Reviews

Phosphorylated macrocycles: structures, complexing properties, and molecular recognition

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Procedures were developed for functionalization of macrocycles by introducing a phosphonic group either directly linked to the aromatic rings (in the case of cyclophanes or calixarenes) or as a pendant arm. For these compounds to be used as artificial receptors for amino alcohols and amino acids, the host molecule must possess not only negative charges arising from the phosphonate moieties but also a hydrophobic binding site, such as electron-rich aromatic residues. We designed *inter alia* new dissymmetric macrocycles capable of being involved in three binding modes with guest molecules, *viz.*, hydrogen bonding, electrostatic attraction, and π-cation interactions. The NMR characterization of the macrocycles, their stereochemistry in solution and in the solid state, and the use as chiral receptors for biologically relevant molecules are described.

Key words: phosphorylated macrocycles, 1,4,8,11-tetraazacyclotetradecane, calix[4]arenes, meta- and paracyclophanes, polyether cyclophanes.

Conformationally flexible macrocycles are of great importance for supramolecular chemistry, and thus the attention of chemists has been focused on a synthetic route to such molecules.[1—3] In particular, considerable study has been given to the synthesis and characterization of constrained macrocycles as specific receptors for selective complexation with neutral guests,[3—5] with emphasis on the binding of a wide variety of biologically relevant molecules. Moreover, chemically robust aromatic macrocycles capable of complexing with cations, in particular, with lanthanides, are useful as luminescence sensors and for diagnostic bioassays[6,7] in medicine, as well as in powerful screening techniques, such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and proton emission tomography (PET) once complexed with radioactive lanthanides and actinides.

A search for rigid receptor molecules for organic dicationic guests is a very fertile field of chemistry. In particular, there exists a need to design three-dimensional

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building blocks containing selected functional groups in order to introduce binding sites suitable for biologically relevant molecules into small stereochemically rigid cyclophanes.[1—5]

Selective recognition of biologically relevant molecules, as well as of cations and, particularly, anions, by synthetic receptors is a very fertile field of investigation in supramolecular chemistry.[8] In particular, high emphasis is placed on the synthesis of conformationally preorganized building blocks, which may be used as precursors of specific hosts with desired properties.

In our approach, among various possible procedures for functionalization, the introduction of a phosphonic group, which is either directly linked to the aromatic rings (in the case of cyclophanes or calixarenes) or as a pendant arm, into a molecule appears to be a rather promising route.

In fact, for an efficient artificial receptor for amino alcohols and dicationic amino acids to be constructed, the host must possess not only negative charges arising from the phosphonate moieties but also a binding site, such as electron-rich aromatic residues.

Since preorganized rigid chiral hosts for biologically relevant molecules are of great interest for biochemistry and pharmacological studies, we designed *inter alia* new dissymmetric macrocycles capable of being involved in three binding modes, *i.e.*, bind guests through electrostatic attraction, hydrogen bonding, and π-cation interactions. For electrostatic interactions, we resorted to the use of a dialkylphosphonate moiety, which can bear a negative charge after hydrolysis to the monoester functionality, ionization of the latter occurring at almost neutral pH values, which is a prerequisite for molecular recognition under physiological conditions.[9]

In the present paper, we review the salient aspects of some macrocycles synthesized in our laboratory, all possessing the phosphonate moiety and being able to act as complexing agents for cations and organic substrates. In particular, NMR characterization of macrocycles, their stereochemistry in solution and in the solid state, and the use as chiral receptors for biologically relevant molecules are described.

Phosphorylated macrocycles

Tetraazacyclotetradecane. Considering that cyclam (1,4,8,11-tetraazacyclotetradecane) and its derivatives have attracted great interest as complexing agents for various applications, the introduction of functional groups at carbon and nitrogen atoms[10] gives rise to "tailor-made" ligands with special properties, *e.g.*, capable of stabilizing unstable oxidation states[11—13] or possessing high selectivity for a certain metal ion.[14] Side chains introduced at the nitrogen atom of cyclam and related compounds are responsible for enhanced thermodynamic stability and kinetic inertness of complexes formed with these ligands. These complexes have found applications as magnetic resonance imaging contrast agents.[15] The design of labeled monoclonal antibodies for radioimmune diagnostics and therapy is another field of application of *N*-functionalized tetraazamacrocycles.[16—18] The introduction of phosphonate instead of carboxylate groups at nitrogen may open new possibilities for the design of potential complexing agents for both the above-mentioned applications.

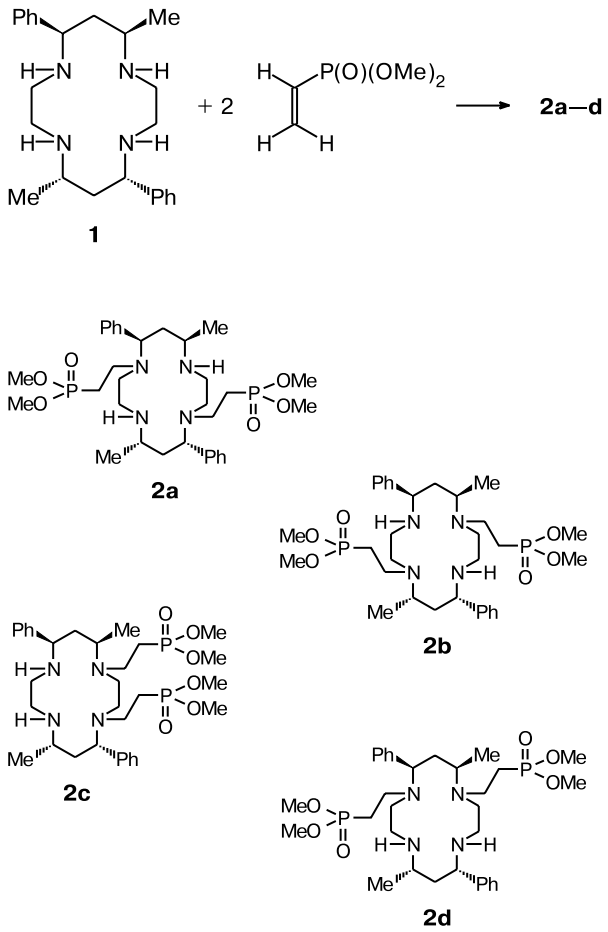
Since, in most cases, the structure of a macrocyclic ligand in solution determines the structure of the resulting complex, the complexation properties of macrocycles can be predicted by analyzing their conformations in solution. We used a method that combines NMR spectroscopy and molecular modeling.[19]

To investigate phosphorylation of substituted cyclam, 7,14-dimethyl-5,12-diphenyl-1,4,8,11-tetraazacyclotetradecane (**1**) was chosen as the starting reagent.[20—22] The reaction of **1** with dimethyl vinylphosphonate in methanol under acidic catalysis affords product **2** (Scheme 1). The presence of two phosphonate pendant arms in the latter was proved by elemental analysis. Unfortunately, it was not possible to grow crystals suitable for X-ray diffraction. Therefore, we tried to differentiate between alternative structures **2a—d** by NMR spectroscopy and molecular modeling.

According to the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, the phosphorylated macrocycle has C_2 symmetry in solution. Therefore, structures **2c** and **2d** can be ruled out because they would give rise to an unsymmetric spectral habitus. An iterative refinement using the DAISY [23] and PERCH [24] program packages allowed us to extract chemical shifts and coupling constants. The conformations of the ethylene bridges are derived from these results by applying the Karplus-type equation modified by Hawkins and Palmer.[25] It enabled us to calculate the N—C—C—N dihedral angle and reveal the *gauche* orientation along both C—C bonds. This rotamer is exclusively populated at room temperature, which is indicative of a very stable structure. Variable-temperature ^{1}H and ^{13}C NMR spectra show no significant changes in the spectral pattern, which is indicative of high stability of the major conformation of the macrocyclic rings.

Unfortunately, it was not possible to discriminate between diastereomers **2a** and **2b** by NMR techniques alone. Therefore, we used molecular modeling to distinguish between these diastereomers. Two different approaches were followed: semiempirical (VAMP [26]) calculations using the AM1 [27] and PM3 [28] parameter sets and force field simulations (DISCOVER [29]). Extensive calculations for molecule **1** with and without consideration for the solvent showed no significant differences for the dihedral angles and energies of the conformations in the presence or absence of solvation for this type of compounds. For struc-

Scheme 1



tures **2**, force field calculations using water as the solvent required excessive computational times (several days). Therefore, since semiempirical optimization (VAMP) again showed no significant differences for the conformers with and without consideration for the solvent, no solvent effects were included in DISCOVER simulations of structures **2a** and **2b**.

Molecular dynamics (MD) calculations were performed for **1**, **2a**, and **2b** to search for minima in the conformational space. Using four representative minima from the 500 K MD simulations as input structures, the geometries of these conformers were optimized with the use of semiempirical and force field programs to avoid misinterpretations resulting from errors of the methods themselves.

For compound **1**, we found a very stable structure of the macrocyclic ring, which is consistent with the experimental data. Figure 1 shows one of the conformers of molecule **1**, which was calculated with the use of the VAMP program (the AM1 parameter set) and is in the best agreement with the NMR spectroscopic data.

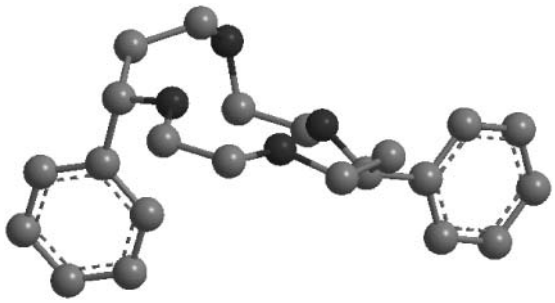


Fig. 1. Most stable conformer of molecule **1** calculated with the use of the VAMP program.

According to the NMR data, a similar geometry should be observed for the macrocyclic ring of **2**. The MD simulation for molecule **2b** revealed a stable arrangement of the ring with *gauche* conformations of both ethylene bridges, which exactly corresponds to the structure type supported by the coupling constants. For **2a**, a different situation arises. The MD simulation showed high conformational flexibility of the macrocycle, resulting in the unfavorable antiperiplanar arrangement of the nitrogen atoms in the ethylene bridges.

