Unusual Directed Synthesis of a Carceplex or a Supramolecule Composed of Calix[4]arene and Resorcin[4]arene Moieties Using Solvent Templation

Hyejae Ihm and Kyungsoo Paek*

Department of Chemistry, Soongsil University, Seoul 156-743, Korea
Center for Biofunctional Molecules, P.O. Box 125, Pohang 790-600, Korea

Received April 10, 1999

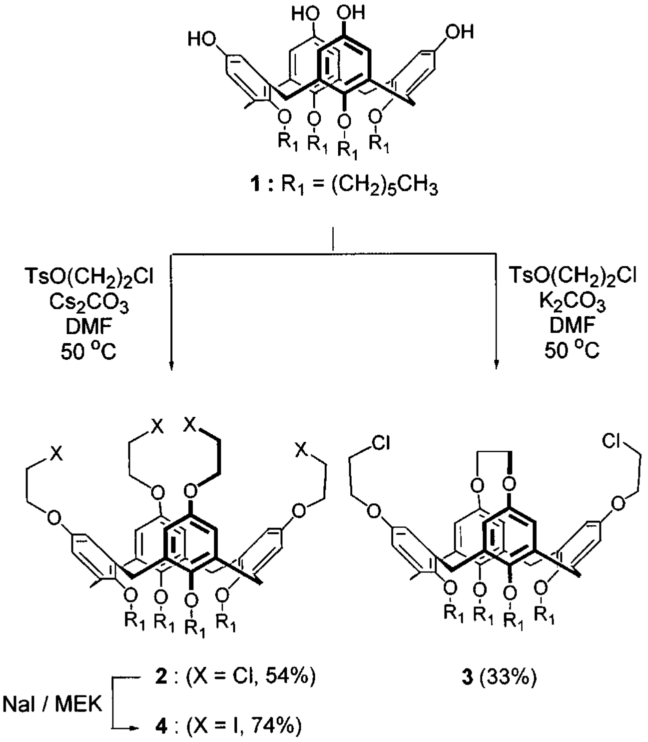
The syntheses of artificial receptor molecules by the modification of simple rigid building blocks such as calixarenes,[1] resorcinarenes,[2] and cyclodextrins[3] have resulted in various host molecules with small cavities suitable for the complexation of alkali metal cations, anions, or small organic molecules. The supramolecular chemistry has been expanded from the combination of calix[4]arenes with other building blocks such as cyclodextrins[4] or porphyrins.[5]

Recently, Reinhoudt *et al.* have reported the supramolecules by the combination of calix[4]arene and resorcin[4]arene moieties.[6,7] The [2 + 2] holand[6] from two calix[4]arene and two resorcin[4]arene moieties has a rigid cavity of nanosize dimensions and the [1 + 1] C_{4v} carcerand[7] having an incarcerated DMF molecules showed the unprecedented carcerostereoisomerism owing to the different orientations of incarcerated guest molecule at low temperature. The [1 + 2] supramolecules from a resorcin[4]arene and two calix[4]arene moieties as well as their complexation of steroids were also reported.[8] Here we report the directed synthesis and structural analysis of a C_{4v} carceplex and a supramolecule composed of a calix[4]arene and two resorcin[4]arene moieties using solvent templation method.

Tetrol **1**[9] obtained from *p*-bromocalix[4]arene hexyl ether was treated with $TsO(CH_2)_2Cl$-Cs_2CO_3-DMF at 50 °C to give tetrachloride **2** in 54% yield (Scheme 1). When potassium carbonate was used as a base at the same condition, the distal ethylene-bridged product **3** and tetrachloride **2** were obtained in 33% and 15% yield, respectively. It seems that the Cs^+ templates in the cavity of the calix[4]arene and prohibits the 1,3-aromatic rings from approaching each other enough to be bridged by ethylene unit. The tetrachloride **2** was refluxed with NaI in methyl ethyl ketone to give tetraiodide **4** in 74% yield. When tetrol **1** was treated with an excess of $TsO(CH_2)_2OTs$-Cs_2CO_3-DMF at 40 °C to obtain a tetratosylate, only a distal bridged analogue of **3** was obtained due to the high reactivity of a tosylate group.

