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Switching from Separated to Contact Ion-Pair Binding Modes with Diastereomeric Calix[4]pyrrole Bis-phosphonate Receptors

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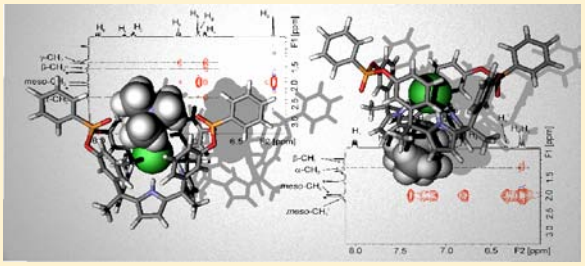
Supporting Information

ABSTRACT: We describe the design, synthesis and conformational assignment of three diasteromeric bis-phosphonate cavitands based on an aryl extended calix[4]pyrrole tetrol scaffold. The diastereoisomers differ in the relative spatial orientation of the P═O groups installed at their upper rims. We demonstrate that these compounds act as heteroditopic receptors for ion pairs forming ion-paired 1:1 complexes with alkylammonium (quaternary and primary) chloride salts in dichloromethane (DCM) solution and in the solid-state. ^{1}H NMR titrations indicate that the complexes are highly stable thermodynamically and kinetically. In the case of tetraalkylphosphonium/ammonium chloride guests, the host featuring the two P═O groups directed outwardly with respect to the aromatic cavity, **4oo**, produces the most thermodynamically stable complexes. Conversely, for the primary alkyl ammonium chloride, the most effective receptor is the diastereoisomer **4ii** with the two P═O groups converging on top of the aromatic cavity. In the nonpolar DCM solvent, the size of the quaternary cation has a strong impact in the thermodynamic stability of the complexes and their binding geometry. We use 2D-ROESY experiments to map out the binding geometries of the 1:1 complexes formed in solution. The 1:1 complexes of the **4oo** host with the chloride salts have a *separated* arrangement of the bound ion-pair. In contrast, those of the **4ii** host display a *close-contact* arrangement. We also investigate the same complexation processes in acetonitrile (ACN) solution. Both the salt and the initially formed anionic complex are fully dissociated in this more polar solvent. The receptors show an analogous trend in their binding affinities for quaternary phosphonium/ammonium chloride salts to the one seen in DCM solution. However, in ACN solution, the magnitudes of the binding affinities are reduced significantly and the size of the cation does not play a role. In addition, the inversion in the trend of relative binding affinities of the complexes, which was revealed in DCM solution, is eradicated in ACN when changing the cation substitution from quaternary to primary.



INTRODUCTION

Ion-pair recognition with heteroditopic receptors is an emerging field of research.[1] The degree of ion pair separation upon complexation is one of the key issues for understanding, controlling and exploiting ion-pair recognition. For ion-paired complexes, three different binding modes are reported in the literature: *ion-separated*, *solvent-bridged*, and *close-contact*.[2] Interestingly, an ion-pair receptor displaying the three types of recognition modes for the cesium cation was recently reported.[3] Nevertheless, the number of examples of ion-pair receptors capable of exhibiting different binding modes is still scarce.[4,5] Typically, the switching between the different binding modes is regulated by changing the anion or the cation of the bound ion-pair. Here, we demonstrate an unprecedented induced regulation of ion-pair binding geometry through modification of the relative spatial configuration of the P═O groups installed at the upper rim of a series of diastereomeric aryl-extended phosphonate calix[4]pyrrole receptors.

Calix[4]pyrroles are a well-known class of neutral receptors for selective anion-binding.[6−8] Anion binding fixes the calix[4]pyrrole scaffold in the cone conformation.[9] In this conformation, the calix[4]pyrrole unit displays a bowl-shaped cavity, delineated by the four pyrrole rings, opposite to the bound anion. This shallow and electron-rich aromatic cavity begs for the inclusion of electropositive guests.

When working in non polar organic solvents, ion-pairing between the negatively charged calix[4]pyrrole•anion complex and the cation must also be taken into account.[10,11] Not surprisingly, under these circumstances, calix[4]pyrroles have been claimed to function as ditopic ion-pair receptors (Figure

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1a).[12] Compared to simple ion receptors, ion-pair receptors usually exhibit improved binding affinities as a consequence of simultaneous binding of both ions.[1,2,13,14]

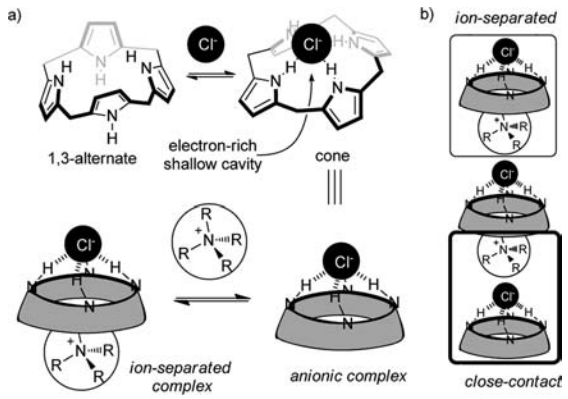


Figure 1. Schematic representations of (a) the conformational change experienced by calix[4]pyrrole receptors in nonpolar solvents upon chloride binding and subsequent ion-paired complex formation; (b) a typical solid-state columnar motif exhibited by ion-paired complexes of calix[4]pyrroles highlighting undistinguishable arrangements of the ion-pair in the 1:1 complex.

In many cases, the columnar crystal packing motif exhibited by the ion-paired calix[4]pyrrole termolecular complexes in the solid-state does not allow one to distinguish unambiguously between *close-contact* and *ion-separated* arrangement for the 1:1 complex (Figure 1b).[15]

Aryl-extended calix[4]pyrroles **1** are obtained by substituting each of the four *meso* carbon atoms of the parent octamethyl compound **2** with one aryl group.[16] When the *α,α,α,α*-isomers of aryl extended calix[4]pyrroles adopt the cone conformation, the additional deep aromatic cavity is open only at one end. The closed end of the cavity is delimited by four convergent pyrrole NHs (Figure 2). The size and volume of this *endo* functionalized cavity is large enough to include halides.

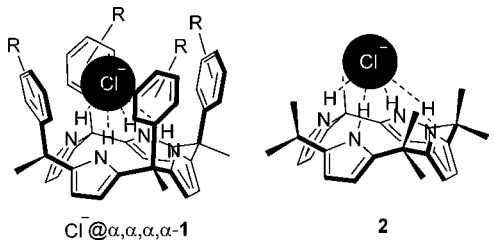


Figure 2. Structures of the *α,α,α,α*-**1**-isomer of aryl-extended calix[4]pyrrole and of the octamethylcalix[4]pyrrole **2** involved in the formation of anionic complexes with chloride.

The structures in solution of ion-paired complexes derived from calix[4]pyrrole receptors and salts are under active investigation. Recent reports suggested the selective inclusion of suitably sized cations in the electron-rich cavity opposite to the bound anion, and hence the concomitant formation of ion-paired complexes with a *separated* arrangement of ions (Figure 1) both in nonpolar[14] or polar organic solvents (i.e., acetonitrile).[17]

Tetraphosphonate cavitands, derived from resorcinarene, are known to be excellent molecular receptors for cationic species such as methylammonium[18,19] or methylpyridinium[20,21] ions or even neutral guests like alcohols.[22−25] The number of bridging P═O groups, placed at the upper rim of the resorcin[4]arene scaffold, and their relative orientation with respect to the aromatic cavity are crucial in defining the binding properties of the receptors. In particular, high stability constants were measured for supramolecular complexes involving intracavity methylammonium and methylpyridium guests if complexation occurs through the cooperative effect of several converging and inwardly directed P═O groups. When active hydrogens are present on the N^+, additional hydrogen bonds with the P═O group set in, enhancing the overall complexation. For this reason, methylammonium salts are preferentially complexed over methylpyridinium ones.[21]

Inspired by these findings, we became interested in designing unprecedented ditopic receptors for ion-pair recognition. We combined the known anion binding properties of aryl-extended calix[4]pyrrole receptors **1** with the recognition characteristics displayed by phosphonate cavitands toward alkylammonium cations. Our synthetic plan involved the installation of several phosphonate groups at the upper rim of an aryl-extended calix[4]pyrrole scaffold. The phosphonate groups are introduced as bridges between two adjacent *meso*-phenyl substituents similarly to the approach used for the resorcinarene based receptors.[26]

In this manuscript, we report the synthesis of a new family of aryl-extended calix[4]pyrroles **4** with two phoshonate groups as bridging groups at their upper rim. Three diastereomeric receptors displaying all possible configurations of the two P═O groups (**ii** = in, in; **io** = in, out; **oo** = out, out) have been prepared. We also report on the binding properties of the three stereoisomers of **4**, both in solution and in the solid state, with several alkylammonium ion-pairs. We have demonstrated that the magnitude of the binding affinities and the location of the cation in the formed 1:1 ion-paired complexes are strongly modulated by the spatial orientation of the P═O groups.

