Synthesis, Conformation, and Binding Properties of Resorcarene Tetrasulfonates. Asymmetric Reorganization of Pendant Sulfonyl Groups via Intramolecular S═O- - -H−O Hydrogen Bonds

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The regioselective reaction of resorcarene octaols **1** with 4 equiv of arylsulfonyl chlorides and Et_3N in MeCN gives in 30−60% yield the C_{2v} symmetrical tetrasulfonates **3**. The mild electrophilic substitution (aminomethylation, bromination) of resorcarene tetrasulfonates **3** and tetraphosphates **2** takes place only in the 2-positions of unsubstituted resorcinol rings yielding distally disubstituted resorcarenes **4.** The acylation of hydroxy groups in compounds **2** and **3** gives C_{2v} symmetrical octaesters **5** including large resorcarene tetracrown-ethers. In the minimized boat conformation of tetrasulfonates **3** the two unsubstituted resorcinol rings are vertical and the sulfonyl fragments are arranged in a C_2 symmetrical manner via intramolecular S═O- - -H−O hydrogen bonds. This structure is proved by NMR and IR spectroscopy. In the case of tetrasulfonate **3c** the two enantiomeric conformations interconvert in $CDCl_3$ with $\Delta G^* = 11.6$ kcal/mol. This is in agreement with the ΔE^* value predicted by molecular mechanics *in vacuo.*

Introduction

Resorcarenes **1**[1] are readily available by acid catalyzed condensation of resorcinol with various aldehydes. The rccc isomers are effectively used as receptors for biologically important molecules[2] as well as for the creation of covalent and self-assembling molecular containers.[3,4] To modify the conformational behavior and binding properties of resorcarenes, chemical modifications can be performed. Many examples of *complete* derivatizations[5] of hydroxy groups and electrophilic substitutions in reactive resorcinol rings[6] have been reported in the literature. Several cases of *partial* reactions including bridging of the neighboring hydroxy groups,[7] alkylations,[8] and bromination [9] have also been described. Partially bridged cavitands undergo further *regioselective* substitutions in the neighboring resorcinol rings.[10]

Regioselective phosphorylation of rccc-resorcarenes **1** was first reported to give the C_4 symmetrical resorcarene tetraphosphates (structure **A**) having the *chair* and *diamond* conformation.[11] This interpretation, however proved to be entirely incorrect and later the C_{2v} symmetrical structure **2** was unambiguously established.[12] Previously, we have reported the conditions for the similar tetrasulfonation only for resorcarene **1a**.[13] Although some of the tetraphosphates and tetrasulfonates

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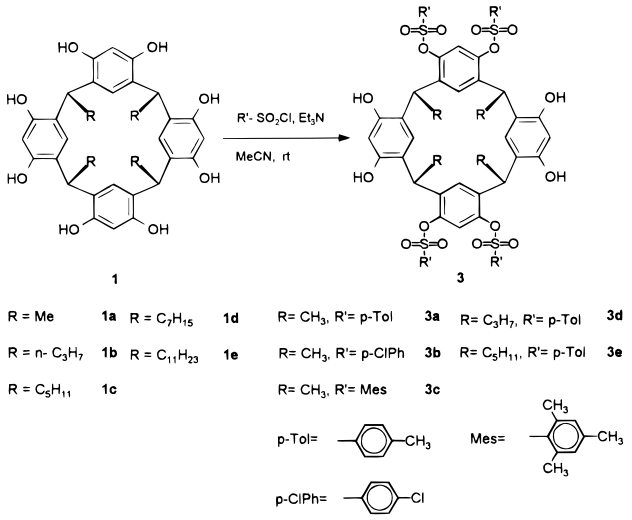
Scheme 1



of resorcarenes can be prepared in gram quantities their binding properties and dynamic stereochemistry still remain unexplored.

Here we describe the synthesis and unique conformational properties of C_{2v} symmetrical resorcarene tetrasulfonates. We demonstrate also that resocarene teterasulfonates and teteraphosphates can be employed as a molecular platform for the design of complex cation receptors containing several binding units of different types.

Results and Discussion

Synthesis and Structure. The addition of Et_3N (4 equiv) to a solution of octaol **1** in MeCN gave a slightly red precipitate. Although these extremely insoluble solids could not be identified they are most probably the salts of the rather acidic[14] resorcarenes **1** and Et_3N.[15] After the addition of arylsulfonyl chloride (4 molar equiv) the reaction mixture became homogeneous and after a while the precipitate of **3**·2Et_3NHCl was formed (Scheme 1). TLC analysis and ^{1}H NMR spectra showed that the filtrate contained many partially acylated resorcarenes that could not be identified.

The highest yields of tetrasulfonates were reached for resorcarene **1a** while in the case of more lypophilic (soluble) compounds **1d**,**e** no individual product could be isolated. The tetraacylation with *p*-chlorobenzene sulfonyl chloride had considerably lower yield compared to the reaction with tosyl chloride (31 and 53%) while in the case of nosyl chloride the reaction was not regioslective. Many attempts to perform partial and complete sulfonation of resorcarene **1a** with benzo-15-crown-5-sulfonyl chloride also failed.

