexes, is in the order $Li^+ \cong Cs^+ < Na^+ \cong K^+$ since the metal complexes of **2b**, as *p*-toluenesulfonates, were isolated in 17%, 18%, 29%, and 27% yield, respectively.

Determination of Extraction Constants. The complexation capability of receptors **2** toward alkali cations was evaluated by using the picrate extraction method reported by Cram et al.[12] Following this procedure, the extraction constants were estimated by measuring the distribution of alkali picrate [(M^+Pic^-); M = Li, Na, K, Cs] between $CHCl_3$ and H_2O in the presence of receptors **2** (equilibrium 1). Control experiments showed that,

$$M^+_{aq} + Pic^-_{aq} + 2_{org} \overset{K_e}{\rightleftharpoons} [(M \subset 2)^+ Pic^-]_{org}$$

under the conditions used, the alkali picrates were not soluble in $CHCl_3$ in the absence of the receptor and that the latter was completely partitioned in the organic phase.

Values of K_e were calculated according to eq 1[9b] by

$$K_e = \frac{[(M \subset 2)^+ Pic^-]_{org}}{[M^+]_{aq}\,[Pic^-]_{aq}\,[2]_{org}}$$

using separately the two isomers of **2a** and the *cis* isomer

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Table 1. Extraction Constants (K_e) and Extent of Complexation for Alkali Picrates by 2a,b[a]

receptor	M^+	K_e (*cis*)	K_e (*trans*)	% complex[b] (*cis*)	% complex[b] (*trans*)
2a	Li^+	3.70×10^4	4.60×10^4	14.7	16.5
2a	Na^+	3.92×10^4	9.14×10^4	15.5	24.0
2a	K^+	3.60×10^4	4.80×10^4	16.7	19.3
2a	Cs^+	2.90×10^4	4.11×10^4	13.2	16.1
2b	Li^+	6.83×10^4		20.5	
2b	Na^+	7.84×10^4		24.2	
2b	K^+	5.30×10^4		20.7	
2b	Cs^+	5.59×10^4		21.3	

[a] Solutions (2.5×10^{-3} M) of ligands in $CHCl_3$ and of alkali picrates in H_2O equilibrated at 20 °C for 72 h. [b] Extent of complexation evaluated as $[M^+ \subset \mathbf{2a}]/[\mathbf{2a}]$.

Table 2. Extraction Constants of *trans*-2a and Na^+ or K^+ Picrates at Different Initial Concentrations

$[\mathbf{2a}]_{CHCl_3}$	$[M^+ Pic^-]_{H_2O}$	K_e (Na^+)	K_e (K^+)
1.76×10^{-3}	1.70×10^{-3}	1.6×10^5	
1.75×10^{-4}	1.67×10^{-4}	1.6×10^8	
1.75×10^{-5}	1.69×10^{-5}	7.4×10^9	
1.73×10^{-3}	2.20×10^{-3}		1.6×10^5
1.77×10^{-4}	2.44×10^{-4}		3.4×10^7
1.77×10^{-5}	2.44×10^{-5}		2.8×10^9

of **2b**. Results are reported in Table 1 and indicate that (i) the values of K_e, under the conditions used, are not so high if compared with those obtained with **1a,b**[9b] and are unaffected by the nature of the lateral groups; (ii) there is no complexation selectivity with respect to the metal cation even though their ionic diameters are very different: 1.20, 1.90, 2.66, and 3.34 Å for Li^+, Na^+, K^+, and Cs^+, respectively.[13] A possible explanation for the low K_e values is that the lateral cavity of receptors **2a–c** is too large; thus the complexed cation is accessible to water molecules, which can compete with the receptor in the complexation process. The lack of selectivity seems to indicate that the nature and the stoichiometry of the complexes may not be the same for all cations.

Indeed eq 1, besides the complete partitioning of the receptors in the organic phase, requires inorganic salts to be completely dissociated in the water phase, and all the salt in the $CHCl_3$ layer to be present as 1:1 complex with the receptor. This might not be the case, at least for Li and Cs cations. Another point that we would like to stress is that the values of K_e are strictly dependent on the initial concentrations of receptors and of picrates. Values of K_e as a function of concentrations obtained for Na^+ and K^+ picrates by using the pure *trans* isomer of **2a** as ligand are reported in Table 2. The dependence of K_e on the picrate concentration may derive from the different ionic strength of the resulting solution.[14]

Complexation of alkali picrates was also studied under solid/liquid two-phases conditions by equilibrating a 2.5×10^{-4} M solution of pure *cis*- and *trans*-**2a** in $CHCl_3$ with solid Na^+ or K^+ picrate; values are reported in Table 3. The amount of the picrate extracted in the organic phase by the ligand was in all cases evaluated by UV-vis spectrophotometric analysis.

Table 3. Extent of Complexation of Alkali Picrates for 2a under Solid/Liquid Two-Phase Conditions[a]

M^+	% complex[b] (*cis*)	% complex[b] (*trans*)
Li^+	20	24
Na^+	82	87
K^+	34	62
Cs^+	2	8

[a] 5 mL of 2.5×10^{-4} M solution of **2a** in $CHCl_3$ were equilibrated, under magnetic stirring, with 100 molar equivalents of solid alkali picrates for 20 h at 20 °C. [b] $[(M^+ \subset \mathbf{2a})Pic^-]/[\mathbf{2a}]$.

Complexation of $NaBPh_4$ by *cis*-**2a** in $CDCl_3$ was studied also by ^{1}H-NMR spectroscopy. The experiment was carried out equilibrating by sonication in an NMR tube equimolecular amounts of *cis*-**2a** and $NaBPh_4$ in $CDCl_3$ and recording ^{1}H-NMR spectra at different times. After 30 min the resonances of the free ligand disappeared and only those of pure $[Na^+ \subset$ *cis*-**2a**$][BPh_4^-]$ were observed.

X-ray Crystallographic Analysis of cis-2*a* and $[Na^+ \subset$ *trans*-2a$][BPh_4^-]\cdot(CH_3COOC_2H_5)$. In order to ascertain the conformational changes associated with the coordination of Na^+ by the receptor we carried out a single-crystal X-ray diffraction experiment on both the free receptor and its Na^+ complex. Unfortunately, we were unable to obtain suitable crystals for the couple of *cis* or, alternatively, *trans* isomers; hence we have determined the crystal structure of *cis*-**2a** and $[Na^+ \subset$ *trans*-**2a**$][BPh_4^-]\cdot(CH_3COOC_2H_5)$, hereafter *cis*-**2a** and $[Na^+ \subset$ *trans*-**2a**$]$.

The structure of *cis*-**2a** presents normal van der Waals contacts like that of the $[Na^+ \subset$ *trans*-**2a**$]$ compound. The latter structure consists of bulky $[Na^+ \subset$ *trans*-**2a**$]$ cations, lying about inversion centers, and of $[BPh_4^-]$ anions and clahtrate $CH_3COOC_2H_5$ solvent molecules, lying about two-fold axes. It is worthwhile to consider the volume *per* "heavy" atom in *cis*-**2a** (19.84 Å^3), $[Na^+ \subset$ *trans*-**2a**$]$ (19.22 Å^3) and $[Na^+ \subset$ **1a**$][ClO_4^-]$ (18.97 Å^3). The computed values, deviating more or less from the 18 Å^3 expected from the Kempster–Lipson rule,[15] have *per se* little meaning; however, their relative values do indicate that the empty receptor, *cis*-**2a**, is more loosely packed than its filled counterpart, $[Na^+ \subset$ *trans*-**2a**$]$, which in turn is less "compact" than $[Na^+ \subset$ **1a**$]$.[9b] These data suggest that the cavity in *cis*-**2a** is partially preformed due to the inabilility of *cis*-**2a** to fold efficiently on itself in order to remove all its "internal" empty space.