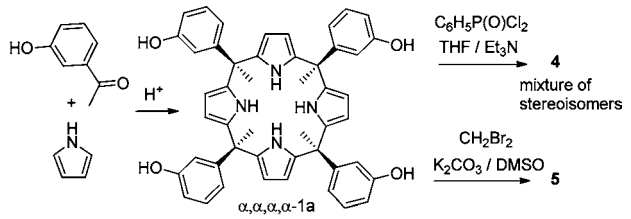
RESULTS AND DISCUSSION

Synthesis. We encountered serious synthetic difficulties in the installation of four phosphonate groups in the upper rim of the known tetramethyl calix[4]pyrrole-resorcinarene hybrid.[27] For this reason, we selected tetrol **1a** as an alternative parent aryl-extended calix[4]pyrrole for the installation of only two phosphonate bridging groups. The synthesis of the three diastereomeric phosphonate cavitands **4** derived from **1a** is depicted in Scheme 1. We also prepared the bis-methylene bridged cavitand **5** as a reference compound for the binding studies.

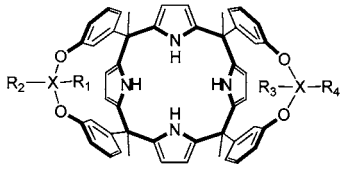
meta-Hydroxyphenylmethylcalix[4]pyrrole **1a** was obtained as a mixture of configurational isomers by condensation of freshly distilled pyrrole with 3-hydroxyacetophenone under acidic conditions following literature procedures.[28] The configurationally pure *α,α,α,α*-**1a** isomer was isolated by crystallization of the mixture of isomers from acetonitrile solution. Room temperature reaction of the *α,α,α,α*-**1a** tetrol and dichloro(phenyl)phosphane oxide[26,29] in the presence of triethylamine in tetrahydrofuran solution during 2 h produced a mixture of the three bis-phosphonate stereoisomers **4ii**, **4io**, and **4oo**. Each pure steroisomer was isolated by semi-preparative HPLC (Spherisorb silica 250 × 20 mm, 5 μm) using DCM/MeOH 99:1 as eluant and crystallized from acetonitrile solution in yields ranging from 10 to 25%.

Bis-methylene bridged cavitand **5** was synthesized from the reaction of *α,α,α,α*-**1a** tetrol with dibromomethane using dry

Scheme 1. Synthetic Scheme for the Preparation of Bis-phosphonate Calix[4]pyrrole Receptors 4 and Bis-methylene Cavitand Analogue 5



	R_1	R_2	R_3	R_4	X
4ii	=O	Ph	=O	Ph	P
4io	=O	Ph	Ph	=O	P
4oo	Ph	=O	Ph	=O	P
5	H	H	H	H	C



potassium carbonate as base in dry DMSO solution heated to 80 °C for 3 h. The pure compound **5** was isolated in 10% yield using semipreparative reverse-phase HPLC. The presence of two methylene bridges in the upper rim of **5** endorsed this cavitand with a conformational rigidity similar to that of the phosphonate receptor series **4**.

Configurational Assignment. We performed the configurational assignment of the three diastereoisomers of **4** by a combination of ^{1}H NMR spectroscopy and single crystal X-ray crystallographic analysis. The solid-state structures of two steroisomers, **4ii** and **4oo**, are shown in Figure 3. In both cases,

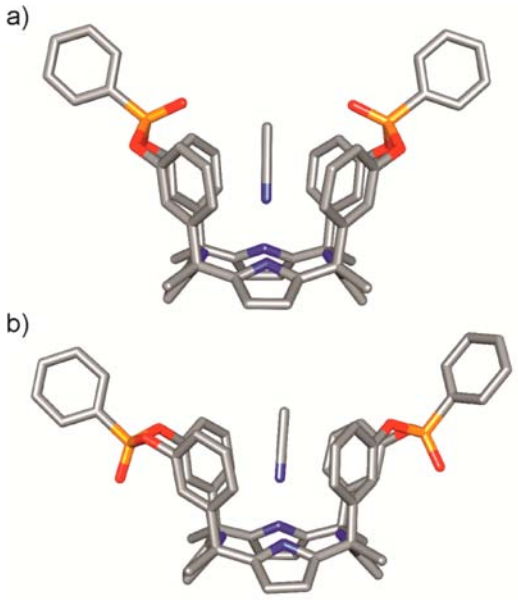


Figure 3. Solid-state structures of the diastereoisomers **4ii** (a) and **4oo** (b). Hydrogen atoms and lattice solvent molecules have been omitted for clarity.

the calix[4]pyrrole core adopts the cone conformation with one molecule of acetonitrile included in the deep aromatic cavity. In the solid state, the 14-membered rings delineated by the bridged phosphonate-group, two *meso*-phenyl groups, their corresponding *meso*-carbons and one pyrrole ring showed a preferred conformation in which the phenyl substituent of the phosphorus atoms is directed away from the pyrrole unit. This conformation is observed for both types of macrocycles, the one having inwardly directed P═O groups and the one with outwardly directed P═O groups. The phosphonate bridges introduced in the upper rim of the receptor also served to significantly reduce the conformational freedom of the cavitand receptors **4**.

Receptors **4ii** and **4oo** possess C_{2v} symmetry and show a reduced number of proton signals in their ^{1}H NMR spectra (Figures S4 and S6, Supporting Information) compared to **4io**. We performed the complete assignment of the signals observed in the ^{1}H NMR spectra of the three diastereomers by means of 2D experiments. As an example, Figure 4 shows the downfield

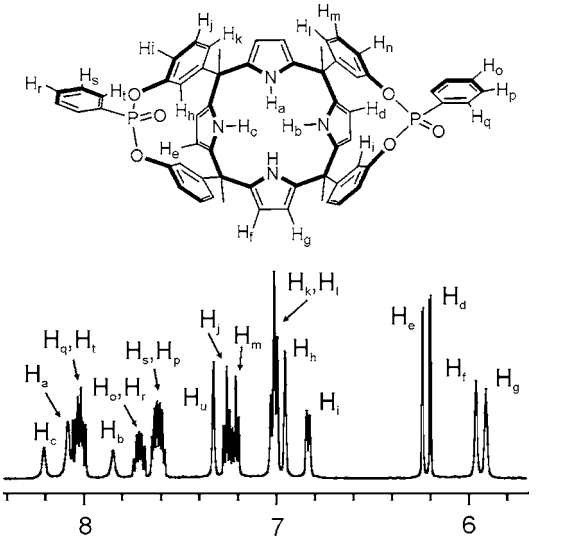


Figure 4. Selected downfield region of the ^{1}H NMR spectrum (400 MHz) of the **4io** stereoisomer at 298 K in DCM solution. The proton assignment is shown in the molecular structure of the **4io** receptor represented on top.

region of the ^{1}H NMR spectra of the **4io** stereoisomer having C_s symmetry. Three broad singlets resonating at δ = 8.29, 8.09, and 7.88 ppm with relative intensities 1:2:1 were assigned to the NH protons. The two pyrrole rings not involved in the 14-member macrocyles display δ-pyrrole protons that are chemically nonequivalent (H_f, H_g) and were assigned to the signals resonating at δ= 5.96 and 5.91 ppm. On the contrary, the other two pyrrole rings that are included in the macrocycles, although experiencing different magnetic environments, have chemically equivalent β-pyrrole protons.

We assigned the signals resonating at δ = 6.24 and 6.2 ppm to the β-pyrrole protons H_d and H_e of the pyrrole rings in the macrocycles containing the phosphonate-out and phosphonate-in bridges, respectively. The ^{31}P NMR of **4io** displays two different signals resonating at δ = 15.5 and 13.2 ppm corresponding to the two chemically nonequivalent phosphorus nuclei. The signals of the *ortho*-protons in the two chemically nonequivalent phenyl phosphonate groups exhibit $^3J_{P-H}$ (~ 14 Hz) coupling.[30]

Binding Studies of Aryl Extended Calix[4]pyrrole 6 with TMPCl and TBACl in DCM Solution. Before exploring the binding properties of receptors **4** with alkylammonium/phosphonium salts in DCM solution, we decided to investigate the complexation between these guests (Figure 5) and aryl-extended calix[4]pyrrole **6**. We wanted to use the obtained data as references in the forthcoming study of receptors **4**.