The structure of tetrasulfonates **3** could be unambiguously proved by ^{1}H and ^{13}C NMR spectroscopy and by FD-mass spectrometry. The ^{1}H NMR spectrum of tetratosylate **3a** contains four singlets for the protons of resorcinol rings, one doublet and one quartet for the protons of the bridges and one set of signals for the tosyl fragments in accordance with a C_{2v} symmetrical structure. This structure was confirmed proved by single-crystal X-ray analysis of bis-benzoxazine derivatives of **3a**.[16] In the case of the pentyl analogue **3e** one doublet of doublets corresponds to the methyne protons of the bridges due to coupling with the diastereotopic protons of the neighboring methylene groups that appear in turn as two well-separated multiplets (Figure 1). The ^{13}C NMR spectra of compounds **3** contain two signals corresponding to the carbon atoms in the 2-positions of the unsubstituted (δ = 103 ppm) and diacylated (δ = 114 ppm) resorcinol rings. This conclusion is additionally supported by comparison with ^{13}C NMR spectra of resorcarene **1a** (δ = 101 ppm) and octatosylate **5g** (δ = 114 ppm).

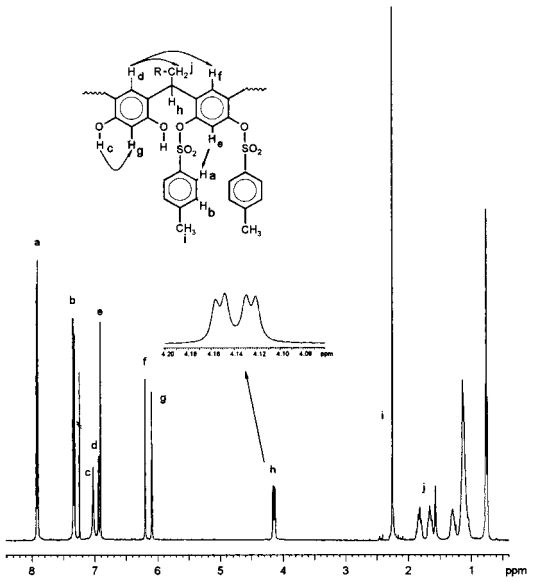
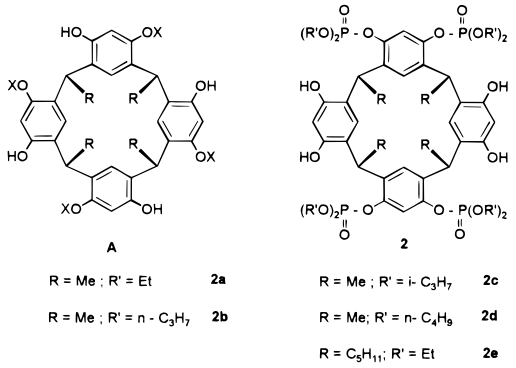


Figure 1. ^{1}H NMR spectrum of tetratosylate **3e** (400 MHz, $CDCl_3$). NOE are shown with arrows: $H_j(H_d)$ = 3.2%, $H_f(H_d)$ = 1.8%, $H_g(H_c)$ = 2.4%; $H_h(H_c)$ = 4.3%, $H_a(H_h)$ = 0.5%.

Chart 1



The tetrasulfonates **3a**−**c** and tetraphosphates **2b**,**d** (Chart 1) undergo acid-catalyzed aminomethylation with secondary amines or bromination with *N*-bromsuccinimide to give the diamines **4a**−**d**,**g** and dibromide **4e** (Chart 2). The reason for this regioselectivity is apparently the much higher reactivity of unsubstituted resorcinol rings over diacylated ones. The *three* singlets for the protons of resorcinol rings in the ^{1}H NMR spectra of compounds **4** are entirely consistent with the proposed structure.

The acylation of tetrasulfonates **3a** and **3c** and tetraphosphates **2b** and **2e** with tosyl chloride, acetyl chloride,

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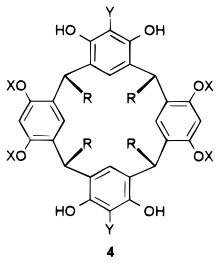
Chart 2



4

R= CH_3, Y= CH_2NEt_2, X = Ts **4a**

R= CH_3, Y= CH_2NEt_2, X= SO_2 p-ClPh **4b**

R= CH_3, Y= CH_2NEt_2, X= SO_2Mes **4c**

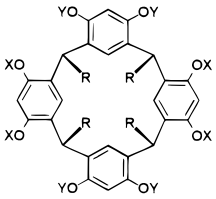
R= CH_3, Y= CH_2NEt_2, X= P(O)$(OPr^i)_2$ **4d**

R= CH_3, Y= Br, X= P(O)$(OBu)_2$ **4e**

R= CH_3, Y= CH_2-l-Pro, X= SO_2 Mes **4f**

l-Pro =

Chart 3



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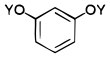


6

Y = SO_2 B-15-C-5

R= C_5H_{11}, X= P(O)$(OEt)_2$, Y= Ac **5a**

R= C_5H_{11}, X= P(O)$(OEt)_2$, Y= Ts **5b**

R= CH_3, X= SO_2Mes, Y= Ts **5c**

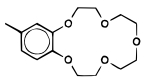
R= C_5H_{11}, X= P(O)$(OEt)_2$, Y= SO_2 B-15-C-5 **5d**

R= CH_3, X= P(O)$(OPr)_2$, Y= SO_2B-15-C-5 **5e**

R= CH_3, X= SO_2Mes, Y= SO_2B-15-C-5 **5f**

R= C_5H_{11}, X= Y= Ts **5g**

B-15-C-5 =



and benzo-15-crown-5-sulfonyl chloride readily gave the C_{2v} symmetrical octaesters **5**[17] (Chart 3). The structure of large receptor molecules **5d**−**f** having molecular weights in the range 2.5−2.6 kDa could be definitely proved by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of compounds **5d**−**f** measured in $CDCl_3$ at room temperature are broad and featureless while in DMSO-d_6, acetone-d_6, and benzene-d_6 they are well resolved and again consistent with C_{2v} symmetrical structure. This solvent effect could be caused by formation of a hydrogen bonded complex between the crown-ether fragments and chloroform molecules. The reactions of tetraphosphates **2a** and **2c** with acetyl chloride and tosyl chloride failed due to their poor solubility in most of organic solvents (except for DMF, DMSO, etc.)