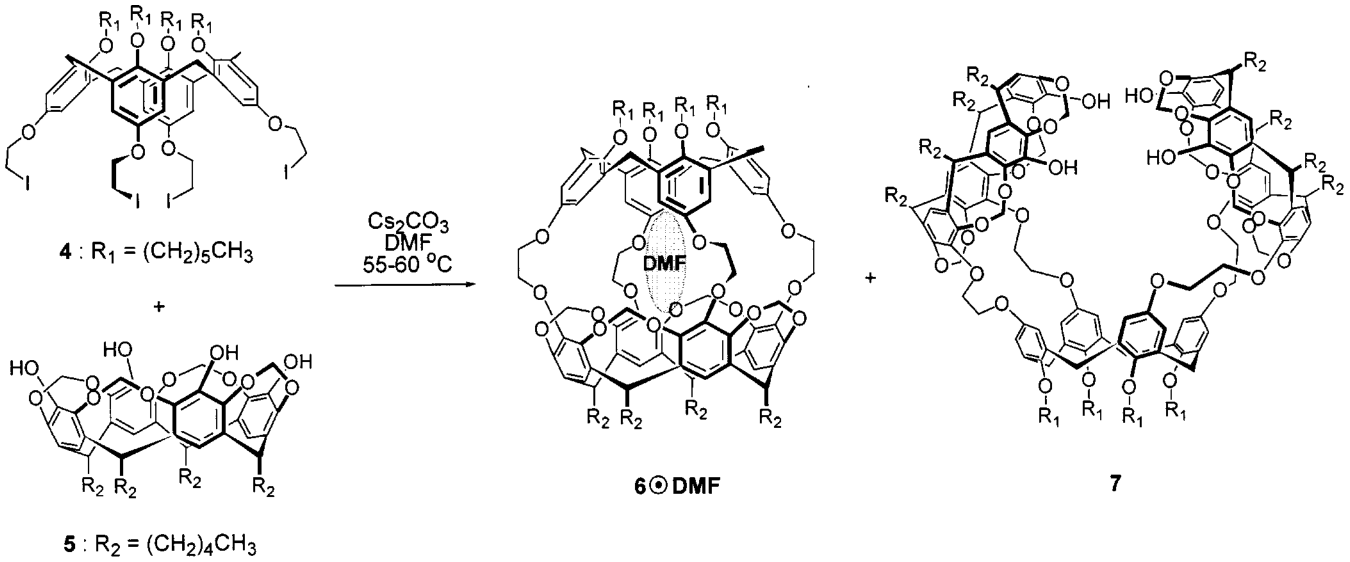
Under high-dilution condition, the shell closing reaction between tetraiodide **4** and tetrol **5**[10] in Cs_2CO_3 / DMF at 55-60 °C produced a carceplex **6□DMF** in 10% yield (Scheme 2). When DMA, NMP, MeCN, or 1,4-dioxane were used as a guest solvent, none of a carceplex or a hemicarceplex was observed.

Pyrazine has been known as the best template in the formation of carceplex based on the resorcin[4]arene.[11] In case of the above reaction in pyrazine (1 mol%)-NMP, any desired carceplex was not isolated, which means both of these potential templates are not good enough for the formation of carcerand **6**.[7] However, the reaction in pyrazine (1 mol%)-DMF produced **6 □ DMF** and a supramolecule **7** in 5% and 2% yield, respectively. As the reaction condition is changed to 1 equiv. of tetraiodide **4** and 2 equiv. of tetrol **5**, the yield of **7** was increased up to 15%. When pyrazine (1 mol%)-DMA was used as a mixed solvent, only the 1 : 2 host **7** was obtained in very low yield. It is probable that pyrazine-calix[4]arene affinity is larger than that of pyrazine-resorcin[4]arene due to the facile squeezability of calix[4]arene to give maximum π-π interactions. This results in the deformation of calix[4]arene to the pinched-cone conformer, which prohibits the [1 + 1] shell-closing reaction.



