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A Water-Soluble Tetraoxa[7.1.7.1]paracyclophane: Synthesis and Host-Guest Interactions with Alicyclic and Cationic Aromatic Guest Molecules in Aqueous Solution

*François Diederich** and *Klaus Dick*

Max-Planck-Institut für medizinische Forschung, Abteilung Organische Chemie, Jahnstr. 29, D-6900 Heidelberg

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As water-soluble macrocyclic host for apolar guest molecules, the tetraoxa[7.1.7.1]paracyclophane **1** was synthesized. In the key reaction of the synthesis, two equivalents of 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine (**4**) and two equivalents of 1-acetyl-4,4-bis[2-(*p*-tolylsulfonyl)ethyl]piperidine (**8**) were cyclized to the tetraoxa[7.1.7.1]paracyclophane **9**. The synthesis of **8** starting from 1-acetyl-4-piperidone is described. **1** was obtained following the reaction sequence **9** → **10** → **11** → **2** → **1**. The temperature dependency of the ^{1}H NMR spectra of **1** is discussed. – ^{1}H NMR studies of host-guest interactions in aqueous solutions between **1** and aromatic guest molecules bearing cationic residues and between **1** and alicyclic guest molecules are described. The association constants K_a ($l \cdot mol^{-1}$) of the complexes were either determined by solid-liquid extraction and from competitive inhibition experiments, or estimated from NMR complexation shifts $\Delta\delta$.

Ein wasserlösliches Tetraoxa[7.1.7.1]paracyclophan: Synthese und Wirt-Gast-Wechselwirkungen mit alicyclischen und kationischen aromatischen Gastmolekülen in wäßriger Lösung

Als wasserlöslicher makrocyclischer Wirt für unpolare Gastmoleküle wurde das Tetraoxa[7.1.7.1]paracyclophan **1** synthetisiert. In der Schlüsselreaktion der Synthese von **1** wurden zwei Äquivalente 1-Acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidin (**4**) mit zwei Äquivalenten 1-Acetyl-4,4-bis[2-(*p*-tolylsulfonyl)ethyl]piperidin (**8**) zum Tetraoxa[7.1.7.1]paracyclophan **9** cyclisiert. Die Synthese von **8**, ausgehend von 1-Acetyl-4-piperidon, wird beschrieben. **1** wurde in der Reaktionsfolge **9** → **10** → **11** → **2** → **1** erhalten. Die Temperaturabhängigkeit der ^{1}H-NMR-Spektren von **1** wird diskutiert. – ^{1}H-NMR-Untersuchungen der Wirt-Gast-Wechselwirkungen in wäßriger Lösung zwischen **1** und aromatischen Gastmolekülen mit kationischen Resten und zwischen **1** und alicyclischen Gastmolekülen werden beschrieben. Die Assoziationskonstanten K_a ($l \cdot mol^{-1}$) der Komplexe wurden entweder durch Fest-Flüssig-Extraktion und über kompetitive Inhibitionsexperimente bestimmt oder anhand der NMR-Komplexierungsverschiebungen $\Delta\delta$ abgeschätzt.

Recently we described the investigations of host-guest interactions in aqueous solution between the macrocyclic host **1** and aromatic guest molecules[1–3]. Host **1** possesses four spiropiperidinium rings locating the water-solubility providing quaternary ammonium nitrogens remote from the cavity. With a value of $7.5 \cdot 10^{-3}$ $mol \cdot l^{-1}$, the critical micelle concentration (CMC) of **1** is considerably higher than

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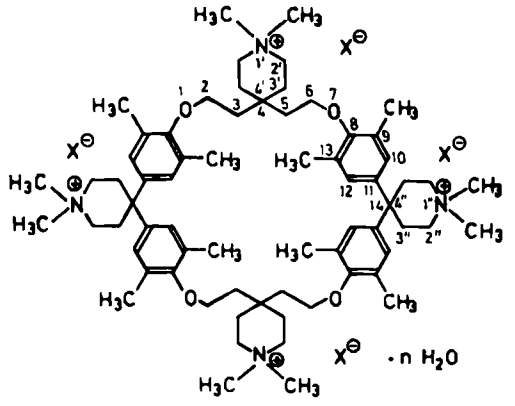
the CMC of the previously reported tetraoxa[n.1.n.1]paracyclophanes (n = 6, 7) with only two spiropiperidinium rings[4]. Below this relatively high CMC of **1**, stoichiometric host-guest complexation could be easily monitored by ^{1}H NMR spectroscopy. With suitably sized guests, exclusively 1:1 host-guest complexation was observed below the CMC in aqueous solution and the association constants K_a ($l \cdot mol^{-1}$) of the complexes were determined. **1** was shown to be a powerful host for neutral aromatic guests as well as for aromatic guests bearing anionic residues. ^{1}H NMR investigations indicated the formation of highly structured complexes with all considered aromatic guests being located in the cavity of **1** in the so-called aromatic guest plane[3]. This plane passes through the two spiro-carbon atoms of the diphenylmethane units and is perpendicular to the mean molecular plane of **1**. Hydrophobic and van der Waals interactions were shown to be the major driving force for the complexation of neutral aromatic guests[2]. The observed strong binding of aromatic guests bearing anionic (sulfonate) residues was explained by additional ion pair interactions between the sulfonate residues of the guests and the quaternary ammonium nitrogens of the spiropiperidinium rings attached to the aliphatic bridges of **1**. As a consequence of the conformational flexibility of the bridges, these spiropiperidinium rings can approach and envelope the enclosed guest molecule either on one or on both sides of the cavity. Two preliminary studies indicated that the complexation between **1** and alicyclic guests or aromatic guests bearing cationic (ammonium) residues is weaker than with neutral or anionic aromatic compounds[2]. In this paper we report on the synthesis of host **1** and on further complexation studies in aqueous solution with alicyclic and cationic aromatic guests.

