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The Host-Guest Chemistry of Resorcinarenes [1]*

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Abstract. Conformations, acid-base and supramolecular properties of phenolic metacyclophanes obtained from the condensation of resorcinol with aldehydes are discussed, including the mechanisms involved in the formation of these macrocycles. The strong binding of choline-type compounds and the inhibition of acetylcholine hydrolysis with the **rccc** stereoisomers is mechanistically evaluated; a **rctt** isomer shows strong conformational coupling for, e.g., choline binding and simultaneous proton release. The presence of larger alkyl residues at the bottom of the **rccc** macrocycle leads to an additional binding site for small lipophilic substrates, which is independent of the upper complexation center for positively charged substrates. Substitution at the upper rim by carboxylic groups at the 2-position of the phenyl rings yields receptors for, e.g., α,ω-diammonium ions with alternate equatorial and axial arylunits. Positively charged substituents at the upper rim, introduced by aminoalkylation, lead to little change of complexation as a result from their orientation away from the binding center. Aminoacid substituents, for the same reason, do not lead to enantioselective complexation, but allow particularly for strong binding of transition metal ions. Preliminary studies show that resorcinarenes bearing a wide array of positive charges are potent groove binders to ds-DNA without intercalative contributions.

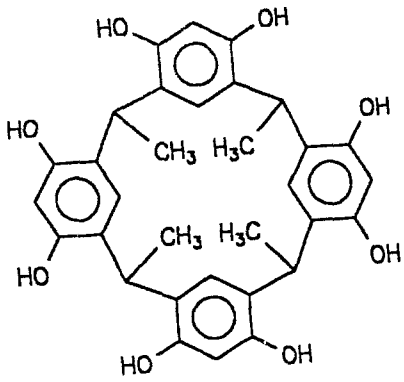
Key words: Acidities, amino acids, binding mechanisms, calixarenes, choline, conformations, copper complexes, NMR, polyphenolates, resorcinarenes, supramolecular complexes.

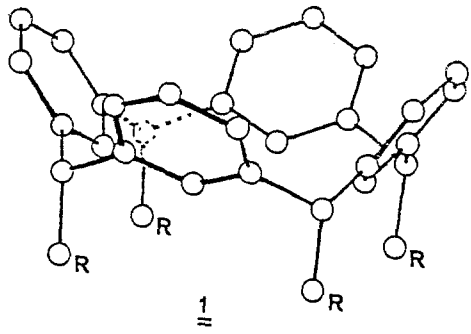
1. Introduction

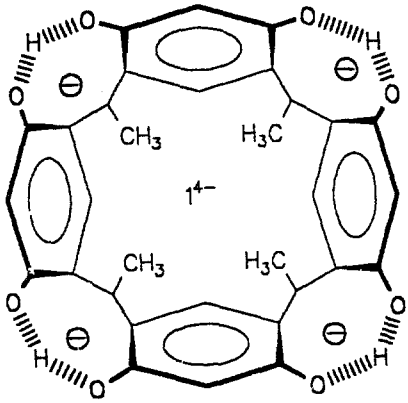
Although Adolf von Baeyer obtained crystalline material from the condensation of resorcinol with aldehydes [2] in 1872 it took almost a century and the efforts of several groups to secure the structure of these products. In 1884 further derivatives were isolated [3], and in 1884 Michael [3a] suggested that they might have a cyclic structure. This was on the basis of molecular weight determinations a supposition supported by Niederl and Vogel in 1940 [4]. Erdtman *et al.* finally proved the metacyclophane structure **1** of derivatives [5] by X-ray analysis. In 1980 Högberg published his NMR studies on the conformational changes of the corresponding esters in chloroform solution [6a] and also clarified some of the acid-catalyzed rearrangememts of the stereoisomers [6b], which later were all characterized, in particular by Mann *et al.* [7].

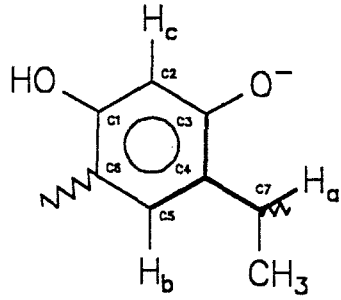
Today, these macrocycles have opened access to promising supramolecular systems and are discussed in recent monographs on cyclophanes [8]. We prefer to call them resorcinarenes and not calixarenes for two reasons: first, the name calixarenes

* This paper is dedicated to the commemorative issue on the 50th anniversary of calixarenes.





