81. Mimicking the Vancomycin Carboxylate Binding Site: Synthetic Receptors for Sulfonates, Carboxylates, and *N*-Protected α-Amino Acids in Water

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The novel H_2O-soluble cyclophanes **1** and **2** incorporating different anion-recognition sites were prepared in short synthetic routes (*Schemes 1* and *2*) as first-generation mimics of the natural, D-Ala-D-Ala binding antibiotic vancomycin. The X-ray crystal structure of **1**, a tris(hydrochloride)salt, revealed an open, preorganized cavity of sufficient size for the incorporation of small aliphatic residues (*Fig. 3*). In the crystal, molecules of **1** are arranged in parallel stacks, generating two types of channels, an 'intra-stack' channel passing through the cyclophane cavities and an 'inter-stack' channel located between cyclophane stacks (*Fig. 4*). The strongest intermolecular interactions between macrocycles in the crystal are C=O···H–N H-bonds between the carboxamide residues of adjacent cyclophanes in neighboring stacks (*Fig. 5*). The 'intra-' and 'inter-stack' channels incorporate the three ordered Cl^- counterions and several, partially ordered solvent molecules (4 MeOH, 1 H_2O) (*Fig. 6*). Counterion Cl(2) is located within the 'intra-stack' channel and interacts with a protonated piperazinium N-atom and both 'intra-stack' MeOH molecules. The two other counterions, Cl(1) and Cl(3), are located within the 'inter-stack' channel. They are connected to two MeOH and one H_2O molecules and also interact both with the NH_2^+ group of the protonated spiropiperidinium ring in **1**, forming an infinite, chain-like H-bonding network ···Cl(1)···HOH···MeOH···Cl(3)···HNH···Cl(1')···. Both 'intra-' and 'inter-stack' MeOH molecules undergo weak CH···π interactions with neighboring aromatic rings. Cyclophane **1** complexed aromatic sulfonates in 0.5M KCl/DCl buffer in D_2O, whereas the tetrakis(quaternary ammonium) receptor **2** bound the sodium salts of aliphatic and aromatic carboxylates and sulfonates, of *N*-acylated α-amino acids as well as of *N*-acetyl-D-alanyl-D-alanine (Ac-D-Ala-D-Ala), a substrate of vancomycin, in pure H_2O. In all of these complexes, ion pairing between the cationic recognition site in the periphery of the cyclophane receptor and the anionic substrates represents the major driving force for host-guest association. The ^{1}H-NMR analysis of complexation-induced changes in chemical shift clearly demonstrated that, in solution, this ion pairing exclusively takes place outside the cavity. Nevertheless, the macrocyclic bridges are essential for the efficiency of the anion-recognition sites in the two cyclophane receptors **1** and **2**. Control compounds **3** and **4** possess nearly the same anion-recognition sites than **1** and **2**, but lack their macrocyclic preorganization; as a consequence, they do not form stable ion-pairing complexes with mono-anionic substrates in the considered concentration ranges (< 50 mM) in D_2O.

1. Introduction. – Binding of small polar molecules such as α-amino acids or small peptides by synthetic receptors in H_2O poses a particular challenge since the small area of their apolar surfaces limits the extent of dispersion forces and hydrophobic desolvation, which are the major driving forces for complexation in aqueous solution. Biological receptors have evolved to accomplish this task, and one prominent example is the natural antibiotic vancomycin [1–3], a glycoheptapeptide with a molecular weight of 1431 D that strongly binds *N*-acetyl-D-alanyl-D-alanine (Ac-D-Ala-D-Ala) in H_2O ($K_a = 3.6 \cdot 10^4$ l mol^{-1}; $\Delta G^\circ = -6.3$ kcal mol^{-1}, 20 mM aqueous citrate buffer, pH 5.1, 298 K) [4]. In this complex, the terminal carboxylate of the substrate forms three ionic H-bonds to NH groups of the peptidic receptor backbone and participates in additional ion pairing with the protonated *N*-methylamino terminus of the antibiotic [5] (*Fig. 1*). Three cyclophane-

type macrocyclic substructures in vancomycin provide a high degree of preorganization to the peptidic backbone and stabilize the complex by apolar interactions (dispersion interactions and hydrophobic desolvation) with the Me groups of the substrate [6] [7]. The complex is further stabilized by additional H-bonds between amide groups of the substrate and the vancomycin backbone [8]. A complete understanding of the extraordinarily strong complexation between vancomycin and Ac-D-Ala-D-Ala in H_2O is a highly desirable objective, since it could greatly enhance the currently poorly developed ability of chemists to design efficient synthetic receptors for the recognition of small polar molecules in H_2O. We intended to contribute to such understanding by model studies [9] [10] which, in a first step, should mimic the carboxylate binding site of the natural antibiotic.

Whereas a great diversity of receptors forms complexes with carboxylic acids [11] and derivatives of α-amino acids [12] [13] in noncompetitive solvents such as $CHCl_3$, only a small number of synthetic hosts is capable of binding these substrates in H_2O, which strongly solvates the H-bonding and charged sites of the interacting partners [14]. A variety of macrocyclic polyammonium receptors is known to complex aromatic and aliphatic carboxylates in H_2O [15–17]. At comparable steric host-guest complementarity, polycarboxylates are generally much better bound than monocarboxylates, which usually only form weak complexes. Only a few reports describe the complexation of α-amino acids, small peptides, and their *N*-functionalized derivatives in competitive, protic solvent environments [18].

Here, we describe the synthesis and binding properties of the polyammonium cyclophanes **1** and **2** [19a] which were designed for the complexation of aromatic and aliphatic carboxylates as well as *N*-protected α-amino acids and small peptides in H_2O. The potential carboxylate-binding site in cyclophane **1** consists of a doubly protonated

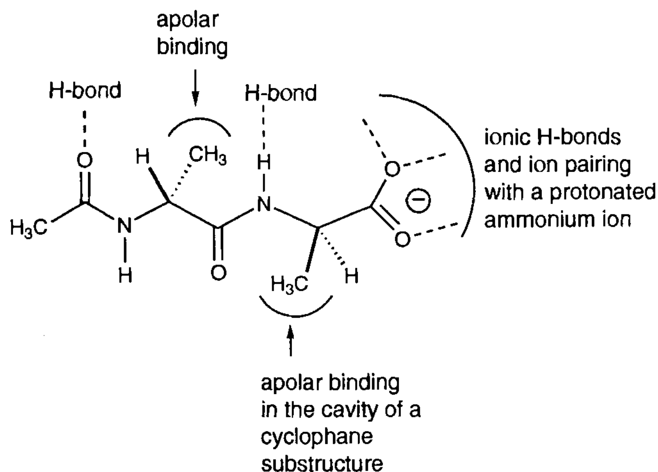
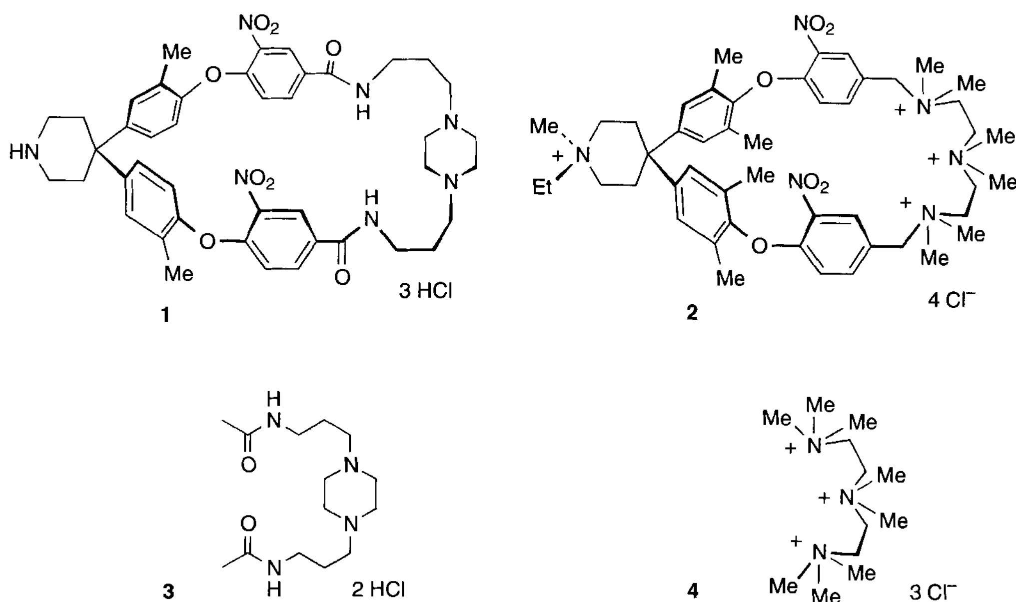


