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Perhydrotriquinacenic Hosts. 2. Synthesis and Complexation Properties of Speleands of *C3* Symmetry.

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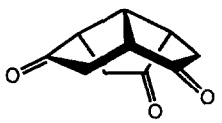
Abstract: The synthesis and complexation properties of four speleands (**13-16**) derived from triol **4** and the chiral C_3 concave cap **3**, linked to the cyclic aza-oxa macrocycle **2** by means of ester-amide bridges, are described.

Introduction

Since the pioneering work of Pedersen, Cram, Vögtle and Lehn, among others, host-guest or supramolecular chemistry has become a rapidly growing field of great interest.[1] In particular, the design, synthesis and use of chiral macrocycles capable of enantioselective recognition of charged or neutral molecules[2] occupies a central position in supramolecular chemistry and in connection to the fundamental chemical interactions occurring in enzymes, antibodies, antigens and asymmetric synthesis. Recently, we have described the application of *all-cis*-tricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-trione[3] (hereafter referred to as triketone **1**) to the synthesis of chiral perhydrotriquinacenic podands of *C3* symmetry.[4] We wish now to report on the use of **1** in the construction of more complex chiral hosts of the *speleand* type.[5]



1

The characteristic features of triketone **1** make this molecule an adequate precursor for the synthesis of criptands. Its triple functionalization allows the anchoring of three chains, which could subsequently be bonded to another cap to build a macrocyclic structure. On the other hand, **1** is a chiral molecule of *C3* symmetry, which can be easily obtained in both enantiomeric forms.[6] As a first approximation to the synthesis of this type of chiral perhydrotriquinacenic criptands, we describe in the present article the preparation of two compounds constituted by a triquinacene cap linked by three chains to a cyclic subunit of the [18]-N_3O_3[7] type. Experiments designed to modelize the crucial triple coupling with the polar moiety [18]-N_3O_3 have led to the preparation of two other criptands whose apolar cap is constituted by a cyclohexane ring.

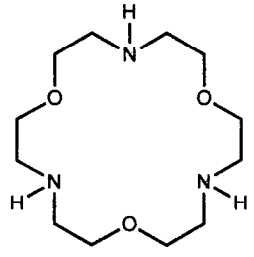
These macrocycles can be included in the family of speleands,[5] since they are formed by a hydrophobic, rigid and concave cap linked to a polar substructure by several anchorage points. The only compounds of this class of macrocycles prepared until now are two "molecular cages" constituted by a cyclotriveratrylene cap bonded to a [18]-N_3O_3 subunit (CTV-[18]-N_3O_3). We describe also the complexation experiments of our criptands with methyl ammonium cation.

Results and Discussion

1. Synthesis

The synthetic sequence designed for the preparation of the new macrocycles involved as a key step a triple-coupling reaction between a triquinanic component and the macrocyclic triamine [18]-N_3O_3 (1,7,13-triaza-4,10,16-trioxacyclooctadecane, **2**)[7]. Since the formation of amides from amines and suitably activated carboxylic acids is a fast and efficient process, adequate for its use in high-dilution conditions, we decided to incorporate three chains in the perhydrotriquinacene skeleton, and subsequently transform the free ends of the chains into acid chlorides in order to allow the condensation with **2**.

The starting product for the synthesis is the *tris-endo* triol **3**, which is easily obtained from **1** by catalytic hydrogenation.[6] Triol **3** retains the C_3 symmetry of the triketone **1**, and moreover presents the requisite *tris-endo* stereochemistry which is necessary in order to take advantage of the concavity of the triquinacene skeleton in the construction of the desired macrocycles. As a model for the incorporation of the three chains and of the subsequent cyclizations, we selected 1,3,5-cyclohexanetriol **4**, à commercially available compound,[8] which in turn has originated a new class of macrocycles.