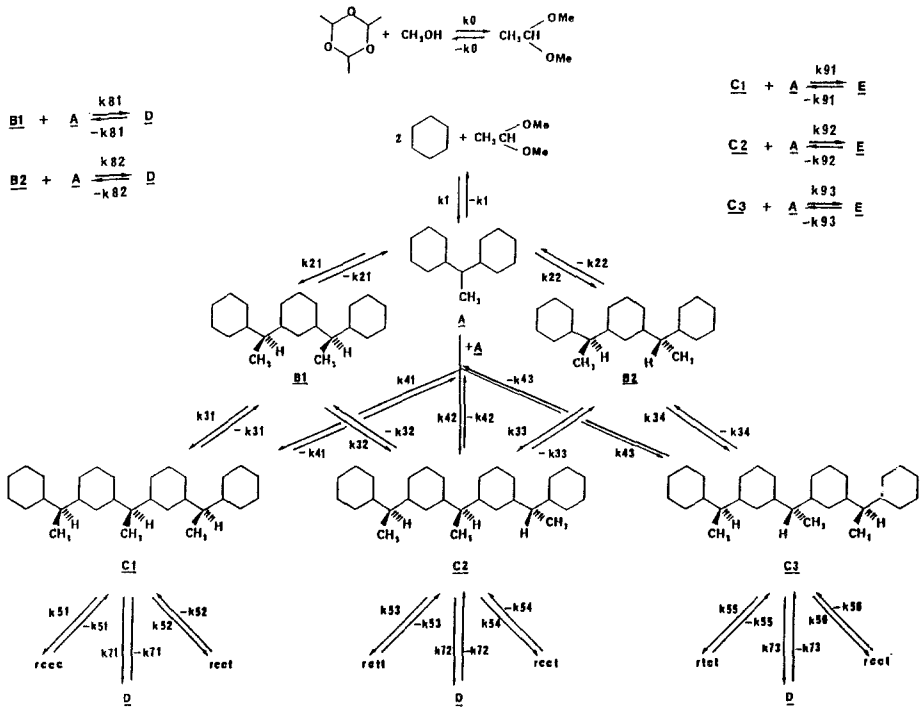




Scheme 1. The structure of the **rccc** product **1**.

was given to the cyclophanes obtained from 4-alkylphenol condensations; second, the cyclic polyphenol systems from resorcinol adopt a vase-like structure only with *one* of the four isomers, and even then only under special conditions (see below). Cram *et al.* have used resorcinarenes as a building block for their cavitands and carcerands [9], which are based on covalent links between the neighbouring phenolic groups of **1** [10]. Aoyama and collaborators have developed efficient sugar binding hosts by condensation of resorcinol with long chain alkanals leading to chloroform-soluble receptors (e.g. **1**, R=$(CH_2)_{10}CH_3$) with 8 well ordered phenolic groups for hydrogen bonding with carbohydrates [11]. Other modifications of the basic resorcin[4]arene skeleton involve binding elements for metals and their complexes [12] and the formation of liquid crystals [13].

The use of the basic resorcin[4]arene skeleton itself as host compound for positively charged substrates was initiated in 1985 in Saarbrücken [14]. The devel-

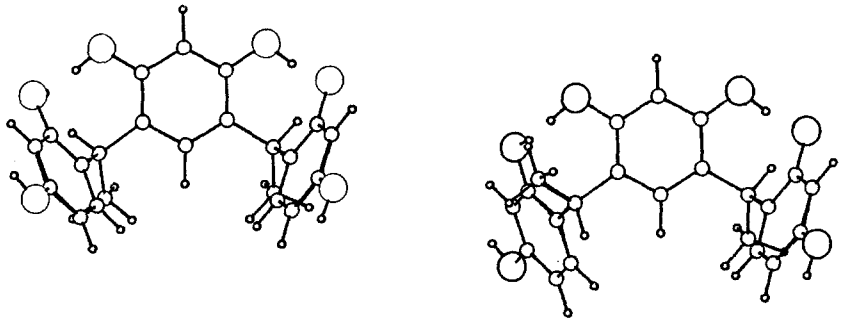


Scheme 2. The buildup of oligomers and macrocycles (see text for explanations).

opment of these systems and of those obtained by substitution both at the top of the macrocycle (at position C-2) and at the bottom (at C-7) will be the focus of the present review. This also reflects our primary interest in the physical characterization of supramolecular complexes in solution, both with respect to the binding mechanisms and energies involved, as well as to the conformations [15]. NMR spectroscopy provides the most important method for this. We also want to point out the possibilities of developing receptors with polytopic and allosteric binding sites from these resorcinarenes.

2. The Mechanisms of Macrocyclization

Before we discuss the supramolecular features of the resorcin[4]arene systems we address the questions of *why and how* the macrocycle containing four resorcinol units forms in such high yields without high dilution and without template effects; these are known to play an important role in calixarene synthesis based on the reaction of 4-alkylphenoles with formaldehyde. Baeyer must have wondered about this, since he isolated crystalline – although at that time unidentified – products only from resorcinol [2], in contrast to the alkylphenol reactions. The conditions which can make such macrocycles available on a large scale, with potential industrial uses [16], are not only of great practical importance, but also fascinating enough



Scheme 3. An illustration of the most stable "folded" (left) and less stable "unfolded" (right) conformations with trimers. The folded structure shows the terminal phenols oriented towards the front side; in the unfolded one phenol is oriented backwards, causing an unfavourable interaction between the hydroxy and methyl groups as well as the absence of a hydrogen bond.

for a mechanistic study. Weinelt, during a stay in Saarbrücken, was in fact able to rationalize on a quantitative basis the peculiarities of such a macrocyclization [17].

