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Tetra-phosphonate Calix[4]pyrrole Cavitands as Multitopic Receptors for the Recognition of Ion Pairs

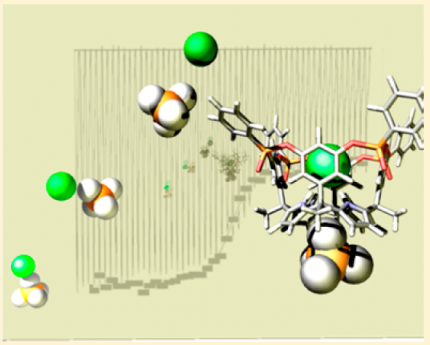
Moira Ciardi,[†,§] Albano Galán,[†] and Pablo Ballester*[,†,‡]

[†]Institute of Chemical Research of Catalonia (ICIQ), Avda. Països Catalans 16, 43007 Tarragona, Spain

[‡]Catalan Institution of Research and Advanced Studies (ICREA), Passeig Lluís Companys 23, 08018 Barcelona, Spain

Supporting Information

ABSTRACT: The synthesis, structural characterization, and binding properties of two unprecedented multitopic receptors for ion-pair recognition are described. We isolated two of the six possible diastereomeric deep cavitand receptors resulting from the installation of four phosphonate groups at the upper rim of a calix[4]pyrrole−resorcin[4]arene hybrid scaffold. The isolated tetra-phosphonate receptors display either three (iooo) or four (oooo) of their P═O groups oriented away from the deep and functionalized aromatic cavity. In contrast to analogous tetra-phosphonate resorcin[4]arene cavitands, the 14-membered macrocyclic rings that contain the P═O groups in the tetra-phosphonate calix[4]pyrrole cavitands are conformationally flexible, always adopting a conformation locating the phenyl substituents in equatorial position. The tetra-phosphonate calix[4]pyrroles exhibited larger affinity constants than the previously reported bis-phosphonate calix[4]pyrrole counterparts in the complexation of both tetramethylphosphonium and octylammonium chloride salts in nonpolar solvents. We demonstrated that the iooo diastereoisomer was able to function as a multitopic receptor for organic chloride salts by switching the geometry of the 1:1 ion-paired complex from receptor-separated to close-contact depending on the quaternary or primary nature of the cobound organic cation. The ion-paired 1:1 complexes formed between the diastereomeric receptors and organic chloride salts were studied and thermodynamically characterized in solution. The determined stability constant values were compared to those obtained for the bis-phosphonate counterparts. The structure of the TMPCl⊂7iooo complex was determined by X-ray structure, and its formation was also evidenced in the gas phase.



INTRODUCTION

During recent years, the design and synthesis of receptors capable of recognizing ion pairs has attracted increasing interest.[1,2] Simple ditopic ion-pair receptors, so-called heteroditopic receptors, contain single sites for the simultaneous recognition of the anion and the cation.[3] On the other hand, multitopic receptors for ion pairs contain more than one binding site for either the cation or the anion.[4] It is widely accepted that both heteroditopic and multitopic receptors exhibit improved properties (affinity and selectivity) for the complexation of ion pairs when compared to monotopic counterparts capable of binding a single cation or anion.[5,6] Cooperative interactions[7] between cobound ions (electrostatic) and cooperative allosteric effects[8] induced by the initial binding of one of the ions are claimed as being responsible for the enhancement in binding properties.[9] In addition, the complexation of the counterion of the targeted ion is also described as a way of reducing binding interferences arising from ion-pairing and solvation effects.[10,11] However, true cooperativity provided by the simultaneous complexation of the cation and the anion is not easy to assess because the formulation of ion-pair binding requires the consideration of several equilibria and involves the multivariable fit of the titration data to elaborated mathematical algorithms.[12]

For the sake of simplicity, the values frequently encountered in the literature and the values reported here for the stability constants of ion-pair complexes correspond to experimental binding constants, $K_{a/exp}$, which are determined using a simple 1:1 theoretical binding model and thus are reported in M^{-1} units.

An interesting example of multitopic ion-pair receptors derived from a calix[4]pyrrole scaffold has been recently described by Sessler et al.[13,14] In this work, crown ethers of different sizes are covalently linked to the *meso*-aryl substituents of "two-wall" aryl extended calix[4]pyrrole resulting in the formation of stable ion-pair complexes with alkali metal (K^+ and Cs^+) fluoride salts, both in the solid state and in solution. Depending on the cobound alkali metal, the cation is coordinated to the oxygen atoms of the crown (K^+) or included in the cone-shaped cavity opposite to the bound anion (Cs^+). In more elaborated designs,[15] one unit of 1,3-alternate calix[4]crown-5 was bridged between the two *para* positions of the *meso*-aryl substituents of a "two-wall" calix[4]pyrrole with ethylenedioxy spacers (Figure 1a). Receptor **1** consist of one anion binding site and, potentially, three cation recognition

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sites displaying different affinities for different alkali metal cations.

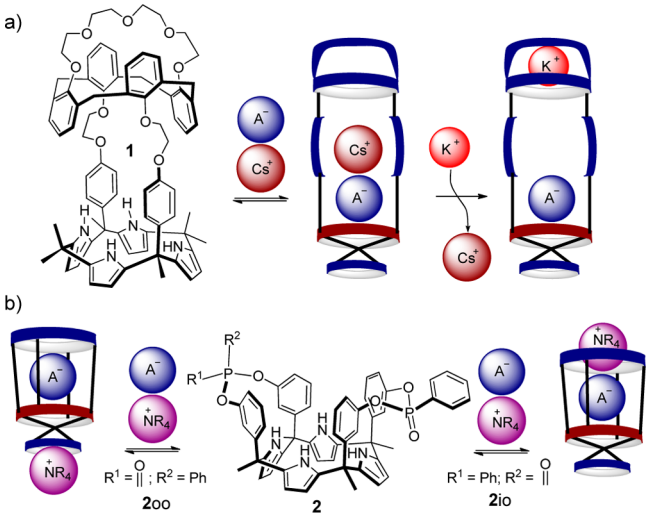


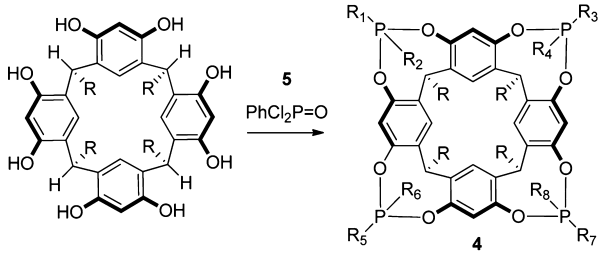
Figure 1. Line drawing structures and schematic representation of multitopic receptors: (a) compound **1** described by Sessler et al.[15] and (b) bis-phosphonate cavitands **2** reported by our group. In both receptors, the different binding sites for the cation are highlighted with blue ribbons. The close-contact binding mode (right) and the host-separated arrangement (left) of the ion pair are shown for the complexes with **2**.

