Accounts

Molecular Recognition Studies on Modified Cyclodextrins

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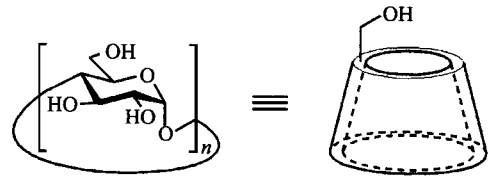
This account describes our research progress in recent years in the areas of the molecular recognition studies on modified cyclodextrins, including positively charged cyclodextrins, cyclodextrin derivatives with hydrophobic substituent, and dimeric cyclodextrins. Calorimetric titration and various spectrometric techniques were employed to determine the complex stability constants, as well as the thermodynamic parameters, for their inclusion complexation with diverse guest molecules. The results obtained have been discussed from the viewpoint of size/shape-matching, induced-fit, geometric compensation, and multiple recognition. Thermodynamically, the compensatory relationship between ΔH and $T\Delta S$ was found to be exhibited in the inclusion complexation of modified cyclodextrin.

Keywords Modified cyclodextrins, molecular recognition, selectivities, cyclodextrin dimers, thermodynamic parameters

Cyclodextrins are truncated cone-shaped cyclic oligosaccharides composed of six or more α-*D*-glucopyranose units, whose exterior, bristling with hydroxy groups, is fairly polar, whereas the interior of the cavity is non-polar. These structural features enable them to accommodate diverse hydrophobic organic and biological molecules to form host-guest or supramolecular complexes in aqueous solution. Owing to this fascinating property, cyclodextrin has been extensively employed as molecular receptors, enzyme mimics, chemical sensors, and drug carriers in science and technology.[1] Cyclodextrins have been modified for a variety of reasons ranging from achieving solubility in a desired solvent to investigating the mechanisms of enzyme-catalyzed reactions. In the past several years, our group has designed and synthesized a series of modified cyclodextrins to explore their molecular recognition ability and inclusion mechanism. We will herein review the molecular recognition studies on modified cyclodextrins to give insight into the molecular recognition of cyclodextrin-based artificial receptors. An excellent review focusing the molecular recognition of native cyclodextrins has been well documented by Connors.[2]

Scheme 1



n=6, α-CD
n=7, β-CD
n=8, γ-CD

Positively charged cyclodextrins

It seems that the simplest positively charged cyclodextrins are the copper(II) complexes of cyclodextrins in alkaline aqueous solution, which were firstly prepared by Matsui *et al*. and named as binuclear copper(II) complexes with cyclodextrins.[3] We have investigated the chiral discrimination of some aromatic *L*/*D*-α-amino acids by using binuclear copper(II) complexes with cyclodextrins **H1** (Cu_2-α-CD) and **H2** (Cu_2-β-CD) as receptors.[4] The results showed that the binuclear copper(II) complexes afford very strong molecular bind-

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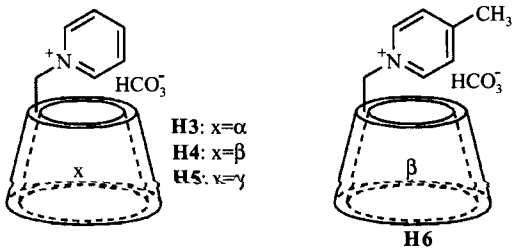
ing ability ($K_S = 2.4 \times 10^4$ L/mol— 1.1×10^5 L/mol), though native cyclodextrins lose their original molecular binding ability in high basic environment such as 1 mol/L NaOH aqueous solution, indicating that the electrostatic interaction between host and guest is now the driving force in the complexation. More interestingly, native cyclodextrins prefer to complex with *L*-enantiomers, while the binuclear copper (II) complexes preferably complex with *D*-enantiomers. This reversed chiral selectivity should be ascribed to the cavity being changed into ellipsoidal form upon complexation with copper(II) ion.

Furthermore, the inclusion complexation of some 4-substituted phenols with binuclear copper(II) complexes with cyclodextrins were studied by spectrophotometric titrations.[5] The results obtained indicate that most model substrates may form much more stable complexes with **H2** than with **H1**. This phenomenon may be interpreted by the size/shape-matching concept since the copper(II) bridge partly occupies the cyclodextrin cavity and the effective cavity of **H2** is therefore suitable to accommodate phenyl residue. Nitrate substituted phenol, however, affords more stable complex with **H1** than with **H2**. Hydrogen bonding interaction is considered as a major driving force as well as electrostatic interaction.

Scheme 2

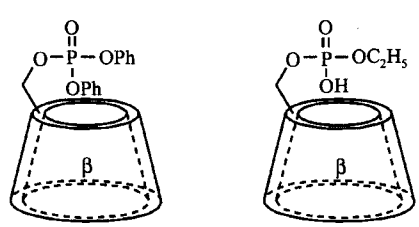


H6

Pyridinio and picolinio groups were introduced onto the primary side of cyclodextrin. The inclusion complexation of these positively charged cyclodextrins (**H3**—**H6**) with various guests, such as amino acids,[6-8] and aliphatic alcohols,[9] were studied by using spectrophotometric and spectropolarimetric titrations. In near neutral buffer solution (pH = 7.20), the complex stability constants of most small size amino acids with hosts **H3**-**H4** are generally in the order **H3** > **H4** > **H5**. On the other hand, among the three pyridinio modified cyclodextrins, **H4** may form the most stable complex ($K_S = 2.1 \times 10^5$ L/mol with isoleucine which possesses a longer hydrophobic chain, indicating that size-fitting between the host and the guest plays a crucial role in molecular recognition. The complex stability constants of amino acids with **H3** are larger than those with parent α-CD by factors from 20 to 50. The stability constants for the complexation of most amino acids with **H3** in acidic aqueous solution (0.1 mol/L H_2SO_4) are slightly higher than those obtained in phosphate buffer solution (pH 7.20).[8] A reasonable explanation may be that an acidic solution can stabilize a positively charged pyridinio moiety and enhance the electrostatic interaction. In the case of aliphatic alcohols as guests, however, positively charged pyridinio group introduced in **H4** and **H6** does not enhance the original binding ability of β-CD, and therefore the electrostatic interaction is not likely to be the major driving force in the inclusion complexation.[9] Pyridinio-modified cyclodextrins (**H3**—**H5**) can recognize not only differences between the molecular size and shape of amino acids, but also the chirality of the *L*- and *D*-amino acid isomer, giving fairly good enantiomer selectivity.[7] The enantioselectivity of **H3** for *L*/*D*-serine is 1.7 in phosphate buffer solution (pH 7.2), while this value is up to 10.3 in acidic solution (0.1 mol/L H_2SO_4).[8]