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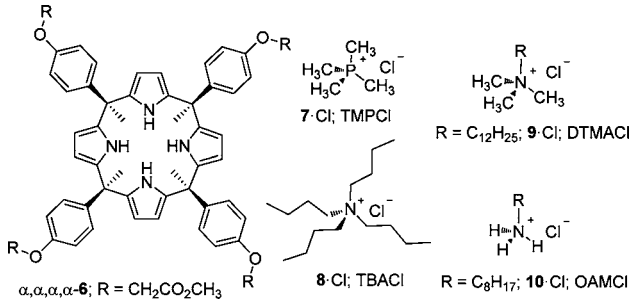


Figure 5. Line drawing structures of aryl-extended calix[4]pyrrole **6**, and the alkylammonium/phosphonium chloride salts used in this study.

The addition of less than 1 equiv of TMPCl, 7·Cl, to a 1 mM DCM solution of **6** produced separated proton signals for the free and bound receptor (Figure 6b). We determined the

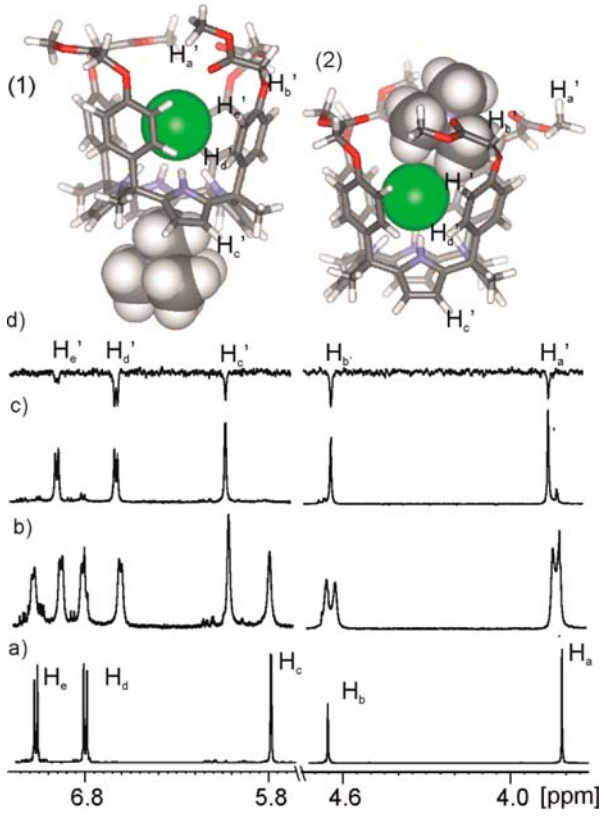
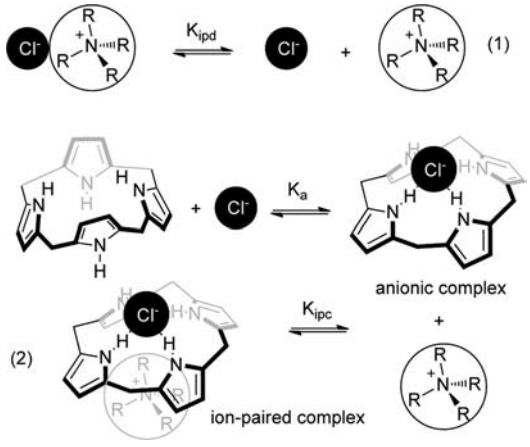


Figure 6. Sections of the ^{1}H NMR spectra acquired during the titration of **6** with TMPCl: (a) 0 equiv; (b) 0.5 equiv; (c) 1 equiv; (d) GOESY experiment with selective excitation of the signal of the methyl protons of TMP of c. Top: Proposed binding geometries for the ion-paired TMPCl@**6** complex in DCM solution (1) ion-separated, (2) close contact.

stoichiometry of the formed complex as 1:1 and estimated an association constant value ($K_{a,exp}$) larger than 10^4 M^{-1} because in the presence of 1 equiv of TMPCl only the signals for the bound receptor were detected in the ^{1}H NMR spectrum of the mixture (Figure 6b). The inclusion of the chloride in the deep aromatic cavity of **6** was evidenced by the observation of a strong downfield shift ($\Delta\delta$ = 3.3 ppm) in the signal of the NH protons and a moderate upfield shifts for the *meso*-phenyl protons of the bound receptor. Evidence of the concomitant complexation of the cation could be inferred from the upfield shift experienced by the signal of the methyl groups of the TMP cation. To map out the preferred location of the TMP cation in the solution binding geometry of the 1:1 complex, TMPCl@**6**, we performed a GOESY (gradient enhanced nuclear Overhauser effect spectroscopy) experiment (Figure 6d). Selective irradiation of the signal of the methyl group of bound TMP produced inverted signals for the β-pyrrole protons, the *meso*-methyl groups, and the signals of the methyl and alpha-methylene protons of the ester groups at the upper rim of **6** (Figure 6d). Taken together, these results gave support to the coexistence of two putative binding geometries for the 1:1 ion-paired TMPCl@**6** complex in DCM solution. One exhibiting an ion-pair separated arrangement (Figure 6(1)) and the other displaying a *close-contact* or intimate arrangement of the ions, both being included in the deep aromatic cavity of receptor **6** (Figure 6(2)). In striking contrast with the observations presented above, the addition of 1 equiv of TBACl, **8**·Cl, to a 1 mM solution of **6** in DCM did not produce noticeable changes in the chemical shift values of the proton signals of the aryl-extended calix[4]pyrrole receptor. This finding indicated that in DCM solution the binding affinity of receptor **6** for TBACl is strongly reduced compared to TMPCl.[31]

Theoretical Binding Models for Ion-Pair Recognition with Neutral Hosts. Sessler, Gale, Schmidtchen, et al. already noticed strong cation size effects in the complexation of **2** with ammonium salts.[6,14] A likely explanation for this significant cation effect was put forward by the same authors suggesting a stepwise binding mechanism, whereby the calix[4]pyrrole receptor binds the chloride anion initially to form a cone-conformation 1:1 anionic complex with an electron-rich bowl-shaped cavity opposed to the bound chloride (Scheme 2). The

Scheme 2. Proposed Equilibria Involved in the Solution Binding of Ion-Pair Salts in Nonpolar Solvents with Ditopic Calix[4]pyrrole Receptor[6,14]



formed 1:1 anionic complex subsequently interacts with the cation to yield an ion-paired complex (Scheme 2). The magnitude of the latter cation complexation is strongly dependent on the match between the cavity and the cation size. In DCM solution, strong ion pairing is expected for both the organic salt (1) and the 1:1 complex (2). The assumption that relatively large cations are more prone to dissociation in nonpolar DCM solution, thus, increasing the available concentration of free anion proved not to be consistent with the reported data and also with the results described here.

Mathematical treatments for the equilibria involved in the complexation of ionic species in nonpolar media by neutral hosts, which explicitly considers both ion pairing processes (1) and (2) have been reported and validated experimentally.[32,33] These studies demonstrated that the existence of ion-pairing processes in solution causes the experimentally determined values in the form of $K_{a,exp}$ (3) to be concentration dependent. For this reason, the application of the complete equilibrium treatment requires the determination of $K_{a,exp}$ values at different concentrations. In this and the following sections of the manuscript, we do not explicitly consider in the measurement of the reported association constant values the ion-pair dissociation equilibrium of the salt (1) or the ion-pairing equilibrium yielding the neutral 1:1 complex (2).[34]

We were restricted by the solubility of the receptors and the sensitivity of ^{1}H NMR spectroscopy to use a reduced range of concentrations for our investigations. For this reason and as frequently encountered in literature, the values reported here for the association constant in DCM solutions correspond to experimental binding constant, $K_{a,exp}$, of the form:

$$H + C^+A^- \leftrightarrow H{\cdot}C^+A^-;$$

$$K_{a,exp} = [H{\cdot}C^+A^-]/[H][C^+A^-] \text{ in } M^{-1} \text{ units} \quad (3)$$

This treatment implicitly assumes that the salt ion-pair is the active component and that the complex is fully ion-paired (an equivalent expression applies when both the guest salt and the complex are 100% dissociated (see effect of the solvent section)); however, this is quite improbable in low dielectric constant solvent.

Effect of the Structure of the Phosphonate Stereoisomers 4 in the Binding with TMPCl. The interaction of the three stereoisomers of **4** with TMPCl, 7·Cl, was probed in DCM solution using ^{1}H NMR and ^{31}P NMR titrations. We initially focused on the evaluation of the binding properties featured by the stereoisomer **4ii**, specifically designed to function as a ditopic receptor for TMPCl. Nevertheless, we also considered the binding properties of the other two stereisomers **4oo** and **4io** with TMPCl. These two latter hosts were very useful in teaching us basic lessons on the fundamental nature of the interactions driving ion-pair recognition with bisphosphonate calix[4]pyrrole receptors **4**.

