A New Cryptophane Receptor Featuring Three *endo*-Carboxylic Acid Groups: Synthesis, Host Behavior and Structural Study

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Dedicated to Professor Leonard F. Lindoy, Sydney on the occasion of his 65th birthday

Abstract: Examples of a new type of cryptophane molecule incorporating aromatic groups in the bridges (**1**–**4**) and, for the first time, being also supplied with three *endo*-positional ionizable carboxylic acid functions (**1**) have been synthesized and characterized. The cryptophane triester **2** yielded a solvate (channel inclusion compound) with trichloromethane and water, the X-ray crystal structure of which is reported. The complexation of **1** with low-molecular-weight alcohols in solution was studied, and the liquid–liquid extraction of different metal ions including alkali (Na^+, Cs^+), alkaline earth (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}), and the lanthanide metal ions Eu^{3+} and Yb^{3+} in an extraction system containing metal nitrate buffer/H_2O/**1**/$CHCl_3$ was examined. Molecular modeling calculations of the cryptophanes **1** and **2**, and of the Eu^{3+} complex of **1** were carried out contributing to the discussion.

Keywords: cryptophanes · molecular modeling · molecular recognition · solvent extraction · structure elucidation

Introduction

Since the pioneering work on crown compounds in the late 1960s[1] strategies and methods[2] have been elaborated to allow the design and synthesis of an enormous variety and complexity of hollow molecules[3] capable of host–guest complexation and more ingenious modes of supramolecular operation.[4]

Among these hosts, the cryptophanes[5] are an outstanding class of compounds being made of two cone-shaped cyclotriveratrylene (CTV) units attached to one another by three bridges, and hence feature a preorganized, three-dimensional enforced cavity suitable for accommodating organic substrates.[6] Cryptophanes are also interesting compounds for their stereochemical properties[5] including conformational behavior, chirality, and the potential for enantioselective complexation.[7] Moreover, cryptophanes are promising as components of materials such as charge-transfer salts[8] and Langmuir films.[9]

In most cases, the cryptophanes are substituted by methoxy groups in a peripheral position owing to the basic structure of the cyclotriveratrylene shaping units. Cryptophanes that have peripherally modified substituents such as carboxylic acid or hydroxyl groups are rare, although this *exo*-polar modification makes them soluble in water[10] or makes available very attractive key compounds for the synthesis of bio-compatible ligands for molecular recognition, as well as for the generation of large supramolecular systems.[11] On the other hand, some modifications of the bridges between the cyclotriveratrylene caps have been made,[5] but mainly regarding the length of the bridging alkyl chains rather than their chemical nature.[12]

Here we report on cryptophanes incorporating aromatic groups in the bridges (**1**–**4**, Scheme 1) and for the first time being supplied with three *endo*-position ionizable carboxylic acid functions in their structure (**1**), giving rise to a new type of *endo*-polar molecular container.[13] Thus, from the structural point of view, the present cryptophane (**1**) is likely to accommodate size-matching metal ions and polar molecules. We describe the synthesis of the new receptor compounds, produce evidence of their structure by single-crystal X-ray analysis and molecular modeling calculation, and show their

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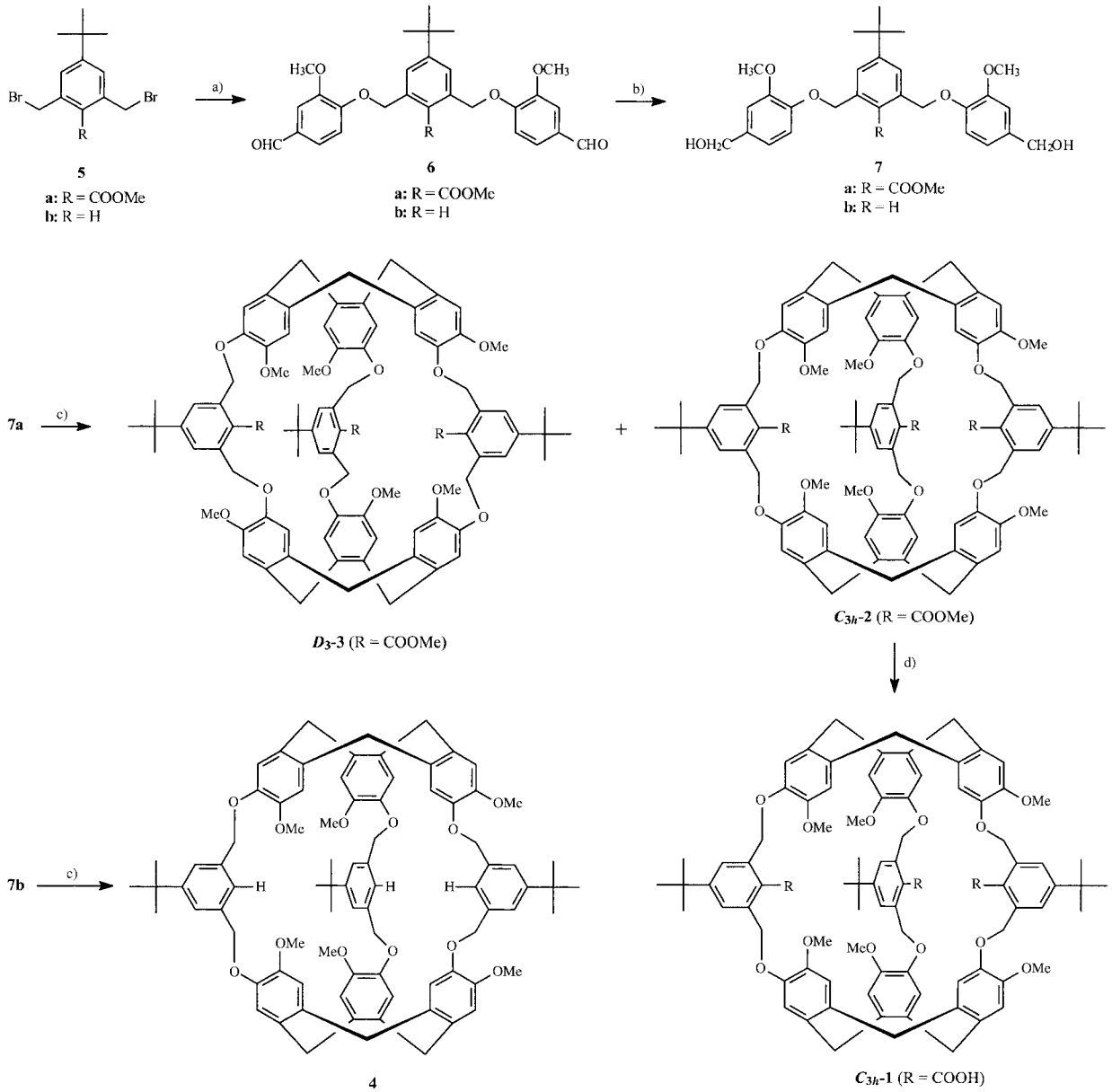

Scheme 1. Synthesis of the cryptophanes: a) K_2CO_3, vanillin; b) $NaBH_4$; c) formic acid; d) KOH, 18C6.

remarkable selectivity behavior in molecular complexation of small alcohols and in the solvent extraction of alkali, alkaline earth, and lanthanide ions.

