Polar Host–Guest Interactions. Solubilization of Some Polar Compounds with Lipophilic Calix[6]arenes containing Polar Groups in Apolar Media†

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Alkylation of three of the six hydroxy groups in calix[6]arene (**2**) with 1-bromo-7,7-di(ethoxycarbonyl)pentacosane (**3**) followed by hydrolysis and subsequent condensation with NH_3 gives rise to a hexa-amide derivative (**6**); the structural formula refers to a mixture of regioisomers of unknown composition. 1-Ethyl-4-methoxycarbonylpyridinium iodide (**12**) and formamide ($HCONH_2$) as polar guests are solubilized in apolar organic solvents such as hexane and CCl_4 *via* host–guest (1:1) complex formation with (**6**) as a lipophilic polar host. The absorption maximum at 365 nm of (**12**) thus solubilized indicates that the binding site of (**6**) for (**12**) is relatively polar. The solubilization of (**12**) and $HCONH_2$ is discussed in terms of micro-solvation interactions of the polar core of (**6**) with the guests.

Host–guest complexation has so far been concerned mainly with the binding of apolar organic molecules and relatively simple ions *via* hydrophobic and electrostatic interactions, respectively; typical hosts are cyclodextrins [1] and cyclophanes [2] for the former and crown ethers and related macrocycles for the latter.[3] We have recently reported that various non-ionic polar compounds including sugars and water-soluble vitamins are solubilized in apolar media *via* the hydrogen-bonding interaction with a polyhydroxy macrocycle (**1**) as a lipophilic polar host.[4] In the present work, we have investigated solubilization of polar compounds by calix[6]arenes modified with flexible alkyl chains having intervening polar groups. We expected that intramolecularly associated polar groups would form a polar core, into which polar compounds could be incorporated by what might be called the micro-solvation effect.§

Results and Discussion

Preparation.—*p*-t-Butylcalix[6]arene (**2**) is a cyclic oligomer arising from the condensation of *p*-t-butylphenol and formaldehyde.[5] It was originally attempted to alkylate the six hydroxy groups in (**2**) with 1-bromo-7,7-di(ethoxycarbonyl)pentacosane (**3**),¶ but, in fact, three of the hydroxy groups underwent facile alkylation when a mixture of (**2**) and (**3**) in acetone was refluxed in the presence of K_2CO_3 and KI for 100 h. The product (**4**) was purified by means of chromotography (silica gel) and gel filtration (Sephadex LH-20). The ^1H n.m.r. spectrum, elemental analysis, and molecular weight of (**4**) determined by vapour-pressure osmometry for a benzene solution (Found: *M*, 2 484. Calc. *M*, 2 458) were consistent with the presence of three moieties of (**3**). Alkaline hydrolysis of (**4**) gave the hexa-acid (**5**), which was further converted into the hexa-amide (**6**) on treatment with NH_3 and dicyclohexylcarbodi-imide (DCC) in CH_2Cl_2. Another type of modified calixarene (**7**) was obtained by alkylating three hydroxy groups of (**2**) with 6-bromo-*N*-stearylhexanamide (**8**).¶

Analytical gel filtration (Sephadex LH-20 and LH-60) of (**4**) purified as above showed a single symmetrical peak, but its h.p.l.c. analysis on silica still gave a rather broad elution curve. After being carefully re-chromatographed on silica, the elution band of (**4**) was arbitrarily separated into five fractions. The ^1H n.m.r. spectra of all fractions were almost identical; especially, the ratios of macrocyclic to side chain moieties were always 1:3. These results suggest that (**4**), and hence (**5**) and (**6**) derived therefrom, are actually mixtures of tri-*O*-substituted regioisomers. In accordance with this, the ^1H n.m.r. spectra of (**4**)–(**7**) even at 100 °C for $(CH_3)_2NCDO$ solutions showed an ill-resolved, complicated pattern for the aromatic protons. The structural formulae of (**4**)–(**7**) are shown as a '1,3,5-' symmetrical regioisomer for purposes of convenience, but they actually refer to a mixture of regioisomers of unknown composition.

It is not clear why (**2**) undergoes only partial alkylation with (**3**) and (**8**). Deactivation of the three hydroxy groups remaining free in (**4**) and (**7**) toward further alkylation may be due to steric effects. Other factors, *e.g.*, hydrogen-bonding interactions between the hydroxy and nearby ester [in (**4**)] or amide groups [in (**7**)] may also come into play.

