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NATURE OF FORCE FIELD OPERATING IN MOLECULAR RECOGNITION BY CYCLODEXTRINS. CONTRIBUTION OF NONPOLAR AND POLAR INTERACTIONS

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Abstract - Significance of polar interaction ($\Delta H_{pol.}$) and nonpolar interaction ($\Delta H_{disp.}$) operating in guest•cyclodextrin complexes in water is investigated. Force field calculation of α-cyclodextrin•p-nitrophenol complex gives ΔH_{disp}= -13.7 kcal/mol and ΔH_{pol} of -0.2 kcal/mol. Minor contribution of ΔH_p between cyclodextrin and even an ionic guest is confirmed by the observed $\Delta H°$ (-4.6 kcal/mol) for Trp-ionic cyclodextrin 1 complexation. ΔH_{pol} between a cyclodextrin bearing cations and anions on C6 carbons and Trp is calculated to be in a range from -2.0 to -5.9 kcal/mol, depending on the local dielectric constant.

Sophisticated molecular recognition by artificial hosts may be achieved by i) regiospecific and/or stereospecific introduction of effective recognition groups onto a host molecule$^{1)}$ and ii) optimization of host-guest interaction by providing appropriate local environment around the recognition center$^{2)}$. As to contribution of polar and nonpolar interactions$^{3)}$ to the total recognition, however, there are contradictory discussions in the literature$^{6,7)}$.

In our current study on sophisticated molecular recognition by use of modified cyclodextrins, we have prepared functionalized cyclodextrins bearing ionic groups fixed in regiospecific positions for specific recognition of hydrophobic amino acids$^{2)}$. The result unexpectedly showed that the Coulombic interaction is very weak, contradictorily to the semiquantitative discussions overestimating polar interaction$^{7a)}$. This finding prompted us to study the nature of driving force operating in complex formation between a cyclodextrin (derivative) and a guest.

In this article, we wish to report computer aided estimation of recognition interaction between an ionic guest and a cyclodextrin derivative in water, in which significance of polar interaction varies depending on local environment. Polar interaction consisting of classical Coulombic interactions — point charge-point charge, point charge-dipole, dipole-dipole interactions etc. is estimated by summation of all possible interactions between partial charge on atom i and that on atom j in this article.

Polar interaction is sensitive to local dielectric constant while nonpolar interaction (London dispersion force) is not. By considering these facts, relative significance of polar and nonpolar interactions must depend on local dielectric constant. This also will be discussed in this article.

RESULTS AND DISCUSSION

Recognition of a Polar Guest by α-Cyclodextrin.

Polar and nonpolar interactions between α-cyclodextrin and a strongly polar guest, p-nitrophenol, were calculated based on the geometry determined by X-ray crystallographic analysis of α-cyclodextrin-p-nitrophenol complex8). Total polar interaction (sum of elemental Coulombic interaction between each pair of atomic charges, q_i and q_j on atom i in α-cyclodextrin and j in a guest molecule, respectively) was calculated from eq.(1), where e is 1.6×10^{-19}C, ε is local (effective) dielectric constant and r_{ij} is distance between atom i and

$$\Delta H_{pol} = \sum \frac{1}{4\pi\varepsilon_0\varepsilon}\,\frac{q_i q_j}{r_{ij}} = \sum \frac{332}{\varepsilon}\,\frac{(q_{i/e})(q_{i/e})}{r_{ij}/\mathrm{\AA}} \qquad \text{(kcal/mol)} \qquad (1)$$

atom j. Atomic charges of α-cyclodextrin9) and atomic charges of p-nitrophenol10) were taken from the literatures. The local dielectric constant (ε) was assumed to be either 18 or 54 as possible extremes, which will give upper and lower limits of the polar interaction. The former value was dielectric constant of isopropanol which has similar bond dipoles (C-O, O-H, C-H, C-C) to those of cyclodextrin, and may represent the most nonpolar local environment where solvent water has no effective influence. The latter value was experimentally determined based on the correlation between dielectric constant of the solvent and fluorescence intensity of strongly hydrophilic zwitter ion, 8-anilino-1-naphthalenesulfonate bound to the cyclodextrin, in methanol-water mixtures2). Considering the fact that some parts of the present guest are exposed to bulk water11), this value may represent the most polar local environment where solvent water has maximal influence. Nonpolar interaction was calculated by use of Hill's equation12) (eq(2)) where E_{ij} is geometrical average of E of atom i and j, and $\alpha_{ij} = r_{ij}/(r_i^* + r_j^*)$. Values of E and r_i^* are taken from the literature12).

$$\Delta H_{disp} = \sum E_{ij}\left(\frac{-2.25}{\alpha_{ij}^{6}} + 8.28 \times 10^{5}\, e^{-\alpha_{ij}/0.0736}\right) \qquad (2)$$

The interaction energies thus calculated were minimized13) by taking atomic coordinates as independent parameters in the range of 0 - 0.2 Å. The calculated dispersion enthalpies together with other enthalpies were listed in Table 1. In Table 1 are also shown the computation results on p-iodoaniline.

