144. Dendrophanes: Water-Soluble Dendritic Receptors

Preliminary Communication

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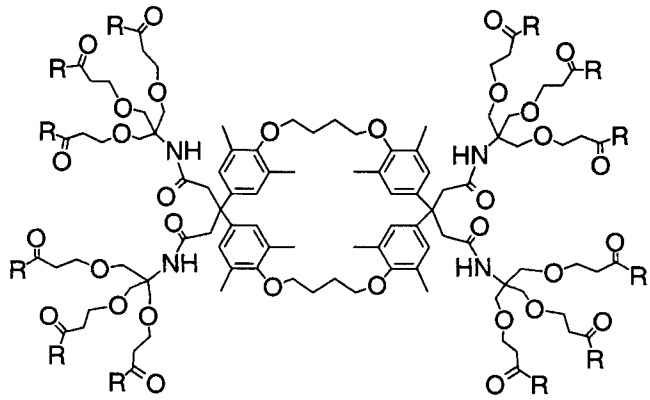
The *dendr*itic cyc*lophanes* (dendrophanes **1–3** containing a [6.1.6.1]paracyclophane as the initiator core embedded in dendritic poly(ether-amide) shells of first (**1**), second (**2**), and third (**3**) generation were prepared and characterized. The X-ray crystal-structure analyses of esters **7** and **4**, derivatives of cyclophane core **9** and first-generation dendrophane **1**, respectively, displayed open cavity binding sites suitable for the inclusion complexation of aromatic substrates. With their carboxylate surface groups, dendrophanes **1–3** were readily soluble in aqueous phosphate buffer (p*H* 8.0), and the complexation of naphthalene derivatives was investigated by ^{1}H-NMR and fluorescence titrations. The binding studies demonstrated that the cyclophane cavity remains open and accessible to appropriate substrates even at higher dendritic generations. The 1:1 complexes formed in aqueous buffer were of similar stability to those formed by the unbranched core **9** (K_a between 1000 and 10000 l mol^{-1}, 300 K). Investigations with the fluorescent probe 6-(*p*-toluidino)naphthalene-2-sulfonate (**12**) showed that the micropolarity at the dendrophane core decreases with increasing generation number.

Water-soluble cyclophanes with hydrophobic cavities are excellent synthetic receptors for apolar aliphatic and aromatic substrates [1] [2]. They contain wide open, solvent-exposed apertures by which substrates can penetrate rapidly, often in a nearly diffusion-controlled way [3], into the binding site, and therefore possess model character for hydrophobic pockets and clefts at the surface of proteins. We became interested in developing model systems for apolar binding sites that are deeply buried within globular proteins and in investigating the influence of a shielding superstructure on kinetics and thermodynamics of inclusion complexation by a cyclophane. To reach this objective, we combined the rapidly developing dendrimer technology [4] [5] with cyclophane chemistry and describe here synthesis and binding properties of the first representatives **1–3** of the dendrophanes (*dendr*imer-cyc*lophanes*)[1]). They possess a cyclophane receptor as initiator core to which dendritic shells with water solubility providing surface groups are covalently attached. In studies with **1–3**, we intended to explore *a*) whether the well-defined cyclophane recognition site remains open and effective at higher dendritic generations, or whether hydrophobic collapse causes the dendritic branches to occupy the binding site, *b*) how the polarity of the binding site changes with increasing dendritic branching and

[1]) A variety of dendrimers with receptor properties have been prepared; see [5]. However, the position of the incorporated guests in these systems is not well defined.