Hydrolysis of tetratosylate **3a** by KOH in MeOH−H_2O at 60 °C gave quantitatively octaol **1a.** However, it was not possible to remove ether the tosyl or phosphoryl groups from the disubstituted compounds **4**. Thus the phosphoryl and arylsulfonyl groups *cannot* be used as protecting groups in the rational synthesis of partly substituted resorcarenes.

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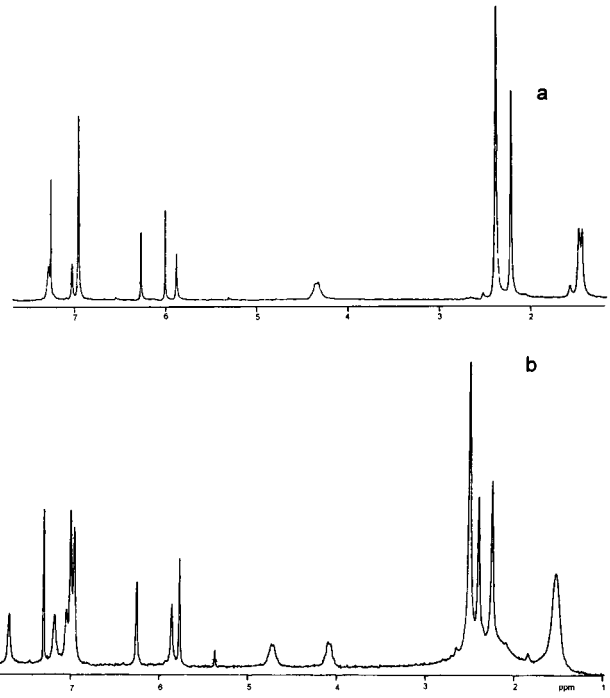

Figure 2. ^{1}H NMR spectrum of tetrasulfonate **3c** (200 MHz, $CDCl_3$): (a) at 295 K; (b) at 203 K.

Dynamic Stereochemistry. The ^{1}H NMR spectra and NOE (Figure 1) suggest that in solution compounds **3** exist in one boat conformation. The singlets for the protons of the lower rim of the calixarene skeleton are strongly separated ($\Delta\delta = 1.0$ ppm) which is characteristic of the rccc boat conformation. By analogy with known rccc-octaesters[18] of resorcarenes, one can conclude that the high-field signal corresponds to the protons of the horizontal resorcinol rings. However, it was not possible to establish from NMR which of the two boat conformations (with horizontal or vertical free resorcinol rings) is actually present in the solution.

At room temperature the ^{1}H NMR spectrum of **3c** is consistent with the C_{2v} symmetrical structure (Figure 2a) while at −60 °C the C_2 symmetrical pattern is observed (Figure 2b). Namely the cooling results in doubling of the signals for the protons of hydroxy groups, the bridges, and mesityl fragments. In contrast the four singlets for the protons of the lower rim do not change considerably either in their shape or in their position within the temperature range 295−205 K, therefore excluding boat−boat transition.[19] Only the signal for the protons of unsubstituted resorcinol rings (upper rim) is shifted upfield by about 0.2 ppm. The signals for the methyne protons of the bridges coalesce at 247 K (200 MHz, $CDCl_3$) which corresponds to ΔG^* of 11.6 kcal/mol.[20] Almost the same ΔG^* (11.2 kcal/mol) was found in toluene-d_8 while

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(19) In the case of resorcarene octatosylates the boat- boat transition took place: Kalchenko, V. I.; Solov'yov, A. V.; Gladun, N. R.; Shivanyuk, A. N.; Atamas', L. I.; Pirozhenko, V. V.; Markowsky, L. N.; Lipkowski, J.; Simonov, Yu. A. *Supramol. Chem.* **1997,** *8*, 269−297