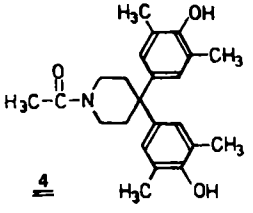
Synthesis of the Macrocyclic Host 1

The key step in the synthesis of **1** was the cyclization of two equivalents of 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine (**4**)[4] with two equivalents of 1-acetyl-4,4-bis[2-(*p*-tolylsulfonyl)ethyl]piperidine (**8**) to the tetraoxa-[7.1.7.1]paracyclophane **9**. The synthesis of **8** starts with the Guareschi reaction of 1-acetyl-4-piperidone with ethyl cyanoacetate in alcoholic ammonia[5]. Acidification of the precipitated imide ammonium salt gave 1′-acetyl-2,6-dioxo-4,4′-spirobi[piperidine]-3,5-dicarbonitril (**5**) in 70% yield. After hydrolysis and decarboxylation of **5** with 55% sulfuric acid, 4,4-piperidinediacetic acid was directly esterified with ethanol/sulfuric acid to yield diethyl 4,4-piperidinediacetate. The crude diester was transformed without further purification with acetic anhydride into diethyl 1-acetyl-4,4-piperidinediacetate (**6**) in 45% yield, starting from **5**. Reduction of **6** with lithiumborohydride in tetrahydrofuran at room temperature yielded 53% of 1-acetyl-4,4-piperidinediethanol (**7**), which was transformed in 73% yield into the desired ditosylate **8** using tosyl chloride in pyridine.

Cyclization of **4** with **8** in the presence of potassium hydroxide and 18-crown-6 in tetrahydrofuran to the tetraoxa[7.1.7.1]paracyclophane **9** was achieved in 18% yield. This represents a remarkably good yield for the cyclization to a thirty two-membered macrocyclic ring, forming four bonds without template-assistance. This yield is a consequence of the favorable geometry of the two cyclization components



1: X = $Cl^{\ominus}$ n = 4
2: X = $FSO_3^{\ominus}$ n = 3
3: X = $BF_4^{\ominus}$ n = 1



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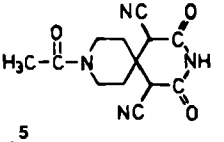

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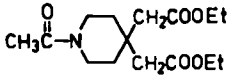

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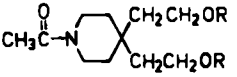
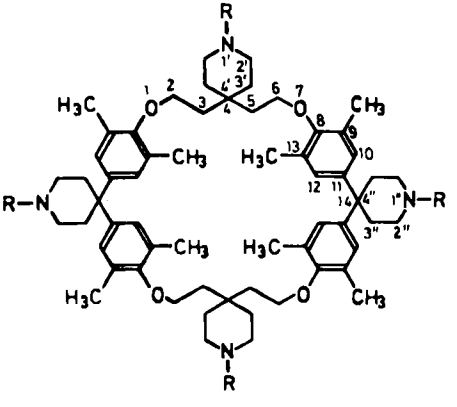


7: R = H
8: R = $-SO_2-C_6H_4-CH_3$



9: R = CH_3CO-
10: R = H
11: R = CH_3

4 and **8**. When **8** was replaced by α,ω-ditosylates of linear alkane chains, such fourfold cyclizations were no longer of synthetic interest as the yields became very low. The ^1H NMR spectrum (360 MHz, $CDCl_3$) of **9** is in accordance with the

assumed macrocyclic structure: δ = 1.5–1.7 (m; 8H; 3′-H), 1.95–2.05 (m; 8H, 3-H), 2.07 (s; 6H, $COCH_3$), 2.10 (s; 6H, $COCH_3$), 2.13 (s; 24H, Aryl-CH_3), 2.2–2.35 (m; 8H, 3″-H), 3.4–3.55 and 3.55–3.7 (two m; each 8H, 2′- and 2″-H), 3.75–3.9 (m; 8H, 2-H), 6.73 (s; 8H, 10-H).

Hydrolysis of the *N*-acetyl groups of **9** with potassium hydroxide in 2-methoxyethanol led to **10** (85%), which by Eschweiler-Clarke methylation was transformed in 92% yield to the tetra(*N*-methylpiperidine) macrocycle **11**. Fourfold quaternization of **11** with methyl fluorosulfonate ("magic methyl") in chloroform gave the corresponding tetrakis(fluorosulfonate) **2** in 79% yield. Addition of a saturated aqueous solution of sodium tetrafluoroborate to an aqueous solution of **2** led to the precipitation of the tetrakis(tetrafluoroborate) **3** (90% yield). Ion exchange chromatography (Dowex 1 X 8, Cl^-) starting from the tetrakis(fluorosulfonate) gave the target host compound **1** as a colourless solid in 77% yield. All salts are hygroscopic and take up stoichiometric amounts of water from the atmosphere. The tetrakis(fluorosulfonate) **2** crystallizes with three equivalents of water, the tetrakis(tetrafluoroborate) **3** with one equivalent and the tetrachloride **1** with four equivalents. Water uptake from the atmosphere beyond these stoichiometric amounts is very slow: elemental analysis gives correct values for all three salts with the above mentioned stoichiometric amounts of water even after one week of exposure of the crystals to laboratory air. The solubility behaviour of the salts **1**–**3** in various organic solvents and in water is similar to that recently described of tetraoxa[n.1.n.1]paracyclophanes with two spiropiperidinium rings[4]. The tetrachloride **1** shows the best solubility in water.