Results and Discussion

Synthesis: Most of the known cryptophanes have been obtained by applying the so-called template and two-step methods including functionalized C_3-cyclotriveratrylenes or dimeric benzyl alcohols as key intermediates.[5] We preferred to use the two-step method,[14] which, aside from its simplicity and shortness, has the advantage of rendering high-dilution conditions superfluous.[15]

Following this method (Scheme 1), methyl-2,6-bis(bromomethyl)-4-*tert*-butylbenzoate (**5a**) was treated with vanillin in acetone in the presence of potassium carbonate to yield 88% of the corresponding bis-vanillyl derivative **6a**. This compound was then reduced with sodium borohydride in methanol to give a quantitative yield of the bis-benzyl alcohol **7a**, which was converted directly in formic acid into a mixture of the diastereomeric cryptophane esters C_{3h}-**2** (*meso*, 14%) and D_3-**3** (racemic, 21%). In a final step of the synthesis, the ester functions of both C_{3h}-**2** and D_3-**3** need to be hydrolyzed; this was not expected to be easy.[16] It must be noted here that ideal symmetry descriptions of both the racemic (C_{3h}) and the chiral (D_3) forms relate only to the shape of the substituent-free host skeleton.

In fact, hydrolysis caused difficulties when using conventional conditions, such as treatment with potassium or cesium hydroxide in refluxing *n*-butanol. However, heating of the cryptophane triester C_{3h}-**2** with potassium hydroxide in *n*-butanol to 90 °C for several hours in the presence of [18]crown-6 readily produced the cryptophane tricarboxylic

acid **1**. Meanwhile, cryptophane triester D_3-**3** was neither affected by this nor other combinations of reagents, including potassium hydroxide/cryptand [2.2.2] or lithium iodide/collidine.[17] Probably the inward ester groups of D_3-**3** are very difficult to access because of steric shielding by the enclosed structure. A molecular modeling study (PM3) of D_3-**3** shows a twisted conformation compressed along the ternary axis leading to very small window openings through which the reagents may not be able to pass.

By using the above sequence of conversions, starting from dibromide **5b**, the unsubstituted cryptophane **4** was obtained in 8% yield. A remarkable fact of this synthesis is that cyclization of **7b**, unlike **7a**, only gave the C_{3h} isomer (meso-compound **4**), the D_3 isomer (racemic compound) was not to be found in the reaction product; this shows the significance of the substituent in affecting the ring-formation reaction.

Structural studies: The high point symmetries of the cryptophanes in hand are clearly reflected in the ^{1}H NMR spectra and are in accordance with previous results.[5] The most characteristic feature of cryptophanes **2** and **3** is a distinct shift of the ester methyl protons to high field (with reference to the basic compound **7a** of about 1.75 ppm); this being indicative of the *endo*-cavity orientation of the functional groups. Considering this, the up-field shift of the corresponding aromatic proton is less (0.43 ppm) when transforming **7a** into cryptophane **4**.

The cryptophane C_{3h}-**2** forms mm-size colorless trigonal plates on crystallizing from a trichloromethane/ethanol/water mixture. These crystals are rather labile and decompose on exposure to air in less than about a minute. Nevertheless, it was possible to carry out an X-ray structure analysis. This showed that the crystals have a trigonal/hexagonal space group that seemed at first to have to be *P*3. All solvents are in a region around an otherwise "empty" threefold axis. The combination of high space group and high molecular symmetry, together with this fairly globular molecular shape makes the crystal very much prone to disorder. Indeed, both independent ⅓ hosts **2** exhibited extensive disorder in the *t*-butyl groups, in the methoxy side wings, in the methylester groups, and even in one of the veratrylene benzene moieties. The electron-density distribution in the central molecular plane bisecting the three slightly tilted methoxycarbonyl groups reflects the presence of a mirror plane in a molecule that may not have this molecular symmetry element. However, it can be easily interpreted as a consequence of a superstructure. This originates from host globes that, while occupying the correct crystallographic sites demanded by the rotation and translation symmetries a exteriori of *P*3, they do accommodate equal-energy 180° rotation dispositioned methoxycarbonyl groups, which interchange fairly randomly and give a disordered interior. Since the assumption of $P\bar{6}$ symmetry (No. 174), which is chemically wrong but reasonable in a time- and space-averaged crystal, reduces the asymmetric unit and thereby the parameter number further to half of the *P*3 variant, we decided to repeat the whole refinement procedure in this space group from the beginnings. The resulting structure model (Figure 1) essentially differed only in that it had a better *R* value of 13.7% against a number of parameters that was a factor of two less than earlier.