Two phosphorus-modified β-cyclodextrins **H7** and **H8** have been synthesized, and their inclusion complexation with some aliphatic amino acids were also studied in aqueous buffer (pH = 7.20).[10] The phosphate group in the host compounds might be expected to enhance complex stability through the electrostatic interaction between the phosphorus possessing a positive center lacking an electron and the amino acid anion accommodated in the cyclodextrin cavity. Since the phosphorus center of **H8** is less positive than that of **H7**, the stability constants for the inclusion complexation of most amino acids with **H7** are higher than those with **H8**. In contrast to the pyridinio-modified cyclodextrins, **H7** and **H8** pre-

Scheme 3



H7 H8

ferably include *D*-amino acids, and the highest enantioselectivity of 3.6 is observed for the complexation of **H7** with *D*/*L*-serine. One possible explanation is that the relative stability is governed by the position of the hydrophobic side chain of amino acid relative to the cyclodextrin cavity, so that inclusion may be allowed only for *D*-enantiomer and not for *L*-enantiomer.

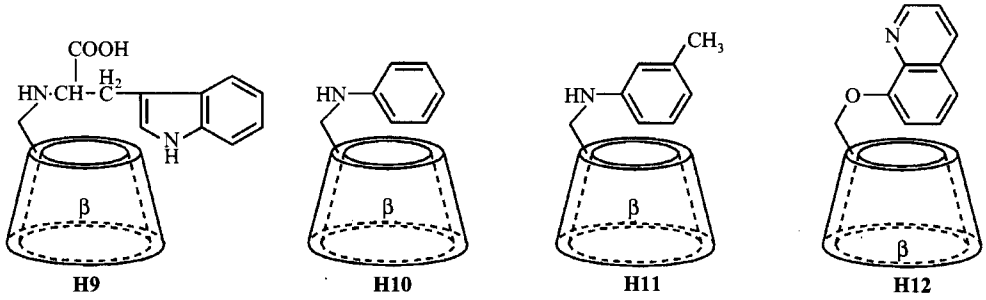
Recently, we have studied the inclusion complexation of diethylenetriamino and triethylenetetraamino mono-modified β-cyclodextrins and their copper (II) complexes with some naphthalenesulfonate derivatives by using spectroflurimetric titration.[11] The results obtained indicate that the electrostatic interaction between the copper cation center in host and the sulfonate anion in the guest significantly enhances the complex stability. The original molecular selectivity of the polyamino cylodextrins without copper(II) was not effectively reserved or enhanced, though there is an additional electrostatic binding site, indicating that the expected multiple recognition is not clear.

Cyclodextrin derivatives with hydrophobic substituents

The chromophoric groups are usually attached to the rim of cyclodextrin, which may suffer substantial conformational change upon inclusion complexation with guest molecule, then can act as spectral probes to determine complex stability constants through spectrometries, such as Ultraviolet-visible, fluorescence, and circular dichroism spectra.[12] In this context, we have prepared some mono-modified cyclodextrins bearing hydrophobic aromatic substituents and studied their molecular recognition ability and inclusion mechanism carefully.

As is well known, the molecular recognition procedure of chemically modified cyclodextrins often takes place in aqueous solution. Therefore, it is essential to elucidate the conformation of chemically modified cyclodextrins in aqueous solution, which is very important for understanding the mechanism of both molecular recognition and enzyme catalysis.[13] In aqueous solution, cyclodextrin's hydrophobic cavity may potentially self-recognize its appendant hydrophobic substituent to form an intramolecular complex. The fluorescence decay profiles obtained with aqueous solution of *L*-tryptophan modified β-cyclodextrin **H9** could be analyzed by a two exponential function and gave two lifetime values of 8.6 ns and 2.8 ns, respectively, indicating that there is a self-inclusion/exclusion equilibrium for the fluorophoric substituent introduced to β-cyclodextrin.[14] In the case of anilino-modified β-cyclodextrin **H10** or toluidino-modified β-cyclodextrin **H11**, however, only one lifetime of 2.8 ns for **H10** or 2.2 ns for **H11** might be observed, indicating that there is only one component in the aqueous solution.[15] It is concluded that the phenyl group in **H10** and **H11** is located outside the cavity and the chromophore plane is aligned perpendicular to the cavity axis on the basis of circular dichroism spectral results. The structure and detailed conformation of **H11** in D_2O were further deduced from the 1-D and 2-D NMR spectra, including TOCSY, COSY, and ROESY techniques. As shown in Fig. 1, the toluidino moiety in **H11** is deeply embeded into the cyclodextrin cavtiy.[15] Then the one lifetime for **H10** and **H11** would indicate the substituents are deeply self-included into the parent cavities.

Scheme 4



H9 **H10** **H11** **H12**

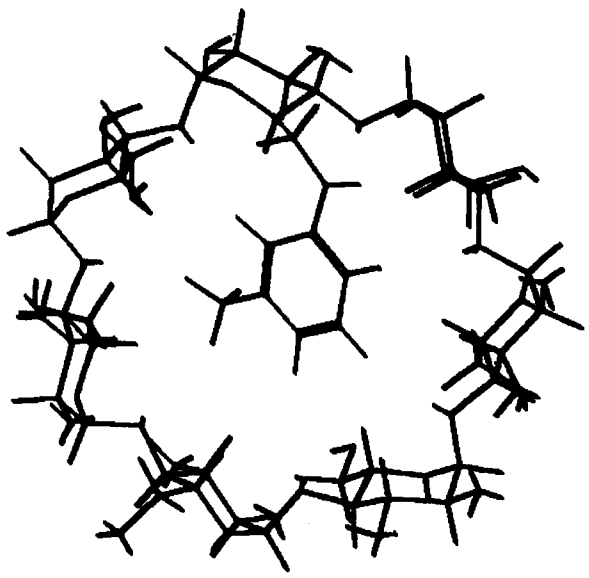


Fig. 1 Conformation of **H11** in aqueous solution deduced from 2D-NMR spectra.