The ^1H NMR spectra of **1** exhibit a large temperature dependency. In [D_4]methanol at 303 K the following spectrum was obtained (360 MHz, tetramethylsilane (TMS) as internal standard): δ = 2.01 (mc; 8H, 3′-H), 2.15 ("t", J = 6.1 Hz; 8H, 3-H), 2.17 (s; 24H, Aryl-CH_3), 2.69 (mc; 8H, 3″-H), 3.18 (s; 12H), N(1″)–CH_3), 3.21 (s; 12H, N(1′)–CH_3), 3.41 (mc; 8H, 2″-H), 3.49 (mc; 8H, 2′-H), 3.89 ("t", J = 6.1 Hz; 8H, 2-H), 6.91 (s; 8H, 10-H). At lower temperature, broadening of specifically all the signals of the protons of the two diphenylmethane units of **1**, N(1″)–CH_3, 2″-H, 3″-H, Aryl-CH_3, and 10-H is observed. The chair inversion of the piperidinium rings of the diphenylmethane units becomes slow on the 360 MHz NMR time scale[4]. Below the coalescence temperature between 265 and 260 K, each signal of these protons splits into two signals of equal intensity. At T_c = 265 K with a distance between the two new singlets of 10-H of Δν = 148 Hz, the rate constant for the chair inversion was estimated as k_{265} = 328 s^{-1}, and the free enthalpy of activation of this process was calculated to be $\Delta G^{\ddagger}_{265}$ = 12.4 kcal·mol^{-1}. This $\Delta G^{\ddagger}$-value is in agreement with the values calculated previously for the chair inversion of spiropiperidinium rings in related macrocycles[4]. Below 250 K, secondary dynamic processes are observed, which now influence the signals of the protons of the aliphatic bridges of **1** and of the protons of the spiropiperidinium rings attached to them. The spectra below 250 K become too complex to be evaluated. For the aromatic protons 10-H as much as eight signals are observed at 193 K.

Host-Guest Interactions of 1 in Aqueous Solution

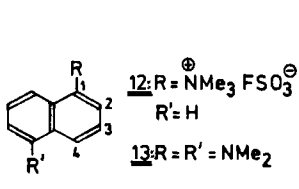
A. With Aromatic Guests Bearing Cationic Residues

The strong complexation between **1** and aromatic guests bearing anionic (sulfonate) residues was explained by additional ion-pair interactions between the anionic groups of the complexed guest and the quaternary nitrogens of the spiropiperidinium rings attached to the aliphatic bridges of **1**[3]. As a consequence of the conformational flexibility of the bridges, these spiropiperidinium rings can approach and envelope the enclosed guest either on one or on both sides of the cavity. Conformations of **1** with the piperidinium rings enveloping the enclosed guest represent also a significant contribution to the actual geometry of **1** in complexes of neutral aromatic guests[3]. This is suggested by the considerable upfield shifts of the signals of N(1′)−CH_3, 2′-H and 3′-H of **1** in the ^{1}H NMR spectra of solutions of **1** and neutral arenes. If the piperidinium rings envelope the enclosed guest, which could provide additional stability to the complex, these protons of **1** are oriented into the shielding region of the guest. Such orientations of the piperidinium rings could be expected to destabilize complexes of **1** with aromatic guests bearing cationic (ammonium) residues, as they would lead to repulsive interactions between cationic centers.

1-(Trimethylammonio)naphthalene fluorosulfonate (**12**) forms a complex with **1** in aqueous solution ($K_a = 1.7 \cdot 10^3$ l·mol^{-1}), which is considerably less stable than the complexes of naphthalene derivatives bearing neutral or anionic substituents (Table 1). With $[H_0] = [G_0] = 4 \cdot 10^{-3}$ mol·l^{-1}, about 68% of host (H) and guest (G) are complexed in aqueous solution and the following changes of the chemical shifts $\Delta\delta$[6] upon complexation are observed in the ^{1}H NMR spectrum (360 MHz, 303 K, D_2O, sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate (TSP) as external standard): $\Delta\delta$ of protons of **1** = +0.04 (3′-H), +0.13 (3-H), ±0.00 (Aryl-CH_3), −0.07 (3″-H), +0.02 (N(1′)−CH_3), ±0.00 (N(1″)−CH_3), +0.03 (2′-H), ±0.00 (2″-H), +0.30 (2-H), −0.16 (10-H); $\Delta\delta$ of protons of **12** = +0.16 (2-H), +0.24 (3-H), +0.49 (4-H), +0.61 (5-H), +0.34 (6-H), +0.44 (7-H), +0.26 (8-H), +0.09 (CH_3). **12** is located in the aromatic guest plane of **1** as indicated by the specific up- and downfield shifts of the protons of **1** upon complexation. The trimethylammonium residue and the part of naphthalene in its proximity are preferably located outside of the cavity. The signals of the protons N(1′)−CH_3, 2′- and 3′-H of **1** are only weakly shifted upfield in the solution of the complex, which might indicate, that the piperidinium rings of the aliphatic bridges of **1** avoid the proximity to the enclosed guest.

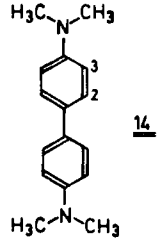
A large difference in complexation was observed in solutions of **1** and 1,5-bis(dimethylamino)naphthalene (**13**) at acidic and basic pH. Solid-liquid extraction[2] with a $1.5 \cdot 10^{-2}$ M aqueous solution of potassium carbonate (pH ≈ 11; [**1**] = $5.02 \cdot 10^{-3}$ mol·l^{-1}) provided a $1.94 \cdot 10^{-3}$ M solution of guest **13**. With a maximum solubility of **13** of $6.0 \cdot 10^{-5}$ mol·l^{-1} in this solution in the absence of host, the binding constant $K_a = 9.7 \cdot 10^3$ l·mol^{-1} (293−295 K) of the 1:1 complex was calculated. In the ^{1}H NMR spectrum of the above mentioned host-guest solution, the specific up- and downfield shifts of the signals of the protons of **1** indicate the

location of **13** in the aromatic guest plane of **1**. The protons of **13** are shifted upfield: $\Delta\delta = +0.97$ (2-H), $+1.04$ (3-H), $+1.13$ (4-H), and $+0.56$ (NCH_3). On the contrary, with dideuterated **13** in acidic solution (KCl/DCl buffer in D_2O, pD = 1.2, $I = 0.27$ mol·l^{-1}, $[H_0] = [G_0] = 4 \cdot 10^{-3}$ mol·l^{-1}), no changes of the chemical shifts of the host and only very weak changes of the chemical shifts upon complexation ($\Delta\delta = +0.01$ and $+0.02$) of the protons of the guest are observed. Under the assumption, that the upfield shifts of the protons of **13** in basic solution, in which almost every guest molecule is complexed, are also the upfield shifts for saturation binding in acidic solution, the association constant for the 1:1 complex of **1** and dideuterated **13** can be estimated as $K_a \approx <10$ l·mol^{-1}. The observed difference in complexation at various pH is due to the deuteration of the guest in the acidic solution and not to the presence of different inorganic salts with different ionic strength. The complexation behaviour of neutral aromatic guests has been found almost insensitive to the pH of the solution and to the nature of inorganic salts up to ionic strengths of 0.5 mol·l^{-1}.



