Spectrophotometric Study of Inclusion Complexation of Aliphatic Alcohols by β-Cyclodextrins with Azobenzene Tether

Yu Liu,* Yan-Li Zhao, Heng-Yi Zhang, Zhi Fan, Guo-Dong Wen, and Fei Ding

Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

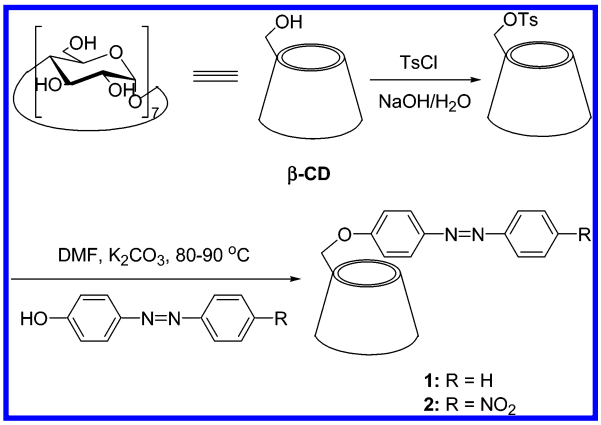
Received: December 24, 2003; In Final Form: April 20, 2004

Two novel β-cyclodextrin (β-CD) derivatives possessing azobenzene functional groups as a spectral probe, i.e., mono{6-*O*-[4-(phenylazo)phenyl]}-β-cyclodextrin (**1**) and mono{6-*O*-[4-((4-nitrophenyl)azo)phenyl]}-β-cyclodextrin (**2**), were synthesized in high yields, and their complexation behaviors with aliphatic alcohols were evaluated by using UV−vis, circular dichroism, and ^{1}H NMR spectroscopy. The induced circular dichroism (ICD) and 2D NMR spectroscopy investigations revealed that azobenzene groups attached to the β-CD rim can be deeply embedded to the β-CD cavity to form the intramolecular inclusion complexes in 10% DMSO aqueous solution. Increasing the ratio of DMSO in solution results in the gradual exclusion of the azobenzene sidearm from the β-CD cavity. Upon complexation with guest adamantanols, modified β-CD **1** or **2** displays two different binding models, that is, the competitive inclusion model for 2-adamantanol and the co-inclusion model for 1-adamantanol. These two different models reasonably explain the different binding behaviors and molecular selectivities of host β-CDs toward guests. Therefore, besides acting as a spectral probe, azobenzene modified β-CDs can also effectively recognize the size/shape of guest molecules, giving good molecular selectivity up to 91 for 2-adamantanol/(+)-borneol pair by **1** and the moderate enantioselectivity ($K^-/K^+ = 2.1$) for (−)-/(+)-borneol pair by **2**.

Introduction

Investigations on the inclusion complexation of native and modified cyclodextrins (CDs) have received much attention in supramolecular chemistry and become the fundamental basis of molecular assembly.[1−4] In the inclusion complexation process, besides several weak intermolecular noncovalent forces, such as dipole−dipole (ion), hydrophobic, electrostatic, van der Waals, and hydrogen bonding interactions, the solvent, environment, and conformations of hosts and guests will also affect the stability of host−guest complexes. The strong binding affinity of CDs to hydrophobic molecules in aqueous media enables them to be effective receptors for organic, inorganic, and biological substrates.[5−8] Furthermore, lots of chemically modified CDs have been designed and synthesized to enhance the original binding ability and the molecular selectivity of parent CD.[9−14] As one of the most important categories, CD derivatives bearing a chromophoric substituent, such as an azo group, can exhibit the appreciable spectral changes upon inclusion complexation with guests, and thus be successfully applied as the versatile spectral probe to investigate the host−guest complexation. As a method to control the stability, solubility, and aggregation of azo dyes, their inclusion complexation with CDs has been widely investigated.[15−20] Recently, Ueno et al. reported several azo dyes modified β-CDs as guest responsive color-change indicators.[21] More recently, Nau and co-workers reported their investigations on the conformational variability of azoalkanes in the presence of β-CD.[22] However, studies on the conformational changes and binding models of self-included azobenzene modified β-CDs in the absence and presence of external guests are rarely investigated,[21] though these studies are very important for discussing the molecular recognition/aggregation mechanism and controlled binding behavior by azobenzene modified β-CDs.

SCHEME 1: Schematic Representation of the Formation of Hosts 1 and 2

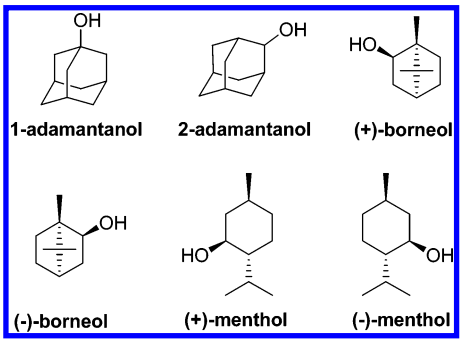


In the present paper, we report the syntheses of two azobenzene modified β-CDs, **1** and **2** (Scheme 1), and their inclusion complexation behaviors with aliphatic alcohols, i.e., 1-adamantanol (1-Ada), 2-adamantanol (2-Ada), (+)-borneol [(+)-Bor], (−)-borneol [(−)-Bor], (+)-menthol [(+)-Men], and (−)-menthol [(−)-Men] (Chart 1). These systematic studies will serve our further understanding of the molecular recognition mechanism and inclusion binding behavior of modified β-CDs.[23−27] On the other hand, the molecular binding model and stability constant of aliphatic alcohols by β-CD derivatives possessing functional azobenzene groups are discussed from the viewpoints of the size/shape matching, hydrogen bonding, and induced-fit interaction between host and guest.

* To whom correspondence should be addressed. Tel: +86-22-23503625. Fax: +86-22-23503625. E-mail: yuliu@public.tpt.tj.cn.

10.1021/jp0380024 CCC: $27.50
Published on Web 05/27/2004

CHART 1: Aliphatic Alcohol Guests



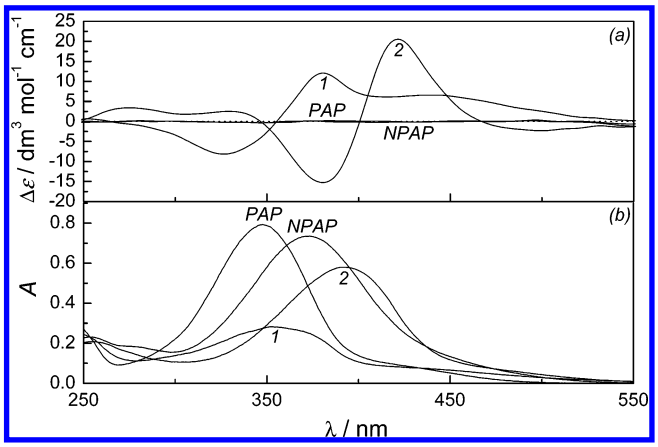


Figure 1. Circular dichroism (a) and absorption (b) spectra of PAP (2.8×10^{-5} mol dm^{-3}), NPAP (2.8×10^{-5} mol dm^{-3}), **1** (2.5×10^{-5} mol dm^{-3}) and **2** (2.3×10^{-5} mol dm^{-3}) in 10% DMSO aqueous solution at 25 °C.