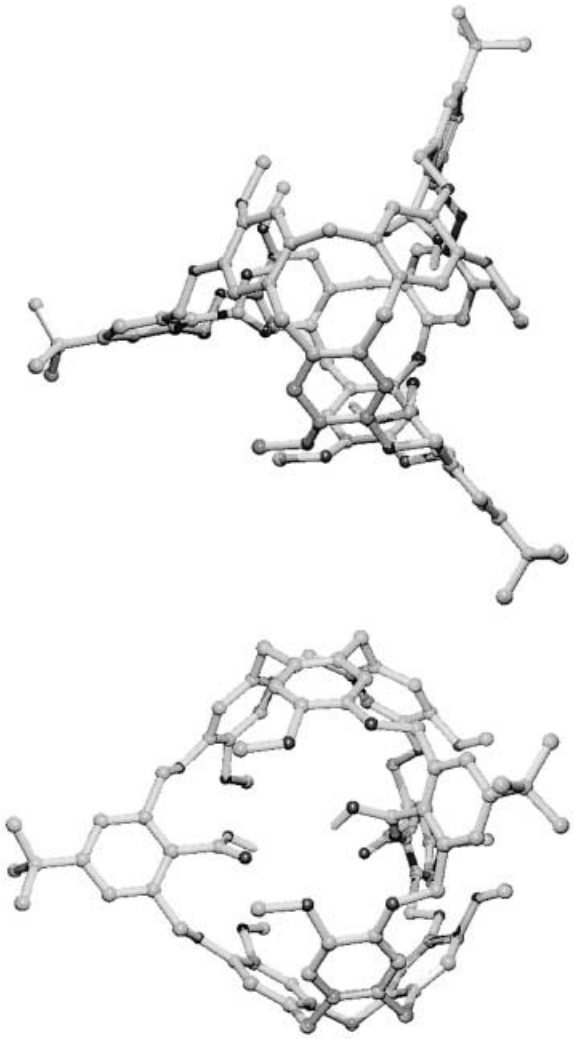

Figure 1. X-ray crystal structure molecular model of molecule **2**: a) seen from the side; b) seen from slightly rotated from the threefold molecular symmetry axis. Only a model of the host molecule is shown. Hydrogen atoms are omitted, oxygen atoms are shown as dark spheres. Disordered methoxycarbonyl groups, *t*ert-butyl moieties, and methoxy side wings are cleaned up so as to show a "real molecule" idealized bonding view. Other components of the asymmetric unit, like disordered solvent guests (dichloromethane molecules, water sites), are all omitted for the sake of clarity.

As compared with other related cyclotriveratrylene crystal structures,[18–21] this is the only structure in which the host assumes, even in spite of the extensive disorder in the crystal, an obviously perfect threefold symmetry (cf. Figure 1b). Neither are molecular symmetries assumed for the analogous cases, not even when a chloroform guest sitting in the cavity assumes a near-perfect threefold symmetry.[19] The molecular cavity is filled here rather effectively with the equilateral triangle of methyl groups (C···C separations are 3.51 Å between these atoms). Another measure of the molecular size is the 10.86 Å separation of the CTV-ring centers along the threefold axis. Channels of the crystal of **2** (Figure 2) are occupied at room temperatures by an obviously almost freely moving mixture of solvent (trichloromethane

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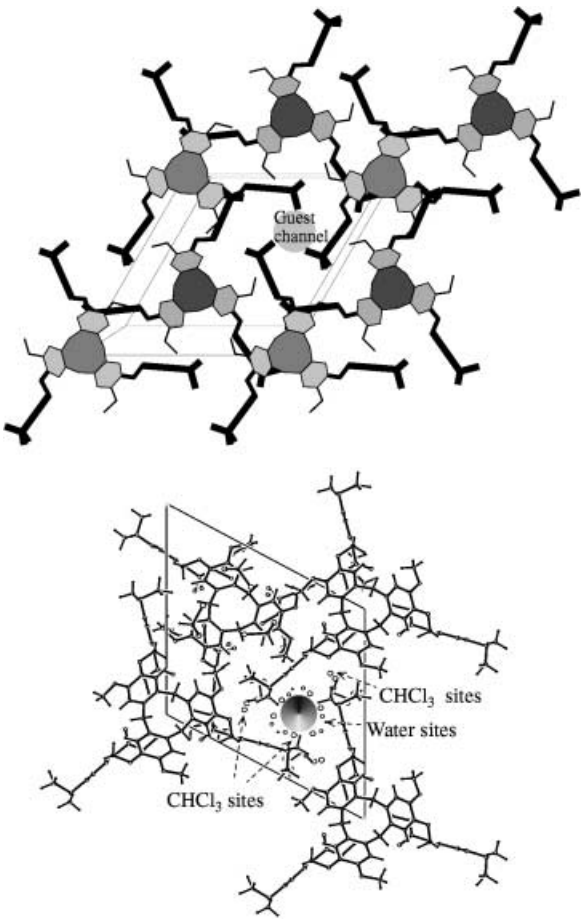

Figure 2. a) Schematic representation of the packing structure of **2** showing channels and the hosts occupying independent crystallographic threefold inversion axes. b) Detail of the lattice channel in the neighborhood of the guest sites.

and water) molecules, which certainly give rise to the overall weak diffraction.

The long list of the disorder as well as the extreme air-sensitivity due to solvent loss is also explained by the structure model. The independent host molecules are sitting on threefold (inversion) axes at 0,0,*z* and ⅓,⅔,*z* while all solvents are placed around the "free" threefold axis at ⅔,⅓ (Figure 2). Thus the channel so formed around this symmetry axis runs unbroken through the whole crystal. It therefore makes solvent removal fairly easy. The "virtual" packing coefficient of the lattice made up of hosts only reduces to 0.51 as compared with the nearly ideal value of 0.66 of the whole model (including solvents in the channel). This also indicates that solvents, albeit hard to model and a handicap for the diffraction experiment still play important role in the formation of the crystal lattice.

In order to compare the structures of cryptophanes **2** (R = COOMe) and **1** (R = COOH), molecular modeling calculations in vacuo have been performed on the basis of density functional theory (DFT). The initial structures were obtained by conformation analysis by using molecular dynamics. The DFT method is applicable to the full range of molecular systems, including hydrogen-bonded aggregates[22] and transition metal complexes,[23, 24] and gives results of quality comparable to ab initio level.[23] Figure 3 shows the calculated "local minima" structures of **2** and **1** from the BP86 functional of the ADF software package.[25] The differences between the two geometries are only small. In the case of **2**, the orientation

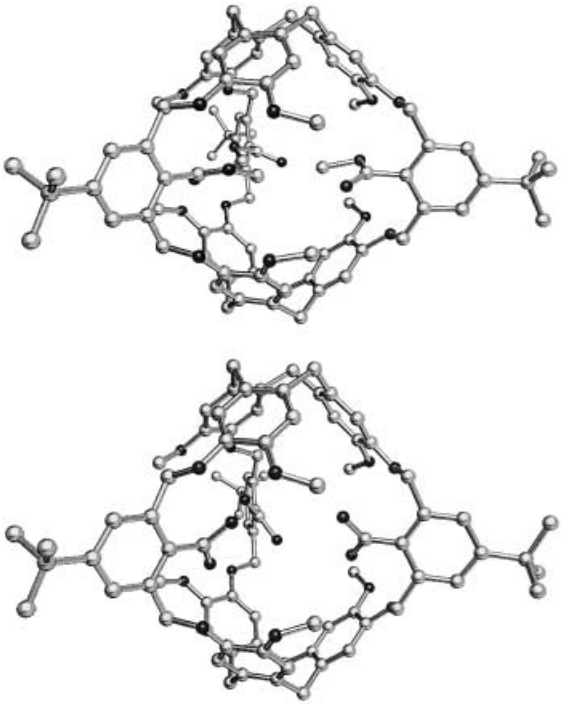

Figure 3. Optimized structures of a) **2** and b) **1** as obtained by DFT calculations. Oxygen atoms are shown as dark spheres.