This conformational behavior is in sharp contrast to the results extracted from the ^{1}H NMR spectrum. Therefore, it is assumed that structure **2a** containing substituents at the nitrogen atoms adjacent to the Ph groups is less favorable than **2b** containing the phosphate moieties in proximity to the less bulky Me groups.

The hints found so far have been supported by further results from geometry optimizations using semiempirical and force field programs. The minimum-energy conformations for structures **2a** and **2b** resulting from optimization with the use of the AM1 method are shown in Fig. 2.

The dihedral angles within the macrocyclic ring of **2a** show that there are significant deviations from the stable structure of the parent cycle **1**, *e.g.*, an antiperiplanar arrangement of the nitrogens in the ethylene bridges and an unfavorable *gauche* conformation along the C—C bonds in the phosphonate groups.

Since all the methods and parameter sets used led to comparable results, it can be assumed that the differences in the conformations of **2a** and **2b** do not stem from the methods themselves, but reflect the inherent properties of the molecules. Therefore, structure **2b** of bis-phosphorylated product **2** is the most stable one. We proved the structural geometry of **2** by a combination of NMR spectroscopy and molecular modeling and established the structure of the diastereomer formed in the reaction.[19]

Calix[4]arenes. Calixarenes, *viz.*, phenol-derived cyclic oligomers,[30] are considered as a versatile class of macrocyclic compounds because of their remarkable ability to form inclusion compounds of the host—guest type.[31] Along with their well-known useful properties,[32] calix-

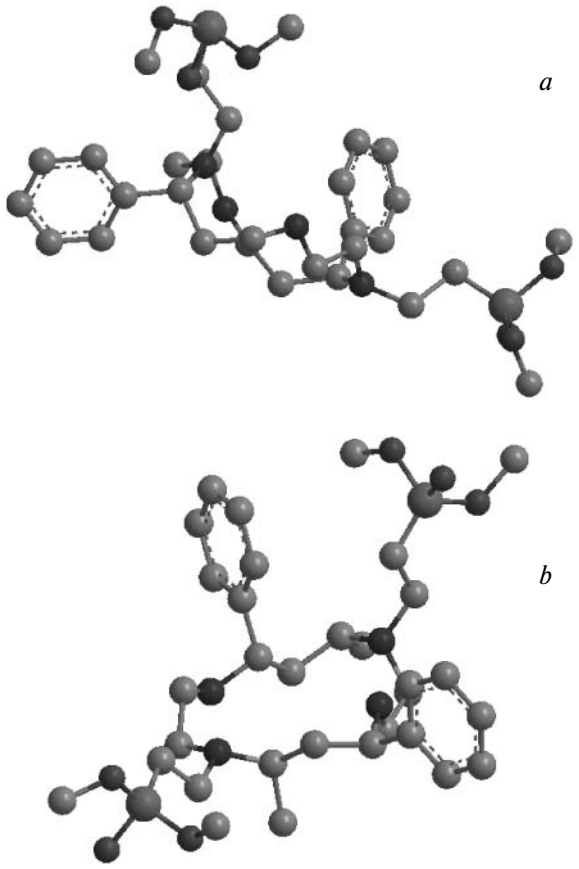


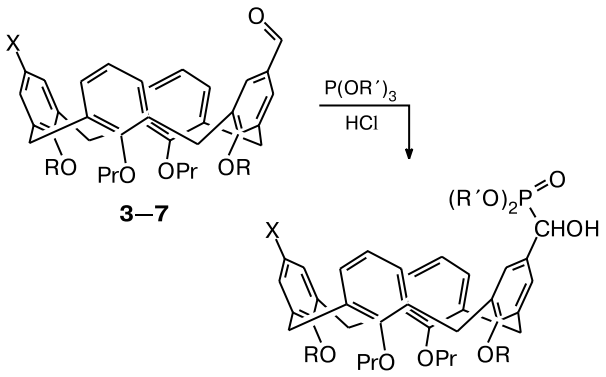
Fig. 2. Minimum-energy conformation resulting from optimizations by the AM1 method: **2a** (*a*) and **2b** (*b*).

arenes possess high biological potential. This potential is *a priori* related to the ability of calixarenes to model natural enzymes[33] and serve as lipophilic containers for transport of bioactive metals and organic molecules through cell membranes. From this point of view, calixarene complexes with bioactive guests[34] and calixarenes chemically modified by bioactive groups are of great interest. At present, calixarenes functionalized at the upper or lower rim of the macrocycle by fragments of natural or artificial biologically active compounds, such as saccharides,[35] ureas,[36] aminoheterocycles,[37] and organophosphorus compounds,[38] are described in literature.

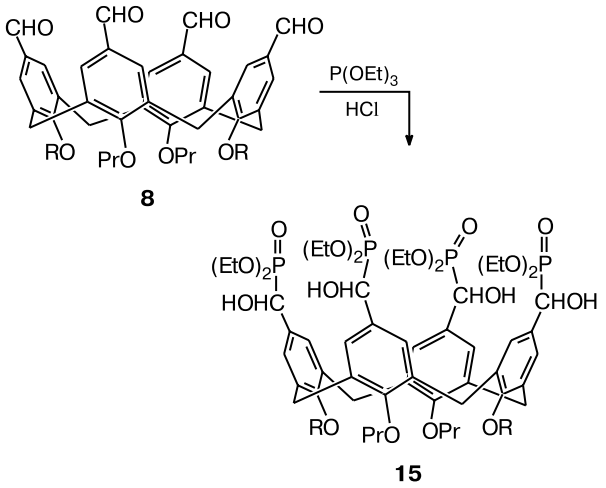
α-Hydroxy- and α-aminophosphonic acid derivatives are known[39] to belong to biologically active compounds. These compounds specifically inhibit certain enzymatic reactions[40] and have high cancerostatic, bacteriostatic, and cytotoxic activities.[40,41] Therefore, we wanted to synthesize calix[4]arenes functionalized at the upper rim of the macrocycle with α-hydroxy- or α-aminophosphonic acid moieties. Below we describe the salient aspects of such hosts.

The reactions of formyl derivatives with trialkyl phosphites provide a convenient synthetic route to the introduction of hydroxymethylphosphonyl fragments at the upper rim of the calixarene ring.[42] The reaction of *p*-formylcalix[4]arenes **3—8** (cone conformers) with trialkyl phosphites in a 1,4-dioxane solution saturated with dry hydrogen chloride at room temperature produced calixarenes **9—15** containing one, two, or four dialkoxyphosphorylhydroxymethyl fragments at the upper rim (Scheme 2).

Scheme 2



	X	R		X	R	R′
3	H	H	**9**	H	Pr	Et
4	H	Pr	**10**	Br	Pr	Et
5	Br	Pr	**11**	$CHOHP(O)(OR')_2$	H	Me
6	CHO	H	**12**	$CHOHP(O)(OR')_2$	H	Et
7	CHO	Pr	**13**	$CHOHP(O)(OR')_2$	H	Pr^i
			14	$CHOHP(O)(OR')_2$	Pr	Et

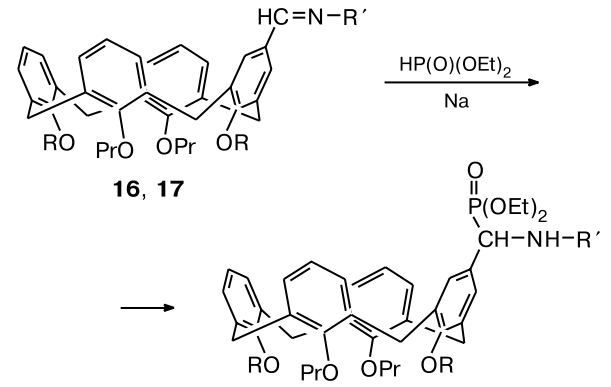


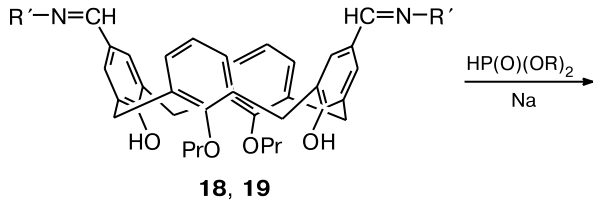
The most important methods for the synthesis of α-aminophosphonic acid derivatives are based on the Pudovik,[43] Mannich,[44] and Kabachnik—Fields reactions.[45] The advantages of phosphorylation using the Pudovik method are high regio- and stereoselectivity, good yields, and accessibility of the reagents. We used this method for the functionalization of the upper rim of

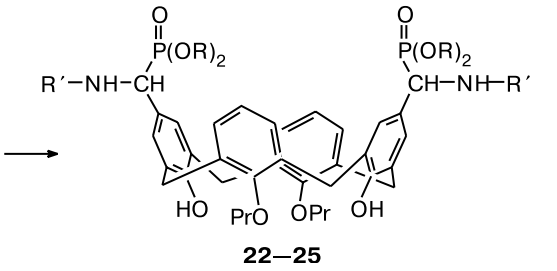
calixarenes with dialkoxyphosphorylaminomethyl fragments.

The precursors, *viz.*, *p*-iminomethylcalixarenes **16—19**, were prepared by refluxing stoichiometric amounts of formylcalixarenes **3—5** with amines in *m*-xylene in the presence of molecular sieves. The dialkoxyphosphorylaminomethyl fragments were introduced into the upper rim by the reaction of *p*-iminomethylcalix[4]arenes **16—19** with dialkyl phosphite in the presence of sodium. As opposed to phosphorylation of *p*-iminodialkoxycalix[4]arenes **16**, **18**, and **19** in the presence of an excess of sodium, a catalytic amount of sodium is sufficient for the reaction of *p*-iminotetraalkoxycalix[4]arene **17** to proceed. The yields of calix[4]arenes **20—25** were 60—65% (Scheme 3).