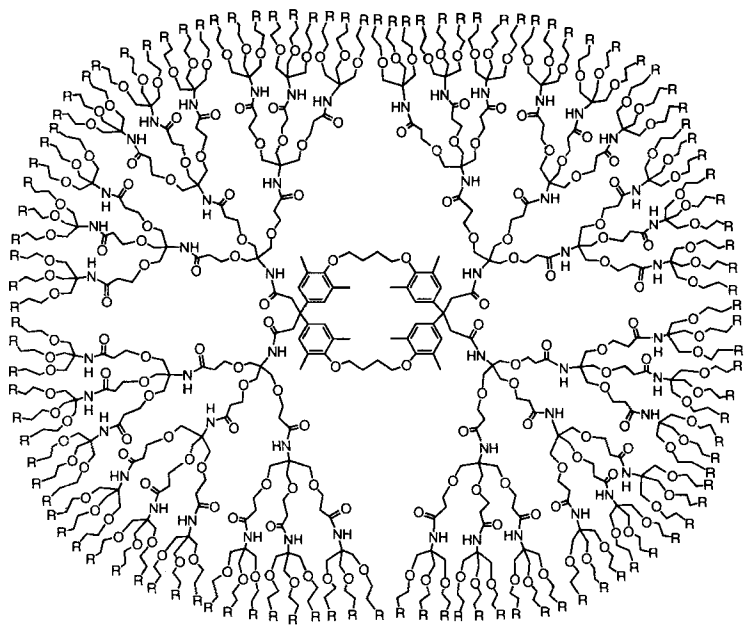


1 R = OH

4 R = OCH_3

2 R = $NHC(CH_2OCH_2CH_2COOH)_3$

5 R = $NHC(CH_2OCH_2CH_2COOCH_3)_3$



3 R = COOH

6 R = $COOCH_3$

shielding from solvent, and *c*) how the kinetics of inclusion complexation is influenced by increased branching.

The synthesis of tetraester **7**, the direct precursor to the cyclophane core **9**, followed closely the method previously described for the preparation of **8** [6][2]). An X-ray crystal-structure analysis was obtained for **7**, which represents the first one for this type of [*n*.1.*n*.1]paracyclophane with four divergent carboxyl residues and shows an open, 8.0 × 9.5 Å wide (distances between the centers of opposite benzene rings) rectangular cavity (*Fig. 1*).

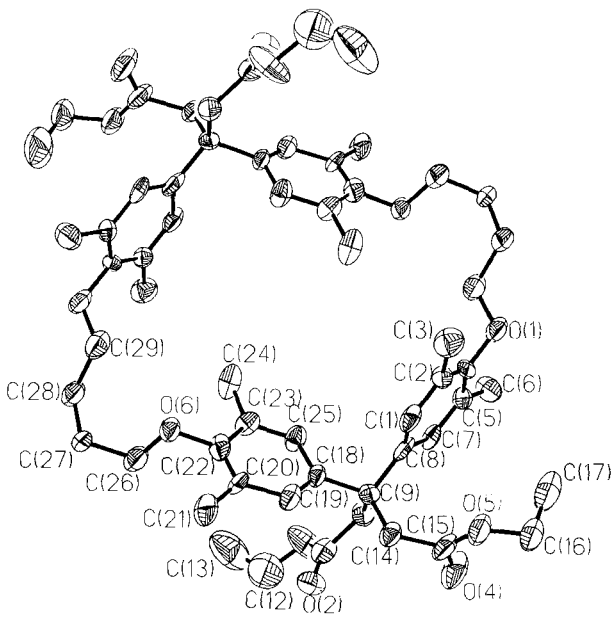


Fig. 1. *Molecular structure of* **7** *in the crystal*

X-Ray crystal-structure analysis of tetraethyl 5,14,20,29,32,33,36,37-octamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-3,5,13,15,18,20,28,30,31,33,35,37-dodecaene-2,2,17,17-tetraacetate (**7**; $C_{58}H_{76}O_{12}$, M_r 965.2): Monoclinic space group $P2_1/n$, $D_c = 1.121$ g cm^{-3}, $Z = 2$, $a = 8.898(13)$, $b = 19.50(3)$, $c = 17.04(2)$ Å, $\beta = 104.74(10)°$, $V = 2859(7)$ Å^3, *Siemens R3m/V* diffractometer, MoK_α radiation, $\lambda = 0.71073$ Å, $2\theta \leq 40°$, 2070 independent reflections, T 298 K. Single crystals were obtained by slow evaporation of a solution of AcOEt/$CHCl_3$. The structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least-squares analysis (heavy atoms anisotropic, H-atoms isotropic with H-atom coordinates based on stereochemical considerations). The EtO groups are disordered (see *Fig. 1*). $R(F) = 0.15$, $wR(F) = 0.15$ for 311 variables and 1617 observed reflections with $F > 4.0\sigma(F)$.