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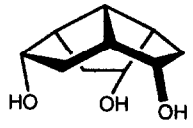
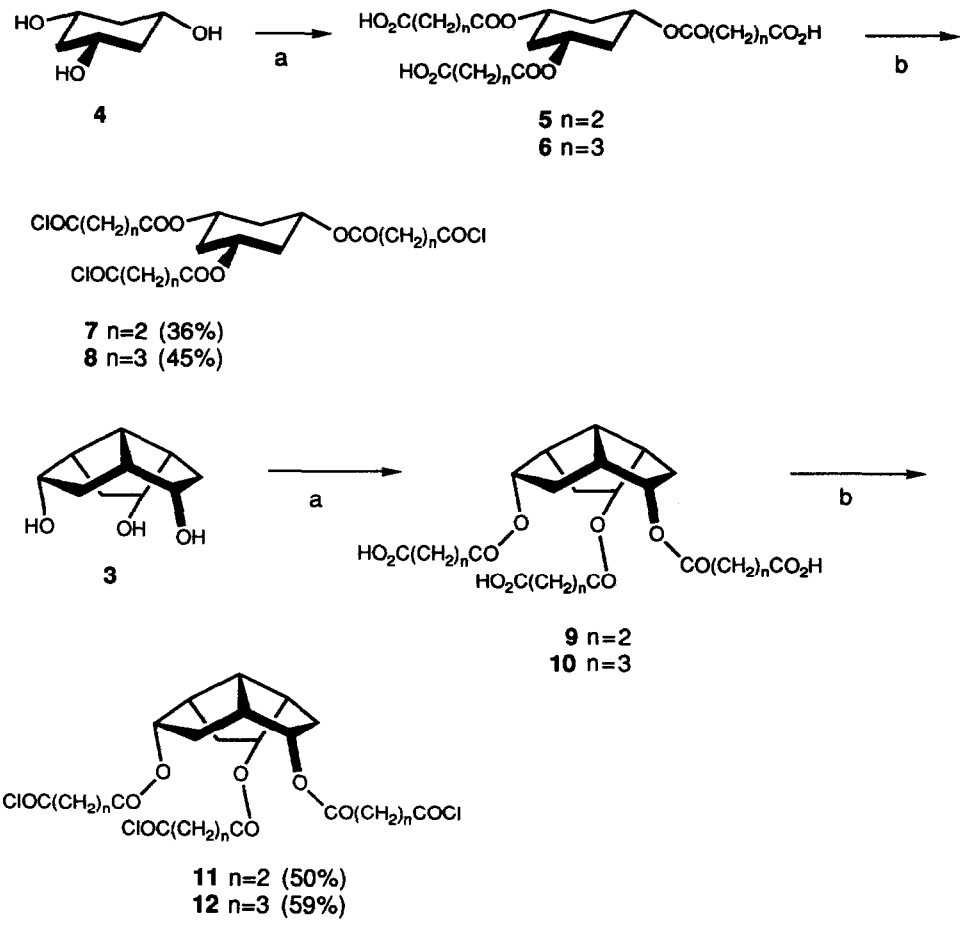


3

4

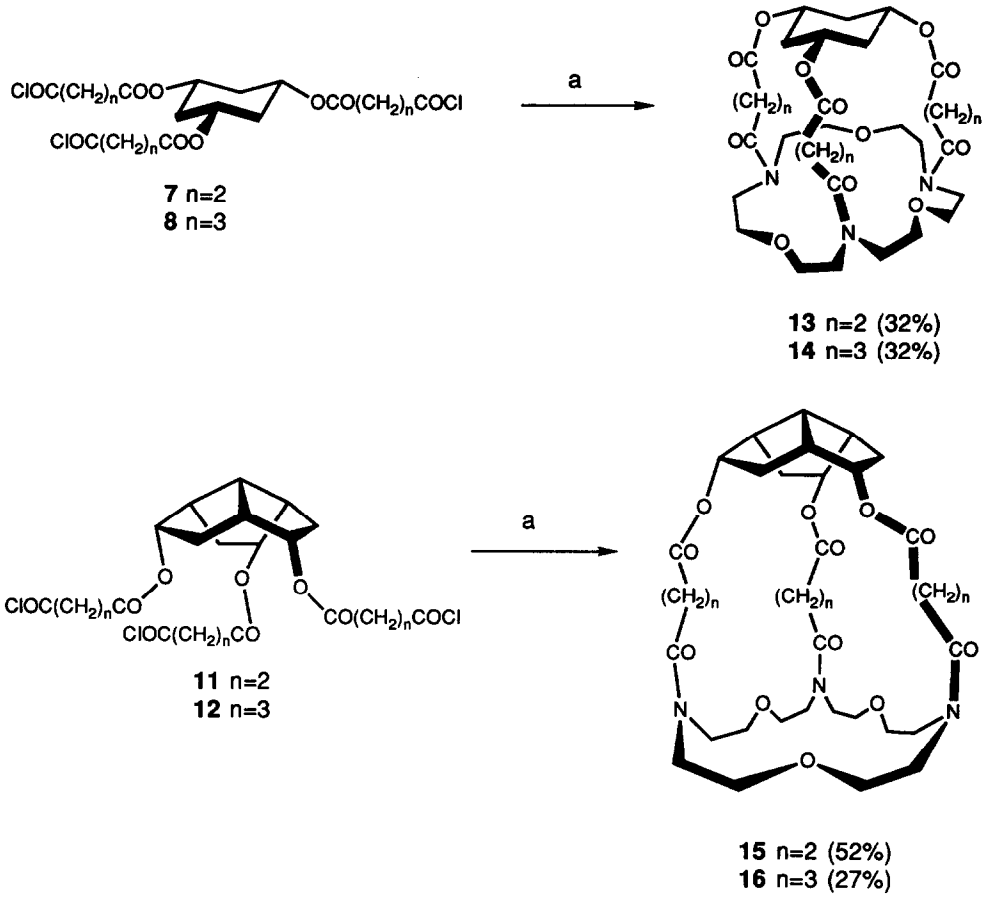
Originally, we planned to build our speleands according to a strategy similar to that of Collet and Lehn,[5] *i. e.*, by a triple alkylation of triols **3** and **4** with a suitable ω-haloester followed by subsequent coupling with **2**. After extensive experimentation it became clear that this approach was not feasible in our case, due to the relatively low nucleophilicity of our secondary alcohols. Thus **3** failed to give the desired triester, even with the strongly electrophilic methyl (*p*-bromomethyl)benzoate, after prolonged reaction times (*n*BuLi, THF, HMPA, 10 days). Since hindered alcohols are known to react easily with activated carboxylic acid derivatives we decided to investigate the reaction of **3** and **4** with cyclic acid anhydrides, which would afford the desired triacids (with chains of variable lengths) in one step.