Table 1. Calculated Enthalpy Change upon Inclusion by α-Cyclodextrin [a]

Guest	ΔH_{disp}	ΔH_{pol}	ΔH_{conf}	$\Delta H_{guest\ sol}$	$\Delta H_{host\ sol}$	ΔH_{total}
p-nitrophenol	-13.7	+0.02[c,e]	+3.6	(+1.4)[b,d]	-8.7	
p-iodoaniline	-10.0		+3.9	+7.1	-8.7	-7.35

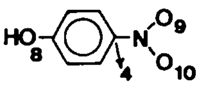
a. kcal/mol, 25°C b. reported by Harata et al9). c. based on the atomic coordinates determined by X-ray crystallography 8).
d. $\Delta H_{aq.soln \rightarrow gas}$ of nitrobenzene is 13 kcal/mol22).
e. ΔH_{pol}=+0.05 kcal/mol if ε=18 (dielectric constant of isopropanol) is assumed. Optimum ΔH_{pol} is -0.06 (ε=56) or -0.2 kcal/mol (ε=18) when the primary hydroxy groups of α-cyclodextrin are freely rotating around C5-C6 axis.

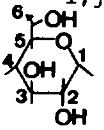
Apparently, the London's dispersion interaction (ΔH_{disp}) is the most important enthalpy term for stabilization of cyclodextrin·p-nitrophenol complex. On the contrary, calculated polar interaction (ΔH_{pol}) is smaller than -0.2 kcal/mol ($\varepsilon = 18$) and larger than -0.06 kcal/mol ($\varepsilon = 54$), being negligibly small even for a very polar guest, p-nitrophenol ($\mu = 5.50$ D). This weak polar interaction is resulted from rather effective cancellation of attractive forces by repulsive forces due to the random orientation of bond dipoles (see Table 2).

Table 2. Coulombic Interaction Energies between Atomic Charges in α-CD·p-nitrophenol Complex

no.[a]	Guest[b]	CD[b]	$\Delta H_{i,j}$[c]	$\sum \Delta H_{i,j}$[c]
1	N	O_6(C)	-0.7460	-0.7460
2	N	O_6(D)	-0.7092	-1.4552
3	N	O_6(F)	-0.6839	-2.1391
4	N	O_6(A)	-0.6766	-2.8158
5	N	O_3(A)	-0.6722	-3.4880
6	O_9	O_6(C)	+0.6454	-2.8426
7	N	O_3(F)	-0.6315	-3.4741
8	N	O_6(B)	-0.6298	-4.1039
9	N	O_3(D)	-0.6205	-4.7245
10	N	O_2(A)	-0.6205	-5.3449
⋮	⋮	⋮	⋮	⋮
20	N	O_2(E)	-0.5643	-10.0289
⋮	⋮	⋮	⋮	⋮
30	N	O_4(F)	-0.4983	-8.9487
⋮	⋮	⋮	⋮	⋮
50	O_9	O_3(C)	+0.4458	-5.2920
⋮	⋮	⋮	⋮	⋮
100	O_9	O_2(E)	+0.3475	+8.0146
⋮	⋮	⋮	⋮	⋮
150	C_4	O_6(F)	-0.2670	+3.9462
⋮	⋮	⋮	⋮	⋮
300	O_9	C_2(F)	-0.1080	+1.4189
1890				-0.2004 (total)

a. listed in decreasing order of $|\Delta H_{i,j}|$, b. notation of atom is as follows





c. unit; kcal/mol

Relatively strong binding of p-nitrophenol to α-cyclodextrin compared to similar benzene derivatives without nitro group is then reasonably explained by the enhanced London's dispersion energy between the nitro group and cyclodextrin.