Results and Discussion

Synthesis. As illustrated in Scheme 1, modified β-CDs **1** and **2** were synthesized in high yields by the reaction of 6-OTs-β-CD with 4-(phenylazo)phenol (PAP) and 4-((4-nitrophenyl)-azo)phenol (NPAP), respectively. The self-included conformation of hosts **1** and **2** are validated by induced circular dichroism (ICD) and 2D NMR results described below.

Conformational Analysis of Azobenzene Modified β-CDs. Circular dichroism spectrometry has become a convenient and widely employed method for the elucidation of the absolute conformation of chiral organic compounds in the past three decades. Moreover, the achiral compounds located in a chiral environment, such as the CD cavity, can also produce ICD signal(s) in the corresponding transition band(s).[28,29] To investigate the structure features of **1** and **2** in solution, their circular dichroism spectra were measured at 25 °C. As can be seen from Figure 1, the circular dichroism spectrum of modified β-CD **1** (2.5×10^{-5} mol dm^{-3}) in 10% DMSO aqueous solution showed a negative Cotton effect peak at 326 nm ($\Delta\epsilon = -8.16$ dm^{-3} mol^{-1} cm^{-1}) and a positive Cotton effect peak at 381 nm ($\Delta\epsilon = 12.05$ dm^{-3} mol^{-1} cm^{-1}). Similarly, **2** (2.3×10^{-5} mol dm^{-3}) showed a negative Cotton effect peak at 381 nm ($\Delta\epsilon = -15.26$ dm^{-3} mol^{-1} cm^{-1}) and a positive Cotton effect peak at 421 nm ($\Delta\epsilon = 20.51$ dm^{-3} mol^{-1} cm^{-1}). Because of the substituent effect of the nitro group, the maximum absorption wavelength of **2** was red-shifted about 50 nm compared to that of **1**, whereas no ICD signal was observed for PAP (2.8×10^{-5} mol dm^{-3}) and NPAP (2.8×10^{-5} mol dm^{-3}) under comparable conditions. According to Kajtár's sector rule[30] on the ICD phenomena of β-CD complexes, we can deduce that the azobenzene moieties in **1** and **2** are deeply embedded in the β-CD cavity with an acclivitous orientation to form self-included complexes.

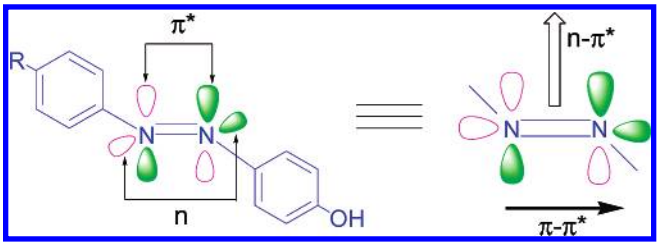


Figure 2. Illustration of the electric transition dipole moment for the $\pi \rightarrow \pi^*$ (solid vector) or n $\rightarrow \pi^*$ (blank vector) electronic transtion of azobenzene moiety.

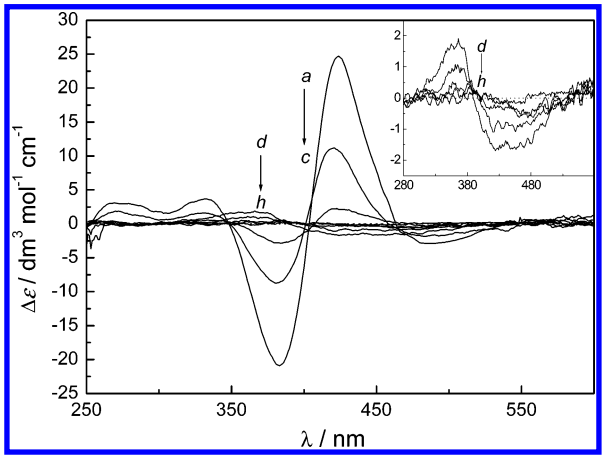


Figure 3. ICD spectra of **2** (3.1×10^{-5} mol dm^{-3}) in DMSO−H_2O solution at 25 °C. DMSO ratio: (a) 10%; (b) 20%; (c) 25%; (d) 30%; (e) 40%; (f) 50%; (g) 80%; (h) 100%.

The broad absorption band of the azobenzene moiety in **1** or **2** in the range of 250−550 nm is composed of two allowed transitions, and their transition dipole moments are perpendicular to each other. That is to say, the transition moments of $\pi-\pi^*$ (parallel to the N=N bond) and n$-\pi^*$ (perpendicular to the N=N bond) of the azobenzene chromophore are perpendicular to each other,[22,31] as illustrated in Figure 2. Therefore, hosts **1** and **2** can induce appreciable positive ICD signals at 381 and 421 nm and negative ICD signals at 326 and 381 nm, which correspond to the n$-\pi^*$ and $\pi-\pi^*$ transition band of the azobenzene group, respectively.

It is well-known that the stability constant of the inclusion complexes formed by β-CDs and guest molecules is influenced by the solvent effect because of the hydrophobic property of the β-CD cavity.[31−33] In this respect, circular dichroism and UV−vis spectra of **1** and **2** in the presence of different amounts of DMSO have been obtained to deduce the conformational variability of the azobenzene group linked to β-CD. Typically, a series of ICD signals of **2** in different DMSO aqueous solutions (DMSO ratio from 10% to 100%) were shown in Figure 3. As can be seen from Figure 3, the ICD signals of host **2** decreased gradually by increasing the DMSO ratio from 10% to 25%, whereas, an opposite ICD signal in 30% DMSO−H_2O was observed, and this ICD signal declined sequentially by further increasing the DMSO ratio from 30% to 100%. One possible explanation for these phenomena is that a competition between the azobenzene group and DMSO must operate upon inclusion complexation with β-CD; that is to say, DMSO gradually excludes the azobenzene moiety from the β-CD cavity.

Furthermore, the UV−vis spectra of **2** in different DMSO aqueous solution also gave interesting phenomena, which were shown in Figure 4. In the experiments, the UV absorption maximum of modified β-CD **2** gradually decreased around 391 nm upon addition of the DMSO ratio from 10% to 30% (a to

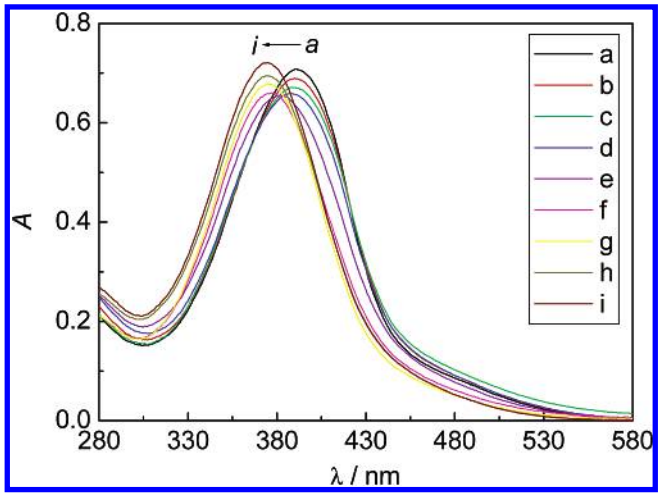


Figure 4. UV−vis spectra of **2** (2.6×10^{-5} mol dm^{-3}) in DMSO−H_2O solution at 25 °C. DMSO ratio: (a) 10%; (b) 15%; (c) 20%; (d) 25%; (e) 30%; (f) 40%; (g) 50%; (h) 70%; (i) 100%.

e), and then increased around 374 nm by further increasing the DMSO ratio from 30% to 100% (e to i), accompanying the obvious blue-shift (about 17 nm) of the absorption peak, which indicated that the chromophoric substituent in **2** entered the hydrophilic region from the hydrophobic cavity due to the binding of guest DMSO.[34] The result obtained supports the above conclusion from the experiments of ICD. In the further studies, the results of 2D NMR experiments showed direct evidence for the phenomena, which is described below.