Our group recently reported the synthesis of three diastereomeric bis-phosphonate cavitands **2** based on the *α,α,α,α*-isomer of a "four-wall" aryl extended calix[4]pyrrole tetrol scaffold (Figure 1b). The diastereoisomers differ in the relative spatial orientation of the P═O groups installed at their upper rim. Because of the reduction of conformational flexibility imposed by the bridging phosphonates, these cavitands possess a permanent deep aromatic cavity closed at one end by the calix[4]pyrrole core.[16]

Bis-phosphonate cavitands **2** qualify as multitopic receptors for ion pairs. They feature a single coordination site for the anion, the calix[4]pyrrole core, but two different binding sites for the organic cation. One of the cation binding sites is provided by the electron-rich cup defined by the four pyrrole rings at the lower rim of the receptor and opposite to the bound anion. The other binding site for the cation is defined by a cleft generated between the bridging phosphonate groups at the upper rim. In this latter binding mode, the cation is in close-contact with the deep included bound anion. We demonstrated that, in dichloromethane solution, the diastereoisomers having one or two P═O groups pointing toward the center of this cavity, **2**io and **2**ii isomers, respectively (o = out, i = in; indicates the orientation of the P═O groups with respect to the cavity), preferentially bound tetraalkylammonium chloride salts with a close-contact arrangement of the ions (Figure 1b, right). This is due to the existence of electrostatic interactions between the converging P═O group/s and the cobound ammonium cation included in the cavity at the upper rim. Conversely, the diastereoisomer with the two P═O groups outwardly directed with respect to the cavity prefers to bind tetraalkylammonium chloride salts with a receptor separated arrangement of ions (Figure 1b, left), thus placing the cobound ammonium in the cup-like cavity at the lower rim opposite to the bound chloride.

When four phenyl phosphonate groups are introduced at the upper rim of resorcin[4]arene **3** (Scheme 1), up to six tetra-

Scheme 1. Reaction Scheme for the Preparation of Tetra-phosphonate Resorcinarene Cavitands 4



	R_1=R_7	R_2=R_8	R_3	R_4	R_5	R_6	Yield (%)
4oooo	=O	Ph	=O	Ph	=O	Ph	2
4iioo	Ph	=O	=O	Ph	=O	Ph	5
4iooo	=O	Ph	=O	Ph	Ph	=O	15
	R_1=R_3	R_2=R_4		R_5=R_7		R_6=R_8	
4iioo	Ph	=O		=O		Ph	8

phosphonate diastereoisomers **4** can be produced.[17−19] The theoretical statistical distribution of isomers is 1[oooo]:1-[iiii]:2[ioio]:4[iiio]:4[iioo]:4[iooo] favoring those with one or more phenyl group inwardly oriented.[18] Conversely, molecular modeling studies disfavored the convergence of two or more phenyl groups in the cavity of related phosphonito cavitands (iioo, ioio, and iooo isomers).[20]

Experimentally, the reaction of resorcin[4]arene **3** with dichlorophenylphosphane **5** in acetone solution and in the presence of triethylamine afforded the **4**iooo isomer, with three phenyl groups oriented toward the cavity interior as the main component of the crude reaction.[18] The isomers with four (**4**iiii) and three phenyl groups (**4**iiio) outwardly oriented with respect to the cavity were not even detected. In toluene solution, the use of 1 equiv of *N*-methylpyrrolidine modified the course of the reaction and resulted in the almost exclusive production of the **4**iiii isomer in a 51% isolated yield most likely due to the template effect of the pyrrolidine guest.[19] The different isomers of the tetra-phosphonate cavitands **4** with inwardly oriented P═O groups are remarkable receptors for linear alcohols,[21,22] *N*-methylammonium salts,[23] primary ammonium salts,[22,24] and cesium cations.[22] They are also used for the construction of selective sensor devices for molecular recognition applications in solid−liquid and solid−gas interfaces.[25] These findings in combination with our previous experience in the synthesis of bis-phosphonate cavitands **2** derived from aryl extended calix[4]pyrroles prompted us to prepare tetra-phosphonate calix[4]pyrrole cavitands.

Herein, we describe the upper rim functionalization of the calix[4]pyrrole−resorcin[4]arene hybrid **6** (Scheme 2) with four phosphonate groups providing two unprecedented diastereomers. We also disclose the superior binding properties of the calixpyrrole tetra-phosphonate cavitands **7** in the complexation of ammonium and phosphonium ion pairs as compared to the structurally closely related bis-phosphonate counterparts **2**. The **7**iooo diastereoisomer acts as a multitopic ion receptor switching from a receptor separated binding mode of the ion pair to a close-contact mode when the cobound tetraalkylammonium cation is replaced by a primary alkylammonium counterpart.

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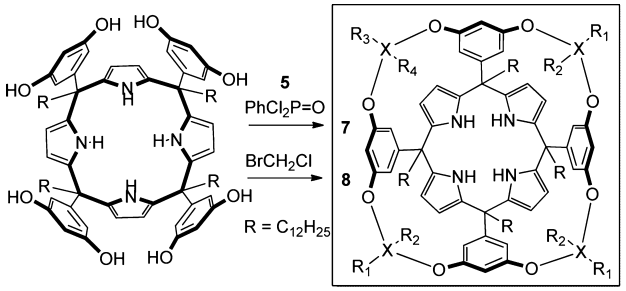
Scheme 2. Reaction Scheme for the Preparation of Tetra-phosphonate Cavitands 7 Based on a Calix[4]Pyrrole Octol Scaffold



	R1	R2	R3	R4	X	Yield(%)
7oooo	=O	Ph	=O	Ph	P	3
7iooo	Ph	=O	=O	Ph	P	9
8	H	H	H	H	C	18

RESULTS AND DISCUSSION

Synthesis. We first attempted the installation of four phosphonate bridges at the upper rim of the methyl-footed octol *α,α,α,α*-**6a** using the same synthetic procedure reported for the preparation of the bis-phosphonate cavitands **2**.[16] The treatment of *α,α,α,α*-**6a** with 5 equiv of dichlorophenylphosphane **5** led to an insoluble and intractable crude reaction mixture. Recently, we reported the synthesis of *α,α,α,α*-**6b**, a lipophilic version[26] of **6a**, as the parent compound in the preparation of a series of deep cavitands having four *ortho*-disubstituted aryl bridging groups. These molecules exhibited excellent solubility in most organic solvents.[27] For this reason, we selected octol **6b** as a suitable aryl-extended calix[4]pyrrole alternative for the installation of the bridging phosphonates. The room-temperature reaction of the lipophilic octol *α,α,α,α*-**6b** and dichlorophenylphosphane **5** (5 equiv) in THF solution in the presence of triethylamine for 2 h produced a crude mixture in which at least two of the six possible tetra-phosphonate diastereoisomers **7** were present. The two pure stereoisomers 7oooo and 7iooo were isolated by semi-preparative HPLC (Spherisorb silica 250 × 20 mm, 5 μm) using hexanes/CH_2Cl_2 60:40 as eluent. The isomers were further purified by crystallization from acetonitrile and obtained in overall yields of 3% and 9%, respectively.

