SHORT PAPER

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Effect of host substituent upon inclusion complexation of aliphatic alcohols with organoseleno β-cyclodextrins†

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The effect of self-including host substituent upon the inclusion complexation of arylseleno β-cyclodextrins with alkanol guests has been investigated in aqueous buffer solution at 25°C, by using spectropolarimetric titrations, and the results show that the stability constants of the host–guest complexes formed are correlated with the Hammett's σ value of the host's substituent.

As macrocyclic compounds built up from D-glucopyranose units, cyclodextrins have attracted much attention for their unique properties of binding various guest molecules to form host–guest or supramolecular complexes in aqueous solution.[1] Consequently, cyclodextrins, especially readily available α, β- and γ-cyclodextrin, were employed as molecular selectors, enzyme mimics, and supramolecular building blocks in diverse fields of science and technology.[2,3] A considerable amount of effort has been devoted to the preparation of chemically modified cyclodextrins in order to improve or enhance the original molecular binding abilities and enantioselectivities of the native cyclodextrins. Among thousands of chemically modified cyclodextrins, the molecular recognition ability and mechanism of chromophore-appended derivatives have been carefully investigated since their complexation behaviour is evaluated conveniently by spectrometric methods such as absorption, circular dichroism, and fluorescence spectroscopy.[4,5] It is generally believed that van der Waals forces, hydrogen bonding, hydrophobic interaction, and the release of distortion energy of cyclodextrin ring upon guest binding cooperatively govern the stability of an inclusion complex. The hydrophobic substituents introduced at the rim of a cyclodextrin can adjust the size and shape of the cylodextrin cavity upon guest accommodation, and the molecular recognition by chromophoric cyclodextrin is achieved through the induced-fit mechanism. However, how the chromophoric substituent affects the binding ability of chemically modified cyclodextrin is still controversial. Hence, it is of particular interest to examine the substitution effects of cyclodextrin derivatives in molecular recognition.

In this paper, we report our results on the systematic investigation of the inclusion complexation of seven structurally related arylseleno β-cyclodextrins (Scheme 1) with several aliphatic alcohols (Scheme 2) by using spectropolarimetric titrations, and reveal the effect of host substituents upon molecular recognition. The seven chemically modified β-cyclodextrins (Scheme 1), *i.e.*, mono(6-benzylseleno-6-deoxy)-β-cyclodextrin (**1**), mono(6-phenylseleno-6-deoxy)-β-cyclodextrin (**2**), mono[6-(*o*-tolylseleno)-6-deoxy)-β-cyclodextrin (**3**), mono[6-(*m*-tolylseleno)-6-deoxy)- β-cyclodextrin (**4**), mono[6-(*p*-tolylseleno)-6-deoxy)-β-cyclodextrin (**5**), mono[6-(*p*-methoxyphenylseleno)-6-deoxy-β-cyclodextrin (**6**), and mono[6-(*p*-chlorophenylseleno)-6-deoxy)-β–cyclodextrin (**7**), were prepared by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]-β-cyclodextrin and the corresponding arylselenolate anion in a mixed solvent of DMF and ethanol according to the literature procedures.[6,7] Circular dichroism spectra were measured in a conventional quartz cell (10 × 10 × 45 mm) on a JASCO J-720S spectropolarimeter equipped with a PTC-348WI temperature controller, which kept the cell temperature at 25°C. A phosphate buffer solution (pH = 7.2, 0.1 M) was used as solvent in the circular dichroism spectral measurement. In the experiment, the stepwise addition of a known amount of the guest to a dilute cyclodextrin solution (0.1–0.2 mM) would cause significant change in circular dichroism, which could be used to determine the binding constant. Assuming the conventional 1:1 stoichiometry, the spectral titration data obtained for each cyclodextrin-alcohol complex were analysed according to a non-linear least squares method reported previously.[7] When repeated meaurements were performed, the K_S value was reproducible within an error of ±5%, which corresponds to an estimated error of 0.12 kJ mol^{-1} in the free energy of complexation (ΔG°). The complex stability constants (K_S) obtained are listed in Table 1, along with the free energy change of complex formation ($-\Delta G°$).

