ARTICLE

OBC
www.rsc.org/obc

Inclusion behavior of water-soluble thiacalix- and calix[4]arenes towards substituted benzenes in aqueous solution

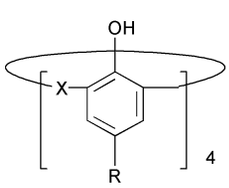
Noriyoshi Kon,* Nobuhiko Iki and Sotaro Miyano*
Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan.
E-mail: miyano@orgsynth.che.tohoku.ac.jp; Fax: +81-(0)22-217-7262; Tel: +81-(0)22-217-7262

Received 21st October 2002, Accepted 16th December 2002
First published as an Advance Article on the web 28th January 2003

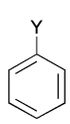
Inclusion abilities of thiacalix- and calix[4]arenetetrasulfonate (**3** and **4**) towards mono-substituted benzenes were investigated in neutral aqueous solution. In general, the hosts regioselectively encapsulated the guests from the aromatic moiety except the complexation of toluene by **4**, in which the guest penetrated from either the aromatic or the methyl group. Stabilities of the inclusion complexes increased with the electron-withdrawing ability of the substituent on the guest, suggesting π–π electronic interaction between the host and guest. In spite of the lower electron density of the aromatic ring, thiacalix[4]arene **3** showed higher inclusion ability than calix[4]arene **4**, suggesting that the size rather than the electron density of the calix framework is a more important factor in determining the inclusion ability.

Introduction

The recognition of molecules by synthetic receptors is a topic of current interest in supramolecular chemistry, in which particular interest is focused on recognition behavior in water, where biological processes take place. In this context, cyclodextrins[1] and water-soluble cyclophanes[2] have been well studied to get deeper insight into molecular recognition processes in the solvent. Calixarenes (*e.g.* **1**) are often described as macrocycles with (almost) unlimited possibility because of their versatility and utility as host molecules.[3] The development of this class of compound relies on the ready availability of various ring sizes and ease of chemical modification at the phenolic OH groups (lower rim) and the *p*-positions (upper rim). Although a number of water-soluble calixarenes have also been prepared *via* various modifications of the aromatic nuclei with charged and neutral functional groups,[3] only limited studies on their complexation behavior towards neutral guests in aqueous systems have been reported.[4]



1: X= CH_2, R= Bu^t
2: X=S, R= Bu^t
3: X= S, R= SO_3^-
4: X= CH_2, R= SO_3^-



Guests: Y= NO_2, CN, Cl, $COOCH_3$, H, CH_3, OMe

Since we reported a practical method for the synthesis of thiacalix[4]arenes (*e.g.* **2**),[5] studies on the chemistry of these new members of the calixarene family have revealed that thiacalix[4]arenes should be regarded as a unique molecular framework for second generation calixarene chemistry, rather than a simple substitute for the conventional calixarenes,[6] because replacement of the methylene linkages of **1** by sulfide provides various intrinsic characteristics of **2**, which cannot be attained by **1**.[6] Recently, we reported that thiacalix[4]arenetetrasulfonate **3** had complexation ability towards halomethanes such as chloroform and dichloromethane[7] as well as water-miscible organic molecules such as alcohols and ketones in water.[8] The preferential inclusion of **3** towards halomethanes enabled highly efficient removal of this class of environmentally hazardous substances from water by treating with **3** to form inclusion complexes, which were then removed by trapping on an anion-exchange resin or salting out by addition of NaCl.[9] In the next step, we realized that basic data on the complexation ability of **3** towards larger molecules, especially benzene derivatives, were essential for the design of a system for the removal of chemical substances of environmental concern. To the best of our knowledge, however, only a few studies on the complexation of mono-substituted benzenes by the conventional calix[4]arene **4** have been reported.[10] Since comparison of the structurally related hosts should provide suggestive information concerning the complexation mechanism, herein we report the results of a study on the inclusion behavior of **3** for mono-substituted benzenes in water compared with that of **4**.