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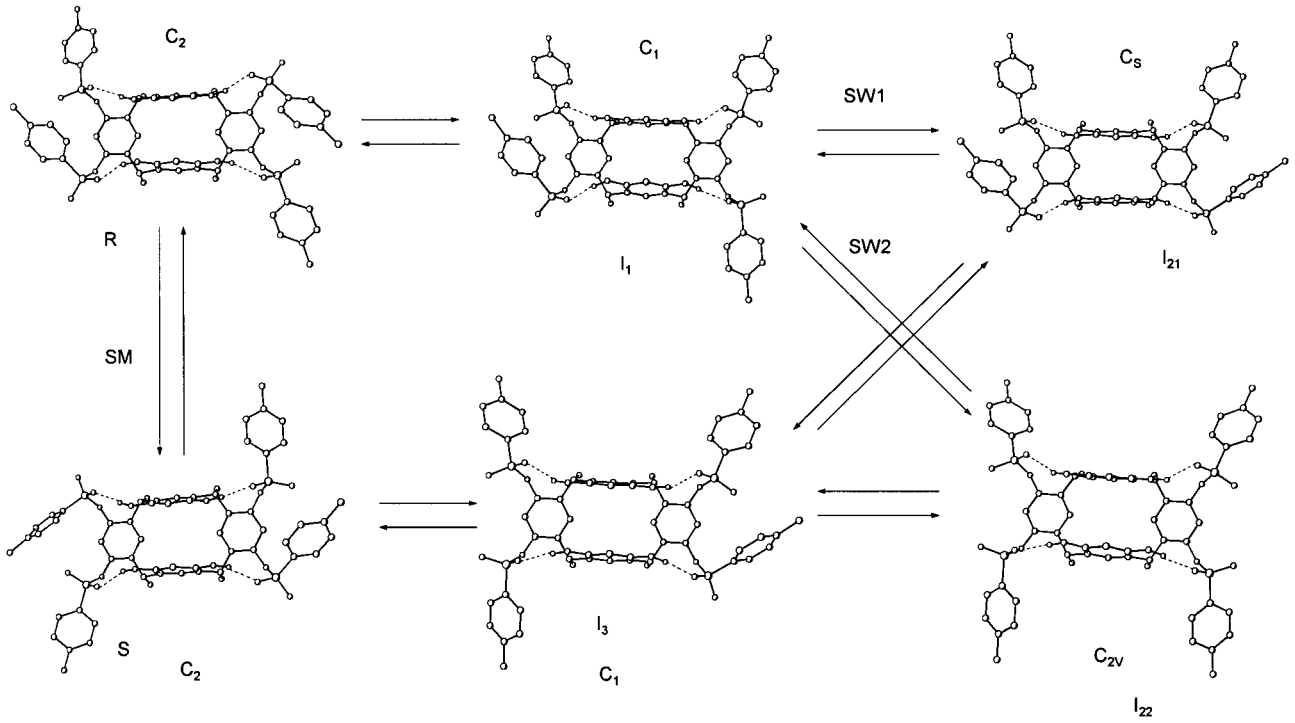

Figure 3. Simultaneous (SM) and stepwise (SW) pathways for the interconversion between C_2 symmetrical enantiomeric conformations of **3**. *R* and *S* refer to the clockwise and counterclockwise orientation of the sulfonyl groups, respectively. Hydrogen bonds are shown in dotted lines.

in pyridine-d_5 (acceptor of hydrogen bonds) no dynamics were observed up to 213 K. This process is much faster ($\Delta G^* < 10$ kcal/mol) for the less sterically hindered tetratosylate **3a** since only broadening of the ^{1}H NMR signals was observed at 213 K ($CDCl_3$, 200 MHz).

The IR spectra of **3b** and **3c** measured in CH_2Cl_2 and CCl_4 contain two clear-cut bands for the OH groups (3410 and 3475 cm^{-1}). The independence of the IR spectra on the concentration and temperature (22−70 °C) reflects the formation of two types of *intramolecular* hydrogen bonds S═O---H−O that are *slightly* different in strength.

The above results could be generally explained by interconversion of two C_2 symmetrical conformers of **3c** different only in the arrangement *of hydrogen-bonded sulfonyl fragments*. To verify this hypothesis we have performed molecular mechanics studies of tetrasulfonates **3a** and **3c**.

Many local energy minima are possible for compounds **3** that are different in the conformation of the resorcarene skeleton and the arrangement of sulfonyl groups. The structures of tetrasulfonates **3a** and **3c** were minimized by MMX force field starting from the two *boat* conformations with parallel and coplanar unsubstituted resorcinol rings. The energy barrier between these conformations was sufficiently high to prevent their interconversion during the geometry optimization.

The lowest energy corresponds to the boat conformation having horizontal diacylated resorcinol rings and C_2 symmetrical propeller-like orientation of the four sulfonyl fragments (Figure 3). Two pairs of intramolecular hydrogen bonds S═O···H−O (O···O of 2.9 and 3.1 Å) are predicted for this structure. It is important to note that a similar arrangement of the sulfonyl fragments was experimentally found in the X-ray crystal structures of bis-benzoxazine derivatives of tetratosylate **3a**.[17] The time-averaged structure of **3** is a mesoform with two *R*- and two *S*-carbon atoms of the bridges. The propeller-like arrangement of the sulfonyl fragments "induces" the chirality of the whole molecule, making the *R*- and *S*-bridging atoms inequivalent. The sulfur atoms also become chiral since one of the S═O oxygens forms the hydrogen bond while the other does not.

The second minimized conformation of **3a** and **3c** with vertical diacylated resorcinol rings (Figure 4a) was found to be about 8 kcal/mol less advantageous. This difference may be attributed partly to the formation of only two intramolecular hydrogen bonds S═O---H−O.

The results of dynamics NMR studies of resorcarene **3c** could be explained by the exchange between two enantiomeric structures differing only in handedness of the propeller-like arrangement of four sulfonyl fragments. The simultaneous and stepwise rotations around $ArSO_2$−OAr′ bonds were considered as possible pathways for this interconversion (Figure 3).

In the simultaneous route all four torsion angles $ArSO_2$−O−Ar′ were constrained every 10° in the range −170 to 70°, while the rest of molecule was minimized. As a result of this procedure the four arylsulfonyl fragments are moving like molecular wind screen wipers. The potential energy surface of this mechanism has a single transition state (Figure 5) with the ΔE^* of 7.5 for **3a** and 11.5 kcal/mol for **3c** which is comparable with the experimental values of ΔG^*.