of the three ester functions inside the cage suggests stabilization by three intramolecular hydrogen bonds between one hydrogen of the methylester function and the neighboring carboxylic oxygen. These interactions lead to a highly symmetric arrangement with CH···O=C separations of practically equal size ranging between 2.414 and 2.416 Å.[26] Such additional interactions are absent in the calculated acid molecule **1**. Because of this, the cage size of **1** is enlarged compared with **2**; this favors the entry of any species into the hole formed. Furthermore, the carboxylic acid functions are twisted by nearly 90° compared with the methyl ester groups of **2**. For the cryptophane **2**, a good fit of the calculated structure with the X-ray structural parameters was observed. The root-mean-square value comes up to 0.666 Å if the distorted ester functions in the crystal are omitted.

Complexation of alcohols: The complexation studies were performed with the cryptophane tricarboxylic acid **1**, which is expected to be a potential host compound for proton-donor and -acceptor guest molecules of which alcohols are typical examples.[16] Owing to the small dimensions of the host cavity (approx. 28 $Å^3$, estimated from the solid-state model), the low-molecular-weight alcohols are considered most promising in this respect. Hence, complexation of the relatively small alcohol molecules methanol, ethanol, and isopropanol in deuterochloroform was determined by ^1H NMR titration. A previous experiment has confirmed that deuterochloroform is

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inefficient and will not compete with the alcohols for steric reasons, while this solvent has been found an effective guest for the more voluminous conventional cryptophanes.[18]

Corresponding to the size relationship, isopropanol, which is the most voluminous of the three alcohols tested, is not complexed by **1**. Evidently this molecule has difficulty passing the narrow openings of the host cavity. On the other hand, the lower homologues ethanol and methanol show formation of complexes with **1**, as indicated by marked up-field shifts of the methylene and methyl protons of the alcohols. Nevertheless the shifts are different, being rather high for methanol and much lower for ethanol. With reference to a 1:1 stoichiometry of the complexes, the shifts are $\Delta\delta(CH_3) = 1.76$ ppm for methanol and $\Delta\delta(CH_2) = 0.18$ ppm for ethanol. This may be accounted for by the depth of penetration of these alcohol molecules into the hollow space of the cryptophane. Such a shift fails to appear in the case of isopropanol, which seems not to be able to penetrate the host.

The stability constants for the complexation of **1** with methanol and ethanol were calculated from the NMR chemical shifts. Based on the linear part (1:1 stoichiometry) of the Benesi – Hildebrand plot and by using the least-squares line-fitting procedure,[27] the stability constants for the 1:1 complexes with methanol and ethanol have been determined to be 7500 and 41 $dm^3 mol^{-1}$, respectively, thus showing that methanol is much more strongly complexed than ethanol.

Small dipolar solvent molecules that have mostly proton-acceptor properties such as acetonitrile, nitromethane, acetaldehyde, or acetone, which were also tested as potential guests, failed to form detectable complexes. This points to the fact that, as well as steric suitability, proton-donor capability is an essential requirement for an effective guest for cryptophane **1**. Compounds **2**, **3**, and **4**, were all found to be inefficient in forming stable complexes under the given conditions.

Solvent extraction of metal ions: Apart from small proton-donor molecules, metal ions are also potential guests for host compound **1**. Since the host possesses proton-ionizable functions (carboxylic acid groups) it is very promising in the extraction of metal ions, rendering superfluous the phase transfer of additional anionic species.[28] Hence extraction experiments were performed with **1** and different metal ions that included alkali and alkaline earth cations as well as the lanthanide metal ions Eu^{3+} and Yb^{3+}. The studied extraction system was metal nitrate/buffer/H_2O/**1**/$CHCl_3$. The pH was adjusted to 8.6 by using a TEA/HCl buffer (for alkali and alkaline earth metal ions) and to 5.6 by using MES/NaOH buffer (Eu^{3+}, Yb^{3+}). A view of the extraction properties of **1** is given in Figure 4. It is clearly shown that there is an increasing extraction tendency of **1** toward alkali and alkaline earth metal ions in the order $Ca^{2+} \sim Sr^{2+} > Mg^{2+} > Ba^{2+} > Cs^{+} > Na^{+}$. The highest extractabilities are observed for Ca^{2+} and Sr^{2+}; this is in agreement with their strong interaction with carboxylate anions. Furthermore, the cavity size of **1** formed by the *endo*-oriented carboxylic acid functions (see Figure 3b) leads to a preorganized coordination pattern with nearly octahedral geometry. This fact has been confirmed by extraction experiments for the metal ions at changing ligand

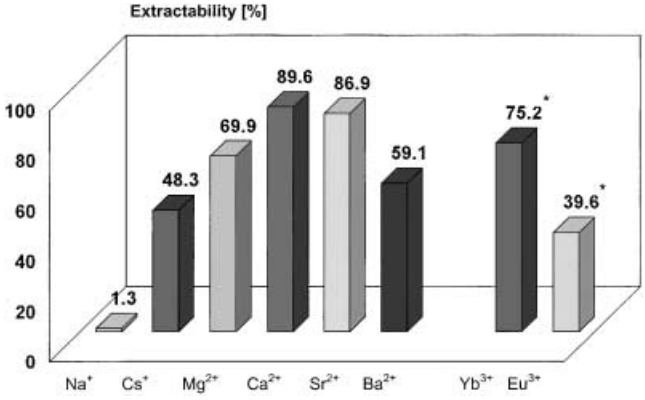

Figure 4. Extractability of metal ions with cryptophane receptor **1**: $[M(NO_3)_n] = 1 \times 10^{-4}$ M (M = Na, Cs, Mg, Ca, Sr, Ba), pH 8.6 (TEA/HCl buffer); $[M(NO_3)_3] = 1 \times 10^{-4}$ M (M = Eu, Yb), pH 5.6 (MES/NaOH buffer); $[\mathbf{1}] = 1 \times 10^{-3}$ M in $CHCl_3$.

concentrations in the organic phase.[29] In all cases clean 1:1 complex formation was detected, as shown by the distribution data summarized in Figure 5 that give lines with an uniform slope of 1 in a $\log D$ against $\log c_L$ diagram at constant pH. Compared with structure-related *endo*-dicarboxylic macrocycles,[28] the extraction selectivities for **1** resulting from single-ion experiments are slightly reduced due to its higher ligand flexibility. However, the observed Ca^{2+} preference is essentially more pronounced under competitive extraction conditions if all metal ions are combined in solution.