The three cavitands **4** are readily soluble in DCM. Titration experiments were performed by adding two doses of 0.5 equiv of TMPCl to NMR tubes containing individual DCM solutions of each stereoisomer. The initial addition of 0.5 equiv of TMPCl to **4ii** induced the appearance of a new set of proton signals in the ^{1}H NMR spectrum of the mixture and two new phosphorus signals in the ^{31}P NMR spectrum. The new signals in the ^{31}P NMR spectrum were assigned to the phosphorus atoms of bound **4ii** (broad, δ = 12.9 ppm) and the phosphorus atom of bound TMP (δ = 24.3 ppm) involved in the TMPCl@**4ii** complex (Figure 7). The phosphorus atoms of free **4ii** and free TMPCl resonated at δ = 14.6 ppm and δ = 26.9 ppm, respectively. In turn, the new set of proton signals was assigned to the protons of the bound receptor in the TMPCl@**4ii** complex. The integral ratio of proton signals for the free and bound **4ii** was 1:1. The signals of the bound pyrrole NHs experienced significant downfield shifts ($\Delta\delta$ > 3.5 ppm) as a result of their involvement in the formation of hydrogen bonds with the included chloride. One of the signals of the β-pyrrole protons and all the signals of the aromatic protons of the *meso*-phenyl substituents of **4ii** experienced noticeable upfield shifts

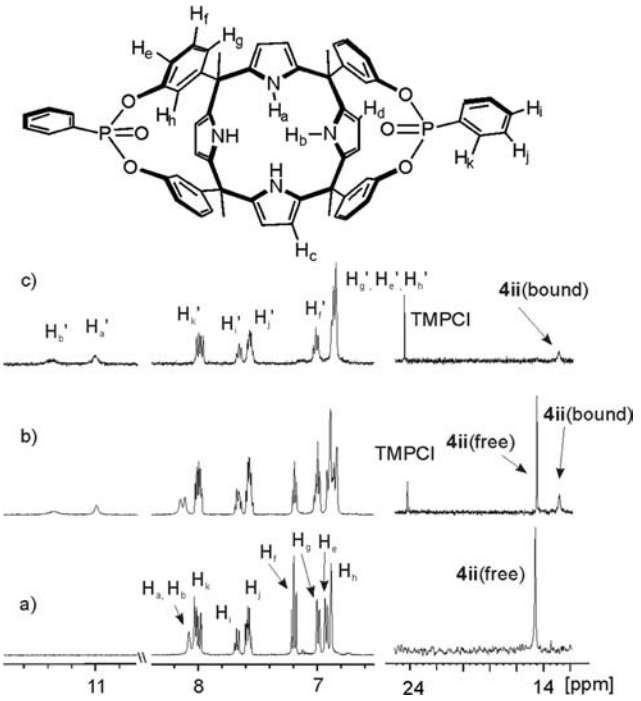


Figure 7. Selected regions of the ^{1}H and ^{31}P NMR spectra acquired during the titration of **4ii** with TMPCl: (a) 0 equiv; (b) 0.5 equiv; and (c) 1 equiv added.

in the bound receptor. On the contrary, the signals of the phenyl-phosphonate protons were almost unaffected (Figure 7). Taken together, these observations suggested the existence of a conformational change of the calix[4]pyrrole core of **4ii**, probably from 1,3-alternate to cone, induced by complexation with TMPCl. The observation of separate proton signals for the free and bound receptor **4ii** indicated that the chemical exchange between them is slow on the ^{1}H NMR time scale. We had observed a similar exchange dynamics with aryl extended calix[4]pyrrole **6**. In addition, the signal of the methyl protons of the TMP cation experienced a significant upfield shift (δ = 1.16 ppm; $\Delta\delta$ = −1.01 ppm, Supporting Information). The addition of 1 equiv of TMPCl induced the exclusive observation of the signals assigned to the proton and phosphorus atoms in the TMPCl@**4ii** complex. These results indicated that the value of the experimental association constant, $K_{a,exp}$, for the TMPCl@**4ii** complex is higher than 10^4 M^{-1} and cannot be measured accurately by ^{1}H NMR titrations. When more than 1 equiv of TMPCl was added, the chemical shifts of the proton signals of the bound **4ii** receptor were not affected. However, the proton signal of the methyl groups of TMP cation and its phosphorus atom shifted downfield. This observation was indicative of the existence of a fast exchange on the ^{1}H NMR time scale between free and bound TMP cations. The inspection of different exchange dynamics between free and bound receptor and between free and bound cation pointed to the existence of two different exchange processes. Because of the inclusion of the anion in the deep aromatic cavity of **4ii**, the chemical exchange between free and bound host requires a conformational change of the calix[4]pyrrole core.[35] Conversely, the chemical exchange between free and bound TMP cation can occur without this requirement. The TMP cation is located at the periphery of the anionic inclusion complex, either close to the phosphonate groups of the upper rim or partially included in the shallow

aromatic cavity distal to the bound anion that is defined by the pyrrole rings of the calix[4]pyrrole core in cone conformation. A 2D ROESY experiment carried out in the sample containing 1 equiv of TMPCl revealed the existence of negative cross peaks between the doublet of the methyl protons of TMP and the aromatic *para* protons (H_e) of the *meso*-phenyl substituent pointing toward the upper rim of the receptor (Figure S15). The existence of this intermolecular close-contact testified for the preferred location of the TMP cation close to the upper rim and the inwardly directed phosphonate groups of **4ii**, experiencing both cation−dipole interactions with the phosphonate groups and charge−charge interactions with the included chloride. We concluded that the preferred binding geometry of the TMPCl@**4ii** complex in solution is that of a *close-contact* ion-pair arrangement.

Single crystals of the TMPCl@**4ii** complex suitable for X-ray diffraction were grown from dichloromethane solution. The binding geometry proposed in solution is supported by the formation of the *endo*-cavity anionic complex TMPCl@**4ii** in the solid state. The packing of the crystal showed the formation of a columnar motif of TMPCl@**4ii** complexes and did not provide an unambiguous evidence for the preferred placement of the TMP cation with respect of the anion in the solid-state (Figure 8).

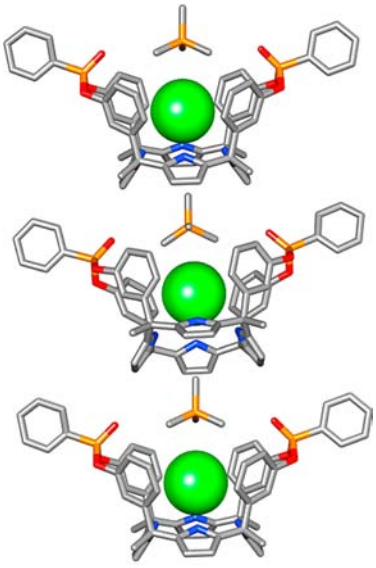


Figure 8. Section of the crystal packing of the TMPCl@**4ii** complex. The columnar arrangement of the TMPCl@**4ii** complexes determination of a preferred location of the TMP cation in the 1:1 complex. For clarity, hydrogen atoms and solvent molecules have been omitted. Chloride is shown as CPK mode.

The general dynamic and thermodynamic trends observed in the NMR titrations of stereoisomer **4io** and **4oo** with TMPCl paralleled those described above for **4ii**. It is worth noting, however, that when 0.5 or 1 equiv of TMPCl are added to 1 mM dichloromethane solutions of **4io** and **4oo**, the chemical shift value of the signal corresponding to the methyl groups of the TMP cation is noticeably upfield shifted ($\delta \approx 0.67$ ppm; $\Delta\delta = -1.5$ ppm) compared to the one registered in the case of **4ii** ($\delta = 1.16$ ppm; $\Delta\delta = -1.01$ ppm, Supporting Information). 2D ROESY experiments performed on equimolar dichloromethane solutions of the receptors **4io** or **4oo** with TMPCl displayed intense cross-peaks between the signal of the methyl protons of TMP and the signals of the β-pyrrole protons of the receptors. For the **4io** receptor, a much weaker cross peak was also spotted between the signals of TMP and the *para* aromatic proton in two of the *meso*-phenyl substituents. Taken together, these results suggested that, in solution, the TMP cation of the 1:1 complexes TMPCl@**4oo** and TMPCl@**4io** is preferentially located in the shallow aromatic cavity defined by the pyrrole rings, stabilized by cation−π interactions. In the specific case of the TMPCl@**4io** complex, the binding geometry locating the TMP in the upper rim close to the inwardly directed phosphonato group was also detected. In short, the energetically favored binding geometries for the complexes TMPCl@**4io** and TMPCl@**4oo** in solution displayed an ion-pair *separated* arrangement.