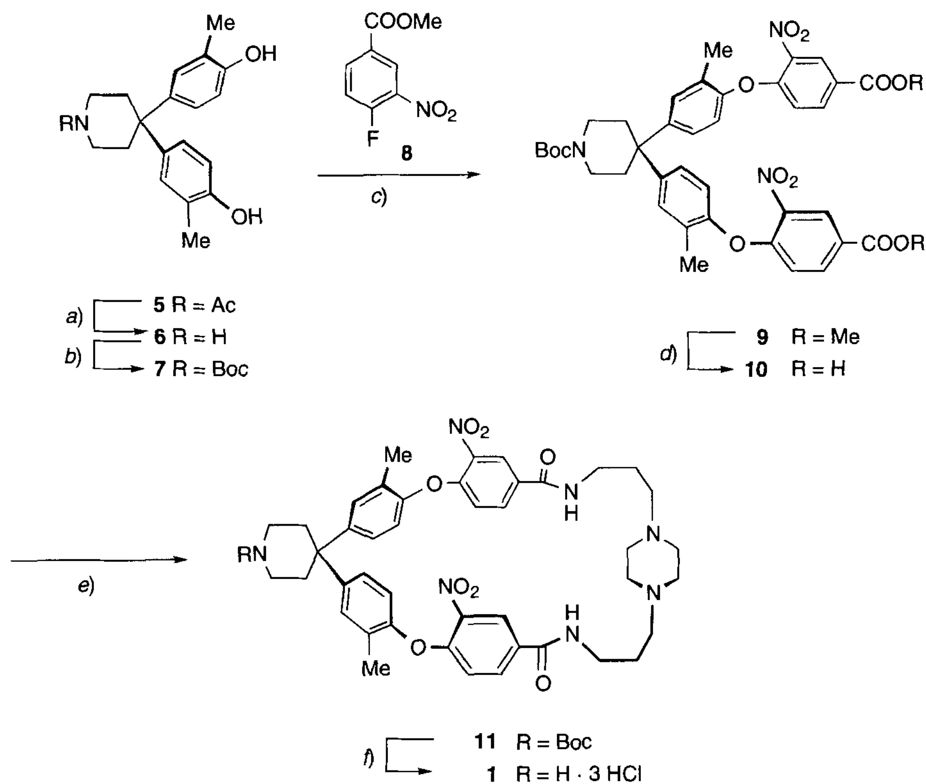
Fig. 1. *Schematic illustration of the intermolecular interactions seen in the complex of Ac-D-Ala-D-Ala with the antibiotic vancomycin* [1–3] [5–7]

piperazinium moiety and two amide H-bonding donor centers, whereas the corresponding recognition site in **2** is formed by three adjacent quaternary ammonium ions. In analogy to vancomycin, the carboxylate-binding sites in **1** and **2** are preorganized through their incorporation into a cyclophane structure. It was of particular interest to explore, in comparative binding studies with model compounds such as **3** and **4** [20], to which extent the hydrophobic cavities shaped by the two diaryl-ether moieties in **1** and **2** would provide additional stability to the formed complexes. Cyclophanes **1** and **2** contain two NO_2 groups which, after successful demonstration of their carboxylate-binding properties, could be reduced to amino groups and thus provide anchors for further construction and extension of the recognition site.



2. Results and Discussion. – 2.1. *Synthesis of Cyclophanes* **1** *and* **2**. The synthesis of **1** (*Scheme 1*) started with bisphenol **5** [19b] which was hydrolyzed to **6** and transformed into the *tert*-butoxycarbonyl(Boc)-protected [21] derivative **7**. Nucleophilic aromatic substitution of **7** with aryl fluoride **8** (2 equiv.) gave bis(diaryl ether) **9**. The highest yields of **9** were obtained when the reaction was performed with K_2CO_3 as base in *N,N*-dimethylformamide (DMF) [22] rather than with KF · Al_2O_3 in MeCN [23]. Hydrolysis of **9** gave dicarboxylic acid **10** which was cyclized with piperazine-1,4-dipropanamine in the presence of diphenylphosphoryl azide (DPPA) [24] under high-dilution conditions to give cyclophane **11** in 32% yield. We found this macrocyclization to work with a variety of other primary α,ω-diamines [25], whereas the use of another coupling reagent such as 2-chloro-*N*-methylpyridinium iodide [26] or conversions with activated esters of **10** [27]

Scheme 1. *Synthesis of Cyclophane* **1**



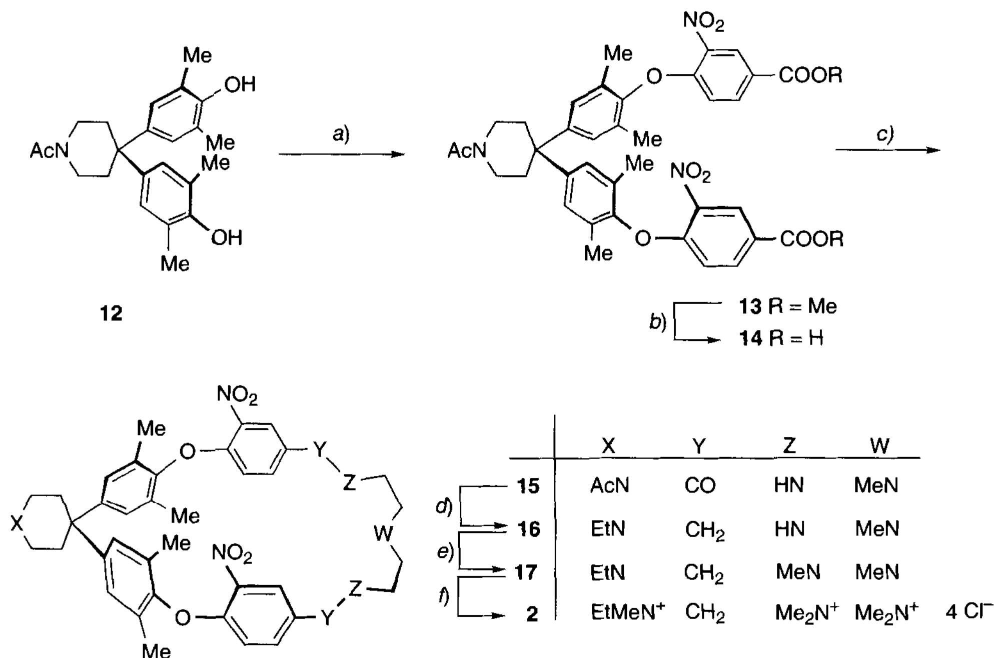
a) NaOH, reflux, 8 h. *b*) $(Boc)_2O$, NaOH, r.t., 4 h; 71% (from **5**). *c*) **8** (2 equiv.), DMF, K_2CO_3, r.t., 14 h; 76%. *d*) KOH, H_2O/MeOH/THF 1:1:1, r.t., 4 h; 98%. *e*) Piperazine-1,4-dipropanamine, DPPA, DMF, Et_3N, high dilution, r.t., 24 h; 32% (from **10**). *f*) HCl (g), MeOH, r.t., 14 h; 98%.

or the corresponding bis(acyl chloride) [28] either failed or gave unreliable results. Deprotection of **11** afforded target compound **1** which was characterized and stored as the hygroscopic tris(hydrochloride)salt.

For the preparation of cyclophane **2** (*Scheme 2*), diol **12** was transformed into bis(diaryl ether) **13** which was hydrolyzed to the cyclization component **14**. Macrocyclization of dicarboxylic acid **14** with *N*-(2-aminoethyl)-*N'*-methylethane-1,2-diamine in the presence of DPPA gave **15** which was reduced with $BH_3 \cdot SMe_2$ [29] to tetramine **16**. *Eschweiler-Clarke* methylation [19b] [30] to **17** followed by quaternization with methyl trifluoromethanesulfonate [19b] [31] and ion-exchange chromatography (Cl^-) yielded the hygroscopic tetrakis(quaternary ammonium) salt **2**.

2.2. *Structural Analysis of Cyclophanes* **1** *and* **2**. Whereas all attempts to grow larger crystals of **2** remained unsuccessful, crystallization of cyclophane **1** from aqueous MeOH yielded platelets suitable for an X-ray structural analysis which was performed at 193 K

Scheme 2. *Synthesis of Cyclophane* **2**



	X	Y	Z	W	
15	AcN	CO	HN	MeN	
16	EtN	CH_2	HN	MeN	
17	EtN	CH_2	MeN	MeN	
2	$EtMeN^+$	CH_2	Me_2N^+	Me_2N^+	4 Cl^-

a) **8** (2 equiv.), K_2CO_3, DMF, r.t., 14 h; 78%. *b*) KOH, H_2O/MeOH/THF 1:1:1, r.t., 4 h. *c*) *N*-(2-aminoethyl)-*N'*-methylethane-1,2-diamine, DPPA, Et_3N, DMF, high dilution, r.t., 24 h; 43% (from **13**). *d*) $BH_3 \cdot SMe_2$, r.t., 72 h; 52%. *e*) HCHO, HCOOH, 100°, 24 h; 92%. *f*) $MeOSO_2CF_3$, $CHCl_3$, sealed vessel, 80°, 8 h; then *Dowex 50W* × *2* (Cl^-); 41%.

(see *Exper. Part*). The crystals contained, besides triprotonated cyclophane **1** and its three Cl^- counterions, 4 equiv. of MeOH and 1 equiv. of H_2O.

In the crystal, **1** displays a rectangularly shaped cavity with an open space of *ca.* 6.1 × 4.1 Å (*Figs. 2* and *3*). This open space is created by a nearly cofacial alignment of the two nitrophenylene moieties. These rings intersect the molecular plane in **1**, defined by C(5), O(16), O(37), and C(47), at angles of 121.3° (ring bearing N(44)) and 123.3° (ring bearing N(13)) (see *Fig. 2*). In contrast, the two phenylene moieties of the 4,4-di(phenylene)piperidinium unit differ strongly in their contribution to the preorganization of an open-cavity binding site. Whereas the ring bearing the Me(23) group is turned into the cavity (dihedral angle C(30)–C(24)–C(20)–C(21) = −10.0°), thus reducing its size, the second ring bearing the Me(36) group adopts a dihedral angle C(31)–C(30)–C(24)–C(20) of 106.8° and keeps the cavity open. The dihedral angle of −10.0° is unusually small; previous X-ray crystal structures all revealed values between 70° and 110° for corresponding dihedral angles in other cyclophanes shaped by 4,4-di(phenylene)piperidinium moieties [32]. At an angle C(20)–C(24)–C(30) of 110.0°, the distance between the O-atoms O(16) and O(37) attached to the 4,4-