Compensation Temperature Tc in α-Cyclodextrin·Guest Complexation

Linear relationship between the enthalpy change and the accompanying entropy change is often observed for a variety of processes in an aqueous solution. The slope of the ΔH° - ΔS° line is called the compensation temperature (Tc), which lies between 250 and 315 K[14]. At Tc, any enthalpy gain must be entirely compensated by the accompanying entropy change, if the linear relationship still holds at Tc. The mechanism of the observed overall compensation of ΔH° by T·ΔS° may be understood by two molecular mechanisms; a) compensation of host-guest interaction enthalpy by the restriction of motional freedom of the guest (or the host)[10] induced by the interaction, and b) compensation of solvation (aquation) enthalpy by the restriction of motional freedom of solvent molecules[15]. It should be noted that the magnitude of Tc is determined not only by solvation (aquation) interactions but also by host-guest interactions. Table 3 summarizes the compensation temperatures determined based on the different data bases. Except for Tc of 403 ± 24 K calculated from data basis C, which is taken by Laufer et al.[7a], Tc calculated from other larger data bases falls to a 250 - 350 K range, that is generally taken as the characteristic of the "aquation" phenomena[14], contrary to the previous arguments[7a]. Therefore, the magnitude of Tc for α-cyclodextrin-organic guest complexation suggests that water molecules play an important role in energetics of complexation and does not necessarily suggest the polar mechanism proposed by Laufer et al[7a].

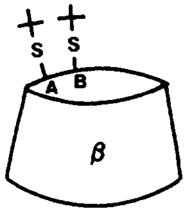
Table 3. The Compensation Temperature Determined by Least-Squares Method. The 95% Confidence Interval[23] (95% CI) and the Correlation Coefficient Are Also Shown.

Data	No. of inclusion complexes for Tc estimation	Tc,°K	correlation coefficient	95% CI
Group				
A[a]	20	403	0.97	352-455
B[b]	59	237	0.93	211-262
C[c]	37	254	0.96	229-280

a. chosen by Laufer[7a] b. all data available[24-29]
c. all data reported for benzene derivatives.

^{13}C NMR Chemical Shift Displacement as a Measure of Induced Dipole Moment on the Guest by Complexation

The observed shift of the ^{13}C NMR absorptions of cyclodextrins and guests upon complexation was sometimes employed to investigate the mechanism of cyclodextrin inclusion[7a]. Inclusion is often accompanied with appreciable or remarkable conformational changes in cyclodextrins, as exemplified by X-ray crystallographic studies[16]. In solution, the cyclodextrin conformation change may be best reflected in the ^{13}C NMR chemical shift change of the skeletal carbons. Typical examples of remarkable ^{13}C NMR chemical shift change were observed for cyclodextrins bearing bulky substituents on A and B rings (4, 5 or 6), in which C1 and C4 absorptions were most affected by the induced conformation change due to repulsive interaction between bulky substituents[17]. With respect to the C1 carbon resonances, it should also be noted that the C1 carbon is most positively charged among the carbons of cyclodextrin based on MO calculation[9], suggesting that the C1 resonance displacements are sensitive to changes in solvation of cyclodextrin and the host-guest polar interaction. A



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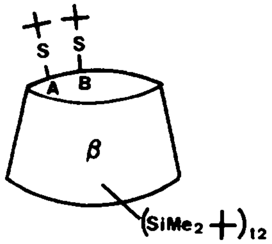

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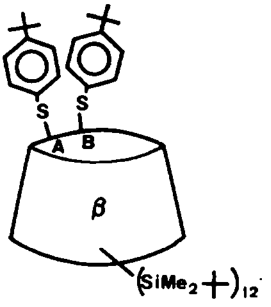


6*

* 2,2',2",2''',2'''',2''''',2'''''',6,6',6",6''',6''''-Dodeca-O-(tert-butyldimethylsilyl) derivatives.

linear correlation was found between the C1 chemical shift displacement ($\Delta\delta_{C1}$) and ΔH° for the complexation of a series of organic guest molecules with slight structural perturbation, and α-cyclodextrin[7a]. This correlation was taken as evidence for the host-guest polar interactions as a sole significant interaction, which causes the remarkable conformational changes in cyclodextrin[7a]. However, as shown in Figure 1, there is no reasonable correlation (correlation

