Syntheses and Aggregation Properties of New Water-soluble Calixarenes

Seiji Shinkai,* Takashi Arimura, Koji Araki, and Hirosuke Kawabata
Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan
Hiroshi Satoh, Takayuki Tsubaki, Osamu Manabe, and Junzo Sunamoto
Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852, Japan

Eighteen water-soluble calixarenes have been synthesized and their aggregation properties in water studied. They are six anionic calixarenes (1_n) having sulphonate groups on the upper rim, nine anionic calixarenes (2_n) having sulphonate groups on the lower rim, and three cationic calixarenes (3_n) having ammonium groups on the upper rim. On the basis of measurements of critical micelle concentrations (c.m.c.s.) by surface tension, conductance, and spectroscopic methods, it was concluded that the aggregation behaviour of these water-soluble calixarenes can be classified into three categories: (*i*) non-micellar calixarenes, (*ii*) micelle-forming calixarenes, and (*iii*) unimolecular micellar calixarenes. The possible structure-aggregation relationships are discussed.

'Calixarenes' are cavity-shaped cyclic molecules made up of benzene units.[1,2] Studies of the host-guest chemistry of calixarenes have been very limited,[3-6] in contrast to cyclodextrins which are known to form a variety of host-guest-type solution complexes. This difference is related to the solvent: the host-guest chemistry of cyclodextrins has been studied in aqueous systems whereas that of calixarenes has been restricted to organic solvent systems.[1,2] In aqueous systems the hydrophobic forces can be expected to encourage host-guest complexation whereas in organic solvents a host must compete with solvent molecules for a guest molecule. The only example of complexation into the calixarene cavity so far obtained in organic solvents is that of t-butylamine acid-base neutralization. This suggests that in order to find evidence for solution complexes, water-soluble calixarenes should be studied.[7,8] Thus, we synthesized water-soluble calixarenes (1_n) by sulphonation of the calixarene *p*-position and found evidence that they complex a variety of guest molecules in aqueous systems.[4-8,†]

As an extension of this study, we synthesized two new water-soluble calixarenes: (2_n) having anionic sulphonate groups on the 'lower rim' of the calixarene cavity in contrast to (1_n) in which they are on the 'upper rim', and (3_n) having cationic ammonium groups instead of anionic sulphonate groups. We here report the syntheses and aggregation properties of these novel water-soluble calixarenes in aqueous solution.

Experimental

Compounds (1_n; $R = Bu$).—These compounds were synthesized from calix[*n*]arene-*p*-sulphonates and butyl bromide in a manner similar to that described previously.[4] We here record the analytical data.

Tetrasodium 25,26,27,28-tetrabutoxycalix[4]arene-5,11,17,-23-tetrasulphonate (1_4; $R = Bu$). Yield 76%, m.p. > 300 °C; $\nu_{max.}$(KBr) 1 050 and 1 180 cm^{-1}(SO); δ_H(D$_2$O, internal standard DSS‡) 1.00 (3 H, t, Me$_3$), 1.4—2.0 [4 H, m, (CH$_2$)$_2$], 3.43 and 4.48 (2 H, 2 × d, ArCH$_2$Ar), 3.97 (2 H, t, OCH$_2$), and 7.31 (2 H, s, ArH) [Found: C, 47.26; H, 5.21. (C$_{11}$H$_{13}$NaO$_4$S)$_4$·3H$_2$O requires C, 47.56; N, 5.26%].

Hexasodium 37,38,39,40,41,42-hexabutoxycalix[6]arene-5,11,17,23,29,35-hexasulphonate (1_6; $R = Bu$). Yield 20%, m.p. > 300 °C; $\nu_{max.}$(KBr) 1 055 and 1 190 (SO); δ_H(D$_2$O, internal standard DSS) 0.66 (3 H, t, Me), 1.1—1.4 [4 H, m, (CH$_2$)$_2$], 3.50 (2 H, t, OCH$_2$), 4.01 (2 H, s, ArCH$_2$Ar), and 7.55 (2 H, s, ArH) [Found: C, 45.15; H, 4.85. (C$_{11}$H$_{13}$NaO$_4$S)$_6$·8.7 H$_2$O requires C, 45.49; H, 5.51%].

(1_n)   (2_n)

(3_n)

(1_4; R = Bu)
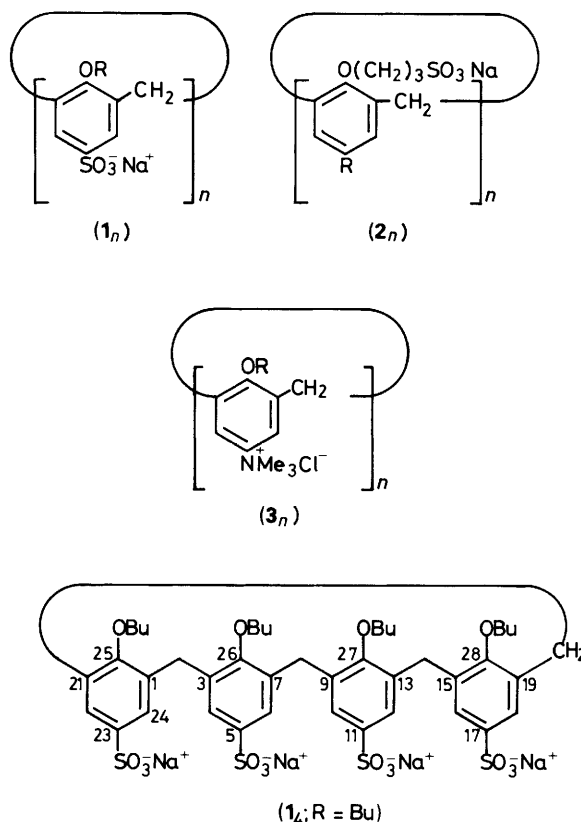
Octasodium-49,50,51,52,53,54,55,56-octabutoxycalix-[8]-arene-5,11,17,23,29,35,41,47-octasulphonate (1_8; $R = Bu$). Yield 20%, m.p. > 300 °C; $\nu_{max.}$(KBr) 1 060 and 1 190 cm^{-1} (SO); δ_H(D$_2$O, internal standard DSS), 0.65 (3 H, t, Me), 1.1—1.4 [4 H, m, (CH$_2$)$_2$], 3.54 (2 H, t, OCH$_2$), 4.07 (2 H, s, ArCH$_2$Ar), and 7.50 (2 H, s, ArH) [Found: C, 46.44; H, 5.26. (C$_{11}$H$_{13}$NaO$_4$S)$_8$-·8H$_2$O requires C, 46.43; H, 5.31%].