Because two protons located closely in space can produce a NOE cross-peak between the relevant protons in the NOESY or ROESY spectra.[35] To study the conformation of modified β-CDs **1** and **2** in different DMSO aqueous solutions, their 2D NMR spectroscopy experiments have also been performed in 10% DMSO-d_6−D_2O solution and pure DMSO-d_6, respectively. In 10% DMSO-d_6−D_2O solution, the NOESY spectrum of **2** (Figure 5a) displays the clear NOE cross-peaks between H5 of β-CD and Ha protons of azobenzene moiety (peaks A), the cross-peaks between H3/H5 of β-CD and Hb and/or Hc protons of azobenzene moiety (peaks B), as well as the cross-peaks between H3 of β-CD and Hd protons (peaks C). On the other hand, peaks D showed the clear NOE cross-peaks between the protons of β-CD and the protons of DMSO, but no NOE cross-peaks between the azobenzene moiety and DMSO could be found. These phenomena indicate that the azobenzene moiety in **2** is deeply self-included in the hydrophobic cavity from the primary side of β-CD (Figure 5b). In pure DMSO-d_6, the NOESY spectrum of **2** (Figure 6a) displays the cross-peaks (peaks A) between the Ha protons of the azobenzene moiety and the hydroxyl groups of the primary side of β-CD, indicating that the azobenzene moiety is located above the β-CD cavity, as illustrated in Figure 6b. Moreover, modified β-CD **1** displayed 2D NMR spectroscopy similar to that of **2**. Therefore, the results of the NOESY experiments not only further support the ICD and UV−vis investigations on the conformations of modified β-CDs **1** and **2** but also may serve to establish correlation between the conformational feature of modified β-CDs and their molecular recognition ability.

Binding Model of Modified β-CDs with Guests. It is well-known that the competitive inclusion and induced fit generally exist in the molecular binding process of modified β-CDs. Therefore, it is very important to investigate the binding models between host β-CDs and guest molecules for elucidating the mechanism of molecular recognition. In this work, ^{1}H NOESY experiments were performed to investigate the conformational

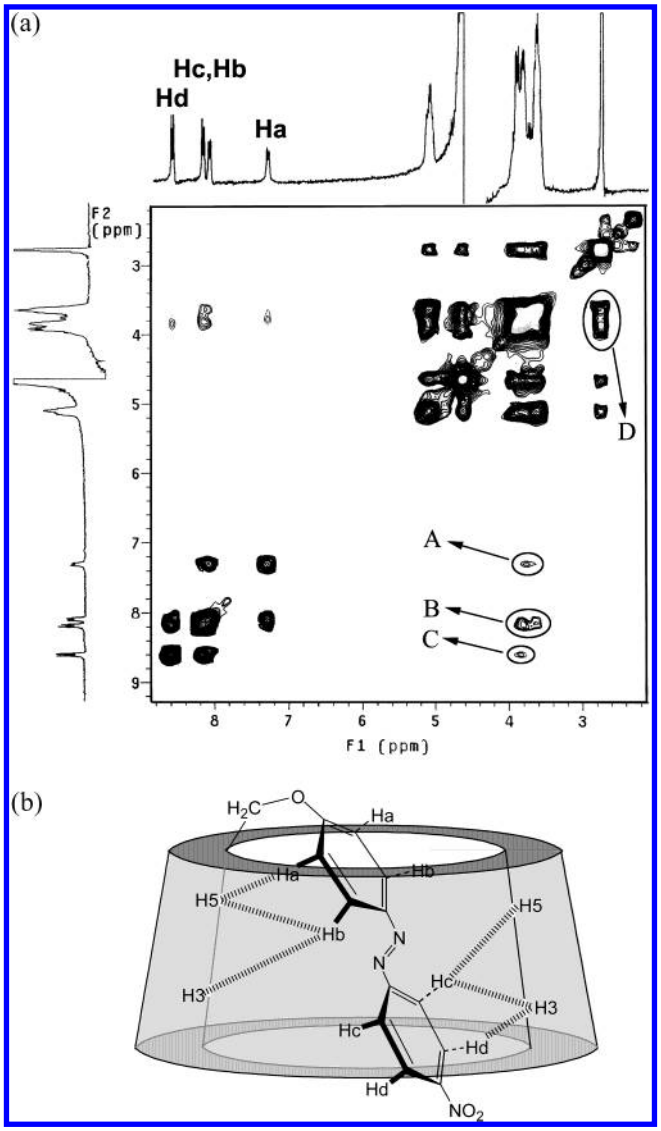


Figure 5. (a) ^{1}H NOESY spectrum of **2** (3.8×10^{-4} mol dm^{-3}) in 10% DMSO-d_6−D_2O solution at 25 °C with a mixing time of 600 ms. (b) Possible structure of **2**.

changes of **1** and **2** upon complexation with the representative guests 2-Ada and 1-Ada, respectively. As illustrated in Figure 7a, the NOESY spectrum of the mixture of **2** (3.7×10^{-4} mol dm^{-3}) and 1-Ada (4.8×10^{-4} mol dm^{-3}) in 10% DMSO-d_6−D_2O solution displays sophisticated NOE cross-peaks. Although the NOE correlations between the H3/H5 of β-CD and the protons in 1-Ada (peaks A) were not clear enough to estimate their relative intensity, we could declare unambiguously that the corresponding NOE correlations actually exist in the present case. Analogical phenomena were also observed between H3/H5 of β-CD and Hb and/or Hc (peaks B) and Ha protons (peaks C) of the azobenzene moiety. However, the clear correlations between Hb (and/or Hc) protons of azobenzene group in host **2** and H_a1 (and/or H_a3) protons in 1-Ada (peaks D) make us deduce reasonably the detailed orientation of the 1-Ada relative to the azobenzene moiety. It is interestingly noted that the clear correlation peaks E between Ha and Hd protons of the azobenzene group were also observed, suggesting that the two benzene rings at the different sides of the azo group must deflect from the original orientation. Moreover, upon addition of 1-Ada, we did not observe any absorption beyond 400 nm in the UV spectra of host **2** (the *cis*-configuration of azobenzene would exhibit an absorption peak around the scope),[19,31b] but only