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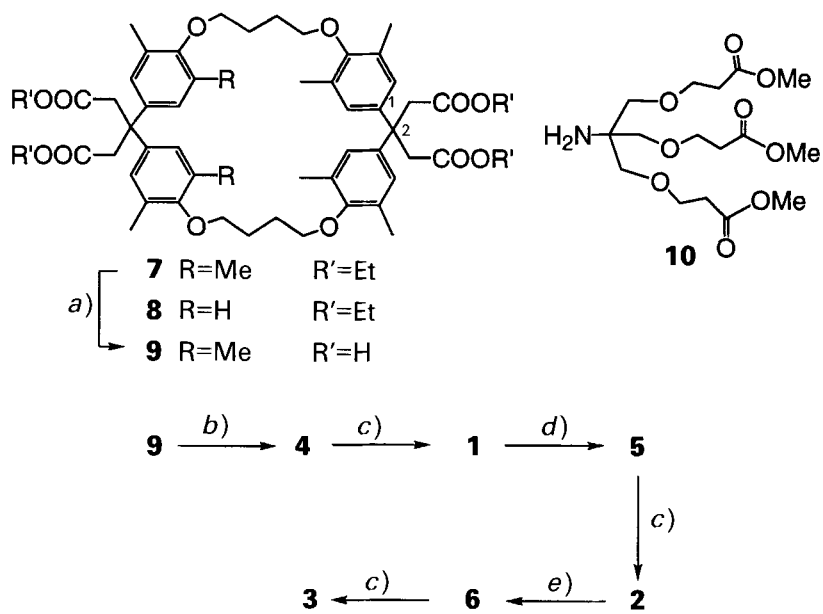
[2]) All new compounds were fully characterized spectroscopically (IR, ^{1}H- and ^{13}C-NMR, EI-, FAB-, or MALDI-TOF-MS) and, with the exception of the dendritic compounds, also by elemental analysis. The dendritic compounds did not give correct elemental analyses due to significant solvent inclusion.

Hydrolysis of the ester groups in **7** afforded tetracarboxylic acid **9**, which served as core for the construction of dendrophanes **1**–**6**. They were prepared following the branching method of *Newkome et al.* [7], under use of building block **10**, previously applied by us to the synthesis of dendrimer-porphyrins [8] (*Scheme*). The various dendritic generations were purified at the stage of the esters (**4**–**6**) by preparative gel-permeation chromatography (GPC, *Biorad Biobeads SX-1*, toluene) until proven homogeneous by ^{1}H- and ^{13}C-NMR spectroscopy (500 and 125.8 MHz, resp., $CDCl_3$; see *Table 1*). In the ^{13}C-NMR spectrum of third-generation dendrophane **6**, 20 of the expected 26 signals, including all four aromatic C-atoms and the CONH, Ar*Me*, and ArO*C*H$_2$ resonances of the cyclophane core, were observed. In addition, all signals of the second- and third-generation branching were clearly identified, whereas those of the first-generation branches were partially masked. In contrast, the ^{1}H-NMR spectrum of **6** showed the complete expected set of signals. The carboxylic acids **1**–**3**, which were obtained by subsequent hydrolysis, also gave the expected ^{1}H- and ^{13}C-NMR spectra (500 and 125.8 MHz, resp., D_2O, 0.066M phosphate buffer, pD 8.4). With the exception of the crystalline ester **4**, all dendritic compounds are colorless oils.

Crystals of first-generation ester **4** suitable for X-ray crystal structure analysis were obtained by slow diffusion of hexane into a toluene solution (*Fig. 2*).

Scheme. *Synthesis of the Water-Soluble Dendrophanes* **1**–**3** *and of Cyclophane Core* **9**



a) NaOH, THF/MeOH/H_2O 1:1:2, 60°, 79%. *b*) **10**, *N*,*N*′-dicyclohexylcarbodiimide (DCC), benzotriazol-1-ol (BtOH), THF, 45°, 60%. *c*) LiOH, THF/MeOH/H_2O 1:1:2, 20°, quant. *d*) **10**, DCC, BtOH, THF, 20°, 70%. *e*) **10**, DCC, BtOH, THF, 20°, 50%.