12: R = $\overset{\oplus}{N}Me_3$ $FSO_3^{\ominus}$, R' = H

13: R = R' = NMe_2



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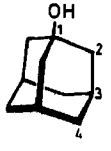

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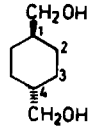

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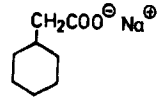

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A similar, although not as drastic, difference in complexation was observed in solutions of **1** and *N,N,N′,N′*-tetramethylbenzidine (**14**) at acidic and basic pH. By solid-liquid extraction, with $[1] = 5.02 \cdot 10^{-3}$ mol·l^{-1} in a $1.5 \cdot 10^{-2}$ M aqueous solution of potassium carbonate, a $4 \cdot 10^{-4}$ M solution of **14** was obtained. Upon consideration of the maximum solubility of the guest in this solution in absence of **1** ($4.2 \cdot 10^{-6}$ mol·l^{-1}), $K_a = 1.7 \cdot 10^4$ l·mol^{-1} was calculated for the 1:1 complex (293–295 K). Due to the small amount of host, which is complexed in the above mentioned solution, the $\Delta\delta$ values of the protons of the host are only very small. The protons of completely complexed **14**, however, show strong and specific complexation shifts: $\Delta\delta = +1.72$ (2-H), $+0.57$ (3-H), and $+0.23$ (NCH_3). **14** is enclosed axially in the cavity of **1** with the dimethylamino groups reaching into the aqueous solution. In acidic solution, complexation is still observed by ^{1}H NMR, although to a weaker extent (KCl/DCl buffer in D_2O, pD = 1.2, $I = 0.27$ mol·l^{-1}, $[H_0] = [G_0] = 4 \cdot 10^{-3}$ mol·l^{-1}). The specific complexation shifts of the protons of **1**

Table 1. Association constants of 1:1 host-guest complexes of **1**

Guest	K_a ($l \cdot mol^{-1}$)	Experimental Conditions
1-(Dimethylamino)naphthalene	$9.3 \cdot 10^3$ [a]	aqueous solution, 293–295 K
Sodium 5-(Dimethylamino)-1-naphthalenesulfonate	$1.4 \cdot 10^5$ [a]	aqueous solution, 292.5 K
1-(Trimethylammonio)naphthalene Fluorosulfonate (**12**)	$1.7 \cdot 10^3$ [a]	aqueous solution, 292.5 K
1,5-Bis(dimethylamino)naphthalene (**13**)	$9.7 \cdot 10^3$ [b]	$1.5 \cdot 10^{-2}$ M aqueous K_2CO_3, pH ≈11, 293–295 K
1,5-Bis(dimethylamino)naphthalene Bis(deuteriochloride)	≈<10 [c]	D_2O/DCl/KCl, pD = 1.2, I = 0.27 $mol \cdot l^{-1}$, 303 K
N,N,N',N'-Tetramethylbenzidine (**14**)	$1.7 \cdot 10^4$ [b]	$1.5 \cdot 10^{-2}$ M aqueous K_2CO_3, pH ≈11, 293–295 K
4,4'-Bis(dimethylamino)biphenyl Bis(deuteriochloride)	≈<$1.5 \cdot 10^3$ [c]	D_2O/DCl/KCl, pD = 1.2, I = 0.27 $mol \cdot l^{-1}$, 303 K
1-Adamantanol (**15**)	$1.6 \cdot 10^2$ [a]	aqueous solution, 292.5 K
trans-1,4-Cyclohexanedimethanol (**16**)	$5.0 \cdot 10^2$ [d]	aqueous solution, 292.5 K
Sodium Cyclohexaneacetate (**17**)	$7.4 \cdot 10^2$ [d]	aqueous solution, pH ≈8.8, 292.5 K

[a] See ref.[2]. – [b] Determined from solid-liquid extraction; for concentrations of host and guest, see text. – [c] Estimated from ^1H NMR complexation shifts, see text. The bis(deuteriochlorides) were prepared by dissolving **13** and **14**, resp., in the buffer. – [d] Estimated from competitive inhibition experiments. The fluorescence of potassium 6-[(4-methylphenyl)amino]-2-naphthalenesulfonate (TNS) is monitored (λ_{exc} = 360 nm, λ_{em} = 445 nm); for the method, see ref.[2]; [TNS] = $2.3 \cdot 10^{-7}$ $mol \cdot l^{-1}$; [**1**] = $2.7 \cdot 10^{-6}$–$2.7 \cdot 10^{-5}$ $mol \cdot l^{-1}$; concentration of inhibitors **16** and **17**: ≈$7 \cdot 10^{-3}$ $mol \cdot l^{-1}$. A solution of **17** is prepared from stoichiometric amounts of cyclohexaneacetic acid and NaOH.

[largest Δδ-values = +0.41 (2-H), −0.41 (10-H)] demonstrate the location of the guest in the aromatic guest plane. The signals of the protons of deuterated **14** are shifted upfield by Δδ = +0.52 (2-H), +0.37 (3-H), and +0.02 $\overset{+}{N}CH_3$). From these shifts, an association constant for the 1:1 complex of $K_a \approx < 1.5 \cdot 10^3$ l·mol^{-1} was estimated as described above.