Results and discussion

Estimation of association constant (*K*)

The complexation behavior of **3** and **4** was investigated by NMR by varying the concentration of the host in D_2O at p*D* = 7.3 (0.1 M phosphate buffer), which was contacted with the bulk of the organic phase (See Experimental section). In all cases, the host to guest ratio of the complex was confirmed as 1 : 1 manner by a Job's plot. Therefore, the host–guest complexation is represented by Eqn. (1), where H, G, and H·G denote the free guest, free host, and host–guest complex, respectively. The association constant (*K*) of H·G is given by Eqn. (2).

$$H + G \rightleftarrows H{\cdot}G \quad (1)$$

$$K = [H{\cdot}G] / [H][G] \quad (2)$$

The average binding number of ($\bar{n}$) of the host is defined by Eqn. (3), where G_T and H_T denote the total concentration of guest and host in the aqueous phase, and are given by Eqns. (4) and (5), respectively.

$$\bar{n} \equiv [\text{guest bound to host}] / [\text{all host}] = (G_T - [G]) / H_T \quad (3)$$

DOI: 10.1039/b210198j

$$G_T = [G] + [H{\cdot}G] \quad (4)$$

$$H_T = [H] + [H{\cdot}G] \quad (5)$$

Here H_T is a known parameter, whereas G_T was estimated by the peak area of the guest in the ^{1}H NMR spectrum. Since the bulk phase of the guest existed after equilibration, [G] is the saturated concentration, namely the solubility of the guest in D_2O. Figs. 1 and 2 show the dependence of G_T on H_T. As H_T

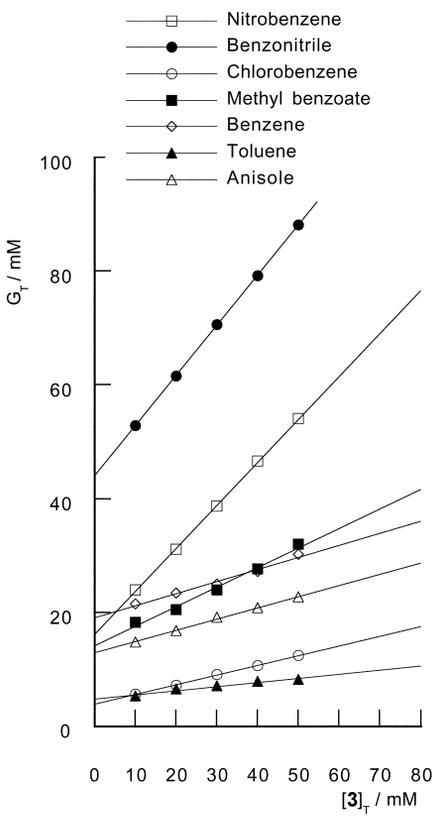


Fig. 1 The plot of G_T *versus* $[\mathbf{3}]_T$ in D_2O at pD= 7.3, 300 K. Correlation coefficients (R^2) of the plots were greater than 0.9645.

increased, G_T also increased linearly, implying that the hosts could solubilize guest molecules into the aqueous phase by complexation. Since Eqn. (3) can be rewritten to Eqn. (6), $\bar{n}$ and [G] are estimated by least square fitting to the data as shown in Figs. 1 and 2.

$$G_T = \bar{n} H_T + [G] \quad (6)$$

The association constant (K) can be obtained by introducing the estimated values of $\bar{n}$ and [G] into Eqn. (7), which is obtained from Eqns. (2)–(5). The estimated $\bar{n}$, [G], and log K are summarized in Table 1.

$$K = \bar{n} / (1 - \bar{n})[G] \quad (7)$$

Complexation modes

^{1}H NMR spectra conveniently provide information on the complexation mode of the guests with the host. In all cases, the guest protons were observed as a single resonance due to fast exchange between a free guest and a complexed one on the NMR time scale. Also, the absorption signals of a guest were shifted upfield compared with those of a free guest as exemplified by the **3**–methyl benzoate system (Fig. 3), suggesting that the guest is encapsulated into the cavity of the hosts to be shielded. Table 2 shows the chemical shift changes ($\Delta\delta$) of