Scheme 3

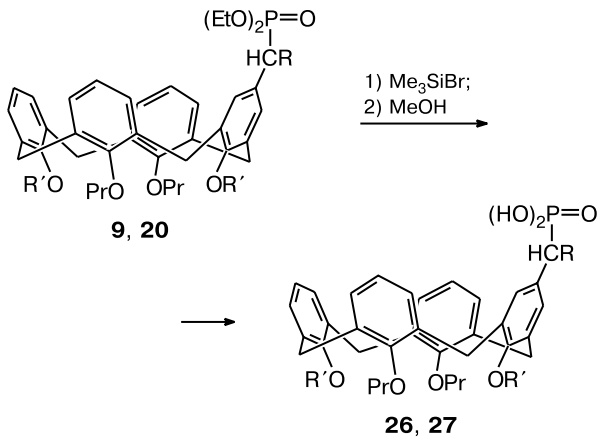


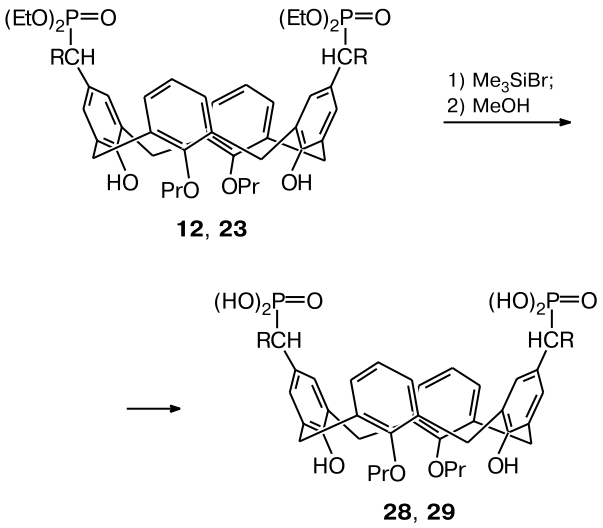




	R	R′		R	R′
16, **20**	H	CHMePh-(–)(L)	**22**	Et	CHMePh-(–)(L)
17, **21**	Pr	*p*-MeC_6H_4	**23**	Et	*p*-MeC_6H_4
18	—	CHMePh-(–)(L)	**24**	Pr	*p*-MeC_6H_4
19	—	*p*-MeC_6H_4	**25**	CH_2Ph	*p*-MeC_6H_4

Scheme 4





9, 26: R = OH, R′ = Pr;
12, 28: R = OH;
20, 27: R = NHCH(Ph)Me-(–)(L), R′ = H;
23, 29: R = *p*-MeC_6H_4NH

Phosphonic acids of the calixarene series **26—29** were synthesized by the reaction of calixarene-containing dialkyl phosphonates **9**, **12**, **20**, and **23** with bromotrimethylsilane in dry chloroform followed by alcoholysis of the resulting silyl esters with methanol (Scheme 4). Dialkoxyphosphoryl(hydroxymethyl)calix[4]arenes **9—15** and dialkoxyphosphoryl(aminomethyl)calix[4]arenes **20—25** are colorless crystalline compounds soluble in many organic solvents. Calix[4]arenes **26—29** containing fragments of free α-amino(hydroxy)phosphonic acids are soluble in polar solvents (DMSO, DMF, and alcohols). Monoaminophosphonic acid **27** of the calix[4]arene series is also soluble in chloroform.

The *syn* orientation of the benzene rings in phosphorylated calixarenes **9—15** and **20—29** is evidenced by the presence of an AB spin system from the nonequivalent axial and equatorial protons of the $ArCH_2Ar$ methylene bridges in the ^1H NMR spectra.

Phosphorylated dipropoxycalix[4]arenes **11—13**, **20**, **22—25**, and **27—29** adopt a flattened cone conformation characteristic of dialkoxy[4]arenes.[32,46] The ^1H NMR spectra show signals for the OH protons at low field (δ >8.0) due to the formation of two strong OH...OPr hydrogen bonds between proximal fragments at the lower rim of the macrocycle. In the ^1H NMR spectra, the distances between the signals for the nonequivalent axial and equatorial protons of the $ArCH_2Ar$ methylene units in calixarenes **11—13**, **20**, **22—25**, and **27—29** ($\Delta\delta$) characterize the dihedral angles formed by the neighboring benzene fragments and are in the range of 0.54—0.97 ppm. The value of $\Delta\delta$ is characteristic of dialkoxycalix[4]arenes adopting a flattened cone (C_{2v} symmetry) conformation. In this conformation, the phosphorylated benzene fragments are forced to be in a coplanar orientation due to the formation of intramolecular OH...OPr hydrogen bonds. The alkoxyalkylated fragments are nearly perpendicular to the main molecular plane of the macrocycle. This conformation was confirmed by molecular mechanics calculations.[42]

The values of $\Delta\delta$ varying in the range of 1.24—1.31 for tetraalkoxycalix[4]arenes **9**, **10**, **14**, **15**, **21**, and **26** indicate the cone conformation (C_{4v} symmetry).[32a] This conformation can be considered as an average structure in a fast flattened cone—flattened cone interconversion characteristic of tetraalkoxycalix[4]arenes.[47]

An important feature of bis-phosphorylated calix[4]arenes **11—13**, **22—25**, **28**, and **29** is the presence of two chiral carbon atoms of the hydroxymethyl or aminomethyl groups at the upper rim of the macrocycle and the possibility of the formation of *d*,*l*-*rac* and (or) *meso* forms during the synthesis.

The addition of dialkoxyphosphates to the C=N bonds of iminocalix[4]arenes **16—19** is highly stereospecific, which has been observed earlier in analogous reactions.[48] Bis-phosphorylation afforded only one of the two possible diastereomers. This result was proved by the fact that the ^1H and ^{31}P NMR spectra of calixarenes **23** and **24** have only one set of signals. Analogous stereospecificity is observed in phosphorylation of monoiminocalix[4]arene **16** containing a chiral carbon atom bound to the nitrogen atom of the imino group. The formation of only one diastereomer of compound **20** was confirmed by the ^1H and ^{31}P NMR spectra.[42]

In contrast with the observations on aminophosphonate derivatives of calixarenes, the ^1H and ^{31}P NMR spectra of bis-hydroxyphosphonates have two sets of signals. The ratio of the intensities of the signals in the ^1H NMR spectra depends on the size of the alkyl groups at the phosphorus atoms and the reaction conditions. The observed spectroscopic characteristics of bis-hydroxyphosphonates **11—14** can be attributed to the formation of a stereoisomeric mixture of the *d*,*l*-*rac* and *meso* forms. One of the diastereoisomers was isolated by crystallization.[42]

Derivatives of α-hydroxyphosphonic acids can form dimeric associates through intermolecular CH—OH...O=P hydrogen bonds.[49] The FAB mass spectra ($[2\ M]^+$ peaks) and IR spectra (signals of associated CH—OH groups at 3310—3360 cm^{-1}) demonstrate that mono(dialkoxyphosphorylhydroxymethyl)calix[4]arenes **9** and **10**, as well as bis(dialkoxyphosphorylhydroxymethyl)calix[4]arenes **11—13**, which adopt the stereochemically rigid flattened cone conformation and have a large distance between the opposite phosphorus atoms (~13 Å), form CH—OH...O=P-hydrogen-bonded dimers (Fig. 3).

The stereochemically flexible cone conformation of bis- and tetrakis(dialkoxyphosphorylhydroxymethyl)tetrapropoxycalix[4]arenes **14** and **15** allows for the formation of two types of associates stabilized by both intermolecular (a dimeric structure analogous to that shown in Fig. 3) and intramolecular (a monomeric structure, Fig. 4) hydrogen bonds.

It should be noted that, in accordance with the results of molecular modeling, this association is possible only if the chiral carbon atoms of the dialkoxyphosphorylhydroxymethyl fragments have the same configuration ($R + R$ or $S + S$, but not $R + S$). The association was confirmed by the formation of CHOH...O=P bonds, which are manifested in the IR spectra at 3310—3360 cm^{-1}.

In contrast to dialkoxyphosphoryl(hydroxymethyl)calixarenes **9—15**, calix[4]arenes **20—25** containing the dialkoxyphosphorylaminomethyl groups are unable to form strong CHNH...O=P associates.[42] No dimers were observed in their FAB mass spectra. Unlike esters **18—23**, aminophosphonic acid **27** forms a dimeric structure through strong intermolecular P=O...HO—P hydrogen

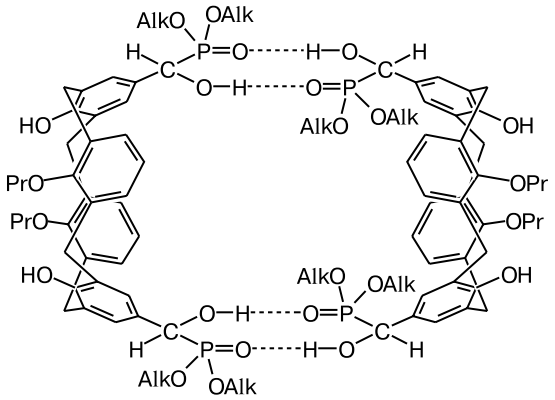


Fig. 3. Dimeric association of bis(dialkoxyphosphorylhydroxymethyl)dipropoxycalixarenes **11—13**.

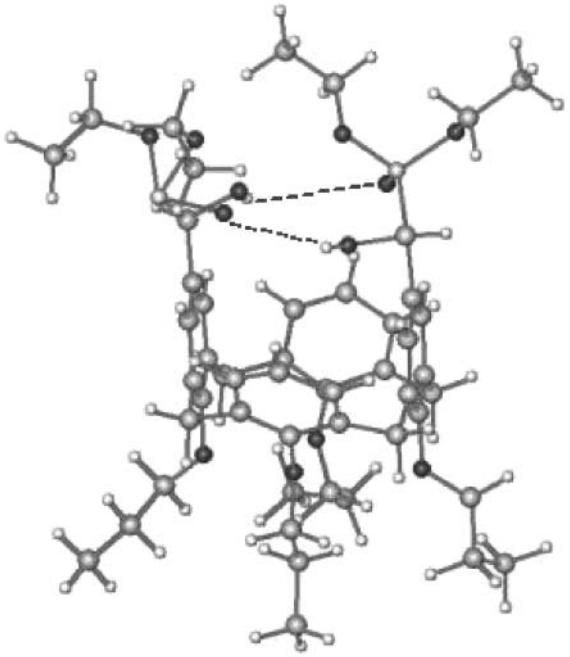


Fig. 4. Energy-minimized structure of calixarene **14** (*S*,*S* diastereomer).

bonds. This was confirmed by the presence of peaks corresponding to the dimer in the FAB mass spectra.