It can be seen from Table 1 that the complex stability constants for each cyclodextrin host are in the order: myrtanol > neomenthol > (cyclooctanol) > cyclohexanol > cyclopentanol. We revealed in previous papers 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.[7,9,10] Therefore, it is not surprising that myrtanol, possessing a bulky and rigid bicyclic skeleton, gives the most stable complexes for all of the hosts used. It has also been revealed that the Gibbs free energy change ($-\Delta G°$) of complexation is usually a linear function of the number of methylenes (N_C) in the guest molecule for the complexation of acyclic and cyclic alcohols with cyclodextrins. In the present case, the unit increment in $\Delta G°$ ($-d\Delta G°/\Delta N_C$) for the complexation of cycloalkanols with the cyclodextrin derivatives is 2.7±0.8 kJ mol^{-1}. Accordingly, we can deduce that the van der Waals and hydrophobic forces mainly contribute to the inclusion complexation by aryseleno β-cyclodextrins, since these two weak interactions are closely related to the distance between host and guest. However, it should be noted that the data obtained above are somewhat smaller than the corresponding value (3.5 kJ mol^{-1}) calculated from the thermodynamic data compiled for native β-cyclodextrin by Rekharsky and Inoue.[8] This discrepancy may be attributable to the competitive self-inclusion of the arylseleno group, which causes steric hindrance upon guest inclusion, although the substituent may enhance the hydrophobicity of the cyclodextrin cavity to a certain extent.

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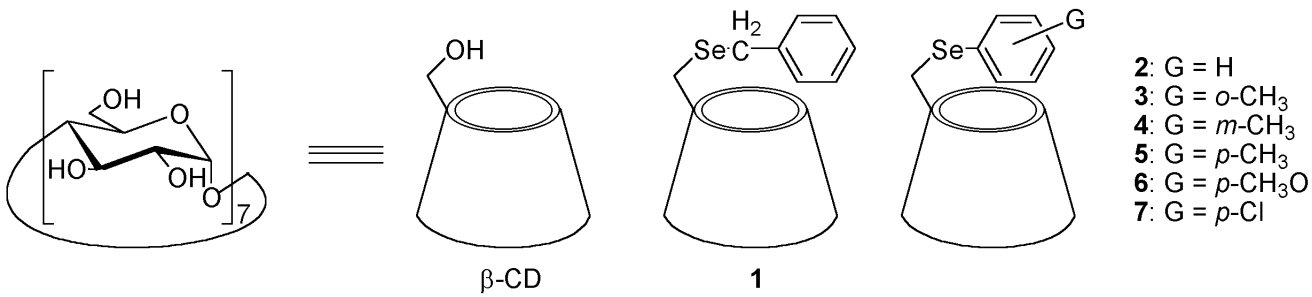
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

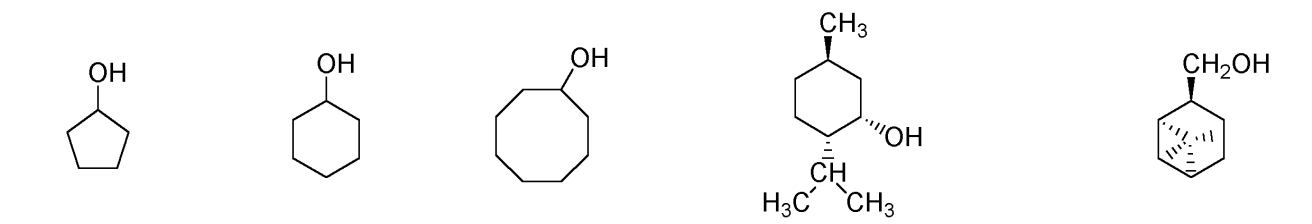
Table 1 The stability constant (K_S) and Gibbs free energy change ($-\Delta G°$) for the inclusion complexation of native β-cyclodextrin and aromatic organoseleno modified β-cyclodextrins (**1**–**7**) with some aliphatic alcohols in aqueous phosphate buffer solution (pH 7.20, 0.1 mol dm^{-3}) at 25°C.