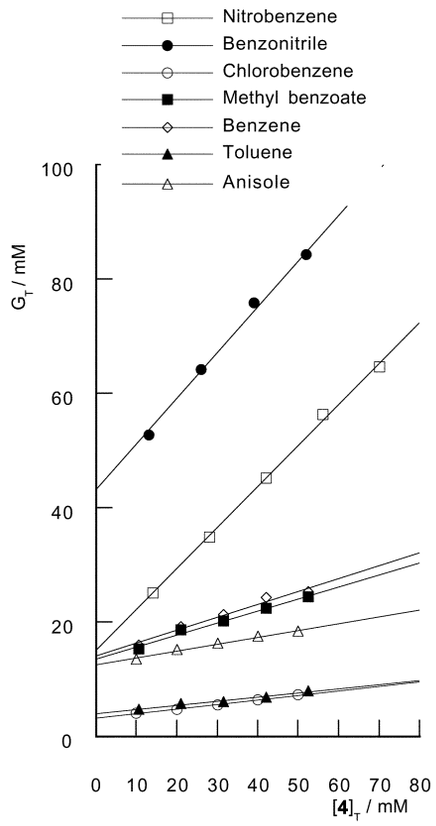


Fig. 2 The plot of G_T *versus* $[\mathbf{4}]_T$ in D_2O at pD= 7.3, 300 K. Correlation coefficients (R^2) of the plots were greater than 0.9798.

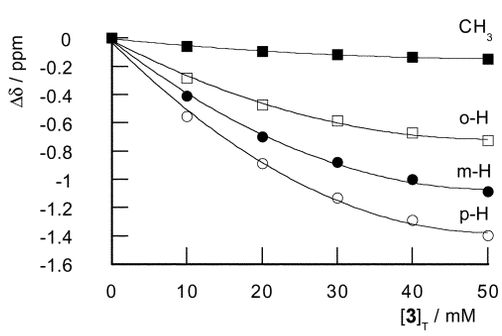


Fig. 3 Chemical shift changes ($\Delta\delta$) of methyl benzoate *versus* $[\mathbf{3}]_T$ in D_2O at pD = 7.3, 300 K.

mono-substituted benzenes in the presence of 50 mM of **3** and **4**, respectively. In the complexation of **3**, the absolute values of $\Delta\delta$ decreased in the order *p*-H > *m*-H > *o*-H> CH_3, indicating that the guests were regioselectively encapsulated into the cavity from the aromatic moiety rather than the side of the substituent Y presumably due to π–π interaction (Scheme 1 (a)).[11]

In the complexes formed by **4**, the orientation of the guests seems to be similar to those formed by **3** except in the case of toluene, where the $|\Delta\delta|$ s are in the order *p*-H ≥ CH_3 > *m*-H ≥ *o*-H (Table 2). The order indicates that toluene is encapsulated from either side of the molecule, that is from the aromatic moiety or methyl group, without regioselectivity as shown in Scheme 1(b). The complexation mode of toluene by **4** might be due to the operation of CH–π interaction in addition to π–π interaction.[12] This sharply contrasts with the fact that **3** regioselectively includes toluene into the cavity from the side of the aromatic moiety, suggesting that the small methyl moiety does not fit comfortably into the enlarged cavity of **3** compared to **4**. This is consistent with the previous results that **4** includes CH_3X-type small guests including methanol, acetonitrile, nitromethane *etc.* [8] more strongly than **3**.

Table 1 The average binding numbers ($\bar{n}$), the saturated guest concentrations ([G]) and association constants (log K) in the complexation of **3** and **4** with mono-substituted benzenes