In Figures 2 and 3 we report ORTEP views of both the free ligand and the Na^+ complex, respectively, oriented in a similar way, in order to allow a fast perception of the major conformational changes due to the Na^+ coordination. In the free receptor none of the oxygen lone pairs is pointing toward the center of the cage and, out of the four nitrogen atoms, only two (N2 and N3) point their lone pairs inside the cage. In the Na^+ complex, however, all the oxygen and nitrogen atoms point a lone pair toward the Na cation and, since the four oxygen and four nitrogen atoms lay on the vertices of two intersecting squares, Na^+ has a distorted cubic coordination. The oxygen atoms are closer (mean 2.42 Å) to the Na cation than the nitrogen ones (mean 2.91 Å), values similar to those found for $[Na^+ \subset$ **1a**$][ClO_4^-]$ (2.46 and 2.79 Å, respectively).

The major differences between the Na-binding sites in $[Na^+ \subset$ *trans*-**2a**$]$ and in $[Na^+ \subset$ **1a**$]$ arise from the

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(14) The extent of complexation under solid–liquid conditions is slightly dependent on the excess of solid picrate. In the case of *trans*-**2a**, values are 60% and 87% for Na^+, and 52% and 62% for K^+, with 2 and 100 mol equiv of picrates, respectively. The extent of complexation remained substantially the same with *cis*-**2b**.

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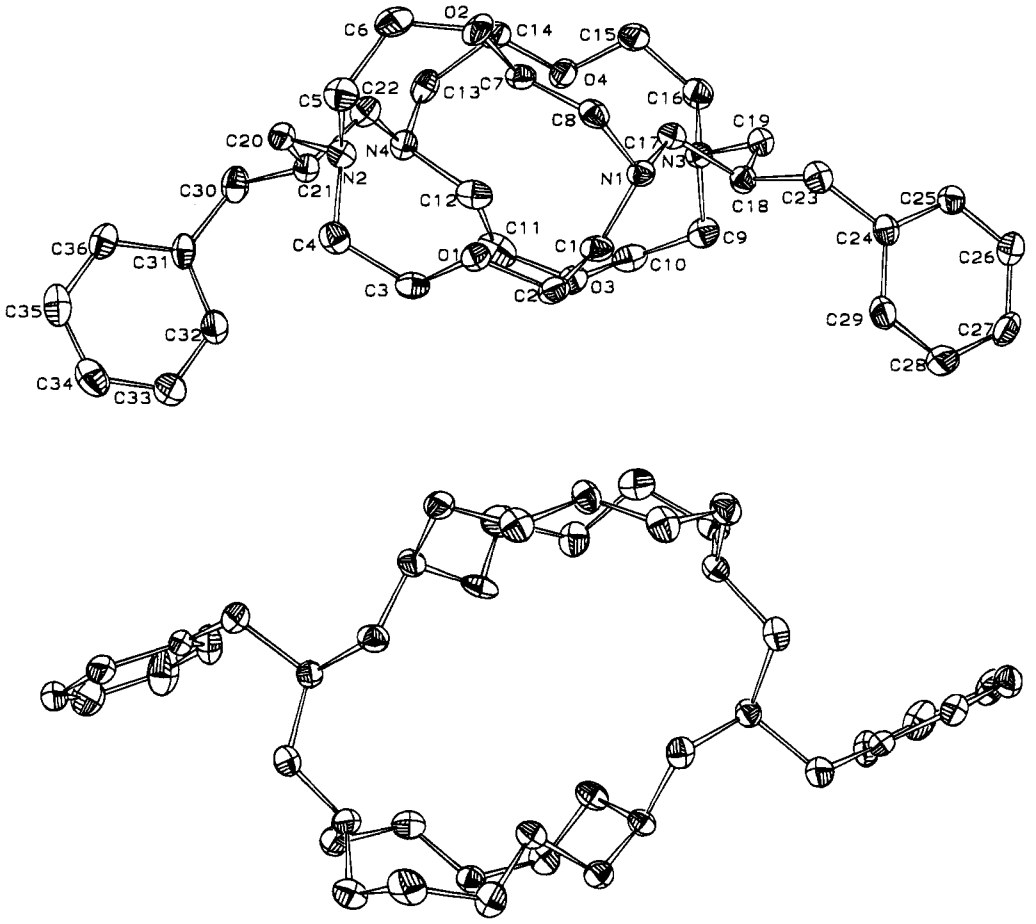

Figure 2. ORTEP view of *cis*-**2a**. Thermal ellipsoids are drawn with 30% probability, and hydrogen atoms are drawn with arbitrary small isotropic thermal parameters for sake of clarity. Two nitrogen lone pairs are pointing outside the cage (N1 and N4) and two inside (N2 and N3) while none of the oxygen lone pairs is pointing toward the center of the cage.

relative length of the two aliphatic chains connecting the two 1,7-dioxa-4,10-diazacyclododecane rings. In particular, on moving from [$Na^+ \subset$ **1a**] to [$Na^+ \subset$ *trans*-**2a**] the Na–O interactions shorten (2.46 vs 2.42 Å) while the Na–N ones lengthen (2.79 vs 2.92 Å). At the same time, the overall conical shape of the [$Na^+ \subset$ **1a**] becomes cylindrical in [$Na^+ \subset$ *trans*-**2a**], as shown by the N···N inter-rings interactions which are markedly different in [$Na^+ \subset$ **1a**] (3.01 and 3.52 Å) but symmetrically equivalent in [$Na^+ \subset$ *trans*-**2a**] (3.39 Å).[16]

Conformational Analysis of Free Receptors 1 and 2. To investigate the degree of preorganization of the binding sites of **2a,b**, we undertook a molecular mechanics computational study on these receptors. We used the MacroModel/Batchmin package[17] and performed a Monte Carlo Multiple-Minimum (MCMM) conformational search, a methodology that allows an efficient sampling of the potential energy surface and has proven to be one of the most effective algorithms at efficiently sampling the accesible conformations of flexible molecules.[18]

The search was started using the united-atom version of AMBER force field[17,19] and saving all conformations within 12 kcal/mol from the global minimum. After addition of hydrogens and lone pairs, the structures were reminimized using MM2.[17,20] In this way, the MCMM search required a relatively small amount of CPU time, while enough structures were saved for reminimization with more suitable force fields such as those that take explicitly into account the hydrogens.[21]

The calculations were run on the *trans* and *cis* isomers of compound **2d** (R = Me; Figure 1), as suitable models for experimentally synthesized *trans*- and *cis*-**2a–c**, by performing 20000 steps of the MCMM search with AMBER united-atom force field. After energy reminimization (EM) of all the minima with MM2, the results obtained were compared with the experimental data, namely the X-ray structure of *cis*-**2a** and the *cis*/*trans* ratio (67/33 at 80 °C for compound **2a**). MM2 gives energetic results in agreement with the experimental data, since a *cis*/*trans* ratio of 78/22 at 80 °C for **2d** is calculated. The two global minima for *cis*- and *trans*-**2d** as calculated with MM2 are shown in Figure 4.