The amide-modified derivatives (**6**) and (**7**) and a hexa-acid (**5**) are highly soluble in apolar solvents such as hexane, CCl_4, and benzene in marked contrast with (**2**) and such references as (**8**), (**9**),¶ and (**10**), which are scarcely soluble in these solvents. The enhanced solubility of (**5**)–(**7**) seems to suggest that the polar groups therein are associated and are insulated from the bulk solvents. The association of side chains is intramolecular in nature as shown schematically for (**5**) and (**6**) in (**11**) (X = CO_2H or $CONH_2$), since vapour-pressure osmometry reveals no aggregation of (**5**) and (**6**) in benzene and (**7**) in $CHCl_3$ (*e.g.*, molecular weight found for (**6**): 2 216. Calc. *M*, 2 283). Regioisomers of (**5**)–(**7**) are expected to form more or less similar polar cores. We investigated their substrate-binding properties in order to see if such polar cores can interact with polar substrates.

Substrate-binding Properties.—The polar substrates investigated were pyridinium salts, simple amides, vitamin B_2 and B_{12}, glutathione, nucleobases, and nucleosides.

† Molecular Recognition. Part 3. Part 2, Y. Aoyama, A. Yamagishi, M. Asagawa, H. Toi, and H. Ogoshi, *J. Am. Chem. Soc.*, 1988, **110**, 4076.

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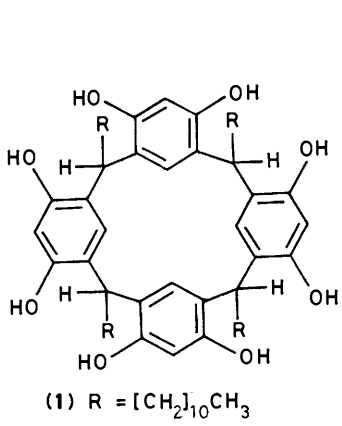
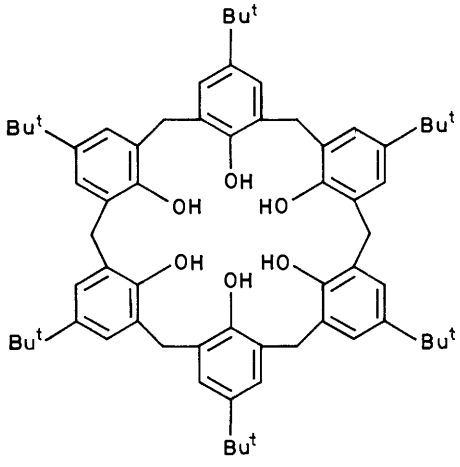
§ Water-soluble calix[6]arene derivatives have been prepared and used as host molecules for hydrophobic guests in aqueous media, S. Shinkai, S. Mori, T. Tsubaki, T. Sone, and O. Manabe, *Tetrahedron Lett.*, 1984, **25**, 5315; S. Shinkai, H. Koreishi, S. Mori, T. Sone, and O. Manabe, *Chem. Lett.*, 1985, 1033; S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki, and O. Manabe, *J. Am. Chem. Soc.*, 1986, **108**, 2409.

¶ Satisfactory ^1H and ^{13}C n.m.r. spectra verified the purity of the material.



(1) R = $[CH_2]_{10}CH_3$



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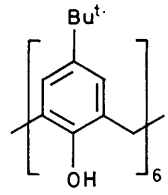

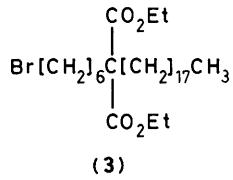

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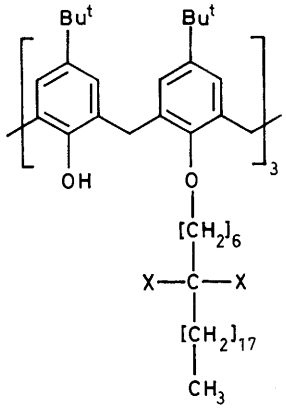
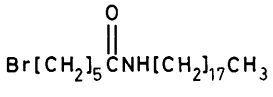