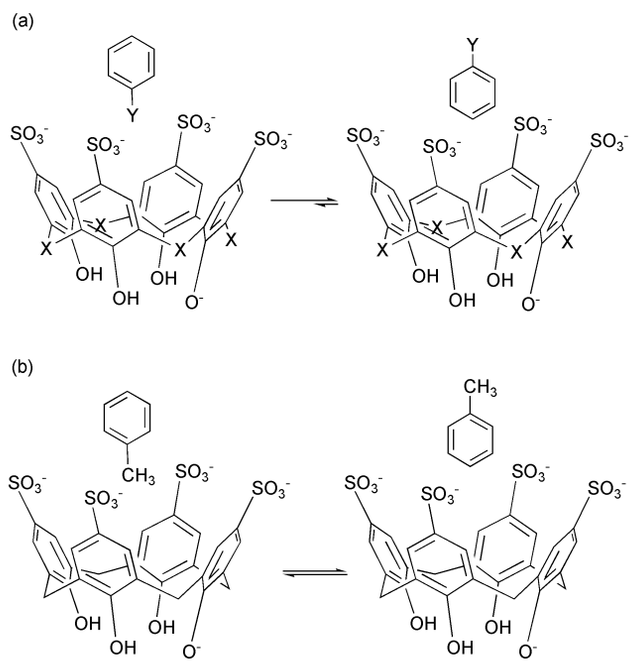
Guest	**3**			**4**		
	$\bar{n}$	[G] / mM	log (K / M^{-1})	$\bar{n}$	[G] / mM	log (K / M^{-1})
Nitrobenzene	0.76	16.2	2.28	0.72	15.1	2.22
Benzonitrile	0.88	44.1	2.22	0.85	43.2	1.96
Chlorobenzene	0.17	3.9	1.72	0.10	3.2	1.45
Methyl benzoate	0.34	14.2	1.57	0.21	13.6	1.30
Benzene	0.27	15.2	1.38	0.22	14.1	1.32
Toluene	0.07	4.8	1.21	0.07	4.0	1.30
Anisole	0.20	13.0	1.28	0.12	12.6	1.04

Aqueous solution buffered at pD = 7.3, 300 K.

Table 2 The chemical shift change ($\Delta\delta$)[a] of mono-substituted benzenes in the presence of 50 mM of **3** and **4**

Guest	**3**				**4**			
	o-H	*m*-H	*p*-H	CH_3	*o*-H	*m*-H	*p*-H	CH_3
Nitrobenzene	−0.987	−1.433	−1.804		−1.005	−1.932	−2.564	
Benzonitrile	−0.701	−1.001	−1.224		−0.712	−1.303	−1.720	
Chlorobenzene	−1.075	−1.245	−1.334		−0.830	−1.422	−1.768	
Methyl benzoate	−0.703	−1.053	−1.355	−0.141	−0.630	−1.264	−1.696	−0.153
Benzene	−0.819				−0.865			
Toluene	−0.990	−0.965	−1.048	−0.823	−0.739	−0.752	−0.860	−0.839
Anisole	−0.634	−0.799	−0.928	−0.408	−0.512	−0.830	−1.096	−0.367

[a] $\Delta\delta = \delta$(presence of 50 mM of host) − δ (free guest). Negative values indicate upfield shift.



Scheme 1 Complexation mode of **3** and **4** toward mono-substituted benzenes (a) except that of **4** towards toluene (b).

Electronic effect of the substituent on the guest

In the complexation of mono-substituted benzenes by **3**, the log K values ranged from 1.21 to 2.28 as shown in Table 1. It may be considered that the hydrophobic effect is a predominant driving force in the complexation of mono-substituted benzenes by **3**, because all of the guest molecules investigated here are relatively hydrophobic.[13] However, log K did not correlate well with hydrophobicity defined as the partition coefficient of a guest between octan-1-ol and water (log P_o).[14] For example, toluene (log P_o = 2.69) is the most hydrophobic among the guests investigated, log K of which, however, is considerably lower than that of benzonitrile (log P_o = 1.56) the least hydrophobic. From these results, it seems that the hydrophobic effect is not a predominant factor in determining the selectivity of **3** towards mono-substituted benzenes. On the contrary, the dependency of log K on the substituent (Y) may be reasonably explained by the electronic effect of Y. For instance, **3** formed the most stable complexes with nitrobenzene (log K = 2.28) and benzonitrile (log K = 2.22) which have highly electron-withdrawing groups, whereas toluene (log K = 1.21) and anisole (log K = 1.28), which have electron-donating groups, formed less stable complexes than benzene (log K = 1.38). The critical role of the electronic effect is clearly supported by Hammett *para*-substituent constants (σ_p);[15] a good linear relationship between log K and σ_p was observed as shown in Fig. 4 (R^2 = 0.9768 except the methyl benzoate complex),[16] suggesting that π–π interaction between **3** and the guest dominates the relative stability of the complexes in water. Methyl benzoate showed a significant deviation from linearity, which may be caused by steric hindrance and/or electric repulsion between the $-SO_3^-$ of the hosts and the –COOMe of the guest.