We also prepared the tetra-methylene bridged cavitand **8** from the reaction of **6b** with chlorobromomethane as previously reported.[27] This compound was used as a reference system in the binding experiments with ion-pair salts.

Configurational Assignment and Structural Characterization. The configurational assignment of the two isolated tetra-phosphonate stereoisomers was performed by combining the data provided by their ^{1}H and ^{31}P NMR spectra with the analysis of single crystal X-ray diffraction data of one of them (7oooo) and of the complex with PMe_4Cl of the other (7iooo).

The ^{1}H NMR spectrum of the first tetra-phosphonate cavitand that eluted from the semipreparative HPLC column exhibited sharp proton signals in a number that was consistent with a C_{4v} symmetry, a clear diagnostic of either the iiii or the oooo isomers (Figure 2). Also consistent with a C_{4v} symmetry, the ^{31}P NMR spectra of the compound revealed the existence of a unique phosphorus signal resonating at δ = 13.7 ppm. By means of 1D and 2D NMR experiments, it was possible to assign all proton signals but not the unequivocal configuration of the P═O groups. In the bis-phosphonate series **2**, we

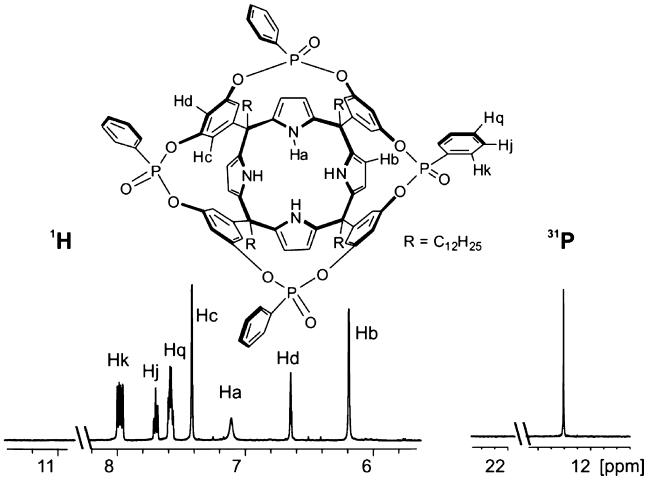


Figure 2. Selected regions of ^{1}H and ^{31}P{^{1}H} NMR spectra of a CD_2Cl_2 solution of tetra-phosphonate 7oooo. Inset: Line drawing structure of 7oooo indicating the proton assignment.

observed that P═O groups directed away from the cavity had phosphorus atoms resonating at higher field, 13.2 ppm for **2**oo and 14.2 ppm for **2**ii.[16] The δ measured for the phosphorus atom of the first isolated tetra-phosphonate isomer (δ = 13.7 ppm) was exactly in the middle of this range.

While studying the structural features of the series of diastereoisomers **2** (bis-phosphonate cavitands), we learned that the orientation of the P═O group with respect to the deep aromatic cavity had a negligible effect on the chemical shift values of the protons in the phenyl groups attached to the P atoms. This is because, as depicted in Figure 3, the 14-membered phosphocine ring of the calix[4]pyrrole phosphonate cavitands is conformationally more flexible than the eight-

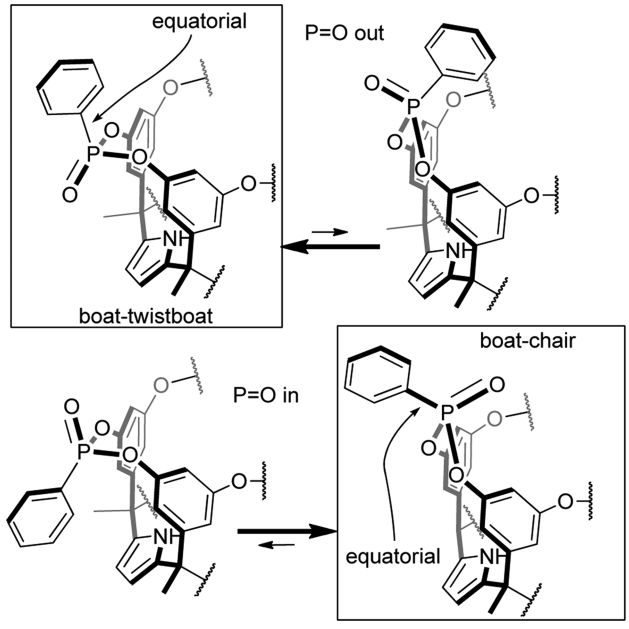


Figure 3. Equilibria involving the two possible conformers, boat-twistboat and boat-chair, of the 14-membered phosphocine rings present in the stereoisomers of bis- and tetra-phosphonate calix[4]-pyrrole cavitands. Top, P═O out(o); bottom, P═O in(i). Notice that the preferred conformation of the ring is dictated by the equatorial position of the phenyl group.

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membered analogue in the resorcin[4]arene phosphonates **4** (see the Supporting Information). Simple molecular modeling calculations (MM3) performed on a mono-phosphonate bridged calix[4]pyrrole cavitand showed that the phosphocine ring adopted two different low energy conformations, boat-chair and boat-twistboat, in response to the relative orientation of the P═O group with respect to the aromatic cavity. Interestingly, in both of them, the phenyl group is oriented in an equatorial position pointing away from the aromatic cavity. This eliminates the possibility of relating the chemical shifts values of the phenyl protons to the orientation exhibited by the P═O group to which it is attached. The X-ray structures previously described for the three stereoisomeric bis-phosphonate **2** testified the exclusive existence, in the solid state, of phosphocine rings having equatorial phenyl groups, that is, a boat-chair conformation for P═O(i) and a boat-twistboat conformation for P═O(o) bridges.[16]

Single crystals from the first eluted stereoisomer suitable for X-ray diffraction grew from acetonitrile solution. The analysis of the diffraction data revealed that the isolated tetra-phosphonate was the 7oooo stereoisomer (Figure 4; see the Supporting Information for the computed energies of the acetonitrile inclusion complexes of the two stereoisomers with C_4 symmetry $CH_3CN\subset$7iiii and $CH_3CN\subset$7oooo). In the solid state, the 7oooo cavitand featured C_4 symmetry with the lone pairs of four of the eight bridging oxygen atoms inwardly directed toward its aromatic cavity providing an example of inherently chiral molecule. The cyclochiral conformer shown is defined to have *M* axial chirality by assigning priority to the oxygen atom with the lone pairs directed toward the cavity.[27] Both cycloenantiomers were observed in the crystal lattice. The 14-membered phosphocine rings adopted a boat-twistboat conformation analogous to the one observed also in the solid state for the bis-phosphonate **2**oo.[16] Probably, when the oxygen atoms of the outwardly oriented P═O group are moved to the axial position, they are forced into the face of the pyrrole ring. To minimize this repulsion, the P═O oxygen atom rotates, the unshared electron pairs of four of the eight phenolic oxygen atoms face inward, and the phosphocine ring adopts a boat-twistboat conformation.