Scheme 1

The structure of **6 □ DMF** was confirmed by spectroscopic and elemental analyses. The FAB(+) mass spectrum of **6□DMF** showed a strong molecular ion peak (*m/z* 1884, 67%) and its IR spectrum showed $\nu_{C=O}$ band of DMF at 1674 cm^{-1}. Its ^1H NMR spectrum shows two singlets for the aromatic protons of the resorcin[4]arene and calix[4]arene at δ 6.72 and 6.43, two doublets (J_{AB} = 7.1 Hz) for the bridging dioxymethylene protons of the resorcin[4]arene moiety at δ



Scheme 2

5.74 (outer OCH_2O) and 4.19 (inner OCH_2O), and two doublets (J_{AB} = 12.0 Hz) for the bridging methylene protons of calix[4]arene moiety at δ 4.34 (H_{endo}) and 3.04 (H_{exo}). Characteristic upfield-shifted guest signals are found (δ 5.35 for formyl H, 0.27 for *cis*-CH_3 and -0.45 for *trans*-CH_3) due to the shielding of the aromatic moieties of the hosts. The incarcerated DMF was not decomplexed at 150 °C for 5 d and the so-called carceroisomerism was not observed up to -70 °C, which is similar to D_{4h} carceplex composed of two resorcin[4]arene moiety connected by dioxyethylene unit.[12]

The FAB(+) mass spectrum of **7** gave its molecular ion peak at m/z 2691 as a base peak, which suggests that it is a trimer consisted of two resorcin[4]arene units and one calix[4]arene unit. For this trimer, three kinds of [1 + 2] isomers, *endo-endo*, *endo-exo* and *exo-exo* isomers, are possible.[6] The *endo-endo* and *exo-exo* isomers have a C_{2v} point group, and the *endo-exo* isomer has a C_s point group.

The ^1H NMR spectrum (500 MHz, $CDCl_3$) of **7** showed two singlets for the aromatic protons of the resorcin[4]arene unit at δ 6.84 and δ 6.61 and two singlets for the aromatic protons of the calix[4]arene unit at δ 6.51 and δ 6.24. Also the dioxymethylene protons of resorcin[4]arene unit appeared as three kinds of doublet of doublets at δ 6.03 (J_{AB} = 7.0 Hz), 5.97 (J_{AB} = 7.2 Hz) and 5.93 (J_{AB} = 6.9 Hz) for outer OCH_2O and at δ 4.53 (J_{AB} = 6.9 Hz), 4.45 (J_{AB} = 7.0 Hz) and 4.34 (J_{AB} = 7.2 Hz) for inner OCH_2O. Also two kinds of doublet of doublets for methylene of calix[4]arene unit were appeared at δ 4.48 (J_{AB} = 13.4 Hz) and 4.39 (J_{AB} = 13.0 Hz) for H_{endo} and at δ 3.16 (J_{AB} = 13.4 Hz) and 3.01 (J_{AB} = 13.0 Hz) for H_{exo}. These ^1H NMR spectral data of **7** shows its C_{2v} point group, which excludes the *exo-endo* isomer.

2D NOESY spectrum of **7** shows a connectivity between the protons (H_a) of the aromatic rings of the calix[4]arene moiety and the bridging outer methylene protons (H_g) of the resorcin[4]arene moiety (Figure 1). The H_a protons also show the cross peaks with H_i and H_j protons. CPK molecular model shows that, if this isomer was an *exo-exo* isomer, the 2D NOESY spectrum should show a connectivity between the H_a protons and the bridging inner methylene protons (H_h). This supports that the *endo-endo* isomer is obtained