The buildup sequence of the macrocycles from acetaldehyde (used as paraldehyde) and resorcinol leads to one dimer **A** and from there to two diastereomeric trimers **B**, further to three tetramers **C**, and then either by ring closure to the four possible stereoisomeric cyclophanes (**rccc,rcct, rctt, rtct**) or further on to pentamers **D**, etc., with more than 50 different rate constants (Scheme 2). Seven of these structures could be identified and their interconversion kinetics followed by NMR; a computerized fitting procedure by numerical integration enabled some rate constants to be obtained and to define the essential conditions for the effective ring closure: (a) under the reaction conditions the higher oligomers **D** etc. degrade back to the tetramers relatively quickly, (b) the tetramers react even faster to form rings, which, (c) open slowly compared to the chain propagation steps. In line with factor (a), there are more polymers under non-homogeneous reaction conditions, e.g. in water instead of methanol as solvent, as the oligomers become less soluble. The reason for the fast cyclization – even in relatively concentrated solutions – became obvious by the conformational preorganization of the open chain precursors: molecular mechanics calculations indicate that they favour folded structures (Scheme 3) in which the terminal phenyl substituents approach each other. There are two factors responsible for this: in the nonfolded conformers hydrogen bonds between phenolic groups are impossible, *and* there is a repulsive 1,5-interaction between the OH and CH_3-substituents which is relieved in the folded form.

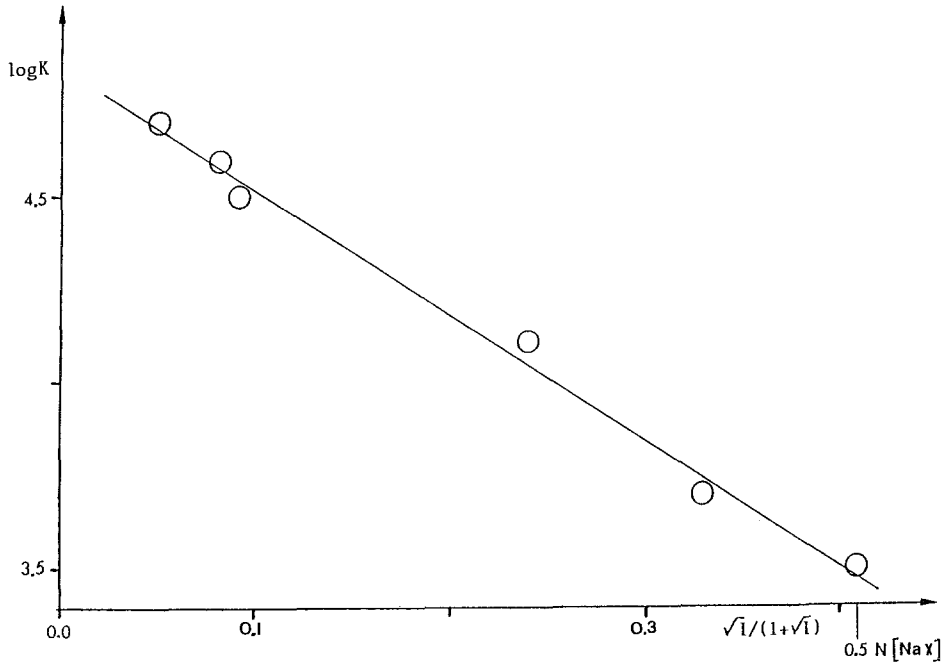


Fig. 1. Equilibrium constants (log K) for **1** + Et_4NBr as function of ionic strength [21].

3. The Basic Skeleton: Conformations and Complexation; An Element of an Allosteric Proton Pump; Choline Binding and Acetlycholine Hydrolysis

In basic solutions **1** forms a stable, calixarene-like "cone" conformation which is still one of the strongest synthetic receptors for choline-type substrates [14, 19], surpassing the natural receptor [19c]. The cavity is quite shallow and the binding free energy ΔG_{cplx} is to 80% due to the formation of four salt bridges; a comparison with a large number of other ion pairs in water [20] showed that this leads to a Coulomb-stabilization of $4 \times 5 = 20$ kJ/mol at low salt concentrations. A comparison with the binding of electroneutral substrates of similar shape such as *tert*-butanol demonstrate that other interactions contribute only about 5 kJ/mol [14]. The ΔG_{cplx} values correlate surprisingly well with Debye–Hückel coefficients of ionic strength (Figure 1) [21]. If the charges are separated by a distance r – as one can study using tetralkylammonium substrates R_4N^+ with different chain length – we see that ΔG_{cplx} decreases as a function of r^{-1}[18]. This is further experimental evidence for dominating Coulomb forces, supported by a realistic dielectric constant obtained from the slope (Figure 2).

A study of the temperature dependence of ΔG shows the binding of choline chloride to be dominated by ΔH (33 kJ/mol), with negligible entropy contributions [22]. The association and dissociation rate constants are, with $k = 2.5 \times 10^8$