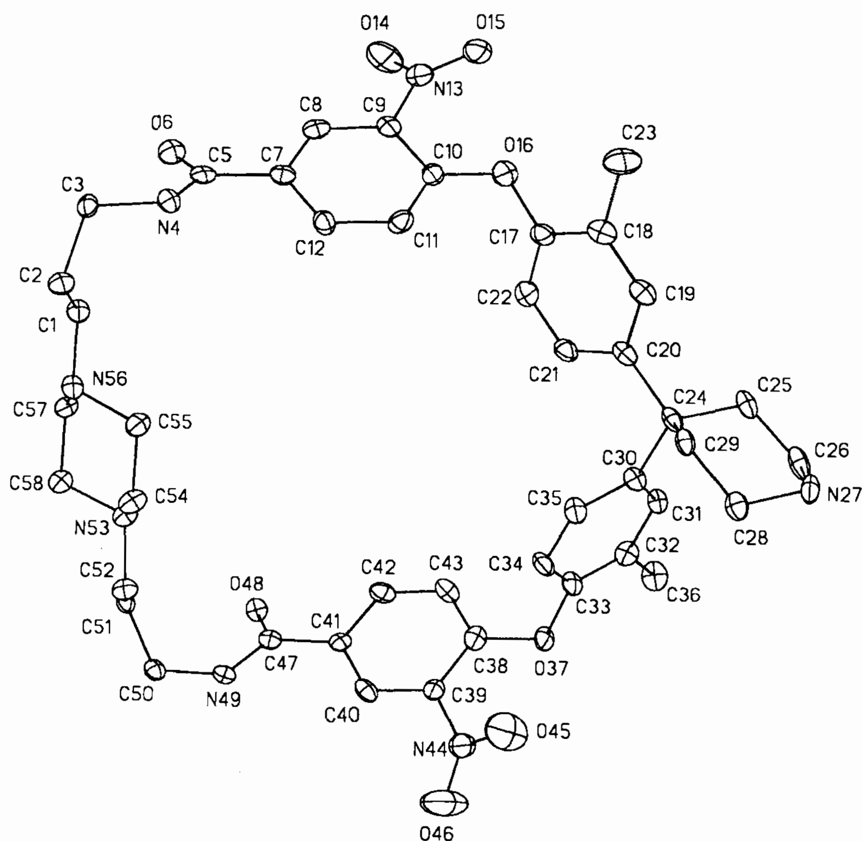


Fig. 2. *Crystal structure of* **1**. Arbitrary numbering. Vibrational ellipsoids are shown at the 30% probability level. Solvent molecules included in the crystal (4 MeOH, 1 H_2O) are omitted for clarity.

di(phenylene)piperidinium moiety amounts to 9.56 Å. Characteristic distances between C-atoms of the parallel nitrophenylene moieties are 9.63 Å (C(10)···C(38)) and 10.03 Å (C(7)···C(41)); selected distances between C-atoms of the piperazinium chair and phenylene C-atoms of the opposite 4,4-di(phenylene)piperidinium spacer are 11.16 Å (C(57)···C(21)) and 10.03 Å (C(58)···C(21)), respectively.

Stacks of cyclophanes **1** form infinite molecular channels in the crystal (*Fig. 4*). This interesting arrangement is not primarily stabilized by contacts between neighboring cyclophanes within a stack: all intermolecular distances between aromatic C-atoms in a stack are longer than 7.3 Å, and short 'intra-stack' contacts are only observed between aromatic CH and NO_2 residues of neighboring macrocycles (distances C(43′)···O(46)NO 2.99 Å, angle C–H···O 123.0° and distance C(11′)···O(14)NO 3.16 Å angle C–H···O 124.0°). A larger energetic contribution to the stability of the observed molecular packing arises from H-bonding between the CONH residues of adjacent

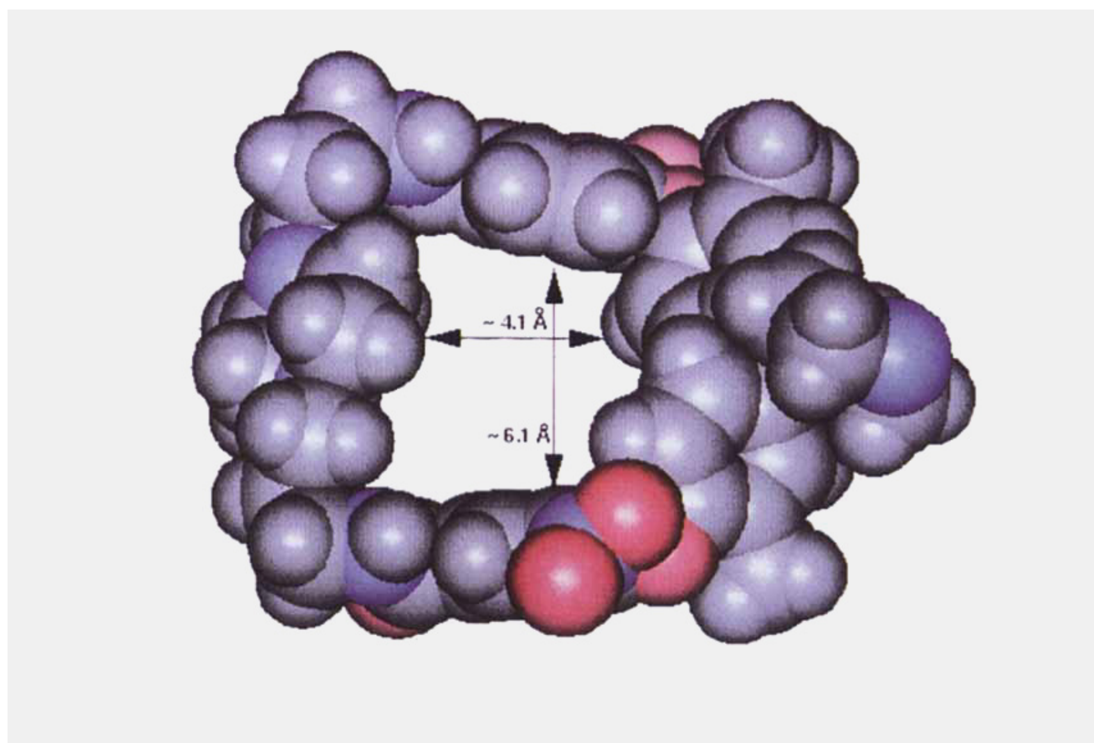


Fig. 3. *Space-filling representation of the molecular structure of* **1** *in the crystal showing the free space in the cavity*

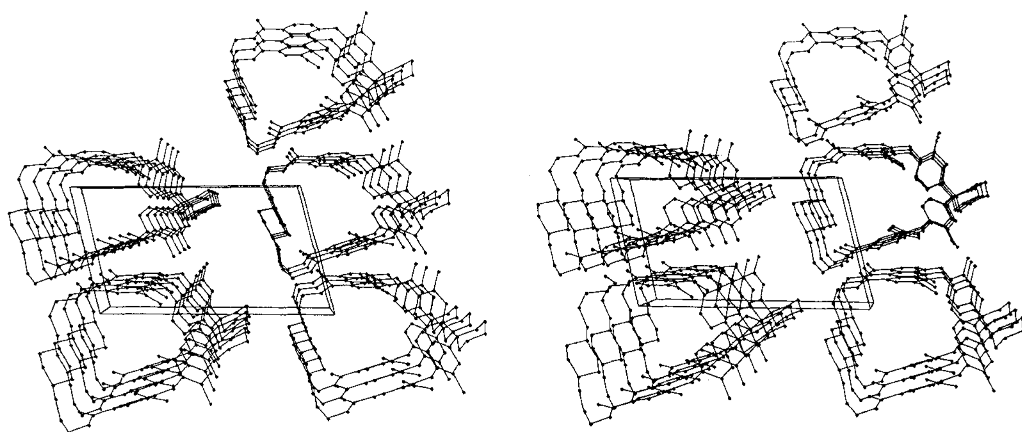


Fig. 4. *Stereoview of the crystal packing of* **1** *along the* a-*axis showing infinite cyclophane channels*. Solvent molecules are omitted for clarity.

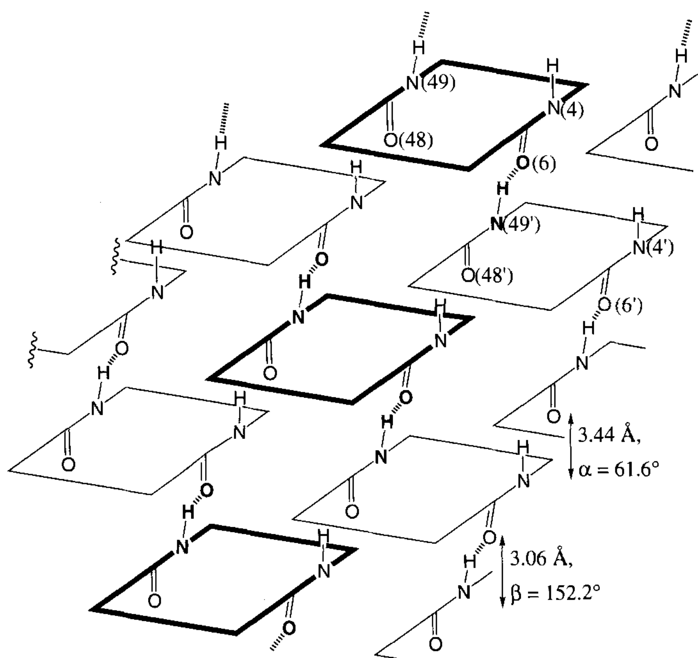


Fig. 5. *Schematic representation of the C=O···H–N interactions between adjacent cyclophane moieties in the crystal of* **1**

cyclophanes in neighboring stacks (*Fig. 5*) [33]. Each macrocycle is linked, *via* two short N–H···O=C H-bonds (distance O(6)···N(49′) 3.06 Å, angle O···H–N 152.2°) to two other adjacent macrocycles located above and below in two neighboring stacks. Two additional contacts between carboxamides of adjacent cyclophanes in neighboring stacks are observed (distance O(48)···N(4′) 3.44 Å) although, at an O···H–N angle of 61.6°, they should be considered as favorable dipolar interactions rather than true H-bonds.