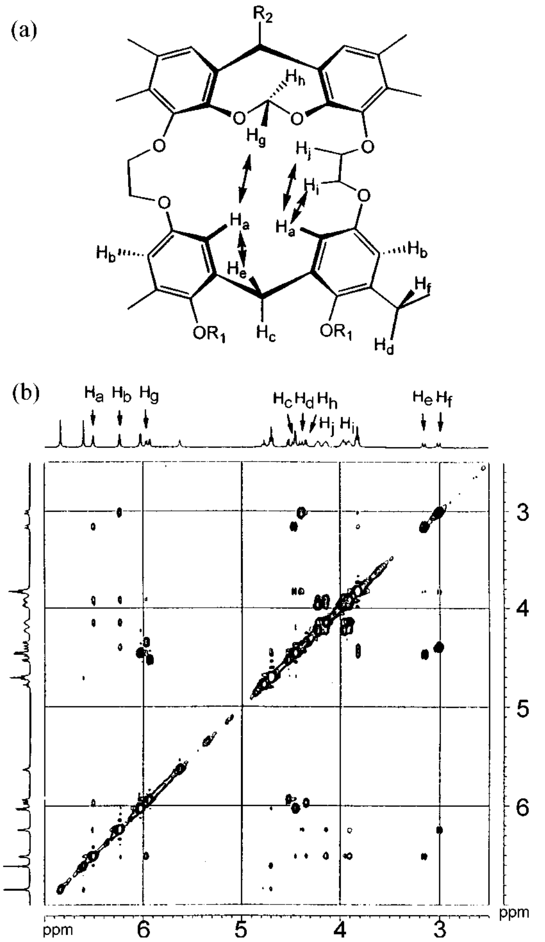


Figure 1. Parts of (a) the NOE Connectivity and (b) 2D NOESY Spectrum (500 MHz) of 7 in $CDCl_3$ at 27 °C.

among the three possible 2 : 1 isomers.[6]

In conclusion, a new calix[4]arene-based C_{4v} carceplex **6□DMF** and an unexpected *endo-endo* supramolecule made of one calix[4]arene unit and two resorcin[4]arene units were obtained using template effect and their structures were determined. Currently the molecular recognition studies as well as the functionalization of hydroxy groups of this supramolecule is in progress.

Experimental Section

General details. All chemicals were reagent grades and used directly unless otherwise specified. All anhydrous reactions were conducted under an argon atmosphere. Melting points were measured on an Electrothermal 9100 apparatus and were uncorrected. IR spectra were taken with a Mattson 3000 FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Bruker Avance DPX300 (300 MHz), JEOL lambda-400 (400 MHz) or Bruker Avance DPX500 (500 MHz) in $CDCl_3$ unless stated otherwise. Residual solvent protons were used as internal standard and chemical shifts are given relative to tetramethylsilane (TMS). FAB mass spectra were run on a HR MS (VG70-VSEQ) at Korea Basic Science Institute using *m*-nitrobenzyl alcohol as a matrix. Gravity column chromatography was performed on silica gel 60 (E. Merck, 70-230 mesh ASTM). Flash chromatography was performed on silica gel 60 (E. Merck, 230-400 mesh ASTM). Thin layer chromatography was done on silica plastic sheets (E. Merck, silica gel 60 F_{254}, 0.2 mm). Elemental analyses were performed by Galbraith Laboratories (Knoxville, Tennessee).

5,11,17,23-Tetrakis(2-chloroethyloxy)-25,26,27,28-tetra(hexyloxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3(28),4,6,9(27),10,12,15(26),16,18,21(25),22-dodecaene (2). To a solution of tetrol **1**[9] (1.0 g, 1.2 mmol) and cesium carbonate (3.9 g, 12 mmol) in DMF (60 mL) was added 2-chloroethane tosylate (4.3 g, 18 mmol) and the reaction mixture was stirred for 3 d at 50 °C. After cooling to room temperature the mixture was partitioned between CH_2Cl_2 (300 mL) and 2 N HCl (2×150 mL). The organic phase was separated, washed with water and brine, and subsequently dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed on a silica gel gravity column using 5% EtOAc/hexane to give the product **2** (0.69 g, 54%); mp 87.5-88.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.26 (s, ArH, 8H), 4.40 (d, *endo*-ArCH, J = 13.1 Hz, 4H), 3.99 (t, OCH_2CH_2Cl, 8H), 3.81 (t, OCH_2, 8H), 3.64 (t, CH_2Cl, 8H), 3.04 (d, *exo*-ArCH, J = 13.1 Hz, 4H), 1.89 (m, CH_2, 8H), 1.38 (br s, CH_2, 24H), 0.93 (t, CH_3, 12H); Anal. Calcd for $C_{60}H_{76}O_8Cl_4C_6H_{14}H_2O$: C, 67.68; H, 7.92. Found: C, 67.41; H, 8.05.