(16) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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(21) The all-atom version of AMBER has been also tested (Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230), but the *trans* isomer was predicted to be the most stable, against what is found experimentally. Moreover, with the united-atom AMBER force-field, the *cis*/*trans* ratio is badly reproduced (97/3 calcd *vs* 67/33 exp at 80 °C), and the X-ray structure of the *cis* isomer did not fit with the minimum energy conformation as resulted from the MCMM search (see below in the text).

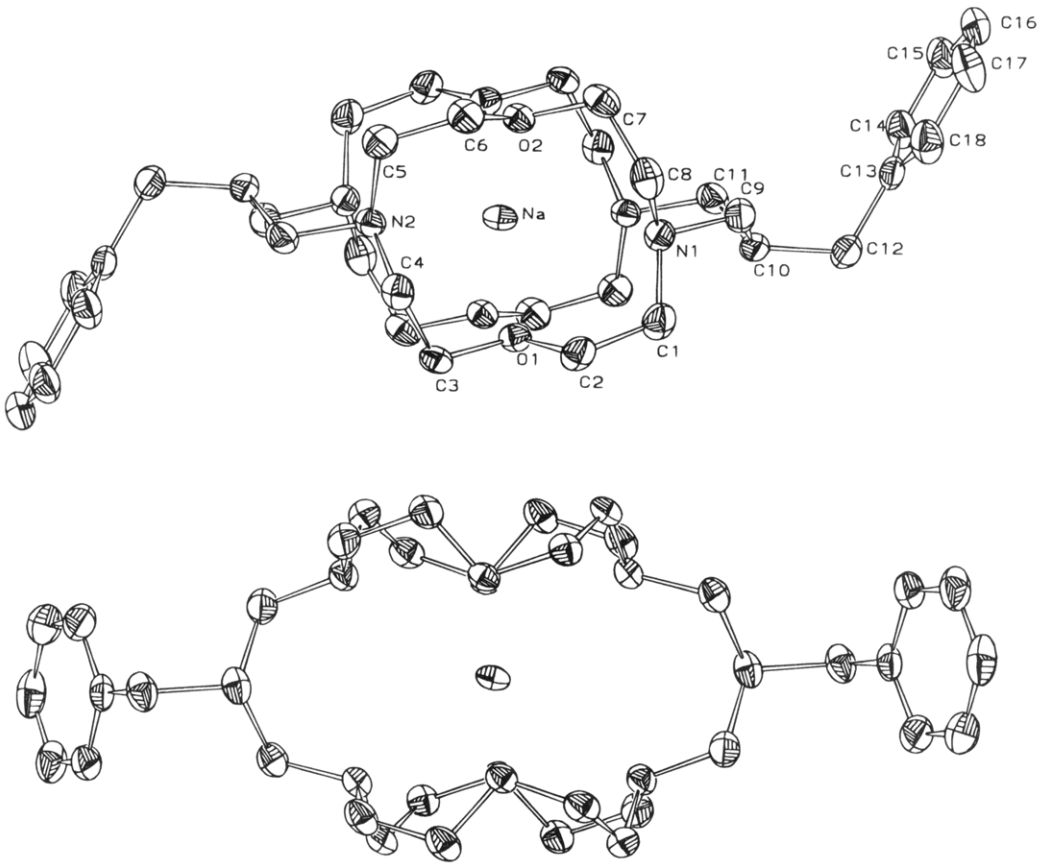

Figure 3. ORTEP view of [$Na^+ \subset$ *trans*-**2a**]. Thermal ellipsoids are drawn with 30% probability, and hydrogen atoms are draw with arbitrary small isotropic thermal parameters for sake of clarity.

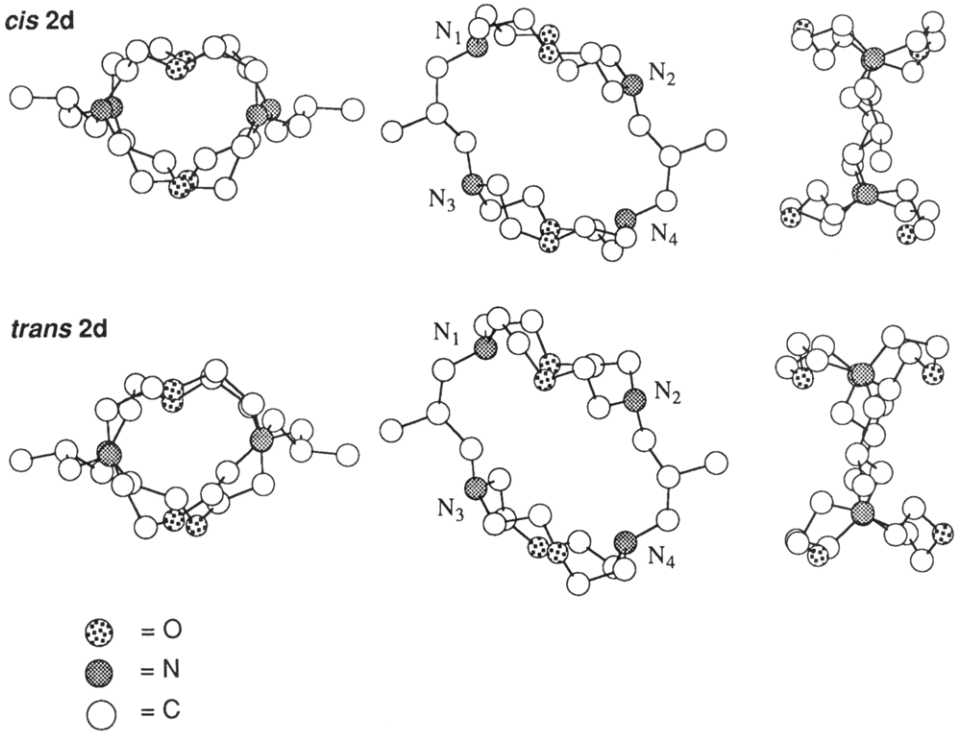

Figure 4. MM2 global minima for *cis*- and *trans*-**2d**.

Examination of the two minima for the *cis* and *trans* isomers of Figure 4 reveals some interesting features for both. The central cavity is slightly different in shape, being more squared in *cis*-**2d** isomer ($N_1 \cdots N_4$: 7.25 Å; $N_2 \cdots N_3$: 6.00 Å) and more elongated in *trans*-**2d** ($N_1 \cdots N_4$: 7.39 Å; $N_2 \cdots N_3$: 5.57 Å), while the orientation of the nitrogen lone pairs is similar. In fact, these lone pairs point alternately inside (N_1 and N_4) and outside (N_2 and N_3) the central cavity; in other words, the central cavity is not strongly preorganized in these compounds. This