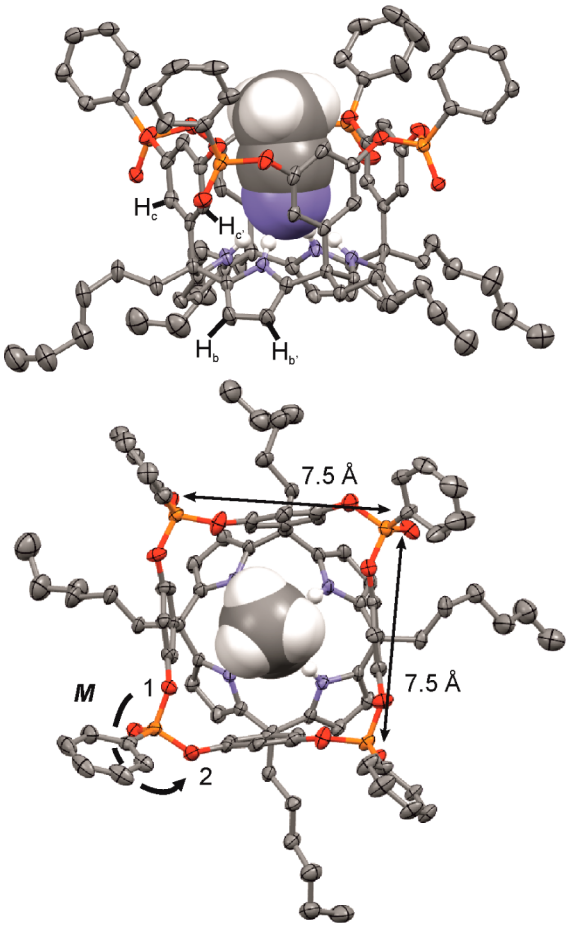

Figure 4. Side and top views of the X-ray structure of tetra-phosphonate 7oooo (C_4 symmetry). Solvent molecules and nonpolar hydrogen atoms are removed. Dodecyl chains are pruned for clarity. The depicted cyclochiral enantiomer is assigned the M configuration.

The two dimensions of the aromatic cavity become almost identical (~7.5 Å between adjacent P atoms).

In the cyclochiral conformation adopted by the 7oooo stereoisomer, the protons H_b,$H_{b'}$ and H_c,$H_{c'}$ are diastereotopic, whereas in the ^{1}H NMR spectrum of the cavitand (Figure 2) they did not resonate as separated signals. This observation suggested that in solution and at room temperature the interconversion between the two cycloenantiomers was occurring at a rate that is fast on the chemical shift NMR time scale, explaining why the ^{1}H NMR spectrum is consistent with a C_{4v} symmetry.

Figure 5 shows the selected regions of the ^{1}H and ^{31}P-decoupled ^{1}H NMR spectra of the second eluted tetra-phosphonate diastereoisomer. The cavitand structure had a reduced symmetry producing more complex NMR spectra. A careful analysis of the number of resonances of the phosphorus atoms and protons led to the ascription of C_s symmetry, diagnostic of the 7iooo and 7iiio isomers. Because of uneven NOE enhancements of the signals by decoupling and long longitudinal relaxation times, the ^{31}P NMR spectra were not suitable for integration. However, qualitatively it can be stated that three of the four phosphorus signals resonated at higher field. As commented above in the bis-phosphonate cavitand series **2**, P═O groups directed away from the cavity had

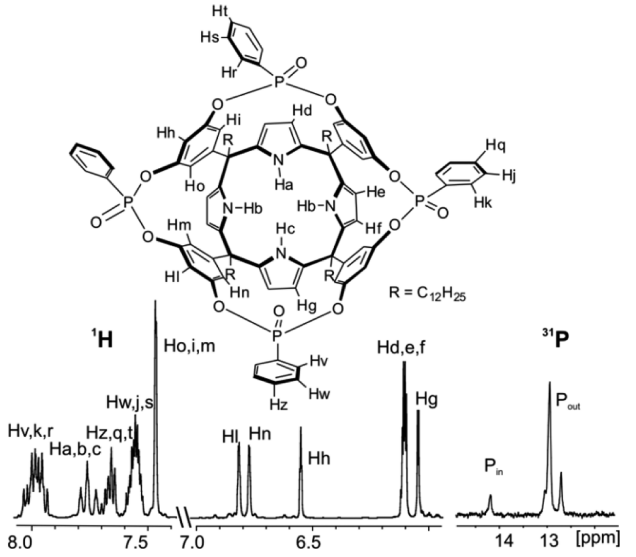

Figure 5. Selected regions of ^{1}H and ^{31}P{^{1}H} NMR of a CD_2Cl_2 solution of tetra-phosphonate 7iooo. Inset: Line drawing structure of 7iooo indicating the proton assignment.

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phosphorus atoms resonating at higher field. Taken together, these results allowed the tentative assignment of this second isomer as 7iooo.

We assigned the more upfield shifted signal (δ = 6.1 ppm) of the β-protons to the pyrrole unit involved in the 14-membered phosphocine ring having the inwardly oriented P═O group. The upfield shift experienced by these protons must be produced by the phenyl substituent at the phosphorus atoms located in equatorial position and facing the pyrrole ring (Figure 3). The high upfield shifts experienced by the aromatic protons H_l and H_n are also consistent with an inward orientation of the bridging P═O group. The configurational assignment of the 7iooo stereoisomer was corroborated by solving the X-ray structure of its complex with PMe_4Cl (vide infra).

Binding Studies with Ammonium/Phosphonium Ion Pairs. We evaluated the newly prepared tetra-phosphonate cavitands 7oooo and 7iooo as multitopic receptors for ion pairs. We selected tetramethylphosphonium chloride (**9**, TMPCl, Figure 6) as a target ion pair because of its increased solubility in dichloromethane solution as compared to tetramethylammonium chloride.

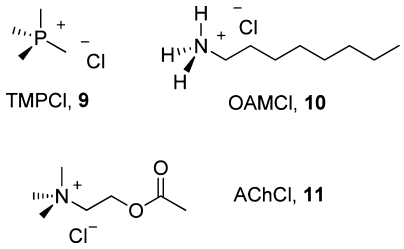

Figure 6. Line drawing structures of the phosphonium and ammonium chloride salts used in this study.

