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Spectroscopic Study of Hydrophobic Interaction of Heterocyclic Amine *N*-Oxides with Cyclodextrins

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Electronic spectra of aromatic amine *N*-oxides show a marked blue shift with the change of solvent polarity from aprotic solvents to protic ones. This is very useful to examine the hydrophobic interaction between the amine *N*-oxides and cyclodextrins (CyD) in water. Among the various systems studied a typical example is the system of 4-nitroquinoline *N*-oxide (4NQO) and 2,6-di-*O*-methyl-β-cyclodextrin in water. A clear red shift of the ultraviolet (UV) spectrum of 4NQO was observed upon inclusion complex formation, indicating directly that the CyD cage environment is much more hydrophobic than in water. Thermodynamic and spectroscopic constants pertinent to those inclusion complex formations were evaluated and the results are discussed in relation to the complex formation mechanisms.

Keywords——electronic spectrum; aromatic amine *N*-oxide; cyclodextrin; hydrophobic interaction; inclusion complex; solvent effect; hydrogen bonding effect; enthalpy change; entropy change; equilibrium constant

The formation of inclusion complexes of organic molecules with cyclodextrin (CyD) in aqueous solutions has been reported by many workers from various viewpoints.[1-11] These studies indicate that the cavity of CyD forms a hydrophobic environment in an aqueous medium and includes various substances. The formation mechanisms of this kind of host–guest complexes have been investigated experimentally and theoretically by using techniques such as spectroscopy, polarography, thermochemistry, X-ray crystal structure analysis, theoretical calculation, *etc.*[1-11] It is also well known that the ultraviolet (UV) spectra of heterocyclic amine *N*-oxides show a marked blue shift with the change of solvent polarity from aprotic to protic,[12] and that the hydrogen bonding of the *N*-oxide group oxygen atom with active hydrogens in protic solvents plays an important role in this general property.[12,13] Thus, if these *N*-oxides form inclusion complexes with CyD's and enter the more hydrophobic environment, a red shift of the UV spectra should be observed. Analysis of the red shift may indicate how hydrophobic the environment around the *N*-oxide molecule in the inclusion complexes is. Thus, we have studied the molecular interactions of aromatic *N*-oxides with CyD's in detail. The results are presented here.

Experimental

Spectral Measurement——Absorption spectra were recorded in a usual manner with a Hitachi spectrophotometer, model 323. The temperature of sample solutions was usually kept at 25 ± 0.1 °C during the measurement by circulating constant-temperature water throughout the cell compartment by the use of a Taiyo thermoleader, model EZL-80. The experiment to determine the temperature dependence of the equilibrium constant K pertinent to the host–guest complex formation was carried out in the range of 5—40 °C by the method mentioned above, 1 cm matched quartz cells equipped with stoppers being usually used. All instrument operations at temperatures lower than room temperature were carried out under an N_2 atmosphere to prevent moisture deposition. The equilibrium study

was carried out in distilled water and also in pH 7 buffer solution composed of "0.1 mol·dm^{-3} Na_2HPO_4+HCl" and adjusted to ionic strength (I) 0.5 with NaCl. All the organic solvents (see footnotes of Figs. 3 and 4) used for spectral measurements were of spectrograde purity except tetrahydrofuran, which was of special grade purity. These were dried over CaH_2 or CaO (only for methanol and ethanol) and then carefully distilled.

Samples——CyD's employed here were α-, β-, and γ-CyD's, 2,6-di-*O*-methyl-α-CyD (DMαCyD), and 2,6-di-*O*-methyl-β-CyD (DMβCyD). Special grade samples of α, β, and γ-CyD's purchased from Wako Pure Chemical were recrystallized from water for β-CyD but from 1-propanol (6)–water (4) mixture for α- and γ-CyD's. Pure DMβCyD for biochemistry research and pure DMαCyD were obtained from Wako Pure Chemical and Toshin Chemical, respectively, and used without further treatment. Heterocyclic amine *N*-oxides studied were 4-nitroquinoline *N*-oxide (4NQO), 4-nitropyridine *N*-oxide (4NPO), quinoline *N*-oxide (QO), and 3-methoxypyridine *N*-oxide (3MOPO). Commercial 4NQO, 4NPO, and QO were purified by the method recommended by Ochiai.[14] For QO, high-vacuum sublimation was also applied. 3MOPO, showing a dominant blue shift of the UV spectrum in the entire region in protic solvents,[15] was synthesized by the reaction of 3-chloropyridine *N*-oxide with CH_3ONa and repeatedly sublimed (mp 102 °C).[16]