The reaction of **4** with succinic and glutaric anhydrides in the presence of triethylamine and 4-*N*,*N*-dimethylaminopyridine led to the triacids **5** and **6** respectively, whose treatment with oxalyl chloride in benzene allowed the preparation of the acid chlorides **7** and **8** in 50 and 59% overall yield, respectively. The same reaction sequence from triol **3** produced the acid chlorides **11** (36% overall yield) and **12** (45% overall yield) (Scheme 1). The synthesis of the triamine **2** was effected following the sequence described by Graf and Lehn,[7b] with some experimental modifications. With all the requisite fragments in hand, we proceeded to test the triple coupling reactions.



SCHEME 1. a: succinic anhydride (n=2) or glutaric anhydride (n=3) / NEt_3 / DMAP/CH_2Cl_2
b: $(COCl)_2$ / benzene

After extensive experimentation using as a model the cyclohexane derivative **7**, the best conditions found for the cyclization required the simultaneous addition, for 9 h at room temperature, of a benzene solution of the acid chloride and of a mixture of triamine **2** and triethylamine, to anhydrous benzene, in such a way that the final concentration was approximately $6x10^{-4}$ M. Following this protocole, the desired speleands **13-16** were obtained (after chromatographic purification) as solids which did not melt below 300 °C with the yields shown in Scheme 2. The four products were characterized by their IR, ^{1}H-NMR, ^{13}C-NMR and MS-FAB spectra, and were found in all cases to be stereoisomerically pure.[9]



SCHEME 2. a: **2**, NEt_3, benzene, high dilution

2. Complexation properties

Compounds **13**, **14**, **15** and **16** are cage molecules which possess (according to CPK molecular models) roughly spheric, rigid intramolecular cavities with diameters of 2, 3, 3 and 4 Å respectively, suitable in principle for the inclusion of small organic molecules. As a matter of fact, we observed during their characterization that they exhibit a strong tendency towards association with neutral molecules: So, elemental analyses of compounds **13** and **15** correspond to complexes with stoichiometries **13**·1$CHCl_3$ and **15**·0.75CH_2Cl_2·0.25AcOEt; on the other hand, the NMR spectrum (in CD_2Cl_2) of **13** (previously dried under vacuum at 40 °C for 2 days) shows the presence of an equivalent of $CHCl_3$.[10]

We decided to study the complexation of speleands **13-16** with methyl ammonium cation, since inspection of CPK molecular models showed that methyl ammonium cation had the appropiate size for its inclusion in the cavities of **13-16**. On the other hand, the [18]-N_3O_3 subunit should be able to interact with cationic species: In fact, the tris-*N*-methyl derivative of the triamine **2** is known to coordinate selectively and efficiently with primary ammonium cations,[11] and the preliminary complexation studies of the speleands CTV-[18]-N_3O_3 with methyl ammonium salts described by Lehn and co-workers[5] showed that complexation took place in these systems.

The studies were effected by mixing each one of the speleands **13-16** with $CDCl_3$ and 1 equivalent of finely divided methyl ammonium picrate. After shaking for 1.5 h and centrifugation, 0.1 mL aliquots were withdrawn and diluted to a final volume of 10 mL with $CHCl_3$; UV spectroscopy allowed us to determine the concentration of extracted picrate. We determined subsequently the solubility of the picrate in $CDCl_3$ by performing the same experiment in the absence of hosts. With those data in hand, we proceeded to evaluate (in a similar way to that used by Gutsche[12] for the determination of aromatic hydrocarbon complexation with water-soluble calixarenes) the association constant (K_c) for the process:

$$H(CDCl_3) + G(CDCl_3) = HG(CDCl_3)$$

$$K_c = [HG](CDCl_3) / ([H](CDCl_3)x[G](CDCl_3)) \qquad \text{(eq. 1)}$$

where the following values are taken at equilibrium:

$[G](CDCl_3)$ = Guest (picrate) solubility in $CDCl_3$.