Interestingly, X-ray crystallographic analysis revealed that the anilino groups of **H10** are consecutively included intermolecularly into the adjacent cyclodextrin cavities in the crystal, thus giving rise to a consolidated column, located on a 2_1-screw axis (Fig. 2).[16]

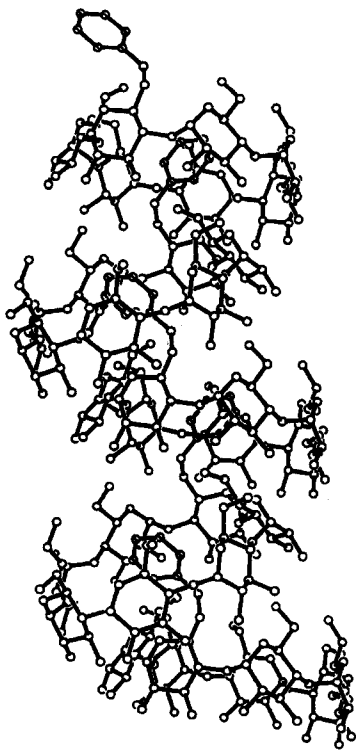


Fig. 2 High-ordered screw structure of **H10** in crystal.

Upon accommodation with guest molecules, the self-included substituent is expected to be driven out of the cavity. The spectral data support this expectation. The relative quantum yield of the longer lifetime component decreased, while that of the shorter lifetime component increased, when guest molecules were added into the fluorescent β-cyclodextrins **H9-H11**. At the same time, the intensities of fluorescence and circular dichroism of the substituted cyclodextrins generally decreased. Therefore, the inclusion complexation procedure of these chromophoric cyclodextrins may be visualized as Fig. 3 (A). If the cavity size is too large relative to the guest, the self-inclusion substituent may penetrate into the cavity more deeply upon guest binding, just as shown in Fig. 3(B).[17] Consequently, we may demonstrate that the hydrophobic substituent may adjust the effective space of the cavity and the molecular recognition procedure is similar with the induced-fit mechanism of enzyme-substrate interaction.

The inclusion complexation behavior of fluorescent cyclodextrins **H9**, **H11** and **H12** has been investigated with acyclic and cyclic alcohols. Fig. 4 illustrates the profile of the stability constants for **H9**,[14] **H11**,[15] and **H12**[9] with some acyclic, cyclic, bicyclic, and tricyclic alcoholic guests. It is noted that although the stability constant (K_S) for each guest differs appreciably from host to host, the profiles of K_S are quite similar to each other, at least for the alcohols employed. This observation is normal, since all of the hosts have a β-cyclodextrin cavity of the same size. However, the stability constant for each guest varies by more than 1 order of magnitude, for which the different structure and hydrophobicity of the substituents introduced are jointly responsible. On the other hand, it is also noted from Fig. 4 that the guest's shape and size appear to be the predominant factors that determine the complex stability upon complexation of such simple guests as alcohols with cyclodextrins. Since the rigid spherical skeleton of adamantane is best size/shape-fitted to the β-cyclodextrin cavity,[18] it is not surprising to observe that **H9**, **H11**, and **H12** give the largest K_S for 1-adamantanol. It is clearly that the order of complex stability is determined mostly by the rigid molecular structure. Thus, among C_{10} guests, tricyclic adamantanol and bicyclic borneol, both having rigid and bulky skeletons, form the most stable complexes, while the flexible nerol and geraniol afford the least stable complex.

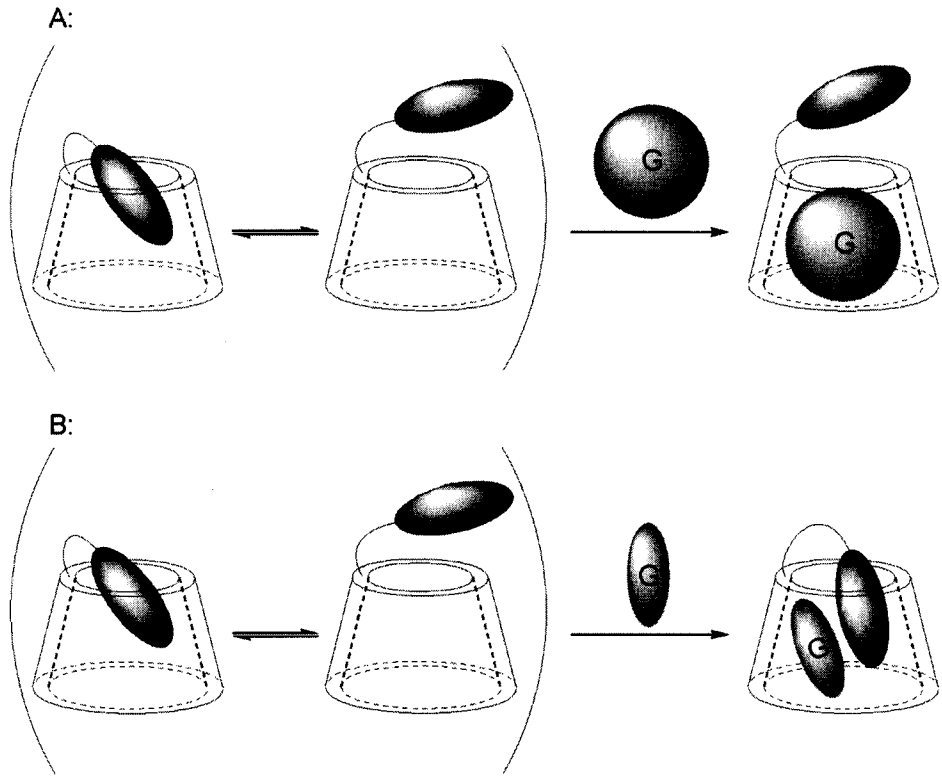


Fig. 3 Conformational change of self-included cyclodextrin derivatives in the absence and presence of guest molecules.