In conclusion, calix[4]arenes bearing the dialkoxyphosphorylhydroxymethyl or bis(dialkoxyphosphorylhydroxymethyl or -aminomethyl) fragments at the upper rim of the macrocycle are similar to calix[4]arenes functionalized with carboxy,[50] acetamide,[51] or (thio)urea[51,52] groups and are able to undergo self-assembly to form dimeric hydrogen-bonded associates. The formation of capsule-type complexes of the compounds with bioactive molecules and their transport through biological membranes are therefore possible.

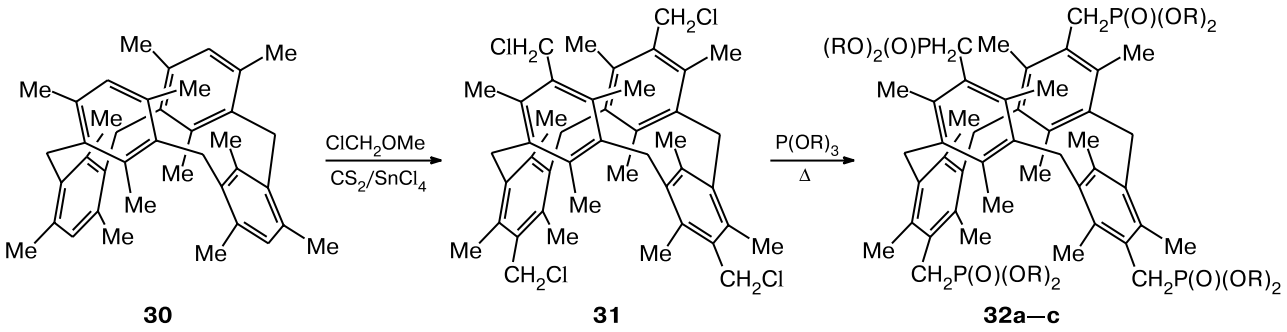
Meta- and paracyclophanes. Macrocycles closely related to calix[4]arenes, that is, tetrameric metacyclophanes containing four methylene-bridged aromatic units can easily be prepared by the Friedel—Crafts reaction.[53] Chloromethylation[54] of cyclophane **30** yielded compound **31**. The Arbuzov reaction of the latter with trialkyl phosphites produced phosphorylated calix[4]arenoid tetramers **32a—c** (Scheme 5).

In previous reports,[55,56] macrocycle **30** has been demonstrated to exist in solution in a fixed "saddle-shape" [54] or 1,3-alternate conformation[55,56] on the NMR time scale in the temperature range from −60 to 150 °C. This is substantiated by upfield resonances for the intra-annular Me groups, which are strongly shielded ($\Delta\delta \approx 1.0$) by the aromatic ring current of two adjacent flanking mesitylene subunits.

Studies by ^{1}H NMR spectroscopy revealed that this type of conformation is retained also in phosphorylated macrocycles **32a—c**. In fact, due to the symmetry of the skeleton (D_{2d}), the bridging methylene protons appear as a sharp singlet at δ ~4.6 and the annular Me groups are observed as two signals at δ 2.4 and ~1.13 in a ratio of 2 : 1, which are assigned to the external and internal methyl groups, respectively. The methylene groups attached to the phosphonic groups appear as a sharp doublet due to spin-spin coupling with phosphorus ($^2J_{H,P}$ = 22.0 Hz), whereas the methyl or methylene protons of the alkyl groups R of the —P(O)(OR)$_2$ fragment are, due to the tetrahedral geometry of phosphorus, in a diastereotopic environment (if R = Pr^i or Et) or are enantiotopic (if R = Me). Hence it follows that the protons of the P(O)(OMe)$_2$ group in macrocycle **32a** appear as a sharp doublet due to coupling with phosphorus ($^3J_{H,P}$ = 10.5 Hz). In the spectra of compound **32b**, the methyl protons of the ethoxy groups appear as a triplet, whereas the methylene protons show up as two distinct multiplets (AB systems coupled with phosphorus). In the spectra of macrocycle **32c**, the methyl protons of the isopropyl groups appear as two doublets ($\Delta\nu = 0.145$, $^2J_{H,H} = 6$ Hz).

Another point of interest in the phosphorylated macrocycles under consideration is their tendency to generate clathrate inclusion compounds with small organic molecules in the solid state. This property may render these

Scheme 5



R = Me (**a**), Et (**b**), Pr^i (**c**)

compounds also of relevant interest as receptors for hydrophobic guests[57] or as water-soluble macrocyclic hosts after hydrolysis of the phosphonic group to the corresponding monoester or to free acid with pH-dependent binding properties.

Macrocycle **32b** was found to form an inclusion compound with cyclohexane, whose stoichiometry (determined by both ^{1}H NMR integration and X-ray diffraction) corresponds to the macrocycle : guest ratio of 1 : 2. Study by NMR spectroscopy demonstrated that compound **32b** crystallizes with water. The importance of this finding, together with the relevance to the molecular architecture of the host, are discussed below. Once again, this finding reveals that the 1,3-alternate conformation of fully aromatic tetrameric macrocycles is very appropriate for the formation of a clathrate, and these compounds can act as molecular receptors.[1] Therefore, considering the interest in the solid-state architecture of **32b** enclathrated with cyclohexane, we studied this compound by X-ray diffraction analysis to determine unequivocally the details of its conformation.

The crystal structure of **32b**$\cdot 2C_6H_{12}\cdot H_2O$ was established by X-ray diffraction at −50 °C. The calixarene molecule, in which the bond lengths and bond angles are within normal ranges, is located on a twofold rotation axis, which is parallel to the [100] crystallographic direction and passes through one pair of the opposite methylene carbon atoms in the inner macrocycle. The arene systems protrude alternately up and down[58] from the macrocycle. The dihedral angle between two systems that are across from each other is 34.8°. Hence, the 1,3-alternate conformation is distinctly different from the more frequent cone or bowl form of calixarenes, in which all the arene moieties are located on the same side of the macrocycle.

The water molecule, which is also present in the crystal structure, lies on a symmetry axis of the same type as the calixarene molecule. The two consecutive hydrogen-bonded molecules are arranged in a one-dimensional array along the [010] direction. The geometric parameters of one independent hydrogen bond donated by the water molecule and accepted by one of the P=O functions are also within normal ranges (O(w)...O(1), 2.72(1) Å). The cyclohexane molecule has a similar chair conformation (C—C, 1.54—1.59(3) Å; C—C—C, 102—113(3)°; C—C—C—C, 61—69(3)°, the absolute values) and was found in a general position (*i.e.*, there are two such molecules per calixarene molecule and water molecule). The incorporation of the cyclohexane molecule into the crystal structure containing the calixarene in the above-described conformation does not conform to a molecular inclusion compound, but rather to a lattice clathrate. Specifically, and as an unusual feature, the cyclohexane molecules are arranged in a tetrahedron-like cluster of four such molecules[58] around a 222-D_2 position of the space

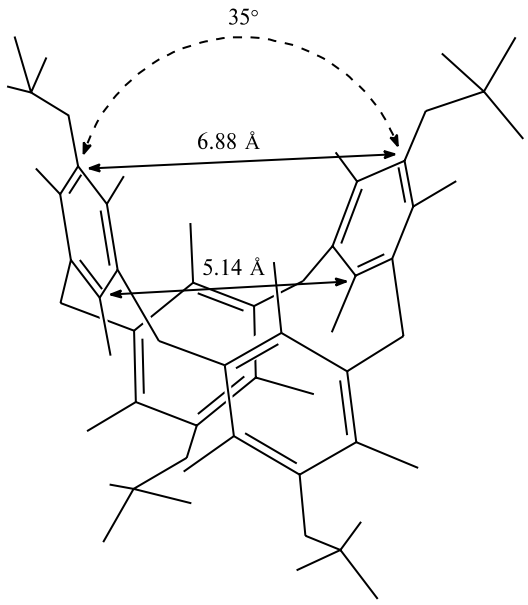


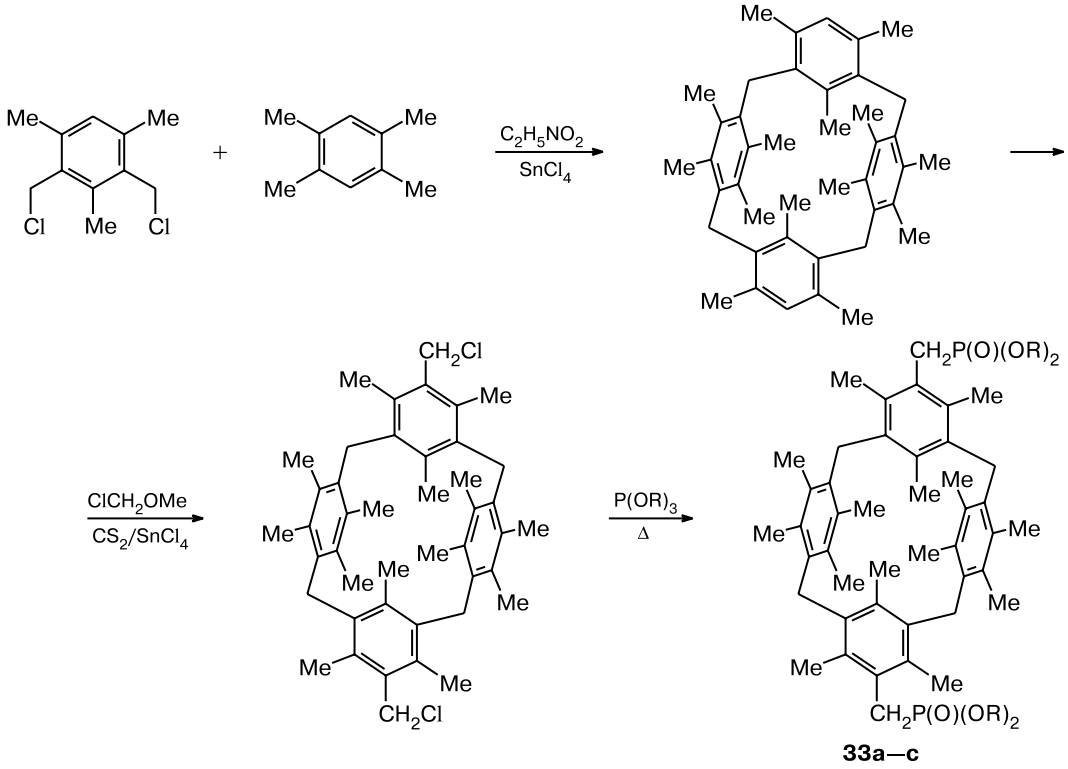
Fig. 5. Line diagram with the geometric parameters for the molecular cavity of macrocycle **32b** (the macrocycle is largely viewed side-on, the ethyl groups and all hydrogen atoms are omitted).