On first view, the weaker complexation between **1** and aromatic guests bearing alkylammonium residues seems explainable by the repulsion between the ammonium nitrogens of the spiropiperidinium rings attached to the aliphatic bridges of **1** and the cationic centers of the enclosed guest. We feel, however, that this repulsive interaction cannot explain alone the almost complete absence of complexation of dideuterated 1,5-bis(dimethylamino)naphthalene.

Previously we also observed no complexation between benzyltrimethylammonium bromide and a tetraoxa[5.1.5.1]paracyclophane without piperidinium rings attached to the aliphatic bridges, whereas other benzene and toluene derivatives with polar or anionic substituents gave, according to ^{1}H NMR, significant complexation with this host[4]. Our experimental results indicate, that there are other effects, which reduce the strength of complexation in aqueous solution between apolar hosts and apolar guests bearing alkylammonium groups which are not well understood at the present stage. A reduction of the strength of hydrophobic interactions as consequence of the influence of the alkylammonium residues on the structure of water around the guest might be one effect contributing to the observed weak complexation[7,8].

B. With Alicyclic Guests[9]

Table 1 gives the association constants K_a of the 1:1 complexes formed between **1** and the alicyclic guests 1-adamantanol (**15**)[2], *trans*-1,4-cyclohexanedimethanol (**16**), and sodium cyclohexaneacetate (**17**) in aqueous solution. These association constants were estimated from competitive inhibition by these compounds of the binding of potassium 6-[(4-methylphenyl)amino]-2-naphthalenesulfonate (TNS) and evaluation of the fluorescence changes of TNS upon addition of **1** by a Benesi-Hildebrand type treatment[2]. The two cyclohexane derivatives form stronger complexes than 1-adamantanol, although the latter guest has a larger apolar surface. The cyclohexane derivatives seem to fit better into the cavity of **1** than the spherical adamantane guest. In addition, ion pairing might be effective in the complex of **17**. In the ^{1}H NMR spectra in D_2O with $[H_0] = [G_0] = 4 \cdot 10^{-3}$ mol·l^{-1}, complexation of **15**−**17** is indicated by upfield shifts of the signals of their protons, e.g. of **15**: Δδ = +0.03 (2-H), +0.06 (3-H), +0.06 (4-H); of **16**: Δδ = +0.09 (CH_2), +0.11 (1,4-H_{ax}), +0.13 (2,3-H_{ax}), and +0.15 (2,3-H_{eq}).

We thank Professor Dr. *H. A. Staab* for the generous support of this work and Mr. *J. Hopisch* for recording the NMR spectra.

Experimental Part

Complexation Studies: The instrumentation and the conditions for the recording of fluorescence and ^1H NMR spectra have been reported before[4]. All NMR spectra in D_2O were recorded at 303 K and δ-values refer to sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate (TSP) in D_2O as external standard placed in a capillary tube inside the NMR tube. The preparation of the samples for fluorescence titrations in the competitive inhibition experiments (T = 292.5 K) has been described[2].

1-(Trimethylammonio)naphthalene fluorosulfonate (**12**)[10], *trans*-1,4-cyclohexanedimethanol (**16**)[11], and 1,5-bis(dimethylamino)naphthalene (**13**)[12] were prepared according to literature procedures. All other guest compounds were commercial products of analytical grade. *N,N,N',N'*-tetramethylbenzidine (**14**) was further purified by chromatography on silica from dichloromethane and recrystallization from ethanol. 1-Adamantanol (**15**) was recrystallized from water.

The determination of association constants by solid-liquid extraction has been described in ref.[2]. The UV bands used for the determination of concentrations of guests were: **13** (*n*-hexane): λ_{max}, nm (ε) = 319 (9400), 238 (28700), 205 (37550); **14** (*n*-hexane): λ_{max}, nm (ε) = 303 (33600), 205 (38580).

The ^1H NMR spectra of pure guests in D_2O solutions are given below (360 MHz, TSP ext.; 303 K; [G] = $4 \cdot 10^{-3}$ mol·l^{-1}).

12 (D_2O): δ = 3.99 (s; N^+-CH_3), 7.66 (t, J = 8.1 Hz; 3-H), 7.76 ("t", $J \approx$ 8 Hz; 6-H), 7.86 ("t", $J \approx$ 8 Hz; 7-H), 8.07 (d, J = 8.2 Hz; 2-H), 8.20 (d, J = 8.2 Hz; 5-H), 8.21 (d, J = 8.3 Hz; 4-H), 8.47 (d, J = 8.8 Hz; 8-H).

13 ([D_4]methanol): δ = 2.88 (s; NCH_3), 7.13 (d, J = 7.4 Hz; 2-H), 7.40 ("t", $J \approx$ 7.9 Hz; 3-H), 7.94 (d, J = 8.4 Hz; 4-H).

14 ([D_4]methanol): δ = 2.97 (s; NCH_3), 6.87 (mc, AA'BB'; 3-H), 7.45 (mc, AA'BB'; 2-H).

13 (DCl/KCl/D_2O; pD = 1.2; I = 0.27 mol·l^{-1}): δ = 3.54 (s; N^+-CH_3), 7.99 ("t", J = 8.1 Hz; 3-H), 8.16 (d, J = 7.9 Hz; 2-H), 8.37 (d, J = 8.7 Hz; 4-H).

14 (DCl/KCl/D_2O; pD = 1.2; I = 0.27 mol·l^{-1}): δ = 3.35 (s; N^+-CH_3), 7.74 (mc, AA'BB'; 3-H), 7.89 (mc, AA'BB'; 2-H).

15 (D_2O): δ = 1.63 (mc; 4-H), 1.72 (mc; 2-H), 2.13 (mc; 3-H).

16 (D_2O): δ = 0.96 ("t", $J \approx$ 10 Hz; 2,3-H_{ax}), 1.45 (mc; 1,4-H_{ax}), 1.80 ("d", $J \approx$ 7.1 Hz; 2,3-H_{eq}), 3.43 (d, J = 6.4 Hz; CH_2).