X-Ray crystal-structure analysis of *dodecamethyl 3,3^{I},3^{II},3^{III},3^{IV},3^{V},3^{VI},3^{VII},3^{VIII},3^{IX},3^{X},3^{XI}-{(5,14,20,29,32,33,36,37-octamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-3,5,13,15,18,20,28,30,31,33,35,37-dodecaene-2,2,17,17-tetrayl)tetrakis{[(1-oxoethane-2,1-diyl)imino(methanetetrayl)]tris(methyleneoxy)}}dodecakis[propanoate]* (**4**; $C_{114}H_{168}N_4O_{44}$, M_r 2298.5): triclinic space group $P\bar{1}$ (No. 2), $D_c = 1.30$ g cm^{-3}, $Z = 1$, $a = 12.772(3)$, $b = 15.452(2)$, $c = 16.180(2)$ Å, $\alpha = 83.33(2)$, $\beta = 69.97(1)$, $\gamma = 79.22(1)°$, $V = 2942.4(8)$ Å^3, *Enraf-Nonius-CAD4* diffractometer, CuK_α radiation, $\lambda = 1.5418$ Å, $\theta \leq 66°$, 10525 independent reflections, T 100 K. The structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least-squares analysis using an isotropic extinction correction and an exponentially modified weight factor $r = 3.5$ A. The molecule contains a center of symmetry; the dendritic branches are disordered. After a series of difference electron density analyses and least-squares refinements, two main orientations could be identified for four (symmetry-independent) ester groups, of which only one is shown in *Fig. 2*. Most heavy atoms were refined anisotropically, disordered ones with half-weight; H-atoms (only those of the ordered molecular skeleton) were refined isotropically, with coordinates based on stereochemical considerations. The high anisotropic atomic displacement parameters of the atoms at the end of the dendrimer branches (see *Fig. 2*) originate mainly from static disorder; the molecular geometry in this region is, therefore, inaccurate. The two orientations of the ester groups could not be resolved with an initial data set measured at 250 K. $R(F) = 0.107$, $wR(F) = 0.124$ for 764 variables and 7497 observed reflections with $F > 4\,\sigma(F)$. Further details of the crystal structure analyses of **7** and **4** are available on request from the Director of the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ (UK), on quoting the full journal citation.

Table 1. *Selected Physical and Spectral Data of Dendrophanes* **5** *and* **6**[a])

Hexatriacontamethyl 3,3^{I},3^{II},3^{III},3^{IV},3^{V},3^{VI},3^{VII},3^{VIII},3^{IX},3^{X},3^{XI},3^{XII},3^{XIII},3^{XIV},3^{XV},3^{XVI},3^{XVII},3^{XVIII},3^{XIX},3^{XX},3^{XXI},3^{XXII},3^{XXIII},3^{XXIV},3^{XXV},3^{XXVI},3^{XXVII},3^{XXVIII},3^{XXIX},3^{XXX},3^{XXXI},3^{XXXII},3^{XXXIII},3^{XXXIV},3^{XXXV}-{(5,14,20,29,32,33,36,37-Octamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-3,5,13,15,18,20,28,30,31,33,35,37-dodecaene-2,2,17,17-tetrayl)tetrakis{[(1-oxoethane-2,1-diyl)imino(methanetetrayl)]tris-{[(methyleneoxy)(1-oxopropane-3,1-diyl)imino(methanetetrayl)]tris(methyleneoxy)}}}hexatriacontakis[propanoate] (**5**): Viscous colorless oil. FT-IR ($CHCl_3$): 1732, 1670 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.60 (*s*, 8 arom. H); 6.45 (*s*, 4 H, NH 1. gen.); 6.17 (*s*, 12 H, NH 2. gen.); 3.81 (*m*, 8 H, ArOCH_2CH$_2$); 3.64 (*m*, 252 H, MeO, CH_2OCH$_2$CH$_2$COO, CH$_2$OCH_2CH$_2$COO); 3.55 (*t*, $J = 6.5$, 24 H, CH$_2$OCH_2CH$_2$CON); 3.39 (*s*, 24 H, CH_2OCH$_2$CH$_2$CON); 3.1 (br. *s*, 8 H, Ar$_2$CCH_2CON); 2.50 (*t*, $J = 6.5$, 72 H, CH$_2$OCH$_2$CH_2COO); 2.33 (*t*, $J = 6.5$, 24 H, CH$_2$OCH$_2$CH_2CON); 2.08 (*s*, 24 H, Ar*Me*); 1.89 (*m*, 8 H, ArOCH$_2$CH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): 172.01; 171.54; 170.92; 153.81; 142.21; 129.67; 127.76; 72.10; 69.10; 68.80; 67.51; 66.74; 59.80; 59.63; 51.63; 46.93; 44.97; 37.15; 34.71; 26.97; 16.74. MALDI-TOF-MS: 6488 (100, $[M + Na]^+$; calc. for $^{13}C_3{}^{12}C_{291}H_{468}N_{16}O_{140}$·Na: 6489).