The formation of chloride *endo* cavity complexes with **4oo** and **4io** receptors in solution was supported by the structures of the complexes obtained in the solid-state. Once again the columnar motif displayed by the packing of the crystals of the complexes TMPCl@**4oo** and TMPCl@**4io** was not conclusive in resolving the issue of the preferred placement of the TMP cation (Figure 9).[36,37]

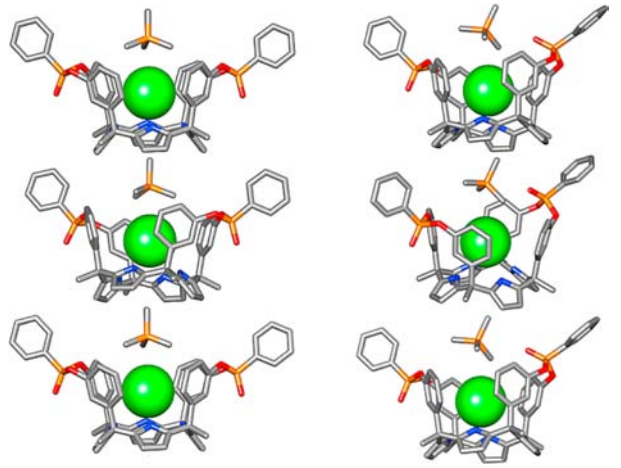


Figure 9. Sections of the crystal packing of the TMPCl@**4oo** complex (left side) and the TMPCl@**4io** (right side). For clarity, hydrogen atoms and solvent molecules have been omitted. Chloride is shown as CPK model.

Relative Magnitudes of the Binding Affinities of Receptor Series 4 for TMPCl. To rank the magnitudes of the binding affinities of receptor series **4** with TMPCl, we performed pairwise competitive binding experiments. We prepared ∼1 mM solutions containing a close to equimolar mixture of two bis-phosphonate receptors and TMPCl in deuterated dichloromethane. The extent of chloride complexation attained by each receptor in the solution was assessed using ^{1}H and ^{31}P NMR spectroscopy. As commented above, the interaction of receptors **4** with chloride induced a considerable downfield shift of the NH proton signals. The NH protons in chloride-bound receptors **4** resonated in the region of 10−12 ppm completely separated from all other signals. In any combination of two receptors, we observed two different sets of signals corresponding to the NH protons hydrogen bonded to chloride in each one of the TMPCl@**4** complexes (Figure 10). In the aromatic region of the ^{1}H NMR spectra of the mixtures, we also could identify separate signals for some protons in the free and bound state of both receptors.

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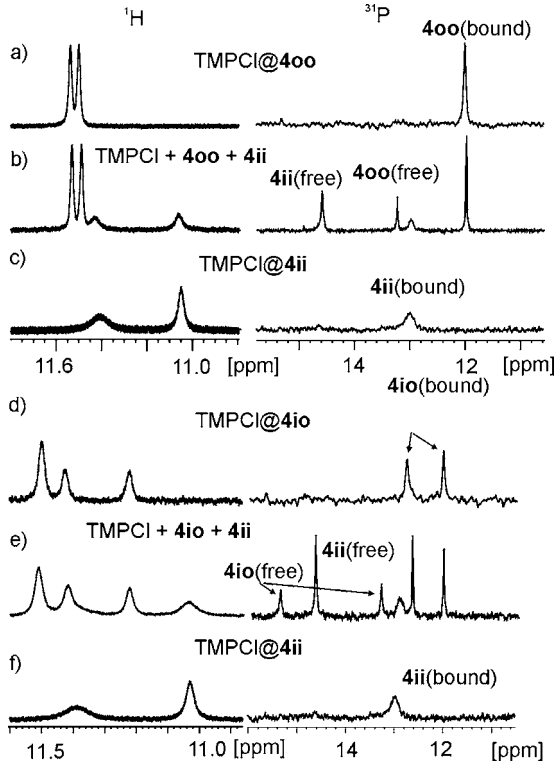

Figure 10. Selected regions of the ^{1}H and ^{31}P NMR spectra of (a) TMPCl@**4oo**, (b) TMPCl + **4oo** + **4ii**, (c) TMPCl@**4ii**, (d) TMPCl@**4io**, (e) TMPCl + **4io** + **4ii**, and (f) TMPCl@**4ii**.

In addition, the ^{31}P NMR spectra of all solution mixtures displayed different signals for the phosphorus atoms of the two receptors, both in the free and bound state (Figure 10). The integral areas of selected proton signals for each receptor, in both free and bound state, were used to calculate the ratio of association constant values for the two TMPCl@**4** complexes present in the pairwise competitive experiments by means of the following eq 4:

$$K_{a,exp}(\text{TMPCl@}\mathbf{4xx})/K_{a,exp}(\text{TMPCl@}\mathbf{4yy}) = \text{FB}(\mathbf{4xx})/\text{FB}(\mathbf{4yy}) \times \text{FF}(\mathbf{4yy})/\text{FF}(\mathbf{4xx}) \quad (4)$$

where FF = fraction free; FB = fraction bound.

Because of uneven NOE enhancements of the signals by decoupling and long longitudinal relaxation times, the ^{31}P NMR spectra of the mixtures were only used to qualitatively corroborate the relative extent in which the two TMPCl complexes were formed in solution that we derived from the ^{1}H NMR analysis of the mixture. We measured that $K_{a,exp}$(TMPCl@**4oo**) is approximately 4-fold larger than $K_{a,exp}$(TMPCl@**4ii**) and that $K_{a,exp}$(TMPCl@**4io**) is 2-fold larger than $K_{a,exp}$(TMPCl@**4ii**). Consequently, $K_{a,exp}$(TMPCl@**4oo**) must be close to 2-fold larger than $K_{a,exp}$(TMPCl@**4io**). The presumed ratio of constants was also confirmed experimentally by a direct pairwise competition experiment between **4oo** and **4io**. In short, the experimentally measured order of binding affinities for the receptor series **4** toward TMPCl is as follows: $K_{a,exp}$(TMPCl@**4oo**) ≈ 2 × $K_{a,exp}$(TMPCl@**4io**) ≈ 4 × $K_{a,exp}$(TMPCl@**4ii**). We performed ITC experiments to assess the magnitude of the binding constant values for the complexes formed between the series of receptors **4** and TMPCl. The ratios between the experimentally measured magnitudes for the binding constants of the complexes are in complete agreement with those derived from the pairwise competitive experiments.[38]

This result was completely unexpected for us. In fact, our expectations were completely opposite. We thought that the **4ii** stereoisomer capable of binding the ion-pair of the salt in a *close contact* arrangement and providing stabilizing cation−dipole and CH···O interactions to the bound TMP moiety when located close to the upper rim should afford the more energetically favorable 1:1 complex, probably followed by the steroisomer **4io**.

We rationalized the experimentally measured order of binding affinities of the receptor series **4** toward TMPCl by invoking a stepwise binding mechanism, as previously proposed for octamethyl calix[4]pyrrole receptor **2**.[6,14] In the case at hand, however, we surmise that the magnitude of the initial binding of the chloride anion to form the 1:1 anionic complex is strongly dependent on the spatial orientation of the phosphonate bridging groups. The subsequent complexation of the TMP cation and its placement within the ion-paired 1:1 complex, which is indeed mandated by the spatial arrangement of the phosphonate groups of the steroisomeric receptor (vide supra), provided an almost constant energetic contribution to the overall binding. In the **4ii** stereoisomer, the two oxygen atoms of the phosphonate groups are pointing inwardly with respect to the deep cavity in which the chloride is included. Most likely, the existence of repulsive electrostatic interactions between the partial negative charges of the inwardly directed oxygen atoms of the phosphonate groups and their dipoles with the included chloride is responsible for the energetic disadvantage of TMPCl@**4ii** complex with respect to TMPCl@**4oo** and TMPCl@**4io**. The orientation of the dipole moment of the phosphonate groups changes substantially on the basis of the molecular structure of stereoisomers **4**. In this sense, for the **4io** and **4ii** stereoisomers one or the two negative ends of the dipoles assigned to the phosphonate groups, respectively, point toward the included chloride. However, for the **4oo** stereoisomer it is the positive end of both dipole moments of the phosphonate groups that are directed toward the included chloride.