Ion pairing between the three protonated ammonium centers in **1** and the three Cl^- counterions as well as ionic H-bonding between these charged centers and the five included solvent molecules certainly make significant contributions to the stability of the observed solid-state structure. Crystals of **1** are indeed only stable in the presence of solvent which is included in the lattice in a partially ordered form. Three different counterion sites are distinguishable (*Fig. 6*). One chloride ion, Cl(2), is bound between two macrocycles within a stack; in *Fig. 6* it is located slightly below the mean molecular plane of the cyclophane molecule shown on the right. It forms H-bonds to MeOH(1) (distance Cl(2)···O 2.96 Å), which is also located slightly below the macrocycle, and MeOH(2) (distance Cl(2)···O 3.08 Å), which is positioned on the mean molecular plane (see also [34]). In addition, Cl(2) undergoes weak ion pairing with the protonated piperazinium N(53)-atom (distance N(53)···C(2) 3.28 Å). The two 'intra-stack' solvent molecules undergo several interactions with the cyclophane molecule: MeOH(1) forms an

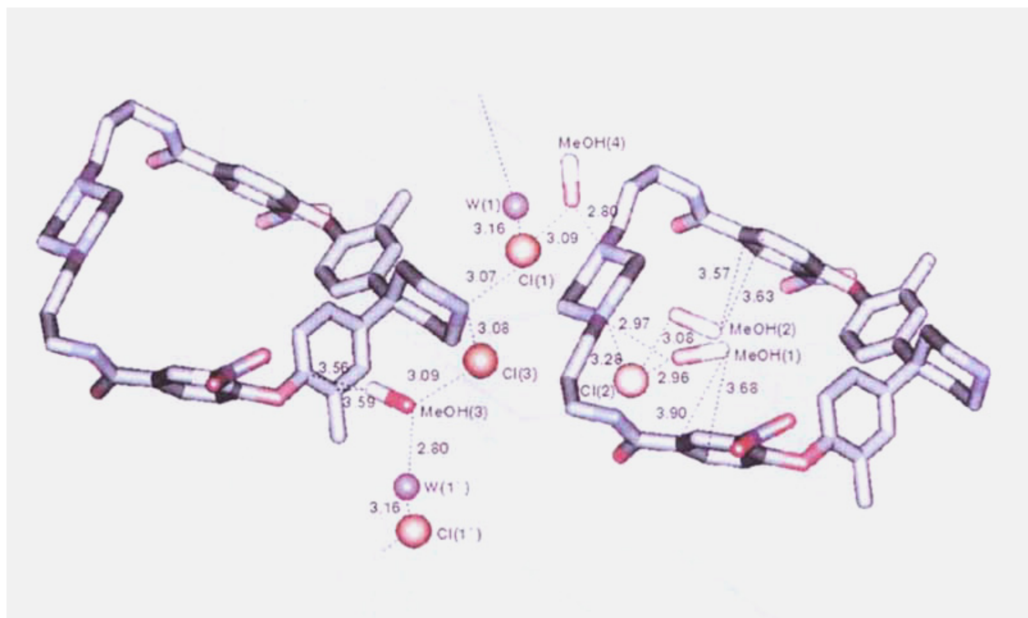


Fig. 6. *View of the three distinct Cl^- counterion recognition sites in the crystal of* **1**. The Cl^- ions interact with neighboring protonated ammonium centers of molecules **1** and four partially ordered MeOH molecules, and one H_2O molecule. The two counterions Cl(1) and Cl(3) outside the cavity participate in a chain-like, infinite H-bonding network.

O···H–N$^+$ H-bond to the axially protonated piperazinium N(53)-atom (distance N(53)···O 2.97 Å). In addition, the Me groups of MeOH(1) and MeOH(2) display multiple, although not very short, C–H···π contacts to the neighboring nitrophenylene moieties (distances HOH_2C–H···C(arom.) *ca.* 3.6–3.9 Å; see also [35]).

The two 'inter-stack' chloride ions Cl(1) and Cl(3) participate in a fascinating chain-type H-bonding network ···Cl(1')···HOH(1')···MeOH(3)···Cl(3)···HN(27')H···Cl(1')··· approximately along the *b*-axis (*Fig. 6*). In detail, both Cl(1) and Cl(3) participate in partially ionic H-bonds to the protonated H_2N^+(27') center of the spiropiperidinium ring (distances Cl(1)···N(27') 3.07 Å and Cl(3)···N(27') 3.08 Å). In addition, Cl(1) accepts H-bonds from H_2O(1) (distance Cl(1)···O 3.16 Å) and MeOH(4) (distance Cl(1)···O 3.09 Å). With its O-atom, the latter solvent molecule participates in another short ionic H-bond with the axially protonated piperazinium N(56) atom (distance N(56)···O 2.80 Å). H-Bonding arrays similar to that observed between the protonated piperazinium N(56) atom, MeOH(4), and counterion Cl(1) have been previously described [36].

The second 'inter-stack' chloride ion Cl(3) forms a H-bond to MeOH(3) (distance Cl(3)···O 3.09 Å). The infinite H-bonding chain is concluded by a short H-bond between the MeOH(3) acceptor and the H_2O(1') donor (distance O···O 2.80 Å). MeOH(3) also exhibits relatively short C–H···π contacts to one of the phenylene moieties of the 4,4-di(phenylene)piperidinium moiety of an adjacent macrocycle.

As described, the 'inter-stack' solvent molecules MeOH(3) and MeOH(4) are involved in an extensive H-bonding network. In comparison, the 'intra-stack' molecules MeOH(1) and MeOH(2) are less strongly bound. The larger atomic displacement parameters observed for MeOH(1) and MeOH(2) also point in this direction.

Based on these X-ray structural data, we expected that **1** would have a cavity of sufficient size and preorganization for full inclusion of small aliphatic carboxylates. However, Monte-Carlo multiple minimum searches (1000 steps) using the AMBER* force field and the volume-based continuum model (GB/SA) for H_2O, as implemented in MacroModel V. 5.0 [37], demonstrated a significant flexibility of **1** leading to a sampling of low-energy conformers with much smaller cavities than observed in the X-ray crystal structure. In particular, the nitrophenylene moieties showed a high propensity to turn into the cavity, thus strongly reducing the size of a potential binding site.

For cyclophane **2**, computer modeling as described for **1** suggested a much more preorganized, open binding site in solution as a result of the electrostatic repulsion between the three adjacent quaternary ammonium centers. The opening of cyclophane-cavity binding sites for anions as well as for neutral apolar molecules as a result of the electrostatic repulsion between multiple adjacent onium centers is well documented in supramolecular chemistry [14–16] [38].

2.3. *Complexation Studies with Cyclophanes* **1** *and* **2** *in Aqueous Solutions.* Stability constants for host-guest complexes of **1** with aromatic sulfonates were determined at 300 K by ^{1}H-NMR binding titrations [39] in a 0.5M KCl/DCl buffer in D_2O at pD 2 [40], to maintain the triprotonated state of the receptor which was held at constant concentration (1 mM) during the titration. Unfortunately, precipitation occurred already at low concentration ranges during several titrations, *e.g.*, with the potassium salts of naphthalene-1-sulfonate and naphthalene-1,5-disulfonate, thus preventing the determination of stability constants in solution [41]. IR and ^{1}H-NMR analyses demonstrated that the precipitates contained both receptor **1** and the substrates. In the absence of X-ray structural data, it cannot be decided whether the substrates in the solid-state complexes, that presumably are formed, are bound within the cavity of **1** or outside the cavity in the crystal lattice, in a clathrate-type fashion [41] [42]. The solution binding studies described in the following, however, strongly suggest that a clathrate-type association should be greatly favored.

The absence of precipitation at lower concentration ranges allowed the determination of the stability of the 1:1 complexes formed between **1** and the aromatic sulfonates **18** and **19** (*Table 1*). The calculated association constants $K_a \approx 45$ l mol^{-1} and binding free energies $-\Delta G° \approx 2.2$ kcal mol^{-1} are quite small and possess considerable uncertainties, since precipitations at higher guest concentrations during the titrations limited the experimentally accessible degree of saturation binding to 30–50%. The data support that **1** and the sulfonate guests undergo ion-pairing interactions but that this association occurs exclusively outside the cyclophane cavity. A large amount of thermodynamic data on the binding or aromatic sulfonates by cationic cyclophane receptors has clearly shown that true inclusion complexation in aqueous solution generates much higher association strength than observed here for the associations with **1** [14a] [19] [43] [44]. In agreement with the proposed ion pairing outside the cavity, the complexation-induced changes in chemical shift of the host protons that occurred during the titrations were very small (*Table 1*). We estimate that competitive inhibition of the ion pairing between **1** and the

sulfonate substrates by the Cl^- ions of the buffer is not a major reason for the measured weak association strength[1]).

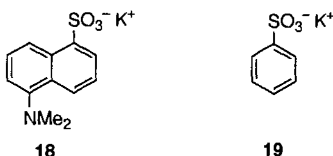
Although the macrocyclic cavity in **1** apparently is not directly involved in the association processes, the introduction of the anion-recognition site into a cyclophane structure nevertheless seems to play an important role by preorganizing this site and, therefore, enhancing its efficiency [45]. This was clearly demonstrated in comparison studies with the more flexible, non-macrocyclic model receptor **3**, for which no association with aromatic and aliphatic sulfonate guests could be observed by ^{1}H-NMR in concentration ranges between 1 and 40 mM.