---

† Similar efforts have been reported;[9,10] the *p*-t-butylcalix[4]arene-tetracarboxylic acid reported in reference 10 is water-soluble, but the solubility is too low, especially in the presence of salts, for its host-guest chemistry to be studied.

‡ DSS is sodium 3-trimethylsilylpropanesulphonate.

Compounds (**2**$_n$).—*p*-Alkylcalix[*n*]arenes were synthesized from formaldehyde and the corresponding *p*-alkylphenols in a manner similar to that reported by Nakomoto *et al.*[11] Compounds (**2**$_n$) were synthesized by the reaction of these *p*-alkylcalix[*n*]arenes with propane-1,3-sultone.

Hexasodium 5,11,17,23,29,35-*hexabutylcalix*[6]*aryloxy*-37,-38,39,40,41,42-*hexakis*(*propane-3-sulphonate*) (**2**$_6$; *R* = *Bu*). *p*-Butylcalix[6]arene (1.50 g, 1.54 mmol) was dissolved in tetrahydrofuran (THF) (100 ml) at 50 °C under a stream of nitrogen. After cooling, sodium hydride (1.20 g, 30 mmol; 60% dispersion in oil) was added and the mixture was stirred until evolution of hydrogen ceased (*ca.* 1 h). Propane-1,3-sultone (2.26 g, 18.5 mmol) was then added dropwise and the mixture was stirred at room temperature for 24 h. Remaining NaH was decomposed by addition of methanol, after which the solvent was evaporated under reduced pressure, and the residue dissolved in hot water (500 ml). Any insoluble material was removed by centrifugation. Finally, (**2**$_6$; R = Bu) was precipitated by the salting-out method with sodium acetate: yield 75%, m.p. > 300 °C; v_{max}.(Nujol) 1 055 and 1 190 cm^{-1} (SO); δ_H(D$_2$O, internal standard DSS) 0.80 (3 H, t, Me), 1.1—1.5 [4 H, br, (CH$_2$)$_2$ of Bu], 2.10 (4 H, br, ArCH$_2$ and CH_2CH$_2$O), 3.10 (2 H, t, SCH$_2$), 4.03 (3H, br, ArCH^{12}Ar and OCH$_2$), and 6.75 (2 H, s, ArH) [Found: C, 53.5; H, 6.55. (C$_{14}$H$_{19}$NaO$_4$S)·3H$_2$O requires C, 53.32; H, 6.39%].

Hexasodium 5,11,17,23,29,35-*hexahexylcalix*[6]*aryloxy*-37,-38,39,40,41,42-*hexakis*(*propane-3-sulphonate*) (**2**$_6$; *R* = *hexyl*). This compound was synthesized from *p*-hexylcalix[6]arene and propane-1,3-sultone: yield 86%, m.p. (decomp.) 265—268 °C; v_{max}.(KBr) 1 050 and 1 180 cm^{-1} (SO) [Found: C, 56.3; H, 7.15. (C$_{16}$H$_{23}$NaO$_4$S)$_6$·2.5H$_2$O requires C, 56.21; H, 7.03%].

Hexasodium 5,11,17,23,29,35-*hexadodecylcalix*[6]*aryloxy*-37,38,39,40,41,42-*hexakis*(*propane-3-sulphonate*) (**2**$_6$; *R* = *dodecyl*). This compound was synthesized from *p*-dodecylcalix[6]arene and propane-1,3-sultone: yield 60%, m.p. (decomp.) 207—212 °C; v_{max}.(Nujol) 1 050 and 1 180 cm^{-1} (SO) [Found: C, 62.9; H, 8.6. (C$_{22}$H$_{35}$NaO$_4$S)$_6$ requires C, 63.13; H, 8.43%].

Compounds (**2**$_n$; R = H) and (**2**$_n$; R = Bu^t) were synthesized from calix[*n*]arene and *p*-t-butylcalix[*n*]arene, respectively, according to the method described above.

Tetrasodium calix[4]*aryloxy*-25,26,27,28-*tetrakis*(*propane-3-sulphonate*) (**2**$_4$; *R* = *H*). Yield 10%, m.p. > 300 °C; δ_H(D$_2$O, internal standard DSS) 2.34 (2 H, m, CH_2CH$_2$O), 3.08 (2 H, t, SCH$_2$), 3.92 (2 H, 2 × d, ArCH$_2$Ar), 4.17 (2 H, t, OCH$_2$), 6.71 (1 H, t, *p*-ArH), and 6.87 (2 H, d, *m*-ArH) [Found: C, 48.15; H, 4.95. (C$_{10}$H$_{11}$NaO$_4$S)$_4$ requires C, 48.00; H, 4.43%].

Hexasodium calix[6]*aryloxy*-37,38,39,40,41,42-*hexakis*(*propane-3-sulphonate*) (**2**$_6$; *R* = *H*). Yield 30%, m.p. > 300 °C; v_{max}.(KBr) 1 050 and 1 200 cm^{-1} (SO) [Found: C, 45.9; H, 4.7. (C$_{10}$H$_{11}$NaO$_4$S)$_6$·3.8H$_2$O requires C, 45.89; H, 4.73%].

Octasodium calix[8]*aryloxy*-49,50,51,52,53,54,55,56-*octakis*-(*propane-3-sulphonate*) (**2**: *R* = *H*). Yield 23%, m.p. > 300 °C; v_{max}.(Nujol) 1 050 and 1 195 cm^{-1} (SO); δ_H(D$_2$O, 60 °C, internal standard DSS) 2.10 (2 H, br, CH_2CH$_2$O), 2.91 (2 H, br, SCH$_2$), 3.75 (2 H, br, OCH$_2$), 4.01 (2 H, br, ArCH$_2$Ar), and 6.84 (3 H, m, ArH) [Found: C, 47.15; H, 5.05. (C$_{10}$H$_{11}$NaO$_4$S)$_8$·2.5H$_2$O requires C, 46.94; H, 4.57%].