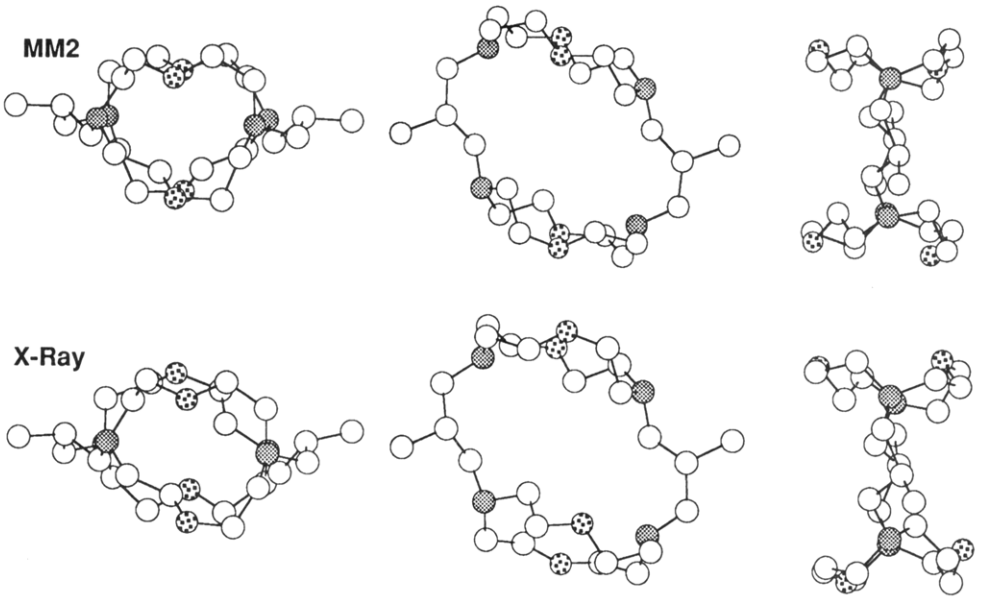

Figure 5. MM2 global minimum for *cis*-**2d** compared with the corresponding X-ray derived structure.

result is of particular interest for our purposes, since no X-ray crystal structure for *trans*-**2a** is available for a comparison with the isomeric *cis*-**2a**. The two isomers can thus be analyzed only by computational means.

A comparison of the global minimum of the MM2 MCMM/EM search for compound *cis*-**2d** with the one derived from the X-ray structure of the *cis*-**2a** (by removal of the phenyl rings and minimization of the local minimum with MM2) is shown in Figure 5. There are some minor differences between the two structures, confined, however, to the azacrown moieties; the X-ray structure of the central cavity, on the other hand, is perfectly reproduced by the calculations; packing forces in the crystal can account for particular conformational preferences of the ethereal moieties that may not be reproduced in a *in vacuo* calculation.

Having thus established the reliability of molecular mechanics procedures in the analysis of the free ligands, we performed a conformational search on compound **1c** as a model for **1a**,**b**. No X-ray crystal structure is available to assess the degree of preorganization of the central cavity for the complexation behavior of these cylindrical cryptands. A 20000 step MM2 MCMM/EM search was performed on compound **1c** (R = Me) by following the same procedure described for **2d**. Two isoenergetic global minima were found, one featuring all the nitrogen lone pairs pointing toward the middle of the central cavity (Figure 6). The other conformation that was found as a global minimum features three of the four nitrogen lone pairs pointing inside the central cavity (N_1, N_3, and N_4), and the same amount of preorganization was observed for the third (ΔE = 0.10 kcal/mol) and fourth (ΔE = 0.50 kcal/mol) conformations. The first minimum energy conformation with a lower amount of preorganization (similar to the one observed for componds **2d**, i.e. two lone pairs only, N_1 and N_4, pointing toward the center of the cage) is the fifth one, 0.6 kcal/mol higher in energy than the MM2 global minima (Figure 6). Its contribution, calculated with a Boltzmann distribution at 298 K, is 6% only. Indeed, compounds **1a**,**b** were experimentally found to be better ligands than **2a**−**c**, at least for the Na cation.[9]

Conclusions

The results reported in the present paper extend the knowledge on the class of lipophilic macrotricyclic cylindrical cryptands featuring short bridges with hydrophobic groups connecting the two diazacoronands, introduced by us several years ago. However some points need to be stressed: (i) The synthesis of compounds described here occurs in appreciable yields even when carried out in a "one-pot" fashion, the assembling of the macrotricyclic structure being driven by the template effect of Na or K metal cations.

(ii) The presence of a substituent on each propylene bridge leads to the formation of *cis* and *trans* isomers. This isomerism is particularly interesting since receptors bearing appropriate lateral groups are suitable starting materials for the synthesis of sophisticated lariat cryptands or polyreceptors.

(iii) The preorganization of the binding sites and the presence of a molecular cavity in the free receptor, ensured by the rigidity of the polycyclic structure, play a major role on the stability and selectivity of complexation. Indeed, molecular mechanics calculations on model compounds **1d** and **2d** evidence a quite different degree of preorganization together with an enlarged molecular cavity of **2d** with respect to **1d**, thus accounting for the decreased extracting capability of cryptands **2a**,**b** toward alkali cations in an aqueous/organic two-phase system with respect to the values previously reported for **1a**,**b**.[9] The extent of complexation of **2a**,**b** is strongly enhanced under solid/liquid conditions. Furthermore, the good agreement between X-ray analysis and molecular mechanics data indicates that this last technique is a powerful tool for explaining the complexation behavior of lipophilic receptors for which it is, in general, very difficult to obtain crystals suitable for X-ray analysis.

(iv) The X-ray structures of the free *cis*-**2a** and of the [Na^+ ⊂ *trans*-**2a**][BPh_4^-] were very important for the unambiguous identifications of the *cis* and *trans* isomers, which would not be otherwise possible.

Work aimed to design new receptors of this class of lipophilic cylindrical cryptands and to study their com-