(4) X = CO_2Et

(5) X = CO_2H

(6) X = $CONH_2$



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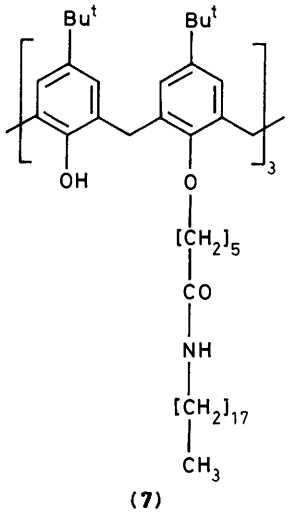

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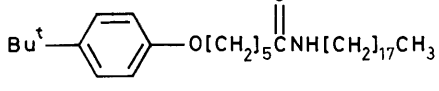

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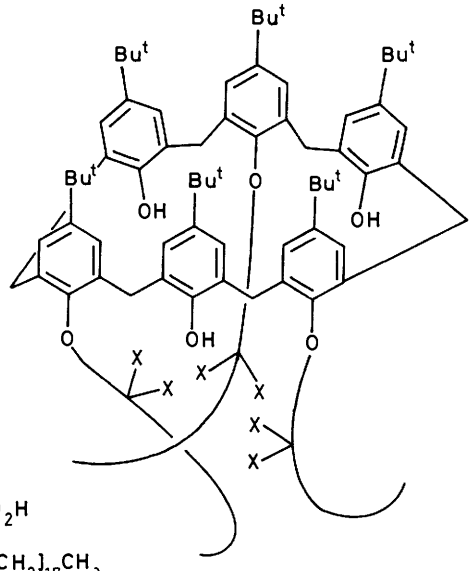

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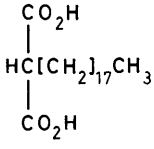
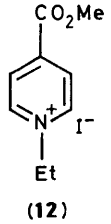


(10)

Table. Charge-transfer absorption maxima of (**12**).

λ_{max}/nm	Solvent	Z^a
302	H_2O	94.6
343	$HCONH_2$	83.3
359	EtOH	79.6
361	AcOH	79.2
368	HCONHMe	77.7
417	$HCONMe_2$	68.5
435	Me_2CO	65.7
452	$CHCl_3$	63.2
529	C_6H_6	54

[a] Solvent Z value; $Z = 28\,590/\lambda_{max}$.



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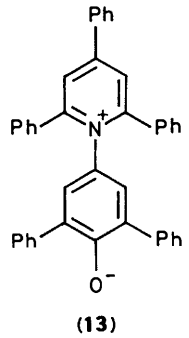

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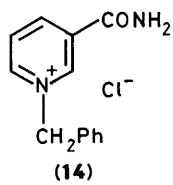

(14)

1-Ethyl-4-methoxycarbonylpyridinium iodide (**12**)[6] provided an interesting case of binding with (**5**)–(**7**). The charge-transfer absorption maximum of (**12**) is known to be sensitive to the solvent polarity (Table).[6] This compound is insoluble in hexane under otherwise identical conditions, but was readily extracted from a concentrated aqueous solution into hexane containing (**6**) and gave the electronic spectrum shown in the Figure. The concentration of (**12**) thus solubilized was determined spectroscopically after re-extraction into a calculated amount of water. The molar ratio of (**6**):(**12**) obtained in this way was *ca.* 1:0.9 at three different concentrations of (**6**) (6×10^{-4}, 1×10^{-3}, and 5×10^{-3} mol dm^{-3}). Such solubilization of (**12**) was also observed when (**5**) or (**7**) was used in place of (**6**), but

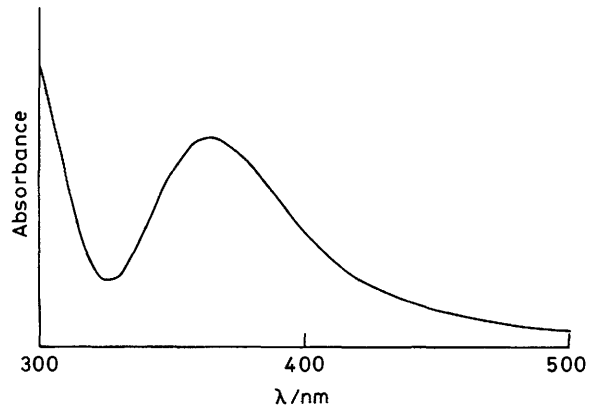

Figure. Electronic absorption spectrum of (**12**) in hexane solubilized with (**6**).