Host	Guest	K_S	log K_S	$-\Delta G°$/ kJ mol^{-1}	Ref.
β-CD	Cyclopentanol	172	2.24	12.8	*a*
	Cyclohexanol	717	2.85	16.3	*a*
	Cyclooctanol	4410	3.64	20.8	*a*
1	Cyclopentanol	68	1.83	10.5	*b*
	Cyclohexanol	138	2.14	12.2	*b*
	Cyclooctanol	996	3.00	17.1	*b*
	(1S,2S,5R)-(+)-neomenthol	1390	3.14	17.9	*c*
	(1S,2S,5S)-(-)-myrtanol	5050	3.70	21.1	*c*
2	Cyclopentanol	300	2.48	14.1	*c*
	Cyclohexanol	840	2.92	16.7	*c*
3	Cyclopentanol	155	2.19	12.5	*c*
	Cyclohexanol	533	2.73	15.6	*c*
	Cyclooctanol	1670	3.22	18.39	*b*
	(1S,2S,5R)-(+)-neomenthol	1820	3.26	18.6	*c*
	(1S,2S,5S)-(-)-myrtanol	15170	4.18	23.9	*c*
4	Cyclopentanol	140	2.15	12.3	*c*
	Cyclohexanol	670	2.82	16.1	*c*
	Cyclooctanol	6520	3.81	21.8	*b*
	(1S,2S,5R)-(+)-neomenthol	1250	3.10	17.7	*c*
	(1S,2S,5S)-(-)-myrtanol	6430	3.81	21.7	*c*
5	Cyclopentanol	113	2.05	11.7	*d*
	Cyclohexanol	590	2.77	15.8	*d*
	Cyclooctanol	4440	3.65	20.8	*d*
	(1S,2S,5R)-(+)-neomenthol	1075	3.03	17.3	*c*
	(1S,2S,5S)-(-)-myrtanol	9450	3.98	22.7	*c*
6	Cyclopentanol	60	1.78	10.1	*d*
	Cyclohexanol	183	2.26	12.9	*d*
	(1S,2S,5R)-(+)-neomenthol	777	2.89	16.5	*c*
	(1S,2S,5S)-(-)-myrtanol	4730	3.67	21.0	*c*
7	Cyclopentanol	340	2.53	14.5	*c*
	Cyclohexanol	1410	3.15	18.0	*c*
	(1S,2S,5R)-(+)-neomenthol	2260	3.35	19.1	*c*
	(1S,2S,5S)-(-)-myrtanol	25400	4.40	25.1	*c*

Data cited from: [a]Ref. 8; [b]Ref. 9; [c]This work; [d]Ref. 7.



Scheme 1



Scheme 2

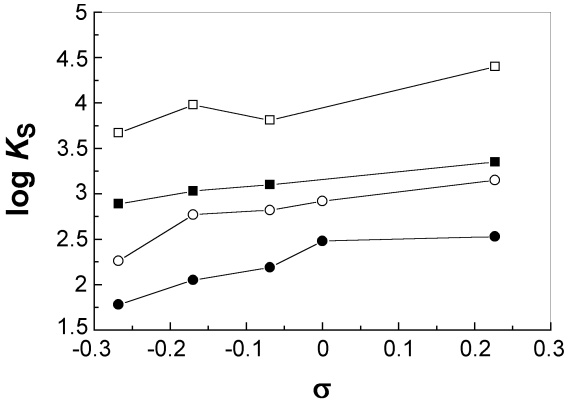


Fig. 1 The stability constants (log K_S) of the host–guest complexes plotted as a function of the Hammett's s value of the host's substituent.

More interestingly, the modified cyclodextrins with different substituents show distinctly different binding abilities toward the same guest molecule, in spite of the apparently similar aryl substituents introduced. Possessing a *p*-methoxyphenyl and *p*-chlorophenyl substituents, the hosts (**6**) and (**7**) gave significantly different complex stability constants (K_S) of 183 and 1410, respectively. Hence it is apparent that the substituent on the phenyl group plays a key role in determining complex stability. Connors *et al.*[11] have observed a linear correlation between log K_S and the Hammett's σ in the inclusion complexation of α-cyclodextrin complexes with 4-substituted benzoic acids and benzoates. Guo *et al.*[12] and Davies *et al.*[13] also employed the Hammett's σ as one of the major parameters for the prediction of K_S for native cyclodextrin complex with substituted benzenes. In this context, it is interesting to examine the possible correlation between Hammett's σ of the host substituent and the stability constant of inclusion complexation with aliphatic alcohol guests. Then, the complex stability constants (log K_S) are plotted as a function of the Hammett's σ of the host substituents. As can be seen from Fig. 1, the complex stability constant (log K_S) gradually increases with increasing σ value. This result indicates 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 *intramolcular* 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.

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