Tetrasodium 5,11,17,23-*tetra-t-butycalix*[4]*aryloxy*-25,26,27,-28-*tetrakis*(*propane-3-sulphonate*) (**2**$_4$; *R* = *Bu*^{t}). Yield 80%, m.p. > 300 °C; v_{max}.(KBr) 1 060 and 1 200 cm^{-1} (SO); δ_H(D$_2$O, internal standard DSS) 1.09 (9 H, s, Bu^t), 2.37 (2 H, m, CH_2CH$_2$O), 3.13 (2 H, t, SCH$_2$), 3.26 and 4.40 (2 H, 2 × d, ArCH$_2$Ar), 4.08 (2 H, t, OCH$_2$), and 6.93 (2 H, s, ArH) [Found: C, 53.25; H, 6.55. (C$_{14}$H$_{19}$NaO$_4$S)$_4$·2H$_2$O requires C, 53.32; H, 6.39%].

Hexasodium 5,11,17,23,29,35-*hexa-t-butylcalix*[6]*aryloxy*-37,38,39,40,41,42-*hexakis*(*propane-3-sulphonate*) (**2**$_6$; *R* = *Bu*^{t}). Yield 75%, m.p. > 300 °C; v_{max}.(KBr) 1 050 and 1 180 cm^{-1}

(SO) [Found: C, 52.2; H, 6.25. (C$_{14}$H$_{19}$NaO$_4$S)$_6$·5H$_2$O requires C, 52.32; H, 6.48%].

Octasodium 5,11,17,23,29,35,41,47-*acta-t-butylcalix*[8]*aryl-oxy*-49,50,51,52,53,54,55,56-*octakis*(*propane-3-sulphonate*) (**2**$_8$; *R* = *Bu*^{t}). Yield 76%, m.p. > 300 °C; v_{max}.(KBr) 1 060 and 1 180 cm^{-1} (SO); δ_H(D$_2$O, internal standard DSS) 0.3—1.7 (9 H, br, Bu^t), 2.3 (2 H, br, CH_2CH$_2$O), 3.2 (2 H, br, SCH$_2$), 3.5—4.6 (4 H, br, OCH$_2$ and ArCH$_2$Ar), and 7.0 (2 H, br, ArH) [Found: C, 53.6; H, 6.65. (C$_{14}$H$_{19}$NaO$_4$S)$_6$·4H$_2$O requires C, 53.32; H, 6.39%].

Compounds (**3**$_n$).—Cationic calixarenes (**3**$_n$) were synthesized from *p*-nitrocalixarenes[12] *via* *p*-aminocalixarenes (see the Scheme).
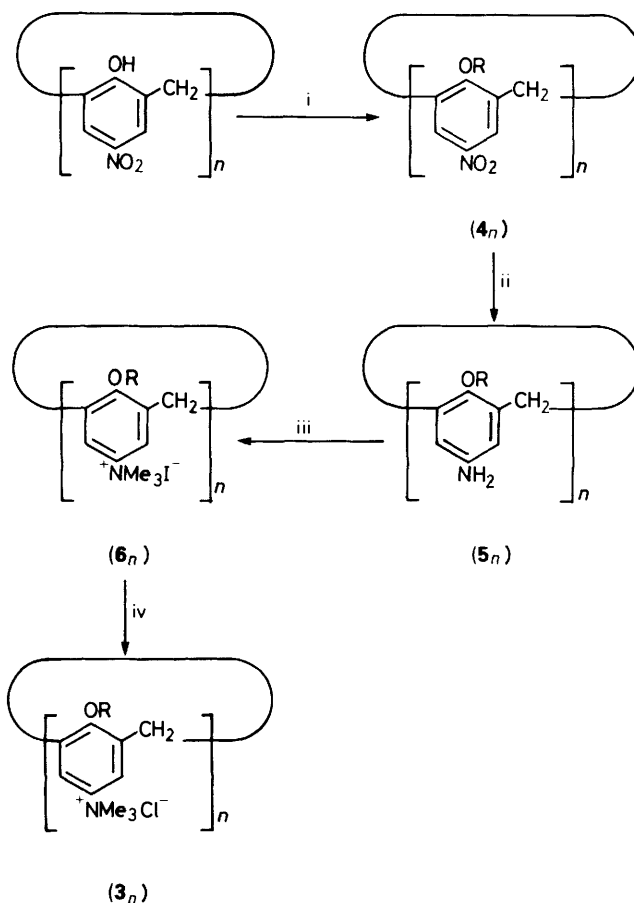
Scheme. *Reagents:* i, RX; ii, N$_2$H$_4$–FeCl$_3$; iii, MeI; iv, ion exchange

37,38,39,40,41,42-*Hexamethoxy*-5,11,17,23,29,35-*hexanitro-calix*[6]*arene* (**4**$_6$; *R* = *Me*). The hexasodium salt of *p*-nitrocalix[6]arene (1.50 g, 1.45 mmol) dispersed in anhydrous sulpholane (30 ml) was treated with methyl iodide (2.0 ml, 40 mmol) at 60 °C. After 6 h, the reaction mixture was cooled and diluted with water. The resulting precipitate was recovered by suction, washed with water and methanol, and dried *in vacuo*: yield 71%, m.p. > 280 °C; v_{max}.(KBr) 1 350 and 1 520 (NO$_2$), and 1 100 cm^{-1} (COC) [Found: C, 57.9; H, 4.15; N, 8.4. (C$_8$H$_7$NO$_3$)$_6$ requires C, 58.18; H, 4.27; N, 8.48%].

25,26,27,28-*Tetramethoxy*-5,11,17,23-*tetranitrocalix*[4]*arene* (**4**$_4$; *R* = *Me*). This compound was synthesized from *p*-nitrocalix[4]arene in a manner similar to (**4**$_6$; R = Me): yield 78%, m.p. > 280 °C; v_{max}.(KBr) 1 350 and 1 520 (NO$_2$), and 1 100 cm^{-1} (COC); δ_H 2.95—4.00 (5 H, m, OMe and ArCH$_2$Ar), and 7.20 (s), 7.85 (d), and 8.35 (d) (2 H, ArH). The complex peak pattern suggests the presence of the conformational isomers which can be discriminated on the n.m.r. time-scale.

5,11,17,23,29,35-*Hexanitro*-37,38,39,40,41,42-*hexakis(octyl-oxy)calix*[6]*arene* (4$_6$; R = *octyl*). This compound was synthesized from *p*-nitrocalix[6]arene and octyl bromide: yield 48%, m.p. 198—199 °C; $\nu_{max.}$(KBr) 1 350 and 1 520 (NO$_2$), and 1 220 cm^{-1} (COC); δ_H(CDCl$_3$) 0.80 (3 H, t, Me), 1.0–2.2 [12 H, m, (CH$_2$)$_6$], 4.00 (4 H, br, OCH$_2$ and ArCH$_2$Ar), and 6.4—8.5 (2 H, br, ArH) [Found: C, 68.45; H, 8.1; N, 5.3. (C$_{15}$H$_{21}$NO$_3$)$_6$ requires C, 68.44; H, 7.98; N, 5.32%].