never with (**9**).* The λ_{max} values observed [365 nm with (**6**) (Figure), 356 nm with (**5**), and 360 nm with (**7**)] in the light of the solvent effects on λ_{max} (Table), indicate that the microenvironments of solubilized (**12**) are rather polar, the polarities roughly corresponding to those of carboxylic acid and amide solvents. These observations suggest that the solubilization of (**12**) is due to its incorporation into the polar cores of (**5**)–(**7**) [*cf.* to (**11**)] with a 1:1 stoicheiometry by what may be called the microsolvation effect. Formamide provided another case of relatively strong binding with (**5**) and (**6**). Vigorous stirring of a two-phase mixture of a solution of (**6**) in CCl_4 and formamide (neat, otherwise practically insoluble in CCl_4) resulted in transfer of the latter into the former solution. The ^1H n.m.r. spectra showed the signals for $HCONH_2$ at δ 8.3 (CH), 5.8 (NH), and 5.3 (NH), the integration of which relative to aromatic protons of (**6**) (12 H) established the stoicheiometry (**6**):$HCONH_2$ = 1:1.1 at three different concentrations of (**6**) (5.0×10^{-3}, 7.8×10^{-3}, and 1.0×10^{-2} mol dm^{-3}). Solubilized formamide could also be extracted with D_2O for further identification. Solubilization of formamide was also observed with (**5**), but was negligible when oleic acid was used in place of (**5**) or (**6**).†

The betaine (**13**)[7] and nicotinamide chloride (**14**) are hydrophobic and hydrophilic pyridinium salts, respectively. In marked contrast with (**12**), there was obtained no evidence for the formation of an association complex of (**13**) or (**14**) with (**5**) or (**6**). Attempts were also made to solubilize vitamin B_2 (riboflavin), vitamin B_{12} (cyanocobalamin), glutathione (a naturally occurring tripeptide), nucleobases (adenine, guanine, cytosine, and thymine), and nucleosides (adenosine, guanosine, citidine, and thymidine), either as solids or in saturated aqueous solutions, into solutions of (**5**) or (**6**) in hexane, CCl_4, or $CHCl_3$. In no case, however, was solubilization observed. These compounds and also (**14**) are too polar to be soluble in apolar organic solvents. On the other hand, (**13**) is relatively apolar and is insoluble in water. It is interesting to note that (**12**) and $HCONH_2$ are amphiphilic, showing good solubilities in a wide range of solvents (from water to $CHCl_3$) except the least polar ones (hydrocarbons and CCl_4). Such amphiphilic guests can be incorporated into the polar cores of (**5**) and (**6**) with a 1:1 stoicheiometry by the microsolvation effect.

* Solubilization of (**12**) does not take place with either the parent calixarene (**2**) or with the diacid (**10**) or amide (**8**) which are insoluble in hexane.

† The ^1H n.m.r. spectrum for solubilized formamide showed signals at δ 8.1, 6.2, and 5.7.

‡ Mixture of regioisomers of unknown composition.

Experimental

N.m.r. spectra (^1H and ^{13}C) were recorded with a JEOL-GX 270 spectrometer with Me_4Si or $CHCl_3$ (δ_H 7.25) and $CDCl_3$ (δ_C 77.0) as internal references, respectively. I.r. spectra were obtained as KBr pellets or liquid films on NaCl plates with a JASCO IR-810 spectrophotometer. Electronic absorption spectra were recorded with a Hitachi 200-10 spectrophotometer. Vapour-pressure osmometry was carried out on a Corona-114 molecular-weight apparatus with benzil as a standard. Wakogel C-200 and Sephadex LH-20 or LH-60 were used for column chromatography and gel filtration, respectively, and the elution was monitored by u.v. absorption at 280 nm. Silica gel 60 F_{254} (Merck) was used for t.l.c. Elemental analyses were performed at the Microanalysis Center of Kyoto University. Solvents were dried by standard procedures; THF and hexane with sodium–benzophenone, acetone with $CaSO_4$, and $(CD_3)_2SO$ with $MgSO_4$ or $CaSO_4$. K_2CO_3 and KI were dried at 100 °C *in vacuo* just prior to use.

1-Ethyl-4-methoxycarbonylpyridinium iodide (**12**),[8] N-[3,5-diphenyl-4-hydroxyphenyl]-2,4,6-triphenylpyridinium betaine (**13**),[7,9] and 1-Benzylnicotinamide Chloride (**14**)[10] were prepared according to the published methods. Vitamins, peptide, nucleobases, and nucleosides were commercial products.