In a stepwise pathway the rotation procedure was applied separately to each arylsulfonyl fragment so that finally three intermediates and four transition states were obtained (Figures 3 and 5). In this case two routes are possible, namely, R−I_1−I_{21}−I_3−S or R−I_1−I_{22}−I_3−S whose energetic characteristics are summarized in the Table 1. Apparently two of those intermediates (I_1 and I_3) are chiral (antipodes) while the two others (I_{21} and I_{22}) are mesoforms. It is important to note that the

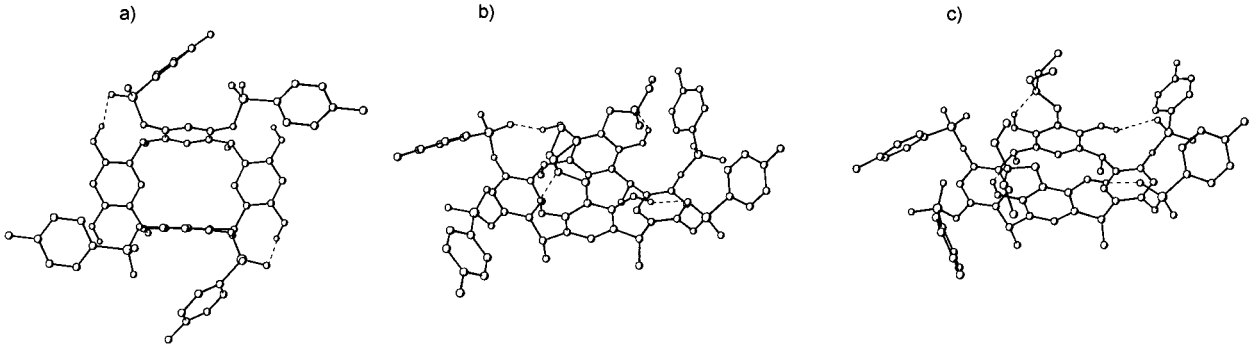

Figure 4. Minimized conformations of tetratosylate **3a** (the second) and diamine **4a** trans form (b) and cis form (c).

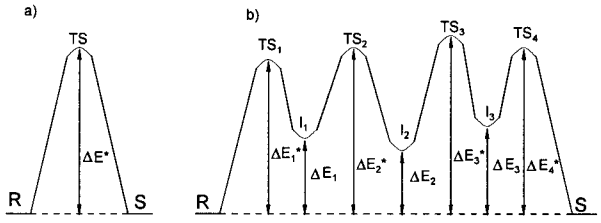

Figure 5. Potential energy profiles of the simultaneous (a) and stepwise (b) pathways.

activation energy per sulfonyl fragment ($\Delta E^*/4$) for the simultaneous mechanism is considerably lower than the average value of the four activation energies for the stepwise pathway (ΔE^*_a). Thus it is reasonable to assume that the interconversion between two enantiomeric conformers of **3** is realized via the *cooperative* simultaneous route.

The ^{1}H NMR spectrum of diamine **4c** recorded at 213 K contains a double set of the signals for the methyne protons of the bridges, hydroxy groups (12.2, 7.01 ppm) and diethylamino fragments. Two doublets with $J = 14.4$ Hz for the benzyl protons of the aminomethyl groups reveal that rotation around the Ar−CH_2 bond is slow on the NMR time scale at this temperature.[21] The three sharp singlets for the protons of resorcinol rings allow the conclusion that the "frozen" conformation has C_2 symmetry. The coalescence data for the protons of the bridging carbon atoms give a ΔG^* value of 11.1 kcal/mol which is comparable to that found for the dynamics of tetrasulfonate **3c**. The IR study of **4c** in CH_2Cl_2 and CCl_4 solutions reveals again intramolecular hydrogen bonding. However in contrast to **3b** and **3c** the two bands for the hydroxy groups are quite distant, most probably due to the large difference in the strength between S═O---H−O ($\nu = 3511$ cm^{-1}) and O−H---N ($\nu = 2800$ cm^{-1}) hydrogen bonds.

Indeed the molecular mechanics calculations predict intramolecular hydrogen bonds between the hydroxy groups and the nitrogen atoms for both C_2 and C_s symmetrical conformations of diamine **4c** (Figure 4b,c). However, the latter is by 3 kcal/mol less advantageous than the former, probably due to the stronger sterical and electrostatic repulsion between diethylamino moieties.

In conclusion the intramolecular hydrogen bonds S═O- - -H−O result in asymmetric reorganization of four pendant arylsulfonyl fragments in molecules **3** and molecular chirality.[22] The two sp^2 oxygens of the sulfonyl group appear to be crucial for this process since in the case of tetraphosphates **2** no dynamics could be detected by ^{1}H NMR spectroscopy.

Complexation Studies

Compounds **5d**−**f** are able to complex alkali cations and NH_4^+ in acetone THF and $CHCl_3$. The ^{1}H NMR titration of tetraphosphates **5d** and **5e** by picrates of Na^+, K^+, Cs^+, Rb^+, and NH_4^+ showed systematic changes in the shape and position of the signals corresponding to the protons of the phosphoryl groups, benzo crown-ether fragments and resorcarene skeleton. The strongest effects were observed in the case of KPic. For example after addition of 2 equiv of KPic all the resonances for the aryl rings of benzo-15-crown-5 were transformed into one broad singlet.