1'-Acetyl-2,6-dioxo-4,4'-spirobi[piperidine]-3,5-dicarbonitril (**5**): 1 l of dry ethanol was saturated with dry gaseous ammonia at 0°C. A mixture of 282.34 g (2.00 mol) of 1-acetyl-4-piperidone and 452.48 g (4.00 mol) of ethyl cyanoacetate was then added rapidly. After standing of the solution in the refrigerator for 3 d, the precipitated imide ammonium salt was collected by filtration, washed once with cold dry ethanol, and dried for 2 h at 50°C/20 Torr. The salt was then dissolved in a minimum amount of boiling water, and the resulting solution was acidified with 2 N HCl. After cooling, precipitated **5** was collected by filtration, washed once with ice-cold water, and dried at 100°C/20 Torr: 383.1 g (70%), m.p. 255°C (dec.). – IR (KBr): ν(C≡N) 2275; ν(C=O) 1710, 1600 cm^{-1}. – ^1H NMR (80 MHz, [D_6]dimethylsulfoxide): δ = 1.5–1.95 (m; 4H), 2.01 (s; 3H), 3.3–3.75 (m; 4H), 5.06 (s; 2H), 12.27 (s; 1H). – MS: m/z = 274 (100%, M^+).

$C_{13}H_{14}N_4O_3$ (274.3) Calcd. C 56.93 H 5.15 N 20.43 Found C 56.63 H 5.40 N 20.47

Diethyl 1-Acetyl-4,4-piperidinediacetate (**6**): A mixture of 43.33 g (0.158 mol) of **5**, 55 ml of conc. sulfuric acid, and 47 ml of water was refluxed for 1 h, after which the solution was diluted with 63 ml of water. Refluxing was continued for additional 5 h. The solution was

cooled to room temperature, neutralized with a 50% aqueous solution of potassium hydroxide, acidified with 2 N HCl, and evaporated to dryness in vacuo. To ensure complete dryness, toluene was added and the remaining water was removed from the boiling mixture with a Dean-Stark trap. After evaporation of the toluene in vacuo, a mixture of 550 ml of absol. ethanol and 60 ml of conc. sulfuric acid was added to the solid residue and the resulting solution was refluxed for 10 h. The sulfuric acid was neutralized with moist sodium hydrogen carbonate, and then 30 g of anhydrous potassium carbonate was added to remove the water from the alcohol. 500 ml of ether was added and the inorganic salts were separated by filtration. After extracting the salts with six 500 ml portions of ether, the combined ethereal extracts were dried over magnesium sulfate and the solvent was removed in vacuo. The residue was taken in 50 ml of cold 0.5 N aqueous solution of sodium carbonate and extracted rapidly with five portions of dichloromethane. The combined dichloromethane extracts were washed once with saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and evaporated *in vacuo*. 24.1 g (59%) of crude diethyl 4,4-piperidinediacetate was obtained as viscous colourless oil, which was used in the next reaction without further purification. – IR (neat): ν(NH) 3325; ν(C=O) 1720 cm^{-1}. – ^1H NMR (60 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz; 6H), 1.45–1.75 (m; 4H), 2.02 (s, br; 1H), 2.55 (s; 4H), 2.7–3.0 (m; 4H), 4.10 (q, *J* = 7.1 Hz; 4H).

42 g (0.163 mol) of the diethyl 4,4-piperidinediacetate together with 100 ml of acetic anhydride were refluxed for 1 h. After evaporation of the excess of acetic anhydride in vacuo, a cold 0.5 N aqueous solution of sodium carbonate was added to the residual oil. The mixture was extracted rapidly with four portions of dichloromethane. The combined organic phases were washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and evaporated. Chromatography on silica from ethyl acetate yielded 36.7 g (45% yield starting from **5**) of **6** as colourless oil, n_D^{20} = 1.4810. – IR (neat): ν(C=O) 1730, 1640 cm^{-1}. – ^1H NMR (80 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz; 6H), 1.55–1.8 (m; 4H), 2.08 (s; 3H), 2.58 (s; 4H), 3.35–3.7 (m; 4H), 4.13 (q, *J* = 7.1 Hz; 4H). – MS: *m/z* = 299 (65%, M^+), 256 (100).

$C_{15}H_{25}NO_5$ (299.4) Calcd. C 60.18 H 8.42 N 4.68 Found C 60.04 H 8.14 N 4.68

1-Acetyl-4,4-piperidinediethanol (**7**): A solution of 10 g (0.459 mol) of lithiumborohydride in 500 ml of absol. tetrahydrofuran was added to a solution of 48.6 g (0.162 mol) of diester **6** in 400 ml of absol. tetrahydrofuran and the resulting mixture was stirred under Ar at 20°C for 2 d. 2 N HCl was added until the solution showed pH 3–4 and the solvent was evaporated in vacuo. In order to destroy the cyclic boric acid esters formed by the product, 600 ml of methanol and 2 N HCl to give pH 3–4 was added to the residue and the mixture was heated for 1 h. The solvent was evaporated in vacuo and a 1 N aqueous solution of sodium carbonate was added to the residue. The resulting mixture was extracted with dichloromethane in a continuous extractor for 2 d, after which the organic solvent was distilled off. Pure crystalline diol **7** was obtained by chromatography of the extracted crude product on silica from ethyl acetate/methanol (3:1): 18.6 g (53%), m.p. 72°C. – IR (KBr): ν(OH) 3660–3060; ν(C=O) 1610 cm^{-1}. – ^1H NMR (80 MHz, [D_4]methanol): δ = 1.35–1.7 (m; 4H), 1.65 (t, *J* = 7.3 Hz; 4H), 2.07 (s; 3H), 3.4–3.65 (m; 4H), 3.65 (t, *J* = 7.3 Hz; 4H). – MS: *m/z* = 215 (50%, M^+), 171 (82), 140 (100).