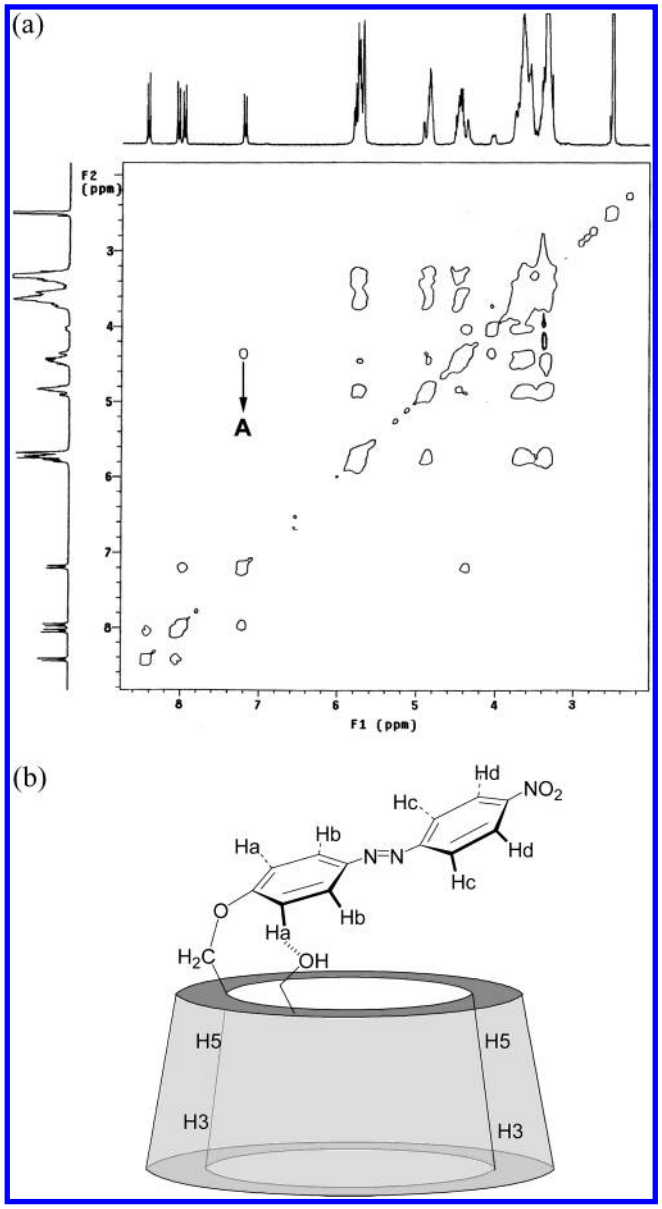


Figure 6. (a) ^{1}H NOESY spectrum of **2** (5.0×10^{-4} mol dm^{-3}) in DMSO-d_6 solution at 25 °C with a mixing time of 300 ms. (b) Possible structure of **2** in DMSO.

found a weak absorption at 275 nm, which indicates that the two benzene rings in **2** are noncoplanar. In addition, the molecular modeling study using the HyperChem Release 6.01 for the Windows Molecular Modeling System was also used to elucidate the plausible binding model for the complexation of host **2** with 1-Ada (Figure 7b). The results show that 1-Ada and the azobenzene group in **2** can be co-included in the β-CD's cavity, which is compatible with 2D NMR experimental results.

Interestingly, host **2** displays a binding model obviously different from that of 2-Ada, although 2-Ada possesses a fairly similar skeleton to 1-Ada. Figure 8a showed the NOESY spectrum of the mixture of **2** (4.0×10^{-4} mol dm^{-3}) and 2-Ada (4.8×10^{-4} mol dm^{-3}). The NOE cross-peaks between H3 and H5 of β-CD and protons (peaks A) of 2-Ada indicated that 2-Ada was included in the CD cavity. However, neither the correlations between β-CD's H3/H5 and the azobenzene protons nor those between 2-Ada's protons and azobenzene protons were found in Figure 8a. These results indicated that the azobenzene

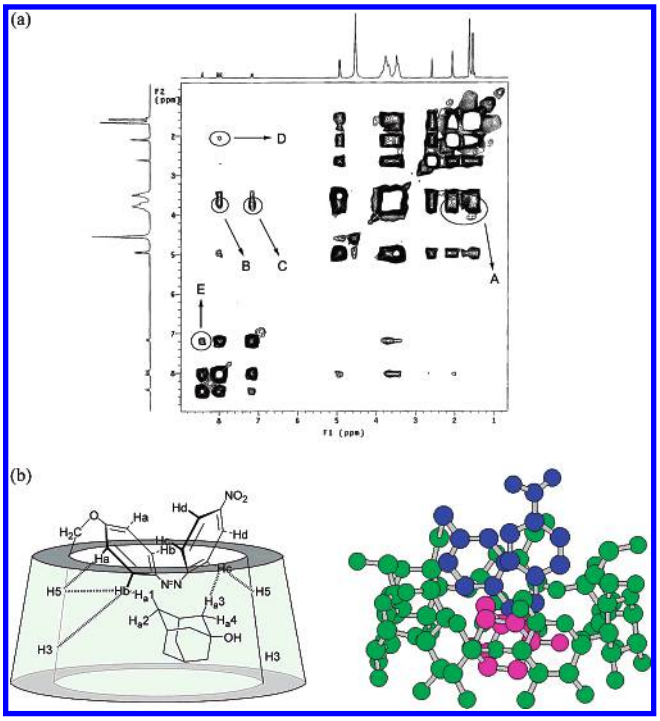


Figure 7. (a) ^{1}H NOESY spectrum of a mixture of **2** (3.7×10^{-4} mol dm^{-3}) and 1-Ada (4.8×10^{-4} mol dm^{-3}) in 10% DMSO-d_6−D_2O solution at 25 °C with a mixing time of 600 ms. (b) Plausible structures of the **2**/1-Ada complex.

moiety has been excluded from the CD cavity upon complexation with 2-Ada (Figure 8b).

As shown in Figure 9a, the NOESY spectrum of **1** with 1-Ada displayed clear NOE cross-peaks between the H5 (peaks A) of β-CD and the Ha, Hc, and Hd protons of the azobenzene moiety in host **1**, which indicates that the azobenzene moiety is shallowly included in the hydrophobic cavity of β-CD. The cross-peaks between the H3/H5 (peaks B) and the protons of 1-Ada showed that 1-Ada is also embedded in the β-CD cavity. On the other hand, the cross-peaks between the Hb, Hc, and Hd protons of the azobenzene group in **1** and protons of 1-Ada (peaks C), and between the Ha and Hd protons of the azobenzene group (peaks D) make us deduce reasonably the detailed orientation of the 1-Ada relative to the azobenzene moiety in the β-CD cavity, illustrated in Figure 9b. In the case of **1** with 2-Ada, the correlation between the H5 of β-CD and the H_b1 and H_b2 of 2-Ada (peaks A and C), as well as correlation between H3/H5 and H_b3 and/or H_b4 (peaks B) were observed (Figure 10a). However, neither the correlations between H3/H5 and the azobenzene protons nor those between 2-Ada's protons and azobenzene protons unequivocally indicate that the azobenzene moiety has been excluded from the β-CD cavity upon complexation with 2-Ada, as illustrated in Figure 10b. Therefore, these different conformations of β-CD derivatives upon guest inclusion may find their potential application for designing the guest-controlled switch in the molecular recognition, although the actual mechanism is still unclear now.

Spectral Titration. For a quantitative assessment of the inclusion complexation behavior of azobenzene modified CDs, UV−vis titrations of **1** and **2** with some optically selected guests were performed at 25 °C in 10% DMSO aqueous phosphate buffer solution (pH 7.20). In the titration experiments, the UV absorption maximum of the modified β-CDs **1** or **2** gradually decreased around 390 or 350 nm upon addition of varying amounts of aliphatic alcohol guests, accompanying the obvious blue shift (5 nm for **1** and 20 nm for **2**) of the absorption peak.