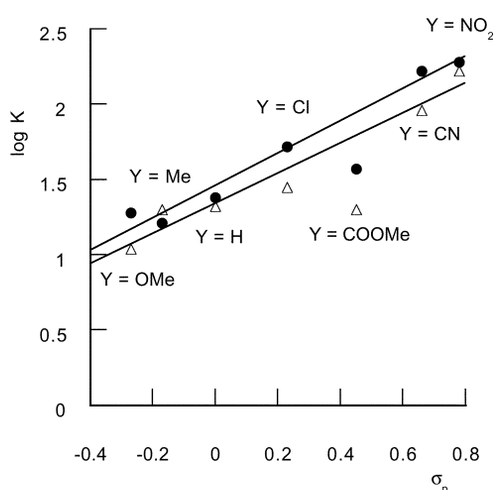


Fig. 4 The linear correlation between log K and σ_p in the complexation of **3** and **4** at pD = 7.3: (●) compound **3**; (Δ) compound **4**.

The plot of log K of **4** *versus* σ_p also showed a good linear correlation, suggesting that π–π electronic interaction also plays the main role in inclusion by **4** (R^2 = 0.956 except methyl benzoate complex, Fig. 4). The deviation of the methyl benzoate complex of **4** from linearity was more significant than that of **3**. This is compatible with the above reasoning based on the steric–electronic effect on the **3**–methyl benzoate complex, considering that the smaller cavity of **4** as compared to that of **3** should probably impose a more severe stereo-electronic effect in the former host.

Size effect of calix framework

As shown above, the complexation ability of **3** and **4** to the guests were dependant on the electron-withdrawing nature of Y on a guest. Therefore, it is expected that the stability of the host–guest complexes also depends on the π electron densities of the hosts. Since the first and second pK_a values for the phenolic OH groups are pK_{a1} = 2.2 and pK_{a2} = 8.5 for **3**,[17] and pK_{a1} = 3.1 and pK_{a2} = 12.0 for **4**,[3d] respectively, both hosts exist as mono-phenolate at pD = 7.3. Therefore, the difference of π electron densities of the hosts should be ascribed to the difference in the bridging groups X. It seems that **3** has more electron-deficient π systems than **4**, because the vacant 3d-orbital of the sulfide linkages of **3** allows a resonance-like interaction with the π-orbital of the adjacent aromatic rings to delocalize negative charges.[18] This in fact results in lower pK_a values of **3** than those of **4**. Contrary to expectation, however, the binding ability of electron-rich **4** was appreciably inferior to that of **3** except in the case of toluene, suggesting that other effects than electronic ones are more effective on the stability of the complexes (Table 1 and Fig. 4). †

Since the host–guest compatibility in size is known to be one of the important factors to determine the stability of the complexes,[19] it seems quite reasonable to expect the cavity size of the host in the present systems to be important. In fact, the replacement of bridging CH_2 groups of **4** with sulfides brings about a 15% enlargement of the cavity size as judged by the bond length between the phenyl group and the bridging group (X): average Ph–X distances are 1.53 Å for **4**[20] and 1.78 Å for **3**.[8] On the basis of X-ray crystallographic analyses of the complexes of **4** with aromatic compounds, **4** seems to be too small to completely encapsulate mono-substituted benzenes.[21] Furthermore, the chemical shift changes of the guests indicated that **4** formed tighter complexes than **3** did because $|\Delta\delta|$ values of *m*- and *p*-aromatic protons of the guest were larger than those of **3** (Table 2), although the $\bar{n}$ and log K values of **4** were smaller than those of **3** except the case of toluene (Table 1). Schneider *et al.*[22] and Collet *et al.*[23] suggested that the degree of freedom of the bound substrate might play a significant role in host–guest complexation. Considering these precedents, the larger cavity of **3** than **4** seems to accommodate the mono-substituted benzenes more comfortably than **4** into the cavity, allowing π–π interaction between the host and guest to operate more effectively with an adequate degree of freedom of the complexed guest. Therefore, it may be concluded that the size of the calix framework has a pronounced effect on the inclusion ability of the host rather than the electronic effect. The larger log K value of the toluene complex of **4** rather than that of **3** might be attributed to the CH–π interaction operating more effectively in **4** than **3** as stated above (Scheme 1 (b)).