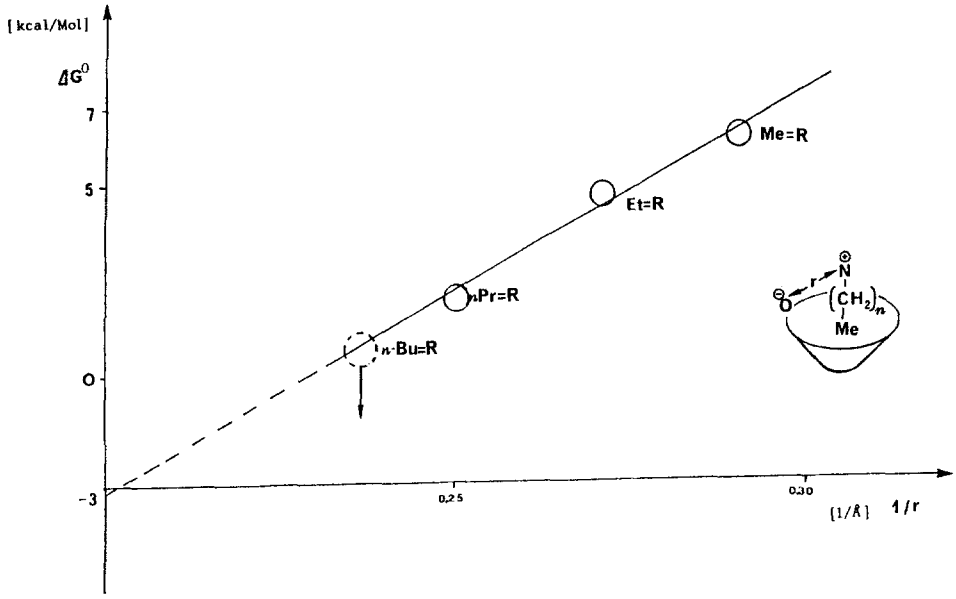
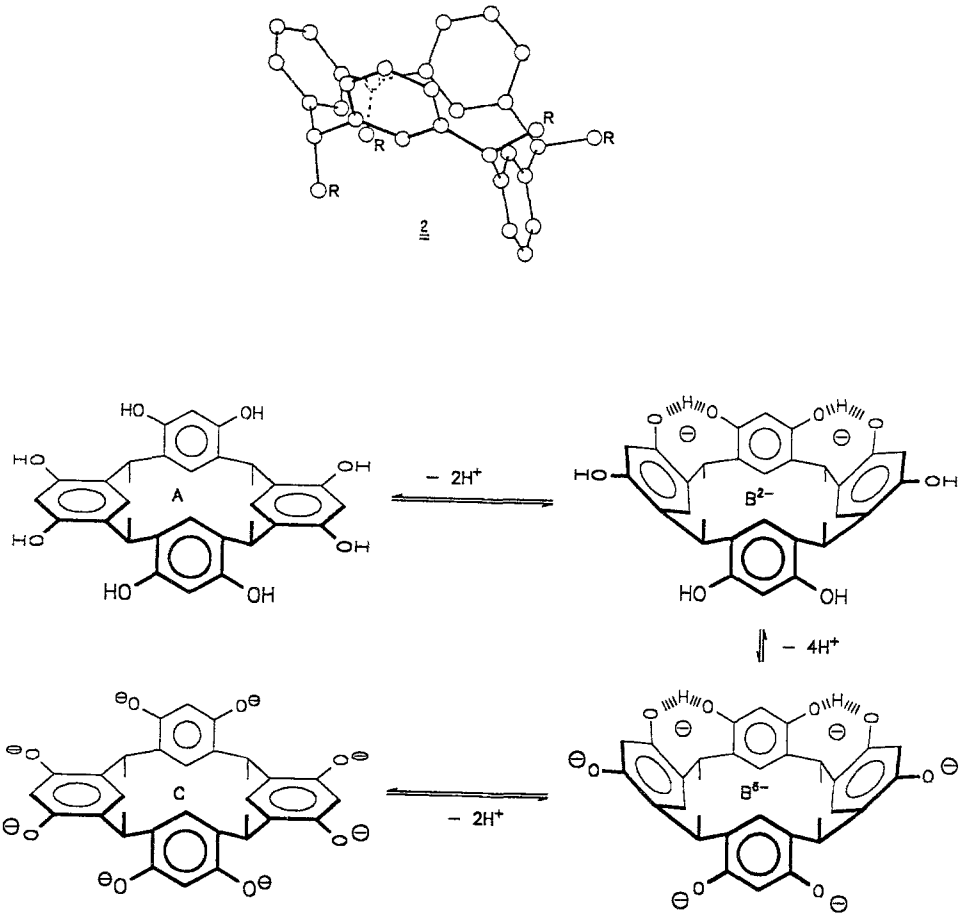


Fig. 2. The dependence of the association free energies between **1** and R_4NCl with R = Me to R = *n*-Bu and the resulting variation of distances r between the charges [18].

$mol^{-1}s^{-1}$, controlled by diffusion, and, with $k = 5 \times 10^3\ s^{-1}$, controlled by the complex stability, respectively, as found by dynamic NMR measurements [18]. *Solvent effects* [21] on the equilibria are characterized by an *increase* of ΔG_{cplx} with increasing water content. This effect, somewhat surprising for an ion pair, is related to the smaller desolvation energy per charge for large organic ions such as $\mathbf{1}^{4-}$ compared to small ions such as bromide, and possibly to still important hydrophobic contributions. Nevertheless, the observed linear correlations with hydrophobicity parameters of binary alcohol-water mixtures exhibit the lowest slope or sensitivity of all host-guest equilibria studied so far, which is in line with particularly strong polar binding contributions here.

The acidities of the phenolic groups in the octol **1** (R = CH_3) reveal the reasons for the particular stabilization of the cone conformation as a consequence of a cyclic hydrogen bonded system (see Scheme 1) with four delocalized negative charges: four protons are dissociating at a pK value *two units below* resorcinol itself, whereas the remaining four cannot be abstracted even by sodium methoxide in methanol solution [18]. The picture changes if phenyl instead of methyl substituents are present (**1**, R = C_6H_5); here one observes slow decomposition in strongly alkaline solutions [22].