Octahecamethyl 3,3^{I},3^{II},3^{III},3^{IV},3^{V},3^{VI},3^{VII},3^{VIII},3^{IX},3^{X},3^{XI},3^{XII},3^{XIII},3^{XIV},3^{XV},3^{XVI},3^{XVII},3^{XVIII},3^{XIX},3^{XX},3^{XXI},3^{XXII},3^{XXIII},3^{XXIV},3^{XXV},3^{XXVI},3^{XXVII},3^{XXVIII},3^{XXIX},3^{XXX},3^{XXXI},3^{XXXII},3^{XXXIII},3^{XXXIV},3^{XXXV},3^{XXXVI},3^{XXXVII},3^{XXXVIII},3^{XXXIX},3^{XL},3^{XLI},3^{XLII},3^{XLIII},3^{XLIV},3^{XLV},3^{XLVI},3^{XLVII},3^{XLVIII},3^{XLIX},3^{L},3^{LI},3^{LII},3^{LIII},3^{LIV},3^{LV},3^{LVI},3^{LVII},3^{LVIII},3^{LIX},3^{LX},3^{LXI},3^{LXII},3^{LXIII},3^{LXIV},3^{LXV},3^{LXVI},3^{LXVII},3^{LXVIII},3^{LXIX},3^{LXX},3^{LXXI},3^{LXXII},3^{LXXIII},3^{LXXIV},3^{LXXV},3^{LXXVI},3^{LXXVII},3^{LXXVIII},3^{LXXIX},3^{LXXX},3^{LXXXI},3^{LXXXII},3^{LXXXIII},3^{LXXXIV},3^{LXXXV},3^{LXXXVI},3^{LXXXVII},3^{LXXXVIII},3^{LXXXIX},3^{XC},3^{XCI},3^{XCII},3^{XCIII},3^{XCIV},3^{XCV},3^{XCVI},3^{XCVII},3^{XCVIII},3^{XCIX},3^{C},3^{CI},3^{CII},3^{CIII},3^{CIV},3^{CV},3^{CVI},3^{CVII}-{(5,14,20,29,32,33,36,37-Octamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-3,5,13,15,18,20,28,30,31,33,35,37-dodecaene-2,2,17,17-tetrayl)tetrakis{[(1-oxoethane-2,1-diyl)imino(methanetetrayl)]tris{[(methyleneoxy)(1-oxopropane-3,1-diyl)imino(methanetetrayl)]tris{[(methyleneoxy)(1-oxopropane-3,1-diyl)-imino(methanetetrayl)]tris(methyleneoxy)}}}}octaheca[propanoate] (**6**): Viscous colorless oil. FT-IR ($CHCl_3$): 1732, 1670 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.54 (*s*, 8 arom. H); 6.3 (br. *s*, 52 H, NH); 3.81 (*m*, 8 H, ArOCH_2CH$_2$); 3.64 (*m*, 900 H, MeO, CH_2OCH$_2$CH$_2$CO, CH$_2$OCH_2CH$_2$CO 2. and 3. gen.); 3.45 (*m*, 24 H, CH$_2$OCH_2CH$_2$CON 1 gen.); 3.39 (*s*, 24 H, CH_2OCH$_2$CH$_2$CON 1. gen.); *ca.* 3.0 (br. *s*, 8 H, Ar$_2$CCH_2CON); 2.78 (*m*, 24 H, CH$_2$OCH$_2$CH_2CON 1. gen.); 2.50 (*t*, $J = 6.5$, 216 H, CH$_2$OCH$_2$CH_2COO); 2.37 (*t*, $J \approx 5$, 72 H, CH$_2$OCH$_2$CH_2CON 2. gen.); 2.08 (*s*, 24 H, ArCH$_3$); 1.89 (*m*, 8 H, ArOCH$_2$CH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): 172.18; 171.99; 171.00; 170.64; 153.83; 142.21; 129.67; 127.5 (br.); 72.10; 69.00; 67.46; 66.70; 59.92; 59.79; 51.60; 37.03; 36.73; 34.64; *ca.* 26.5; 16.65. MALDI-TOF-MS: 18958 (100, M^+; calc. for $^{13}C_9{}^{12}C_{825}H_{1368}N_{52}{}^{18}O_1{}^{16}O_{427}$: 18971) and fragment ions from successive loss of each three NHC(CH$_2$OCH$_2$CH$_2$CO$_2$CH$_3$)$_3$ moietics.

