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Analyses of the Acid Dissociation Constants of Multisubstituted Diarylamines Measured in Solvents and Micellar System

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The acid dissociation constants of a number of multisubstituted diarylamines measured in an α-dodecyl-ω-hydroxyocta(oxyethylene) micellar system ($\log K_A^m$) were compared with those measured in 50% (v/v) EtOH–water mixture ($\log K_A^e$). The electronic effects of substituents on $\log K_A^m$ values were similar to, whereas the steric effect of substituents was larger than, those examined previously on the $\log K_A^e$ values. The acid dissociation constant of each compound was generally larger in the less polar (ε: ca. 28) micellar system than that in 50% EtOH–water mixture (ε: ca. 52). To understand this phenomenon, solvent effects on the dissociation constant of compound **37** as a model were examined. We found that compound **37** forms a hydrogen-bonded or proton-transfer complex with DMSO in $CHCl_3$. The anionic form of compound **37** was favored in partition at a higher DMSO content in a DMSO–water mixture compared to the neutral form. These results suggest that contributions of such as hydrogen bonding and dispersion force are of primary importance regarding the effect on the acid dissociation of the series of compounds in the micellar system.

There are a number of biologically active chemicals the acid-base dissociation behavior of which in the biomembranous phase has been proposed to play a significant role in their activities.[1—5] Among them, one of the most remarkable examples is the uncoupler of the oxidative phosphorylation of mitochondria. We previously showed that the variations in the uncoupling potency of diarylamines[4] are well-correlated with variations in the $\log K_A$ values measured in α-dodecyl-ω-hydroxyocta(oxyethylene) (hereafter abbreviated as $C_{12}E_8$) micellar system. The result suggests that the variations in $\log K_A$ values of these compounds in the mitochondrial membrane phase are satisfactorily approximated by those $\log K_A$ values measured in the above system. To investigate the physicochemical properties of the biomembranous phase, the surfactant micellar systems have been widely used as a simple model.[6—8] However, there is less information available on the substituent and substructural effects on the acid dissociation of a systematically selected series of acidic compounds in the micellar system.

In the previous studies,[4,9] we have found that the diarylamines had a larger ionization constant in the $C_{12}E_8$ micellar system than that in 50% EtOH–water system though the dielectric constant (ε) is larger in the latter case. The purpose of this report is to elucidate the factors affecting the acid dissociation in the micellar system. We will examine the relationship between the ionization constant measured in nonionic micellar system ($\log K_A^m$) and those measured in 50% EtOH–water ($\log K_A^e$), in groups which are divided according to their substitution patterns as shown below. Also, we will study the possible solute–solvent interactions affecting the acid dissociation in the micellar system using compound **37** as a model (Chart 1).

Materials and Methods

Compounds and Chemicals: The diarylamines were the same samples previously used.[9] $C_{12}E_8$ was from Nikko Chemical Co. 2-Hexadecyl-6-quinolinol (H_6HQ) was kindly supplied by Dr. C. Drummond (Division of Chemicals and Polymers, CSIRO Australia). All organic solvents were spectroscopic analysis grade from Wako Pure Chemical Industries. Other reagents were of the purest grade commercial available.

Measurements of the Acid Dissociation in the Micellar System: The acid dissociation constants of diarylamines in a $C_{12}E_8$ micellar system. K_A^m, were from the earlier study.[4] The dielectric constant, ε, of the micellar interfacial region of $C_{12}E_8$ was determined using a solvatochromic indicator H_6HQ by the method of Drummond et al.[7] The mean value of ε was 28, which was close to 29 reported.[7]

Measurements of the Acid Dissociation Constant in Various Organic Solvent–Water Mixtures: The acid dissociation constant of compound **37** in various water-miscible organic solvent–water mixtures was measured spectrophotometrically with a Shimadzu UV-3000 spectrophotometer by the method described previously[9] except for the estimation of the pH-meter readings of the media. The proton concentrations in dioxane–water mixtures were obtained

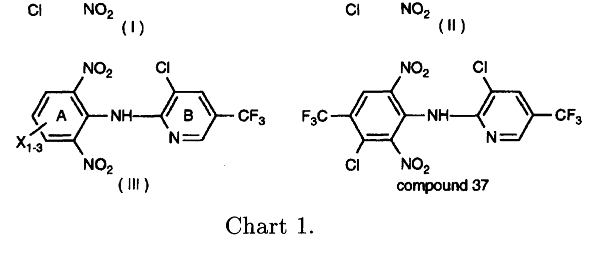

Chart 1.

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by correcting the pH-meter readings using the method described.[10,11] The pH-readings in MeOH– and EtOH–water mixtures were corrrected by the method of Gelsama et al.[12] For the estimation of the apparent $\log K_\mathrm{A}$ value in DMSO–water mixtures, the pH-meter readings were not corrected.