The ^{31}P NMR signal of **5d** and **5e** was shifted downfield by about 1 ppm upon titration with MPic clearly showing saturation. However, no reliable thermodynamic parameters could be obtained from these dilution experiments, most probably, due to the presence of more than one complex under the host−guest ratios studied.

Inspection of CPK− models and MM- calculations for the receptors **5d**−**f** showed that complexation of the cations can be realized in several ways (Figure 5).

A. Sandwich-like complex with two crown-ether fragments connected to the same resorcinol ring.

B. Sandwich-like complex with two crown-ether fragments connected to the opposite resorcinol rings. This type of complexation is possible only when the receptor adopts the boat conformation with vertical sulfonated resorcinol rings.

C. Lariat complex with one crown-ether fragment and neighboring P═O or S═O groups.

To reveal the mode of 1:1 cation complexation we have carried out a UV study of interaction of MPic with excess of the ligand.

Addition of receptor **5d** (10 molar equiv) to the solution of alkali and ammonium picrates in THF resulted in considerable bathochromic shifts ($\Delta\lambda_{max}$) of the absorption maximum for the picrate anion (see Table 2) due to the separation of contact ion pair M^+Pic^-. The strongest shifts were observed for KPic (24 nm) and RbPic (20 nm), while relatively small or no changes were found for LiPic

(21) This rotation is much more hindered in the completely aminomethylated resorcarenes: Leigh, D. A.; Linnane, P.; Pritchard, R. G.; Jackson, G. *J. Chem. Soc. Chem. Commun.* **1994**, 389−390.

(22) About the "supramolecular chirality" in the crystalline state via *intermolecular* hydrogen bonding between achiral compounds, see: Suarez, M.; Branda, N.; Lehn, J.-M.; Decian, A.; Fischer, J. *Helv. Chim. Acta* **1998,** *81*, 1−13.

Table 1. Energetic Characteristics (in kcal/mol) for the Interconversion of Tetrasulfonates 3a,c

	ΔE_1*	ΔE_1	ΔE_2*	ΔE_2	ΔE_3*	ΔE_3	ΔE_4*	ΔE_4
3a								
route 1	3	2	3.5	2.5	4	2.5	3.5	3.5
route 2	3	2	4.5	4	4.5	2.5	3.5	3.875
ΔE*/4				1.87				
min ($4\Delta E^*_a - \Delta E^*$)				6.5				
3c								
route 1	4	3	5	0.5	3.5	3	5	4.375
route 2	4	3	7	6	8.5	3	5	6.125
ΔE*/4				2.875				
min ($4\Delta E^*_a - \Delta E^*$)				6				

Table 2. Absorption Maxima for Picrate Anion λ_{max} and Their Bahochromic Shifts $\Delta\lambda_{max}$ Induced by Complexation of Receptors 5d,f and Model Compound 6 with MPic in THF

	cation					
ligand	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+
5d[b]	348[1]	356[5]	380[24]	376[20]	372[12]	362[12]
5f[b]	347[0]	354[3]	369[12]	376[20]	368[8]	357[7]
6[c]	347[0]	354[3]	369[12]	356[0]	360[0]	350[0]

[a] Concentration of MPic = 2×10^{-4} M. [b] MPic/ligand = 1:10. [c] MPic/ligand = 1:20.

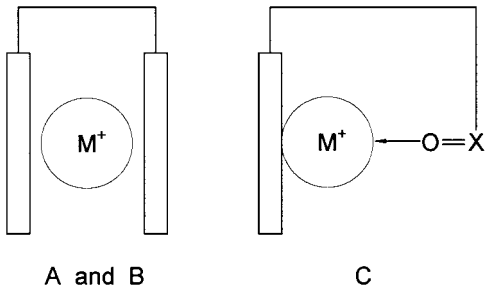

Figure 6. Possible mechanisms for the complexation of the cation by resorcarene tetracrown ethers.

and NaPic. The tetracrown-ether **5f** showed similar effects; however, in the case of KPic, the $\Delta\lambda_{max}$ was two times smaller under exactly the same conditions.

In the model expereiment the addition of bis crown-ether **6** (*isolated binding unit of type A*) to the solution of KPic in THF induced $\Delta\lambda_{max}$ of 12 nm however no changes were detected for the other cations. These results suggest that complexes tetracrown-ethers **5d**−**f** with Rb^+, Cs^+, and NH_4^+, are of type B or (and) C (Figure 6).

The complexation of KPic by receptor **5f** is most probably realized in way A since the $\Delta\lambda_{max}$ is the same as for the biscrown ether **6**. The difference in $\Delta\lambda_{max}$ (KPic) for tetraphosphate **5d** and tetramesityl sulfonate **5f** gives a hint in a favor of lariat complexation (type C) of K^+ by **5d.** This is in accordance with the fact that the phosphoryl group is a much better donor of the electron pair than the sulfonyl goup.

Concluding Remarks

The tetrasulfonates and tetraphosphates of resorcarenes are promising molecular platforms for preorganization of various modules (for example cation binding sites) via modiffication of the hydroxy groups and unsubstituted resorcinol rings. The intramolecular hydrogen bonding between the neighboring sulfonyl and hydroxy groups in tetrasulfonates **3** makes possible the asymmetric arrangement of all arylsulfonyl fragments which is unprecedented in the chemistry of resorcarenes.