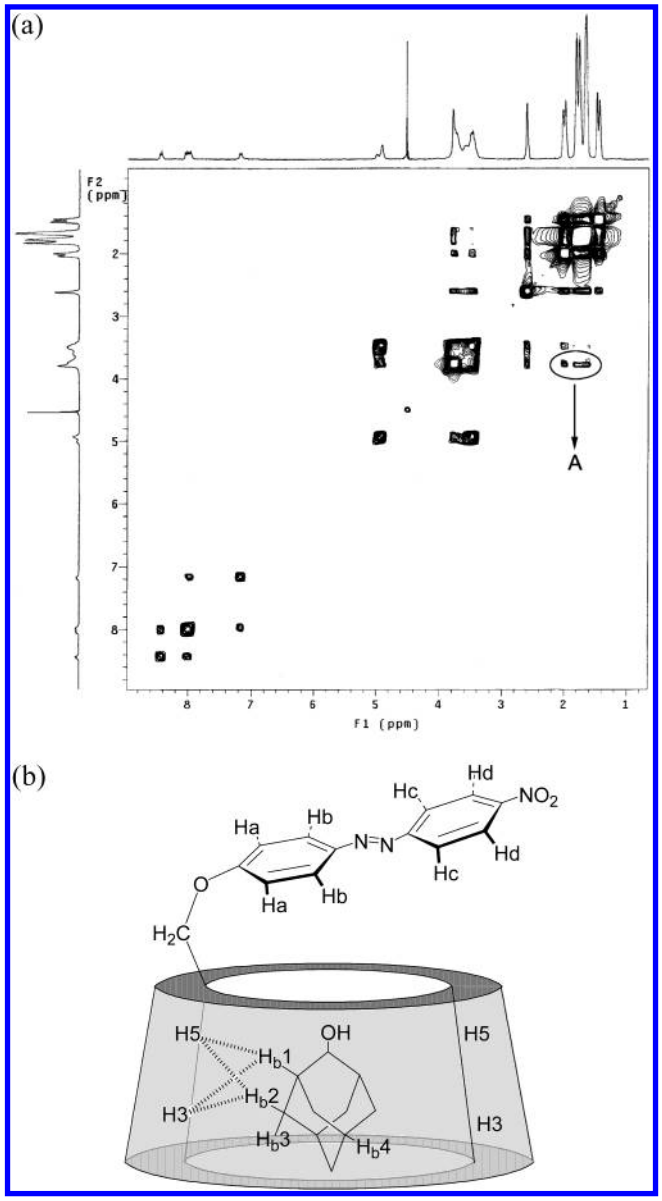


Figure 8. (a) ^{1}H NOESY spectrum of a mixture of **2** (4.0×10^{-4} mol dm^{-3}) and 2-Ada (4.8×10^{-4} mol dm^{-3}) in 10% DMSO-d_6−D_2O solution at 25 °C with a mixing time of 600 ms. (b) Plausible structures of the **2**/2-Ada complex.

These results indicated that the modified β-CDs form the inclusion complexes with guest molecules. Typical UV−vis spectral changes of host **2** upon addition of (−)-Bor are shown in Figure 11a.

Assuming the conventional 1:1 host/guest stoichiometry, the complexation of aliphatic alcohols (AA) with β-CD hosts (CD) can be expressed by

$$\mathrm{CD} + \mathrm{AA} \overset{K_S}{\rightleftharpoons} \mathrm{CD{\cdot}AA} \qquad (1)$$

The UV spectral changes (ΔA) upon addition of aliphatic alcohols are proportional to the concentration of complex formed and the difference of molar extinction coefficients between the free host and complexed one may be taken as the proportionality coefficient, i.e., $\Delta A = \Delta\epsilon[\mathrm{CD{\cdot}AA}]$. Thus, the complex stability constant (K_S) should be defined by using[36]

$$K_S = \frac{[\mathrm{CD{\cdot}AA}]}{[\mathrm{CD}][\mathrm{AA}]} = \frac{[\mathrm{CD{\cdot}AA}]}{([\mathrm{CD}]_0 - [\mathrm{CD{\cdot}AA}])([\mathrm{AA}]_i - [\mathrm{CD{\cdot}AA}])} = \frac{\Delta A/\Delta\epsilon}{([\mathrm{CD}]_0 - \Delta A/\Delta\epsilon)([\mathrm{AA}]_i - \Delta A/\Delta\epsilon)} \qquad (2)$$

After some manipulation, eq 2 yields

$$\frac{[\mathrm{CD}]_0[\mathrm{AA}]_i}{\Delta A} = \frac{1}{K_S\Delta\epsilon} + \frac{[\mathrm{AA}]_i}{\Delta\epsilon} \qquad (3)$$

where $[\mathrm{CD}]_0$ and $[\mathrm{AA}]_i$ denote the initial concentrations of β-CD host and aliphatic alcohols, respectively. Using the nonlinear least squares curve-fitting method, we obtained the complexation stability constant for each host−guest combination from eq 2. Figure 11b illustrates a typical plot of experimental and calculated data obtained by using eq 2, and no serious deviations are observed. A good correlation between the experimental and calculated result strongly indicates not only that the stability constants obtained are reliable but also that the host−guest complexation proceeds through the 1:1 stoichiometry. The stability constants (K_S) and Gibbs free energy changes ($-\Delta G°$) obtained for the complexation of β-CD derivatives (**1** and **2**) with aliphatic alcohols are compiled in Table 1. When repeated measurements were made, the K_S values were reproducible within an error of ±4%.

Binding Ability. Much research indicates that the host−guest size/shape matching and induced-fit interaction can dominate the stability of the complex formed between substituted β-CD and model substrates, leading to the stronger van der Waals and hydrophobic interactions, because these interactions are closely related to the distance and contacting surface area between the host and guest.[10,37] As can be seen from Table 1, the complex stability constants for the complexation of modified β-CDs with aliphatic alcohols are variable according to the guest structure, showing a sequence of binding ability:

2-Ada > 1-Ada, (−)-Bor > (+)-Bor, (+)-Men > (−)-Men

The adamantyl group of adamantanol has a diameter of ca. 7 Å, and strong binding affinities were shown for β-CD and its derivatives,[11,21b,21c,38−40] which is consistent with the near-perfect match between the cavity of β-CD and the guest diameter. One can note that the complexes of 2-Ada with both **1** and **2** are more stable than those of 1-Ada, indicating that the hosts can recognize the minor difference in the substituent position of guest molecules. Host **1** affords the highest stability constant up to 138 000 M^{-1} upon complexation with 2-Ada and the highest molecular selectivity up to 91 for the 2-Ada/(+)-Bor pair, which will be attributed to the strict size/shape fit between 2-Ada and the β-CD cavity. The high molecular selectivity for the 2-Ada/1-Ada pair ($K_s^{(2-\mathrm{Ada})}/K_s^{(1-\mathrm{Ada})} = 12$) by **1** should be due to the two different binding models of azobenzene modified β-CDs upon complexation with adamantanols. According to the results of 2D NMR experiments, the 2-Ada molecule in the cavity locates near the primary hydroxyl side of β-CDs **1** and **2**, and the azobenzene moieties of the two hosts were excluded from the β-CD cavity, which would make the hydrogen bonding interaction between the hydroxyl group of 2-Ada and the hydroxyl groups of the primary side of β-CD possible.[40a] In the presence of the 1-Ada molecule, the azobenzene moieties of **1** and **2** were embedded shallowly into the cavity, preventing hydrogen bonding between the hydroxyl group of 1-Ada and