In dichloromethane solution at millimolar concentration, both the TMPCl and its complexes with the cavitands are expected to be almost completely ion-paired. The interaction of the two stereoisomers **7** with TMPCl (**9**) in CD_2Cl_2 solution was probed using ^1H and $^{31}P\{^1H\}$ NMR in separated titration experiments. The addition of 0.5 equiv of salt **9** to a millimolar CD_2Cl_2 solution of 7oooo produced separated proton and phosphorus signals for the free and bound cavitand in the corresponding NMR spectra. When 1 equiv of **9** was added, only the signals assigned to bound 7oooo were observable (Figure 7a). Taken together, these observations indicated that the chemical exchange between free and bound phosphonate cavitand was slow on the ^1H and ^{31}P NMR chemical shift time scales and that the magnitude of the stability constant for the **9**⊂7oooo complex was greater than 10^4 M^{-1}.

The large downfield shift experienced by the pyrrole NH protons ($H_{a'}$ $\Delta\delta$ = 4.15 ppm) upon chloride binding indicated the formation of hydrogen-bonding interactions, which required the inclusion of the chloride in the calix[4]pyrrole deep aromatic cavity. The $^{31}P\{^1H\}$ NMR spectrum revealed that the phosphorus signal assigned to the P═O groups in the bound receptor moved slightly upfield ($\Delta\delta$ = −1.49 ppm) with respect to the free receptor. Likewise, the phosphorus signal of the TMP cation in the **9**⊂7oooo complex was also shifted upfield ($\Delta\delta$ = −4.0 ppm, Supporting Information Figure S9).[28] A 2D ROESY experiment (Supporting Information Figure S10) showed close-contact cross-peaks between the methyl protons of the TMP cation and the β-pyrrole protons of the 7oooo

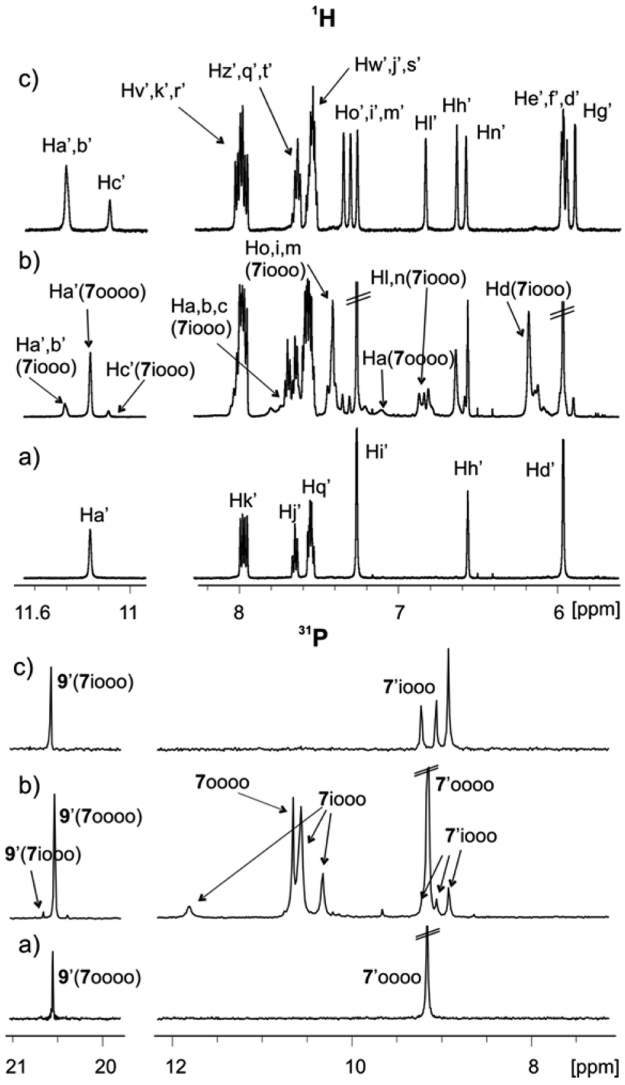

Figure 7. Selected regions of the ^1H and $^{31}P\{^1H\}$ NMR spectra in CD_2Cl_2 solution of equimolar mixtures of (a) 7oooo and **9**, (b) 7oooo, 7iooo, and **9**, and (c) 7iooo and **9**. Primed letters indicate the signals corresponding to the protons involved in complex formation. See Figures 2 and 5 for proton assignment.

($H_{b'}$). This finding suggested a preferential location of the TMP cation in the electron-rich shallow bowl of the calixpyrrole opposite to the bound chloride resulting in a **9**⊂7oooo complex displaying host-separated ion-pair geometry.

The complexation of TMPCl with the 7iooo stereoisomer was also probed using NMR spectroscopy (Figure 7c). The obtained results demonstrated that the kinetic and thermodynamic behavior of the binding process was comparable to that described for 7oooo (see the Supporting Information). Previous work with the bis-phosphonate series of stereoisomers **2**[16] evidenced that the presence of one or two P═O groups inwardly directed led to a switching of the ion-pair arrangement in the complex. In short, the ion pair was bound with receptor separated binding geometry by **2**oo but preferentially with close contact arrangement by **2**ii and **2**io. The complexation-induced shifts (^1H and $^{31}P\{^1H\}$) experienced by the bound TMP cation in complexes **9**⊂7oooo and **9**⊂7iooo cation were completely analogous. Moreover, a 2D ROESY experiment performed on the **9**⊂7iooo complex demonstrated exclusive intermolecular contacts between the TMP cation and the β-pyrrole protons

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(Supporting Information Figure S11). We concluded that both tetra-phosphonate stereoisomers 7oooo and 7iooo recognized the TMPCl salt displaying a host-separated arrangement of the ions. In summary, the inward orientation of one P═O group did not produce the switching of the ion-pair binding mode for the tetra-phosphonate diastereoisomers 7oooo and 7iooo binding TMPCl.