group at 1/4, 3/4, 1/2 (3/4, 1/4, 1/2). Since the macrocycles under study are of interest as molecular receptors, we characterized the cavity by selected geometric parameters. Figure 5 shows that the molecular cavity with an opening angle of ~35° is quite large and wide at the entrance and gets smaller when moving inside, which is typical of a cone conformation. The distance between the two aryl carbon atoms attached at the methylene carbons of the $-CH_2-P(O)(OEt)_2$ groups of the opposite mesitylene rings is 6.88 Å, whereas this distance between the inner aryl carbon atoms bearing the methyl groups is reduced to 5.14 Å (see Fig. 5). The distance between the opposite methylene carbon atoms in the inner macrocycle are 7.18(2) and 7.13(2) Å. The shortest distance between the adjacent methylene carbons is 4.55(1) Å.

Metaparacyclophanes containing two mesitylene and two durene units linked by methylene bridges were prepared using analogous synthetic procedures.[53] Bis-phosphonated macrocycles **33** were synthesized according to a procedure presented in Scheme 6.

Our study by NMR spectroscopy at room temperature demonstrated[59] that macrocycles **33a—c** show restricted rotation of the durene rings, as evidenced by the presence of two sharp singlets for the durene methyl groups at δ 1.43 and 2.34 in a ratio of 1 : 1. In addition, these data show that one set of signals is substantially shifted upfield, resulting from the aromatic ring current effect. Analogous shielding is observed for the mesitylene methyl groups located inside the methylene bridging groups, which resonate at δ 0.87, *i.e.*, the signals are shifted upfield by ~1.46 ppm compared to the signals for the pertinent methyl groups in the linear parent subunit model, *viz.*, dialkyl

Scheme 6



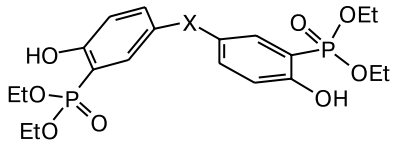
33a—c

R = Me (**a**), Et (**b**), Pr^i (**c**)

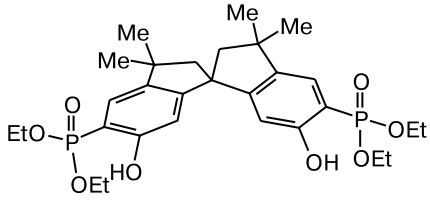
2,4,6-trimethylbenzylphosphonate. These data allowed us to interpret the conformation of macrocycles **33a—c** in solution as a 1,3-alternated saddle-shaped geometry, in which two durene units are perpendicular to the plane passing through four methylene groups, whereas the mesitylene rings deviate alternatively up and down, their inner methyl groups pointing inward the aromatic ring current of the durene rings. The methylenephosphonic groups also deviate alternatively up and down relative to the cage in strategic positions for complexation with neutral guests.

Due to the symmetry of the skeleton, the bridging methylene protons appear as two doublets at δ ~4.08, the methylene groups attached to the phosphonic fragments appear as a sharp doublet due to spin-spin coupling with phosphorus ($^2J_{H,P}$ = 21.5 Hz), whereas the Me or CH_2 groups of the alkyl groups R of the $—P(O)(OR)_2$ moiety are, due to the tetrahedral geometry of the P atom, in a diastereotopic environment, if R is Pr^i or Et, whereas they are enantiotopic if R = Me.

Polyether cyclophanes. It is well known[60] that dialkyl aryl phosphates can be rearranged upon treatment with lithium diisopropylamide (LDA) or butyllithium to give dialkyl *o*-hydroxyaryl phosphonates, which, in turn, can be easily hydrolyzed to *o*-hydroxyarylphosphonic acids. Bis-hydroxyaryl diphosphonates **34** and **35** thus prepared[61] were used for synthesizing new macrocyclic polyethers. The latter bear phosphonic groups, which improve their water solubility or their complexing properties toward particular cations,[62] such as lanthanides, which is extensively used in diagnostic medicine.[6,63]



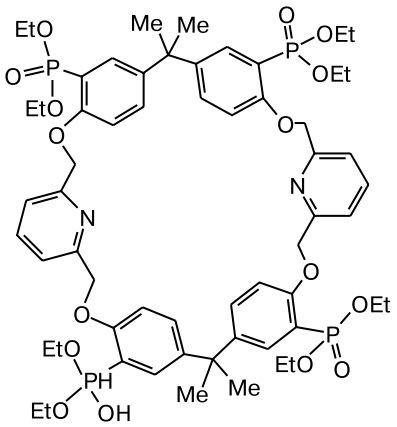
34a—c



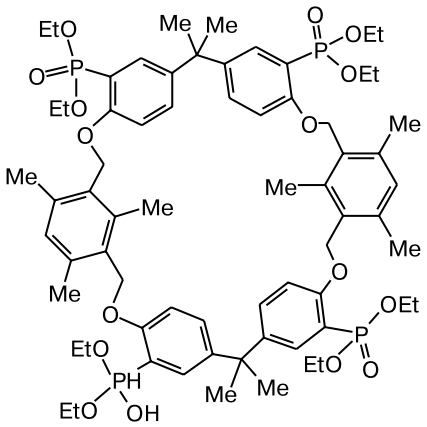
35

X = CMe_2 (**a**), S (**b**), SO_2 (**c**)

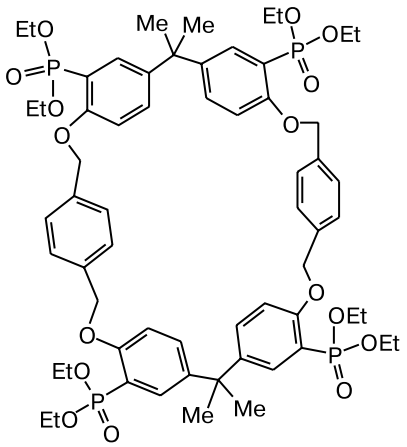
We prepared new polyether macrocycles **36—38** by condensation of bis-phenol **34a** with 2,6-bis(bromomethyl)pyridine, 2,4-bis(chloromethyl)-1,3,5-trimethylbenzene, and α,α′-dibromo-*p*-xylene, respectively.



36



37



38

Three novel macrocycles **36—38** [57] are of interest in supramolecular chemistry due to the presence of phosphonate groups, which can generate, after hydrolysis to phosphonic acids, novel architectures through hydrogen bonding. These macrocycles are also able to incorporate neutral molecules into the cavity, which was demonstrated by X-ray diffraction study of compound **36**.

The ^{1}H NMR spectrum (500 MHz) of macrocycle **36** at room temperature in $CDCl_3$ shows a triplet at δ 1.34 and a multiplet at δ 4.20 of the ethoxy groups linked to the phosphorus atoms, a sharp singlet at δ 1.64 of the methyl groups attached to the bridgehead quaternary carbons, a single sharp peak at δ 5.27 of the benzylic protons linked to the pyridine moiety, and the expected multiplicity for the aromatic hydrogens. This pattern, coupled with the ^{13}C and ^{31}P NMR spectra, clearly indicates high mobility of macrocycle **36**, which undergoes interconversions between various possible conformations in solution. Interestingly enough, the NMR spectrum of crystals of **36** grown from a cyclohexane—AcOEt solution shows the presence of the enclathrated saturated hydrocarbon in a molar ratio of 1 : 1. The same observation was also made in the study by thermogravimetric analysis, which showed a total loss of one mole of cyclohexane in two steps at 170.3 and 179.0 °C.

The ^{1}H, ^{13}C, and ^{31}P NMR spectra of macrocycles **37** and **38** can also be interpreted in terms of high conformational mobility in solution at room temperature (a single sharp signal for the benzylic protons, only one peak for phosphorus, *etc.*). Contrary to **36**, macrocycle **37** containing the pyridine nitrogen atoms that lack polarity is unable to form clathrates, at least with a large number of organic solvents tried so far (benzene, toluene, ethyl acetate, cyclohexane, *etc.*).

The selective inclusion of cyclohexane was observed when compound **36** was crystallized from a cyclohexane—AcOEt mixture. Taking advantages of this property, [2+2]-macrocycle **36** can be selectively isolated from the reaction mixture due to the formation of an inclusion complex with cyclohexane in an ethyl acetate solution. Under these conditions, crystallization of macrocycle **36** was nearly quantitative. In other words, "supramolecular" purification can be used for compound **36**. On the contrary, macrocycles **37** and **38** should be isolated by chromatography, because they are unable to include any solvent used so far.

The structure of **36**, which includes one cyclohexane molecule, was unambiguously established by single-crystal X-ray diffraction study.[57] The final refinement confirmed that there is considerable static disorder in molecule **36**, resulting in that the pendant ethoxy groups in the phosphite fragments have different conformations. The guest cyclohexane molecule fits nicely into the hydrophobic cavity of host macrocycle **36**, all intermolecular distances being smaller than the expected van der Waals distances, *i.e.*, there are no strong intermolecular interactions, and only weak nonpolar—nonpolar interactions are present.