† It is known that donor–acceptor interactions are not always dominant in Ar–Ar interactions.[11] For instance, a review by Hunter introduces cases in which electrostatic repulsion between aromatic rings plays a more significant role than electron donor–acceptor interactions.[11c] In our case, however, electrostatic interactions may not govern the stability of the complex H·G because, compared to host **3**, electron-rich host **4** formed tighter complexes, in which the guest penetrated more deeply into the cavity showing a higher degree of overlapping between the aromatic rings of the host and guest.

Conclusion

Herein we have shown the inclusion behavior of **3** and **4** toward mono-substituted benzenes in water. The guests are encapsulated into the cavity of the host from the side of the aromatic moiety except the **4**-toluene system. Stabilities of the complexes of **3** and **4** depend on the electronic effect of substituent (Y) on a guest, suggesting that π–π interaction between the host and the guest is a predominant factor for the complexation of mono-substituted benzenes by the particular host. The stability constants reveal that thiacalix[4]arene **3** is more efficient for the complexation of mono-substituted benzenes than calix[4]arene **4**, although **3** has lower electron density of the aromatic ring. Favorable complexation by **3**, rather than by **4**, is attributed to the size of the calix framework, which is more affective on inclusion ability than electron density of the host. The conclusions presented here will be helpful for understanding molecular recognition processes in water and the design of artificial receptors for substituted benzenes.

Experimental

Materials

Tetrasodium 25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiacalix-[4]arene-5,11,17,23-tetrasulfonate (**3**) was prepared as described in the literature.[7] Tetrasodium 25,26,27,28-tetrahydroxycalix-[4]arene-5,11,17,23-tetrasulfonate (**4**) was obtained from Sugai Chemie Inc. (Wakayama, Japan). All mono-substituted benzenes were commercially available and purified by distillation.

NMR titration

A D_2O solution of hosts ($H_T \approx$ 0–70 mM) adjusted to pD = 7.3 with 0.1 M H_3PO_4–NaOD buffer was saturated with a guest at 300 K by addition of a few drops of the guest. After equilibration, an aliquot of the D_2O phase was subjected to ^{1}H NMR with 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an external reference to determine the chemical shift (δ) and the total concentration of the guest (G_T).

Acknowledgements

This work was supported by the Grants-in-Aid for Scientific Research (Exploratory Research, No. 14655332) provided by the Japan Society for the Promotion of Science, and also by the Industrial Technology Research Grant Program in 2002 from the New Energy and Industrial Technology Development Organization (NEDO) of Japan. N. K. thanks the Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

References

1 Reviews: (*a*) W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344; (*b*) V. Mikhail and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875.
2 Review: F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 362.
3 (*a*) C. D. Gutsche, *Calixarenes, Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1989; (*b*) C. D. Gutshe, *Calixarene Revisited, Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1998; (*c*) L. Mandolini and R. Ungaro, *Calixarene in Action*, Imperial College Press, London, 2000; (*d*) *Calixarenes 2001*, eds. Z. Asfari, V. Böhmer, J. Harrowfield and J. Vicens, Kluwer Academic, Dordrecht, 2001.
4 (*a*) C. D. Gutsche and I. Alam, *Tetrahedron*, 1988, **44**, 4689; (*b*) S. Shinkai, H. Kawabata, T. Arimura, T. Matsuda, H. Satoh and O. Manabe, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1073; (*c*) B.-L. Poh and L.-S. Koay, *Tetrahedron Lett.*, 1990, **31**, 1911; (*d*) B.-L. Poh and C. M. Tan, *J. Inclusion Phenom.*, 1994, **18**, 93; (*e*) G. Arena, A. Casnati, A. Contino, D. Sciotto and R. Ungaro, *Tetrahedron Lett.*, 1997, **38**, 4685; (*f*) G. Arena, A. Contino, F. G. Gulino, A. Magrì, D. Sciotto and R. Ungaro, *Tetrahedron Lett.*, 2000, **41**,