5,11,17,23,29,35-*Hexa-amino*-37,38,39,40,41,42-*hexamethoxycalix*[6]*arene* (5$_6$; R = *Me*). (4$_6$; R = Me) (1.0 g, 1.0 mmol) was dissolved in 2-methoxyethanol (100 ml) containing FeCl$_3$·6H$_2$O (0.50 g, 1.87 mmol), hydrazine monohydrate (2.0 ml, 50 mmol), and activated charcoal (0.50 g), and the reaction mixture was refluxed for 12 h. The hot solution was filtered, and the filtrate concentrated under reduced pressure. The residual solution (*ca.* 10 ml) was poured into water, and the precipitate was filtered off: yield 75%, m.p. > 280 °C; $\nu_{max.}$(KBr) 3 200—3 500 cm^{-1} (NH$_2$); δ_H(CD$_3$OD) 3.28 (3 H, s, Me), 3.75 (2 H, s, ArCH$_2$Ar), and 6.30 (2 H, s, ArH) [Found: C, 68.75, H, 6.85; N, 9.75. (C$_8$H$_9$NO)$_6$·1.5H$_2$O requires C, 68.80; H, 6.86; N, 10.02%].*

5,11,17,23-*Tetra-amino*-25,26,27,28-*tetramethoxycalix*[4]-*arene* (5$_4$; R = *Me*). This compound was synthesized from (4$_4$; R = Me) in a manner similar to (5$_6$; R = Me): yield 37%, m.p. > 280 °C; $\nu_{max.}$(KBr) 3 200—3 500 cm^{-1} (NH$_2$); δ_H[(CD$_3$)$_2$SO] 3.32 (3 H, s, Me), 3.2—4.0 (2 H, br, NH$_2$), 4.35 (2 H, br s, ArCH$_2$Ar), and 6.10 (2 H, s, ArH) [Found: C, 70.75; H, 6.7; N, 10.7. (C$_8$H$_9$NO)$_4$ requires C, 71.11; H, 6.67; N, 10.37%].

5,11,17,23,29,35-*Hexa-amino*-37,38,39,40,41,42-*hexakis(octyl-oxy)calix*[6]*arene* (5$_6$; R = *octyl*). This compound was synthesized from (4$_6$; R = octyl) in a manner similar to (5$_6$; R = Me): yield 90%, m.p. 208—209 °C; $\nu_{max.}$(KBr) 3 400 cm^{-1} (NH$_2$); δ_H(CDCl$_3$) 0.84 (3 H, t, (Me), 1.2—1.8 [12 H, m, (CH$_2$)$_6$], 2.60 (2 H, br, NH$_2$), 3.72 (4 H, br, OCH$_2$ and ArCH$_2$Ar), and 6.00 (2 H, br, ArH) [Found: C, 74.9; H, 10.0; N, 5.2. (C$_{15}$H$_{23}$NO)$_6$·2.5H$_2$O requires C, 74.84; H, 9.91; N, 5.82%].

37,38,39,40,41,42-*Hexamethoxy*-5,11,17,23,29,35-*hexakis-(trimethylammonio)calix*[6]*arene Hexachloride* (3$_6$; R = *Me*). (5$_6$; R = Me) (0.50 g, 0.6 mmol) and methyl iodide (5.0 ml, 0.090 mol) were dissolved in *N,N*-dimethylformamide (DMF) (20 ml) and the reaction mixture was heated at 60 °C for 5 h in the presence of powdered K$_2$CO$_3$ (1.00 g, 5.0 mmol). The solution was concentrated under reduced pressure and the residual solid was recrystallized from water–DMF. The crystals thus obtained were subjected to the Cl$^-$-type anion-exchange column. The product (an oil) was crystallized from acetone: yield 45%, m.p. > 280 °C; $\nu_{max.}$(KBr) 1 600 and 1 630 (C=C), and 1 220 cm^{-1} (COC); δ_H(D$_2$O, internal standard DSS) 3.38 (3 H, s, OMe), 3.58 (9 H, s, N$^+$Me$_3$), 4.12 (2 H, s, ArCH$_2$Ar), and 7.57 (2 H, s, ArH) [Found: C, 56.6; H, 7.7; N, 5.95. (C$_{11}$H$_{16}$ClNO)$_6$· 6H$_2$O requires C, 57.02; H, 7.78; N, 6.05%].

25,26,27,28-*Tetramethoxy*-5,11,17,27-*tetrakis(trimethylam-monio)calix*[4]*arene tetrachloride* (3$_4$; R = *Me*). This compound was synthesized from (5$_4$; R = Me) in a manner similar to (3$_6$; R = Me): yield 29%, m.p. > 280 °C; $\nu_{max.}$(KBr) 1 600 and 1 630 (C=C), and 1 230 cm^{-1} (COC); δ_H(D$_2$O, internal standard DSS) 3.0—3.8 (12 H, m, OMe and N$^+$Me$_3$), 3.40 and 4.52 (2 H, 2 × d, ArCH$_2$Ar), and 7.80 (2 H, s, ArH) [Found: C, 51.7; H, 7.85; N, 5.55. (C$_{11}$H$_{16}$ClNO)$_4$·9.5H$_2$O requires C, 51.51; H, 8.16; N, 5.46%].

37,38,39,40,41,42-*Hexakis(octyloxy)*-5,11,17,23,29,35-*hexa-kis(trimethylammonio)calix*[6]*arene hexachloride* (3$_6$; R = *octyl*). This compound was synthesized from (5$_6$; R = octyl)

in a manner similar to (3$_6$; R = Me): yield 76%, m.p. > 280 °C; $\nu_{max.}$(KBr) 1 600 (C=C) and 1 210 cm^{-1} (COC); δ_H(CD$_3$OD) 0.85 (3 H, t, Me), 1.3—1.8 [12 H, m, (CH$_2$)$_6$], 3.0—4.2 (13 H, m, OCH$_2$, N$^+$Me$_3$, and ArCH$_2$Ar), and 6.5—8.0 (2 H, m, ArH) [Found: C, 63.45; H, 9.9; N, 4.2; Cl, 9.6. (C$_{18}$H$_{30}$ClNO)$_6$·9.8-H$_2$O requires C, 63.36; H, 9.76; N, 4.11; Cl, 10.40%].