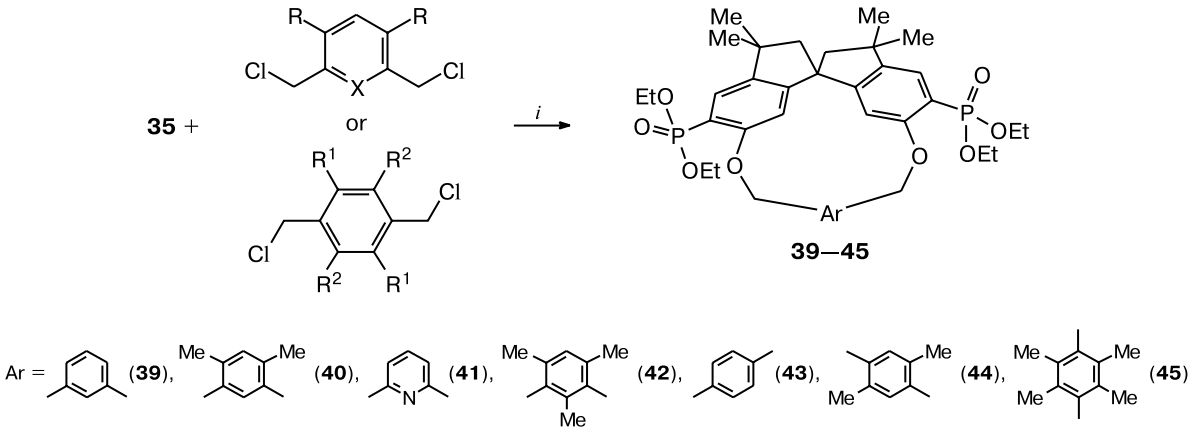
Williamson condensation using stereochemically constrained spirobisindane monomer **35** and 1,3- or 1,4-bischloromethylated arenes produced rigid [1+1]-cyclophanes in high yields (Scheme 7).

Compounds **39—45** were characterized in solution by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy.[64] Macrocycles **39—41** show mobility of the aryl rings, and their π radian rotation averages the signals for the benzylic bridging protons as well as the spirobisindane phosphonic groups.

Interestingly enough, the signal for the inner aromatic proton located between two benzylic bridging groups is strongly shifted upfield by δ ~0.6 due to the aromatic ring current effect of the cavity, which indicates that this proton is pointing inside the cage.

On the contrary, macrocycle **42**, as well as the macrocycles prepared by condensation of dihydroxy monomer **35** with 1,4-bis(chloromethyl)arene derivatives

Scheme 7



Reagents and conditions: *i*. Refluxing MeCN, K_2CO_3, 24 h.

(compounds **43—45**), are stereochemically rigid on the NMR time scale. In particular, restricted rotation of the 1,3-bridged mesitylene ring in compound **42** renders the molecule asymmetric, as evidenced by the fact that all nuclei are chemically and magnetically nonequivalent, which is confirmed by the ^1H, ^{13}C, and ^{31}P NMR spectra. The inner methyl group of the mesitylene ring resonates at δ 1.59, *i.e.*, at much higher field compared to δ for other mesitylene methyl protons (δ 2.54 and 2.43). Two bridging benzylic groups are not anymore homotopic and their diastereotopic H_a and H_b protons (as well as H_a' and H_b') give rise, in the ^1H NMR spectrum, to two doublets of doublets centered at δ 5.20 and 5.33, respectively.

Macrocycles **43—45** have a dissymmetric structure (point-group symmetry C_2), and kinetically restricted rotation of the 1,4-bridged aromatic ring is observed for all these compounds, as evidenced by the presence of two sets of signals for the nuclei at positions 2 and 3.

The stereochemical pattern in the macrocycles under consideration is quite intriguing due to the presence, in the same molecule, of the C_2-symmetric spirobisindane unit (which is in itself chiral) and the xylylene bridging moiety, which can impart planar chirality to the compound. Hence, it follows that, when choosing an appropriate unit (*i.e.*, the 2,5-disubstituted 1,4-xylylene bridge) under the conditions of restricted rotation of this unit, two different diastereomers are possible for macrocycle **44**. Actually, in the series under consideration, the xylylene bridging unit lacks a local C_2 axis passing through the CH_2 bridges only in compound **44**.

Structures **44a** and **44b** are depicted in Fig. 6. In **44a**, two homotopic methyl groups of the 1,4-substituted *p*-xylylene ring are pointing out of the molecular cavity and are far from the ring shielding cone of the spirobisindane moiety. The opposite situation arises for structure **44b**. After work-up of the reaction mixture, only one diastereomer with a sharp melting point (m.p. 158—159 °C) was isolated. This compound showed only one set of signals for all the diastereotopic nuclei.[64]

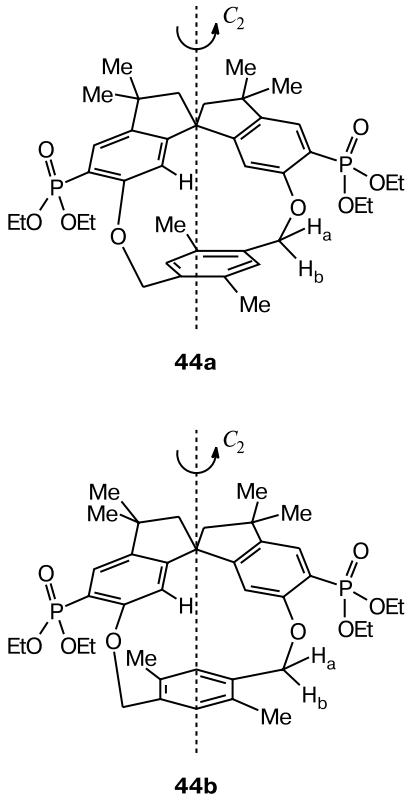


Fig. 6. Two possible diastereomers of macrocycle **44**.

The aryl Me groups resonate at normal values of δ and do not show upfield shifts due to the aromatic ring current effect. On the contrary, this effect is observed for the aromatic ring protons. From NOE experiments, which

reveal that the aryl methyl protons are spatially close to the spirobisindane hydrogens in *ortho* positions with respect to the oxygen bridge, we tentatively conclude that the diastereomer isolated has structure **44a**, which is the only one formed in the cyclization reaction.[64]

With the aim of elucidating the preferred geometry in the solid state, we studied macrocycle **42**, which is complexed with two moles of cyclohexane, and compound **44** by X-ray diffraction.[64]

The overall view of the molecular conformation of host **42** shows that the molecule is asymmetric (C_1), and the inner mesitylene methyl group is pointing inside the cavity under the shielding cone of the spirobisindane aromatic ring. Thus, the solution geometry determined by NMR spectroscopy is consistent with that found in the solid state. The structure belongs to the triclinic system, space group $P\bar{1}$, $Z = 2$. All bond lengths and bond angles are within normal ranges.[64]

We determined the cavity size in molecule **42** from X-ray diffraction data and found that this cavity is large, but is insufficiently large to include small organic solvent molecules, such as cyclohexane molecules. This explains why two cyclohexane molecules enclathrated by host **42** are present in the crystal lattice exterior to molecule **42**. Once we realized that host **42** includes cyclohexane, we examined the ability of the cyclophanes under study to enclathrate small organic molecules in some more detail. Only macrocycle **40** was found to form inclusion complexes with one mole of cyclohexane, as evidenced by the ^{1}H NMR integration. Some other solvents (benzene, chloroform, ethyl acetate, *etc*.) were tested, but NMR analysis did not detect the presence of these solvents as guests in molecules **40** and **42**.

Earlier, we have postulated that only diastereomer **44a** would be expected to be formed for macrocycle **44** through a stereospecific coupling reaction. X-ray diffraction study of the diastereomer isolated with m.p. 158—159 °C demonstrated that its structure is consistent with that deduced by NMR observations in solution.[64]

A comparison of the geometry of macrocycles **42** and **44** reveals that the *para*-substituted planes in **44** are quite hindered with respect to π rotation of the 1,4-substituted aryl ring, which flattens the structure and, in turn, reduces the cavity size of the macrocycle. Thus, the *meta*-substituted planes of this series generally present a higher degree of rotational freedom and provide a large cavity size, which was found experimentally.

Considering that spirobisindane phosphonate monomer **35** is a preorganized dissymmetric molecule, which exists as a pair of enantiomers, this compound can be used as a chiral template for building chiral polycondensates or inducing chirality in replicant strands. The resulting macrocycles could also be of interest for chiral recognition and chiral separation. Therefore, we resolved the macrocycles by HPLC using chiral columns and demonstrated that compounds **39** and **40**, in which internal mobility of the aromatic rings is observed on the NMR time scale, are not separated into enantiomers. Compound **41**, in spite of the fact that it also contains the mobile aromatic ring, is characterized by good separation. This can be due to stronger interaction between the 2,6-disubstituted pyridine ring and the 3,5-dimethylphenyl end groups of the carbamate moieties of the chiral stationary phase. Stereochemically rigid compounds **42—45** are well separated, and an increase in the polarity of the mobile phase has a beneficial effect on their separation factors.[64]

The good resolution factor (1.5) and short elution times for the enantiomeric pair of compound **42** provide quantitative separation of the enantiomers by repeated 50-μL injections of the racemic compound (0.2 mg for each injection) and collection of the eluates. The CD spectra of both eluates were measured. It appeared that they were almost mirror images of each other, which is indicative of the enantiomeric relationship between the two eluates. The specific rotations of the two enantiomers are −189.8 and 190.3, respectively.[64]

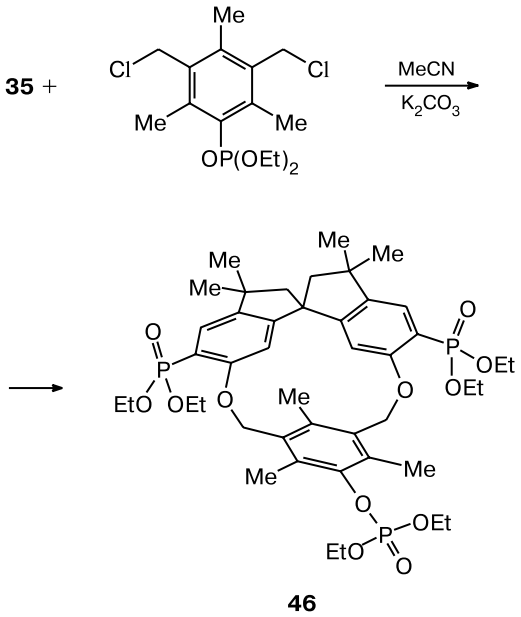
Analogously, a similar isolation procedure was applied to compound **35**. The measured specific rotations are 25.9 and −24.0 for the first and second enantiomers eluted, respectively. Analytical HPLC reruns of the eluates indicated enantiomeric purity (100%) for both peaks of compound **42**. For the first and second eluted peaks of compound **35**, *ee* are 98 and 88%, respectively.