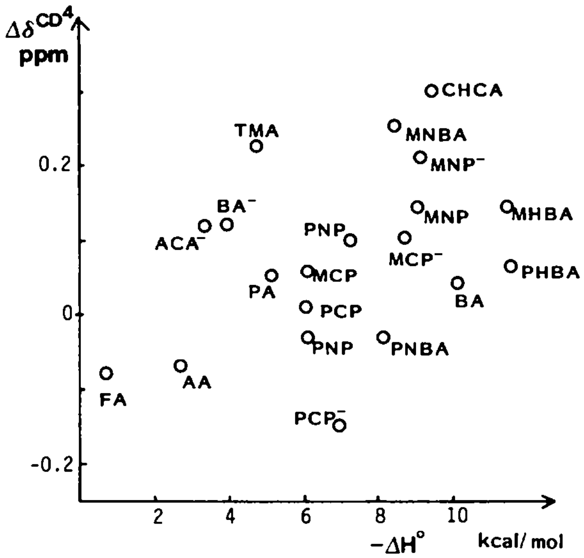


Fig. 1. Correlation of cyclodextrin C4 ^{13}C NMR displacement $\Delta\delta_{C4}$ vs. ΔH° for the complexations. Values of $\Delta\delta_{C4}$ and ΔH° are taken from ref. 7a. The abbreviations are as follows: FA; formic acid, AA ; acetic acid, PA ; propionic acid, CHCA ; cyclohexanecarboxylic acid, TMA ; trimethylacetic acid, ACA ; adamantanecarboxylic acid, BA ; benzoic acid, PHBA ; p-hydroxybenzoic acid, PNP ; p-nitrophenol, PCP ; p-cyanophenol, PNBA; p-nitrobenzoic acid, MNP; m-nitrophenol, MCP ; m-cyanophenol, MNBA ; m-nitrobenzoic acid, and corresponding anions are shown as PNP⁻ .

coefficient r = 0.34) between ΔH° and $\Delta\delta_{C4}$, the latter is also sensitive to the conformation change of a cyclodextrin molecule. And it is not logical to imagine that the conformational change of cyclodextrin is induced in such a way that only bond angles and torsional angles around C1 are strongly twisted while those around C4 are not twisted appreciably. Therefore, it is highly questionable to ascribe $\Delta\delta_{C1}$ to conformational change exclusively as speculated[7a].

The largest atomic charge in a substitutent (Fig. 2) or the sum of absolute values of atomic charges of a substituent (Fig. 3)[18] on each guest molecule (the substituent having higher charges is chosen if there are two substituents) is plotted against observed -ΔH°. There is no or rather negative correlation (r = -0.59 or -0.43 for Figs. 2 and 3, respectively) and negative correlation further becomes clearer if PCP is excluded (r = -0.91 or -0.92, respectively). The results suggest that a more polar substituent weakens the binding. This

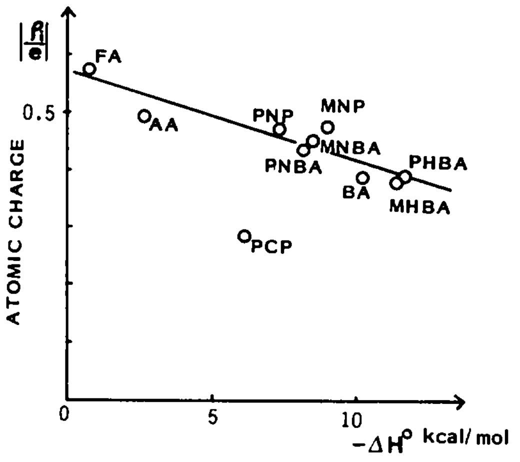


Fig. 2. Correlation of the largest atomic charge of substituent of guest molecules $|\rho_i|$ vs. $-\Delta H°$ for the complexations. Atomic charges of FA, AA[30], PNP, MNP[9], BA, PHBA, MHBA, PNBA, MNBA[31] and PCP[32] are reported values. Values of $\Delta H°$ are taken from ref. 7a. The line drawn represents a least square fit to 9 complexes except PCP.