[a]) Matrixes for MALDI-TOF-MS were 2-(4-hydroxyphenylazo)benzoic acid (for **5**) or α-cyano-4-hydroxycinnamic acid (for **6**).

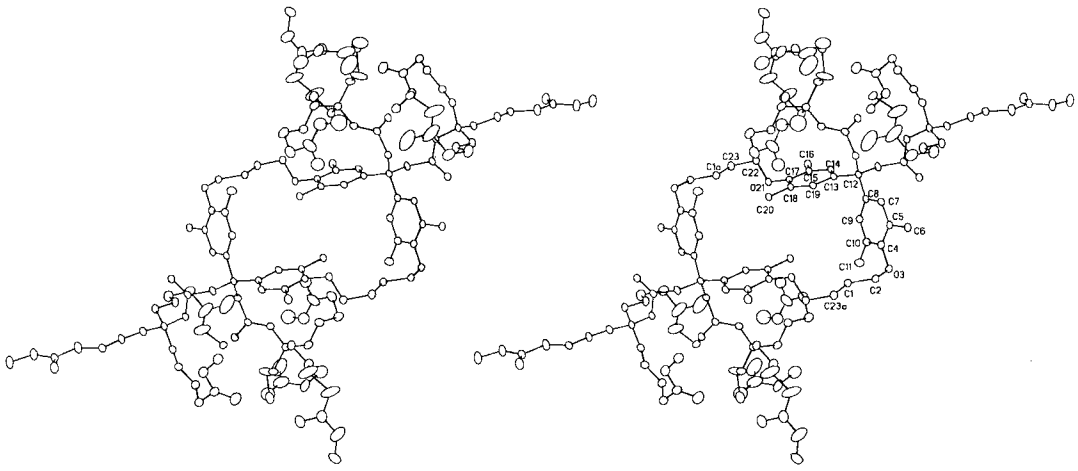


Fig. 2. *Stereo-representation of the molecular structure of* **4** *in the crystal*

The *ca.* 7 × 10 Å large cavity in **4** is somewhat distorted as compared to that in **7** but remains open for guest incorporation. Although the branches start covering the cavity openings, the dendritic shell in **4** is not yet sufficiently extended to fully surround the cyclophane. According to computer models [9], a densely packed, full encapsulation of the binding site occurs only at the stage of generation 3. Among the very few known solid-state structures of dendrimers [10], **4** is the largest whose X-ray crystal structure could be solved so far. The high structural disorder at the ends of the dendritic branches in **4** suggests that in general, solving the solid-state structures of higher generation dendrimers is unlikely [11].