The hydrogen-bonding interaction and the deep inclusion of the chloride proposed for the 9⊂7iooo complex formed in solution were fully supported by the X-ray structure of the complex in the solid state (Figure 8). Unfortunately, the

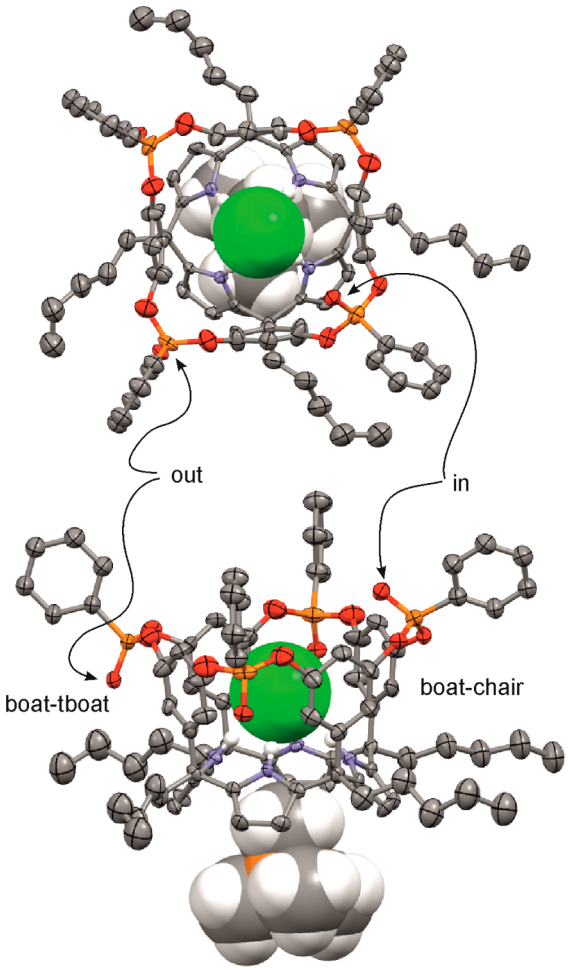

Figure 8. Solid-state structure of the complex 9⊂7iooo. The cavitand is depicted in stick-ellipsoid style at 50% probability level for all atoms, whereas the TMPCl salt is shown as a space-fill model.

packing of the crystal showed a columnar motif, which did not provide unambiguous evidence of the ion-pair arrangement in such complex. It was rewarding to observe that in the solid state the phosphocine rings in the 9⊂7iooo adopted the two different conformations expected as a function of the relative orientation of the P═O group with respect to the cavity (boat-chair for P═O(i) and boat-twistboat conformer for P═O(o) bridges). As discussed above, in both ring conformations the phenyl substituent occupies an equatorial position. The formation of anionic $[Cl⊂7oooo]^-$ and cationic $[TMP⊂7oooo{\cdot}CH_3CN]^+$ complexes was also evidenced in the gas phase through the detection of the corresponding ion peaks and their expected isotopic distributions using ESI−MS with negative and positive modes, respectively, to analyze a solution containing the tetra-phosphonate cavitand and TMPCl (see the Supporting Information).

We used isothermal titration calorimetry experiments to assess accurately the stability constant values for the 9⊂7oooo and 9⊂7iooo complexes in CH_2Cl_2 solution (see the Supporting Information). At the concentrations required for the accurate calculation of the stability constants of the complexes, the heat released (0.3−0.5 μcal) after each injection of TMPCl to a solution of **7** was small, close to the detection limit of the calorimeter, and of the same order of the heat released by the simple dilution of the injected salt. These limitations are inherent to the systems under study and complicated the measurement of reliable data. Nevertheless, we obtained a reasonable fit of the integrated heat data, after subtracting the heat of dilution, to theoretical binding isotherms for the formation of 1:1 complexes (Supporting Information). The binding curves were monosigmoidal and showed an inflection point centered at a molar ratio [**9**]/[receptor] close to 1. As was already mentioned, we considered that in CH_2Cl_2 solution both the salt and the complex are ion-paired; thus a 1:1 binding model, although not ideal, is suitable for the mathematical analysis of titration data. The values calculated for the stability constant of the different complexes, the free energies of binding, and their associated enthalpy and entropy terms are summarized in Table 1.

Table 1. Stability Constant Values (K_a, M^{-1}), Free Energies of Binding (ΔG, kcal/mol), and Corresponding Enthalpic (ΔH, kcal/mol) and Entropic ($T\Delta S$, kcal/mol) Components Determined for the 1:1 Complexes of TMPCl 9 with Diastereomeric Tetra-phosphonates 7oooo, 7iooo, and Cavitand 8 in Dichloromethane Solution (298 K)

receptor	$K_a \times 10^{-7}$	ΔG	ΔH	$T\Delta S$
7oooo	16.0 ± 5	−11.2 ± 0.2	−7.2 ± 0.1	4.0 ± 0.2
7iooo	3.3 ± 1.1	−10.2 ± 0.2	−5.7 ± 0.1	4.5 ± 0.2
8	0.2 ± 0.1	−8.5 ± 0.3	−3.3 ± 0.1	5.2 ± 0.3

The complexation of TMPCl by the receptor series **7** was both enthalpically and entropically favorable. The strong and favorable entropic component measured for the two complexation processes suggested that solvation/desolvation effects must play a crucial role in binding. To verify the ratio between the stability constant values determined for the 9⊂7oooo and 9⊂7iooo complexes using ITC experiments, we performed a pairwise competitive binding experiment. We analyzed a ∼1 mM CD_2Cl_2 solution containing a close to equimolar amount of the two tetra-phosphonate receptors and TMPCl using ^1H and $^{31}P\{^1H\}$ NMR spectroscopy. The NHs in the bound-chloride receptors are the most downfield shifted signals of the spectrum and resonate completely separate of any other proton signal. We observed two different sets of signals for the NHs corresponding to each one of the complexes. In addition, the $^{31}P\{^1H\}$ NMR spectrum displayed different signals for the phosphorus atoms of the two receptors, both in the free and in the bound state (Figure 7b). The integral values of the NH proton signals for each receptor, in both the free and the bound state, were used to calculate the ratio of association constants. In good agreement with the ITC results, we determined that $K_{a,exp}$(9⊂7oooo)/$K_{a,exp}$(9⊂7iooo) ≈ 4. Previous studies with bis-phosphonate calix[4]pyrroles **2** had shown that the inward orientation of one P═O group produced an energetic

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disadvantage to a similar extent.[16] We hypothesized that the existence of repulsive electrostatic interactions between the negative end of the dipole moment of the inwardly directed P═O group and the included chloride was responsible for the reduction in binding affinity.

The calix[4]pyrrole cavitand **8** (Scheme 2) was used as a model system to quantify the electrostatic effect provided by the four phosphonate groups in the **9**⊂7oooo complex. ITC experiments assigned a stability constant of $(0.2 \pm 0.1) \times 10^7$ M^{-1} to the **9**⊂**8** complex.[29] This value is approximately 80-fold smaller (2 orders of magnitude) than the one calculated for the **9**⊂7oooo complex. Therefore, the stabilizing electrostatic effect provided by the four phosphonate group was quantified to be ∼ −2.5 kcal/mol. This value nicely doubles the −1.4 kcal/mol calculated for the introduction of two P═O groups in the bis-phosphonate cavitands **2**.[16]

Interestingly, receptor 7oooo was also very effective in CH_2Cl_2 solution for the complexation of acetylcholine chloride (**11**, Figure 6), a biorelevant trimethylalkylammonium salt.[30,31] Using ^{1}H NMR spectroscopy, we estimated a stability constant value larger than 10^4 M^{-1} for the 1:1 complex **11**⊂7oooo. The analysis of the ^{1}H NMR titration data assigned a host-separated geometry for the ion pair in the complex. One of the methyl groups in the trimethylammonium knob of the acetylcholine can be accommodated easily by the shallow aromatic π-cavity provided by the calix[4]pyrrole core opposite to the deep included chloride (Supporting Information).