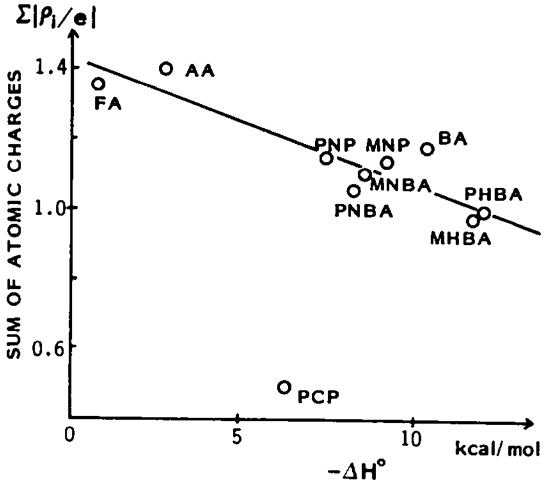


Fig. 3. Correlation of the sum of atomic charges of guest molecules $\Sigma|\rho_i|$ vs. $-\Delta H°$ for the complexations. For ρ_i, $\Delta H°$ and the line, see foot note in Fig 2.

conclusion is compatible both with a general trend that polar guest molecules with large $|\rho_i|$ are bound more weakly than apolar ones[1c)] and with our forcefield calculation[6b)]. Since ^{13}C NMR chemical shift can be used as a measure of electron density of the carbon atom, the chemical shift displacement of the guest carbons ($\Delta\delta_{ipso}$) on complexation should be closely related to a measure of induced dipoles of the bound guest. No correlation was found between $\Delta\delta_{C1}$ and $\Delta\delta_{ipso}$ (Fig. 4), again strongly suggesting that the major interaction affecting $\Delta\delta_{C1}$ (i,e. conformation of cyclodextrin) is not polar in nature.

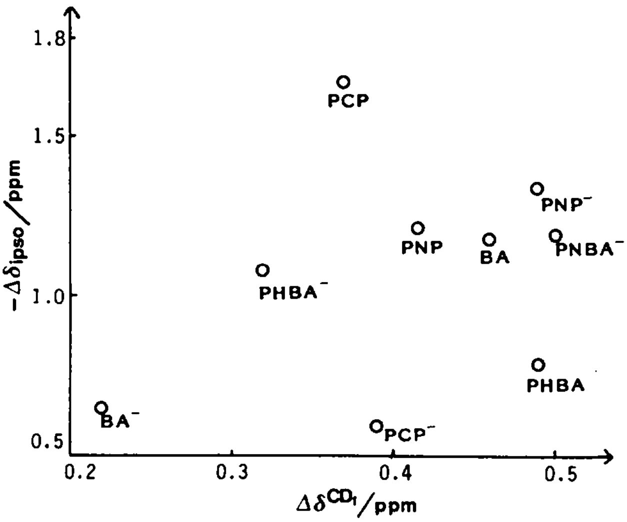
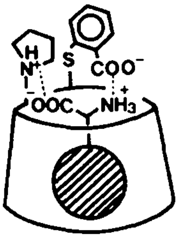


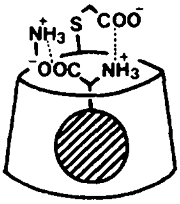
Fig. 4. Correlation of α-cyclodextrin C1 displacement $\Delta\delta_{C1}$ vs. ipso carbon displacement of included guest molecules $\Delta\delta_{ipso}$. $\Delta\delta_{C1}$ and $\Delta\delta_{ipso}$ are reported values[7a)].

Coulombic Interaction Between a Charged Cyclodextrin and a Charged Guest

We now focus on the polar interaction between a charged cyclodextrin and a charged guest. Polar interactions are considered to have crucial significance for recognition of substrates by enzymes[19)]or recognition of trigger molecules by receptors. However, an important point to note for these biological recognitions is that the agonist-antagonist interaction is achieved in relatively hydrophobic environment. As mentioned above, we have estimated maximum and minimum polar interaction energies for CD guest complexes by use of eq. (1) by taking lower and upper limits of local dielectric constant. As a typical example, total Coulombic interaction between the ammonium and the carboxylate groups on the β-CD (1) and the carboxylate and the ammonium groups on the guest, Trp, respectively, was calculated based on a rough estimation of local dielectric constant (ε) to be 18 or 54, (vide supra). The calculation yields $\Delta H_{pol.}$ = -2.0 kcal/mol (for ε = 54) or -5.9 kcal/mol (for ε = 18). The calculated total recognition energy due to the polar interaction may be obtained from the calculated Coulombic interaction energy discussed above, desolvation energy ($-\Delta H_{sol}$) and the calculated intramolecular Coulombic interaction energies of the host and the guest, as shown in eqn 3. In eqn 3, ΔH_{sol} for the host• guest complex is neglected. Since all of the other terms (second to fifth terms) give positive contribution, ΔH(polar recogn) must be less negative than ΔH(H-G Coulombic). From the comparison between ΔH_{pol} observed (-4.5 kcal/mol for 1•Trp) and ΔH_{pol} calculated (between -2.0 and -5.9 kcal/mol), therefore, it may be safely concluded that the direct Coulombic interaction between charged groups on the host and those on the guest is one of the most important interactions operating between a charged host and a charged guest.