$[HG](CDCl_3)$ = Extracted picrate concentration as determined by UV.

$[H](CDCl_3)$ = Initial $[H](CDCl_3)$ - $[HG](CDCl_3)$

The results obtained for each one of the speleands **13-16** are summarized in Table I. The complexation is rather efficient, although there are no striking differences between the four compounds, which could be indicative of the formation of *exo* complexes, i. e. complexes in which the ammonium cation coordinates to the external face of the polar subunit. In fact, no appreciable changes can be found in the host signals of NMR spectra of free and complexed speleands.

TABLE I. Association constants (L/mol) of speleands **13-16** with methyl ammonium cation.

Host	**13**	**14**	**15**	**16**
$K_c x 10^{-3}$	2.3	2.0	3.6	2.9

In summary, we have shown in the present paper that speleands able to complex to organic molecules can be easily constructed from the concave chiral cap **3** (and from *sym*-cyclohexanetriol **4**). Suitable structural modifications (including length and functional group modification of the chains in order to enlarge the cavities and to enhance the complexation properties) should enlarge the already interesting perspectives of this class of compounds in the field of molecular recognition.

Experimental

Ultraviolet spectra were obtained with a Perkin-Elmer Lambda 5 spectrometer. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on a Varian XL-200 instrument. Infrared spectra were obtained with a Perkin-Elmer 681 apparatus. Mass spectra were run on a Hewlett-Packard 5988A spectrometer, using both FAB and chemical ionization techniques. Elemental analyses were performed with a 1106 Carlo Erba microanalyzer instrument. All chromatographic purifications were performed on silicagel (Merck, 230-400 mesh ASTM), using (except where indicated) hexane-ethyl acetate mixtures of increasing polarity as eluent.

1. Synthesis of acid chlorides 7, 8, 11 and 12.

***All-cis*-3-(3,5-di(3-carboxypropanoyloxy)cyclohexoxycarbonyl)propanoic acid, 5.**

A mixture of triol **4** (0.60 g, 4.54 mmol), succinic anhydride (1.36 g, 13.6 mmol), trietylamine (1.78 mL, 13.6 mmol), 4-(dimethylamino)pyridine (63 mg, 0.52 mmol) and dry methylene chloride (6 mL) was stirred at room temperature during 24 h. The reaction mixture was then poured over a mixture of diethyl ether (30 mL) and 2 M aqueous hydrochloric acid (30 mL), and the two phases were separated. The aqueous phase was extracted with diethyl ether (2x30 mL), and the combined organic phases were dried over anhydrous magnesium sulfate. Evaporation of the solvents gave a crude material (1.05 g) which after washing with chloroform and water yielded the triacid **5** as a white solid (0.854 g, 43% yield) of m. p. 83-85 °C. IR (KBr): 3700-2300, 2960, 1750-1700, 1420, 1365, 1170, 1145, 1100, 870, 840 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.55 (q, J = 11.4 Hz, 3H), 2.39 (d of t, J = 11.4 Hz, J' = 4.5 Hz, 3H), 2.66 (m, 12H), 4.90 (m, 3H), 5.1 (broad s, 3H + water). ^{13}C-NMR (CD_3OD) δ: 30.6 (t), 31.1 (t), 38.1 (t), 69.4 (d), 174. 1 (s), 176.8 (s). MS (c. i., NH_3): 450 (M+18), 349.

***All-cis*-4-(3,5-di(4-carboxybutanoyloxy)cyclohexoxycarbonyl)butanoic acid, 6.**

Using a similar procedure to that described above, starting from triol **4** (0.50 g, 3.8 mmol), glutaric anhydride (1.36 g, 11.9 mmol), 4-(dimethylamino)pyridine (100 mg, 0.82 mmol), triethylamine (1.5 mL, 11.9 mmol) and anhydrous methylene chloride (5 mL), crude triacid **6** (1.84 g) was obtained as a solid, which was used without further purification for the preparation of the corresponding acid chloride. ^{1}H-NMR (CD_3COCD_3) δ: 1.43 (q, J = 12 Hz, 3H), 1.82 (m, 6H), 2.33 (m, 15 H), 4.83 (t of t, J = 12 Hz, J' = 4 Hz, 3H). ^{13}C-NMR ($CDCl_3$ / CD_3OD) δ: 21.4 (t), 34.2 (t), 34.7 (t), 37.6 (t), 68.4 (d), 173. 7 (s), 176.7 (s). MS (c. i., NH_3) : 492 (M+18).