In addition to the NMR data, mass-spectrometric investigations provided support for the structures assigned to the dendrimers of second and third generation. The matrix-assisted laser-desorption-ionization time-of-flight mass spectrum (MALDI-TOF-MS) of **5** depicted the sodium-molecular ion complex as base peak at m/z 6488 (calc. for $^{13}C_3{}^{12}C_{291}H_{468}N_{16}O_{140}\cdot Na$: 6489), and the spectrum of **7** displayed the molecular ion as parent ion at m/z 18958 (calc. for $^{13}C_9{}^{12}C_{825}H_{1368}N_{52}{}^{18}O_1{}^{16}O_{427}$: 18971) besides fragment ions resulting from successive loss of $NHC(CH_2OCH_2CH_2CO_2Me)_3$ moieties. The monodispersity of **4**–**6** was additionally supported by sharp peaks in the GP chromatogram.

The complexation properties of dendrophanes **1** and **2**, and, in comparison, of cyclophane **9** were first investigated at 300 K by 500-MHz ^{1}H-NMR titrations in 0.066M phosphate buffer in D_2O (pD 8.4) in the presence of small quantities of organic solvent (*Table 2*)[3]). Titrations at either constant guest or constant host concentration were

[3]) Accurate weighting-ins for titrations were rendered very difficult by the high hygroscopicity of dendrophanes **1**–**3**. Furthermore, **2** and **3**, in particular, showed a high tendency for solvent incorporation. Therefore, concentrations of dendrophanes in titration solutions were best determined by ^{1}H-NMR integration relative to the guest signals taken as internal standard. Small amounts of organic solvents were required for the preparation of stock solutions of the guests for ^{1}H-NMR titrations with variable guest concentration.

evaluated by nonlinear least-squares curve-fitting and yielded similar results [12]. Both naphthalene-2,7-diol (**11**; in D_2O buffer/$(CD_3)_2SO$ 97.3:2.7) and 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS; **12**; in D_2O buffer/CD_3OD 85:15) formed 1:1 complexes with **1** and **2** revealing stabilities (K_a between 10^3 and 10^4 l mol^{-1}, T 300 K) similar to those measured for complexes of cyclophane **9**. The complexation-induced changes in ^{1}H-NMR chemical shifts observed for protons of both cyclophane and substrate provided unambiguous evidence for specific inclusion complexation in the cavity of the cyclophane core. In titrations with **1** and **2** at constant guest concentration, downfield shifts of 0.20 to 0.26 ppm (at *ca.* 80% saturation binding) for the *s* of the eight aromatic cyclophane H-atoms were measured; such changes in chemical shift are characteristic for [*n*.1.*n*.1]cyclophane-arene complexation. In titrations at constant host concentration, the guest protons were strongly and differentially shifted upfield (*Fig. 3*). These characteristic changes in ^{1}H-NMR chemical shift would not be observed in case of nonspecific guest incorporation outside the cavity binding site within the dendritic branches. With increasing degree of branching, the complexation rates were significantly lowered as indicated by the line broadening of the ^{1}H-NMR resonances at comparable complexation strength. Titrations with **9** and **1** gave sharp, resolved signals whereas in titrations with **2**, the peaks were already strongly broadened. Titrations with **3** no longer displayed resolved signals at all, due to slow exchange processes on the ^{1}H-NMR time scale.

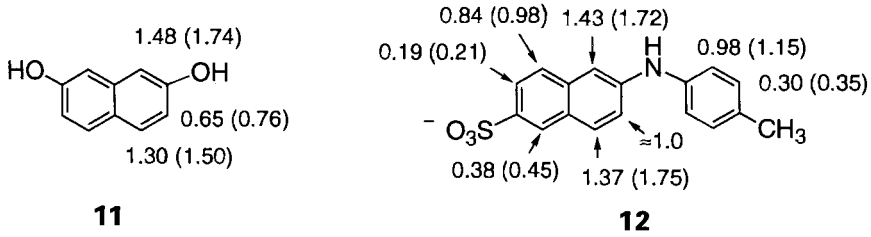


Fig. 3. *Maximum observed upfield shifts* ($\Delta\delta_{max\,obs}$) *and, in parenthesis, upfield shifts calculated for saturation binding* ($\Delta\delta_{sat}$) *of protons of* **11** *and* **12** *in the* ^{1}*H-NMR spectra of complexes of dendrophane* **1**. In a soln. with [**2**] = 1.14 mM and [**11**] = 0.48 mM in D_2O buffer/$(CD_3)_2SO$ 93.2:6.8, the following upfield shifts of the naphthalene protons are observed: 0.74 (H–C(1)), 0.43 (H–C(3)), 0.80 (H–C(4)).