Experimental Section

Reagents and Methods. The ^{1}H and ^{13}C NMR, ^{1}H NOE, HETCOR, and APT spectra were recorded with Varian XR-300 (300 and 75.4 MHz), Varian-200 (200 and 50.0 MHz), Bruker 200 (200 and 50 MHz), and Bruker 400 (400 and 100 MHz) instruments with TMS as internal standard. The ^{31}P NMR spectra were recorded by Bruker WP-200 (81.026 MHz) with 85% H_3PO_4 as external standard. The ^{1}H and ^{13}C NMR spectra in CCl_4 were recorded using a capillary with TMS. The UV and IR spectra were measured by Specord M-40 and Specord M-80 instruments, respectively. FD mass spectra were recorded with a Finnigan MAT 90 (5 kV/10 mA/min). Melting points were determined with a MEL TEMP 2 capillary melting point apparatus and are uncorrected. Compounds **1** were obtained by known procedures.[23]

General Procedure for Tetrasulfonylation of Resorcarenes. To a solution of resorcarene **1a** (5.45 g, 0.01 mol) in dry MeCN (100−150 mL) Et_3N (4.04 g, 0.04 mol) was added. A slightly red precipitate was formed, and the reaction mixture was stirred for 15 min. A solution of tosyl chloride (7.68 g, 0.04 mol) in MeCN (50 mL) was added immediately to the suspension of precipitate, and the reaction mixture was intensively stirred to facilitate disolution of the precipitate. In 2−3 min a colorless precipitate formed. The reaction mixture was stirred at room temperature for 12 h, the precipitate formed was filtered off, washed with MeCN (2 × 20 mL) water and dried in a vacuum. The product obtained in this way is a complex of tetratosylate **2a** with 2 equiv of Et_3NHCl. The salt ether was removed by reprecipitation of a DMF solution of the complex with water or by chloroform/water extraction.

The reaction with nosyl chloride and benzo-15-crown-5-sulfonyl chloride were carried out in a similar manner. However, after addition of sulfonyl chloride no precipitate was formed. The reaction mixture was evaporated in vacuo. The TLC analysis and ^{1}H NMR spectroscopy showed that inseparable mixtures of many partially acylated compounds were formed.

4,6,16,18-Tetrahydroxy-10,12,22,24-tetrakis(*p*-tolylsulfonyloxy)-2,8,14,20-(tetramethyl)calix[4]arene 3a. Yield 53%; mp 310−313 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 4H), 7.80 (d, J = 7.5 Hz, 8H), 7.50 (d, J = 7.5 Hz, 8H), 6.91 (s, 2H), 6.85 (s, 2H), 6.84 (s, 2H), 5.93 (s, 2H), 4.30 (q, J = 6.9 Hz, 4H), 2.39 (s, 12H), 1.20 (d, J = 6.9 Hz, 12H); ^{13}C NMR (100, MHz, DMSO-d_6) δ 152.90, 145.46, 143.72, 138.31, 132.83, 130.06, 127.83, 127.65, 124.02, 120.25, 112.84, 101.92, 29.66, 20.99, 20.42. MS (FD) 1160.6 (100%) [M^+, 1161.3]. Anal. Calcd for $C_{60}H_{56}O_{16}S_4$: C, 62.05; H, 4.86; S, 11.04; Found: C, 61.95; H, 4.88; S, 11.15.

4,6,16,18-Tetrahydroxy-10,12,22,24-tetrakis(di-*n*-propylphosphoryloxy)-5,17-(methylenediethylamino)-2,8,14,20-(tetramethyl)calix[4]arene 4d. To a solution of tetraphosphate **2b** (0.5 g, 4.3 mmol) in EtOH (30 mL) was

(23) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305−1312.

added Et_2NH (2 mL) and the solution was brought to reflux. To the clear solution phormaline (40%, 3 mL) was added in one portion followed by AcOH (0.5 mL). Reaction mixture was stirred at room temperature for 20 h and then was poured into water (200 mL). The emulsion formed was extracted with ether (5 × 20 mL) and the combined ether solutions were dried over Na_2SO_4 and evaporated in vacuo. Yield 63%; mp 127−128 °C; ^{1}H NMR (CCl_4) δ 0.87 (t, J = 7.5 Hz, 12H), 0.94, 0.96 (two t, J = 7.8 Hz, 24H), 1.37 (d, J = 7.1 Hz, 12H), 1.61−1. 88 (m, 16H), 2.30 (q, J = 7.5 Hz, 8H), 3.52 (s, 4H), 3.93−4.12 (m, 16H), 4.44 (q, J = 7.1 Hz, 4H), 6.31 (s, 2H), 6.90 (s, 2H), 7.22 (t, J = 1.0 Hz, 2H), 9.10 (br s, 4H); ^{13}C NMR (CCl_4) δ 8.01, 9.30, 18.85, 21.64 (d, J_{CP} 7.0 Hz), 29.36, 44.41, 48.77, 67.60 (d, J_{CP} 7.0 Hz), 68.05 (d, J_{CP} 7.0 Hz), 106.05, 109.82, 116.35, 121.46, 124.33, 134.52 (d, J_{CP} 5.9 Hz), 143.79 (d, J_{CP} 6.2 Hz), 151.90; ^{31}P NMR (CCl_4) δ −5.15. Anal. Calcd for $C_{66}H_{110}O_{20}P_4N_2$:C, 57.62; H, 8.06; P, 9.01; N, 2.03. Found: C, 57.62; H, 8.06; P, 9.01; N, 2.03.