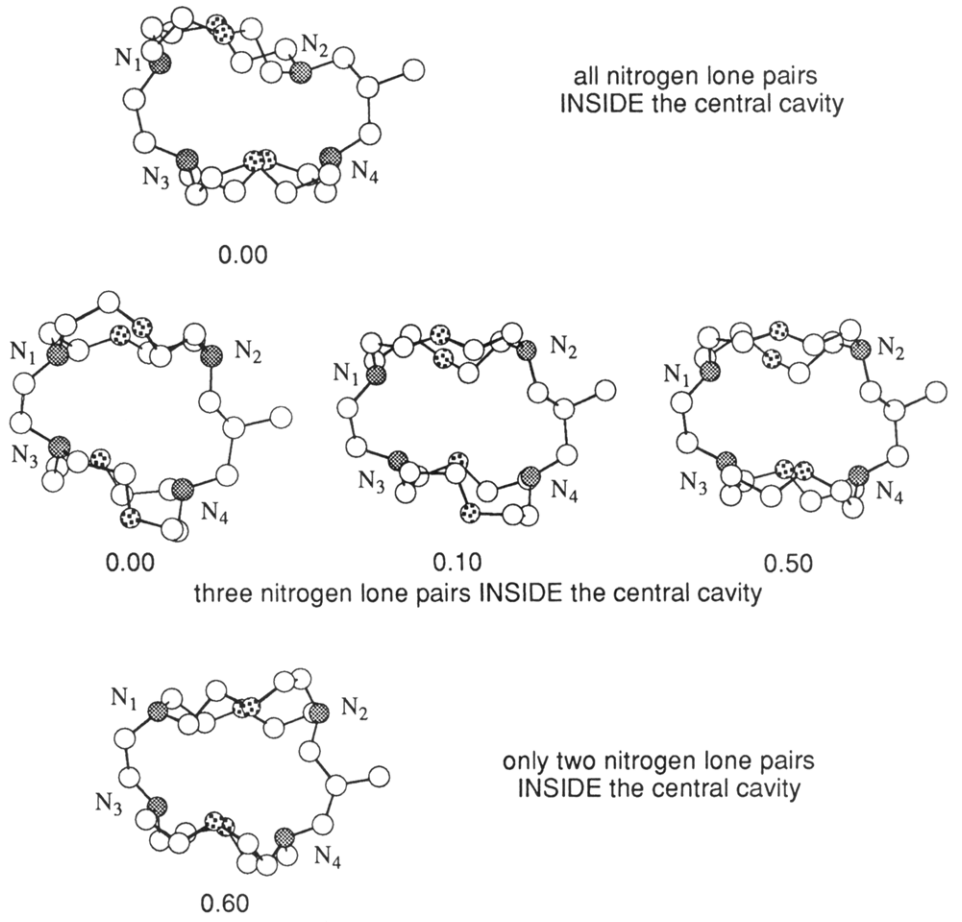

Figure 6. A comparison of the first 5 conformers from the MM2 MCMM/EM search of **1c**. ΔE values in kcal/mol.

plexation behavior toward other metal cations is currently in progress.

Experimental Section

All reactions employing dry solvents were run under nitrogen. THF was distilled twice from Na; Et_2O was distilled from Na and then from $LiAlH_4$; both solvents were stored on molecular sieves. Commercial acetonitrile was used without additional purification and stored on molecular sieves; pyridine was stored on KOH. Purifications of compounds by column chromatography were performed with 60−230 mesh silica gel (Merck).

^1H NMR spectra were recorded at 80 and 300 MHz in $CDCl_3$; ^{13}C NMR spectra were recorded at 75.43 MHz in $CDCl_3$. Chemical shifts are reported in δ relative to TMS.

6-(Benzyloxy)hexan-1-ol (6). To a sample of hexane-1,6-diol (59 g, 500 mmol), heated with stirring to fusion, Na (2.3 g, 100 mmol) was carefully added under nitrogen. The solution was heated to 80 °C and stirred for 5 h and then benzyl chloride (12.7 g, 100 mmol) was added. The reaction mixture was stirred at 80 °C for 15 h. After cooling to rt, the mixture was acidified with 25% aqueous H_2SO_4; CH_2Cl_2 (100 mL) was added, and a triphase system was obtained. The organic layer was separated, washed with 5% aqueous $NaHCO_3$ (2 × 50 mL) and then with H_2O (2 × 50 mL), dried ($MgSO_4$), and concentrated to give 20.1 g of crude product. Purification by column chromatography (hexanes/Et_2O 9/1, then 7/3 as eluant) afforded 14.6 g (70%) of **6** as a colorless oil. ^1H NMR (80 MHz): δ 7.30−7.20 (m, 5H); 4.50 (s, 2H); 3.70−3.35 (br s, 1H); 3.60−3.30 (m, 4H); 1.80−1.20 (m, 8H). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.02; H, 9.64.

Diethyl 2-[6-(Benzyloxy)hexyl]propane-1,3-dioate (7). A solution of methanesulfonyl chloride (5.3 g, 46 mmol) in 10 mL of pyridine was added dropwise to a stirred solution of **6** (8.13 g, 42 mmol) in 50 mL of pyridine, the temperature being kept between 0 and 5 °C. The reaction mixture was stirred overnight at 0 °C. After addition of 150 g of ice and acidification with 37% aqueous HCl, the mixture was extracted with CH_2Cl_2 (2 × 50 mL), washed with 5% aqueous $NaHCO_3$ (30 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded 11.2 g (93%) of 6-(benzyloxy)hexan-1-ol methanesulfonate as a thick oil. ^1H NMR (80 MHz): δ 7.30−7.10 (m, 5H), 4.50 (s, 2H), 4.20 (t, 2H, J = 5.6 Hz), 3.60 (t, 2H, J = 5.6 Hz), 3.00 (s, 3H), 1.90−1.30 (m, 8H). Anal. Calcd for $C_{14}H_{22}O_4S$: C, 58.72; H, 7.74. Found: C, 58.69; H, 7.76.

A mixture of 6-(benzyloxy)hexan-1-ol methanesulfonate (10.0 g, 35 mmol), diethyl malonate (5.1 g, 32 mmol), K_2CO_3 (13.0 g, 96 mmol), and tetrabutylammonium bromide (0.5 g, 1.5 mmol) in 100 mL of acetonitrile was stirred and refluxed for 3 d. After cooling to rt, the reaction mixture was filtered, the solid precipitate carefully washed with CH_2Cl_2, and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL), washed with H_2O (2 × 50 mL), dried over $MgSO_4$, and concentrated to give a crude oil. Purification by column chromatography (hexanes/Et_2O 8/2 as eluant) afforded 9.6 g (85%) of **7** as a clear oil. n^{20}_D 1.4800. ^1H NMR (80 MHz): δ 7.30−7.10 (m, 5H), 4.5 (s, 2H), 4.2 (q, 4H, J = 6.5 Hz), 3.60−3.20 (m, 3H), 2.10−1.00 (m, 16H). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.66.

2-[6-(Benzyloxy)hexyl]propane-1,3-diol Bis(4-methylbenzenesulfonate) (3c). A solution of **7** (25.8 g, 740 mmol) in 150 mL of anhydrous THF was slowly added, under nitrogen, to a stirred suspension of $LiAlH_4$ (5.6 g, 148 mmol) in 70 mL of anhydrous THF. The reaction mixture was stirred and refluxed for 15 h, and then, after cooling at 0 °C, the excess of $LiAlH_4$ was destroyed with AcOEt (CAUTION!). The salts were dissolved with 10% aqueous H_2SO_4, and the organic phase was separated. The aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic phases were washed with 5% aqueous $NaHCO_3$ (2 × 50 mL) and water (2

× 50 mL) and dried over $MgSO_4$. The solvent was evaporated to afford a solid crude product that, after crystallization from cyclohexane, gave 14.0 g (71%) of 2-[6-(benzyloxy)hexyl]propane-1,3-diol as a white solid: mp 47–49 °C. ^1H NMR (80 MHz): δ 7.30–7.10 (m, 5H), 4.40 (s, 2H), 3.80–3.30 (m, 6H), 2.60 (br s, 2H), 1.80–1.00 (m, 11H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.17; H, 9.83.

A solution of *p*-toluenesulfonyl chloride (24.4 g, 128 mmol) in 70 mL of CH_2Cl_2 was added at rt to a stirred solution of 2-[6-(benzyloxy)hexyl]propane-1,3-diol (11.4 g, 428 mmol) and Et_3N (21.34 g, 211 mmol) in 80 mL of CH_2Cl_2. The reaction mixture was stirred overnight at rt and then washed with 3 N aqueous HCl (2 × 50 mL) and with water (2 × 50 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a crude residue which was purified by column chromatography (hexanes/Et_2O 9/1 and then 1/1 as eluant). **3c** was obtained as a white solid (21.4 g, 87%): mp 42–43 °C. ^1H NMR (80 MHz): δ 7.70 (d, 4H, *J* = 7.4 Hz), 7.30–7.00 (m, 9H), 4.40 (s, 2H), 3.90 (br d, 4H, *J* = 5.3 Hz), 3.40 (br t, 2H, *J* = 5.0 Hz), 2.45 (s, 6H), 2.00–1.00 (m, 11H). Anal. Calcd for $C_{30}H_{38}O_7S_2$: C, 62.69; H, 6.66. Found: C, 62.72; H, 6.64.

