185. *SPELEANDS.* Macropolycyclic Receptor Cages Based on Binding and Shaping Sub-units. Synthesis and Properties of Macrocycle-Cyclotriveratrylene Combinations

Preliminary communication

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Summary

Combination of a receptor unit with a rigid shaping unit produces a new type of receptor molecules of the cryptand class, hollow macropolycyclic molecules termed *speleands,* capable of substrate inclusion. Two members of this category of compounds **1** and **2**, have been synthesized by connecting in a single step, a macrocyclic [18]-N_3O_3 binding unit with a rigid cyclotriveratrylene unit *via* three bridges. Compound **1** binds the methylammonium cation forming both external and internal complexes; for the latter a *'speleate'* structure, schematically represented by **15**, may be proposed.

Cryptates are defined as inclusion complexes in which the substrate species is (are) contained in the intramolecular cavity of a macropolycyclic receptor molecule. Introduced originally for alkali and alkaline-earth complexes of macrobicyclic cryptands, this general concept has since been extended to inclusion complexes of a large variety of substrates (other inorganic cations, organic cations, as well as anionic species) with macropolycyclic molecules of various shapes and sizes, designed so as to display molecular recognition processes [1]. The molecular architecture of these macropolycycles is based on the combination of various sub-units possessing specific structural properties and containing defined binding sites, in order to achieve receptor-substrate complementarity for both geometry and interactions. Furthermore, ligand dynamics, *i.e.* the rigidity/flexibility balance, influence substrate binding and exchange rates.

Within this general class of cryptand molecules, the connection of polar *binding sub-units* to large, concave, more or less rigid and hydrophobic *shaping*

[1]) GR 20 of the CNRS.

[2]) ERA 265 of the CNRS.

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components, should produce a new type of hollow macropolycyclic receptors, capable of substrate inclusion. We propose the terms *speleands* (from σπήλαιον = cave) and *speleates* for individualizing this sub-class of cryptands and of inclusion complexes. The binding sub-units may be derived from chelating, tripodal or macrocyclic arrangements of binding sites (as for instance in polynucleating cryptands [2]). The shaping components may belong to different types of framework like phenol-aldehyde condensation products, cyclodextrins [3] or functionalized porphyrins and tetrapyrroles [4]. The former are of special interest since, in addition to known representatives (*e.g.* veratrole-formaldehyde cyclotriveratrylene [5–10], phenol-formaldehyde [11] [12] calixarene [13] [14] or resorcinol-aldehyde [15–17] condensation products), many intriguing variations remain to be investigated. Furthermore, such substances form clathrate inclusion compounds with organic molecules in the solid state (*cf.* [14] [18]) a property which may confer additional binding potential to speleands, especially towards hydrophobic substrates.

We now report preliminary results on the synthesis and substrate-binding properties of two members of this family of macropolycycles (compounds **1** and **2**) which result from the connection of a macrocyclic binding sub-unit of type [18]-N_3O_3 (**3**, [19]) to the cyclotriveratrylene (CTV) derivative **4** [9] [20] by three bridges. Triply bridged coreceptors incorporating two [18]-N_3O_3 rings and forming molecular cryptates have been described [21], as well as a molecular cage formed by two triply connected CTV units [20].

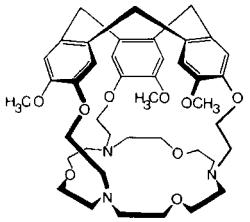
The racemic (C_3)-tricarboxylic acid (±)**5** [20] was converted into the trichloride **6** by treatment with thionyl chloride. Condensation of **6** with **3** in high dilution conditions [22] afforded the tricarboxamide **7** (m.p. ≈325° (dec.)) in 35% yield after purification by chromatography over alumina. Reduction of **7** with diborane [22], gave the CTV-[18]-N_3O_3 molecular cage **1** (m.p. ≈230°) in 85% yield.

The CTV unit bearing longer branches was prepared as follows. Treatment of the sodium salt of vanillin with $ICH_2CH_2OCH_2CO_2CH_3$ (for the corresponding chloro-analog see [23]) gave **8** (m.p. 85°; 85%) which was reduced to the alcohol **9** (m.p. 40°; quantitative yield) with H_2/*Raney* nickel. Trimerization of **9** with perchloric acid in methyl orthoformate solution at room temperature for 20 h gave the CTV trimer **10** in 40% yield (m.p.: 98°). The crude triacid **11**, obtained as a glassy solid by basic hydrolysis of **10** (NaOH in methanol/water 95 : 5), was converted to the corresponding trichloride **12** by treatment with thionyl chloride. Following the same reaction sequence as for **1**, **12** was condensed with **3** to give the tricarboxamide **13** (glass; 40%), which was reduced to the larger CTV-[18]-N_3O_3 cage **2** (glass; 65%). All new compounds had physical properties in agreement with the proposed structures.