Results and Discussion

CyD Complexes with Aromatic *N*-Oxides and Their Spectral Behavior

A typical example of the experiments on three-component systems consisting of CyD's and *N*-oxides in aqueous solvents is the complex formation of 4NQO with DMβCyD in water. The basicity of 4NQO is weak, and its pK_a was reported to be -1.03,[17] so that only the neutral form of 4NQO exists in water. The shift of electronic spectra caused by the complex formation should be therefore ascribed to the change of the electronic state of neutral 4NQO. Figure 1 illustrates the spectral change of 4NQO upon complex formation with DMβCyD in water. We can see there that the spectrum of 4NQO shifts to longer wavelengths with the addition of DMβCyD through an isosbestic point, showing that the 1 : 1 complex between them is formed in an aqueous solvent.[10a,18,19] This kind of spectral behavior was also observed in the other systems studied here (*vide post*). Although the concentration of DMβCyD is of the order of 10^{-3}—10^{-1} mol·dm^{-3}, that of 4NQO is 6.37×10^{-5} mol·dm^{-3} (see Fig. 1), so that we can safely write equation 1 for the equilibrium constant $K=C_{GH}/C_G\cdot C_H$.

$$K=C_{GH}/C_GC_H^0 \qquad (1)$$

where C_G, C_H, and C_{GH} are the equilibrium concentration of 4NQO (guest), DMβCyD (host), and the guest–host inclusion complex, respectively. The analytical concentration of DMβCyD is C_H^0, and $C_H=(C_H^0-C_{GH})$ is equal to C_H^0 to a good approximation, because $C_H^0\gg C_{GH}$ (*vide supra*). However, it is easily understood that $C_G=(C_G^0-C_{GH})$ is very different from C_G^0. CyD's do not show UV absorption in the near UV region, so that applying the Lambert–Beer law to the light absorption due to 4NQO and the complex, we can get Eq. 2, since $(C_G/C_{GH})=$

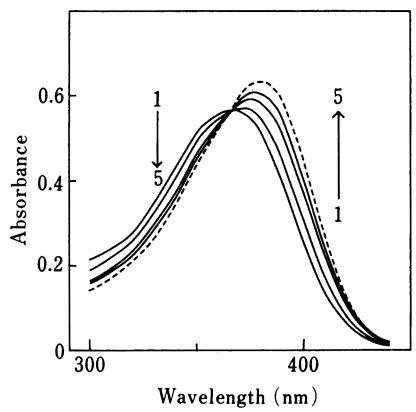

Fig. 1. UV Spectra of 4NQO at Various Concentrations of DMβCyD in Water at 25 °C and 1 cm Cell Length

Concentrations of DMβCyD were 0, 1.97×10^{-2}, 7.89×10^{-2} and 1.58×10^{-1} mol·dm^{-3} for curves 1—4, respectively. Curve 5 is for the complex itself calculated from the equilibrium constant K. The concentration of 4NQO is constant at 6.37×10^{-5} mol·dm^{-3}.