The CD spectrum of compound **35** showed pronounced Cotton effects. Actually, CD splitting gives a positive Cotton effect ($\Delta\varepsilon$ + 60 at 215 nm and $\Delta\varepsilon$ − 78 at 205 nm) for the less retained enantiomer. A negative Cotton effect is observed for the most retained enantiomer. A similar behavior can be envisaged for compound **42**, although CD splitting cannot be observed due to shorter wavelengths of the CD bands.[64]

To improve the complexing properties of the macrocycles, specially, for longer biologically relevant α,ω-diamine dications, we wanted to introduce an additional binding site into one of the congested cyclophanes in a particularly strategic position, *i.e.*, we synthesized novel sterically congested cleft-like receptor molecule **46** (Scheme 8).

The NMR data confirmed that macrocycle **46** is stereochemically rigid on the NMR time scale. In particular, the restricted rotation of the 1,3-bridged mesitylene ring renders the molecule asymmetric, as evidenced by the fact that all nuclei are chemically and magnetically different. The two bridging benzylic groups, as well as the two phosphorus atoms attached to the C_2-symmetric spirobisindane unit, are no longer homotopic. Thus, their diastereotopic hydrogens appear as two different doublets of doublets, while the phosphorus atoms give rise to two sharp singlets at δ 18.97 and 17.74, respectively.

Scheme 8



46

The molecular structure of compound **46**, which was solved by X-ray diffraction,[65] is almost completely identical to that of bis(5,5′-diethoxyphosphoryl)-6,6′-(2,4,5-trimethyl-1,3-benzyloxy)-3,3,3′,3′-tetramethyl-1,1′-spirobisindane. Although molecule **46** is chiral, it regularly alternates with its optical antipode in the centrosymmetric space group $P2_1/c$, giving rise to a racemic crystal. The macrocycle has a usual heart-like shape, and the steric hindrance of the ring atoms does not allow guest molecules to be enclathrated, so that no solvent molecules were found in the crystal structure. Moreover, a degree of tension is present in the macrocycle, resulting in slight distortion of the mesitylene ring, the latter being not exactly planar.

The survey of the macrocycles so far described reveals that, although [1+1]-macrocycles **39—45** are chiral, their cavities are not large enough to include bulky guests. On the other hand, [2+2]-macrocycles **36—38** have a larger cavity, but they are achiral.

Thus, with the idea of synthesizing chiral bis-chelating phosphonate macrocycles, which can include neutral guests and, after hydrolysis to tetramonoesters, could become water-soluble receptors for positively charged molecules, we adopted a new strategy for the synthesis of different types of robust inherently chiral cyclophanes, which are able to act as potential resolving agents for antipodes of biologically relevant molecules.

Condensation of spirobisindane monomer **35** with 1,3- or 1,4-dibenzyl halides afforded only [1+1]-cyclization products,[64] whereas the reaction with the use of 2,2-bis(3-diethoxyphosphono-4-hydroxyphenyl)propane (**34a**) as the condensation agent afforded the [2+2]-macrocycle as the major product.[57] Hence it follows that the synthesis of novel macrocycles containing both unit **34a** and unit **35** in the scaffold cannot be performed by a one-pot method.

Scheme 9 gives a schematic description of the synthetic strategy followed for the preparation of the macrocycles. The idea is to synthesize initially a bis-halomethylated derivative containing moiety **34a** or **35** and then perform cyclization to prepare the desired cyclophanes **54—59**. The two synthetic paths differ only in the sequence of the addition of the same reagents.

According to the path *A*, Williamson condensation of 10 equiv. of *m*- or *p*-bis(halomethyl)benzene and one equivalent of phosphorylated bis-phenol **34a** in acetonitrile in the presence of solid K_2CO_3 as a base afforded cleft-shaped precursor molecules **47—52** in high yields (60—80%). These compounds were isolated from the reaction mixture and fully characterized.[66] Then precursors **47—52** were allowed to react with spirobisindanol **35** under high dilution conditions to give macrocycles **54—59**.

Under the same conditions, following the path *B*, various cleft-shaped precursor molecules **53** were prepared in only 16% yield. The reaction again afforded [1+1]-macrocycles as the major products, which were obtained in high yields under conditions unfavorable for cyclization.

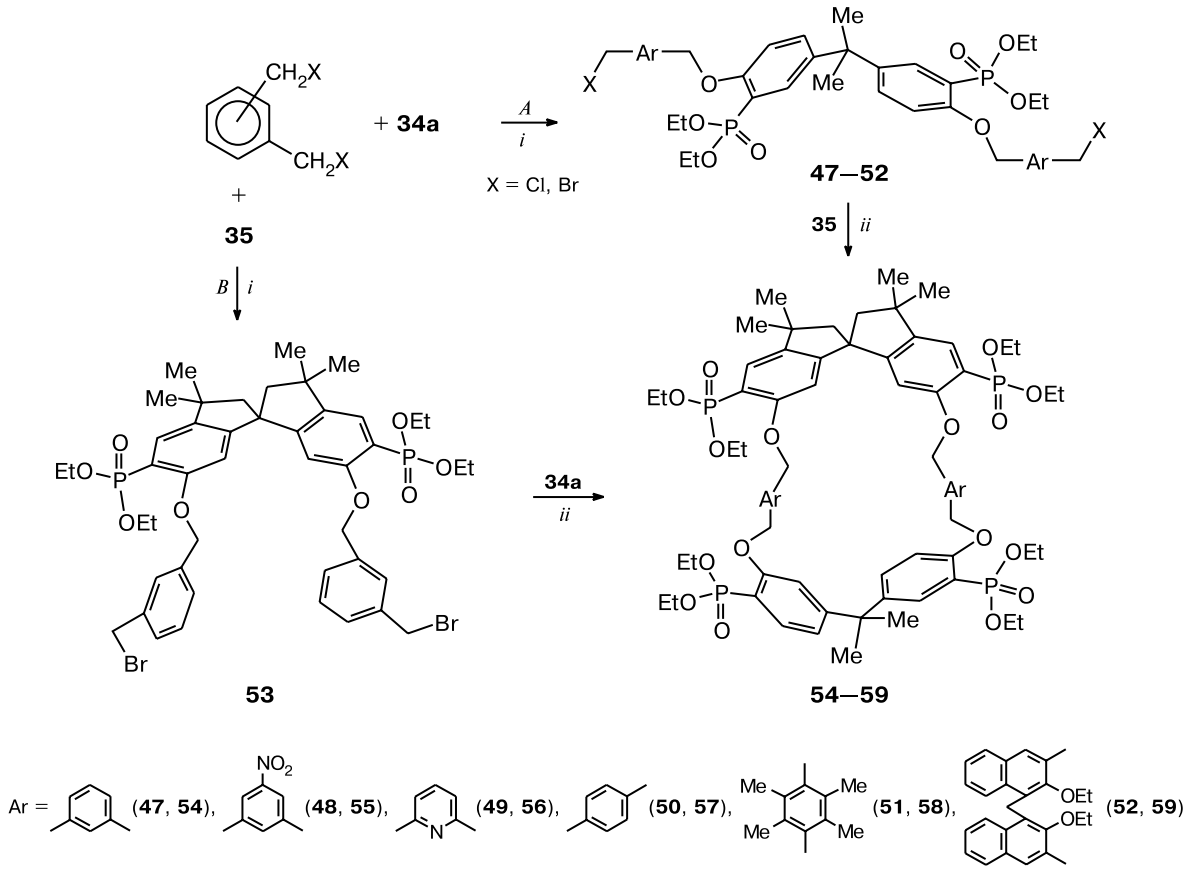
Therefore, we used only the path *A* for preparing a large variety of the desired chiral cyclophanes. All these compounds are inherently chiral and differ in the size and polarity of the cavity.

The ^1H, ^{13}C, and ^{31}P NMR spectra, FAB mass spectra, and X-ray diffraction data confirmed the structures of the resulting compounds.[66]

The ^1H NMR spectrum (500 MHz) of macrocycle **57** in $CDCl_3$ at room temperature shows two triplets (δ 1.31 and 1.36) and a multiplet (δ 4.10—4.28) of the ethoxy groups bound to the phosphorus atoms, three sharp singlets for the methyl groups attached to the bridgehead quaternary carbons, a doublet of doublets for the methylene hydrogens of the spirobisindane unit centered at δ 2.16 and δ 2.45, a couple of two different doublets of doublets for the benzylic protons bound to the *p*-xylene moiety centered at δ 4.80, 4.93, 5.21, and 5.28, and the expected multiplicities for the aromatic hydrogens. This spectral pattern, coupled with the ^{13}C and ^{31}P NMR spectra, clearly indicates a dissymmetric structure (point-group symmetry C_2) and high mobility of macrocycle **57**, which undergoes interconversions between various possible conformations in solution.