It is worth mentioning that the extractabilities of the lanthanide ions Yb^{3+} and Eu^{3+} are significantly higher even at lower pH values of the aqueous solution. As shown in

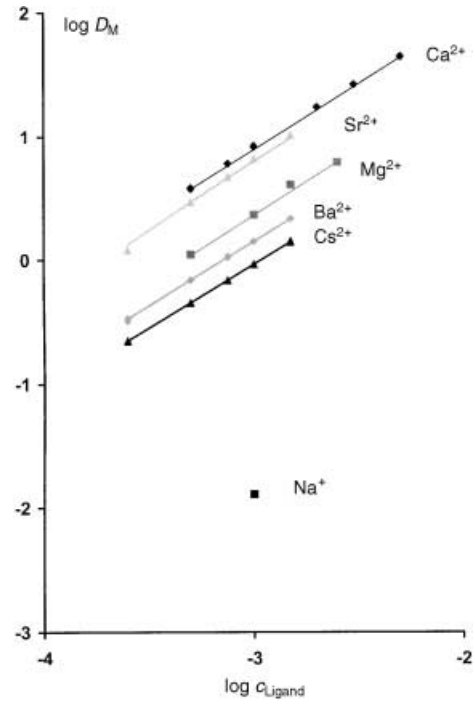

Figure 5. Variation of $\log D_M$ with ligand concentration for the extraction of metal ions with cryptophane receptor **1**: $[M(NO_3)_n] = 1 \times 10^{-4}$ M (M = Na, Cs, Mg, Ca, Sr, Ba), pH 8.6 (TEA/HCl buffer); $[\mathbf{1}] = 2.5 \times 10^{-4} \ldots 5 \times 10^{-3}$ M in $CHCl_3$.

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Figure 4, the Yb^{3+} and Eu^{3+} extractabilities at pH 5,6 are 75,2% and 39.6%, respectively. These results point to a pronounced complex-formation behavior of **1** toward such trivalent hard metal ions giving neutral lipophilic 1:1 complexes. The in vacuo calculated complex structure for Eu^{3+} with **1** obtained in the same way as for the free ligand is in full agreement with this interpretation. As illustrated in Figure 6, the carboxylic groups, being coplanar to their aromatic unit,

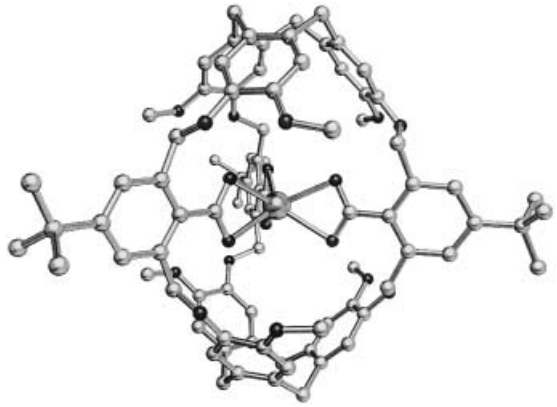

Figure 6. Optimized structure of the europium complex with **1** as obtained by DFT calculations. Oxygen atoms are shown as dark spheres; the metal ion is illustrated as a large sphere.

wrap around the metal ion in a symmetric octahedral environment leaving space for additional water or solvent coordination on the metal center; this can lead to a more optimum coordination number of between seven and nine. In consequence of the metal complexation, the host molecule has increased slightly in size compared with the free ligand. As expected, the cryptophanes **2**, **3**, and **4** are inefficient in the extraction of metal ions; this points to the requirement for both cavity space available for guest accommodation and suitable binding sites not being fulfilled in these compounds.

Conclusion

In summary, prototype compounds of a new type of cryptophanes incorporating aromatic units in the bridges between the two cyclotriveratrylene caps (**1**–**4**) have been presented. Within the scope of the new structure type, the cryptophane **1**, which has three *endo*-positional carboxylic functions is another structural innovation. Solution ^{1}H NMR spectroscopy and crystal-structure studies clearly indicate the intracavity orientation of the ester groups of **2**. A corresponding property also resulted from molecular modeling calculations both of compounds **1** and **2**. Complexation studies in solution by using ^{1}H NMR titration show the cryptophane **1** to be a rather selective host for methanol and ethanol, which are included in the cavity unlike isopropanol, which is evidently too big to be included. Solvent extraction of metal ions in a metal nitrate/buffer/H_2O/extractant/$CHCl_3$ system proved the cryptophane **1** to be a very efficient carrier for more highly charged, hard metal ions of matching size, such as divalent alkaline earth or trivalent lanthanide metal ions, in particular Ca^{2+}, Sr^{2+}, and Yb^{3+}. The determined 1:1 complex formation of **1** is consistent with the optimized structure of the Eu^{3+} complex, which assumes such a stoichiometry and binding mode. In contrast to **1**, the other cryptophanes described here are inefficient both in the complexation of alcohols or other polar compounds and in the extraction of metal ions due to their structural insufficiency for binding and inclusion.

On the other hand, the remarkable binding properties of **1** offer interesting options for separation and transport applications that are based both on a stable binding of the species and an effective shielding from the environment[1c, 30] fairly comparable to that of the spherand-type containers.[31] However, the latter generally do not display intracavity-ionizable or other functional groups. Thus, the present cryptophanes, in particular compound **1**, can be seen as spherical analogues of the *endo*-functional cyclophanes described earlier,[16, 28] but having the advantage as above. Extension of the structural concept by enlargement of the bridges, modification of the bridging aromatic units or exchange of the functional groups are promising tasks that remain to be done.

Experimental Section

General methods and procedures: Melting points (uncorrected) were determined on a Kofler melting-point apparatus. IR spectra were recorded on a Nicolet FTIR instrument. NMR spectra were obtained with Bruker MSL 300 (^{1}H: 300 MHz, ^{13}C: 75.15 MHz) and Bruker AM 400 (^{1}H: 400 MHz, ^{13}C: 100.61 MHz) spectrometers with $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were recorded on Kratos Concept ^{1}H (FAB; mNBA/NaOAc) and HP 59987A (ESI) instruments. Elemental analyses were performed on a Heraeus CHN-O-Rapid.

All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica gel 60 F254-coated plates. Merck silica gel (particle size 40–63 μm) was used for column chromatography. All reagents were commercial products and were utilized without further purification. The solvents used were purified or dried by common literature procedures.