Fluorescence Polarization.—All fluorescence polarization measurements, with pyrene as a probe, were carried out on a Hitachi spectrophotometer equipped with polarizers and a thermostatic cell holder for control of temperature at 30 ± 0.1 °C. With excitation at 310 nm, the emission maximum (374 nm in water) shifted to longer wavelengths with increasing calixarene concentrations. The fluorescence polarization (*P*) was calculated by equation (1), where I is the fluorescence

$$P = (I_{VV} - C_fI_{VH})/(I_{VV} + C_fI_{VH}) \tag{1}$$

intensity and the subscripts V and H refer to the orientation, vertical and horizontal, respectively, for the excitation and analyser polarizers in this sequence; C_f is the grating correction factor given by I_{HV}/I_{HH}.

Results and Discussion

The ^{1}H n.m.r. peak for the ArCH$_2$Ar protons has been used as an indication of the calixarene conformation: a pair of doublets is assigned to a conformationally-fixed 'cone' whereas a singlet resonance is assigned to a conformationally-labile 'alternate'.[1,2,13] All water-soluble calix[6]arene and calix[8]-arene derivatives studied herein afforded a singlet resonance, although some of them were significantly broadened. This implies that each benzene unit in these calixarenes can rotate through the annulus. In contrast, the ^{1}H n.m.r. data for calix[4]arene derivatives are quite different: (1$_4$; R = Bu), (2$_4$; R = H), and (2$_4$; R = Bu^t) afforded a pair of doublets for the ArCH$_2$Ar protons at *ca.* 3.4 and 4.4 p.p.m. As the spectrum pattern was scarcely affected by temperature change (0—70 °C in D$_2$O), one can conclude that the conformation is fixed as a 'cone'.[1,2,14] This indicates that the ring of calix[4]arenes is too small for the *O*-substituted benzene unit to rotate.

It is known that the temperature-dependent ^{1}H n.m.r. for the ArCH$_2$Ar protons in *p*-t-butylcalix[4]arene displays a pair of doublets at low temperature and a singlet resonance at high temperature.[1,2,13] This behaviour may be interpreted in terms of a conformational change from 'cone' to 'alternate': that is, the 'cone' structure is fairly stable at low temperature but the rotation of the hydroxybenzene unit becomes possible at high temperature. *O*-Methylation of *p*-t-butylcalix[4]arene results in conformational isomers, indicating that the isomers can be fixed by the steric hindrance of the *O*-methyl groups;[15] In this case, the ArCH$_2$Ar protons give a complicated split pattern. As expected, the ^{1}H n.m.r. peak for the ArCH$_2$Ar protons in (4$_4$; R = Me) was very complex, indicating that (4$_4$; R = Me) also consists of a mixture of conformational isomers.
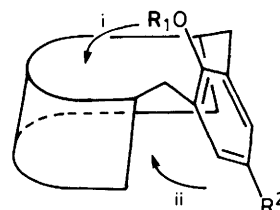
Figure 1. Schematic representation of two possible rotation mechanisms: i, 'oxygen through the annulus' rotation; ii, '*para*-substituent through the annulus' rotation

---

* We reduced *p*-nitrocalix[6]arene to *p*-aminocalix[6]arene by the same method; however, the product was so sensitive to air oxidation that good analytical data could not be obtained.
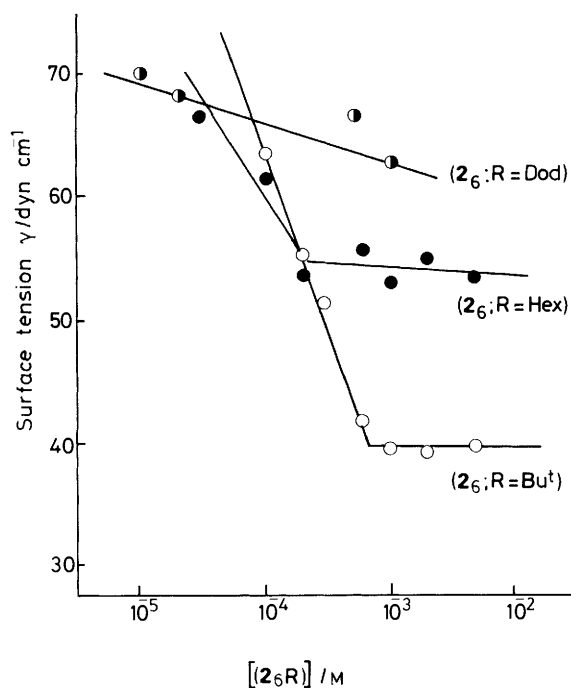
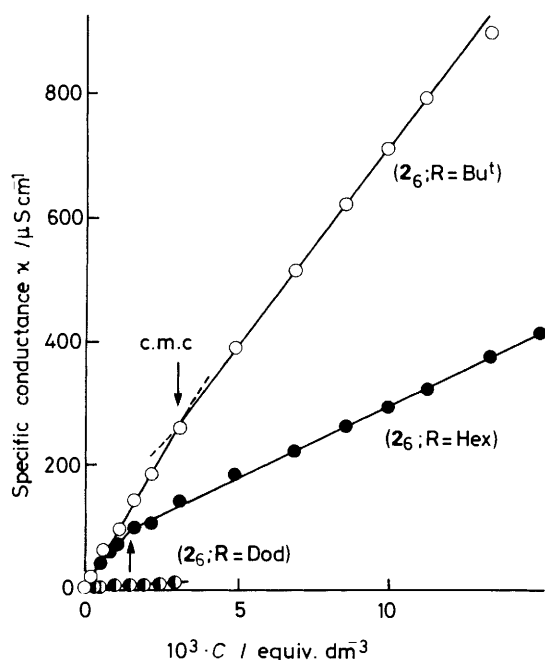**Figure 2.** Surface tension plotted against calixarene concentration at 30 °C

Figure 3. Specific conductance plotted against calixarene concentration (C, equiv. dm^{-3}; $C = 6[2_6R]$) at 30 °C

Surprisingly, we found that for the ArCH$_2$Ar protons of (5$_4$; R = Me), having amino groups at the p-position, gave a singlet resonance (although broad) whereas (3$_4$; R = Me), having trimethylammonio groups at the p-position, gave a pair of doublets. It is very difficult to rationalize why (5$_4$; R = Me) can

---

* Matsuoka et al.[18] found that (1$_6$; R = dodecyl), when dissolved in water by sonication (up to 0.5M), forms an ellipsoid aggregate with dodecyl groups in the core and sulphonate groups at the surface.