Complexation studies with **2** rapidly showed that, similar to the findings with **1**, the macrocyclic structure was not providing an active cavity site for substrate inclusion. Rather, the macrocyclic bridging again assisted host-guest association by enforcing a high degree of preorganization in the tris(quaternary ammonium) recognition site which seems required for efficient ion pairing with anionic guests outside the cavity. As a distinct advantage over **1**, the presence of four quaternary ammonium moieties in **2** allowed binding studies with carboxylates, sulfonates, and *N*-substituted α-amino acids to be performed in aqueous solutions at neutral pH and in the absence of buffer which could possibly compete for the binding site. The 500-MHz ^{1}H-NMR binding titrations at either constant host or guest concentration (1 mM) under variation of the second binding partner ([guest] 1–40 mM or [host] 1–20 mM) provided for many of these substrates highly reproducible data points which could be nicely fitted to a 1:1 host-guest binding model. In titrations at constant host concentration, the chemical shifts of the benzylic CH_2 protons of **2** were best monitored, whereas in the titrations at constant guest concentration, the shift of the proton in α-position to the carboxylate was usually evaluated. However, due to the ion pairing outside the cavity of **2**, the complexation-induced

Table 1. *Association Constants* K_a [l mol^{-1}] *and Complexation Free Enthalpies* ΔG° [kcal mol^{-1}] *for Complexes of Cyclophane* **1** *with Sulfonates* **18** *and* **19** *in 0.5 M KCl/DCl Buffer in* D_2O (pD 2) *at 300 K as well as the Calculated and the Maximum Observed Complexation-Induced Upfield Shifts* $\Delta\delta_{sat}$ *and* $\Delta\delta_{max\ obs}$ [ppm], *Respectively, for the Resonances of* **1** *Monitored during the Titrations*[a])

Guest	K_a [l mol^{-1}]	ΔG° [b]) [kcal mol^{-1}]	$\Delta\delta_{sat}$ ($\Delta\delta_{max\ obs}$) [ppm]	Protons of **1** monitored
18	47	−2.3	−0.047 (−0.022)	NCH_2CH_2N
19	42	−2.2	−0.122 (−0.036)	$CONHCH_2$

[a]) [**1**] = 1 mM; [substrate] = 1–20 mM. [b]) Uncertainties in ΔG°: ±0.2 kcal mol^{-1}.



[1]) It should, however, be noted that inhibition of inclusion complexation by Br^- counterions was observed in anion-binding studies with an octacationic cyclophane [41], and that halide-ion association to polyammonium receptors has previously prevented the evaluation of association constants by pH titrations [15c].

changes in ^{1}H-NMR chemical shifts observed in both types of titrations were, with a few exceptions, extremely small, amounting in many cases only to calculated values at saturation binding of $\Delta\delta_{sat} \approx 0.02$ to 0.03 ppm (*Table 2, Fig. 7*).

A series of initial experiments, therefore, addressed the questions whether the evaluation of such small changes in chemical shift was meaningful, and whether they truly represented a variable directly proportional to the degree of 1:1 complexation. Firstly, in the concentration range between 1 and 50 mM, no self-complexation of **2** or the guests shown in *Table 2* was observed in D_2O by 500-MHz ^{1}H-NMR; all chemical shifts remained constant within ±0.001 ppm. Secondly, to investigate nonspecific salt effects, the changes in chemical shift of host and several guest protons were monitored as a function of increasing NaCl concentration. At [NaCl] < 50 mM, no changes in chemical shift (±0.001 ppm) were observed (*Fig. 7*) which eliminated nonspecific ionic-strength contributions, unrelated to stoichiometric complex formation, to the $\Delta\delta$ values measured in the titrations. Above [NaCl] > 50 mM, resonances of **2** started moving upfield, indicating ion-pairing interactions between the receptor and the chloride anions. Finally, all titration results could be reproduced within a narrow range of uncertainty in duplicate or triplicate runs, and both titration modes, *i.e.*, either at constant host or guest concentration, yielded similar results. We, therefore, are confident that the thermodynamic quantities calculated for 1:1 host-guest complexation from the small changes in chemical shift shown in *Table 2* represent meaningful data.

In pure D_2O, 1:1 complexation occurred with the sodium salts of aliphatic and aromatic monocarboxylates (*Entries 1–6*), small α,ω-dicarboxylates (*Entries 7* and *8*), *N*-protected α-amino acids (*Entries 10* and *11*), and the dipeptide Ac-D-Ala-D-Ala (*Entry 12*). The observed weak complexation-induced changes in chemical shift support

Table 2. *Association Constants* K_a [l mol^{-1}] *and Complexation Free Enthalpies* $\Delta G°$ [kcal mol^{-1}] *for Complexes of Cyclophane* **2** *in* D_2O *at 300 K as well as the Calculated and the Maximum Observed Complexation-Induced Shifts* $\Delta\delta_{sat}$ *and* $\Delta\delta_{max\ obs}$ [ppm], *Respectively, for the Benzylic* CH_2 *Resonance in Titrations at Constant Concentration of* **2** (type *A*)[a]) *and for the Given Substrate Resonance in Titrations at Constant Substrate Concentration* (type *B*)[b])

Entry	Guest (Na$^+$ salts)	Titration type	K_a [l mol^{-1}]	$\Delta G°$[c]) [kcal mol^{-1}]	$\Delta\delta_{sat}$ ($\Delta\delta_{max\ obs}$)[d]) [ppm]
1	$HCOO^-$	*A*	22	−1.9	−0.025 (−0.016)
2	$MeCOO^-$	*A*	30	−2.0	−0.020 (−0.012)
3	$MeCH_2COO^-$	*A*	42	−2.2	−0.021 (−0.013)
4	Me_2CHCOO^-	*A*	61	−2.5	−0.022 (−0.015)
		B	66	−2.5	−0.039 (−0.020) (Me signal)
5	Cyclopentyl-COO^-	*A*	33	−2.1	−0.023 (−0.015)
6	$PhCOO^-$	*A*	35	−2.1	−0.192 (−0.103)
		B	55	−2.4	−0.043 (−0.022) (H_o signal)
7	$^-OOCCH_2COO^-$	*A*	230	−3.2	+0.056 (+0.050)
8	$^-OOCCH{=}CHCOO^-$ (*Z*)	*A*	1800	−4.5	+0.107 (+0.103)
9	$Me_2CHSO_3^-$	*A*	56	−2.4	−0.026 (−0.018)
10	Ac-D-Ala	*B*	74	−2.6	−0.023 (−0.011) (C^*–H signal)
11	Ac-D-Val	*A*	30	−2.0	−0.015 (−0.008)
		B	36	−2.1	−0.032 (−0.014) (C^*–H signal)
12	Ac-D-Ala-D-Ala	*A*	51	−2.3	−0.017 (−0.011)

[a]) [**2**] = 1 mM; [substrate] = 1–40 mM. [b]) [Substrate] = 1 mM; [2] = 1–20 mM. [c]) Uncertainties in $\Delta G°$: ±0.2 kcal mol^{-1}. [d]) Negative sign: upfield shift.

that ion-pairing association between the anionic center of the substrate and the tris(quaternary ammonium) site of the receptor occurs outside rather than inside the cyclophane cavity. Nevertheless, the increase in binding free energy from sodium formate ($-\Delta G^\circ = 1.9$ kcal mol^{-1}) to sodium 2-methylpropionate ($-\Delta G^\circ = 2.5$ kcal mol^{-1}) suggests that some hydrophobic contacts, presumably mainly with the non-aromatic tris(quaternary ammonium) site of **2**, contribute to the association strength.

Larger complexation-induced changes in chemical shift were observed in the titration with sodium benzoate (*Entry 6*), in which the benzylic CH_2 protons of **2**, held at constant concentration, were shifted upfield by 0.192 ppm at saturation binding. This considerable upfield shift suggests that the substrate preferentially binds from above the cyclophane. Model examinations indeed indicate that the tricationic recognition site in **2** is best preorganized for ion pairing with substrates approaching from atop the macrocyclic ring. The $\Delta\delta$ values observed in the titrations with the disodium salts of malonic and maleic acid (*Entries 7* and *8*) are also more substantial than those seen in the titrations with the aliphatic monocarboxylates. Interestingly, the benzylic CH_2 protons of **2** move downfield in these titrations. The complexes formed by the two dianions at the tricationic recognition site of **2** are expectedly much more stable than those of the monocarboxylates [15] [16].

Whereas the sodium salts of Ac-D-Ala and Ac-D-Val as well as of the vancomycin substrate Ac-D-Ala-D-Ala underwent complexation with **2** (*Entries 10–12*), binding of unprotected zwitterionic α-amino acids was not observed.

In concentration ranges up to 50 mM, no binding interactions were observed by ^{1}H-NMR between the tricationic model receptor **4** and the substrates shown in *Table 2*. The superiority of cyclophane **2** over **4**, with a nearly identical anion-recognition site, underlines once more the important role of the preorganization imposed on this site in **2** by the macrocyclic structure [16].

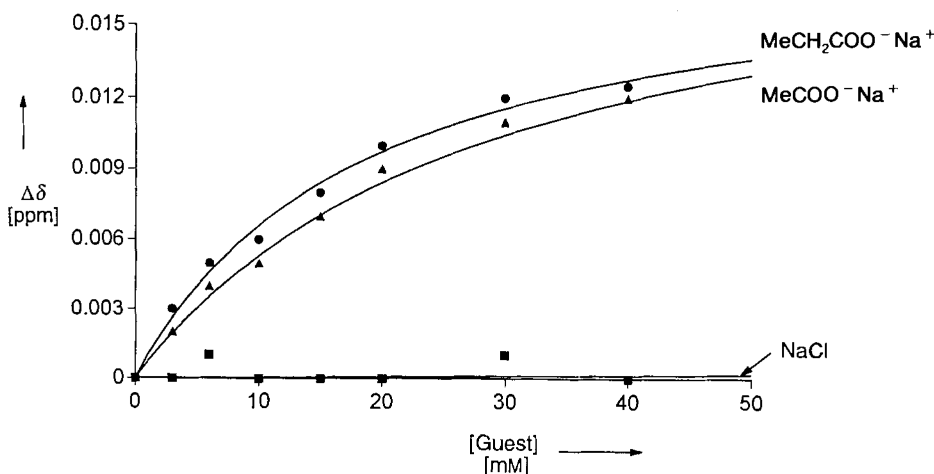


Fig. 7. *500-MHz ^{1}H-NMR Binding titrations (T = 300 K) of* **2** *with sodium acetate and propionate at constant host concentrations* (c = 1 mM). The complexation-induced upfield changes in δ(H) of the benzylic CH_2 of **2** are plotted against increasing substrate concentration (c = 1–50 mM). In the same concentration range, NaCl does not bind to **2**, and nonspecific ion-strength effects are not influencing ($\Delta\delta \pm 0.001$) the position of its benzylic CH_2 resonance.