4,6,16,18-Tetrahydroxy-10,12,22,24-tetrakis(di-*n*-butylphosphoryloxy)-5,17-dibromo-2,8,14,20-(tetramethyl)-calix[4]arene 4e. To a solution of the tetraphosphate **2d** (1 g, 0.76 mmol) in acetone (20 mL) *N*-bromosuccinimide (1 g, 4.4 mmol) was added in one portion and the reaction mixture was stirred overnight at room temperature. Solvent was removed in vacuo and the remaining material was recrystallized from EtOH/H_2O. Yield 84%; mp 216−218 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (br s, 4H), 7.25 (s, 2H), 7.07 (s, 2H), 6.13 (s, 2H), 4.57 (q, J = 6.8 Hz, 4H), 4.30−4.10 (m, 16H), 1.81−1.62 (m, 16H), 1.45 (d, J = 7.16 Hz, 12H), 1.52−1.31 (m, 16H), 0.93 (t, J = 7.3 Hz, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.55, 18.61, 20.05, 29.55, 32.13, 32.16, 32.30, 32.35, 68.61 (d, J = 6.4 Hz), 68.84 (d, J = 6.4 Hz), 101.11, 112.0, 119.72, 123.60, 126.08, 135.67 (d, J = 5.4 Hz), 146.1 (d, J = 8.2 Hz), 150.18; FD-MS m/z 1471.3 (100%) [M^+ 1471.2]. Anal. Calcd for C_{64} $H_{98}O_{20}P_4Br_2$: C, 48.94; H, 12.72. Found: C, 49.13; H, 12.94.

4,6,16,18-Tetrahydroxy-10,12,22,24-tetrakis(*p*-tolylsulfonyloxy)-5,17-bis(*N*-L-prolylmethyl)-2,8,14,20-(tetramethyl)calix[4]arene 4f. To a solution of tetratosylate **3a** (0.3 g, 0.26 mmol) in ethanol (20 mL) formaline (0.5 mL, 0.26 mmol) and 2 or 3 drops of acetic acid were added. Then a solution of L-proline (0.59 g, 5.2 mmol) in ethanol (5 mL) was added with stirring. The mixture was stirred at reflux for 5 min and at room temperature for 24 h. The solvent was evaporated in vacuo, and the solid formed was recrystallized from cold methanol. Violet solid; yield 89%; mp 180−184 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.34 (d, J = 6.2 Hz, 12H), 1.78 (br, s, 4H), 2.07 (br s, 4H), 2.46 (s, 12H), 2.84 (br s, 2H), 3.33 (br s, 2H), 4.17 (s, 4H), 4.20−4.60 (m, 6H), 5.96 (s, 2H), 6.82 (s, 2H), 7.12 (s, 2H), 7.38 (d, J = 7.2 Hz, 8H), 7.82−7.90 (m, 8H). Anal. Calcd for: $C_{72}H_{74}O_{20}N_2S_4$: C, 61.09; H, 5.27; S, 9.06; N, 1.98. Found: C, 61.00; H, 5.16; S, 9.22; N, 1.90.

4,6,16,18-Tetrakis(benzo-15-crown-5-sulfonyloxy)-10,12,22,24-tetrakis(dipropoxyphosphoryloxy)-2,8,14,20-(tetramethyl)calix[4]arene 5d. To a solution of tetraphosphate **2** (0.9 g, 0.77 mmol) in dry $CHCl_3$ (10 mL) Et_3N (0.9 mL, 6.1 mmol) was added followed by benzo 15-crown-5-sulfonyl chloride (2.3 g, 6.3 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated in vacuo, and the crude product was taken up in THF (30 mL). A precipitate formed (Et_3NHCl) was filtered off, and the filtrate was evaporated in vacuo. The crude product was recrystallized from diethyl ether. Yield 55%; mp 148−150 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 0.96, 0.98 (two t, J = 7.0 Hz, 24H), 1.40 (d, 12H, J = 7.0 Hz), 1.65−1.85 (m, 16H), 3.69−4.24 (m, 80H), 4.57 (q, J = 7.1 Hz, 4H), 6.20 (br s, 2H), 7.04−7.52 (m, 18H); ^{31}P NMR (acetone-d_6) δ −5.20; Anal. Calcd for $C_{112}H_{156}O_{48}P_4S_4$: C, 53.32; H, 6.23; S, 5.08; P, 4.91. Found: C, 53.55; H, 6.14; S, 5.15; P 4.72.

Molecular Mechanics Calculations. Molecular mechanics calculations were performed using MMX force field as implemented in PCMODEL 5.13.[24] Geometry optimization was accomplished with a conjugate gradient procedure. A root-mean-square (RMS) gradient of 0.001 kcal/mol or less was assumed as a condition of energy convergence. A value of 1.5 D was assumed for the dielectric constant.

For optimization of the arrangement of the arylsulfonyl groups the dihedral driver procedure has been applied during which two torsions for the Ar−OTs and ArO−Ts bonds were changed with the step of 30°. From the 144 conformers, the lowest energy one was minimized with no constrains and taken, in turn, as starting point for the following rotations of remaining tosyl groups.

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Supporting Information Available: Synthetic procedures, spectral and analytical data for compounds **2d, 3b−d, 5a−c, 4a, 4b, 5e−g,** and **6** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS; see any current masthead page for ordering information.

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(24) (a) PCMODEL is distributed by Serena Software, Dr. Kevin E. Gilbert, P. O. 3076, Bloomington, IN 47402. (b) *Discover*, version 2.9.5; Biosym Technologies: 9685 Scranton Road, San Diego, CA 92121-4778, May, 1994.