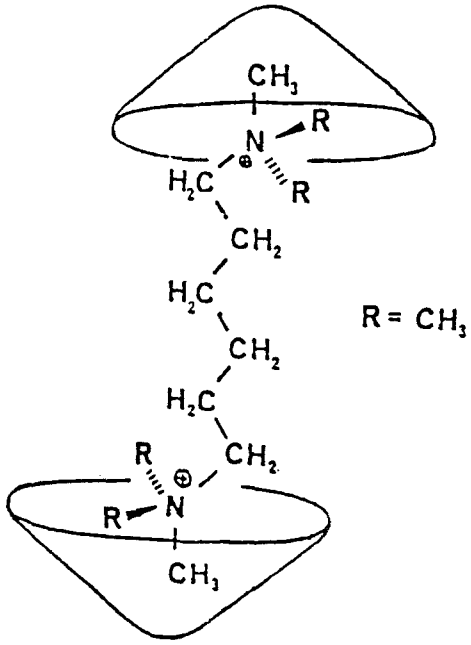
The **rctt** stereoisomer **2** (R = CH_3) shows, in neutral as well as in strongly basic solution, two sets of equally intense ^1H and ^{13}C NMR signals for the phenyl rings, demonstrating slowly interconverting C_{2v} conformations **A** and **C** (Scheme 4). Abstraction of two protons from **A** leads to conformer **B**, which is retained in the



Scheme 4. The **rctt** isomer **2** and its interconversions.

hexaphenolate in more basic solution, before converting to the octaphenolate form **C** after adding more base. The corresponding interconversion from **C** to **B** occurs if instead of sodium hydroxide a methylammonium substrate such as choline is added.

The system represents a very simple allosteric element of a proton pump. The mechanistic origin for the strong conformational coupling between the uptake of protons and of positively charged substrates is the repulsion between the pseudo-axial methyl substituents and either -OH or O^- groups of the two pseudoaxial phenylrings in **B**, which becomes acceptable only if either two hydrogen bonds are formed between the three axial phenol units, or if the system gains energy by the complexation of the $^+NR_4$ substrates. Therefore, this complexation leads to the uptake of protons and *vice versa*. Only the "half-cone" structure **B** can efficiently bind choline; on the other hand the thus enforced vicinity of the neighbouring phenolic groups is stabilized by proton dissociation leading to hydrogen bonds.

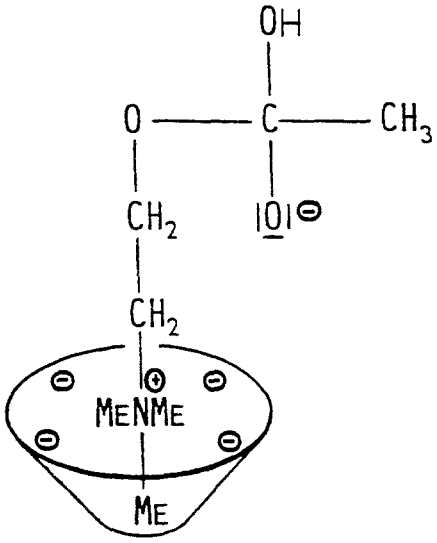


Scheme 5. An illustration of a ditopic complexation of 1,5-bis(trimethylammonium)pentane by the **rccc** isomer **1**.

In contrast to the **rccc** isomer **1**, the addition of sufficient base to the **rctt** isomer **2** leads to the abstraction of *all* eight protons, because again the unfavourable interaction of the axial methyl groups in **2** would be enhanced two times if the last phenyl ring in this "partial cone" conformer **B** turned upwards for the sake of additional hydrogen bonds.

The "cone" conformations for the tetraphenolates **1** were confirmed in solution for R = $CH_3$and R = C_6H_5 by an analysis of the vicinal coupling between C-4 *or* C-5 and H-a. The value of (4 + 0.5) Hz for *both* couplings and *both* derivatives indicate angles which are similar and around 25° or 150°, in agreement with force field modelled geometries [22]. The tetraphenolate **1** binds not only ammonium compounds but also, e.g., phosphonium derivatives with the same high affinity of about 25 kJ/mol as long as there is at least one methyl group on the onium center.

Ditopic onium derivatives are, as expected, complexed twice at the two ends (Scheme 5), with negligible weakening of ΔG at the second binding site. The complexation of choline is so strong that significant retardation is observed for the hydrolysis of acetylcholine. The kinetically derived inhibition constant is close to the spectrocopically determined thermodynamic equilibrium value [23]. This rarely



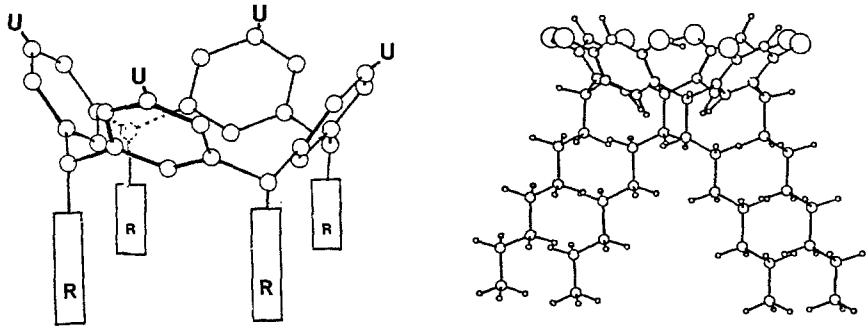
Scheme 6. A transition state model for the hydrolysis of acetylcholine; the normal stabilization by attraction between the N^+ and the O^- charges is diminished by the four negative charges of receptor $\mathbf{1}^{4-}$ with a subsequent lower hydrolysis rate.

observed reaction retardation, not to be confused with the much more frequent inhibition of a catalyst, is based on the diminuition of the activating effect of the $^+NMe_4$ charge on the ester group by the four-fold negative charge of the receptor $\mathbf{1}^{4-}$ (Scheme 6).