5,11,17,23-Tetrakis(2-iodoethyloxy)-25,26,27,28-tetra(hexyloxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3(28),4,6,9(27),10,12,15(26),16,18,21(25),22-dodecaene (4). A solution of sodium iodide (155 mg, 1.0 mmol) in MEK (30 mL) was refluxed for 1 h. To a refluxing solution was added tetrachloride **2** (110 mg, 0.10 mmol) and refluxed for 3 d. After evaporation of the solvent the crude mixture was taken up in CH_2Cl_2 (100 mL), washed with water (2×100 mL) and brine (25 mL) and subsequently dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed on a silica gel gravity column using hexane-CH_2Cl_2 (2 : 1, v/v) and then recrystallized from CH_2Cl_2-MeOH to afford the product **4** (110 mg, 74%) as a white powder; mp 71.6-73.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.22 (s, ArH, 8H), 4.37 (d, *endo*-ArCH, J = 13.2 Hz, 4H), 4.02 (t, OCH_2CH_2I, 8H), 3.78 (t, OCH_2, 8H), 3.22 (t, CH_2I, 8H), 3.02 (d, *exo*-ArCH, J = 13.2 Hz, 4H), 1.86 (m, CH_2, 8H), 1.34 (br s, CH_2, 24H), 0.89 (t, CH_3, 12H); FAB(+) MS 1440 (M^+, 100).

Calix[4]arene-based Carcerand 6□DMF. Under argon atmosphere, a solution of tetraiodide **4** (170 mg, 0.12 mmol) and tetrol **5**[10] (114 mg, 0.13 mmol) in DMF (50 mL) was added dropwise to a suspension of Cs_2CO_3 (384 mg, 1.2 mmol) in DMF (80 mL) for 6 h at 55-60 °C and the mixture was stirred for 12 h. Then the temperature was increased into 80 °C and the mixture was stirred for 3 h. After cooling to room temperature, the residue was taken up in CH_2Cl_2 (250 mL) and the solution was washed with 2 N HCl (50 mL), H_2O (3×150 mL), and brine (50 mL), and then dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed on a silica gel column using hexane-EtOAc (9 : 1, v/v) and the recrystallization from CH_2Cl_2-MeOH gave the product **6□DMF** (21 mg, 10%); mp >268 °C dec.; FT-IR (KBr) 1674 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.72 (s, ArH, 4H), 6.43 (s, ArH, 8H), 5.74 (d, OCH_2O, J = 7.1 Hz, 4H), 5.31 (s, COH, 1H), 4.61 (t, ArCH, 4H), 4.34 (d, *endo*-ArCH, J = 12 Hz, 4H), 4.32 (m, OCH_2, 8H), 4.19 (d, OCH_2O, J = 7.1 Hz, 4H), 4.05 (m, OCH_2, 8H), 3.72 (t, OCH_2, 8H), 3.04 (d, *exo*-ArCH, J = 12 Hz, 4H), 2.08 (m, CH_2, 8H), 1.96 (m, CH_2, 8H), 1.57-1.29 (m, CH_2, 48H), 0.84 (m, CH_3, 24H), 0.22 (s, NCH_3, 3H), -0.49 (s, NCH_3, 3H); FAB (+) MS, m/z 1884 (19□DMF$^+$, 67), 1906 (19□DMF+Na$^+$, 100); Anal. Calcd for $C_{115}H_{151}O_{21}N_1 \cdot CH_2Cl_2 \cdot Na_1$: C, 69.97; H, 7.74. Found: C, 69.64; H, 7.48.

2 : 1 Supramolecule (7). Under argon atmosphere, a solution of tetraiodide **4** (150 mg, 0.10 mmol), tetrol **5** (193 mg, 0.22 mmol), and pyrazine (650 mg) in DMF (50 mL) was added dropwise to a suspension of Cs_2CO_3 (339 mg, 1.0 mmol) and pyrazine (650 mg) in DMF (80 mL) for 6 h at 50 °C. The mixture was stirred for another 1 d and then cooled to room temperature. The mixture was taken up in CH_2Cl_2 (250 mL), washed with 2 N HCl (50 mL), water (3×150 mL), and brine (50 mL) and dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed on a silica gel column using hexane-EtOAc (5 : 1, v/v) and then the recrystallization from CH_2Cl_2-MeCN gave the product **7** (42 mg, 15%); mp 266.7 °C; FT-IR (KBr) 3462 cm^{-1} (ν_{OH}); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84 (s, resorcin-ArH, 4H), 6.61 (s, resorcin-ArH, 4H), 6.51 (s, calix-ArH, 4H), 6.24 (s, calix-ArH, 4H), 6.02 (d, OCH_2O, J = 7.0 Hz, 4H), 5.95 (two d, OCH_2O, J = 7.0 Hz, 4H), 5.63 (br s, OH, 4H), 4.78 (t, CH, 2H), 4.70 (t, CH, 6H), 4.53 (d, OCH_2O, J = 7.0 Hz, 2H), 4.48 (d, *endo*-ArCH, J = 13.1 Hz, 2H), 4.45 (d, OCH_2O, J = 7.0 Hz, 2H), 4.39 (d, *endo*-ArCH, J = 13.1 Hz, 2H), 4.34 (d,