Methyl 2,6-bis(bromomethyl)-4-*tert*-butylbenzoate (5a) and 1,3-bis(bromomethyl)-5-*tert*-butylbenzene (5b) were obtained from methyl 2,6-dimethyl-4-*tert*-butylbenzoate or 3,5-dimethyl-1-*tert*-butylbenzene by *N*-bromosuccinimide bromination in 70 and 47% yield, respectively, according to literature descriptions.[32]

Methyl 2,6-bis(4′-formyl-2′-methoxyphenoxymethyl)-4-*tert*-butylbenzoate (6a) and 1,3-bis(4′-formyl-2′-methoxyphenoxymethyl)-5-*tert*-butylbenzene (6b)

General procedure: A mixture of vanillin (6.1 g, 40 mmol) and K_2CO_3 (13.8 g, 100 mmol) in dry acetone (150 mL) was stirred for 5 min. The corresponding bis(bromomethyl) compound (**5a** or **5b**) (20 mmol) was added, and the suspension was stirred at *RT* for 2 d. The solvent was evaporated, and the residue was partitioned between dichloromethane and water. The organic layer was separated, washed with water, and dried (Na_2SO_4). On concentration of the solution and addition of diethyl ether, the products precipitated. Purification was effected by column chromatography (SiO_2, chloroform).

*Data for **6a***: 88% yield; m.p. 111 °C; $R_f = 0.08$ (chloroform); IR (KBr): $\tilde{\nu} =$ 3086, 2959, 2868, 2066, 1724, (C=O), 1683 (C=O), 1587 (Ar), 1464, 1397, 1342, 1268, 1136, 1033, 972, 892, 814, 779, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.20$ (s, 9H; *t*-Bu), 3.66 (s, 3H; COOMe), 3.85 (s, 6H; OMe), 5.29 (s, 4H; CH_2), 6.92 (d, $J = 5$ Hz, 2H; ArH), 7.33 (d, $J = 5$ Hz, 2H; ArH), 7.34 (s, 2H; ArH), 7.46 (s, 2H; ArH), 9.76 (s, 2H; CHO); ^{13}C NMR (100.15 MHz, $CDCl_3$): $\delta = 31.14$ (CMe_3), 34.95 (CMe_3), 52.07 (COO*Me*), 55.99 (OMe), 69.63 (CH_2), 109.30, 112.30, 125.51, 126.66, 127.54, 130.47, 135.38, 150.02, 153.46, 154.10 (Ar), 168.36 (*C*OOMe), 190.95 (CHO); MS (FAB): $m/z = 521.2$ [M^++H]; elemental analysis (%) for $C_{30}H_{32}O_8$ (520.2): C 69.21, H 6.20; found: C 69.02, H 6.48.

Data for **6b**: 79% yield; m.p. 110 °C; $R_f = 0.51$ (chloroform); IR (KBr): $\tilde{\nu} =$ 2963, 2865, 2059, 1676 (C=O), 1596, 1508 (Ar), 1464, 1272, 1135, 1031, 964, 870, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ (s, 9H; *t*-Bu), 3.93 (s, 6H; OMe), 5.22 (s, 4H; CH_2), 6.97 (d, $J = 8.16$ Hz, 2H; ArH), 7.31 – 7.42 (m, 7H; ArH), 9.83 (s, 2H; CHO); ^{13}C NMR (75.15 MHz, $CDCl_3$): $\delta = 31.28$ (CMe_3), 34.79 (CMe_3), 56.07 (OMe), 71.23 (CH_2), 109.73, 112.76, 123.48, 124.30, 126.35, 130.49, 136.29, 150.23, 152.29, 153.70 (Ar), 190.75 (CHO); MS (FAB): $m/z = 463$ [M^++H]; elemental analysis (%) for $C_{28}H_{30}O_6$ (462.5): C 72.71, H 6.63; found: C 72.36, H 6.67.

Methyl 2,6-bis(4′-hydroxymethyl-2′-methoxyphenoxymethyl)-4-*tert*-butylbenzoate (7a) and 1,3-bis(4′-hydroxymethyl-2′-methoxyphenoxymethyl)-5-*tert*-butylbenzene (7b)

General procedure: A solution of $NaBH_4$ (284 mg, 7.5 mmol) in aqueous NaOH (2 M, 0.2 mL) and water (1 mL) was added dropwise to a stirred suspension of dialdehyde **6a** or **6b** (10 mmol) in methanol (50 mL). The solution obtained was concentrated, suspended in water, and acidified with diluted hydrochloric acid. The precipitate was extracted with dichloromethane, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave quantitative yields (as shown by NMR) of the compounds as viscous oils pure.

Data for **7a**: $R_f = 0.15$ (ethyl acetate/chloroform 1:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (s, 9H; *t*-Bu), 1.76 (br s, 2H; OH), 3.76 (s, 3H; COOMe), 3.86 (s, 6H; OMe), 4.58 (s, 4H; CH_2OH), 5.23 (s, 4H; CH_2O), 6.80, 6.88 (d, $J = 8$ Hz, 4H; ArH), 6.92 (s, 2H; ArH), 7.53 (s, 2H; ArH); ^{13}C NMR (75.15 MHz, $CDCl_3$): $\delta = 30.99$ (CMe_3), 34.87 (CMe_3), 51.90 (COO*Me*), 55.93 (OMe), 65.20 (CH_2OH), 69.77 (CH_2O), 114.16, 119.37, 120.43, 125.06, 127.56, 134.37, 135.96, 147.73, 149.88, 153.54 (Ar), 168.65 (*C*OOMe); MS (ESI): $m/z = 541$ [M^++Na].

Data for **7b**: $R_f = 0.10$ (chloroform); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (s, 9H; *t*-Bu), 1.82 (br s, 2H; OH), 3.87 (s, 6H; OMe), 4.58 (s, 4H; CH_2OH), 5.12 (s, 4H; CH_2O), 6.77 (d, $J = 8.12$, 2H; ArH), 6.79 (d, $J = 8.12$ Hz, 2H; ArH), 6.91 (s, 2H; ArH), 7.29 (s, 1H; ArH), 7.37 (s, 2H; ArH); ^{13}C NMR (75.15 MHz, $CDCl_3$): $\delta = 31.31$ (CMe_3), 34.72 (CMe_3), 56.16 (OMe), 65.25 (CH_2OH), 71.70 (CH_2O), 111.23, 114.67, 119.37, 123.68, 124.01, 134.33, 137.11, 147.89, 150.03, 151.75 (Ar); MS (ESI): $m/z = 489$ [M^++Na].