† We also synthesized (3$_6$; R = dodecyl) but the aqueous solution gelled.

adopt an 'alternate' conformation. It is known that rotation of the benzene unit occurs by two different mechanisms: 'oxygen through the annulus rotation' and '$para$-substituent through the annulus rotation' (Figure 1).[13,16,17] The conformational isomers produced by O-alkylation are due to the steric inhibition of the 'oxygen through the annulus rotation' mechanism. Thus, the alternate conformation observed for (5$_4$; R = Me) may be accommodated by the '$para$-substituent through the annulus' mechanism. The amino group is sterically smaller than the nitro group but much greater than hydrogen. Therefore, the above explanation is incompatible with the fact that the conformation of (2$_4$; R = H) is fixed as a 'cone' and is not subject to the '$para$-substituent through the annulus rotation' mechanism. At present we cannot explicitly account for the ^{1}H n.m.r. spectrum of (5$_4$; R = Me). On the other hand, the 'cone' conformation of (3$_4$; R = Me) is explained by selective alkylation of the 'cone' conformation of (5$_4$; R = Me) —this conformation is then fixed by steric hindrance.

We previously determined the c.m.c.s. of (1$_6$; R = Me, hexyl, and dodecyl),[4] and established that (1$_6$; R = Me) does not form a micelle (at concentrations < 0.2M), (1$_6$; R = hexyl) has a c.m.c. at 6 × 10^{-4}M, and (1$_6$; R = dodecyl) has no detectable c.m.c. and behaves as a unimolecular micelle (at concentrations < 1 × 10^{-3}M).* In order to obtain an insight into their aggregation properties, we determined the c.m.c.s of (2$_n$) and (3$_n$) in addition to those of (1$_n$), mainly using surface tension and electric conductance measurements. Typical examples are illustrated in Figures 2 and 3 and the results are summarized in Tables 1—3.

Examination of Tables 1—3 reveals that the aggregation properties of anionic and cationic calixarenes can be classified into three categories: (*i*) calixarenes which do not bear long aliphatic chains have no detectable c.m.c. [*e.g.* (1$_6$; R = Me), (2$_n$; R = H), and (3$_n$; R = Me)], (*ii*) calixarenes which possess moderate aliphatic chains have c.m.c.s. at *ca.* 10^{-4}M [*e.g.* (1$_n$; R = Bu), (1$_6$; R = hexyl), (2$_n$; R = t-Bu), (2$_6$; R = hexyl), and (3$_6$; R = octyl)], and (*iii*) calixarenes which possess long aliphatic chains behave as a unimolecular micelle (*e.g.* (1$_6$; R = dodecyl) and (2$_6$; R = docecyl)].† In category (*i*), each calixarene has 4 to 8 ionic groups, so that the electrostatic repulsion overcomes the hydrophobic interaction. In category (*iii*), the surface tension for (2$_6$; R = dodecyl) was only slightly lower than that for pure water (71 dyn cm^{-1}): similar behaviour was observed for (1$_6$; R = dodecyl).[4] This indicates that these calixarenes are not surface-active and are stable in water as a monomer or as an oligomer. Conceivably, a single molecule of these calixarenes, having six dodecyl chains can form a stable, micelle-like closed shell by itself. On the other hand, calixarenes in category (*ii*) have alkyl groups which are insufficiently long enough to form a close shell, and thus interact intermolecularly to form micellar aggregates. Figure 4 shows plots of the ^{1}H n.m.r. chemical shifts *vs.* (1$_4$; R = Bu) concentration. Above the c.m.c (2.5 × 10^{-3}M) some protons are shifted to higher magnetic field with increasing calixarene concentration. H$_{exo}$ and OCH$_2$ Protons are particularly subject to large upfield shifts. This suggests that the butyl groups form the micellar core and the calixarene rings form stacks at the micellar surface. This image is compatible with that depicted by Matsuoka et al.[18] on the basis of the small-angle X-ray scattering study.

Vibronic band intensities in pyrene monomer fluorescence are frequently used as a probe to determine c.m.c. values because the ratio (band III: band I) changes drastically at the c.m.c. from 0.63—0.66 (in water) to 0.90 [above c.m.c. in aqueous SDS (sodium dodecyl sulphate)].[19] The c.m.c. of SDS determined by this method (7.6 × 10^{-3}M) was equal to that determined by other methods (5.6—6.6 × 10^{-3}M) within allowable experimental error. As shown in Figure 5, a plot of III/I ratio *vs.* [(1$_6$; R = hexyl)] showed a sigmoid curvature,

Table 1. Critical micelle concentrations (c.m.c., M) for (1_n) at 30 °C

Calixarene	Method		
	Surface tension	Conductance	Spectroscopy [c]
$(1_6; R = Me)$	>0.2	>0.2	
$(1_4; R = Bu)$		2.5×10^{-3}	
$(1_6; R = Bu)$		1.0×10^{-3}	
$(1_8; R = Bu)$	5.0×10^{-4}	7.0×10^{-4}	
$(1_6; R = hexyl)$	5.0×10^{-4a}	6.7×10^{-4a}	ca. 5×10^{-4a}
$(1_6; R = dodecyl)$	n.d.[b]	n.d.[b]	
SDS	5.6×10^{-3a}	6.6×10^{-3a}	7.6×10^{-3a}

[a] Cited from reference 4. [b] The c.m.c. was not detected because of the unimolecular micelle formation. [c] Determined by the fluorescence intensity of pyrene.

Table 2. Critical micelle concentrations (c.m.c., M) for (2_n) at 30 °C

Calixarene	Method	
	Surface tension	Conductance
$(2_4; R = H)$	>0.1	>0.1
$(2_6; R = H)$	>0.1	>0.1
$(2_8; R = H)$	>0.1	>0.1
$(2_6; R = Bu)$		4.3×10^{-4}
$(2_4; R = Bu^t)$	5.6×10^{-4}	5.5×10^{-4}
$(2_6; R = Bu^t)$	6.1×10^{-4}	5.8×10^{-4}
$(2_8; R = Bu^t)$	1.5×10^{-4}	4.0×10^{-4}
$(2_6; R = hexyl)$	2.1×10^{-4}	2.5×10^{-4}
$(2_6; R = dodecyl)$	n.d.[a]	n.d.[a]

[a] The c.m.c. was not detected because of the unimolecular micelle formation.