Influence of the Cation Size in the Binding Affinity Values Displayed by Receptor Series 4. We also wanted to evaluate the influence of the cation size on the absolute and relative binding affinities of the receptor series. For this reason, we investigated the complexation properties of the receptor series **4** with two additional chloride salts: tetrabutylammonium chloride, **8**·Cl, TBACl and 1-dodecyltrimethylammonium chloride, **9**·Cl, DTMACl. The results of the binding experiments with receptor series **4** and DTMACl (dynamics, thermodynamics and complex geometries) were analogous to the ones we described above for TMPCl. By means of pairwise competitive binding experiments, we determined the following relationship of binding constants for DTMACl as guest: $K_{a,exp}$(DTMACl@**4oo**) ≈ 2 × $K_{a,exp}$(DTMACl@**4io**) ≈ 4 × $K_{a,exp}$(DTMACl@**4ii**). The analogy of the results obtained with DTMACl and TMPCl as guests indicated that although the two cations of these salts have different sizes both can be similarly accommodated in the cationic binding pockets of the receptors. That is, if the DTMA cation directs the long alkyl chain away from the binding pockets of the receptor it becomes almost equal in size and shape to the TMP cation.[39] Because of statistical effects, however, we surmise that the complexes of

receptors **4** with TMPCl should be slightly more stable thermodynamically than with DTMACl.

The results obtained in the complexation experiments of the receptor series **4** with TBACl are worth describing in more detail. Addition of 0.5 equiv of TBACl to separated 1 mM deuterated dichloromethane solutions of the three stereoisomers produced the appearance of diagnostic signals of complex formation, in the corresponding ^{1}H NMR spectra of the mixtures. All the exchange dynamics of the complexation processes were slow/intermediate on the ^{1}H NMR time scale. We observed separated signals for some protons in the free and bound receptors and broadening of other proton signals. Integration of selected proton signals for free and bound receptor after addition of 1 equivalent of TBACl, allowed us to estimate that the binding constant $K_{a,exp}$ for TBACl@**4oo** is in the order of 10^4 M^{-1} while the $K_{a,exp}$ for TBACl@**4io** had a value of $2 \pm 0.5 \times 10^3$ M^{-1}. Conversely, the addition of 1 equiv of TBACl to the solution of **4ii** induced the formation of the 1:1 complex TBACl@**4ii** to a much reduced extent, $K_{a,exp}$(TBACl@**4ii**) $\approx 5 \pm 1 \times 10^2$ M^{-1}. We also performed a pairwise competitive experiment between receptors **4oo** and **4io** with TBACl (Figure 11) demonstrating the superior

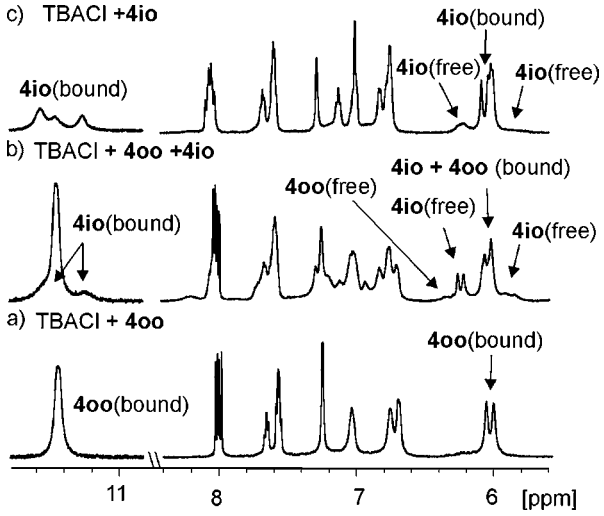

Figure 11. Selected regions of the ^{1}H NMR spectra of (a) TBACl + **4oo**, (b) TBACl + **4oo** + **4io**, and (c) TBACl + **4io**.

binding affinity of **4oo** for this salt ($K_{a,exp}$(TBACl@**4oo**)/$K_{a,exp}$(TBACl@**4io**) ≈ 5). These results demonstrated that the general trend in binding affinities determined above for the receptor series **4** with TMPCl and DTMACl was also maintained for TBACl. However, the magnitude of the binding affinities of **4ii** and **4io** toward TBACl were significantly reduced compared to those estimated for TMPCl and DTMACl. Most likely, the mismatch that exists between the size of the TBA cation and that of the receptor's binding sites significantly reduced the energetics of complexation.

Remarkably, the magnitude of the binding affinity featured by the phosphonate receptor **4oo** toward TBACl was 3 and 2 orders of magnitude larger than those determined for the more conformationally flexible aryl-extended calix[4]pyrrole **6** and the *meso*-octamethylcalix[4]pyrrole **2**, respectively.

Study of the Conformational and Electrostatic Factors Influencing the Complexation Process of Receptor 4oo with Ion-Pair Salts. In an attempt to dissect the electrostatic contributions and conformational rigidity imparted by the phosphonate groups of the **4oo** receptor to the overall binding energy of the TMPCl salt, we also determined the binding properties of the synthesized cavitand calix[4]pyrrole **5** toward this salt. The comparison of the binding properties exhibited by **5** with those of **4oo** should reveal the effect provided mainly by the electrostatic factors of the phosphonate groups to the ion-pair binding.

Bis-methylene bridged host **5** formed a 1:1 complex with TMPCl in deuterated DCM for which we could estimate, using ^{1}H NMR titrations, a binding affinity constant value $K_{a,exp}$(ClTMP@**5**) $> 1 \times 10^4$ M^{-1}. We observed slow exchange dynamics for the binding process. The signal of methyl protons of bound TMP cation resonate at $\delta = 0.67$ ppm suggesting its inclusion in the shallow aromatic cavity provided by the pyrrole rings in cone conformation that is distal to the bound chloride. In the downfield region of the ^{1}H NMR spectrum of the TMPCl@**5** complex, we detected two signals for the pyrrole NH protons hydrogen bonded to the chloride resonating at $\delta =$ 11.62 and 11.20 ppm. We performed competitive pairwise binding experiments involving receptors **6**, **4oo**, and **5** with TMPCl in DCM solution. The ratio of the integrals for selected signals of the protons in the free and bound receptors and the application of eq (4) allowed us to derive the following relationship for the stability constants values of the complexes $K_{a,exp}$(TMPCl @**4oo**) $\approx 10 \times K_{a,exp}$(TMPCl@**5**) $\approx 40 \times K_{a,exp}$(TMPCl @**6**).

Thus, we concluded that the phosphonate groups installed at the upper rim of the **4oo** receptor offered electrostatic and conformational advantages compared to **6**, which can be quantified in −2.2 kcal/mol. The overall gain in binding energy of **4oo** with respect to **6** can be dissected in the two components by the use of receptor **5** as reference. We had considered that receptor **4oo** and **5** are similarly restricted conformationally (preorganized) for the binding of TMPCl. Complexation of TMPCl with **5**, however, lacks the electrostatic interactions provided by the phosphonate groups installed in **4oo**. We assigned the measured difference in the binding energies of TMPCl with **4oo** and **5**, −1.4 kcal/mol, mainly to the existence of electrostatic interactions in the TMPCl@**4oo**. Consequently, the preorganization effect build into the scaffolds of bridged receptors **4oo** can be quantified approximately as $-2.2 - (-1.4) = -0.8$ kcal/mol using aryl-extended calix[4]pyrrole **6** as reference. These back of the envelope calculations indicate that both effects, preorganization and electrostatic interactions, are important for the effective binding of organic ion-pairs by receptor **4oo**.

Effect of Hydrogen Bonding as an Additional Driving Force for the Recognition of a Primary Alkylammonium Salt by Receptor Series 4. Phosphonate cavitands derived from resorcinarene are well-known hydrogen-bonding receptors for alkylammonium ions.[40] By means of gas-phase binding studies, it was shown that the number and spatial orientation of the P═O binding groups in these receptors have a dramatic influence on their ability to form hydrogen bonded complexes with primary, secondary and tertiary methylammonium ions.[41,42] Thus, we became interested in evaluating the effect that the geometrical differences provided by the calix[4]pyrrole phosphonate cavitand series **4** could produced in the complexation of octylammonium chloride OAMCl ion-pair, **10**·Cl, in DCM solution. We also wanted to determine, if possible, the relative thermodynamic stabilities of the complexes formed by the receptor series **4** with primary and tertiary alkylammonium salts. Molecular modeling studies

indicated that OAMCl can be engaged in an interaction of its alkylammonium group (hydrogen bonds, CH··O and cation—dipole interactions) simultaneously with the two P═O groups of diastereoisomer **4ii** (Figure 12a). Geometrical constraints eliminate this bidentate binding possibility for the other two diastereoisomeric receptors.