1•Trp



2•Trp

$$\Delta H_{(\text{polar recogn})} = \Delta H_{(\text{H-G Coulombic})} - \Delta H_{(\text{H sol})} - \Delta H_{(\text{G sol})} - \Delta H_{(\text{G Coulombic})} - \Delta H_{(\text{H Coulombic})} \qquad (3)$$

Comparison of the host-guest Coulombic interaction between 1•Trp (ΔH_{pol} = -4.5 kcal/mol) and 2•Trp complex (-0.9 kcal/mol) confirms that even a small change in local environment (local dielectric constant) is extremely important for host-guest recognition.

Compensating Entropy Loss in Polar Recognition

Although observed (and calculated) polar recognition enthalpy change is of considerable significance for charged host•charged guest complex having hydrophobic local environment, -ΔH (1•D-Trp) = 4.5 kcal/mol, the observed polar recognition free energy change, -ΔG(1•D-Trp) = 0.9 kcal/mol, is much less important. This is due to the compensating unfavorable entropy change, ΔS(1•D-Trp) = -12 cal/mol•deg, in the tight complexation. Most probable origin of the observed unfavorable entropy change seems to be loss of one rotational freedom of the guest around z axis (see Fig. 5) upon complexation via triple recognition. We have calculated the one dimensional rotational entropy of Trp from the moment of inertia, I = 7.25 × 10^{-45} kg m^2 20). The rotational entropy amounts to S_{rot} = 10.7 eu, the entire loss of which is equivalent to ΔG° = 3.2 kcal/mol destabilization of the complex at 25°C, in an excellent agreement with the observed entropy loss which corresponds to ΔG° = +3.6 kcal/mol.

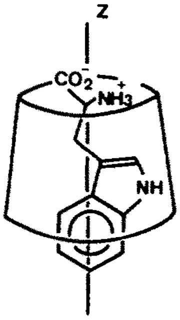


Fig. 5. One dimensional rotation of Trp in the complex. z-Axis is drawn so as to connect C_α and the center of gravity of Trp.

We have investigated the molecular dynamics of a guest bound to cyclodextrins by observing deuterium NNR relaxation time. Preliminary results suggest that even such a bulky guest as 2,3,5,6-tetramethyl-1-benzenesulfonate 3 has rotational freedom in the cavity of 6A,6C-bis(trimethylammonio)-6A,6C-dideoxy-β-cyclodextrin as freely as the cavity of parent β-cyclodextrin21). These observations indicate that Coulombic interaction ($-\Delta H_{pol}$) between an anion and a cation is less important than loss of one rotational freedom. Two important conclusions may be drawn from these observations; (i) any specific interaction between a dipolar guest and a cyclodextrin derivative at fixed position under similar circumstances has no significance and (ii) any charge-charge interaction under similar circumstances can not overcome loss of rotational entropy.

The observed compensating entropy loss upon tight host-guest complexation via triple recognition suggests that such strong molecular recognition as seen in biological agonist-antagonist binding is only achieved via quadruple (or higher multiple) recognition and/or recognition in strongly nonpolar local environment, in order to afford large negative enthalpy change to overcome large negative entropy change due to entire loss of motional freedom of the guest (agonist).

CONCLUSION

Polar and nonpolar interactions operating in cyclodextrin•guest complexes were calculated for two extreme cases, one for uncharged CD•uncharged guest complexes and the other for charged CD•charged guest complexes. For the former, the magnitude of polar interaction was much smaller than that of nonpolar interaction. This conclusion is further supported by the magnitude of Tc and absence of $\Delta\delta_{C1}$ - $\Delta\delta_{ipso}$ correlation. On the other hand, for charged•CD charged guest complexes, polar interaction becomes important where the local environment at the recognition site is nonpolar. In triple recognition of an amino acid by the doubly charged cyclodextrin, the Coulombic interaction makes the formation enthalpy of the complex more negative by at least 2 kcal/mol, but it is considerably compensated by entropy decrease (-T•ΔS = 3.2 kcal/mol) due to loss of rotational freedom of amino acid. For strong recognition of amino acids in water, quadruple (or higher multiple) recognition is preferable.

ACKNOWLEDGEMENT

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