$C_{11}H_{21}NO_3$ (215.3) Calcd. C 61.37 H 9.83 N 6.51 Found C 61.48 H 9.56 N 6.62

1-Acetyl-4,4-bis[2-(p-tolylsulfonyl)ethyl]piperidine (**8**): A solution of 29 g (0.152 mol) of tosyl chloride in 140 ml of dry pyridine was added dropwise below 0°C to a solution of 13.6 g (63.2 mmol) of diol **7** in 140 ml of dry pyridine. The mixture was stirred for 5 h at 0 to −5°C, stored overnight in the refrigerator, then poured onto 200 g of crushed ice, and

the resulting aqueous solution was extracted five times with dichloromethane. The combined organic phases were washed twice with ice-cold 6 N HCl, twice with cold water, once with a cold 1 N aqueous solution of sodium hydrogen carbonate, and finally with a cold saturated aqueous solution of sodium chloride. The organic solution was dried over magnesium sulfate and evaporated. Chromatography on silica from ethyl acetate/ethanol (10:1) gave 24.2 g (73%) of **8** as a colourless glass. – IR (neat): ν(C=O) 1640; ν(SO_2O) 1355, 1175 cm^{-1}. – ^1H NMR (80 MHz, $CDCl_3$): δ = 1.15–1.55 (m; 4H), 1.73 (t, *J* = 6.6 Hz; 4H), 2.05 (s; 3H), 2.46 (s; 6H), 3.2–3.6 (m; 4H), 4.05 (t, *J* = 6.6 Hz; 4H), 7.25–7.5 and 7.6–7.85 (AA'BB'; 8H).

$C_{25}H_{33}NO_7S_2$ (523.7) Calcd. C 57.34 H 6.35 N 2.67 S 12.25
Found C 57.53 H 6.76 N 2.77 S 11.97

1',1'',1''',1''''-Tetraacetyl-9,13,17,19,29,33,37,39-octamethyltetraspiro[1,7,21,27-tetraoxa-[7.1.7.1]paracyclophane-4,4':14,4'':24,4''':34,4''''-tetrakispiperidine] (**9**): A mixture of 11.66 g (31.7 mmol) of 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine (**4**), 4.33 g (65.6 mmol) of potassium hydroxide (85%), and 2.5 g of 18-crown-6 in 1400 ml of absol. tetrahydrofuran containing 6 ml of water was heated to reflux. After 1 h, a solution of 16.60 g (31.7 mmol) of ditosylate **8** in 500 ml of absol. tetrahydrofuran was added dropwise within 1 h. After stirring the reaction mixture at reflux for 2 d under Ar, the solvent was evaporated in vacuo and the residue was partitioned between chloroform and 2 N NaOH. The organic layer was washed once with 2 N NaOH, three times with water, dried over magnesium sulfate, and evaporated in vacuo. Chromatography from chloroform/ethyl acetate/methanol (5:4:1) on silica followed by recrystallization from ethanol/ether afforded 6.29 g (18%) of **9**, m.p. 310°C (after drying at 170°C/10^{-3} Torr). – IR (KBr): ν(C=O) 1640 cm^{-1}. – ^1H NMR (360 MHz, $CDCl_3$): see general part. – MS: *m/z* = 1093 (M^+).

$C_{68}H_{92}N_4O_8$ (1093.5) Calcd. C 74.69 H 8.48 N 5.12 Found C 74.57 H 8.25 N 5.34

9,13,17,19,29,33,37,39-Octamethyltetraspiro[1,7,21,27-tetraoxa[7.1.7.1]paracyclophane-4,4':14,4'':24,4''':34,4''''-tetrakispiperidine] (**10**): A solution of 3.0 g (2.74 mmol) of **9** and 7.88 g (0.119 mol) of potassium hydroxide (85%) in 100 ml of 2-methoxyethanol was heated to reflux for 5 h. 40 ml of the solvent was distilled off and 40 ml of water was slowly dropped into the remaining solution at ≈80°C. Upon cooling, the product crystallized and was collected by filtration. The product was washed with water until the washing solution showed neutral pH, dried at 100°C/20 Torr and recrystallized from ethanol/ether: 2.17 g (85%) of colourless **10**, m.p. 345°C (after drying at 170°C/10^{-3} Torr). – IR (KBr): ν(NH): 3360, 3320 cm^{-1}. – ^1H NMR (360 MHz, $CDCl_3$): δ = 1.45–1.6 (m; 8H, 3'-H), 1.61 (s, br; 4H, NH), 1.99 ("t", *J* = 6.7 Hz; 8H, 3-H), 2.13 (s; 24H, Aryl-CH_3), 2.15–2.3 (m; 8H, 3''-H), 2.75–3.0 (m; 16H, 2'- and 2''-H), 3.84 ("t", *J* = 6.7 Hz; 8H, 2-H), 6.73 (s; 8H, 10-H). – MS: *m/z* = 925 (M^+).

$C_{60}H_{84}N_4O_4$ (925.4) Calcd. C 77.88 H 9.15 N 6.06 Found C 77.60 H 9.21 N 5.83

1',1'',1''',1'''',9,13,17,19,29,33,37,39-Dodecamethyltetraspiro[1,7,21,27-tetraoxa[7.1.7.1]-paracyclophane-4,4':14,4'':24,4''':34,4''''-tetrakispiperidine] (**11**): A mixture of 4.5 g (4.86 mmol) of **10**, 5.15 g (0.112 mol) of formic acid (98–100%), and 4.02 g (46.85 mmol) of a 35% aqueous solution of formaldehyde was heated slowly with stirring until the beginning of the evolution of carbon dioxide (≈60°C). Stirring without heating was continued until the end of the evolution of gas and the mixture was then heated to 100°C for 12 h. After cooling, the reaction mixture was added to 80 ml of 2 N NaOH. The aqueous suspension was extracted four times with chloroform. The combined chloroform phases were washed twice with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated in vacuo. Chromatography on neutral alumina (Brockmann, activity II–III)

from ethyl acetate/chloroform (1 : 1) followed by recrystallization from toluene/ethanol (95%) afforded 4.38 g (92%) of **11** as colourless needles, m.p. 254°C (after drying at 130°C/10^{-3} Torr). – IR (KBr): ν(NCH_2–H) 2795 cm^{-1}. – ^1H NMR (360 MHz, $CDCl_3$): δ = 1.55–1.7 (m; 8H, 3′-H), 1.95 ("t", *J* = 6.7 Hz; 8H, 3-H), 2.12 (s; 24H, Aryl-CH_3), 2.20 (s; 6H, NCH_3), 2.31 (s; 6H, NCH_3), 2.25–2.4 (m; 8H, 3″-H), 2.35–2.5 (m; 16H, 2′- and 2″-H), 3.83 ("t", *J* = 6.7 Hz; 8H, 2-H), 6.73 (s; 8H, 10-H). – MS: *m/z* = 981 (M^+).