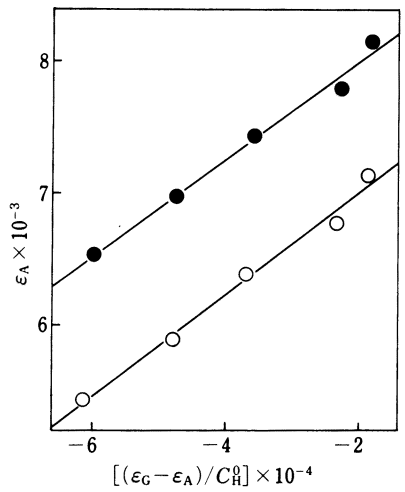

Fig. 2. Linear Relation of ε_A Values to $(\varepsilon_G-\varepsilon_A)/C_H^0$ at 395 (Open Circles) and 390 nm (Closed Circles) for 4NQO–DMβCyD Complexes

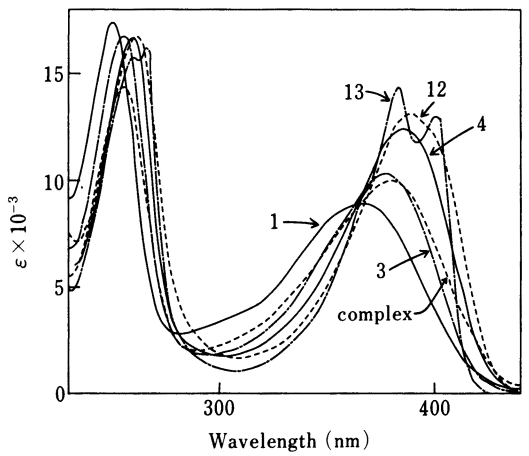

Fig. 3. Solvent Effect on the UV Spectrum of 4NQO at Room Temperature

Curves 1, 3, 4, 12, and 13 are, respectively, for water, ethanol, acetonitrile, dioxane, and cyclohexane (refer to the footnote of Fig. 4). The spectrum of the 4NQO–DMβCyD complex itself in water is given by the curve labelled "complex".

$[(\varepsilon_{GH}-\varepsilon_A)/(\varepsilon_A-\varepsilon_G)]$.[19]

$$\varepsilon_A=(1/K)[(\varepsilon_G-\varepsilon_A)/C_H^0]+\varepsilon_{GH} \quad (2)$$

Here, ε_G and ε_{GH} are the molecular absorption coefficients of the guest and inclusion complex, respectively, ε_A being the apparent one. Using the slope and intercept of the ε_A *vs.* $(\varepsilon_G-\varepsilon_A)/C_H^0$ linear plot we can easily evaluate K and ε_{GH}. An example of the linear plot is illustrated in Fig. 2 for the data of Fig. 1. Wavelengths employed for determining K and ε_{GH} values are those where the intensity change upon the addition of DMβCyD is quite large. The absorption spectrum of the inclusion complex itself was then calculated using the equilibrium constant K, and the result is shown in Fig. 1. The same system as in Fig. 1 was also studied in pH 7 buffer solution with $I=0.5$. In addition, these studies were extended to the systems composed of QO plus DMβCyD, 4NPO plus DMβCyD or DMαCyD, and 3MOPO plus DMβCyD or DMαCyD in water. In any case, a clear red shift of the *N*-oxide spectra is caused by the host–guest interaction, and only the neutral form of these *N*-oxides exists in water on the basis of their reported pK_a values.[14b,c] All the experimental results are listed in Table I. When we employed α- and β-CyD's as hosts the spectral change (red shift phenomenon) caused by the host–guest interactions was small in comparison with that for dimethylated CyD's, so accurate analyses were not done. The main reason for this is that the solubility of these unmethylated CyD's is small compared with that of the dimethylated CyD's, and the present K values are relatively small (less than 30 in water; Table I), so that the addition of sufficient α- or β-CyD to bring about such spectral change as is seen in Fig. 1 is impossible.