4. Substitution at the Bottom: A Second, Lipophilic Binding Site

The condensation of resorcinol with "longer" aldehydes than acetaldehyde provides a convenient entry to the construction of narrow lipophilic binding centers at the bottom of the **rccc** isomer **1**. Benzaldehyde furnishes only a weak complexer even for small substrates like acetonitrile [24] or diethylether, and an intracavity-inclusion is not proven here. Phenyl rings directly attached at the bottom of **1** do not leave enough space, as is evident also from molecular models; even with the 4-phenyl-benzaldehyde product (R = biphenyl) we detect no measurable NMR shift changes upon the addition of e.g. benzylalcohol [22]. In contrast, more flexible bottom substituents R leave enough room (Scheme 7) and several lipophilic substrates are efficiently bound (Scheme 8).

As expected from the conformationally mobile sidechains and the predominantly lipophilic and/or hydrophobic binding mechanism there is relatively little selectivity, apart from an increase of ΔG with increasing lipophilicity of the substrate. Nevertheless, this is probably the *first* host system for which the inclusion of open chain substrates like diethylether has been proven by NMR shielding variations [22]. NMR measurements at host concentrations between 5×10^{-2} M^{-1} and



Scheme 7. The structures of the **rccc** isomer with substituents R at the bottom (QUANTA /CHARMm simulation for R = C_7H_{15}).

R = →	$-(CH_2)_5CH_3$	$-(CH_2)_{11}CH_3$	$-CH_2-C_6H_5$
$(CH_3CH_2)_2O$	9.9	10.1	9.7
$C_6H_5-CH_2OH$	8.4	9.7	5.7
$C_6H_5-(CH_2)_3OH$	15.7		9.7

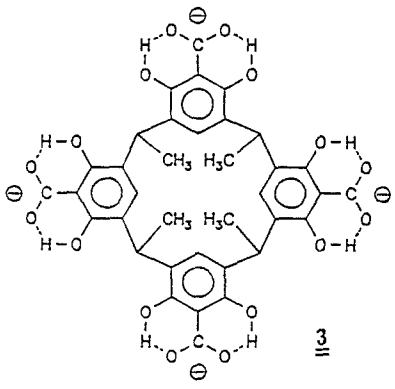
Scheme 8. Complexation free energies ΔG [kJ mol^{-1}] for the bottom-substituted **rccc** isomers with different substituents R and different substrates.

$8 \times 10^{-5}\ M^{-1}$ showed no evidence for micelle formation. The upper binding site of host **1** is not involved in the complexation, as is evident from a separate experiment in which the binding of diethylether in the presence of tetramethylammonium salt was measured and found to be the *same* as without the occupied upper site. This shows that there is no cooperativity in these ditopic receptors.

5. Substitution at C-2: the Upper Rim

5.1. Alternating Tetracarboxylate Conformations/Salt Bridges

The **rccc** isomer with four carboxylic acid functional groups at C-2 is unable to form a cone-like tetraphenolate **1** as all phenolic groups are involved in hydrogen bonding to the disssociated carboxylates. This is anolgous to the behaviour of salicylic acid, and the pK value measured for **3** is indeed similar to that of salicylic acid. The NMR spectrum of **3**, which above pH 5 is present as a tetraanion, shows



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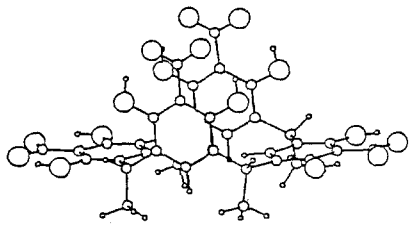
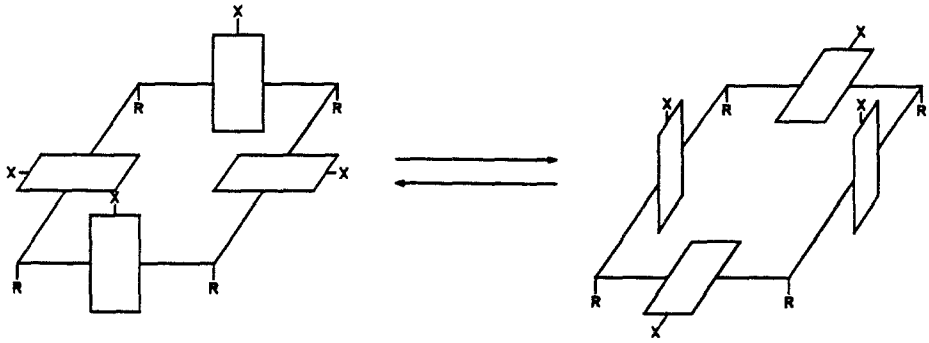
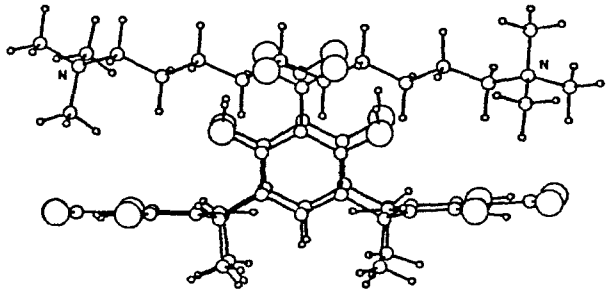