Table 3. Critical micelle concentrations (c.m.c., M) for (3_n) (30 °C)

Calixarene	Method		
	Surface tension	Conductance	Spectroscopy [a]
$(3_4; R = Me)$	>0.2	>0.2	>0.2
$(3_6; R = Me)$	>0.2	>0.2	>0.2
$(3_6; R = octyl)$	1.0×10^{-4}	1.6×10^{-4}	n.d.[b]
HTAB	1.2×10^{-3}	1.2×10^{-3}	1.2×10^{-3}

[a] Determined by the absorbance of DCPI. [b] A plot of OD_{640} vs. $[(3_6; R = octyl)]$ provided a simple saturation curve.

although the jump at the c.m.c. $(6 \times 10^{-4}M)$ was not as clear as with SDS. The sigmoid dependence implies that the aggregated $(1_6; R = hexyl)$ is more hydrophobic than monomeric $(1_6; R = hexyl)$. On the other hand, the jump at the c.m.c. was not detected for $(2_6; R = hexyl)$. This result could be explained in two different ways: (i) the hydrophobicity of the binding-site (conceivably, the calixarene cavity) in $(2_6; R = hexyl)$ is not changed below and above the c.m.c. or (ii) added pyrene induces the aggregation of $(2_6; R = hexyl)$ and reduces the c.m.c. We carefully examined the III:I band ratio for $[(2; R = hexyl)] = 10^{-6}$—$10^{-4}M$ in the presence of pyrene $(1.92 \times 10^{-6}M)$ and found that a sigmoidal change exists at $[(2_6; R = hexyl] = 3 \times 10^{-5}M$: this value is ca. one order of magnitude lower than the c.m.c. in the absence of pyrene. Presumably, the structure of $(2_6; R = hexyl)$, appended by hexyl groups at the p-position, is especially favourable to the binding of pyrene leading to intermolecular aggregation.

Is there any difference in the binding-site between the conventional micelle and the calixarene-based micelle? The fluorescence polarisation (P) reflects the viscosity of micro-environments around the bound fluorescence probe: the higher
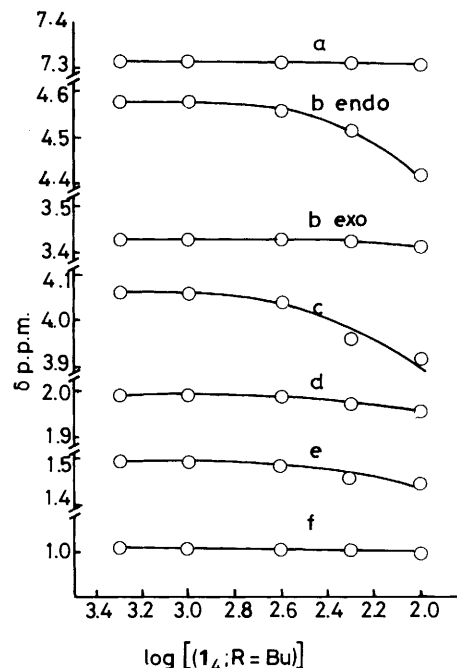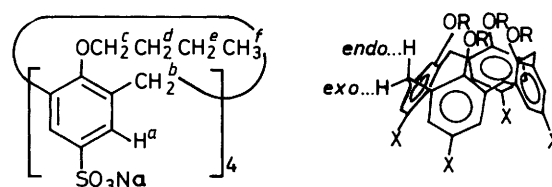
Figure 4. [1]H N.m.r. chemical shift (p.p.m.) vs. $(1_4; R = Bu)$ concentration at 20.9 °C in D_2O
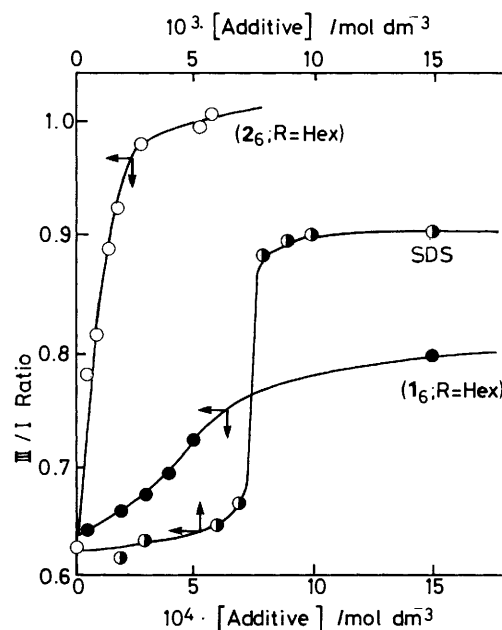
Figure 5. Plots of III/I band vs. additive concentration in pyrene fluorescence at 30 °C: [pyrene] = 1.92×10^{-6} M, excitation 310 nm

the P value, the more viscous the site.[20] As shown in Table 4, P in an aqueous SDS micelle (0.020) is somewhat greater than that in water, indicating that the micelle interior is more viscous than bulk water. P Values presented by monomeric calixarenes are

**Table 4.** Fluorescence polarization (P) of pyrene as a probe in an aqueous system at 30 °C[a]

Calixarene	P (calixarene conc., mM)	
	below c.m.c.	above c.m.c.
None	0.008	
(1_6; R = hexyl)	0.023 (0.247)	0.046 (1.49)
(2_6; R = hexyl)	0.051 (0.100) [b]	0.106 (0.495)
(2_4; R = Bu^t)	0.011 (0.200)	0.020 (0.990)
(2_6; R = Bu^t)	0.013 (0.200)	0.033 (0.990)
(2_8; R = Bu^t)	0.020 (0.075)	0.072 (0.990)
SDS		0.020 (19.8)
HTAC[c]		0.016 (10.0)

[a] [Pyrene] = 1.92×10^{-6}M, excitation 310 nm. [b] This concentration is below the c.m.c. in the absence of pyrene but may be higher than the c.m.c. in the presence of pyrene (see text). [c] Hexadecyltrimethylammonium chloride.

smaller than that for the SDS micelle, whereas they are significantly enhanced above the c.m.c.s of calixarenes. The largest P value was observed for (2_6; R = hexyl), the micelle formation of which was induced by pyrene addition. The results clearly support the view that the calixarene-based micelle is generally more viscous than the conventional surfactant micelle.

Table 3 shows that (3_4; R = Me) and (3_6; R = Me) have no detectable c.m.c., indicating that they belong to category (i), whereas (3_6; R = octyl) has a c.m.c. comparable with those of (1_6; R = hexyl) and (2_6; R = hexyl).