$\mathrm{OCH_2O}$, $J = 7.0$ Hz, 2H), 4.18 (two t, $\mathrm{OC}H_2\mathrm{CH_2O}$, 8H), 3.94 (two t, $\mathrm{OCH_2C}H_2\mathrm{O}$, 8H), 3.83 (t, lower-$\mathrm{OCH_2}$, 8H), 3.16 (d, *exo*-ArCH, $J = 13.1$ Hz, 2H), 3.01 (d, *exo*-ArCH, $J = 13.1$ Hz, 2H), 2.18 (m, $\mathrm{CH_2}$, 16H), 1.90 (m, $\mathrm{CH_2}$, 8H), 1.43-1.35 (m, $\mathrm{CH_2}$, 72H), 0.93 (m, $\mathrm{CH_3}$, 36H); FAB(+) MS, m/z 2691 (M^+, 100).

Acknowledgment. The financial support from Korea Science and Engineering Foundation (Project No. 96-0501-04-01-3 and through CBM) is gratefully acknowledged.

References

1. Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon: Oxford, 1996; Vol. 2. Chap. 4.
2. (a) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry Press: Cambridge, 1994; Vol. 4. (b) Maverick, E. F.; Cram, D. J. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon: Oxford, 1996; Vol. 2. Chap. 12.
3. In *Comprehensive Supramolecular Chemistry, Cyclodextrins*; Szejtli, J., Ed.; Pergamon: Oxford, 1996; Vol. 3.
4. (a) Van Dienst, E.; Shellink, B. H. M.; Von Piekartz, I.; Grote Gansey, M. H. B.; Venema, F.; Feiters, M. C.; Nolte, R. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem*. **1995**, *60*, 6537. (b) Van Dienst, E.; Shellink, B. H. M.; Von Piekartz, I.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 1151.
5. (a) Nagasaki, T.; Fujishima, H.; Shinkai, S. *Chem. Lett.* **1994**, 989. (b) Milbradt, R.; Weiss, J. *Tetrahedron Lett*. **1995**, *36*, 2999. (c) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem*. **1995**, *60*, 6585. (d) Gale, P. A.; Sessler, J. L.; Lyneh, V.; Sansom, P. I. *Tetrahedron Lett.* **1996**, *37*, 7881.
6. (a) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, W. P.; Reinhoudt, D. N. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1292. (b) Timmerman, P.; Nierop, K. G. A.; Brinks, E. A.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, W. P.; Reinhoudt, D. N. *Chem. Eur. J*. **1995**, *1*, 132. (c) Higler, I.; Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **1998**, 2689.
7. (a) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2345. (b) van Wageningen, A. M. A.; Timmermann, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Chem. Eur. J*. **1997**, *3*, 639.
8. Timmerman, P.; Brinks, E. A.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 417.
9. Ihm, H.; Paek, K. *Bull. Korean Chem. Soc.* **1995**, *16*, 71.
10. (a) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1403. (b) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc*. **1991**, *113*, 2167.
11. (a) Chapman, R. G.; Chopra, N.; Cochien, E. D.; Sherman, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 369. (b) Chapman, R. G.; Sherman, J. *J. Org. Chem*. **1998**, *63*, 4103.
12. Paek, K.; Joo, K.; Kwon, S.; Ihm, H.; Kim, Y. *Bull. Korean Chem. Soc.* **1997**, *18*, 80.