Demonstration of inclusion complexation by the third-generation dendrophane **3** was obtained in fluorescence titrations with the fluorescent probe TNS **12** [13] in pure aqueous phosphate buffer (0.066M, pH 8.0) at 300 K. Upon changing from **1** to **2** and to **3**, the stability of the formed 1:1 complexes only varied slightly (*Table 2*). Whereas the dendrophanes did not give any indication for formation of TNS complexes with higher host-guest stoichiometry, comparison cyclophane **9** in both fluorescence and ^{1}H-NMR titrations demonstrated a strong tendency for formation of host-guest complexes with 2:1 stoichiometry in which the two apolar moieties of the substrate are included in cavity binding sites. The dendritic branches apparently prevent an on-top-stacking of two cyclophanes, needed for a 2:1 host-guest complexation.

Table 2. *Association Constants* K_a [l mol^{-1}] *and Complexation Free Enthalpies* $\Delta G°$ [kcal mol^{-1}] *for Dendrophane Complexes in Aqueous Phosphate Buffer* (0.066M, pH 8.0) *at 300 K*[a])

Dendrophane	Guest	K_a [l mol^{-1}]	$\Delta G°$ [kcal mol^{-1}]
^{1}H-NMR Titrations[b])			
9	**11**[c])	4300	−5.0
1	**11**[c])	1800	−4.4
2	**11**[c])	1700	−4.3
1	**12**[d])	8000	−5.3
2	**12**[d])	2200	−4.6
Fluorescence Titrations[e])			
1	**12**	10500	−5.5
2	**12**	8000	−5.3
3	**12**	5500	−5.1

[a]) Uncertainties in $\Delta G° \pm 0.1$ kcal mol^{-1}.
[b]) Concentration of the component held constant 0.5–1.0 mM and of the variable component 0.25–2.5 mM.
[c]) In D_2O buffer/$(CD_3)_2SO$ 97.3:2.7.
[d]) In D_2O buffer/CD_3OD 85:15.
[e]) In pure aqueous phosphate buffer, [**12**] = $1 \cdot 10^{-5}$ M, [dendrophane] = 10^{-5} to $2 \cdot 10^{-4}$ M.

Fluorescence titrations with TNS, whose emission maximum is strongly polarity dependent, provided indication that the microenvironment around the cavity binding site becomes more apolar with increased branching [8b]. Thus, the maximum of the fluorescence emission of TNS is sequentially blue-shifted when changing from the complex of cyclophane **9** (λ_{max} *ca.* 450 nm in the sections of the titrations where 1:1 association is predominant) to those of dendrophanes **1** (λ_{max} 443 nm), **2** (λ_{max} 435 nm), and **3** (λ_{max} 432 nm). In comparison, the maximum of the fluorescence emission of TNS in H_2O occurs at *ca.* 500 nm, in MeOH at 443 nm, and in EtOH at 429 nm [13]. Our findings suggest that a dendritic shell can influence [14] and, in our case, reduce the micropolarity near specific receptor sites such as cyclophanes.

The preliminary investigations with dendrophanes show that the cyclophane cavity binding site in the interior of a dendritic superstructure remains open and accessible for large aromatic substrates and that complexation occurs specifically in this cavity. With increasing density, the dendritic shell reduces the micropolarity of the binding site. Since decomplexation rates are still quite rapid ($k_{decompl}$ in the range between 10 and 1000 sec^{-1}), even at the stage of the third-generation dendrophane, it will be interesting to transform these novel systems in future work, by attachment of functional groups to the cyclophane core [6] [15], into dendrophanes that are true catalytically active mimics of globular enzymes.

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