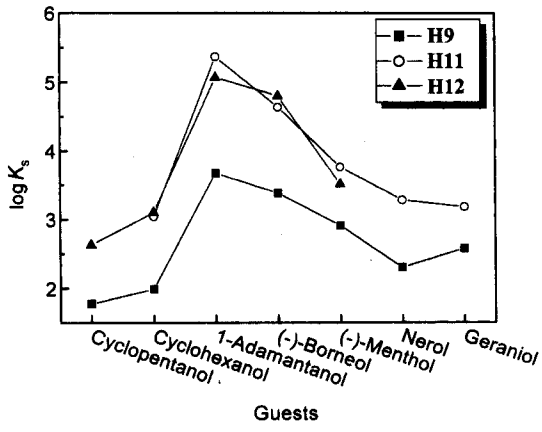
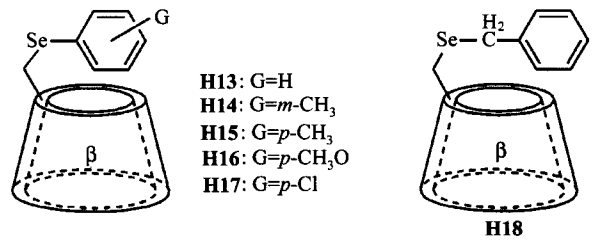


Fig. 4 Comparison of the complexation stability constants of chemically modified β-cylodextrins **H9**, **H11** and **H12**.

In order to further investigate the effect of host substituent upon inclusion complexation of model substrates with modified cyclodextrins, a series of structurally related aromatic organoselenium-modified β-cyclodextrin have been synthesized and used as hosts to recognize aliphatic alcoholic guests.[19-23] One important reason for choosing organoselenium-modified cyclodextrins as hosts is that selenium, possessing a larger atomic radius and lower electronegativity than carbon, can lead to a C—Se bond which is longer and more flexible than a C—C bond.

Scheme 5



In Fig. 5, the stability constants ($\log K_S$) for the complexation of organoseleno β-cyclodextrins **H3**—**H17** with cyclopentanol and cyclohexanol are plotted as a function of the Hammett's σ value of the host's substituent. As can be seen from Fig. 5, the complex stability constant gradually increases with increasing σ value, indicating that the electron density of substituent affects the complex stability. As we have pointed out above, the hydrophobic substituent of cyclodextrin

derivative is usually self-included into the cavity to form an intramolecular inclusion complex, and will be driven out upon guest binding. In summary, the stability of the original intramolecular inclusion complex affects the competitive intermolecular inclusion of alkanol guests, and therefore the introduction of a strongly self-including substituent to cyclodextrin discourages the subsequent intermolecular guest inclusion.

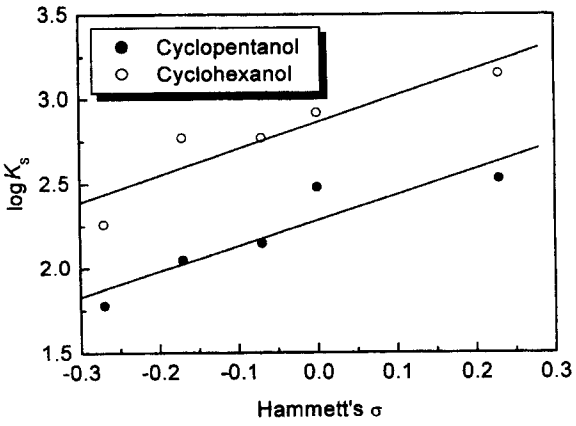


Fig. 5 Stability constants ($\log K_S$) of the host-guest complexes plotted as a function of the Hammett's σ value of the host (**H13**—**H17**)'s substituent.

The complex stabilities ($-\Delta G$) for the complexation of acylic and cyclic alcohols with arylseleno β-cyclodextrins increase practically linearly with increasing the number of methylenes (N_C) in the guest molecule, which means that van der Waals and hydrophobic forces mainly contribute to the inclusion complexation, since these two weak interactions are closely related to the distance between host and guest. To quantitatively recognize the guest's size/shape effect, the unit increments per methylene ($-\mathrm{d}\Delta G/\mathrm{d}N_C$) for hosts **H15**, **H16** and **H18** are calculated from the stability constants obtained. Since the substituent is introduced and therefore the conformation of cyclodextrin derivatives **H15**, **H16** and **H18** are different considerably, the unit increments are somewhat different accordingly. The unit increments obtained are 2.4 kJ/mol for alkanols with **H15** and **H16**, 3.0, 2.8, and 2.3 kJ/mol for cycloalkanols with **H15**, **H16** and **H18**, respectively.[20,21] These values are somewhat smaller than the corresponding values (3.1 and 3.5 kJ/mol, respectively) for native β-cyclodextrin calculated from the thermodynamic data compiled by Rekharsky and Inoue.[24] Although we have no clear explanation for these small but distinct discrepancies, the selenium substitution would affect the van der Waals interaction.

Enantioselective recognition of amino acids by organoselenium modified β-cyclodextrins were also investigated by spectrometries. These hosts show fairly well chiral discrimination, among the aryseleno β-cyclodextrins used, mono[6-(*o*-tolylseleno)-6-deoxy]-β-cyclodextrin affords the highest enantioselectivity of 27 for *L*-alanine over the antipodal *D*-alanine.[25] Arylseleno groups have also been introduced at C-2 of β-cyclodextrin,[26] but their enantiomer selectivities for *L*/*D*-tryptophan are badly. A probable explanation is that the substituent attached at the secondary side of cyclodextrin affect the original chirality of the cavity. All in all, organoselenium modified cyclodextrins made a new route to molecular recognition.