***All-cis, tris-endo*-3-(5,8-di(3-carboxypropanoyloxy)tricyclo[5.2.1.0^{4,10}]decyl-2-oxycarbonyl) propanoic acid, 9.**

Using a similar procedure to that described above, starting from triol **3** (0.15 g, 0.81 mmol), succinic anhydride (0.37 g, 3.66 mmol), 4-(dimethylamino)pyridine (16 mg, 0.13 mmol), triethylamine (0.48 mL, 3.66 mmol) and dry methylene chloride (1 mL), were obtained 0.360 g of crude material which was treated with chloroform. The insoluble fraction was identified as the triacid **9** (0.251 g, 56% yield) in the form of a white solid. Recrystallization from hot methanol afforded an analytically pure sample of m. p. 186-190 °C. IR (KBr): 3600-2300, 2980, 1780-1700, 1490, 1440, 1370, 1310, 1240, 1160, 1090, 1050, 1020, 1000, 970, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75-2.07 (m, 4H), 2.65-2.90 (m, 6H), 2.67 (m, 12H), 5.0 (broad s, 3H acid + water), 5.05 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ: 29.7 (t), 30.0 (t), 30.1 (t), 41.8 (d), 46.7 (d), 78.0 (d), 173.8 (s), 175.9 (s). Anal. calcd. for $C_{22}H_{28}O_{12}$: C, 54.54; H, 5.78 %. Found: C, 54.23; H, 5.88 %.

***All-cis, tris-endo*-4-(5,8-di(4-carboxybutanoyloxy)tricyclo[5.2.1.0^{4,10}]decyl-2-oxycarbonyl) butanoic acid, 10.**

Using a similar procedure to that described above, starting from triol **3** (0.30 g, 1.62 mmol), glutaric anhydride (0.60 g, 5.1 mmol), 4-(dimethylamino)pyridine (33 mg, 0.27 mmol), triethylamine (0.66 mL, 5.1 mmol) and anhydrous methylene chloride (3 mL), crude triacid **10** (0.808 g) was obtained as a dense oil which was used without further purification for the preparation of the corresponding acid chloride. ^{1}H-NMR ($CDCl_3$) δ: 1.58-1.92 (complex signal, 12 H), 2.33 (t, J = 7 Hz, 6H), 2.34 (t, J = 7 Hz, 6H), 2.60-2.78 (m, 4H), 4.96 (m, 3H), 10.9 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 19.9 (t), 28.8 (t), 32.8 (t), 33.2 (t), 40.3 (d), 45.3 (d), 76.3 (d), 172.8 (s), 175.5 (s).

[*All-cis*-3,5-di(3-chloroformylpropanoyloxy)cyclohexyl] (3-chloroformyl)propanoate, 7.

A mixture of triacid **5** (0.400 g, 0.92 mmol, previously dried under vacuum for 6 h), oxalyl chloride (0.44 mL, 3.2 mmol) and anhydrous benzene (12 mL).was stirred under nitrogen during 3 days at room temperature. After elimination of solvent, the residue was digested with anhydrous diethyl eher and filtered.

Evaporation of the solvent gave the desired acid chloride **7** (0.380 g, 36% overall yield from **4**) as a colourless oil which was used without further delay due to rapid hydrolysis. IR (film): 2960, 2940, 2870, 1790, 1470, 1360, 1140, 1045 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.45 (q, J = 12 Hz, 3H), 2.6 (m, 9H), 3.2 (t, J = 6 Hz, 6 H), 4.8 (m, 3H).

[*All-cis*-3,5-di(4-chloroformylbutanoyloxy)cyclohexyl] (4-chloroformyl)butanoate, 8.

Using an analogous procedure to that described for **7**, starting from 0.220 g of crude triacid **6**, trichloride **8** (0.110 g, 45 % overall yield from **4**) was obtained as a yellow oil which was not further purified. IR (film): 2960, 2910, 1780, 1470 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.1-3.2 (complex signal, 24H), 4.8 (m, 3H).

***All-cis*, *tris-endo*-5,8-di(3-chloroformylpropanoyloxy)tricyclo[5.2.1.$0^{4,10}$]dec-2-yl (3-chloroformyl)propanoate, 11.**

Using an analogous procedure to that described for **7**, starting from 0.220 g (0.45 mmol) of triacid **9**, trichloride **11** (0.200 g, 50 % overall yield from **2**) was obtained as a yellowish oil which was not further purified. IR (film): 2960, 2910, 1780, 1740, 1470, 1380, 1260 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.75-2.30 (complex signal, 4H), 2.70 (m, 12H), 3.20 (t, 6H), 5.10 (m, 3H).