Comparison of the Binding Affinity of Tetra-phosphonate 7oooo versus Bis-phosphonate 2oo toward TMPCl. The ratio of the stability constants determined from ITC experiments $K_{a,exp}$(**9**⊂7oooo)/$K_{a,exp}$(**9**⊂**2**oo)[16] is ∼200. To further verify the energetic advantage provided by the introduction of two additional phosphonate groups, we performed a direct competitive binding experiment between the 7oooo and **2**oo receptors. The analysis of a CD_2Cl_2 solution containing an equimolar mixture of the two receptors and TMPCl using ^{1}H NMR and ^{31}P{^{1}H} NMR revealed the exclusive formation of **9**⊂7oooo (Supporting Information Figure S12). Consequently, and in complete agreement with the ITC results, the value of the $K_{a,exp}$(**9**⊂7oooo) is more than 2 orders of magnitude larger than $K_{a,exp}$(**9**⊂**2**oo). The measured difference in binding affinities is greater than expected for the electrostatic gain provided by the introduction of two additional P═O groups (−1.4 kcal/mol, corresponding to a 10-fold increase in binding affinity). The superior binding properties displayed by the tetra-phosphonate calix[4]pyrrole 7oooo for the complexation of TMPCl, in comparison to the bis-phosphonate **2**oo counterpart, resulted from the combination of an increase in the number of favorable electrostatic interactions and the reduction of conformational flexibility. In short, the tetra-phosphonate isomer 7oooo shows superior binding properties for TMPCl than the bis-phosphonate analogue **2**oo.

Effect of Hydrogen Bonding as an Additional Driving Force for the Recognition of Primary Ammonium Salts and Switching of the Ion-Pair Binding Mode. The iiii stereoisomer of tetra-phosphonate resorcin[4]arene cavitands and other phosphonate derivatives with at least one P═O group inwardly directed are known to interact with primary alkylammonium cations by establishing simultaneously NH···O hydrogen bonds and cation−dipole interactions.[25,32] We became interested in assessing the effect provided by one inwardly oriented P═O group on the complexation of a primary ammonium salt, that is, octylammonium chloride (OAMCl, **10**, Figure 6), by the tetra-phosphonate calix[4]-pyrrole 7iooo cavitand. We learned from previous studies with the series of bis-phosphonate calix[4]pyrrole cavitands **2** that octylammonium chloride **10** formed a 1:1 complex with the **2**io isomer that was approximately 2-fold thermodynamically more stable than the analogous complex with the **2**oo isomer. In addition, while the **10**⊂**2**oo complex showed in solution a receptor-separated binding mode, the **2**io isomer bound the primary salt **10** in a close-contact geometry. That is, the chloride was included in the deep aromatic cavity of **2**io, and the cobound cation was located close to the upper rim, establishing a combination of ion−dipole and hydrogen-bond interactions with the inwardly oriented P═O group.

A pairwise competitive experiment carried out in CD_2Cl_2 solution between the diastereoisomers 7oooo and 7iooo toward **10** (Supporting Information Figure S21) uncovered an analogous trend in stability constants for the tetra-phosphonate series binding a primary ammonium chloride, that is, $K_{a,exp}$(**10**⊂7iooo) ≈ 2$K_{a,exp}$(**10**⊂7oooo). The switching of the ion-pair binding mode in the tetra-phosphonate series also became evident by comparison of the complexation induced shift experienced by methylene protons α to the nitrogen atom in the bound octylammonium cation, $\Delta\delta$ = −0.45 ppm and $\Delta\delta$ = −2.2 ppm for **10**⊂7iooo and **10**⊂7oooo, respectively. The highest upfield shift of the methylene protons α to the nitrogen atom in the **10**⊂7oooo complex is caused by their preferential inclusion in the shallow cup-like of the calix[4]pyrrole opposite to the bound chloride (host-separated binding mode, Figure 9).

A direct competition experiment performed between the best receptors of the bis- and tetra-phosphonate series, **2**ii and 7iooo, respectively, toward the octylammonium chloride **10** assigned a 2-fold thermodynamic advantage to the **10**⊂**2**ii complex (Supporting Information Figure S22). A similar experiment performed between **2**io and 7iooo (Supporting Information Figure S23) established a superior binding ability of the tetra-phosphonate receptor toward the primary ammonium chloride salt **10**, $K_{a,exp}$(**10**⊂7iooo) ≈ 10$K_{a,exp}$(**10**⊂**2**io). Taken together, these results demonstrated that the reduction of conformational flexibility and the presence of additional outwardly oriented P═O groups featured by the tetra-phosphonate receptors, as compared to the bis-phosphonate analogs, increased the binding affinity toward ion-pair **10**. However, these two effects were not enough to outperform the inward orientation of two P═O groups present in the **2**ii diastereoisomer. Therefore, the synthesis of tetra-phosphonate isomers featuring more than one P═O group inwardly oriented may lead to the discovery of calix[4]pyrrole receptors with binding properties superior to those of the bis-phosphonate isomer **2**ii toward primary ammonium ion pairs.

Effect of the Solvent in the Selective Binding of TMPCl by Tetra- versus Bis-phosphonate Receptors. It is well-known that the nature of the solvent has a strong impact on the behavior of the salts in solution. In low permittivity media (i.e., CH_2Cl_2), ion-pair formation is likely to occur. Conversely, in high permittivity solvents (i.e., CH_3CN), alkylphosphonium salts at 1 mM concentration are expected to be fully dissociated. For solubility reasons, we could only investigate the binding of TMPCl, **9**, with the 7oooo isomer in CD_3CN solution. The 7iooo was not soluble in CD_3CN at the concentration required to perform NMR experiments. The interaction of the receptor 7oooo with **9** was probed using ^{1}H NMR spectroscopy. The results obtained indicated: (a) the