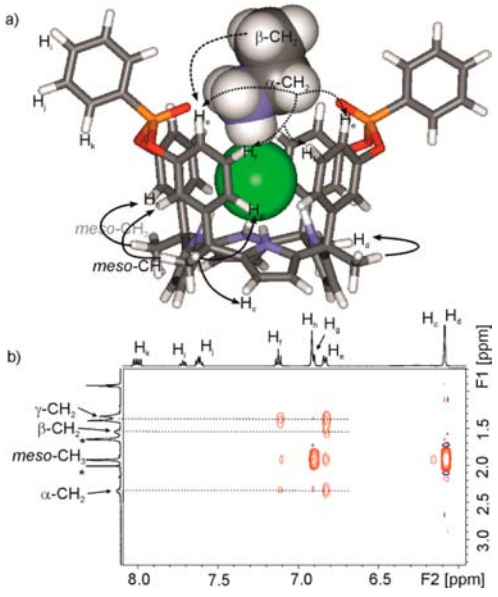

Figure 12. (a) CAChe energy minimized structure (PM6) of the OAMCl@**4ii** complex highlighting the bidentate binding mode of the alkylammonium cation located at the upper rim. For clarity, the alkyl group shown for OAM cation is ethyl and the salt ion-pair is displayed as CPK model. (b) Selected region of a 2D-ROESY experiment performed on a dichloromethane solution containing an equimolar mixture of **4ii** and OMACl. Intermolecular (dotted lines) and intramolecular (solid lines) NOEs (nuclear Overhauser effect) are indicated by arrows in panel a.

We performed ^{1}H NMR titration experiments by sequential addition of two doses of 0.5 equivalent of OAMCl to individual 1 mM solutions of stereoisomers **4oo** and **4ii** in deuterated DCM. We observed that both complexation processes featured slow exchange dynamics on the ^{1}H NMR time scale. In particular, for stereoisomer **4ii** the addition of 1 equiv of the salt induced the exclusive observation of proton signals corresponding to the bound host. This result indicated that the binding constant value for the 1:1 complex of OAMCl@**4ii** can be estimated as higher than 10^4 M^{-1}. The complexation induced shifts observed for the signals of some protons in the octylammonium cation **10** were significant. The signal of the ammonium group moved upfield $\Delta\delta$ = −2.0 ppm, as well as that of the methylene in α position, $\Delta\delta_\alpha$ = −0.73 ppm, and the one for beta methylene, $\Delta\delta_\beta$ = −0.26 ppm. The placement of the cation in the upper rim and the *close-contact* ion-paired geometry assigned to the OAMCl@**4ii** complex were supported by the existence of intermolecular close contacts between the *meso*-phenyl protons (*para* and *meta*) and the methylene protons (mainly alpha and beta) of the alkyl chain of **10**, which produced the corresponding cross-peaks in the ROESY spectrum of the complex (Figure 12b).

In striking contrast, the addition of 1 equiv of OAMCl to the DCM solution of receptor **4oo** revealed the coexistence of proton signals both for the free and bound host. Integration of proton signals for free and bound host allowed us to determine the stability constant value for the 1:1 complex as $K_{a,exp}$(OAMCl@**4oo**) = 2 ± 1 × 10^3 M^{-1}. A careful analysis of the ^{1}H NMR spectrum of **4oo** containing 0.5 equivalent of OMACl revealed that the signals of the methylene protons of the cation in alpha and beta position with respect to the ammonium group were massively upfield shifted, $\Delta\delta_\alpha$ = −2.2 and $\Delta\delta_\beta$ = −0.91 ppm, suggesting inclusion in the shallow and electron rich aromatic cavity opposite to the bound chloride (Figure 13a). The signal for the protons of the ammonium

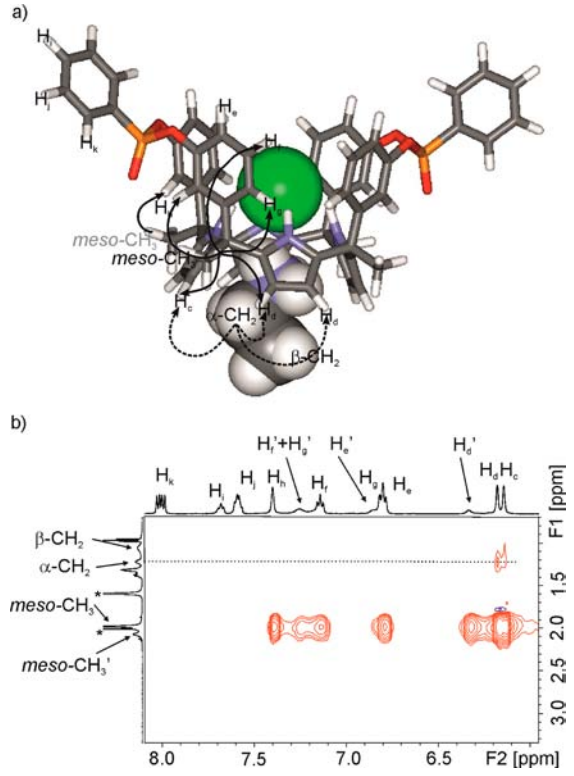

Figure 13. (a) CAChe energy minimized structure (PM6) of the OAMCl@**4oo** complex with the alkylammonium cation located in the electron-rich aromatic cup distal to the bound chloride. For clarity, the alkyl group shown for OAM is ethyl and the salt ion-pair is displayed as CPK model. (b) Selected region of a 2D-ROESY experiment performed on a dichloromethane solution containing an equimolar mixture of **4oo** and OAMCl. Separate signals for the free and bound protons of the receptors are still distinguishable. Primed letters indicate proton signals of the free receptor. Intermolecular (dotted lines) and intramolecular (solid lines) NOEs are indicated by arrows in panel a.

group of OAMCl also experienced a dramatic upfield shift ($\Delta\delta$ = −5.6). Probably, the complexation induced shift of the ammonium protons signals is partially caused by the shielding effect of the aromatic cavity in which the cation is located. Nevertheless, we propose that the change in geometry experienced by the ion-pair of the salt free in solution to the *ion-separated* arrangement that experiences in the ion-paired complex OAMCl@**4oo** must play an important role in the observed chemical shift change. In complete agreement with the proposed *ion-separated* binding geometry assigned to the OAMCl@**4oo**, the ROESY experiment carried out on a solution containing an equimolar mixture of the two binding partners (∼ 75% complex formation) displayed the exclusive existence of intermolecular cross peak between the signals of

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the β-pyrrole protons of the host and the alpha methylene protons in the octylammonium cation (Figure 13b).

Pairwise competitive binding experiments of receptor series **4** with OAMCl were used to determine the following order of the binding affinity magnitudes, $K_{a,exp}$(OAMCl@**4ii**) ≈ 50 $K_{a,exp}$(OAMCl@**4io**) > 100 $K_{a,exp}$(OAMCl@**4oo**).

From all the results of the above experiments, we concluded that the spatial location of the cation in the 1:1 complexes formed by the receptor series **4** and quaternary ammonium salts is analogous to that of the complexes derived from a primary alkylammonium salt. Most likely, ion-dipole interactions with or without the assistance of hydrogen bonding interactions with the phosphonato groups are responsible for the selective spatial location of both types of cations. Interestingly, the trend of the relative thermodynamic stabilities of the complexes is completely reversed on changing from quaternary to primary ammonium salts. Thus, quaternary ammonium salts formed the more thermodynamically stable complexes with the **4oo** receptor. On the contrary, a primary ammonium salt binds more tightly with the **4ii** receptor. Favorable hydrogen bonding interactions established between the primary alkylammonium residue and the phosphonate groups[43] in the **4ii** receptors compensate for the reduced binding energy provided in the initial interaction of the chloride with this receptor compared to **4oo**. Unfortunately, pairwise competitive binding experiments in solution were not conclusive for rating the binding affinities of **4ii** with respect to TMPCl and OAMCl, that is a quaternary versus a primary ammonium salt.

Effect of the Solvent in the Binding of Alkylammonium Ion-Pairs with Receptor Series 4. The nature of the solvents has a strong impact on the behavior of 1:1 electrolytes. In low permittivity media, such as DCM, ion pair formation is likely to occur. The extent of ion-pair formation is concentration dependent and, based on existing information, it is reasonable to consider that at 1 mM concentration alkylammonium/phosphonium salts are mainly ion-paired.[44−46] On the contrary, in high permittivity solvents, such as acetonitrile (ACN) alkylammonium/phosphonium salts at 1 mM concentration are predominantly ionic species. Conductance measurements are practical in establishing these points. The absence of ions in solution correlates with the observation of no conductance.