Solvent Effect on UV Spectra of Heterocyclic Amine *N*-Oxides and Their Hydrophobic Interaction with CyD's

It is well known that the UV spectra of aromatic amine *N*-oxides shift markedly to shorter wavelength with increasing solvent polarity, and the hydrogen bonding interaction written as $\gg N\rightarrow O\cdots HOR$ plays an important role in this.[12,13,20] The solvent dependence of the spectrum of 4NQO is depicted in Fig. 3. Of the parameters scaled as an index for solvent

TABLE I. Spectroscopic and Equilibrium Constants as Regards the Inclusion Complex Formation of Aromatic Amine *N*-Oxides with Dimethylated α- and β-CyD's[a]

Sample	Temp. (°C)	In water		In DMβCyD complex				In DMαCyD complex				log $P^{e)}$
		$\tilde{\nu}_{max}$ (10^3 cm^{-1})	ε_{max}[b]	$K^{c)}$	$\tilde{\nu}_{GH.max}$ (10^3 cm^{-1})	ε_{max}[b]	$\Delta\tilde{\nu}^{d)}$ (cm^{-1})	$K^{c)}$	$\tilde{\nu}_{GH.max}$ (10^3 cm^{-1})	ε_{max}[b]	$\Delta\tilde{\nu}^{d)}$ (cm^{-1})	
4NQO	25.5	27.26	8890	26.4	26.32	9840	940	—[g]				1.02
	26.0	27.36[f]	9230[f]	34.0[f]	26.49[f]	9920[f]	870[f]	—[g]				
QO	25.0	32.05	7640	12.3	30.63	7770	1420					0.39
4NPO	25.0	31.74	11100	8.5	30.85	10800	890	7.7	30.41	11300	1330	−0.57
3MOPO	25.0	39.17	10900	5.7	38.58	9270	590	5.1	38.39	10100	780	

a) See text for the abbreviations of compounds. *b*) Molecular absorption coefficient (dm^3·mol^{-1}·cm^{-1}). *c*) Equilibrium constant (dm^3·mol^{-1}). These are the average values calculated at several wavelengths, where the change of optical density with the complex formation is large. The standard deviation (S.D.) is 1.0 (maximum)—0.4 (minimum) except for that (S.D. = 2.7) in the buffer solution. *d*) Red shift of the longest wavelength high-intensity UV band with the change of environment from water to the complex formed in water. *e*) *P* is the partition coefficient between the octanol and buffer solutions (pH 7). See reference 30. *f*) These are experimental values obtained in pH 7 buffer solutions with ionic strength 0.5. See the text for details. *g*) A reliable *K* value could not be obtained in this DMαCyD system.

polarity, E_T (Dimroth's E_T)[21] and AN (Gutmann's acceptor number)[22] values are quite good descriptors for the solvent effect on the above UV spectra, because proton donors in interaction systems such as hydrogen bonding are well interpreted as electron acceptors based on charge transfer theory.[12,23] Also, note that the E_T and AN values are well correlated to each other.[22] We have now recorded the spectra of *N*-oxides, employed here, in various solvents, and the maximum wave numbers (cm^{-1}) of their intramolecular CT bands,[12,15] as well as those observed in the host–guest complex itself, were plotted against E_T or AN values. There was always a good correlation in such plots, an example being shown in Fig. 4. In this figure such solvents as cyclohexane, carbon tetrachloride, *etc.* lie well away from the straight line. This might indicate that the solvent effect on electronic spectra in these aprotic inert solvents could be better explained by the application of McRae's theory[12,24] or other approaches[12,25] using Onsager's reaction field model rather than the present treatment. Now, we are able to estimate the E_T or AN values of the environments in which the *N*-oxides exist in CyD complexes. The results are given in Table II, from which it seems possible to say that 4NQO and QO in their DMβCyD complexes dissolved in water are in a hydrophobic environment roughly equivalent to ethanol,[26,27] but in the cases of 4NPO and 3MOPO complexes with DMβCyD or DMαCyD they are in a hydrophobic environment roughly equivalent to methanol.[26,27] It is well known that the *N*-oxide group oxygen atom in heterocyclic amine *N*-oxides is quite a good proton acceptor for hydrogen bond formation,[12] but the hydrogen bonding ability of an NO_2 group is very weak.[12,28] So, the N→O group in CyD complexes may be in a configuration where it protrudes more or less from the CyD cage and still interacts with water molecules as well as free OH groups (3-OH) of a dimethylated CyD framework.