Scheme 9. The **rccc** isomer with four carboxylic substituents at C-2.

at, e.g. 270 K, two sets of equally intense phenyl protons, which coalesce at 293 K (400 MHz ^{1}H-NMR). This indicates an equilibrium of pseudorotating conformers with alternate equatorial and axial phenyl rings (Scheme 9), interconverting with a barrier of $\Delta G^* = 72$ kJ/mol. This value, measured in water, comes close to the pseudorotation barrier of $\Delta G = 60$ kJ/mol observed by Högberg [6a] for the butyrates of **1** in chloroform.

The tetrabenzoate host **3** can bind ammonium ions either by a double salt bridge from one onium center to two opposing axial benzoate units (with tetramethylammonium salts), or with α,ω-diammonium-alkanes, to the pseudoequatorial benzoate functionalities with one salt bridge at each end. A maximum ΔG is found if the alkane chain length matches approximately the distance between the two eq. COO^- groups (Scheme 10). However, whereas the complexation with the small cation $^+NMe_4$ corresponds exactly to the general [20] increment of 5 kJ/mol per salt bridge, the α,ω-alkyldications show additional stabilization (Scheme 10). Molecular modelling indicates that this may be the result of a contact between the



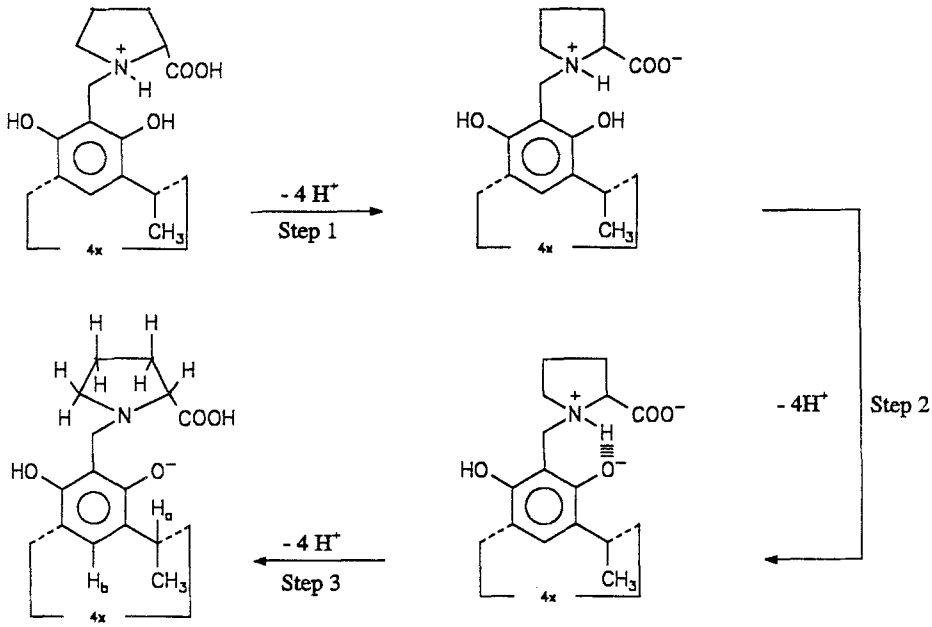
Substrates	d [Å]	$-\Delta G$ [kJ · mol^{-1}]
$Me_4\ N^{\oplus}$ *0.3*		11.6
$Me_3\ N^{\oplus}$ *0.6* — *0.5* — *0.5* — $N^{\oplus}\ Me_3$	5.5	12.0
$Me_3\ N^{\oplus}$ *0.4* — *0.8* — *1.0* — *1.4* — $N^{\oplus}\ Me_3$	9.9	16.0
$Me_3\ N^{\oplus}$ *0.3* — *1.0* — *1.3* — *0.9* — *0.9–1.2* — *0.9–1.2* — $N^{\oplus}\ Me_3$	14.6	14.7

Scheme 10. QUANTA/CHARMm simulation of the complex **3** + Me_3N-$(CH_2)_{10}NMe_3$ and complexation free energies [kJ/mol] of **3** with substrates of different chainlength. Complexation induced NMR shifts (all upfield CIS, in [ppm]) are in *italics*.

pseudoaxial phenylrings and the alkane chain; the observed complexation-induced NMR shifts support this (Scheme 10).