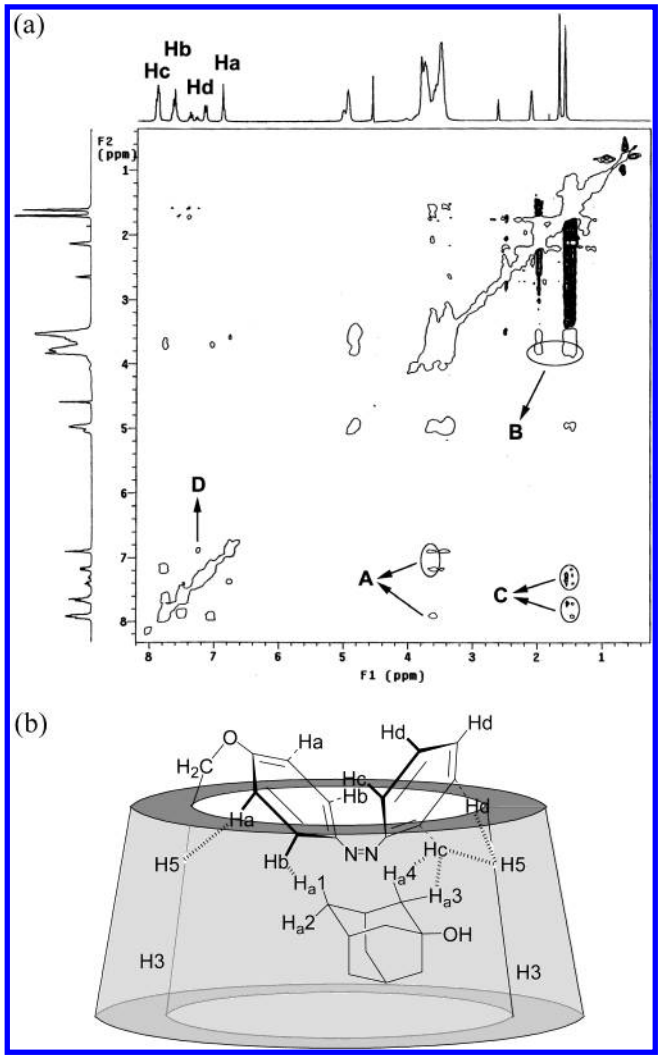


Figure 9. (a) ^{1}H NOESY spectrum of a mixture of **1** (6.2×10^{-4} mol dm^{-3}) and 1-Ada (6.5×10^{-4} mol dm^{-3}) in 10% DMSO-d_6−D_2O solution at 25 °C with a mixing time of 300 ms. (b) Plausible structures of the **1**/1-Ada complex.

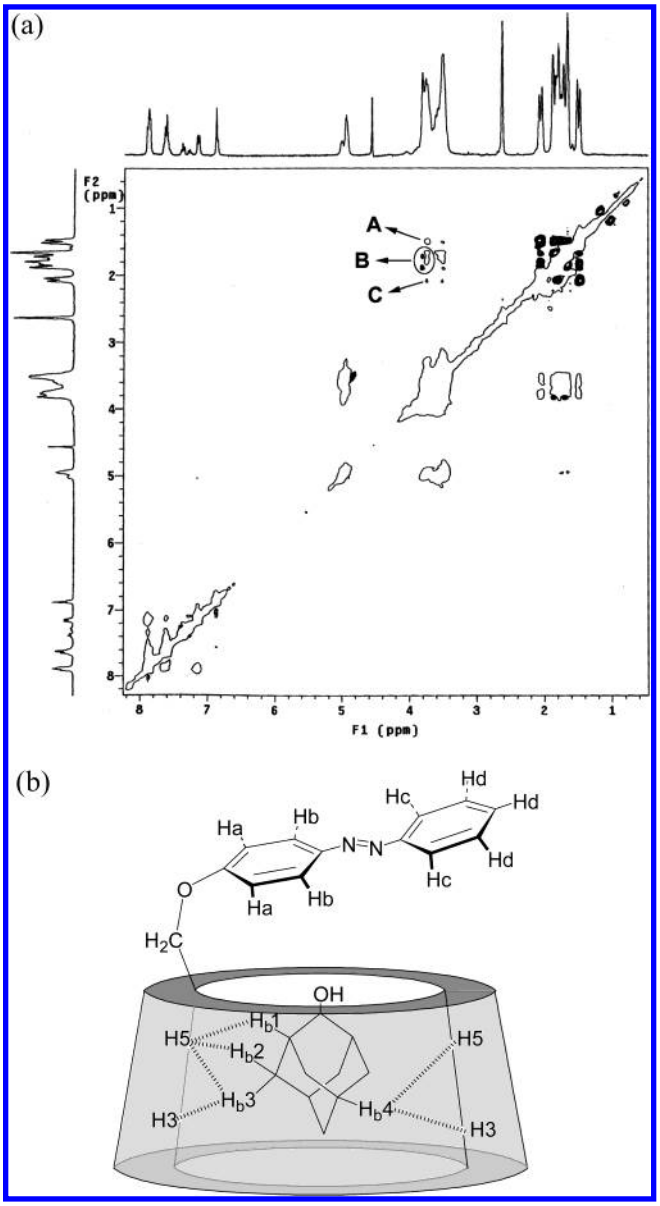


Figure 10. (a) ^{1}H NOESY spectrum of a mixture of **1** (6.5×10^{-4} mol dm^{-3}) and 2-Ada (7.0×10^{-4} mol dm^{-3}) in 10% DMSO-d_6−D_2O solution at 25 °C with a mixing time of 300 ms. (b) Plausible structures of the **1**/2-Ada complex.

the hydroxyl groups of the primary side of β-CD. Consequently, it is reasonable that the binding affinity of 2-Ada with **1** and **2** is greater than that of 1-Ada.

As compared with guest adamantanols, chiral borneols and menthols show relatively low binding ability and molecular selectivity upon inclusion complexation of hosts **1** and **2**. For example, hosts **1** and **2** give moderate enantioselectivity ($K_s^-/K_s^+ = 1.6-2.1$) for the (−)-Bor/(+)-Bor pair and the low enantioselectivity ($K_s^-/K_s^+ = 1.1-1.2$) for the (+)-Men/(−)-Men pair. It is inferred that the modification at the rim affects the chiral microenvironment of the β-CD cavity and the self-including substituent contributes to the fixation of the included guest molecules, behaving as a spacer.[10a,41] On the other hand, from the data listed in Table 1, we can see that the complexes of **1** with guests are more stable than those of **2**. This may be explained as host **2**, possessing a hydrophilic nitro group, being more hydrophilic and sterically hindered than **1**, which jointly reduces the hydrophobic interaction and extent of desolvation upon complexation.

Conclusions

In summary, two novel azobenzene modified β-CD derivatives **1** and **2** were synthesized in high yields, and their original conformations and molecular binding models were investigated by using spectroscopic techniques. Studies on binding models of **1** and **2** in the presence of 1-Ada and 2-Ada indicate that the size/shape matching, hydrogen binding, and induced-fit mechanisms play a crucial role in the molecular recognition process of the azobenzene modified β-CDs. Therefore, the azobenzene moiety attached to β-CD can not only act as a spectral probe but also dominate the molecular/chiral and size/shape recognition of guests.