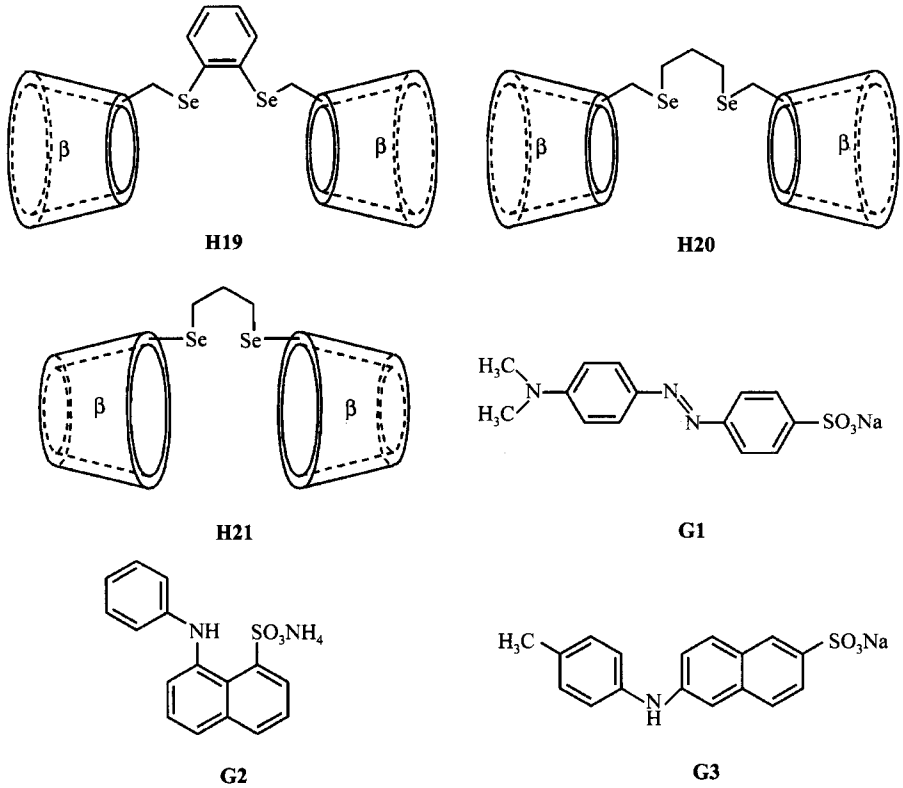
L-Methionine, *L*-proline, and *L*-isoleucine modified β-cyclodextrins have been synthesized, and their molecular binding behavior with several dyes was investigated through fluorescence spectrometry.[27,28] This kind of chemically modified β-cyclodextrins are shown to generally decrease the binding ability as compared with the parent β-cyclodextrin, which should be ascribed to either the self-inclusion of substituent or the carboxylate group's effect. It has been found that a hydrophilic substituent may marginally attenuate the binding of guests within the cyclodextrin cavity.[29]

Dimeric cyclodextrins

Possessing dual hydrophobic cavities in a close vicinity, bridged cyclodextrin dimers have been demonstrated to greatly enhance the original molecular binding ability of the parent cyclodextrin through the cooperative binding of one guest molecule in the closely located two cyclodextrin cavities.[30] In this context, we synthesized organoselenium-bridged bis(β-cyclodextrin)s **H19**—**H21** and the corresponding platinum(IV) complexes and investigated their molecular recognition behavior with some dye guests (**G1**—**G3**).[31,32]

Fig. 6 gives the fluorescence spectra of TNS in the absence and presence of β-cyclodextrin and bridged bis(β-cyclodextrin)s **H19**—**H21**. As shown in Fig. 6, upon addition of the bridged bis(β-cyclodextrin)s **H19**—**H21**, the fluorescence intensity of TNS(**G3**) is dramatically enhanced, accompanying significant hypochromic shifts of the fluorescence peak. However,

Scheme 6



the addition of native β-cyclodextrin only caused a moderate fluorescence enhancement and less-extensive hypochromic shift. Furthermore, the fluorescence decay revealed that bridged bis(β-cyclodextrin)s **H19—H21** induce ANS (**G2**) to exhibit much longer lifetime than that β-cyclodextrin does.

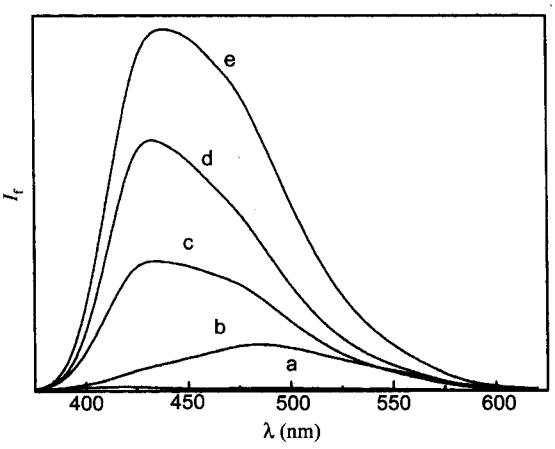


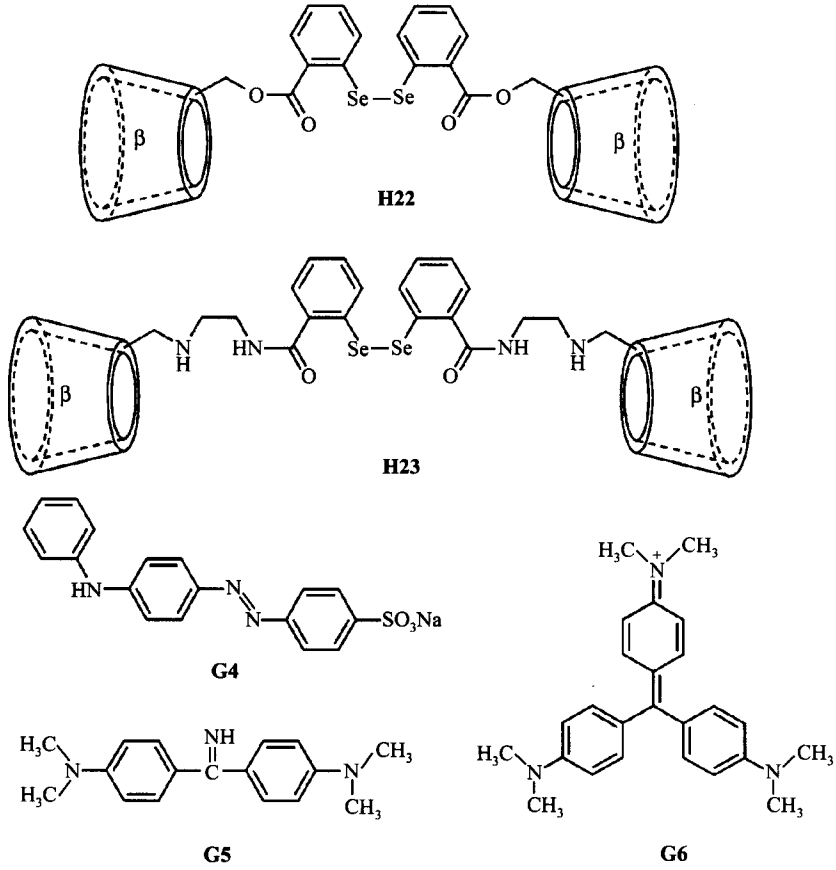
Fig. 6 Fluorescence spectra of TNS in the absence and presence of β-cyclodextrin and bridged bis(β-cyclodextrin)s, (a) TNS (10 μmol/L); (b) (a) + β-CD (450 μmol/L); (c) (a) + **H21** (24 μmol/L); (d) (a) + **H20** (26 μmol/L); (e) (a) + **H19** (26 μmol/L).