Diethyl 1-Bromopentacosane-7,7-dicarboxylate (**3**).—A mixture of diethyl stearylmalonate (30 g, 73 mmol), 1,6-dibromohexane (38 g, 0.16 mol), and sodium ethoxide prepared from Na (1.8 g) in dry ethanol (200 cm^3) was refluxed until the mixture was neutral to wet litmus. Most of the ethanol was removed, water (300 cm^3) was added to the residue, and the mixture was extracted with ether. Work-up and removal of excess dibromohexane under reduced pressure gave an oily residue, which was chromatographed on silica gel with $CHCl_3$ as the eluant to give (**3**) (22 g, 53%); ν_{max}(NaCl) 1 725 cm^{-1} (CO); δ_H(270 MHz; $CDCl_3$) 4.18 (4 H, q, CO_2CH_2), 3.35 (2 H, t, $BrCH_2$), 1.84 [4 H, m, $CH_2C(CO_2Et)_2$], 1.26 (44 H, m, CH_2 and $CO_2CH_2CH_3$), and 0.88 (3 H, t, Me); δ_C(67.8 MHz; $CDCl_3$) 171.9 (CO_2Et), 60.9 [$(CH_2)_2C(CO_2Et)_2$], 57.5 ($CO_2CH_2CH_3$), 33.6–22.7 (CH_2), and 14.1 (Me).

Tris-O-[7,7-di(ethoxycarbonyl)pentacosanyl]calix[6]arene (**4**).‡—A mixture of 5,11,17,23,29,35-hexa-t-butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (**2**) (5.0 g, 5.1 mmol), (**3**) (41 g, 72 mmol), K_2CO_3 (8.6 g, 62 mmol), and KI (5.0 g, 30 mmol) in acetone (250 cm^3) was refluxed for 100 h with vigorous stirring. The mixture was neutralized with dilute hydrochloric acid and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with $CHCl_3$ as the eluant to eliminate unchanged (**3**). Further purification by means of repeated gel filtration with $CHCl_3$–MeOH (1:1) as the eluant afforded (**4**) as an oily material (6.6 g, 52%) (Found: C, 76.7; H, 10.75. $C_{159}H_{258}O_{18}$ requires C, 77.70; H, 10.58%); ν_{max}(NaCl) 1 738 cm^{-1} (CO); δ_H(270 MHz; $CDCl_3$) 7.1 (12 H, br, ArH), 4.3–3.1 (18 H, br m, $ArCH_2Ar$ and OCH_2), 4.12 (12 H, distorted q, CO_2CH_2), 2.2–0.7 (*ca.* 150 H, m, CH_2, $CO_2CH_2CH_3$, and Me_3C), and 0.90 (9 H, t, Me); the osmometric molecular weight for a benzene solution was 2 484 (Calc. 2 458). The ^1H n.m.r. spectrum for a $(CD_3)_2NCHO$ solution at 100 °C still gave a poorly resolved broad signal for aromatic protons.

Tris-O-(7,7-dicarboxypentacosanyl)calix[6]arene (**5**).‡—A mixture of (**4**) (3.7 g, 1.5 mmol) and KOH (5.0 g, 88 mmol) in ethanol (50 cm^3) was refluxed for 50 h. Most of the ethanol was removed and the residue was acidified by the addition of dilute hydrochloric acid. The mixture was extracted with ether. Work-up gave (**5**) as a glassy material (3.0 g, 88%) (Found: C, 75.45;

H, 10.3. $C_{147}H_{234}O_{18}\cdot 3H_2O$ requires C, 75.34; H, 10.32%); ν_{max}(NaCl) 1 703 cm^{-1} (CO); δ_H(270 MHz; $CDCl_3$) 7.1 (12 H, br, ArH), 4.3–3.2 (18 H, br m, $ArCH_2Ar$ and OCH_2), 2.1–0.7 (*ca.* 132 H, m, CH_2 and Me_3C), and 0.90 (9 H, t, Me); the osmometric molecular weight for a benzene solution was 2 265 (calc. 2 289). The ^1H n.m.r. spectrum for a $(CH_3)_2NCDO$ solution at 100 °C still gave a poorly resolved broad signal for the aromatic protons.