When the guest salt and the complex are both 100% dissociated, eq 5 applies referring to the 1:1 complexation process of an anion:

$$H + A^- \leftrightarrow H\cdot A^-;$$

$$K_{a,exp} = [H\cdot A^-]/[H][A^-] \text{ in units of } M^{-1} \quad (5)$$

The application of eq 5 explicitly assumes that the host is present as a monomer and the cation is not participating in the binding process. The selection of ACN as solvent allows the direct assessment of the selectivity of the receptor series **4** toward chloride without having to worry about the effect of the different cations.[10]

At 298 K, only receptor **4oo** is significantly soluble in ACN. The solubility of receptor **4io** is 0.5 mg/mL (∼ 0.5 mM) and receptor **4ii** is not soluble enough to be detected by ^{1}H NMR spectroscopy. The ^{1}H NMR titrations of receptors **4oo** and **4io** in ACN solution with TMPCl showed slow exchange dynamics for the binding process. From the integral values of selected signals for protons in the free and bound receptors, we calculated the following binding constant values $K_{a,exp}$(TMPCl@**4oo**) = 6.0 ± 2 × 10^3 M^{-1} and $K_{a,exp}$(TMPCl@**4io**) = 2.0 ± 1 × 10^3 M^{-1}.[47] The magnitudes of the binding constants are significantly reduced compared to the values we estimated/determined in DCM solution. However, the ratio of binding constant values $K_{a,exp}$(TMPCl@**4oo**)/$K_{a,exp}$(TMPCl@**4io**) is similar to the one we calculated in DCM solution. This result is in support of our hypothesis stating that the binding of the quaternary ammonium cation to the initially formed anionic complex Cl^-@**4xx** in DCM solution, although not site-identical is energetically similar in the three diastereoisomeric complexes.

The two receptors, **4oo** and **4io**, were also titrated against the battery of all alkylammonium salts in ACN solutions. In all cases, the interaction of the anion with the receptor induced a large downfield shift of the NH protons and produced the observation of two different set of proton signals assigned to the free and bound host. The values of the measured binding constants were in the order of 10^3 M^{-1}, reinforcing the idea that the cation is not significantly involved in the formation of ion-paired complexes in ACN solution. For any salt, the value for the binding constant with the **4oo** receptor was between 2- to 3-fold larger than with **4io**. In the specific case of TBACl, this ratio was also evaluated through a direct pairwise competitive experiment affording $K_{a,exp}$(TBACl@**4oo**)/$K_{a,exp}$(TBACl@**4io**) ≈ 3 (Figure 14).

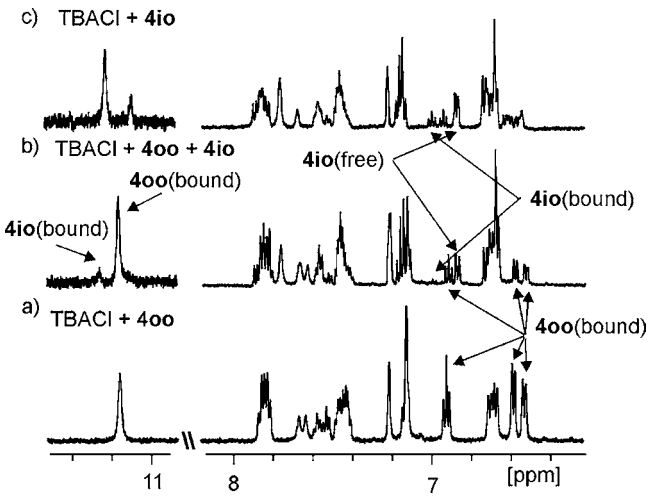

Figure 14. Selected regions of the ^{1}H spectra in ACN solution at 298 K of mixtures containing equimolar amounts of (a) TBACl +**4oo**, (b) TBACl + **4oo** + **4io**, (c) TBACl + **4io**.

■ CONCLUSIONS

We have designed and synthesized a new class of heteroditopic ion-pair receptors combining the anion binding properties of calix[4]pyrroles with the cation affinity of phosphonate cavitands. The combination of the two binding sites in a single molecule imparts to these receptors peculiar complexation properties toward ion pairs. The relative orientation of the P═O units with respect to the aromatic cavity dictates the ion-pair binding mode and modulates the strength of the interaction in connection with the H-bonding ability of the cationic guest. Thus, the **4ii** stereoisomer provided the smallest magnitudes in binding constant for the 1:1 complex with the chloride quats and displayed a *contact* arrangement of the ion-pair. The **4oo**

host produced the more thermodynamically stable 1:1 complexes with the same chloride salts and displayed a *separated* arrangement of the ion-pair. We rationalize the observed trend in binding affinities as a consequence of stepwise binding mechanism. The magnitude of the initial binding of the chloride to form the 1:1 anionic complex must be strongly dependent on the spatial orientation of the phosphonate bridging groups. The subsequent complexation of the quat cation and its placement within the ion-paired 1:1 complex, which is indeed mandated by the spatial arrangement of the phosphonate groups, should afford an almost constant energetic contribution to the overall binding regardless of the P═O spatial orientation. For a primary alkylammonium chloride, the arrangement of the ion-pair in the complexes is similarly controlled by the relative orientation of the P═O groups in the hosts. However, the trend in binding affinities for their 1:1 complexes is reversed compared to that measured for the quaternary ammonium salts. Favorable hydrogen bonding interactions established between the primary alkylammonium residue and the phosphonate groups in the **4ii** receptors overpower the reduced binding energy provided by the initial interaction of the chloride with this receptor compared to **4oo**. In ACN solution where the cation is not significantly involved in the binding process, the determined $K_{a,exp}$ values are of the order of 10^3 M^{-1} both for quaternary and primary ammonium ions. However, the superior binding properties displayed by the **4oo** isomer in DCM are maintained in ACN. In conclusion, the introduction of phosphonate units at the upper rim of aryl-extended calix[4]pyrrole receptors widens and sharpens the molecular recognition properties of this class of heteroditopic receptors toward phosphonium/ammonium salts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for the synthesis of all the compounds and their characterization data; ^{1}H and ^{31}P NMR spectra corresponding to the binding studies of **4** and the competitive pairwise experiments performed with different chloride salts that are discussed in the text in both dichloromethane and acetonitrile solutions; ITC experiments of **4** with TMPCl; experimental details for the reported X-ray structures; figures of the columnar packing motifs observed in the solid-state structures of the complexes of **4** with methyl-pyridinium chloride and octylammonium chloride with **4ii**; CIF files of the diastereomeric receptors **4**, their complexes with TMPCl, methyl pyridinium chloride, the OAMCl@**4ii** complex and the pyridine oxide complex of **4io**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(37) The ditopic character of **4oo** was also evidenced in ESI−MS experiments of a solution containing TMPCl (Supporting Information). We used negative and positive detection modes with capillary voltages from 0 to 500 V. We observed ion-peaks at m/z 1019 corresponding to the anionic complex Cl^{-}@**4oo** and at m/z 1075 corresponding to the cationic complex TMP+@**4oo** in negative and positive detection modes, respectively.
(38) We performed isothermal titration calorimetry (ITC) experiments at 298 K to assess the magnitudes of the binding constants for the receptor series 4 with TMPCl in DCM solution (Supporting Information). From the results of these experiments, we were also able to determine the thermochemical data for the complexation. In general, the binding processes showed a reduced heat release (heat vs time). We obtained a good fit for the integrated heat to a theoretical binding isotherm corresponding to the formation of a 1:1 complex. The inflection point of the sigmoideal binding isotherms coincides with a molar ratio value close to 1. $K_{a,exp}$(TMPCl@**4oo**) = $8 \pm 1 \times 10^{5}$ M^{-1}; $\Delta G = -8.0$ kcal/mol; $\Delta H = -3.3$ kcal/mol; $T\Delta S = -4.7$ kcal/mol; $K_{a,exp}$(TMPCl@**4io**) = $5 \pm 1 \times 10^{5}$ M^{-1}; $\Delta G = -7.7$ kcal/mol; $\Delta H = -3.1$ kcal/mol; $T\Delta S = -4.6$ kcal/mol; $K_{a,exp}$(TMPCl@**4ii**) = $2 \pm 0.5 \times 10^{5}$ M^{-1}; $\Delta G = -7.2$ kcal/mol; $\Delta H = -1.9$ kcal/mol; $T\Delta S = -5.3$ kcal/mol. The obtained trend and ratio of the determined binding affinity values are in complete agreement with the results obtained in the pairwise competitive experiments that were analyzed by ^{1}H NMR spectroscopy. All processes were both enthalpically and entropically driven. The strong and favourable entropic component measured for all complexation processes suggests that solvation/desolvation effects must play a crucial role.
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