It is at present not clear why some of the small aliphatic carboxylates, such as acetate, propionate, or 2-methylpropionate do not complex with their hydrophobic moieties fully inserted into the cavity of **2**. Computer model examinations strongly suggested that these substrates possess the necessary steric complementarity to the open cyclophane cavity. In Monte Carlo multiple-minimum searches within MacroModel in H_2O, the hydrophobic isopropyl residue of 2-methylpropionate stays preferentially bound inside the cavity of **2**. To explain the experimental results, which contradict the modeling, we propose that the energetic costs for the complete desolvation of the carboxylate, which would be necessary upon full substrate inclusion, might be too high. The first objective in the continuation of this work must be the preparation of improved mimics of vancomycin, in which cyclophane structures not only help preorganizing the anion-recognition sites as in **1** and **2**, but also enhance the complex stability by fully incorporating hydrophobic residues such as the Me groups of Ac-D-Ala-D-Ala. In the vancomycin complex of this substrate in aqueous solution, the δ(H) of the Me group at the terminal D-Ala residue shifts upfield by −0.57 ppm as a result of its incorporation into one of the three shielding cyclophane subsites of the antibiotic [7].

3. Conclusions. – The new cyclophanes **1** and **2**, incorporating different anion-recognition sites, have been prepared as a first step towards the development of H_2O-soluble synthetic mimics of the natural antibiotic vancomycin. Whereas **1**, as the tris(hydrochloride salt), complexes aromatic sulfonates in 0.5M KCl/DCl buffer in D_2O, the tetrakis-(quaternary ammonium) receptor **2** binds the sodium salts of aliphatic and aromatic carboxylates and sulfonates, of *N*-acylated α-amino acids as well as of Ac-D-Ala-D-Ala, a good substrate of vancomycin, in pure H_2O. In all of these complexes, ion-pairing interactions between the cationic-recognition site of the cyclophane receptor and the anionic substrates represent the major driving force for host-guest association. Although the X-ray crystal structure of **1** revealed an open, preorganized cavity with the potential for incorporation of hydrophobic aliphatic residues of the size of an isopropyl group, ion-pairing complexation by **1** and **2** exclusively took place at the outside of the cavity. This is clearly demonstrated by the very small complexation-induced changes in chemical shift observed in the ^{1}H-NMR binding titrations. Presumably, the costs for full desolvation of the anionic centers in the substrates, which would be required upon full inclusion in the host cavity, are too high. On the other hand, the macrocyclic bridges in **1** and **2** are essential for the efficiency of their anion-recognition sites. Control compounds **3** and **4** possess anion-binding sites very similar to those in **1** and **2** but, due to a lack of preorganization in the absence of a macrocyclic bridge, do not form stable ion-pairing complexes. Receptors **1** and **2** present only partial mimics of vancomycin; their cyclophane structure preorganizes the carboxylate-binding site but does not provide a cavity for inclusion of apolar residues. In contrast, one of the three macrocyclic bridges in the natural antibiotic both contributes to the preorganization of the carboxylate-binding site and provides an apolar inclusion site for the Me group of the terminal D-Ala residue in its D-Ala-D-Ala substrate. In the development of a next generation of vancomycin mimics, we now target H_2O-soluble cyclophanes capable of both preorganizing an efficient carboxylate-binding site and providing an active apolar cavity inclusion site.

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Experimental Part

General. See [13]. Solvents were purified according to standard procedures [46]. All operations were performed under N_2 unless otherwise stated. Evaporations and concentrations *in vacuo* were done at water-aspirator pressure. Unless stated otherwise, foams and solids were dried for 24 h at 60°/5 · 10^{-2} Torr prior to spectral and anal. characterization. The Chemical Abstracts Registry Service assisted in naming some of the new compounds.

X-Ray Crystal Structure of **1**. X-Ray crystal data for $(C_{44}H_{55}N_7O_8)^{3+} \cdot 3\ Cl^- \cdot 4\ MeOH \cdot H_2O$ (M_r 1062.1): triclinic space group $P1$ (No. 1), $D_c = 1.33$ g cm^{-1}, $Z = 1$, $a = 7.511$ (4), $b = 10.434$ (2), $c = 17.801$ (7) Å, $\alpha = 75.47$ (3)°, $\beta = 83.10$ (3)°, $\gamma = 81.33$ (3)°, $V = 1330.1$ (9) Å^3, *Enraf-Nonius-CAD4* diffractometer, CuK_α radiation, $\lambda = 1.5418$ Å, $T = 193$ K. Single crystals were obtained by slow evaporation of a MeOH/H_2O soln. of **1**. The structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least-squares analysis using an isotropic extinction correction and an exponentially modified weight factor $r = 5.0$ Å^2; heavy atoms were refined anisotropically, H-atoms (only those within the skeleton of **1**) were refined isotropically, whereby H-positions are based on configurational considerations. Final $R(F) = 0.062$, $wR(F) = 0.082$ for 628 variables and 3369 observed reflections with $F > 4\sigma(F)$ and $\theta < 60°$.

Complexation Studies. All ^{1}H-NMR titration data were acquired on a *Bruker* 500-MHz NMR spectrometer thermostated to ±0.1 K at 300 K. Commercially available sodium carboxylates were purchased from *Fluka, Aldrich,* and *Bachem.* All other sodium salts were prepared by ion-exchange chromatography (*Dowex 50W* × *2*, Na^+ form) from commercially available carboxylic acids. For each binding study, 8–12 titration samples were prepared with *Gilson Pipetman* (200 and 1000 µl) pipettors from stock solns. which were obtained by weighing the compounds into 1–5 ml volumetric flasks on a *Mettler-AT20* microbalance. Quantitative binding data (K_a, $\Delta G°$, $\Delta\delta_{sat}$) were obtained by nonlinear least-squares curve fitting of the titration data [39].

*1-[(*tert*-Butoxy)carbonyl]-4,4-bis(4-hydroxy-3-methylphenyl)piperidine* (**7**). A soln. of **5** [19b] (5.00 g, 14.7 mmol) in 1M aq. NaOH (30 ml) was heated to reflux for 8 h and then cooled to r.t. To the formed soln. of crude **6**, $(Boc)_2O$ (3.84 g, 17.6 mmol) was added, and the mixture was stirred for 4 h at r.t. Extraction with AcOEt, washing with sat. aq. NaCl soln., drying ($MgSO_4$), evaporation, and recrystallization from $(i\text{-}Pr)_2O$ afforded **7** (5.19 g, 71%). White powder. M.p. 93–96°. IR (KBr): 3391, 2940, 1659, 1506, 1427, 1245, 1155, 1109. ^{1}H-NMR (200 MHz, CD_3OD): 6.92 (*s*, 2 H); 6.87 (*d*, *J* = 8.3, 2 H); 6.64 (*d*, *J* = 8.3, 2 H); 3.45–3.35 (*m*, 4 H); 2.26–2.18 (*m*, 4 H); 2.12 (*s*, 6 H); 1.44 (*s*, 9 H). ^{13}C-NMR (50 MHz, CD_3OD): 157.1; 154.7; 139.7; 130.8; 126.6; 125.6; 115.7; 81.2; 44.6; 37.6; 28.9; 23.3; 16.7. EI-MS (70 eV): 397 (M^+), 341 ([MH – Me_3C]$^+$), 297 ([MH – Me_3COCO]$^+$). Anal. calc. for $C_{24}H_{31}NO_4 \cdot (Me_2CH)_2O$ (499.69): C 72.11, H 9.08, N 2.80; found: 71.82, H 8.83, N 2.78.

Methyl 4-Fluoro-3-nitrobenzoate (**8**). To 4-fluoro-3-nitrobenzoic acid (1.00 g, 5.41 mmol) in Et_2O (100 ml) was added under ice cooling 2.1M CH_2N_2 in Et_2O [47]. Evaporation and recrystallization (hexane) yielded **8** (1.07 g, 99%). Yellow crystals. M.p. 65–68°. IR (KBr): 3062, 1714, 1623, 1542, 1438, 1250, 1128, 755. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.78–8.68 (*m*, 1 H); 8.35–8.25 (*m*, 1 H); 7.45–7.32 (*m*, 1 H); 3.95 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 163.8; 160.5; 155.0; 136.3 (*d*, *J*(C,F) = 10); 127.5; 126.9 (*d*, *J*(C,F) = 4); 118.5 (*d*, *J*(C,F) = 21); 52.6. EI-MS (70 eV): 199 (M^+), 168 ([M – OMe]$^+$). Anal. calc. for $C_8H_6FNO_4$ (199.14): C 48.23, H 3.04, N 7.04; found: C 48.40, H 3.12, N 7.08.