2,2-Dibutylpropane-1,3-diol (8). A mixture of diethyl malonate (6.4 g, 40 mmol), butyl bromide (13.7 g, 100 mmol), K_2CO_3 (16.6 g, 120 mmol), and tetrabutylammonium bromide (0.6 g, 2 mmol) in 120 mL of acetonitrile was stirred and refluxed for 5 d. After cooling to rt, the reaction mixture was filtered, the solid precipitate carefully washed with CH_2Cl_2, and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL), washed with H_2O (2 × 50 mL), dried over $MgSO_4$, and concentrated to give a crude oil. Purification by column chromatography (hexanes/Et_2O 95/5 and then 9/1 as eluant) afforded 7.6 g (70%) of diethyl 2,2-dibutylpropane-1,3-dioate as a thick reddish oil. ^1H NMR (80 MHz): δ 4.11 (q, 4H, *J* = 7.1 Hz), 2.00–1.75 (m, 4H), 1.60–1.00 (m, 8H), 1.15 (t, 6H, *J* = 7.1 Hz), 0.90 (bt, 6H, *J* = 5.9 Hz). Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 68.17; H, 10.34.

A solution of diethyl 2,2-dibutylpropane-1,3-dioate (8.8 g, 32 mmol) in 100 mL of anhydrous Et_2O was slowly added, under nitrogen, to a stirred suspension of $LiAlH_4$ (1.7 g, 45 mmol) in 50 mL of anhydrous Et_2O. The reaction mixture was stirred overnight, and then the excess of $LiAlH_4$ was destroyed with AcOEt (CAUTION!). The salts were dissolved with 10% aqueous H_2SO_4, and the organic phase was separated. The aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic phases were washed with 5% aqueous $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL) and dried over $MgSO_4$. The solvent was evaporated to afford 6.1 g (100%) of **8** as a thick oil. ^1H NMR (80 MHz): δ 3.50 (br s, 6H), 1.50–1.00 (m, 12H), 0.90 (br t, 6H, *J* = 5.9 Hz). Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.19; H, 12.84.

2,2-Dibutylpropane-1,3-diol Bis(4-Methylbenzenesulfonate) (3d). A solution of *p*-toluenesulfonyl chloride (13.4 g, 70 mmol) in 50 mL of pyridine was added to a stirred solution of **8** (6.0 g, 32 mmol) in 15 mL of pyridine and kept at 0 °C. The reaction mixture was stirred overnight at rt, poured into a mixture of ice (20 mL) and 36% aqueous HCl (65 mL), and extracted with CH_2Cl_2 (2 × 70 mL). The organic phase was washed with H_2O (2 × 50 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a crude solid which was crystallized from EtOH. **3d** was obtained as a solid (8.2 g, 52%): mp 93–96 °C. ^1H NMR (80 MHz): δ 7.80 (d, 4H, *J* = 8.2 Hz), 7.30 (d, 4H, *J* = 8.2 Hz), 3.80 (s, 4H), 2.50 (s, 6H), 1.50–0.90 (m, 12H), 0.80 (br t, 6H, *J* = 5.8 Hz). Anal. Calcd for $C_{25}H_{36}O_6S_2$: C, 60.46; H, 7.31. Found: C, 60.50; H, 7.28.

Synthesis of 1,7-Dioxa-4,10-diazacyclododecane (4). To a stirred solution of $LiAlH_4$ (7.0 g, 183 mmol) in anhydrous THF (120 mL) was added solid **9**[9b] (12.0 g, 36 mmol) under nitrogen, and the mixture was refluxed for 2 d. After cooling to rt, a solution of THF (30 mL) and water (13 mL) was slowly added (CAUTION!). Filtration through a sintered glass filter funnel and removal of the solvent under reduced pressure gave **12** (6.15 g, 97%) that was used without further purification. ^1H NMR (80 MHz): δ 3.65–3.50 (m, 8H), 2.80–2.65 (m, 8H), 2.50 (br s, 2H). Anal. Calcd for $C_8H_{18}N_2O_2$: C, 55.14; H, 10.41; N, 16.08. Found: C, 55.17; H, 10.43; N, 16.04.

Synthesis of 5a–c. General Procedure. A mixture of the desired tosylate (**3a** or **3b** or **3c**, 8 mmol) and **4** (1.4 g, 8 mmol) were refluxed in 120 mL of acetonitrile in the presence of Na_2CO_3 (8.5 g, 80 mmol) for 4 d. After cooling at rt, the mixture was filtered through a Celite pad and the residue washed with acetonitrile (100 mL). The solvent was evaporated under vacuum and the residue dissolved in CH_2Cl_2 (150 mL). To exchange the anion the solution was treated under stirring with aqueous 10% $NaClO_4$ (2 × 100 mL). The solvent was then removed and the crude purified by column chromatography (CH_2Cl_2/MeOH 9/1 as eluant). Yields are collected in Scheme 1. The *cis*/*trans* ratio was 2:1 in all cases.

cis-**5a**: ^1H NMR (300 MHz): δ 7.32–7.10 (m, 10H), 3.67–3.49 (m, 16H), 2.84–2.76 (m, 4H), 2.60–2.41 (m, 20H), 2.35–2.28 (m, 4H), 2.12–1.08 (m, 2H). ^{13}C NMR (75.43 MHz): δ 36.4 (d), 40.7 (t), 52.9 (t), 56.0 (t), 68.2 (t), 68.4 (t), 69.0 (t), 126.4 (br t), 128.5 (dd), 129.1 (br d), 139.6 (br s). *m*/*z* 631 (M^+); calcd for $C_{36}H_{56}N_4O_4Na$ 631.

trans-**5a**: ^1H NMR (300 MHz): δ 7.31–7.10 (m, 10 H), 3.88–3.66 (m, 8H), 3.44–3.32 (m, 8H), 3.14–2.98 (m, 8H), 2.66 (d, 2H, *J* = 12.3 Hz), 2.63 (d, 2H, *J* = 12.3 Hz), 2.43 (d, 4H, *J* = 7.6 Hz), 2.34–2.15 (m, 6H), 1.81 (t, 8H). ^{13}C NMR (75.43 MHz): δ 33.0 (d), 40.5 (t), 50.9 (t), 53.2 (t), 65.4 (t), 67.7 (t), 69.4 (t), 126.3 (br t), 128.4 (dd), 129.1 (br d), 139.6 (br s). *m*/*z* 631 (M^+); calcd for $C_{36}H_{56}N_4O_4Na$ 631.

cis-**5b**: ^1H NMR (300 MHz): δ 3.71–3.51 (m, 20H), 2.89–2.83 (m, 4H), 2.71–2.47 (m, 10H), 2.43–2.27 (m, 6H), 1.74–1.60 (m, 2H), 1.34–1.16 (m, 60H), 0.85 (t, 6H, *J* = 6.6 Hz). *m*/*z* 899 (M^+); calcd for $C_{54}H_{108}N_4O_4Na$ 899.