Cryptophanes 2 – 4

General procedure: Under an atmosphere of Ar, benzylic dialcohol **7a** or **7b** (7 mmol) was dissolved in formic acid (800 mL), and the solution was stirred at *RT* for 2 – 10 d. That the reaction is proceeding is shown by precipitation of the product, which may be perceptible only after 2 days' stirring. The formic acid was evaporated in vaccuo at 50 °C. In order to remove any traces of formic acid, in several runs, chloroform was added and evaporated each time. Compounds **2** – **4** were purified, and the diastereomers C_{3h}-**2** and D_3-**3** were separated by column chromatography (SiO_2, ethyl acetate/chloroform 1:1).

Data for C_{3h}-**2**: 14% yield; m.p. 290 °C (dec.); $R_f = 0.60$ (ethyl acetate/chloroform 1:1); IR (KBr): $\tilde{\nu} = 2957$, 2871, 2039, 1721 (C=O), 1631 (Ar), 1508, 1463, 1397, 1365, 1300, 1214, 1147, 1084, 1038, 887, 843, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (s, 27H; *t*-Bu), 2.02 (s, 9H; COOMe), 3.43 (d, $J = 13.54$ Hz, 6H; H_e-CH_2O), 3.59 (s, 18H; OMe), 4.66 (d, $J = 13.54$ Hz, 6H; H_a-CH_2O), 4.77 (d, $J = 10.34$ Hz, 6H; H_e-CH_2), 5.00 (d, $J = 10.34$ Hz, 6H; H_a-CH_2), 6.74 (s, 6H; ArH), 6.79 (s, 6H; ArH), 7.41 (s, 6H; ArH); ^{13}C NMR (100.15 MHz, $CDCl_3$): $\delta = 31.18$ (CMe_3), 34.72 (CMe_3), 36.30 (CH_2), 50.04 (COO*Me*), 56.10 (OMe), 67.93 (OCH_2), 111.50, 113.10, 127.17, 131.34, 131.39, 131.80, 134.89, 146.07, 147.07, 152.09 (Ar), 167.23 (*C*OOMe); MS (FAB): $m/z = 1465.6$ [M^+]; MS (ESI): $m/z = 1466$ [M^++H], 1488 [M^++Na]; elemental analysis (%) for $C_{90}H_{96}O_{18}$ (1465.7): C 73.57, H 6.60; found: C 73.68, H 6.57.

Data for D_3-**3**: 21% yield; m.p. 320 °C (dec.); $R_f = 0.92$ (ethyl acetate/chloroform 1:1); IR (KBr): $\tilde{\nu} = 2964$, 2854, 1707, (C=O), 1402 (Ar), 1510, 1445, 1202, 1152, 1096, 871, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$ (s, 27H; *t*-Bu), 2.04 (s, 9H; COO*Me*), 3.43 (d, $J = 13.53$ Hz, H_e-CH_2O), 3.70 (s, 18H; OMe), 4.51 (d, $J = 9.35$ Hz, H_e-CH_2), 4.67 (d, $J = 13.53$ Hz, 6H; H_a-CH_2O), 5.62 (d, $J = 9.35$ Hz, 6H; H_a-CH_2), 6.75 (s, 6H; ArH), 6.84 (s, 6H; ArH), 7.28 (s, 6H; ArH); ^{13}C NMR (100.15 MHz, $CDCl_3$): $\delta = 31.20$ (CMe_3) 34.85 (CMe_3), 36.39 (CH_2), 50.51 (COO*Me*), 56.64 (OMe), 70.31 (OCH_2), 114.30, 114.38, 127.66, 132.10, 132.26, 132.63, 134.38, 147.89, 148.14, 152.72 (Ar), 168.16 (*C*OOMe); MS (FAB): $m/z = 1465.6$ [M^+]; MS (ESI): $m/z =$ 1466 [M^++H], 1488 [M^++Na]; elemental analysis calcd (%) for $C_{90}H_{96}O_{18}$ (1465.7): C 73.57, H 6.60; found: C 73.68, H 6.57.

Data for **4**: 8% yield; m.p. 298 °C (dec.); $R_f = 0.71$ (ethyl acetate/chloroform 1:1); IR (KBr): $\tilde{\nu} = 2961$, 2865, 2039, 1608 (Ar), 1509, 1477, 1464, 1445, 1397, 1364, 1266, 1216, 1142, 1087, 1024, 868, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (s, 27H; *t*-Bu), 3.36 (d, $J = 13.70$ Hz, 6H; H_e-CH_2O), 3.49 (s, 18H; OMe), 4.58 (d, $J = 13.70$ Hz, 6H; H_a-CH_2O), 4.93 (d, $J = 12.62$ Hz, 6H; H_e-CH_2), 5.04 (d, $J = 12.62$ Hz, 6H; H_a-CH_2), 6.43 (s, 6H; ArH), 6.65(s, 6H; ArH), 6.86 (s, 3H; ArH), 7.30 (s, 6H; ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 31.39$ (CMe_3), 34.73 (CMe_3), 36.26 (CH_2), 56.30 (OCH_3), 71.16 (OCH_2), 113.60, 115.00, 122.81, 123.14, 131.59, 132.38, 137.41, 146.82, 148.18, 151.71 (Ar); MS (FAB): $m/z = 1291.3$ [M^+]; MS (ESI): $m/z = 1314$ [M^++Na]; elemental analysis calcd (%) for $C_{84}H_{90}O_{12}$ (1291.6): C 73.57, H 6.60; found: C 73.57, H 6.46.

Cryptophane 1: A mixture of cryptophane triester C_{3h}-**2** (56 mg, 0.038 mmol), aqueous KOH (10 M, 1.5 mL, 15 mmol), a few small grains of [18]crown-6 and *n*-butanol (50 mL) was heated to reflux under stirring until a clear solution had formed. Stirring and reflux were continued for an additional 6 – 10 h. The solvent was evaporated. In order to remove traces of *n*-butanol, water and then ethanol were added and evaporated in succession. The solid residue was stirred in 5% hydrochloric acid (10 mL), extracted with chloroform, and dried (Na_2SO_4). Concentration, column chromatography (SiO_2, chloroform/ethyl acetate 4:1), and recrystallization from acetone yielded 77% of a colorless solid: m.p. > 330 °C; $R_f = 0.31$ (chloroform/ethyl acetate 4:1); IR (KBr): $\tilde{\nu} = 2966$, 1637 (Ar), 1510, 1265, 1096, 857, 807 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (s, 27H; *t*-Bu), 3.50 (d, $J = 13.43$ Hz, 6H; H_e-CH_2O), 3.57 (s, 18H; OMe), 4.72 (d, $J = 13.43$ Hz, 6H; H_a-CH_2O), 4.83 (d, $J = 9.03$ Hz, 6H; H_e-CH_2), 5.29 (d, $J = 9.03$, 6H; H_a-CH_2), 6.84 (s, 6H; ArH), 6.89 (s, 6H; ArH), 7.49 (s, 6H; ArH), 10.89 (br s, 3H; COOH); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 31.17$ (CMe_3), 34.66 (CMe_3), 35.92 (CH_2), 56.27 (OMe), 71.15 (OCH_2), 113.23, 114.16, 127.99, 131.31, 131.59, 132.47, 137.31, 148.00, 148.55, 151.16 Ar), 174.27 (COH); MS (FAB): $m/z = 1405.7$ [$M^+ - H_2O$]; MS (ESI): $m/z = 1438$ [M^++H_2O], 1455 [M^++Na]; elemental analysis calcd (%) for $C_{87}H_{90}O_{18}$ (1423.7): C 73.40, H 6.37; found: C 73.54, H 6.23.