*Dimethyl 4,4'-{{1-[(*tert*-Butoxy)carbonyl]piperidin-4-ylidene}bis(2-methyl-4,1-phenyleneoxy)}bis[3-nitrobenzoate]* (**9**). To a soln. of **7** (8.85 g, 22.3 mmol) in DMF (100 ml) was added **8** (8.86 g, 44.6 mmol) and K_2CO_3 (5.60 g, 40.6 mmol), and the mixture was stirred for 14 h at r.t. Dilution with AcOEt, washing with 0.1M aq. HCl and sat. aq. NaCl soln., evaporation, and chromatography (SiO_2, CH_2Cl_2/THF 20:1) gave **9** (12.79 g, 76%). White powder. M.p. 124°. IR (KBr): 3437, 2954, 1728, 1691, 1619, 1491, 1435, 1363, 1262, 1157, 1118, 818, 765. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.53 (*d*, *J* = 2.0, 2 H); 8.04 (*dd*, *J* = 8.7, 2.0, 2 H); 7.18 (*s*, 2 H); 7.13 (*d*, *J* = 8.7, 2 H); 6.93 (*d*, *J* = 8.3, 2 H); 6.78 (*d*, *J* = 8.3, 2 H); 3.89 (*s*, 6 H); 3.87 (*m*, 4 H); 2.36 (*m*, 4 H); 2.14 (*s*, 6 H); 1.42 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 165.0; 155.2; 154.9; 150.5; 144.8; 139.9; 135.4; 130.9; 130.6; 127.8; 126.7; 124.5; 120.9; 117.5; 79.8; 52.8; 44.4; 41.2; 36.3; 28.6; 16.5. FAB-MS: 756 (25, MH$^+$), 700 (100, [M – C_4H_7]$^+$). Anal. calc. for $C_{40}H_{41}N_3O_{12}$ (755.78): C 63.57, H 5.47, N 5.56; found: C 63.52, H 5.69, N 5.70.

*4,4-{{1-[(*tert*-Butoxy)carbonyl]piperidin-4-ylidene}bis(2-methyl-4,1-phenyleneoxy)}bis[3-nitrobenzoic Acid]* (**10**). To **9** (2.00 g, 2.64 mmol) in H_2O/MeOH/THF 1:1:1 (100 ml) was added KOH (1.47 g, 26.3 mmol), and the clean soln. was stirred for 4 h at r.t. Acidification with 0.1M aq. HCl, extraction with AcOEt, washing with sat. aq. NaCl soln., drying ($MgSO_4$), and evaporation yielded **10** (1.88 g, 98%) as an off-white foam which was used without further purification. IR (KBr): 3422, 2975, 1697, 1618, 1537, 1495, 1426, 1353, 1260, 1158, 1115. ^{1}H-NMR (200 MHz, CD_3OD): 8.46 (*d*, *J* = 2.1, 2 H); 8.06 (*dd*, *J* = 8.6, 2.1, 2 H); 7.31 (*s*, 2 H); 7.25 (*d*, *J* = 8.6, 2 H); 6.94 (*d*, *J* = 8.7, 2 H); 6.79 (*d*, *J* = 8.7, 2 H); 3.50 (*m*, 4 H); 2.42 (*m*, 4 H); 2.19 (*s*, 6 H); 1.46 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.3; 155.6; 155.4; 150.5; 144.8; 139.9; 135.9; 130.9; 130.7; 128.5; 126.8; 124.1; 121.1; 117.5; 80.4; 44.5; 36.3; 28.7; 21.0; 16.5. FAB-MS: 728 (12, MH$^+$), 672 (100, [M – C_4H_7]$^+$).

*1'-[(*tert*-Butoxy)carbonyl]-4,10-dimethyl-14,33-dinitrospiro[2,12-dioxa-18,22,25,29-tetraazahexacyclo[29.2.2.2^{3,6}.2^{8,11}.2^{13,16}.2^{22,25}]tritetraconta-3,5,8,10,13,15,31,33,34,38,40,42-dodecaene-7,4'-piperidine]-17,30-dione* (**11**). Two solns. of **10** (1.00 g, 1.38 mmol) and piperazine-1,4-dipropanamine (2.75 mg, 1.38 mmol) each in DMF (20 ml) were added at r.t. simultaneously over 24 h to a soln. of Et_3N (2 ml) and DPPA (1.67 g, 6.07 mmol) in DMF (100 ml). Evaporation and chromatography (SiO_2, CH_2Cl_2/MeOH/28% aq. NH_3 soln. 100:10:1) gave **11** (394 mg, 32%) as a foam which was used without further purification. IR (KBr): 3422, 2933, 1655, 1527, 1483, 1344, 1261, 1150. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.40 (*d*, J = 2.1, 2 H); 7.87 (*dd*, J = 8.7, 2.1, 2 H); 7.47 (*s*, 2 H); 7.20 (*s*, 2 H); 6.98 (*dd*, J = 8.7, 2.1, 2 H); 6.69 (*d*, J = 8.7, 2 H); 6.65 (*d*, J = 8.7, 2 H); 3.52 (*m*, 8 H); 2.61–2.42 (*m*, 16 H); 2.20 (*s*, 6 H); 1.82 (*m*, 4 H); 1.44 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.9; 154.9; 152.7; 151.7; 143.7; 140.6; 132.5; 129.6; 129.2; 129.1; 125.7; 125.0; 120.1; 118.5; 79.6; 57.0; 53.3; 43.9; 41.2; 39.8; 34.5; 28.5; 25.1; 16.3. FAB-MS: 892 (MH$^+$).

4,10-Dimethyl-14,33-dinitrospiro[2,12-dioxa-18,22,25,29-tetraazahexacyclo[29.2.2.2^{3,6}.2^{8,11}.2^{13,16}.2^{22,25}]-tritetraconta-3,5,8,10,13,15,31,33,34,38,40,42-dodecaene-7,4'-piperidine]-17,30-dione Tris(hydrochloride) (**1**). HCl gas was bubbled for 2 h through a soln. of **11** (350 mg, 0.39 mmol) in MeOH (30 ml), then the mixture was stirred for 12 h at r.t. and evaporated. Crystallization (aq. MeOH) gave **1** (381 mg, 98%) as white hygroscopic platelets, which were dried at 60°/5 · 10^{-2} Torr for 48 h. M.p. > 250°. IR (KBr): 3433, 2955, 1655, 1616, 1527, 1483, 1350, 1255, 1111. ^{1}H-NMR (500 MHz, D_2O): 8.44 (*d*, J = 1.6, 2 H); 7.89 (*m*, 2 H); 7.47 (*s*, 2 H); 7.33 (*d*, J = 8.8, 2 H); 7.07 (*d*, J = 8.8, 2 H); 6.82 (*d*, J = 8.8, 2 H); 3.82 (*s*, 8 H); 3.6 (*s*, 4 H); 3.51 (*s*, 4 H); 3.34 (*s*, 4 H); 2.76 (*s*, 4 H); 2.20 (*s*, 4 H); 2.09 (*s*, 6 H). FAB-MS: 792.6 (100, $[M - 2H - 3Cl]^+$). Anal. calc. for $C_{43}H_{52}Cl_3N_7O_8 \cdot 5\,H_2O$ (990.35): C 52.10, H 6.26, N 9.87; found: C 52.32, H 6.49, N 9.81.

X-Ray: see *Figs. 2–6*.

Dimethyl 4,4'-[(1-Acetylpiperidin-4-ylidene)bis(2,6-dimethyl-4,1-phenyleneoxy)]bis[3-nitrobenzoate] (**13**). A mixture of **8** (5.41 g, 27.2 mmol), K_2CO_3 (9.38 g, 67.9 mmol), and **12** (5.00 g, 13.6 mmol) in DMF (100 ml) was stirred for 14 h at r.t. Dilution with AcOEt, washing with 0.1M aq. HCl and sat. aq. NaCl soln., evaporation, and chromatography (CH_2Cl_2/THF 10:1) gave **13** (7.69 g, 78%). Foam. IR (KBr): 3295, 2866, 1727, 1644, 1611, 1533, 1477, 1433, 1355, 1261. ^{1}H-NMR (200 MHz, CDCl): 8.60 (*d*, J = 2.1, 2 H); 8.04 (*dd*, J = 8.7, 2.1, 2 H); 7.01 (*s*, 4 H); 6.58 (*d*, J = 8.7, 2 H); 3.91 (*s*, 6 H); 3.68 (*m*, 4 H); 2.38 (*m*, 4 H); 2.10 (*s*, 15 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.3; 165.1; 154.4; 148.2; 144.7; 139.0; 135.6; 131.2; 128.1; 124.1; 115.4; 112.4; 52.8; 44.4; 43.8; 38.8; 36.9; 36.1; 21.6; 16.7. FAB-MS: 726 (100, MH$^+$). HR-FAB-MS: 726.2633 (MH$^+$, $C_{39}H_{40}N_3O_{11}^+$; calc. 726.2663).

1'-Acetyl-4,10,21,33,36-pentamethyl-14,28-dinitrospiro[2,12-dioxa-18,21,24-triazapentacyclo[24.2.2.2^{3,6}.2^{8,11}.2^{13,16}]hexatriaconta-3,5,8,10,13,15,26,28,29,31,33,35-dodecaene-7,4'-piperidine]-17,25-dione (**15**). A soln. of **13** (4.08 g, 5.63 mmol) and KOH (3.00 g, 53.6 mmol) in H_2O/MeOH/THF 1:1:1 (100 ml) was stirred for 4 h at r.t. Acidification with 0.1M aq. HCl under ice-cooling, extraction with AcOEt, washing with sat. aq. NaCl soln., drying ($MgSO_4$), and evaporation yielded **14** (3.87 g, 99%) as a foam which was used without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.46 (*d*, J = 2.0, 2 H); 8.00 (*dd*, J = 8.8, 2.0, 2 H); 7.24 (*d*, J = 8.8, 2 H); 6.82 (*m*, 4 H); 3.69 (*m*, 4 H); 2.47–2.36 (*m*, 4 H); 2.11 (*s*, 12 H); 2.08 (*s*, 3 H).