trans-**5b**: ^1H NMR (300 MHz): δ 3.89 (br t, 4 H), 3.72 (t, 4H, *J* = 11.7 Hz), 3.47–3.36 (m, 8H), 3.21–3.09 (m, 8H), 2.59–2.52 (m, 4H), 2.21 (d, 4H, *J* = 12.6 Hz), 2.02 (d, 4H, *J* = 13.0 Hz), 1.89–1.78 (m, 6H), 1.34–1.17 (m, 60H), 0.86 (t, 6H, *J* = 6.6 Hz). *m*/*z* 900 ($M^+ + 1$); calcd for $C_{54}H_{108}N_4O_4Na$ 899.

cis-**5c**: ^1H NMR (300 MHz): δ 7.37–7.20 (m, 10H), 4.48 (s, 4H), 3.82–3.43 (m, 20H), 3.20–2.28 (m, 24H), 1.63-1.24 (m, 22H). *m*/*z* 830 ($M^+ - 1$); calcd for $C_{48}H_{80}N_4O_6Na$ 831.

trans-**5c**: ^1H NMR (300 MHz): δ 7.37–7.20 (m, 10H), 4.50 (s, 4H), 3.87 (t, 4H, *J* = 11.0 Hz), 3.70 (t, 4H, *J* = 11.0 Hz), 3.46–3.34 (m, 12H), 3.18–3.06 (m, 8H), 2.57–2.50 (m, 4H), 2.19 (d, 4H, *J* = 12.6 Hz), 2.00 (d, 4H, *J* = 12.6 Hz), 1.87–1.76 (m, 6H), 1.62–1.53 (m, 4H), 1.38–1.22 (m, 12H), 1.14–1.07 (m, 4H). *m*/*z* 831 (M^+); calcd for $C_{48}H_{80}N_4O_6Na$ 831.

Synthesis of 2a–c. General Procedure. 2a–c were obtained in quantitative yields from **5a–c** as described in ref 9b.

cis-**2a**: ^1H NMR (300 MHz): δ 7.30–7.10 (m, 10H), 3.81–3.74 (m, 4H), 3.72–3.63 (m, 8H), 3.58–3.50 (m, 4H), 2.94–2.86 (m, 4H), 2.81–2.72 (m, 4H), 2.69–2.57 (m, 16H), 2.29–2.22 (dd, 4H, *J* = 12.5 Hz, *J* = 6.7 Hz), 1.96 (m, 2H). ^{13}C NMR (75.43 MHz): δ 36.5 (d), 36.9 (t), 53.5 (t), 58.0 (t), 59.3 (t), 68.4 (t), 68.9 (t), 125.5 (dt), 128.0 (dd), 129.3 (dt), 140.9 (br s). *m*/*z* 609 ($M^+ + 1$); calcd for $C_{36}H_{56}N_4O_4$ 608. Anal. Calcd for $C_{36}H_{56}N_4O_4$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.05; H, 9.25; N, 9.22.

trans-**2a**: ^1H NMR (300 MHz): δ 7.30–7.10 (m, 10H), 3.82–3.70 (m, 8H), 3.59–3.48 (m, 8H), 3.13–3.04 (m, 4H), 2.82–2.74 (m, 4H), 2.69–2.46 (m, 16H), 2.26–2.20 (dd, 4H, *J* = 12.6 Hz, *J* = 6.5 Hz), 1.90 (m, 2H). ^{13}C NMR (75.43 MHz): δ 37.4 (t), 37.9 (d), 54.1 (t), 56.2 (t), 59.2 (t), 66.3 (t), 69.0 (t), 125.5 (dt), 128.0 (dd), 129.3 (dt), 141.1 (br s). *m*/*z* 609 ($M^+ + 1$); calcd for $C_{36}H_{56}N_4O_4$ 608. Anal. Calcd for $C_{36}H_{56}N_4O_4$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.00; H, 9.28; N, 9.25.

cis-**2b**: ^1H NMR (300 MHz): δ 3.80–3.58 (m, 12H), 3.60–3.50 (m, 4H), 2.99–2.72 (m, 8H), 2.68–2.50 (m, 12H), 2.28–2.18 (m, 4H), 1.63–1.50 (m, 2H), 1.24–1.18 (m, 60H), 0.86 (t, 6H, *J* = 6.6 Hz). *m*/*z* 877 ($M^+ + 1$); calcd for $C_{54}H_{108}N_4O_4$ 876. Anal. Calcd for $C_{54}H_{108}N_4O_4$: C, 73.92; H, 12.41; N, 6.39. Found: C, 73.95; H, 12.39; N, 6.41.

trans-**2b**: Using the procedure described in ref 9b, only a mixture of *trans*-**2b** and of *trans*-**5b** was obtained.

cis-**2c**: The decomplexation of *cis*-**5c** was never performed.

trans-**2c**: ^1H NMR (300 MHz): δ 7.37–7.20 (m, 10H), 4.50 (s, 4H), 3.81–3.70 (m, 8H), 3.60–3.44 (m, 10H), 3.45 (t, 4H, *J*

= 6.6 Hz), 3.14–3.04 (m, 4H), 2.89–2.81 (dt, 4H, J = 13.8 Hz, J = 4.7 Hz), 2.69–2.57 (m, 8H), 2.50–2.45 (br d, 4H, J = 14.6 Hz), 2.21–2.14 (dd, 4H, J = 12.5 Hz, J = 6.2 Hz), 1.64–1.48 (m, 6H), 1.38–1.20 (m, 14H). m/z 807 ($M^+ - 1$); calcd for $C_{48}H_{80}N_4O_6$ 808. Anal. Calcd for $C_{48}H_{80}N_4O_6$: C, 71.25; H, 9.96; N, 6.92. Found: C, 71.28; H, 9.98; N, 6.89.

Alkali Picrates Extraction under Liquid/Liquid Two-Phase Conditions. General Procedure. Into a 20-mL centrifuge tube, equipped with a small magnetic stirring bar, were introduced 5.0 mL of a 2.5 × 10^{-3} M solution of the required ligand (**2a–c**) in $CHCl_3$ and 5.0 mL of a 2.5 × 10^{-3} M aqueous solution of the appropriate alkali picrate. The tube was then stoppered to prevent evaporation; the mixture was stirred for 72 h at 20 °C and then centrifuged at 3000 rpm for 10 min. A 1.0-mL aliquot of the aqueous layer was diluted 1:100 with water. The UV absorption of each solution was measured against the appropriate blank solution at the appropriate wavelength (Li, Cs: 356 nm; Na: 354 nm; K: 355 nm). Calculations were performed as described in ref 9b. All data are collected in Table 1. The same procedure was applied to the study of the concentration effect on the complexation rates; all data are reported in Table 2.

Alkali Picrates Extraction under Solid/Liquid Two-Phase Conditions. General Procedure. A 5.0 mL 2.5 × 10^{-4} M solution of *cis*- or *trans*-**2a** in $CHCl_3$ was placed in a 10-mL centrifuge tube, equipped with a magnetic stirring bar. A 100 molar excess of the appropriate solid alkali picrate was then added, and the mixture stirred at 20 °C for 20 h. A 1-mL aliquot of the solution was diluted 1:10 with $CHCl_3$. The UV absorption of each sample was measured as described in ref 12. All data are collected in Table 3.