***All-cis*, *tris-endo*-5,8-di(4-chloroformylbutanoyloxy)tricyclo[5.2.1.$0^{4,10}$]dec-2-yl (4-chloroformyl)butanoate, 12.**

Using an analogous procedure to that described for **7**, starting from 0.330 g of crude triacid **10**, trichloride **12** (0.230 g, 59 % overall yield from **2**) was obtained as a yellow oil which was not further purified. IR (film): 2960, 2940, 1790, 1470, 1360 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.5-3.2 (complex signal, 31H), 5.0 (m, 3H).

2. Synthesis of triamine 2

3-Oxapentylene 1,5-di-*p*-toluenesulfonate, 17.

To an stirred mixture of diethylene glycol (30 g, 0.28 mol) and pyridine (104 g) were slowly added 132 g (0.69 g) of *p*-toluenesulfonyl chloride at 0 °C. After stirring overnight at room temperature, the reaction mixture was poured over a mixture of water (150 mL) and methylene chloride (150 mL). The aqueous phase was separated and washed with additional methylene chloride. The combined organic phases were successively washed with water and 2 M aqueous hydrochloric acid, and dried over magnesium sulfate. Elimination of solvents gave a solid residue which was recrystalized (dichlorometane/hexane) to afford the ditosylate **17** (48.4 g, 41% yield) as a white solid. ^1H-NMR ($CDCl_3$) δ: 2.4 (s, 6H), 3.6 (m, 4H), 4.05 (m, 4H), 7.25-7.75 (AA'BB' system, 8H).

3-Oxa-1,5-pentanediazide, 18.

A mixture of ditosylate **17** (38.4 g, 0.093 mol), sodium azide (24.10 g, 0.371 mol), tetrabutylammonium bromide (5.37 g) and water (125 mL) was heated to reflux for 20 h. After cooling, the mixture was extracted with chloroform to afford, after drying and elimination of solvent, a crude product (26 g) which was purified by chromatography. Azide **18** (14.6 g, 98% yield) was thus obtained as a colorless oil. IR (film): 2940, 2880, 2110, 1450, 1300, 1230, 925 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.4 (t, 4H), 3.65 (t, 4H).

3-Oxa-1,5-pentanediamine, 19.

A mixture of diazide **18** (14.6 g, 0.093 mol), 10 % Pd/C (2.0 g) and ethanol (200 mL) was stirred for three days at room temperature under hydrogen athmosphere. Filtration and elimination of solvents produced the diamine **19** (7.2 g, 74% yield) as a colorless oil. IR (film): 3380, 3290, 2930, 2870, 1600, 1450, 1350, 1120 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.55 (s, 4H), 2.85 (t, J = 5 Hz, 4H), 3.50 (t, J = 5 Hz, 4H).

1-*p*-Toluenesulfonyl-4,10,16-trioxa-1,7,13-triazacyclooctadecane-6,14-dione, 20.[7b]

In a three-necked, round-bottomed 1 L reaction flask were introduced 500 mL of dry benzene. Dry nitrogen was bubbled through the solution for 1 h, and subsequently a solution of *p*-toluenesulfonyl-3,9-dioxa-6-azaundecanedioyl dichloride[7b] (6 g, 14.6 mmol) in dry benzene (160 mL) and a solution of diamine **19** (3.06 g, 29.4 mmol) in the same volume of dry benzene were added dropwise and simultaneously during three hours. The precipitated hydrochloride was filtered off and the solvent was eliminated to give a residue which was taken up in chloroform and filtered through alumina, affording the cyclic diamide **20** (3.8 g, 59% yield) as a colorless oil. Recrystallization from benzene / chloroform produced a white solid of m. p. = 117-118 °C. IR (film): 3430, 3380, 2930, 2880, 1680, 1600, 1450, 1340, 1150, 1125, 1095, 1030, 990, 945, 925, 820, 735, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (s, 3H), 3.58 (m, 16H), 3.96 (s, 4H), 7.12 (broad s, 2H), 7.26-7.79 (AA'BB' system, 4H).