Experimental Section

Materials. All aliphatic alcohols, i.e., 1-adamantanol (1-Ada), 2-adamantanol (2-Ada), (+)-borneol [(+)-Bor], (−)-borneol [(−)-Bor], (+)-menthol [(+)-Men], and (−)-menthol [(−)-Men] were used as received. 4-(Phenylazo)phenol (PAP) and 4-((4-nitrophenyl)azo)phenol (NPAP) were commercially available and used without further purification. β-CD of reagent grade was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use. Mono[6-*O*-(tolyl-*p*-sulfonyl)]-β-cyclodextrin (6-OTs-β-CD) was prepared by the reaction of

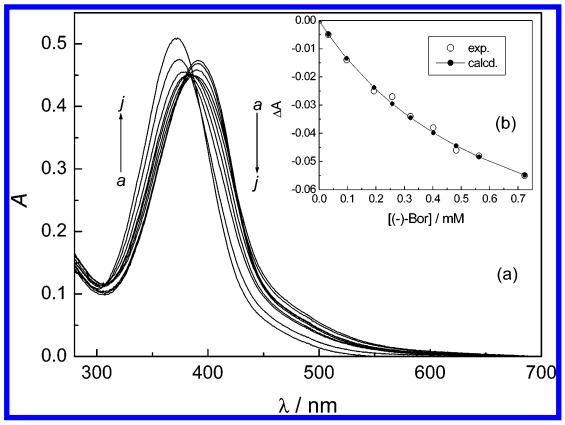


Figure 11. (a) UV−vis spectra of **2** (1.6×10^{-5} mol dm^{-3}) in the presence of (−)-Bor (0, 0.3, 1.0, 1.9, 2.6, 3.2, 4.0, 4.8, 5.6, and 7.2×10^{-4} mol dm^{-3} from (a) to (j). (b) Curve-fitting analyses for the complexation of host **2** with (−)-Bor in 10% DMSO phosphate buffer aqueous solution (pH 7.20) at 25 °C, λ_{max} 390.5 nm.

TABLE 1: Complex Stability Constant (K_S) and Gibbs Free Energy Change ($-\Delta G°$) for the Inclusion Complexation of Azobenzene Modified β-CDs (1 and 2) with Some Aliphatic Alcohols in 10% DMSO Phosphate Buffer Aqueous Solution (pH 7.20) at 25 °C

host	guest	K_S/M^{-1}	log K_S	$-\Delta G°$/kJ mol^{-1}
1	2-Ada	138 000	5.14	29.3
	1-Ada	11 885	4.07	23.2
	(+)-Bor	1510	3.18	18.1
	(−)-Bor	2420	3.38	19.3
	(+)-Men	2870	3.46	19.7
	(−)-Men	2630	3.42	19.5
2	2-Ada	17550	4.24	24.2
	1-Ada	3130	3.49	20.0
	(+)-Bor	769	2.89	16.5
	(−)-Bor	1580	3.20	18.3
	(+)-Men	2350	3.37	19.2
	(−)-Men	1980	3.30	18.8

p-toluenesulfonyl chloride with β-CD in alkaline aqueous solution.[42] *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were dried over calcium hydride for 2 days and then distilled under a reduced pressure prior to use.

Instruments. Circular dichroism and UV−vis spectra were recorded in a conventional quartz cell (light path 10 mm) on a JASCO J-715S spectropolarimeter and a Shimadzu UV-2401PC spectrophotometer equipped with a PTC-348WI temperature controller to keep the temperature at 25 °C. Elemental analysis was performed on a Perkin-Elmer 2400C instrument. NMR spectra were performed on a Varian Mercury VX300 spectrometer.

Mono{6-*O*-[4-(phenylazo)phenyl]}-β-cyclodextrin (1). To a solution of DMF (30 mL) containing 2.0 g of 6-OTs-β-CD and 0.214 g of K_2CO_3 was added 0.307 g of PAP; the resultant mixture was stirred at 80−90 °C for 3 days under nitrogen. The solution was poured into 300 mL of acetone, and the precipitate was collected by filtration to give a yellow powder. The crude product was washed with water (100 mL) and dried in vacuo to give a pure sample (yield 78%). UV−vis (10% DMSO aqueous solution), λ_{max}/nm (log ϵ): 348.5 nm (4.27). ^{1}H NMR (300 MHz, DMSO-d_6, TMS, ppm): δ 3.2−3.9 (m, 42H), 4.0−4.6 (m), 4.7−4.9 (m, 7H), 5.5−5.8 (m), 7.1−7.2 (m, 2H), 7.5−7.6 (m, 3H), 7.8−7.9 (m, 4H). FT-IR (KBr, cm^{-1}): ν 3343, 2932, 2909, 2836, 1600, 1585, 1501, 1418, 1365, 1330, 1300, 1252, 1154, 1079, 1032, 944, 840, 759, 704, 581. Anal. Calcd for $C_{54}H_{78}O_{35}N_2 \cdot 3H_2O$ (1369.2): C, 47.37; H, 6.18; N, 2.05. Found: C, 47.65; H, 6.47; N, 2.67.

Mono{6-*O*-[4-((4-nitrophenyl)azo)phenyl]}-β-cyclodextrin (2). 2 was prepared as a deep yellow in 74% yield from NPAP and 6-OTs-β-CD according to a similar procedure described above. UV−vis (10% DMSO aqueous solution), λ_{max}/nm (log ϵ): 390.5 nm (4.35). ^{1}H NMR (300 MHz, DMSO-d_6, TMS, ppm): δ 3.3−3.9 (m, 42H), 4.0−4.6 (m), 4.8−4.9 (m, 7H), 5.6−5.8 (m), 7.2−7.3 (m, 2H), 7.9−8.0 (m, 2H), 8.0−8.1 (m, 2H), 8.4−8.5 (m, 2H). FT-IR (KBr, cm^{-1}): ν 3343, 2936, 2904, 2833, 1600, 1525, 1501, 1455, 1421, 1344, 1255, 1153, 1079, 1031, 944, 861, 755, 705, 580. Anal. Calcd for $C_{54}H_{77}O_{37}N_3 \cdot 5H_2O$ (1450.3): C, 44.72; H, 6.05; N, 2.90. Found: C, 44.58; H, 6.46; N, 2.82.

Acknowledgment. This work was supported by the NNSFC (No. 90306009 and 20272028), which are gratefully acknowledged.