These observations clearly indicate that the two adjacent cyclodextrin units of dimeric cyclodextrins could cooperatively work to encapsulate one guest. Therefore, the bridged bis(β-cyclodextrin)s **H19**, **H20** and **H21** form more stable inclusion complexes with **G1—G3** than native β-cyclodextrin by factors from 3 to 17, through the cooperative binding by two β-cyclodextrin units. While their platinum(IV) complexes give yet higher stability constants than the corresponding bis(β-cyclodextrin)s. Among the bis(β-cyclodextrin)s used, the 2,2′-bridged bis(β-cyclodextrin) **H21** and its Pt(IV) complex show the highest affinities toward **G2**, which should be attributable to the wider openings of the 2,2′-bridged bis (β-cyclodextrin) derivatives than the 6,6′-bridged counterparts. The increased hydrophobicity of the bridging group (*o*-phenylene) of **H19** also favors the inclusion complexation with **G3**.

Since bridged bis(cyclodextrin)s bearing diselenoyl group (Se—Se) are potentially good mimics of glutathione peroxidase, the investigation on the inclusion complexation behavior of diselenoyl bridged bis(β-cyclodextrin)s such as **H22** and **H23** would be essential for understanding the interaction between the cy-

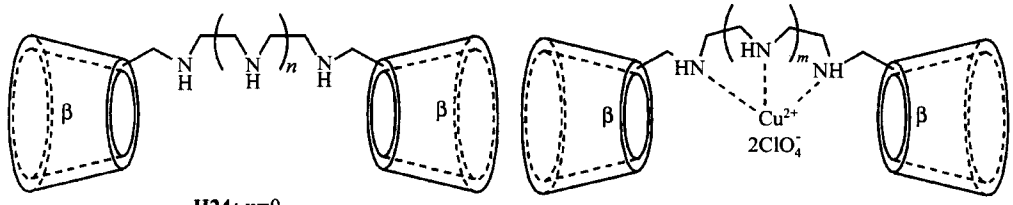
clodextrin-based selenium-containing enzyme model and substrates.[33] Although circular dichroism spectra revealed that the spacer of **H22** was shallowly self-included into the cavity, while the spacer of **H23** was exposed out of the cavity due to the longer tether, the binding ability of **H22** is higher than that of **H23** with the different size/shape guests such as **G1** and **G4**—**G6**. The fact that the binding ability of cyclodextrin dimers **H22** and **H23** decreased with the extending bridged chain moiety may be ascribed to the gradually declining cooperative binding ability with the extending distance between the two cyclodextrin cavities.

Scheme 7



There is an inherent advantage for the oligo(ethylenediamine) tether incorporated in a bis(cyclodextrin), since the tether group can be coordinated to transition metal ions, thus enabling us to modify, and potentially switch, the original binding ability through the metal ligation. In this context, a series of oligo(ethylenediamino) tethered bis(β-cyclodextrin)s (**H24**-**H27**) and two of their copper(II) complexes (**H28** and **H29**) were synthesized. The coordination of the ligand tether of **H25** and **H26** to Cu(II) further enhances the binding ability of **H28** and **H29** by a factor of 1.2—1.7 for ANS and TNS. This further enhancement is attributable to conformational fixation by metal ligation, electrostatic interaction with the ligated Cu(II), and/or ligation of the anilino-nitrogen of ANS/TNS to Cu(II) in **H28** and **H29**. If one of the latter two mechanism is operative, the metallobis(β-cyclodextin)s **H28** and **H29** could be hosts with ternary recognition (two hydrophobic and one electrostatic/coordination) sites. Thus, the TNS/ANS selectivity is enhanced from 11 for **H25** to 13 for **H28** and from 13 for **H26** to 17 for **H29**, respectively.

Scheme 8



H24: n=0
H25: n=1
H26: n=2
H27: n=3

H28: m=1
H29: m=2

The binding mode of bridged bis(β-cyclodextrin)s **H24—H27** with Methyl Orange (**G1**) was elucidated from circular dichroism spectra. Both native β-cyclodextrin and bridged bis(β-cyclodextrin) **H24** induce appreciable CD at the π-π* transition band of the azo group in methyl orange, while no CD is seen in the absence of cyclodextrin. However, the ICD signals of methyl orange induced by β-cyclodextrin and **H24** are distinctly different. From the rule of circular dichroism induced by cyclodextrins, it can be deduced that the two aromatic groups in methyl orange are included into the adjacent cavities of bis(cyclodextrin) **H24**, respectively, while the azo group is exposed outside the cyclodextrin cavity. As shown in Fig. 7b. In the case of β-cyclodextrin, however, the azo group is expected to be included into the cavity. This result indicates that the two cyclodextrin cavities cooperatively work to encapsulate an appropriate geometric guest.

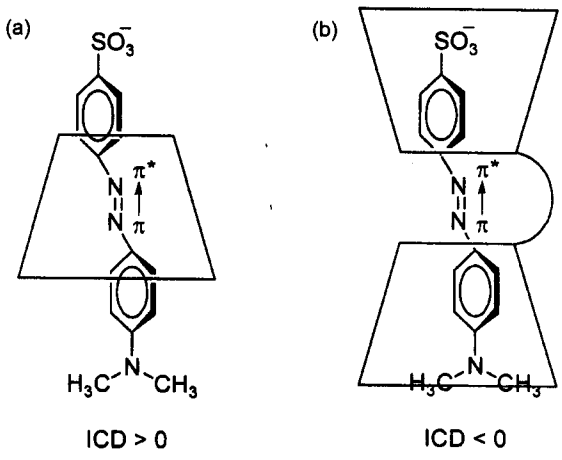


Fig. 7 Possible structures of inclusion complexes between methyl orange and (a) β-cyclodextrin; and (b) dimeric β-cyclodextrins.