Spectroscopic Measurements: The UV/vis spectroscopic measurements were performed in solvent systems of DMSO–, dioxane–, EtOH–, and MeOH–$\mathrm{CHCl_3}$ of various compositions with a Shimadzu UV-3000 at 25±0.5°C. ^{1}H NMR spectra were measured at 400 MHz with JEOL (GSX-400) NMR spectrometer using the pulsed Fourier-transform mode.

Measurements of the Partition Coefficient in Systems of Heptane–Water and Heptane–Aqueous DMSO Solvents: The partition coefficient (P) of compound **37** between a heptane (10 ml) and aqueous or DMSO–water mixture phases was measured using essentially the same procedure as described by Watarai and Suzuki.[13] Heptane containing various amounts of compound **37** was vigorously agitated with aqueous solution in a thermostated shaker bath (25±1°C) for 2 h. The partition coefficients of the anionic [$P_{(\mathrm{R}^-)}$] and the neutral (P_RH) forms were determined in 0.01 M NaOH and HCl solutions, respectively (1 M=1 mol dm^{-3}). The volume ratios of heptane to the aqueous solution or DMSO–water mixture were 1 : 1 and 1 : 2 for $P_{(\mathrm{R}^-)}$ and P_RH measurements, respectively. For each partition coefficient, four different concentrations over a range of about tenfold from 0.05 to 2 mM were used, which were dependent on the DMSO content and the measurement of the forms of compound **37**. The $\log P$ value was the average of the values of two series measurements.

For the estimation of P_RH, the concentration of compound **37** in water or a DMSO–water mixture phase was determined spectrophotometrically by alkalinization of the acidic phase with small portions of concentrated NaOH solution and that in the heptane phase was estimated from the difference between the total amount and the amount in the aqueous or aqueous DMSO phase. The concentrations in the aqueous and heptane phases were directly measured for the determination of $P_{(\mathrm{R}^-)}$ between the heptane phase and the aqueous phase, but for the estimation of $P_{(\mathrm{R}^-)}$ between heptane and DMSO–water mixtures only the concentration in the heptane phase was determined.

Procedure of the Analyses of Substituent Effects: The analyses of the substituent effects on the acid dissociation in the micellar system were performed by the same procedures used for the analyses of those in 50% EtOH–water.[9] In the analysis of the relationship between $\log K_\mathrm{A}^\mathrm{m}$ and $\log K_\mathrm{A}^\mathrm{e}$, we used the $\log K_\mathrm{A}^\mathrm{e}$ as an independent parameter in the same way as other substituent parameters. The electronic effect parameter that was used depended upon the locations relative to the NH side chain and the substitution patterns. The Taft–Kutter–Hansch E_s steric parameter was used to reflect the steric effect of an *ortho* substituent.[14] For the compounds of Series I, the *ortho* substituents were divided into $E_\mathrm{s}(\mathrm{L})^\mathrm{ortho}$ for the larger and $E_\mathrm{s}(\mathrm{S})^\mathrm{ortho}$ for the smaller ones according to their bulkiness. For the compounds of Series III, the steric effects of the both *meta* and *para* substituents were shown to relayed to the *ortho* nitro group through the *meta* substituent, thereby affecting the nitro group's stereoelectronic properties. The cross-product $E_\mathrm{s}^\mathrm{m} \cdot E_\mathrm{s}^\mathrm{p}$ was used to reflect the buttressing steric effect of *meta* and *para* substituents. The results of the correlations are reported only when each of the parameters was found to be significant above the 95% level by F-test.[15]

Results and Discussion

1) Regression Analyses of the Acid Dissociation Constants of Diarylamines in the $\mathrm{C_{12}E_8}$ Micellar System. The correlation results deduced from $\log K_\mathrm{A}^\mathrm{m}$ showed that the electronic effects of substituents on the dissociation constants are not so different from those deduced from $\log K_\mathrm{A}^\mathrm{e}$. Here, we will show only the results obtained by comparison analyses of the dissociation constants measured in the two systems. The $\log K_\mathrm{A}^\mathrm{m}$ and $\log K_\mathrm{A}^\mathrm{e}$ values of Series I, II, and III compounds are listed respectively in Tables 1, 2, and 3, along with the parameters used.

The best correlation equation for each series of compounds is shown below.

Series I:

$$\mathrm{p}K_\mathrm{A}^\mathrm{m} = \underset{(0.054)}{1.056}\mathrm{p}K_\mathrm{A}^\mathrm{e} + \underset{(0.171)}{0.288}E_\mathrm{s}(\mathrm{S})^\mathrm{ortho} - \underset{(0.507)}{1.697} \tag{1}$$

$$n = 23,\ s = 0.116,\ r = 0.998,\ \text{and}\ F_{2,20} = 2821.2$$

In this and the following equations, n is the number of compounds included in the correlation, s is the standard deviation, and r is the correlation coefficient. The figures in parentheses are the 95% confidence intervals.