2,6-Dichlorophenolindophenol (DCPI) is an excellent probe to detect hydrophobic domains with a cationic surface in aqueous solutions: for example, the c.m.c. of cationic micelles in dilute HCl solution can be determined on the basis of the colour change from light red (undissociated phenol: 517 nm) to blue (phenolate anion: around 640 nm.)[21] This dissociation is induced by complexation between DCPI and cationic surfactants.

517nm   640nm
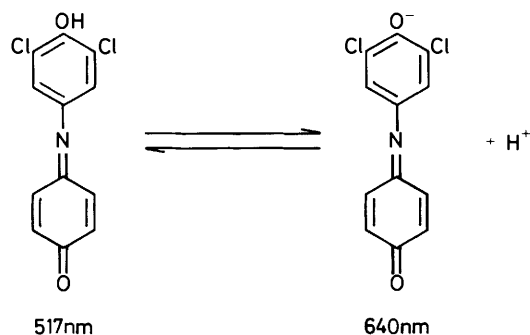
As shown in Figure 6, a plot of OD_{640} vs. [HTAB] (hexadecyltrimethylammonium bromide)] provides a sharp jump at 1.2×10^{-3}M which is in good accord with the c.m.c. determined by other physical methods. In contrast, (3_4; R = Me) and (3_6; R = Me) could not induce dissociation of DCPI. This implies that these cationic calixarenes are not hydrophobic enough to complex 'neutral' DCPI. On the addition of (3_6; R = octyl) (below the c.m.c.), however, the distinct blue colour appeared ($\lambda_{max.}$ 643 nm; $\lambda_{max.}$ 635 nm in HTAB). A plot of OD_{640} vs. [(3_6; R = octyl)] showed a simple saturation curve, indicating that even monomeric (3_6; R = octyl) displays strong binding ability towards DCPI. The continuous variation plot at [DCPI] + [(3_6; R = octyl)] = 1.08×10^{-4}M (where [(3_6; R = octyl)] was maintained below the c.m.c.) in 0.15mM HCl
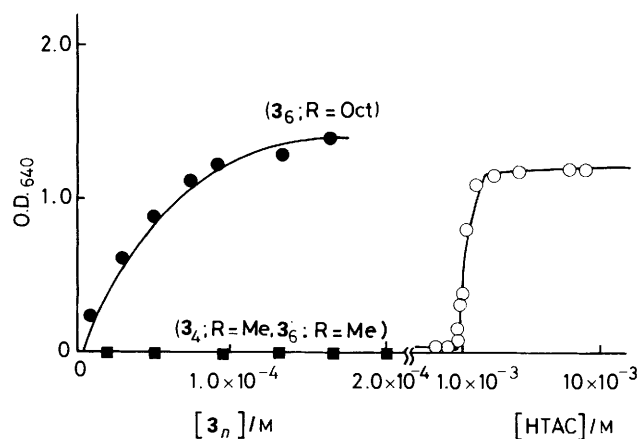
Figure 6. Plots of OD_{640} vs. additive concentration in DCPI absorbance at 30 °C: [DCPI] = 1.00×10^{-4}M, [HCl] = 3.00×10^{-4}M

solution established the formation of a 1:1 complex between DCPI and (3_6; R = octyl). The association constant was thus determined to be 2.00×10^4M^{-1}. These results indicate that (3_6; R = octyl) provides a strong cationic binding-site as well as a hydrophobic binding-site and acts as an excellent host for anionic guest molecules.

In conclusion, the present paper demonstrates that water-soluble calixarenes can be synthesized by introducing anionic or cationic groups into the upper or lower rim of calixarenes. Their aggregation properties in water are classified into three categories: (i) non-micellar calixarenes, (ii) micelle-forming calixarenes, and (iii) unimolecular micellar calixarenes. The aggregation properties are profoundly related to the calixarene architecture, especially the length of introduced alkyl groups. Their application as new host molecules is currently being studied in these laboratories.

Acknowledgements

References

1 C. D. Gutsche, Acc. Chem. Res., 1983, 16, 161.
2 C. D. Gutsche, 'Host Guest Complex Chemistry/Macrocycles,' Springer-Verlag, Berlin, 1985, p. 375.
3 C. D. Gutsche, M. Iqbal, and I. Alam, J. Am. Chem. Soc., 1987, 109, 4314.
4 S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki, and O. Manabe, J. Am. Chem. Soc., 1986, 108, 2409.
5 S. Shinkai, K. Araki, and O. Manabe, J. Am. Chem. Soc., 1988, 110, 7214.
6 S. Shinkai, T. Arimura, H. Satoh, and O. Manabe, J. Chem. Soc., Chem. Commun., 1987, 1495.
7 S. Shinkai, Pure Appl. Chem., 1986, 58, 1523.
8 S. Shinkai and O. Manabe, Nippon Kagaku Kaishi, 1988, 1917.
9 C. D. Gutsche and I. Alam, Tetrahedron, 1988, 44, 4689.
10 A. Arduini, A. Pochini, S. Reverberi, and R. Ungaro, J. Chem. Soc. Chem. Commun., 1984, 981.
11 Y. Nakamoto, T. Kozu, S. Oya, and S. Ishida, Netsu Kokasei Jushi, 1985, 6, 73.
12 S. Shinkai, K. Araki, T. Tsubaki, T. Arimura, and O. Manabe, J. Chem. Soc., Perkin Trans. 1, 1987, 2297.
13 C. D. Gutsche and L. J. Bauer, J. Am. Chem. Soc., 1985, 107, 6052.
14 A. Arduini, A. Pochini, S. Reverberi, and R. Ungaro, Tetrahedron Lett., 1986, 42, 2089.
15 R. N. Reinhoudt, P. J. Dijkstra, P. J. A. in't Veld, K. Bugge, S. Harkema, R. Ungaro, and E. Ghidini, J. Am. Chem. Soc., 1987, 109, 4761.

16 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.* 1985, **107**, 6059.

17 T. Arimura, S. Shinkai, T. Matsuda, T. Hirata, H. Satoh, and O. Manabe, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3733.

18 H. Matsuoka, M. Tsurumi, and N. Ise, *Phys. Rev.*, 1988, **B38**, 6279.

19 K. Kalyanasundaram and J. K. Thomas, *J. Am. Chem. Soc.*, 1977, **99**, 2039.

20 T. Azumi and S. P. McGlynn, *J. Chem. Phys.*, 1962, **37**, 2413.

21 M. L. Corrin and W. D. Harkins, *J. Am. Chem. Soc.*, 1947, **69**, 679.