9327; (*g*) J.-Z. Zheng, J.-S. Wu, K. Toda and I. Sanemasa, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 505.
5 (*a*) H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama and S. Miyano, *Tetrahedron Lett.*, 1997, **38**, 3971; (*b*) N. Iki, C. Kabuto, T. Fukushima, H. Kumagai, H. Takeya, S. Miyanari, T. Miyashi and S. Miyano, *Tetrahedron*, 2000, **56**, 1437; (*c*) N. Kon, N. Iki and S. Miyano, *Tetrahedron Lett.*, 2002, **43**, 2231.
6 Reviews: (*a*) N. Iki and S. Miyano, *J. Chem. Soc. Jpn., Chem. Ind. Chem.*, 2001, 609; (*b*) N. Iki and S. Miyano, *J. Inclusion Phenom. Macrocyclic Chem.*, 2001, **41**, 99.
7 N. Iki, T. Fujimoto and S. Miyano, *Chem. Lett.*, 1998, 625.
8 N. Iki, T. Suzuki, K. Koyama, C. Kabuto and S. Miyano, *Org. Lett.*, 2002, **4**, 509.
9 N. Iki, T. Fujimoto, T. Shindo, K. Koyama and S. Miyano, *Chem. Lett.*, 1999, 777.
10 (*a*) H. J. Schneider, F. Werner and T. Blatter, *J. Phys. Org. Chem.*, 1993, **6**, 590; (*b*) M. Baur, M. Frank, J. Schatz and F. Schidbach, *Tetrahedron*, 2001, **57**, 6985.
11 (*a*) C. A. Hunter, *Chem. Soc. Rev.*, 1994, 101; (*b*) C. A. Hunter, K. R. Lawson, J. Perkins and C. J. Urch, *J. Chem. Soc., Perkin Trans. 2*, 2001, 651; (*c*) C. A. Hunter, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1584.
12 M. Nishio, M. Hirota and Y. Umezawa, *The CH/π Interaction: Evidence, Nature and Consequences*, Wiley-VCH, New York, 1998.
13 (*a*) C. Tanford, *The Hydrophobic Effect*, *2nd ed*, Wiley-VCH, New York, 1991; (*b*) S. Shinkai, K. Araki, T. Matsuda and O. Manabe, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 3856.
14 A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, 1971, **71**, 525.
15 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
16 The linear correlations between log *K* and dipole moments (μ) were also observed. $R^2 = 0.975$ for **3** and 0.9363 for **4**, respectively.
17 H. Matsumiya, Y. Terazono, N. Iki and S. Miyano, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1166.
18 (*a*) W. von E. Doering and K. C. Schreiber, *J. Am. Chem. Soc.*, 1955, **77**, 514; (*b*) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 1955, **77**, 521.
19 J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, 1995.
20 A. W. Coleman, S. G. Bott, S. D. Morley, C. M. Means, K. D. Robinson, H. Zhang and J. L. Atwood, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1361.
21 (*a*) S. Shinkai, K. Araki, T. Matsuda, N. Nishiyama, H. Ikeda, I. Takasu and M. Iwamoto, *J. Am. Chem. Soc.*, 1990, **112**, 9053; (*b*) J. L. Atwood, G. W. Orr, R. K. Juneja, S. G. Bott and F. Hamada, *Pure Appl. Chem.*, 1993, **65**, 1471; (*c*) J. L. Atwood, L. J. Barbour, M. J. Hardie and C. L. Rason, *Coord. Chem. Rev.*, 2001, **222**, 3.
22 H.-J. Schneider, T. Blatter and S. Simova, *J. Am. Chem. Soc.*, 1991, **113**, 1996.
23 L. Garel, B. Lozach, J.-P. Dutasta and A. Collet, *J. Am. Chem. Soc.*, 1993, **115**, 11652.