Interestingly enough, crystals of **57**, which were grown from a cyclohexane—ethyl acetate solution, contain the enclathrated saturated hydrocarbon in a ratio of 1 : 1, as evidenced by the NMR spectrum. A similar observation was also made by thermogravimetric analysis, which showed a total loss of one mole of cyclohexane at 120 °C. Besides, TGA showed a loss of two moles of water in a

Scheme 9



Reagents and conditions: *i*. Refluxing MeCN, K_2CO_3, 12 h. *ii*. High dilution, refluxing MeCN, K_2CO_3, 24 h.

wide temperature range (30—90 °C). The molecular structure of **57** was solved by X-ray diffraction techniques.[66] Due to the presence of the spiro-carbon atom and a large number of sp^2-hybridized carbon atoms, the macrocycle has a nonplanar ring structure and is heavily puckered. Its cavity is rather closed.

Moreover, recrystallization of compounds **54—59** from a mixture of cyclohexane with other organic solvents (ethyl acetate, chloroform, dichloromethane, benzene, *etc.*) demonstrated that these macrocycles are able to form inclusion complexes only with cyclohexane.

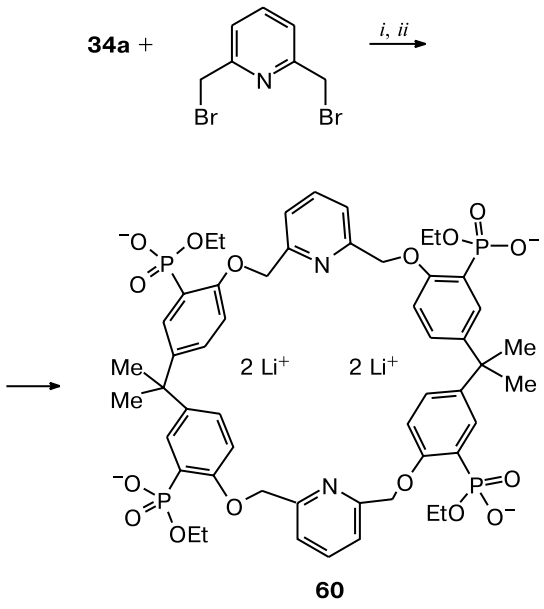
Taking into account that an efficient and selective molecular recognition of amino acids in water by synthetic receptors is of great interest,[67] we prepared the tetraanion corresponding to macrocycle **36** (Scheme 10). According to the results of X-ray diffraction data and molecular modeling for its octaethyl ester precursor, the tetraanion adopts an open conformation[57] favorable for the highly efficient formation of a chelate complex with a cationic group of biologically relevant amino acids.

This tetraanion should be able to perform an induced fit on approach of a dication with an appropriate spacer. Thus, a highly stable 1 : 1 complex could be formed, possibly even in water. Heating of a hexan-2-one solution of the octaethyl ester precursor with 4 equiv. of dry lithium bromide for one week afforded, after recrystallization and dialysis, pure receptor **60** as the tetralithium salt. This compound is readily soluble in polar solvents, such as methanol and water, but is insoluble in DMSO and MeCN.

Significant complexation-induced shifts of the signals for the CH protons both of the amino acid and the receptor molecule are observed in the ^{1}H NMR spectra of a 1 : 1 mixture of receptor **60** with lysine methyl ester dihydrochloride. To check the stoichiometries of the complexes with lysine, arginine, ornithine, and histidine, we derived Job plots for each amino acid complex with tetraanion **60**. The result was remarkable: smaller amino acids, *viz.*, histidine, ornithine, and arginine, produce complexes with 2 : 1 stoichiometry, and only lysine was bound by **60** to give the pure 1 : 1 complex.[68]

Only in lysine, two cationic groups are able to span the distance from one bis-phosphonate moiety to the other one. By contrast, the smaller amino acids, such as

Scheme 10



Reagents and conditions: *i*. K_2CO_3, MeCN. *ii*. LiBr, hexan-2-one.

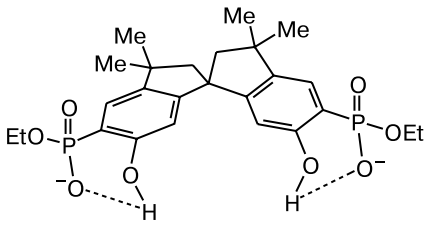
arginine, ornithine, and histidine, can reach only one bisphosphonate moiety at a time, so that two amino acid molecules can be bound by receptor molecule **60**.

Histidine remarkably well forms a 2 : 1 complex. This is probably due to the specific arrangement of the imidazolium ion. According to the results of force-field calculations, two histidine molecules each can be involved in a double chelate assembly with three phosphonate groups. The ammonium functionality is complexed with bisphosphonate, whereas the imidazole ring acts a hydrogen-bond-donor bridge to one of the phosphonate fragments at the opposite end of the receptor molecule.[68]

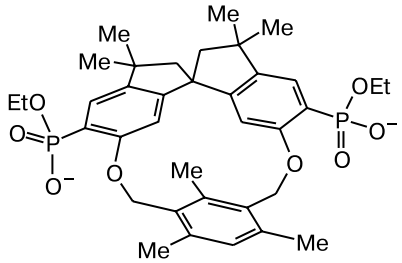
We performed NMR titration for each of the four amino acid complexes with molecule **60** in methanol. In this solvent, all amino acids are strongly bound by molecule **60**. The four-point interaction in the lysine complex with **60** is stronger than the two-point interaction in the related assemblies with ornithine and arginine. However, in spite of the 2 : 1 stoichiometry, histidine is even superior to lysine. In addition to a stronger electrostatic attraction, histidine is able to form two strong hydrogen bonds between the imidazole moiety and the bis-phosphonate ions. This may contribute to its high binding constant.

The replacement of methanol with water does not change the stoichiometry of all complexes but leads to a 20—50-fold drop in the association constants of the four amino acid esters under consideration. However, lysine forms complexes, which are 5—7 times stronger than those of ornithine and arginine and even two times stronger that that of histidine. If hydrophobic forces are weak, as in our case, the contribution of hydrogen bonds in water is negligible, while electrostatic interactions represent the major attractive force. In our case, the electrostatic attraction exerted by the second ammonium functionality of lysine is obviously much stronger than that of the guanidinium ion of arginine and even than that of the imidazolium ion of histidine. Thus, receptor molecule **60** is moderately selective for lysine in water.

A new class of cleft-like receptor molecules **61** and **62** based on bis-phosphonates, which are fully tailored for multipoint binding of their dicationic substrates, were obtained by careful monodealkylation of the corresponding cleft-like tetraalkyl bis-phosphonates with LiBr.[69]



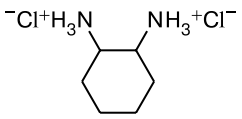
61



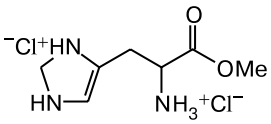
62

The spirobisindane skeleton of molecules **61** and **62** ensures high rigidity, which should lead to pronounced preorganization of different binding sites. A series of NMR binding experiments revealed a remarkably different behavior of two new hosts with respect to their chemoselectivity and enantioselectivity.

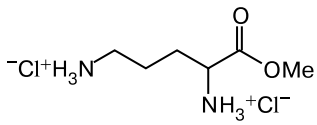
The Job plots for **61** and **62** and several α,ω-diammonium compounds proved that molecule **61** always forms 1 : 1 complexes, whereas host **62** binds two guest molecules until they are shorter than lysine or arginine.[69] This divergent behavior can be attributed to the difference in steric accessibility of the cleft in **61** and **62**. In molecule **61**, there is ample room for both cationic groups to approach the phosphonate anions from within the cleft, with the effect that small α,ω-diammonium compounds should provide the highest binding enthalpy governed mainly by the optimum electrostatic interactions. On the contrary, the cleft in molecule **62** is closed by the rigid mesitylene bridge, so that only long α,ω-dicationic guests can reach



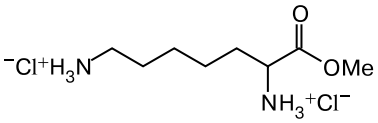
(±)-Cyc



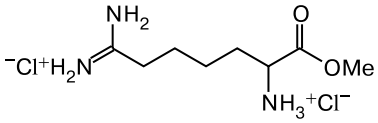
L-His



L-Orn



L-Lys



L-Arg

from one phosphonate group to another. At the same time, their carbon chains are in close contact with the mesitylene bridge, so that the molecular recognition would be expected to be more sensitive. We performed NMR titration of various dicationic guests with a successively increasing distance between their positively charged nitrogen atoms.

The dependence of the total binding energy on the structure of the guest for host **61** differs substantially from that for host **62**. The open-chain host (**61**) is selective for short rigid α,ω-diamines (K_a to $8 \cdot 10^3$ L mol^{-1}). However, macrocycle **62** prefers longer dications (K_a up to $1.2 \cdot 10^4$ L mol^{-1}).

No enantiodiscrimination is found for open-chain host **61**, and even host **62** can only distinguish between enantiomeric guests with an $N^+ \ldots N^+$ distance longer than five bonds. The results of force field calculations suggest that only lysine and arginine are long enough to span the bridged cleft of **62**, so that two salt bridges can be formed between their cationic groups and the respective phosphonates. This indicates once again that two binding sites in C_2-symmetric open-chain host molecule **61** are not sufficient for efficient chiral recognition. Only the additional third binding site present in C_1-symmetric macrocycle **62** due to the chiral surface of the mesitylene bridge allows noticeable enantiomeric discrimination. Although the enantiomeric excesses are not very high (**62** : L-Arg, 17%; **62** : L-Lys, 33%), well-resolved NMR signals were produced during NMR titration. Hence, optically pure compound **62** can be used as a shift reagent for the quantitative determination of the enantiomeric purity of arginine and lysine derivatives.[69]

In summary, we present a new class of rigid receptor molecules for organic dicationic guests. Depending on the accessibility of their clefts, these hosts are selective for either short or long α,ω-diammonium and guanidine compounds. Due to their inherent chirality, we could examine their potential for chiral discrimination and found that only those host—guest combinations, which allow a three-point interaction, are efficient. Therefore, bridged macrocycle **62** can act as a chiral shift reagent for arginine and lysine derivatives.

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