4NQO and QO have an extra benzene ring compared with 4NPO and 3MOPO, and therefore the former two are naturally more hydrophobic than the latter two, so that 4NQO and QO may show a stronger interaction with DMβCyD than 4NPO and 3MOPO. As expected (Table I), the equilibrium constant *K* values for 4NQO and QO are larger than those for 4NPO and 3MOPO. In other words, the hydrophilic interaction of an ≫N→O group in the complex itself with surrounding water molecules or free OH groups of a dimethylated CyD framework is smaller for the former two than the latter. In the case of the molecular interactions of the above-mentioned aromatic *N*-oxides with unmethylated CyD's such as α-

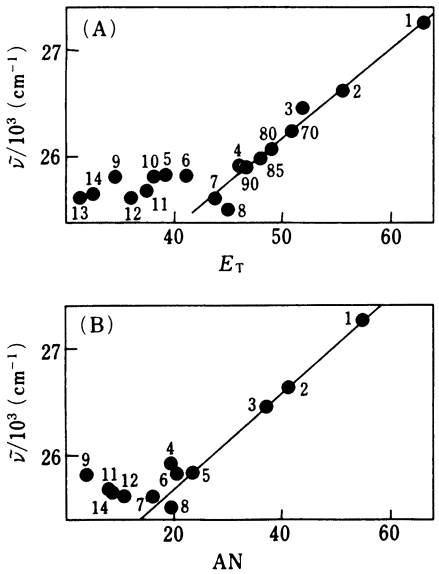

Fig. 4. Correlation of the Longest Wavelength High-Intensity UV Band Maximum to the Solvent Polarity Scales E_T (A) and AN (B)

Each number denotes the solvent given in parentheses: 1 (H_2O), 2 (CH_3OH), 3 (C_2H_5OH), 4 (CH_3CN), 5 ($CHCl_3$), 6 (CH_2Cl_2), 7 ($HCON(CH_3)_2$), 8 ($(CH_3)_2SO$), 9 ($C_2H_5OC_2H_5$), 10 ($CH_3COOC_2H_5$), 11 (tetrahydrofuran), 12 (dioxane), 13 (cyclohexane), 14 (CCl_4), 70 (70% (v/v) aqueous dioxane), 80 (80% dioxane), 85 (85% dioxane), 90 (90% dioxane). For solvent 13, the weighted-mean wave number of the absorption band with vibrational structures is adopted as the band maximum.

TABLE II. E_T and AN Values Evaluated for the Aromatic Amine *N*-Oxides in the Inclusion Complexes with Dimethylated CyD's[a] Formed in Water[b]

Samples	DMβCyD		DMαCyD	
	E_T	AN	E_T	AN
4NQO	51.6	34.2		
	53.9[c]	38.4[c]		
QO	51.6			
4NPO	57.9	46.1	55.1	41.7
3MOPO	58.6	47.5	57.2	45.2

a) See the text for the abbreviations of compounds. *b*) The E_T and AN values of water, methanol, ethanol, and acetonitrile are as follows: 63.1, 55.5, 51.9 and 46.0 for E_T, and 54.8, 41.3, 37.1 and 19.3 for AN, respectively. *c*) These were evaluated from the data in pH 7 buffer solutions with ionic strength 0.5. See the text for details.

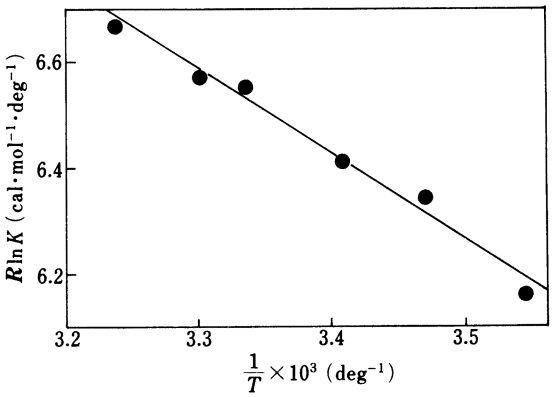

Fig. 5. Linear Relation of $R\ln K$ to $1/T$ Pertaining to the 1:1 Complex Formation of 4NQO with DMβCyD in Water