It is also interesting to note from Fig. 8 that the Gibbs free energy changes for the inclusion complexation of ANS and TNS with bis(β-cyclodextrin)s **H24—H27** decrease linearly, but the unit decrement of complex stability per ethylene are somewhat different, *i.e.* 0.99 kJ/mol for ANS and 0.44 kJ/mol for TNS, respectively. A probable explanation for this phenomenon is that the longer flexible tether of dimeric cyclodextrins may penetrate into its own cavity to form a spacer self-inclusion complex and then the guest molecule must overcome much resistant when accessing to the host cavity.[35]

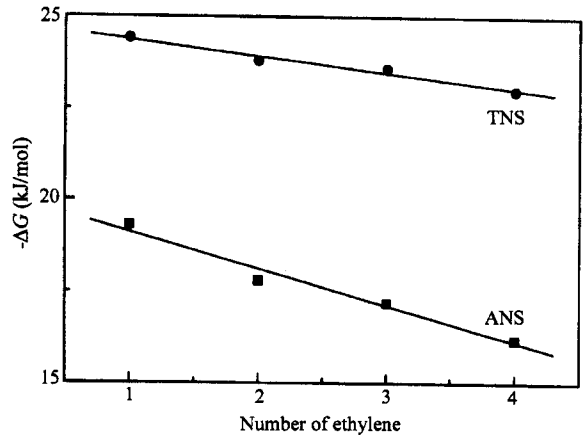


Fig. 8 Gibbs free energy changes ($-\Delta G$) for the inclusion complexation of ANS and TNS plotted as a function of the number of enthylene in the tethers of **H24—H27**.

Thermodynamic studies

A wide variety of experimental methods, including calorimetry and spectrometries like electronic absorption, fluorescence, and nuclear magnetic resonance, have been employed in the determination of thermody-

namic quantities for the complexation reactions of cyclodextrins, in which the thermodynamic parameters are obtained from the complexation constants (K_S) at different temperatures through van't Hoff equation.[6,7] Although calorimetry is the only direct method for determination of the reaction enthalpy, this technique has not been widely used for studying the complexation thermodynamics of cyclodextrins, which is probably due to a combination of the need for a relatively large amount of sample and sophisticated and delicate equipment.[24] We have investigated the inclusion complexation behavior of native cyclodextrins[36] and modified cyclodextrins[37,38] with various aromatic guests through calorimetric titrations to give the complex stability constants and thermodynamic parameters. The results obtained show that the complex stability constants, relative selectivity, and thermodynamic parameters for the inclusion complexation of the guest molecules with modified cyclodextrins are influenced by several factors: relative size between the cyclodextrin's cavity to the guest molecule, induced dipole of functional side arm attached to the edge of cyclodextrin cavity, spatial conformation, microenvironmental hydrophobicity, van der Waals, hydrogen-bonding interactions, and so on. Thermodynamically, the inclusion complexation for both of native cyclodextrins and modified cyclodextrins is mainly enthalpy-driven with a negative or minor positive entropic contribution. Although hydrophobic binding is often believed to be driven by entropy, the unfavorable entropy contribution observed would probably mean that there are compensating solvation effects whose enthalpy/entropy consequences determine the complex stability in some cases.

The thermodynamic parameters for the inclusion complexation of a wider variety of both guests and simple modified cyclodextrins exhibit a compensatory relationship between ΔH and $T\Delta S$. As shown in Fig. 9, the entropy change ($T\Delta S$) was plotted against the enthalpy change (ΔH) to give an excellent regression line (correlation coefficient (r) = 0.993) of a large slope (α = 1.02) and intercept ($T\Delta S_0$ = 17.7 kJ/mol),[38] which are much larger than those for native cyclodextrins.[36] The slope of unity and the intercept of 17.7 reveal that the inclusion complexation with simple modified cyclodextrins accompanies substantial changes in conformation and solvation. This seems reasonable, since the appended side arm, either self-included or excluded in the cavity, is considered to change its conformation upon guest inclusion.

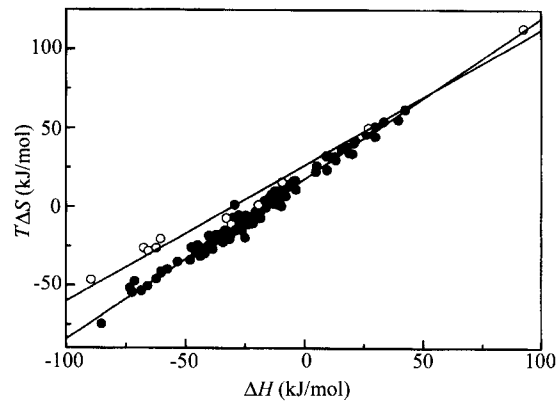


Fig. 9 Enthalpy-entropy compensation plots for simple modified cyclodextrins (●) and bridged bis(cyclodextrin)s (○).

More recently, we have measured the thermodynamic parameters for the inclusion complexation of several bis(β-cyclodextrin)s tethered by 2,2′-bipyridine-4,4′-dicarboxy spacer with Rodamine B and Acridine Red guests.[39] The enthalpy-entropy compensation plot for these data, along with Breslow's results,[40] is also shown in Fig. 9. As can be seen from Fig. 9, the slope for bis(β-cyclodextrin)s (α = 0.86) is appreciably smaller than that for modified mono-β-cyclodextrins (α = 1.02), but rather close to that for native β-cyclodextrin (α = 0.80).[24] On the other hand, bis(β-cyclodextrin)s show much larger intercept ($T\Delta S_0$ = 26.3 kJ/mol) than those for native β-cyclodextrin ($T\Delta S_0$ = 11 kJ/mol) and modified mono-β-cyclodextrin ($T\Delta S_0$ = 17.7 kJ/mol). These results indicate that bis(β-cyclodextrin)s experience moderate conformational changes and most extensive desolvation upon inclusion complexation. Since the present analysis was done by using the limited number (11) of data, the result should be taken with some reserve when being extended to other systems.