Liquid – liquid extraction: The extraction studies were performed at 25 ± 1 °C in 2 mL micro-reaction vials by means of mechanical shaking. The phase ratio $V_{(org)}/V_{(W)}$ was 1:1 (0.5 mL each); the shaking time was 30 min. The extraction equilibrium was attained within this period. All samples were centrifuged after extraction. The metal concentrations in both phases were determined radiometrically by using β emission (^{45}Ca; liquid scintillation counter Tricarb 2500/Canberra – Packard) and γ radiation (^{22}Na, ^{137}Cs, ^{85}Sr, ^{133}Ba, ^{152}Eu, ^{169}Yb; NaI (Tl) scintillation counter Cobra II/Canberra – Packard). The radioisotopes were supplied by Medgenix Diagnostics GmbH, Rathingen. The magnesium concentration was only determined in the aqueous phase by atomic adsorption spectrometry (AAS 2100/Perkin Elmer). The pH of the aqueous solution was adjusted by using 0.05 M 2-(*N*-morpholino)ethanesulfonic acid (MES)/NaOH (pH 5.6), and triethanolamine (TEA)/HCl buffer (pH 8.6).

X-ray crystallographic study: Crystals of **2** suitable for structural determination were obtained by slow evaporation of a solution of **2** in chloroform/ethanol/water to yield trigonal plates of a solvate with chloroform and water. A crystal was mounted on a glass fiber. Diffraction data were collected with a CAD-4 instrument (Enraf Nonius; graphite monochromator, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å) at 133(2) K. Cell parameters were determined by least-squares of the setting angles of 25 ($8.86 \le \theta \le 38.93°$) reflections. Intensity data were collected in the range $5.11 \le \theta \le 75.04°$ using $\omega/2\theta$ scans. Backgrounds were measured for half the total time of the peak scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated no crystal decay. A total of 11927 reflections were collected, of which 7008 were unique ($R(\mathrm{int}) = 0.0520$, $R(\sigma) = 0.0659$). The intensities of 5897 reflections were greater than $2\sigma(I)$. Completeness to $\theta = 0.980$.

Crystal data: $C_{61}H_{64.67}Cl_{7.33}O_{14}$, $M_r = 1281.76$, colorless, rhombic plate, size: $0.30 \times 0.40 \times 0.40$ mm, hexagonal, space group: $P\bar{6}$, $a = 17.315(2)$, $b = 17.315(2)$, $c = 19.600(4)$ Å, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 120.00°$, $V = 5089.0(13)$ Å^3, $Z = 3$, $F(000) = 2002$, $D_x = 1.255$ Mg m^{-3}, $\mu = 3.274$ mm^{-1}.

An initial structure model was developed by the application of recycling procedure in a direct method[33] and was completed in a stepwise manner by several subsequent difference syntheses. A properly substituted benzene fragment was localized on one of the threefold axes of the *P*3 space group. This fragment was subsequently recycled several times into direct methods,

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finally yielding a starting model with two independent 1:3 host **2** molecules and some electron density that was assigned to trichloromethane solvent. The initial model was developed in several subsequent steps of restrained least-squares refinements and consecutive difference electron-density maps into a final structure model in the initial *P*3 space group ($R =$ 0.16 %). This model showed some water solvent molecules and some more disordered $CHCl_3$ located near the first $CHCl_3$ site. As the *P*3 model suggested a prospective mirror symmetry going through the molecular center, the refinement was continued in the $P\bar{6}$ space group. Anisotropic full-matrix least-squares refinement[34] on F^2 for all non-hydrogen atoms yielded $R_1 = 0.1368$ and $wR^2 = 0.3508$ for 5897 [$I > 2\sigma(I)$] and $R_1 = 0.1479$ and $wR^2 = 0.3613$ for all 7008 intensity data (number of parameters = 410, GOF = 1.478, absolute structure parameter $x = 0.13(4)$, the maximum and mean shift/esd are 0.109 and 0.020). The maximum and minimum residual electron densities in the final difference map were 0.971 and -0.862 e Å^{-3}. The weighting scheme applied was $w = 1/[\sigma^2(F_o^2) + (0.2000P)^2 + 0.0000P]$ in which $P = (F_o^2 + 2F_c^2)/3$. Hydrogen atomic positions were calculated from assumed geometries for those sites where it was deemed reasonable. Hydrogen atoms were included in structure-factor calculations but they were not refined. Isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq) value of the atom they were bonded to.

CCDC-172075 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

Computational Studies: All calculations were performed with the Amsterdam Density Functional 2000.02 (ADF) program package[25] on a Silicon Graphics Origin 2000 computer (56 MIPS R10000 64-Bit CPU with 195 MHz and 17 GB memory). The molecular orbitals were expanded in an uncontracted set of Slater type orbitals (STOs) containing diffuse functions. The basis was of triple-zeta quality, augmented with one polarization function [basis set IV (TZ + P)].[35] The cores were treated by the frozen-core approximation. The numerical integration was performed by using the procedure developed by Baerends et al.[36] The Becke–Perdew (BP86) functional with Becke's gradient correction for the local expression of the exchange energy[37] and Perdew's gradient correction for the local expression of the correlation energy[38] was used for the calculations. The convergence criteria for geometry optimizations, which use analytical derivatives,[39] were set to 1×10^{-3} hartree for the changes in energy, 1×10^{-3} hartree Å^{-1} for the energy gradient, 1×10^{-3} Å for the changes between old and new bond lengths, and 0.3° for changes in bond and dihedral angles.

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