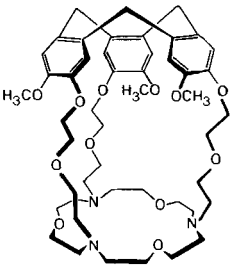
Compounds **1** and **2** represent a new type of macropolycyclic mesomolecules [1], *speleands,* containing both a receptor site and a rigid shaping unit. They combine the features of bis-[18]-N_3O_3 cylindrical macrotetracycles [21] and of the bis-CTV molecular cage [20].

The *overall shape* of **1** and **2** may be described as a circular component topped by the CTV unit in its usual 'crown'-type conformation (as shown by the characteristic *AB*-quadruplet of the methylene bridges at about 4.7 and 3.5 ppm, $J = 14$ Hz in the ^{1}H-NMR. spectrum [9] [20]).

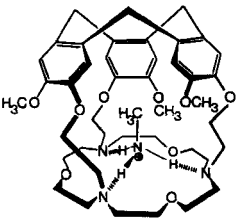
Compounds **1** and **2** are *hollow molecules*, whose intramolecular cavity is maintained by the rigid CTV unit [9]. The flexible bridges permit adjustment of the cavity height along the C_3-axis; the maximum size is clearly larger for **2** (≈ 8 Å) than for **1** (≈ 5 Å).



1
7[a])

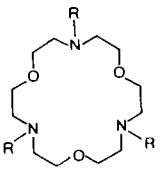


2
13[a])

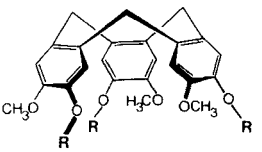


15

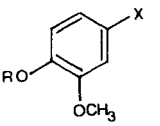
[a]) The three N⌒O⌒ bridges between the CTV unit and [18]-N_3O_3 stand for N–$COCH_2O$.



3 R = H
14 R = CH_3



4 R = H
5 R = CH_2COOH
6 R = CH_2COCl
10 R = $CH_2CH_2OCH_2COOCH_3$
11 R = $CH_2CH_2OCH_2COOH$
12 R = $CH_2CH_2OCH_2COCl$



R = $CH_2CH_2OCH_2COOCH_3$

8 X = CHO
9 X = CH_2OH

The [18]-N_3O_3 macrocyclic sub-unit of **1** and **2** may serve as receptor site for cationic species. Indeed, the tris(*N*-methyl) derivative **14** binds metal cations and is especially well-suited for selective complexation of primary ammonium cations [19]. The latter property is of particular interest in the present case, since binding of R-NH_3^+ by anchoring of the NH_3^+ head group into the [18]-N_3O_3 ring, may occur either inside or outside the central cavity depending on the nature of the R residue. Preliminary experiments have shown that **1** dissolves about 1 equivalent $CH_3NH_3^+$ picrate into $CDCl_3/CD_3OD$ 9:1 or into CD_2Cl_2 yielding a mixture (about 2:1) of two species giving CH_3–NH_3^+ NMR. signals around 2.3 ppm and -0.1 ppm (ill-resolved quadruplet, $J \approx 6$ Hz in CD_2Cl_2). They may be identified respectively as the *exo*- and the *endo*-complexes, if we accept that the large shift to high field is diagnostic of inside binding, thus placing the CH_3 group of the substrate into the shielding region of the aromatic rings, as observed for the diammonium cryptates of cylindrical coreceptors [21] [24]. A schematic representation of this cryptate-type inclusion complex, the *methylammonium speleate* of **1**, is given by structure **15**. R-NH_3^+ substrates with R larger than CH_3 apparently do not bind inside (experi-

ments in progress). Double-irradiation ^{1}H-NMR. experiments indicate that *endo*- and *exo*-bound $CH_3NH_3^+$ species exchange slowly (saturation transfer), and that the protons of *exo*- and *endo*-NH_3^+ groups undergo respectively fast and slow exchange with the solvent. The binding properties of **2** are being investigated together with further studies of **1**, in particular by low-temperature NMR.

Developments of the chemistry of speleands may be concerned with: *i)* the incorporation of rigid rather than flexible bridges, as in **1** and **2**, or rigidification of the basic components by structural modifications (for a recent example on calixarenes see [25]), in order to enforce more strongly a preformed cavity; *ii)* the synthesis of optically active **1** and **2** since the basic CTV unit is chiral and has been resolved [9]; *iii)* the introduction of polar groups in order to confer solubility in water and to permit operation of hydrophobic effects. In a broader view, a great variety of other combinations of receptor and architectural units may be envisaged, as briefly mentioned above, adding another facet to the chemistry of molecular receptors.

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