Conclusion

In summary, we have systematically studied the molecular recognition and inclusion behavior of three series of modified cyclodextrins, and found that the introduction of functional substituent to the rim of cyclodextrin will alter not only the original binding ability, but also the enantioselectivity. Therefore, we may potentially control the inclusion behavior of cyclodextrin by intro-

ducing suitable substituents. As cyclodextrin itself is rigid and not flexible enough to allow allosteric conformational changes like those to exist in biological supramolecular systems, it will provide much effective artificial receptors and enzyme mimics through the modification of cyclodextrin. Furthermore, dimeric cyclodextrins possessing the typical characters of multiple recognion should receive much attention in the future. By adjusting the size, shape, and hydrophobicity of the spacer and the complexation/decomplexation of metal ions, we can obtain novel host compounds, which may potentially be used as receptors, artificial enzymes, and molecular devices in science and technology. At the same time, the thermodynamic origin studies of the molecular multiple recognition by dimeric cyclodextrins is another interesting topic which need to be further explored.

References and notes

1 For a recent series of comprehensive reviews on all aspects of cyclodextrin chemistry, see: *Chem. Rev.* **1998**, *98*, 1741—2076.

2 Connors, K. N. *Chem. Rev.* **1997**, *97*, 1325.

3 Matsui, Y.; Suemitsu, D. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1658.

4 Liu, Y.; Li, B.; Zhang, Y. M.; Bu, X. H.; Li, Y. M.; Chen, Y. T. *Chin. Sci. Bull.* **1996**, *41*, 117.

5 Liu, Y.; You, C. C.; Han, B. H.; Li, Y. M.; Li, B.; Chen, R. T. *Chem. J. Chin. Univ.* **1997**, *18*, 1316.

6 Liu, Y.; Zhang, Y. M.; Sun, S. X.; Li, Y. M.; Chen, R. T. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1609.

7 Liu, Y.; Zhang, Y. M.; Sun, S. X.; Zhang, Z. H.; Chen, R. T. *Acta Chim. Sin.* **1997**, *55*, 779 (in Chinese).

8 Liu, Y.; Han, B. H.; Qi, A. D.; Chen, R. T. *Bioorg. Chem.* **1997**, *25*, 155.

9 Liu, Y.; You, C. C.; Wada, T.; Inoue, Y. *Supramol. Chem.* **2001**, *12*, 243.

10 Liu, Y.; Li, B.; Han, B. H.; Li, Y. M.; Chen, R. T. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1275.

11 You, C. C.; Zhang, M.; Liu, Y. *Acta Chim. Sin.* **2000**, *58*, 338 (in Chinese).

12 Liu, Y.; Zhang, Y. M.; Qi, A. D.; Chen, R. T.; Yamamoto, K.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1997**, *62*, 1826.

13 Liu, Y.; You, C. C. *Sci. China, Ser. B: Chem.* **2000**, *43*, 27.

14 Liu, Y.; Han, B. H.; Sun, S. X.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 1487.

15 Liu, Y.; You, C. C.; Kunieda, M.; Nakamura, A.; Wada, T.; Inoue, Y. *Supramol. Chem.* **2001**, *12*, 299.

16 Liu, Y.; You, C. C.; Zhang, M.; Weng, L. H.; Wada, T.; Inoue, Y. *Org. Lett.* **2000**, *2*, 2761.

17 Ikeda, H.; Nakamura, M.; Ise, N.; Oguma, N.; Nakamura, A.; Ikeda, T.; Toda, F.; Ueno, A. *J. Am. Chem. Soc.* **1996**, *118*, 10980.

18 Liu, Y.; Zhang, Y. M.; Qi, A. D.; Wang, Q. C.; Chen, R. T. *Chin. Sci. Bull.* **1998**, *43*, 286.

19 Liu, Y.; Li, B.; Li, Z. Y.; Chen, R. T. *Chin. Sci. Bull.* **1998**, *43*, 1011.

20 Liu, Y.; Li, B.; Han, B. H.; Wada, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **1999**, 563.

21 Liu, Y.; You, C. C.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 3630.

22 Liu, Y.; You, C. C.; Wada, T.; Inoue, Y. *J. Chem. Res. (S)* **2000**, 90.

23 Liu, Y.; Li, B.; Wada, T.; Inoue, Y. *J. Inclusion Phenom. Macrocyclic. Chem.* **2000**, *36*, 311.

24 Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.

25 Liu, Y.; Li, B.; Wada, T.; Inoue, Y. *Supramol. Chem.* **1999**, *10*, 173.

26 You, C. C.; Liu, Y. *Chem. J. Chin. Univ.* **2000**, *21*, 249 (in Chinese).

27 Liu, Y.; Jin, L.; Sun, S. X. *Microchem. J.* **2000**, *64*, 59.

28 Jin, L.; Sun, S. X.; Liu, Y. *Chem. J. Chin. Univ.* **2000**, *21*, 412 (in Chinese).

29 Liu, Y.; You, C. C. *J. Phys. Org. Chem.* **2001**, *14*, 11.

30 Breslow, R.; Halfon, S.; Zhang, B. *Tetrahedron* **1995**, *51*, 377.

31 Liu, Y.; Li, B.; Wada, T.; Inoue, Y. *Supramol. Chem.* **1999**, *10*, 279.

32 Liu, Y.; You, C. C.; Chen, Y.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 7781.

33 Liu, Y.; Li, B.; You, C. C.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2001**, *66*, 225.

34 Liu, Y.; You, C. C.; Wada, T.; Inoue, Y. *Tetrahedron Lett.* **2000**, *41*, 6869.

35 Liu, Y.; You, C. C.; Li, B. *Chem. Eur. J.* **2001**, *7*, 1281.

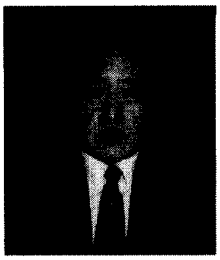
36 Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L. H.; Shen, B. J.; Jin, D. S. *J. Am. Chem. Soc.* **1993**, *115*, 475.

37 Inoue, Y.; Liu, Y.; Tong, L. H.; Shen, B. J.; Jin, D. S. *J. Am. Chem. Soc.* **1993**, *115*, 10637.

38 Liu, Y.; Han, B. H.; Li, B.; Zhang, Y. M.; Zhao, P.; Chen, Y. T.; Wada, T.; Inoue, Y. *J. Org. Chem.* **1998**, *63*, 1444.

39 Liu, Y.; Chen, Y.; Li, B.; Wada, T.; Inoue, Y. *Chem. Eur. J.* **2001**, *7*, in press.

40 Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353.



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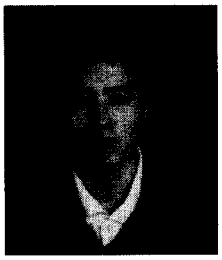

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