4,10,16-Trioxa-1,7,13-triazacyclooctadecane, 2. [7b]

A mixture of lihium aluminum hydride (5.7 g, 0.15 mol), amide **20** (3.8 g, 8.6 mmol) and anhydrous THF (60 mL) was heated at reflux for 16 h. After cooling, water (10 mL) and 10% aqueous LiOH (10 mL) were added carefully dropwise. After 10 minutes of stirring, magnesium sulfate (3 g) was added. Filtration (the precipitate was thoroughly washed with chloroform) and elimination of solvents gave a residue which was taken up in water and acidified with 1 M aqueous HCl. Washing with chloroform (to eliminate *p*-methylthiophenol), basification with solid LiOH (until pH = 11) and extraction with chloroform gave, after elimination of solvent, amine **2** (1.68 g, 75% yield) as a colorless oil. Recrystallization from benzene / chloroform produced a white solid of m.p. = 135-136 °C. IR (film): 3600-3200, 2890, 1680, 1460, 1340, 1250, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (broad s, 3H), 2.77 (t, 12H), 3.58 (t, 12H).

3. High-dilution cyclizations.

Preparation of speleand 13.

A three-necked, round-bottomed 1 L reaction flask was charged with 300 mL of dry benzene. Dry nitrogen was bubbled through the solution for 1 h, and subsequently a solution of acid chloride **7** (0.360 g, 0.74 mmol) in dry, deoxygenated benzene (100 mL) and a solution of amine **2** (0.182 g, 0.71 mmol) and triethylamine (0.244 g, 2.42 mmol) in anhydrous, deoxygenated benzene (100 mL) were added dropwise and simultaneously during 9 hours. The precipitated hydrochloride was filtered off and the solvent was eliminated to give a residue which was purified by chromatography on silicagel, eluting with a 94:5:1 mixture of $CHCl_3$/MeOH/aq. NH_3, affording the speleand **13** (90 mg, 20% yield) as a white solid which did not melt below.300 °C. A sample was pulverized and dried for 2 h under vacuum, to give a material with elemental analysis according to the formula **13**·1$CHCl_3$. IR ($CHCl_3$): 2950, 1750, 1655, 1430, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (q, J = 12 Hz, 3H), 2.19-3.43 (complex signal, 18H), 3.75 (m, 18H), 4.21 (d of t, J = 14 Hz, J' = 5 Hz, 3H), 4.79 (t of d, J = 12 Hz, J' = 5 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ: 27.3 (t), 29.3 (t), 34.6 (t), 47.7 (t), 48.9 (t), 65.8 (d), 68.7 (t), 69.7 (t), 168.8 (s), 171.2 (s). MS/FAB m/e: 640 (M+1, 18%), 327(13%), 294(11%), 281(14%), 267(15%), 251(13%), 249(11%), 207(34%), 193(31%), 191(29%), 177(25%), 147(30%). Anal. calcd. for $C_{30}H_{45}N_3O_{12}$: C, 56.33; H, 7.04; N, 6.57%. Anal. calcd. for $C_{30}H_{45}N_3O_{12}$·1$CHCl_3$: C, 49.04; H, 6.06; N, 5.54%. Found: C, 49.63; H, 5.98; N, 4.85%. When the sample was dried during 24 h (55 °C, 1 mm Hg) the analysis was: C, 55.22; H, 6.80; N, 5.15; Cl, 3%.

Preparation of speleand 14.

Using a similar procedure to that described for **13**, starting from acid chloride **8** (0.220 g, 0.41 mmol), triamine **2** (0.104 g, 0.40 mmol) and triethylamine (0.132 g, 1.3 mmol), speleand **14** (0.090 g, 32% yield) was obtained as a semisolid oil. IR ($CHCl_3$): 2950, 2880, 1730, 1650, 1450, 1420, 1375, 1240, 1135, 1100, 1060, 925, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5-4.5 (complex signal, 48H), 4.9 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ: 20.7 (t), 31.9 (t), 32.8 (t), 34.9 (t), 49.4 (t), 50.1 (t), 65.3 (d), 68.9 (t), 69.9 (t), 172.3 (s), 173.4 (s). MS/FAB m/e: 682 (M+1, 77%), 500 (59%), 345(18%), 271(25%), 257(37%), 243(86%).

Preparation of speleand 15.