Tris-O-(7,7-*dicarbamoylpentacosanyl*)*calix*[6]*arene* (**6**).‡—Into a solution of (**5**) (2.2 g, 1.0 mmol) and dicyclohexylcarbodiimide (2.3 g, 11 mmol) in CH_2Cl_2 (80 cm^3) was introduced gaseous NH_3 for 6 h. The mixture was stirred for 20 h, washed with dilute hydrochloric acid, and extracted with $CHCl_3$. The extract was dried and evaporated. The residue was taken up in hexane and purified by means of gel filtration with $CHCl_3$–MeOH (1:1) as the eluant to give (**6**) as a glassy material (1.5 g, 67%) (Found: C, 76.6; H, 10.25. $C_{147}H_{240}N_6O_{12}$ requires C, 77.32; H, 10.59%); ν_{max}(NaCl) 1 682 cm^{-1} (CO); δ_H(270 MHz; $CDCl_3$) 7.0 (12 H, br, ArH), 4.6–3.1 (18 H, br m, $ArCH_2Ar$ and OCH_2), 2.2–0.7 (*ca.* 132 H, m, CH_2 and Me_3C), and 0.90 (9 H, m, Me); the osmometric molecular weight for a benzene solution was 2 216 (calc. 2 283). The ^1H n.m.r. spectrum for a $(CH_3)_2NCDO$ solution at 100 °C still gave poorly resolved broad signal for aromatic protons.

6-*Bromo*-N-*stearylhexanamide* (**8**).[11]—To a solution of stearylamine (32 g, 0.12 mol) and triethylamine (31 g, 0.31 mmol) in CH_2Cl_2 (150 cm^3) was added dropwise a solution of 6-bromohexanoyl chloride (25 g, 0.12 mol) in CH_2Cl_2 (150 cm^3) at 30–35 °C in a period of 3 h. The mixture was stirred under reflux for 4 h, allowed to cool to room temperature, and washed successively with aqueous solutions of $NaHCO_3$ (5%), NaCl (saturated), citric acid (5%), and NaCl (saturated). Work-up and recrystallization of the residue from CH_2Cl_2 afforded (**8**) (25 g, 47%), m.p. 74–75 °C; ν_{max}(KBr) 3 300 (NH) and 1 630 cm^{-1} (CO); δ_H(270 MHz; $CDCl_3$) 5.42 (1 H, br, NH), 3.41 (2 H, t, $BrCH_2$), 3.23 (2 H, q, $NHCH_2$), 2.17 (2 H, t, CH_2CO), 1.85, 1.61, 1.47, and 1.25 (38 H, m, CH_2), and 0.80 (3 H, t, Me); δ_C(67.8 MHz; $CDCl_3$) 172.5 (CONH), 39.6 (CH_2NH), 36.6 (CH_2CO), 33.6–22.7 (CH_2), and 14.1 (Me).

Tris-O-[5-(N-*stearylcarbamoyl*)*pentyl*]*calix*[6]*arene* (**7**).‡—A mixture of (**2**) (200 mg, 0.21 mmol),[5] (**8**) (740 mg, 1.7 mmol), K_2CO_3 (1.0 g, 7.2 mmol), and KI (0.3 g, 1.8 mmol) in acetone (30 cm^3) was stirred under reflux for 100 h. After addition of water (100 cm^3) the mixture was acidified with dilute HCl solution and extracted with $CHCl_3$. Work-up and chromatography with $CHCl_3$ as the eluant gave an excess (**8**) (450 mg, 1.0 mmol). The crude product eluted with MeOH was purified by means of gel filtration, with $CHCl_3$–MeOH (1:1) as the eluant, to give (**7**) as a glassy material (300 mg, 70%) (Found: C, 79.0; H, 11.05; N, 2.0. $C_{138}H_{225}N_3O_9$ requires C, 79.92, H, 10.95; N, 2.03%); ν_{max}(KBr) 3 300 (NH) and 1 640 cm^{-1} (CO); δ_H(270 MHz; $CDCl_3$) 7.0 (12 H, br, ArH), 4.3–3.3 (18 H, br m, $ArCH_2Ar$ and OCH_2), 3.20 (6 H, br m, $CONHCH_2$), 2.20 (6 H, br m, CH_2CONH), 2.0–0.7 (*ca.* 170 H, m, CH_2 and Me_3C), and 0.90 (9 H, t, Me). The ^1H n.m.r. spectrum for a $(CH_3)_2NCDO$ solution at 100 °C still gave a poorly resolved broad signal for the aromatic protons.