References and Notes

(1) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803−822.
(2) Breslow, R. *Science* **1982**, *218*, 532−537.
(3) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344−362.
(4) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875−1917.
(5) Huskens, J.; Deij, M. A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4467−4471.
(6) (a) Franchi, P.; Lucarini, M.; Pedulli, G. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1842−1845. (b) Lucarini, M.; Mezzina, E.; Pedulli, G. F. *Eur. J. Org. Chem.* **2000**, 3927−3930.
(7) Brewster, R. E.; Teresa, B. F.; Schuh, M. D. *J. Phys. Chem. A* **2003**, *107*, 10521−10526.
(8) (a) Yamauchi, A.; Hayashita, T.; Kato, A.; Nishizawa, S.; Watanabe, M.; Teramae, N. *Anal. Chem.* **2000**, *72*, 5841−5846. (b) Tong, A.-J.; Yamauchi, A.; Hayashita, T.; Zhang, Z.-Y.; Smith, B. D.; Teramae, N. *Anal. Chem.* **2001**, *73*, 1530−1536. (c) Yamauchi, A.; Hayashita, T.; Nishizawa, S.; Watanabe, M.; Teramae. *J. Am. Chem. Soc.* **1999**, *121*, 2319−2320. (d) Hayashita, T.; Qing, D.; Minagawa, M.; Lee, J. C.; Ku, C. H.; Teramae, N. *Chem. Commun.* **2003**, 2160−2161.
(9) Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417−1474.
(10) (a) Liu, Y.; Song, Y.; Wang, H.; Zhang, H.-Y.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 3687−3690. (b) Liu, Y.; Chen, G.-S.; Li, L.; Zhang, H.-Y.; Cao, D.-X.; Yuan, Y.-J. *J. Med. Chem.* **2003**, *46*, 4634−4637. (c) Liu, Y.; Han, B.-H.; Chen, Y.-T. *J. Phys. Chem. B* **2002**, *106*, 4678−4687.
(11) Hamasaki, K.; Ikeda, H.; Nakamura, A.; Ueno, A.; Toda, F.; Suzuki, I.; Osa, T. *J. Am. Chem. Soc.* **1993**, *115*, 5035−5040.
(12) (a) Breslow, R.; Yang, Z.; Ching, R.; Trojandt, G.; Odobel, F. *J. Am. Chem. Soc.* **1998**, *120*, 3536−3537. (b) Leung, D. K.; Yang, Z.; Breslow, R. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 5050−5053.
(13) West, L. C.; Wyness, O.; May, B. L.; Clements, P.; Lincoln, S. F.; Easton, C. J. *Org. Biomol. Chem.* **2003**, *1*, 887−894.
(14) de Jong, M. R.; Engbersen, J. F. J.; Huskens, J.; Reinhoudt, D. N. *Chem. Eur. J.* **2000**, *6*, 4034−4040.
(15) Anderson, S.; Claridge, T. D. W.; Anderson, H. L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1310−1313.
(16) Yoshida, N. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2249−2256.
(17) Sanchez, A. M.; de Rossi, R. H. *J. Org. Chem.* **1996**, *61*, 3446−3451.
(18) Hirai, H.; Toshima, N.; Uenoyama, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1156−1164.
(19) Liu, W.; Bian, S.; Li, L.; Samuelson, L.; Kumar, J.; Tripathy, S. *Chem. Mater.* **2000**, *12*, 1577−1584.
(20) Takei, M.; Yui, H.; Hirose, Y.; Sawada, T. *J. Phys. Chem. A* **2001**, *105*, 11395−11399.
(21) (a) Ueno, A.; Kuwabara, T.; Nakamura, A.; Toda, F. *Nature* **1992**, *356*, 136−137. (b) Aoyagi, T.; Nakamura, A.; Ikeda, H.; Ikeda, T.; Mihara, H.; Ueno, A. *Anal. Chem.* **1997**, *69*, 659−663. (c) Kuwabara, T.; Nakajima, H.; Nanasawa, M.; Ueno, A. *Anal. Chem.* **1999**, *71*, 2844−2849. (d) Kuwabara, T.; Nakamura, A.; Ueno, A.; Toda, F. *J. Phys. Chem.* **1994**, *98*, 6297−6303.
(22) (a) Zhang, X.; Nau, W. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 544−547. (b) Nau, W. M.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 8022−8032. (c) Mayer, B.; Zhang, X.; Nau, W. M.; Marconi, G. *J. Am. Chem. Soc.* **2001**, *123*, 5240−5248. (d) Zhang, X.; Gramlich, G.; Wang, X.; Nau, W. M. *J. Am. Chem. Soc.* **2002**, *124*, 254−263.
(23) Liu, Y.; Yang, Y.-W.; Cao, R.; Song, S.-H.; Zhang, H.-Y.; Wang, L.-H. *J. Phys. Chem. B* **2003**, *107*, 14130−14139.
(24) Fujimoto, T.; Sakata, S.; Kaneda, T. *Chem. Lett.* **2000**, 764−675.
(25) Hoshino, T.; Miyauchi, M.; Kawaguchi, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* **2000**, *122*, 9876−9877.

(26) (a) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *J. Am. Chem. Soc.* **1988**, *110*, 4323−4328. (b) Ikeda, H.; Matsuhisa, A.; Ueno, A. *Chem. Eur. J.* **2003**, *9*, 4907−4910. (c) Ikeda, H.; Nakamura, M.; Ise, N.; Oguma, N.; Nakamura, A.; Ikeda, T.; Toda, F.; Ueno, A. *J. Am. Chem. Soc.* **1996**, *118*, 10980−10988.

(27) (a) Wang, Y.-H.; Zhang, H.-M.; Liu, L.; Liang, Z.-X.; Guo, Q.-X.; Tung, C.-H.; Inoue, Y.; Liu, Y.-C. *J. Org. Chem.* **2002**, *67*, 2429−2434. (b) Wang, Y.-H.; Zhu, M.-Z.; Ding, X.-Y.; Ye, J.-P.; Liu, L.; Guo, Q.-X. *J. Phys. Chem. B* **2003**, *107*, 14087−14093.

(28) Harata, K.; Uedaira, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 375−378.

(29) Kodaka, M. *J. Phys. Chem. A* **1998**, *102*, 8101−8103.

(30) Kajtár, M.; Horvath-Toro, C.; Kuthi, E.; Szejtli, J. *Acta Chim. Acad. Sci. Hung.* **1982**, *110*, 327−355.

(31) (a) Tran, C. F.; Fendler, J. H. *J. Phys. Chem.* **1984**, *88*, 2167−2173. (b) Bortolus, P.; Monti, S. *J. Phys. Chem.* **1987**, *91*, 5046−5050.

(32) Siegel, B.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 6869−6870.

(33) Eftink, M. R.; Harrison, J. C. *Bioorg. Chem.* **1981**, *10*, 388−398.

(34) Fujita, K.; Ueda, T.; Imoto, T.; Tabushi, I.; Toh, N.; Koga, T. *Bioorg. Chem*. **1982**, *11*, 72−84.

(35) Schneider, H.-J.; Hacket, F.; Rüdiger, V.; Ikeda, H. *Chem. Rev.* **1998**, *98*, 1755−1785.

(36) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703−2707.

(37) (a) Liu, Y.; Han, B.-H.; Li, B.; Zhang, Y.-M.; Zhao, P.; Chen, R.-T.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1998**, *63*, 1444−1454. (b) Liu, Y.; Li, B.; You, C.-C.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2001**, *66*, 225−232. (c) Liu, Y.; You, C.-C.; Li, B. *Chem. Eur. J.* **2001**, *7*, 1281−1288.

(38) Chung, W.-S.; Turro, N. J.; Silver, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1990**, *112*, 1202−1205.

(39) Tanabe, T.; Touma, K.; Hamasaki, K.; Ueno, A. *Anal. Chem.* **2001**, *73*, 1877−1880.

(40) (a) Liu, Y.; You, C.-C.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 3630−3634. (b) Liu, Y.; Han, B.-H.; Sun, S.-X.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 1487−1493.

(41) Inoue, Y.; Yamamoto, K.; Wada, T.; Everitt, S.; Gao, X.-M.; Hou, Z.-J.; Tong, L.-H.; Jiang, S.-K.; Wu, H.-M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1807−1816.

(42) Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860−3868.