TABLE III. Thermodynamic Data Obtained from the Temperature Dependence of the Equilibrium Constant for 1:1 Inclusion Complex Formation of 4NQO with DMβCyD in Water

	K[a]						$\Delta H°$	$\Delta S°$
Temp. (°C)	9.1	15.2	20.4	25.5	29.9	35.8	(kcal·mol^{-1})	(cal·K^{-1}·mol^{-1})
4NQO	22.2	24.3	25.2	27.0	27.3	28.7	1.62 (±0.13)	11.94 (±0.46)

a) The K values were calculated at 390 nm, where the change in optical density upon complex formation is by far the largest.

or β-CyD, accurate equilibrium constant (K) values could not be determined. As mentioned in the foregoing section one of the main reasons is the lower solubility of α- or β-CyD in water, making it difficult to evaluate K values of the order given in Table I. So, in the present stage, the ability of α- or β-CyD to include the *N*-oxides is not clear, but we suppose from the

spectral experiments that the complexing ability of α- or β-CyD is rather less than that of DMβCyD or DMαCyD for the present *N*-oxides. Anyway, reliable results were obtained with DMαCyD and DMβCyD, which are more hydrophobic than α- and β-CyD's. Since there are many reports showing quite large K values for inclusion complex formation of aromatic and aliphatic substances, such as benzene and naphthalene derivatives, alcohols, *etc.*,[1-11,29] with α and β-CyD's in aqueous solutions, the *N*-oxides studied seem to have weaker inclusion complex formation ability than the other organic compounds. The main reason for this may be the specific nature of aromatic *N*-oxides, the N→O bond in which is very polar and a good hydrogen bond acceptor. Thus, these *N*-oxide groups are quite hydrophilic, and the partition coefficients (log P) between organic and water solvents are also small in comparison with those of usual organic substances having similar structures.[30,31]

Temperature Dependence of Equilibrium Constants

For studying the mechanism of inclusion complex formation the temperature dependence of the equilibrium constant K was investigated on the typical system of 4NQO and DMβCyD. The result is given in Table III, and the correlation of $\boldsymbol{R}\ln K$ *vs.* $1/T$ is depicted in Fig. 5, where we can see a good linear relation with a correlation coefficient of 0.986. From the slope and intercept, the changes of enthalpy (ΔH°) and entropy (ΔS°) pertinent to the complex formation were assessed as $\Delta H^\circ = 1.62$ (± 0.13: kcal·mol^{-1}) and $\Delta S^\circ = 11.94$ (± 0.46: cal·K^{-1}·mol^{-1}). These data indicate that since a free energy change ($\Delta F^\circ = -\boldsymbol{R}T\ln K$) due to complex formation is divided into $\Delta F^\circ = \Delta H^\circ - T\Delta S^\circ$, the stabilization caused by the above complex formation in the water system ($K = 27.0$ at 25.5 °C) would arise from the term $-T\Delta S^\circ$, and the contribution from the term ΔH° is less than that from ΔS°, because the value is positive, though it is quite small as was observed for the inclusion complex formation of β-CyD with 1-alkanols.[31] Of the various factors contributing to host–guest interactions in aqueous media[4,5,7,9] the dehydration process of 4NQO seems to play an important role in the inclusion complex formation in the present case. As has been discussed above, the polar *N*-oxide dative bond in a 4NQO molecule is considered to be well hydrated, and this water should be removed in order to include the molecule into a DMβCyD cage; this may account for the positive ΔS° and ΔH°. Needless to say, the process of the replacement of some H_2O molecules present in a DMβCyD cage by a guest molecule can not be neglected in explaining the positive ΔS°. Strictly speaking, we must deal with the energy cycle taking into consideration both the gas and water phases to estimate ΔH° and ΔS° pertinent to the complex formation.[9,32] As a compensation of each step energy value in the energy cycle, we think that there is a small positive ΔH° value in the present case. In the gas phase, however, the ΔH° value would turn out to be negative, *i.e.*, the interaction potential energy between the host and guest molecules may be negative.

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