4-t-*Butyl* 5-(N-*Stearylcarbamoyl*)*pentyl Ether* (**9**).—A mixture of *p*-t-butylphenol (1.0 g, 6.7 mmol), (**8**) (3.0 g, 6.7 mmol), K_2CO_3 (1.1 g, 8.0 mmol), and KI (0.3 g, 1.8 mmol) in acetone (30 cm^3) was stirred under reflux for 48 h. Most of the acetone was removed under reduced pressure and water (50 cm^3) was added to the residue. The mixture was extracted with benzene. Work-up, chromatography with CH_2Cl_2 as the eluant, and recrystallization from CH_2Cl_2 afforded (**9**) (2.5 g, 73%), m.p. 80–80.5 °C; ν_{max}(KBr) 3 300 (NH) and 1 630 cm^{-1} (CO); δ_H(270 MHz; $CDCl_3$) 7.27 and 6.81 (4 H, AB system, ArH), 5.41 (1 H, br, NH), 3.94 (2 H, t, OCH_2), 3.20 (2 H, m, $NHCH_2$), 2.18 (2 H, m, CH_2CO), 1.8, 1.7, 1.49, and 1.27 (47 H, m, CH_2 and Me_3C), and 0.86 (3 H, t, Me); δ_C(67.8 MHz; $CDCl_3$) 172.7 (CONH), 126.2 and 114.0 (aromatic), 67.6 (CH_2O), 39.6 (CH_2NH), 36.8 (CH_2CO), 34.0–22.7 (CH_2), and 14.1 (Me).

Solubilization of (**12**).—To a hexane solution (3 cm^3) of a calix[6]arene derivative [(**5**), (**6**), or (**7**)] (6×10^{-4} to 5×10^{-3} mol dm^{-3}) was added the probe (**12**) (150 mg, 0.51 mmol) and water (0.05 cm^3). The mixture was sealed, stirred vigorously for 48 h, and centrifuged. The clear hexane solution was separated and its u.v. spectrum indicated that the solubilization of (**12**) had taken place. The hexane solution was diluted with more hexane (30 cm^3) and the solubilized probe (**12**) was extracted into a calculated amount of water and its concentration was determined from the absorbance at 276 nm (ε 4 330). The water added (0.05 cm^3) was found not to be essential, but solubilization of (**12**) was much faster in its presence. No solubilization of (**12**) was observed when (**9**) (saturation amount) was used under otherwise identical conditions.

Solubilization of Formamide.—A two-phase mixture of a CCl_4 solution (2 cm^3) of (**5**) or (**6**) (5×10^{-3} to 1×10^{-2} mol dm^{-3}) and formamide (neat liquid, 280 mg) was stirred vigorously for 24 h. The mixture was allowed to stand for 6 h to achieve separation of the two phases. The CCl_4 layer was analysed directly by n.m.r. spectroscopy.

Interaction of (**13**) *with* (**6**).—A solution of (**13**) (1.0×10^{-5} mol dm^{-3}) in chlorobenzene with λ_{max} 762 nm underwent a red (bathochromic) shift of λ_{max} by 34 nm upon addition of (**6**) (1.0×10^{-3} mol dm^{-3}, *i.e.*, 6.0×10^{-3} mol dm^{-3} with respect to the amide moiety). This shift could not be taken as evidence for the formation of an association complex of particular stoicheiometry between (**6**) and (**13**), since a similar shift (24 nm) was also observed with *N*-methylacetamide (6.0×10^{-3} mol dm^{-3}) in place of (**6**).

Attempted Solubilization of (**14**), *Vitamins, Peptides, Nucleobases, and Nucleosides.*—Water (0.1 cm^3) with an excess amount of (**14**), vitamin B_2, B_{12}, glutathione, nucleobase, or nucleoside was added to a solution of (**5**) or (**6**) (5×10^{-3} mol dm^{-3}) usually in CCl_4 (3 cm^3). The mixture was stirred vigorously for 24 h, allowed to stand for 6 h, and passed through a membrane filter to remove any excess of substrate. The organic layer was analysed by means of u.v.–vis spectroscopy (for vitamins) or n.m.r. spectroscopy [for (**14**), peptide, nucleobase, or nucleoside]. In no case was there any evidence to suggest solubilization of the substrate in the organic layer.

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