5.2. Cationic Substituents at C-2/Aminoacids and Metal Complexes

A large number of amino-methylsubstituents were introduced by the Mannich reaction which works as smoothly with the resorcinarene **1** as it had been reported for calixarenes [25]. From the eight aminoderivatives thus prepared and investigated [22] we restrict ourselves here to the L-proline compound **4** which was obtained without any racemization. The system can adopt four different protonation states (Scheme 11) which were all characterized. Computer-aided potentiometric titrations yielded the relevant pK values with an average error of +0.2 units, with excellent fits assuming the same value for the different independently treated phenyl units in the macrocycle. ^{1}H-NMR titrations allowed the different steps as shown in Scheme 12 to be identified. Due to the betaine formation the pK of the



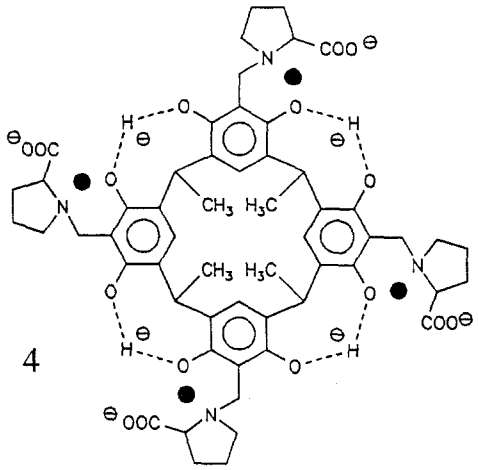
Scheme 11. The protonation steps for the proline-substituted macrocycle **4.**

	pK_S - Values		
Dissociating Group	**4**	Resorcinol	Proline
COOH	1.8	--	1.9
OH	6.3	9.9	--
NH	13.0	--	10.8

Scheme 12. Comparison of pK values of **4** , resorcinol, and proline.

carboxylic group is as low as in proline itself; the basicity of the nitrogen, however, is even higher as a result of the extra-stabilization by the negative phenolate charge. Acidity increases by the presence of additional proton donors, such as for **1** or **4** in comparison to resorcinol alone, have been reported also for structurally related calixarenes [26].

Although the macrocycle **4** contains four chiral units in a well ordered arrangement, all attempts to discriminate between enantiomers of racemic substrates bearing suitable charges, such as D,L-carnitine, ephidrinium or 1-phenylethylammonium bromides failed: even at 400 MHz the ^{1}H-NMR spectra showed no line splitting of the quite stable (usually $K>10^3\ M^{-1}$) complexes with **4** in water. This is consistent with the complexation free energies observed with many alkylamino-analogs to **4**, where the presence of additional charges such as in the piperazine derivative **5** showed little changes compared to the unsubstituted ring **1**. In general accordance



4

● : Cu^{2+}

pK values for Cu^{2+} -complexes:

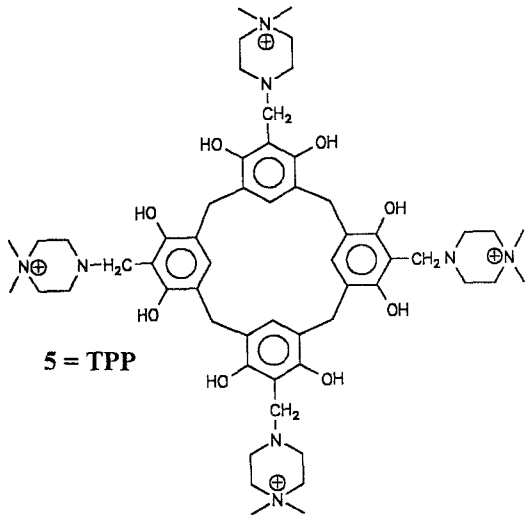
with 4:	15.0
with proline:	9.0

Scheme 13. Structure and binding pK values for the complex **4** with copper(II) ions.

with the observed NMR shifts the substituents point away from the cavity and the substrate binding center; in particular, if they can expose in this way an additional charge to the aqueous environment.

One of the attractive features of the aminoacid-substituted macrocycles is the possibility to provide strong and chiral binding elements for transition metal ions. Potentiometric titrations with **4** showed a stability increase from Zn^{2+} to Cu^{2+} to Fe^{3+}, similar to the parent aminoacid complexes [27]. However, the stabilities themselves are considerably increased, e.g. with Cu^{2+} by six units (Scheme 13). This is the result of the additional Coulomb attraction by the phenolate (half)-anions in the macrocycle, leading to four independent strong tridentate binding sites. Attempts to use transition metal ions implemented in the macrocycle for the catalysis of acetylcholine hydrolysis showed moderate success, consisting essentially in the removal of the inhibition discussed above for bound acetylcholine.

Finally, we discuss briefly the first attempts to use resorcinarenes as ligands for double-stranded DNA. The piperazinium-derivative **5** seems to be a particular attractive species in view of the extended array of positive charges for groove binding and the aryl units which may lend themselves to intercalation. Preliminary investigations (B. Palm, [28]) show only slight increases of viscosity and *no* NMR upfield shifts of any ligand signals, ruling out intercalative mechanisms. Both fluorescence binding assays and the melting point increases are similar to those observed with several azoniacyclophanes which also bear four ammonium groups in a macrocycle. The latter have been shown to fit into a regular affinity scheme of polyamine groove binders [29], characterized again by a salt bridge increment value of 4–6 kJ/mol.



Experiments with Calf Thymus DNA; MWav $9*10^6$

A: Affinity (assay with Ethidiumbromide); $1/C_{50}$ = A

ΔT_M: Melting point changes (with 10^{-6} M Ligand)

Ligand	$A*10^{-6}$	ΔT_M
TPPi	**0.8**	**1.6**
CP66	0.7	3.0
CP55	0.11	1.4
CP44	3.7	5.1
CP33	0.14	2.2
$+N_4$-open chain-av.	0.5	5-10

No intercalation: a) NMR $\Delta\vartheta < 0.1$ ppm

b)Viscosity increase too small (L/Lo = 0.95 to 1.05 with intercalator ≥ 1.15)

Scheme 14. Binding of the resorcarene **5** to **DNA**.

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