Complexation of $NaBPh_4$ by *cis*-2a. A 0.015 mmol amount of *cis*-**2a** (9.13 mg) was dissolved in a NMR tube with 0.5 mL of $CDCl_3$, and 0.015 mmol (5.13 mg) of $NaBPh_4$ was added. The solution was sonicated, and ^1H NMR (300 MHz) spectra were recorded after 5, 20, and 30 min. After this time the complexation was complete. ^1H NMR (300 MHz): δ 7.43–7.37 (m, 7H), 7.31–7.17 (m, 6H), 7.10–7.00 (m, 11H), 6.92–6.85 (m, 6H), 3.51–3.25 (m, 16H), 2.54–2.52 (m, 4H), 2.49–2.14 (m, 24H), 2.20–1.89 (m, 2H).

X-ray Crystallographic Analysis of *cis*-2a and [$Na^+ \subset$ *trans*-2a][BPh_4^-] ($CH_3COOC_2H_5$). The diffaction experiments were performed on an Enraf–Nonius CAD-4 diffractometer, using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The unit-cell parameters, reported in Table 4, were determined from the setting angles of twenty-five intense reflections having a θ value in the range 10.0–14.0°. The diffracted intensities were collected at rt with variable scan speed out to a maximum 2θ angle of 50°. Three standard reflections were monitored every 120 min and no crystal decay or long range fluctuations of the primary beam intensity were observed. Details on the data collections are reported on Table 4. The diffracted intensities were corrected for Lorentz, polarization, and background effects. Scattering factors for neutral atoms and anomalous dispersion corrections for scattering factors were taken from refs 22 and 23, respectively.

The structures were solved by direct methods using SHELXS86[24] and refined by full-matrix least-squares, minimizing the function $\sum w(F_o - k|F_c|)^2$. Weights assigned to individual observations were $1/\sigma^2(F_o)$, where $\sigma(F_o) = [\sigma^2(I) + (pI)^2]^{1/2}/2F_oL_p$, $\sigma^2(I)$ is the standard deviation for each reflection as derived from counting statistics, p is a coefficient for improving the goodness of fit, and L_p is the Lorentz-polarization factor. Anisotropic thermal parameters were assigned to all non hydrogen atoms. Hydrogen atoms were placed in idealized positions and refined riding on their parent atom with fixed isotropic thermal parameters (B = 5.0 Å^2). Most of the calculations were performed on a PDP11/73 computer using the SDP-Plus Structure Determination Package.[25]

Table 4. Summary of Crystal Data and Data-Collection/Analysis Parameters for *cis*-2a and [$Na^+ \subset$ *trans*-2a][BPh_4^-]·($CH_3COOC_2H_5$)

formula	$C_{36}H_{56}O_4N_4$	$[C_{36}H_{56}O_4N_4Na]^+[C_{24}H_{20}B]^-C_4H_8O_2$
M	608.87	1039.21
crystal system	orthorhombic	monoclinic
space group	*Pbca* (No. 61)	*C2/c* (No. 15)
a/Å	13.814(2)	19.290(3)
b/Å	22.021(2)	16.874(2)
c/Å	22.959(2)	18.068(2)
β/deg	–	96.47(2)
U/Å^3	6984(1)	5844(1)
Z	8	4
D_c/g cm^{-3}	1.158	1.181
F(000)	2656	2240
crystal dimensions/mm	0.30 × 0.20 × 0.15	0.25 × 0.15 × 0.15
μ(Mo Kα)/ cm^{-1}	0.704	0.760
absorption correction	no	no
θ-range/deg	3-25	3–25
scan mode	w	w
scan range/deg	0.75 + 0.35 tan θ	0.85 + 0.35 tan θ
required $\sigma(I)/I$	0.01	0.01
max scan time/s	90	80
octants of recipr space collected	h,k,l	h,k,l
crystal decay	no	no
no. collected reflections (at rt)	6593	5313
no. unique observed reflns	1857 [$I > 2\sigma(I)$]	2465 [$I > 3\sigma(I)$]
no. of refined parameters	397	354
fudge p factor	0.035	0.050
max shift/error	<0.1	<0.2
R[a]	0.056	0.046
R'[b]	0.050	0.058
goodness of fit	1.445	1.628
max peak diff Fourier map/e Å^{-3}	0.22	0.23

[a] $R = \sum(|F_o - k|F_c||)/\sum F_o$. [b] $R' = [\sum w(F_o - k|F_c|)^2/\sum wF_o^2]^{1/2}$. Goodness of fit = $[\sum w(F_o - k|F_c|)^2/(N_o - N_v)]^{1/2}$ where N_o and N_v are the number of observations and refined parameters, respectively. $w = 4F_o^2/\sigma^2(F_o^2)$ where $\sigma(F_o^2) = [\sigma^2(I) + (pI)^2]^{1/2}/L_p$.

Molecular Mechanic Calculations. The MCMM searches were performed on *cis*- and *trans*-**2d** and on **1c** using the 3.1 version of Batchmin.[17] A Monte Carlo global search (MCMM) was performed by randomly varying 5 ± 1 dihedral angles at each step out of a total of 16 dihedrals, starting from a random conformation.[26] Chirality check (CHIG) was active to prevent *cis*/*trans* isomerization during each search. In the case of *cis*-**2d**, the search was started from a modification of the X-ray structure of *cis*-**2a** by replacing the benzyl groups with methyls. Each search was the result of five searches of 4000 MCMM steps each: after the first 4000 steps the new global minimum was selected as a new starting structure for the subsequent search. After a total of about 10000 steps, in each of the three MCMM searches (*cis* and *trans*-**2d** and **1c**) no new low-energy minima were found; in particular, the global minimum was left unchanged from the one found in the first 4000 steps. The subsequent 10000 steps were thus performed by varying different dihedral angles. In this way, all the torsions were taken into account at the end of the conformational analysis, and artificial duplication of the results was avoided. In the latter 10000 steps the global minimum was always unchanged in each of the three searches, and all the found conformations were sampled several times, thus ensuring convergence of the conformational analysis.

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(25) Frenz, B. A. and Associates. *SDP Plus Version 1.0, Enraf Nonius,* 1980.

(26) The structures of the minimum energy conformations obtained in the MCMM/EM seaches for compounds *cis*- and *trans*-**2d** (Figure 4), and the first five minimum energy conformations of the MCMM/EM search for compound **1c** (Figure 6) are available in PDB format at ECTOC1 - The First Electronic Conference on Trends in Organic Chemistry (http://www.ch.ic.ac.uk/ectoc/papers/raimondi/), started on June 12, 1995. The material presented at ECTOC1 will remain available for two years.

The MCMM searches were perfomed with AMBER united-atoms force field, due to the need of minimizing the required amount of CPU time. All conformations were saved that differed up to 50 kJ/mol (12 kcal/mol) from the global minimum: this range was large enough to ensure that in the subsequent minimizations with the other force fields no significant minima were lost (as clearly results from inspection of the output files). After addition of hydrogens and lone pairs (HADD), all the structures were reminimized with MM2, using the MULT (Multiconformer Minimization) option of Batchmin. Symmetry of the structures was taken into account only for elimination of duplicate conformers, so as not to bias the search toward highly symmetric structures. To eliminate duplicate structures, a comparison was made on heavy atoms only. The default gradient criteria were met at the end of each minimization with both force fields ($\leq$0.01 kJ/Å mol). Macromodel 3.0 was used to evaluate the nature of the conformations within 2.5 kcal/mol from each global minimum: all these points were found to have no imaginary frequencies.[26]

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