Two solns. of **14** (3.87 g, 5.60 mmol) and N-(2-aminoethyl)-N'-methylethane-1,2-diamine (656 mg, 5.60 mmol) each in DMF (20 ml) were added at r.t. simultaneously over 24 h to a soln. of Et_3N (2 ml) and DPPA (6.16 g, 22.4 mmol) in DMF (100 ml). Evaporation followed by chromatography (CH_2Cl_2/MeOH 10:1) afforded **15** (1.87 g, 43%). Foam. IR (KBr): 3422, 2922, 2866, 1650, 1611, 1522, 1483, 1250. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.58 (*d*, J = 2.0, 2 H); 8.01 (*dd*, J = 8.8, 2.0, 2 H); 7.11 (*s*, 4 H); 7.02 (*s*, 2 H); 6.15 (*d*, J = 8.8, 2 H); 3.65 (*m*, 8 H); 2.55 (*m*, 4 H); 2.21 (*m*, 4 H); 2.11 (*s*, 3 H); 2.08 (*s*, 15 H). ^{13}C-NMR (75 MHz, $CDCl_3$/CD_3OD 1:1): 165.2; 163.4; 153.3; 148.5; 144.7; 139.4; 131.8; 129.5; 126.9; 123.9; 114.7; 57.8; 45.9; 43.7; 40.6; 38.8; 36.8; 33.9; 31.6; 16.4; 8.5. FAB-MS: 779 (100, MH$^+$). HR-FAB-MS: 779.3427 (MH$^+$, $C_{42}H_{47}N_6O_9^+$; calc. 779.3404).

1'-Ethyl-4,10,21,33,36-pentamethyl-14,28-dinitrospiro[2,12-dioxa-18,21,24-triazapentacyclo[24.2.2.2^{3,6}.2^{8,11}.2^{13,16}]hexatriaconta-3,5,8,10,13,15,26,28,29,31,33,35-dodecaene-7,4'-piperidine] (**16**). A mixture of **15** (300 mg, 0.39 mmol) and $BH_3 \cdot SMe_2$ (2.00 ml, 32.9 mmol) was stirred for 72 h at r.t. After evaporation, MeOH (30 ml) and conc. H_2SO_4 soln. (0.2 ml) were added and the soln. heated to reflux for 16 h. After addition of 1M aq. NaOH (50 ml), the basic mixture was extracted with AcOEt, washed with 0.1M aq. NaOH, and dried ($MgSO_4$). Chromatography (SiO_2, CH_2Cl_2/MeOH/28% aq. NH_3 soln. 100:10:1) yielded **16** (147 mg, 52%). Colorless foam. IR (KBr): 3411, 2788, 1527, 1477, 1238. ^{1}H-NMR (200 MHz, CD_3OD): 7.84 (*d*, J = 2.1, 2 H); 7.43 (*dd*, J = 8.7, 2.1, 2 H); 7.23 (*s*, 4 H); 6.24 (*d*, J = 8.7, 2 H); 3.77 (*s*, 4 H); 2.62 (*m*, 12 H); 2.42 (*m*, 6 H); 2.08 (*s*, 12 H); 2.02 (*s*, 3 H); 1.15 (*t*, J = 7.2, 3 H). ^{13}C-NMR (50 MHz, CD_3OD): 151.3; 149.8; 147.9; 140.6; 135.3; 134.6; 132.3; 128.8; 126.9; 116.5; 59.2; 53.7; 52.9; 51.5; 47.1; 44.9; 41.3; 35.5; 16.6; 12.2. FAB-MS: 737 (100, MH$^+$). HR-FAB-MS: 737.4049 (MH$^+$, $C_{42}H_{53}N_6O_6^+$; calc. 737.4026).

1'-Ethyl-4,10,18,21,24,33,36-heptamethyl-14,28-dinitrospiro[2,12-dioxa-18,21,24-triazapentacyclo-[24.2.2.2^{3,6}.2^{8,11}.2^{13,16}]hexatriaconta-3,5,8,10,13,15,26,28,29,31,33,35-dodecaene-7,4'-piperidine] (**17**). A mixture of 40% aq. HCHO soln. (30 ml) and **16** (500 mg, 0.68 mmol) in HCOOH (30 ml) was heated to 100° for 24 h, then made basic by addition of 1M aq. NaOH. Extraction with AcOEt, drying ($MgSO_4$), evaporation, and chromatography (SiO_2, CH_2Cl_2/MeOH/28% aq. NH_3 soln. 100:10:1) gave **17** (478 mg, 92%). White foam. IR (KBr): 3422, 2933, 2788, 1527, 1344, 1238, 1133. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.76 (*d*, *J* = 2.1, 2 H); 7.51 (*dd*, *J* = 8.7, 2.1, 2 H); 7.07 (*s*, 4 H); 6.29 (*d*, *J* = 8.7, 2 H); 3.49 (*s*, 4 H); 2.53 (*m*, 16 H); 2.37 (*q*, *J* = 7.2, 2 H); 2.16 (*s*, 6 H); 2.11 (*s*, 15 H); 1.09 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 150.3, 148.1; 138.0; 134.4; 132.3; 130.7; 126.9; 125.7; 115.6; 61.6; 56.3; 55.3; 52.3; 49.9; 43.3; 41.9; 40.9; 34.7; 16.5; 12.0. FAB-MS: 765 (100, MH^+). HR-FAB-MS: 765.4355 (MH^+, $C_{44}H_{57}N_6O_6^+$; calc. 765.4339).

1'-Ethyl-1',4,10,18,18,21,21,24,24,33,36-undecamethyl-14,28-dinitrospiro[2,12-dioxa-18,21,24-triazoniapentacyclo[24.2.2.2^{3,6}.2^{8,11}.2^{13,16}]hexatriaconta-3,5,8,10,13,15,26,28,29,31,33,35-dodecaene-7,4'-piperidinium Tetrachloride (**2**). A soln. of **17** (200 mg, 0.26 mmol) and CF_3SO_3Me (426 mg, 2.60 mmol) in CH_2Cl_2 (2 ml) was stirred in a sealed vessel at 80° for 8 h. The dark mixture was diluted with MeOH and the crude product precipitated by addition of Et_2O. Ion-exchange chromatography (*Dowex 50W × 2*, Cl^- form, MeOH/H_2O 4:1) followed by reversed-phase (*C_{18}*) chromatography (H_2O/MeCN 10:1) afforded crude product which was taken up in a minimum amount of H_2O and precipitated by addition of MeCN. Drying for 24 h at 20°/5 · 10^{-2} Torr afforded **2** (113 mg, 41%). White hygroscopic powder. M.p. > 250°. IR (KBr): 3422, 3011, 2955, 1616, 1533, 1477, 1350, 1250. ^{1}H-NMR (200 MHz, CD_3OD): 8.36 (*s*, 2 H); 8.14 (*d*, *J* = 7.8, 2 H); 7.43 (*s*, 4 H); 6.62 (*d*, *J* = 7.8, 2 H); 4.90 (*s*, 4 H); 4.48 (*m*, 8 H); 4.06 (*m*, 8 H); 3.51 (*q*, *J* = 7.0, 2 H); 3.39 (*m*, 18 H); 3.15 (*s*, 3 H); 2.17 (*s*, 12 H); 1.17 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 153.7; 149.9; 140.7; 133.1; 132.9; 131.9; 128.4; 128.1; 121.9; 117.9; 68.2; 66.9; 59.9; 59.2; 54.4; 51.7; 43.7; 29.8; 16.7; 15.6; 8.1. FAB-MS: 931 ([M – Cl]$^+$). Anal. calc. for $C_{48}H_{68}Cl_4N_6O_6 \cdot 5\,H_2O$ (1054.45): C 54.63, H 7.46, N 7.97; found: C 54.64, H 7.40, N 8.27.

N,N'-*[(Piperazine-1,4-diyl)propan-3,1-diyl]bis[acetamide] Dihydrochloride* (**3**). Acetyl chloride (0.8 ml, 11.0 mmol) was added under ice-cooling to piperazine-1,4-dipropanamine (2.00 g, 10.0 mmol) in CH_2Cl_2 (100 ml), and the mixture was stirred for 14 h at r.t. Evaporation followed by recrystallization from aq. MeOH yielded **3** (2.87 g, 62%). M.p. 252–255°. ^{1}H-NMR (300 MHz, CD_3OD/D_2O 1:1): 3.69 (*m*, 8 H); 3.36 (*m*, 4 H); 3.07 (*s*, 4 H); 2.15 (*m*, 4 H); 1.92 (*s*, 6 H). ^{13}C-NMR (75 MHz, CD_3OD/D_2O 1:1): 177.2; 57.2; 51.4; 38.7; 26.2; 24.5. FAB-MS: 285 (100, [M – H – 2 Cl]$^+$). Anal. calc. for $C_{14}H_{30}Cl_2N_4O_2 \cdot 2$ MeOH (421.41): C 45.60, H 9.09; found: C 45.28, H 8.65.

N,N,N,N',N'-*Pentamethyl*-N'-*[2-(trimethylammonio)ethyl]ethane-1,2-diaminium Trichloride* (**4**) [20]. A soln. of MeI (1.17 ml, 18.8 mmol) and *N*-(2-aminoethyl)-*N'*-methylethane-1,2-diamine (383 mg, 6.27 mmol) in CH_2Cl_2 (10 ml) was stirred for 14 h at 80° in a sealed vessel. The mixture was diluted with MeOH, stirred for additional 14 h at r.t. and then evaporated. Ion-exchange chromatography (*Dowex 50 W × 2*, Cl^- form, MeOH/H_2O 4:1, followed by recrystallization from aq. MeOH afforded **4** (1.64 g, 70%). Hygroscopic powder. M.p. > 250°. ^{1}H-NMR (300 MHz, D_2O): 4.33 (*m*, 4 H); 3.55 (*m*, 4 H); 3.44 (*m*, 24 H). ^{13}C-NMR (75 MHz, D_2O): 59.8; 59.2; 55.1; 53.9. Anal. calc. for $C_{12}H_{32}Cl_3N_3 \cdot H_2O \cdot$ MeOH (374.35): C 41.66, H 10.22, N 11.21; found: C 41.48, H 9.90, N 11.55.

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