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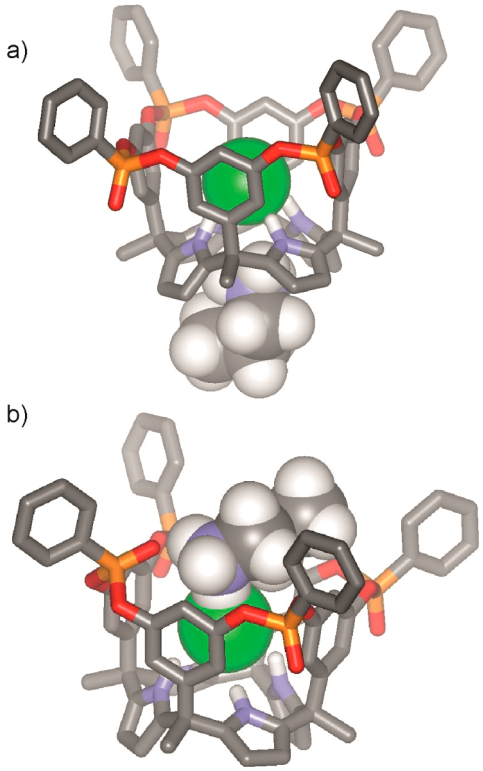

Figure 9. Energy-minimized structures at the BP86/dev2-SVP level of theory of the complexes: (a) **10**⊂7oooo showing a receptor separated geometry for the bound ion pair and (b) **10**⊂7iooo featuring close-contact arrangement of the ion pair. The P═O group inwardly oriented in **10**⊂7iooo is hydrogen bonded to the OAM cation. The octyl substituent in **10** was modeled as a propyl residue and the *meso*-dodecyl chains in **7** as methyl groups to reduce calculation time.

existence of a chemical exchange between the free and bound receptor that was slow on the chemical shift time scale, and (b) the formation of a 1:1 anionic complex Cl^-⊂7oooo with a stability constant that was estimated to be higher than 10^4 M^{-1} (see the Supporting Information). The lack of involvement of the cation in the anionic complex Cl^-⊂7oooo was inferred from the absence of complexation-induced changes in the proton signals of the TMP. A pairwise competitive experiment performed with receptors 7oooo and **2**oo toward **9** in CD_3CN allowed the determination of the ratio of the stability constants of the corresponding chloride complexes as $K_{a,exp}(Cl^-⊂7oooo)/K_{a,exp}(Cl^-⊂2oo) \approx 6$, a value that gauges the energy gain provided by the conformational rigidification of the receptor and the introduction of two additional P═O groups. Interestingly, the same ratio of stability constants determined above in CD_2Cl_2 solution is approximately 200. The measured difference in the values of the constant ratios indicated that the binding of the TMP cation occurring in low polarity solvents, which afforded ion-paired complexes with the same binding mode, is not isoenergetic for the tetra- and bis-phosphonate cavitands. The recognition of the TMP cation seems to be the determining step for the high selectivity for 7oooo toward TMPCl measured in CD_2Cl_2. This finding is in complete agreement with recent computational studies on bis-phosphonate calix[4]pyrrole cavitands **2**.[33] Taking as reference the value of $K_{a,exp}(Cl^-⊂2oo) = (6.0 \pm 2) \times 10^3$ M^{-1} determined in a previous work,[16] we calculated a stability constant value $K_{a,exp}(Cl^-⊂7oooo) = 3.6 \times 10^4$ M^{-1} in acetonitrile. Not surprisingly, the stability constant determined for the 1:1 anionic complex that is formed in the polar solvent is reduced by 3 orders of magnitude as compared to the one calculated for the 1:1 ion-paired counterpart $K_{a,exp}$(**9**⊂7oooo) = $(16.0 \pm 5) \times 10^7$ M^{-1} in CD_2Cl_2 solution. In short, the nature of the solvent has a strong impact in both binding affinity and characteristics of the complex.

■ CONCLUSIONS

We have synthesized two unprecedented diastereoisomeric tetra-phosphonate cavitands 7oooo and 7iooo based on a calix[4]pyrrole octol scaffold **6b**. The solid-state structures available for phosphonate resorcin[4]arene cavitands and the X-ray structures reported here for tetra-phosphonate calixpyrrole cavitands revealed significant differences in the conformations adopted by their phosphocine rings. The eight-membered phosphocine rings present in the phosphonate resorcin[4]arene cavitands always adopted a boat-chair conformation. In contrast, the 14-membered phosphocine ring of the calix[4]pyrrole phosphonate cavitands is conformationally flexible. Two different low energy conformations, boat-chair and boat-twistboat, are observed in response to the relative orientation of the P═O group with respect to the aromatic cavity. Interestingly, in both of them, the phenyl group is oriented in an equatorial position pointing away from the aromatic cavity. The complexation of tetramethylphosphonium chloride by the tetra-phosphonate calix[4]pyrrole receptors 7oooo and 7iooo was probed using NMR spectroscopy both in CH_2Cl_2 and in CH_3CN solutions. In CH_2Cl_2 solution, ion-paired complexes **9**⊂**7** with 1:1 stoichiometry are formed, in which the ion pair displayed a host-separated binding mode independent of the relative orientation of the P═O groups. Using ITC experiments, we assessed accurately the binding constant values of TMPCl with the two tetra-phosphonate calix[4]pyrrole diastereoisomers. The 7oooo receptor showed higher affinity, most likely due to the existence of repulsive interactions between the negative end of the dipole moment of the inwardly directed P═O in 7iooo and the included chloride. Interestingly, the complexation of the primary ammonium chloride **10** by the tetra-phosphonate isomers **7** featured a switching of the ion-pair binding mode. The receptor 7oooo bound **10** in host-separated mode, while 7iooo produced a close-contact arrangement of the ions in the complex. This behavior demonstrated the use of the tetra-phosphonate cavitands **7** as multitopic receptors. Because of reduction in conformation flexibility and increase of electrostatic interactions, the tetra-phosphonate isomers **7** outperformed their bis-phosphonate analogues **2** (**2**io and **2**oo) in the binding of **10**. However, the **2**ii isomer still showed a superior binding affinity for **10** than 7iooo. Binding experiments performed in CH_3CN with the 7oooo receptor and TMPCl revealed the formation of anionic complexes Cl^-⊂7oooo. The comparison of the stability constants determined for the Cl^-⊂7oooo (CH_3CN) and TMPCl⊂7oooo (CH_2Cl_2) complexes indicated that ion-pair binding is determinant for the high selectivity exhibited by this receptor in nonpolar solvents toward TMPCl.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for the synthesis of the cavitands and their characterization data; ^1H and ^{31}P NMR spectra of the binding studies of **7** and **8** with TMPCl; competitive experiments performed in both dichloromethane and acetoni-

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trile solutions between the two diastereoisomers **7**, as well as with the bis-phosphonate calix[4]pyrroles **2**; ITC experiments of **7** with TMPCl; ^{1}H and ^{31}P NMR spectra of the binding studies of **7** with acetylcholine chloride; ESI−MS experiments; conformational studies of resorcinarene cavitands **4**; and computational study details and coordinates of the energy minimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*pballester@iciq.es

Present Address

[§]Institute of Condensed Matter and Nanosciences, Université Catholique de Louvain, Croix du Sud, 1 B-1348 Louvain-la-Neuve, Belgium.

Notes

The authors declare no competing financial interest.

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