A three-necked, round-bottomed 1 L reaction flask was charged with 300 mL of dry benzene. Dry nitrogen was bubbled through the solution for 1 h, and subsequently a solution of acid chloride **11** (0.200 g, 0.36 mmol) in dry, deoxygenated benzene (100 mL) and a solution of amine **2** (94 mg, 0.35 mmol) and triethylamine (0.122 g, 1.21 mmol) in anhydrous, deoxygenated benzene (100 mL) were added dropwise and simultaneously during 9 hours. The precipitated hydrochloride was filtered off and the solvent was eliminated to give a residue which was purified by chromatography on silicagel, eluting with a 94:5:1 mixture of CH_2Cl_2/MeOH/aq. NH_3, affording the speleand **15** (0.134 g, 52% yield) as a semisolid oil. Recrystallization from choloroform/ethyl acetate gave white crystals which did not melt below 300 °C. A sample was pulverized and dried for 6 h under vacuum, to give a material with elemental analysis according to the formula **15**·0.75CH_2Cl_2·0.25AcOEt. IR ($CHCl_3$): 2990, 2950, 2900, 1745, 1660, 1480, 1430, 1300, 1270, 1220, 1190, 1150, 1130, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.45-4.2 (complex signal, 46H), 4.79 (d of t, J = 11 Hz, J' = 7 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ: 27.8 (t), 28.0 (t), 29.8 (t), 39.4 (d), 45.0 (d), 48.6 (d), 49.6 (t), 68.8 (t), 69.4 (t), 77.38 (d), 77.4 (d), 171.5 (s), 172.1 (s). MS/FAB m/e: 692 (M+1), 309. Anal. calcd. for $C_{34}H_{49}N_3O_{12}$: C, 59.04; H, 7.09; N, 6.08%. Anal. calcd. for $C_{30}H_{45}N_3O_{12}$·0.75CH_2Cl_2·0.25AcOEt: C, 55.45; H, 6.79; N, 5.40; Cl, 6.39%. Found: C, 54.95; H, 6.56; N, 5.08; Cl, 6.23%.

Preparation of speleand 16.

In the same conditions described above, starting from acid chloride **12** (0.230 g, 0.40 mmol), amine **2** (0.102 g, 0.38 mmol) and triethylamine (0.132 g, 1.30 mmol), using 570 mL of anhydrous benzene, the resulting crude product was purified by column chromatography on silicagel, eluting with CH_2Cl_2/MeOH/aq. NH_3 mixtures of increasing polarity, to afford speleand **16** (80 mg, 27% yield) as an amorphous white solid which did not melt below 300 °C. IR ($CHCl_3$): 2940, 2880, 1740, 1650, 1470, 1420, 1245, 1220, 1155, 1130, 1065, 1045, 925, 735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.3-4.1 (complex signal, 52H), 5.0 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ: 21.0 (t), 29.6 (t), 31.1 (t), 32.4 (t), 41.0 (d), 44.4 (d), 48.1 (t), 50.4 (t), 69.5 (t), 71.3 (t), 76.0 (d), 172.6(s), 173.0 (s). MS/FAB m/e: 734 (M+1, 8%), 486 (8%), 309 (9%), 294 (14%).

4. Complexation studies.

Methyl ammonium picrate.

To a saturated solution of picric acid in ethanol (50 mL) aqueous 40% methylamine (2 mL) was added. After stirring for 30 minutes at room temperature, the resulting precipitate was filtered and recrystallized from 90% aqueous ethanol, to give methyl ammonium picrate (1.3 g, 38% yield) as a yellow solid of m. p. = 211 °C.

Complexation of methyl ammonium picrate with speleands 13-16.

In a centrifuge tube were introduced the speleand (10 mg), $CDCl_3$ (0.7 mL) and 1 equivalent of finely powdered methyl ammonium picrate. After stirring for 1.5 h and centrifugation, the solution was decanted and filtered, and the ^{1}H-NMR spectrum was recorded. A 0.1 mL aliquot was then withdrawn of the solution and diluted to 10 mL with $CHCl_3$. The absorbance at λ = 354 nm (ε = 15600) gave the picrate concentration in $CDCl_3$ for each of the speleands **13-16**. The solubility of picrate in host-free $CDCl_3$ was determined in a similar experiment performed in the absence of speleand, obtaining a mean value of 2.687×10^{-5} M in these conditions. These data were implemented in eq. 1 to give the constants shown in Table I.

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8. The commercial product (Fluka) is a hydrate which must be dried under vacuum prior to subsequent use.

9. It is interesting to observe that in principle the cyclization of **7** and **8** can occur in two different ways. In effect, the coupling with **2** can take place either in the face of the cyclohexane ring which contains the three chains (giving rise to an isomer which we shall call IN) or in the opposite face (leading to a different configurational isomer which we shall denominate OUT). Inspection of molecular models shows that whereas both configurations are possible for **13** and **14** (but of course not for **15** and **16**), the IN configuration is less strained than the OUT. For this reason, we represent in Scheme 2 the IN form of **13** and **14**.

10. NMR complexation studies of CH_2Cl_2 and $CHCl_3$ with criptands **13-16** in $C_2D_2Cl_2$ solution, according to the method of Collet and co-workers (Canceill, J.; Lacombe, L.; Collet, A. *C. R. Acad. Sci. Paris* **1987**, *304*, 815), did not show significative differences in the chemical shifts of the guests. These results do not rule out however the existence of inclusion complexes, because in the absence of aromatic rings in the host the chemical shift displacements can be very small.

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