$C_{64}H_{92}N_4O_4$ (981.5) Calcd. C 78.32 H 9.45 N 5.71 Found C 78.30 H 9.18 N 5.72

1′,1′,1″,1″,1‴,1‴,1⁗,1⁗,9,13,17,19,29,33,37,39-Hexadecamethyltetraspiro[1,7,21,27-tetraoxa[7.1.7.1]paracyclophane-4,4′:14,4″:24,4‴:34,4⁗-tetrakispiperidinium] Tetrakis(fluorosulfonate) (**2**): 0.29 ml (0.412 mg, 3.61 mmol) of methyl fluorosulfonate was added via syringe under Ar to a stirred solution of 300 mg (0.306 mmol) of **11** in 50 ml of dry chloroform, and the mixture was stirred for 20 h at 20°C. 30 ml of dry ether was added and after the solution had stood for 1 h, the precipitated product was isolated by filtration and washed with dry ethyl acetate. Recrystallization from methanol/ether yielded 360 mg (79%) of **2** as hygroscopic solid. For elemental analysis, the crystals of **2** were exposed to laboratory air for 1 h; m.p. 276°C. – ^1H NMR (360 MHz, [D_4]methanol): δ = 1.9–2.1 (m; 8H, 3′-H), 2.13 ("t", *J* = 5.9 Hz; 8H, 3-H), 2.16 (s; 24H, Aryl-CH_3), 2.6–2.75 (m; 8H, 3″-H), 3.18 (s; 12H, $\overset{+}{N}CH_3$), 3.20 (s; 12H, $\overset{+}{N}CH_3$), 3.3–3.45 and 3.45–3.6 (two m; each 8H, 2′- and 2″-H), 3.89 ("t", *J* = 5.9 Hz; 8H, 2-H), 6.90 (s; 8H, 10-H).

$C_{68}H_{104}F_4N_4O_{16}S_4 \times 3\ H_2O$ (1491.9) Calcd. C 54.75 H 7.43 N 3.76 S 8.60
Found C 54.69 H 7.76 N 3.74 S 8.48

1′,1′,1″,1″,1‴,1‴,1⁗,1⁗,9,13,17,19,29,33,37,39-Hexadecamethyltetraspiro[1,7,21,27-tetraoxa[7.1.7.1]paracyclophane-4,4′:14,4″:24,4‴:34,4⁗-tetrakispiperidinium] Tetrakis(tetrafluoroborate) (**3**): 20 ml of an aqueous solution of sodium tetrafluoroborate, saturated at 100°C, was added to a solution of 200 mg (0.13 mmol) of **2** in 5 ml of water. The product, which had precipitated upon standing in the refrigerator, was collected by filtration, dried at 100°C/20 Torr and recrystallized from acetonitrile/ethanol. Drying at 170°C/10^{-3} Torr yielded 170 mg (90%) colourless needles, m.p. 265°C. – ^1H NMR (360 MHz, [D_3]acetonitrile): δ = 1.85–2.0 (m; 8H, 3′-H), 2.05 ("t", *J* = 6.1 Hz; 8H, 3-H), 2.15 (s; 24H, Aryl-CH_3), 2.5–2.7 (m; 8H, 3″-H), 3.06 (s; 12H, $\overset{+}{N}CH_3$), 3.08 (s; 12H, $\overset{+}{N}CH_3$), 3.2–3.45 (m; 16H, 2′- and 2″-H), 3.79 ("t", *J* = 6.1 Hz; 8H, 2-H), 6.90 (s; 8H, 10-H).

$C_{68}H_{104}B_4F_{16}N_4O_4 \times 1\ H_2O$ (1406.9) Calcd. C 58.05 H 7.59 B 3.08 N 3.98
Found C 58.29 H 7.86 B 3.00 N 4.06

1′,1′,1″,1″,1‴,1‴,1⁗,1⁗,9,13,17,19,29,33,37,39-Hexadecamethyltetraspiro[1,7,21,27-tetraoxa[7.1.7.1]paracyclophane-4,4′:14,4″:24,4‴:34,4⁗-tetrakispiperidinium] Tetrachloride (**1**): 200 mg (0.13 mmol) of **2** was chromatographed on ion exchange resin Dowex 1X8 (Cl^-, 200–400 mesh) from water. Recrystallization from methanol/ether gave 130 mg (77%) of **1** as hygroscopic colourless solid. For elemental analysis, crystals of **1** were exposed to laboratory air for 1 h; m.p. 270°C (dec.). – ^1H NMR (360 MHz, D_2O, 303 K, $<7.5 \cdot 10^{-3}$ $mol \cdot l^{-1}$): δ = 1.90 (mc; 8H, 3′-H), 1.99 ("t", *J* = 7 Hz; 8H, 3-H), 2.08 (s; 24H, Aryl-CH_3), 2.70 (mc; 8H, 3″-H), 3.16 (s; 24H, $\overset{+}{N}(1')-CH_3$ and $\overset{+}{N}(1'')-CH_3$), 3.43 (mc; 16H, 2′- and 2″-H), 3.91 ("t", *J* = 7 Hz; 8H, 2-H), 6.99 (s; 8H, 10-H).

$C_{68}H_{104}Cl_4N_4O_4 \times 4\ H_2O$ (1255.5) Calcd. C 65.05 H 8.99 Cl 11.30 N 4.46
Found C 65.24 H 8.91 Cl 11.27 N 4.45

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