Table 1. Observed and Calculated $\mathrm{p}K_\mathrm{A}$ Values and Substituent Parameters of Series I Compounds[a]

No.	Compound	$\mathrm{p}K_\mathrm{A}^\mathrm{m}$			$\mathrm{p}K_\mathrm{A}^\mathrm{e}$	$-E_\mathrm{s}(\mathrm{S})$
		Obsd	Calcd[b]	Dev.		
1	3-$\mathrm{CF_3}$	8.71	8.88	−0.17	10.01	0
2	4-Cl, 3-$\mathrm{CF_3}$	8.10	7.94	0.16	9.12	0
3	3, 5-$\mathrm{(CF_3)_2}$	7.05	7.12	−0.07	8.35	0
4	4-Br	9.20	9.14	0.06	10.26	0
5	4-Cl	9.32	9.17	0.15	10.29	0
6	4-$\mathrm{CF_3}$	8.38	8.33	0.05	9.49	0
7	4-$\mathrm{OCF_3}$	9.23	9.40	−0.17	10.50	0
8	2-Br	8.86	8.78	0.08	9.92	0
9	2-Cl, 5-$\mathrm{CF_3}$	7.39	7.49	−0.10	8.70	0
10	2, 4-$\mathrm{Cl_2}$, 5-$\mathrm{CF_3}$	6.62	6.66	−0.04	7.91	0
11	2-Cl, 4-$\mathrm{CF_3}$	7.00	7.01	−0.01	8.24	0
12	2, 4-$\mathrm{F_2}$	8.75	8.64	−0.11	9.78	0
13	2-$\mathrm{CF_3}$	8.13	8.16	−0.03	9.33	0
14	4-Cl, 2-$\mathrm{CF_3}$	7.07	7.10	−0.03	8.33	0
15	2,4,6-$\mathrm{Br_3}$,3-$\mathrm{CF_3}$	4.89	4.93	−0.04	6.59	1.16
16	2,6-$\mathrm{Br_2}$, 4-$\mathrm{CF_3}$	4.90	4.86	0.04	6.52	1.16
17	2-Br,4-Cl,6-$\mathrm{CF_3}$	4.96	5.04	−0.08	6.69	1.16
18	2-Br,6-Cl,4-$\mathrm{CF_3}$	4.92	5.04	−0.12	6.64	0.97
19	2,4,6-$\mathrm{Cl_3}$	6.36	6.50	−0.04	8.02	0.97
20	2,4-$\mathrm{Cl_2}$,6-$\mathrm{CF_3}$	5.01	5.04	−0.03	6.64	0.97
21	2,6-$\mathrm{Cl_2}$,4-$\mathrm{NO_2}$	3.32	3.14	0.18	4.84	0.97
22	2,4,6-$\mathrm{Cl_3}$,3-$\mathrm{CH_3}$	6.97	6.76	0.21	8.27	0.97
23	2,4,6-$\mathrm{Cl_3}$,3,5-$\mathrm{(CF_3)_2}$	3.56	3.58	−0.02	5.26	0.97

a) Parameters were from Ref. 9. b) Calculated by use of Eq. 1.

Table 2. Observed and Calculated pK_A Values and Substituent Parameters of Series II Compounds[a]

No.	Compound	pK_A^m Obsd	Calcd[b]	Dev.	pK_A^e	$-E_s$
24	6-Cl,5-CF_3	7.24	7.03	0.21	7.65	0
25	5-Br	8.75	8.80	−0.05	9.10	0
26	5-Cl	8.87	8.74	0.13	9.05	0
27	5-NO_2	6.20	6.13	0.07	6.91	0
28	5-CF_3	8.28	8.04	0.24	8.48	0
29	3-Br,5-Cl	7.05	6.92	0.13	7.78	1.16
30	3-Br-5-CF_3	6.11	6.05	0.06	7.07	1.16
31	3-Br,6-Cl, 5-CF_3	4.90	4.98	−0.08	6.19	1.16
32	3-Cl,5-Br	7.02	7.18	−0.16	7.96	0.97
33	3,5-Cl_2,4-Me	7.56	7.53	0.03	8.25	0.97
34	3,5-Cl_2,4,6-Me_2	7.99	8.19	−0.20	8.79	0.97
35	3,5,6-Cl_3,4-CF_3	4.47	4.52	−0.05	5.77	0.97
36	3,5-Cl_2,6-Me	7.59	7.63	−0.04	8.33	0.97
37	3-Cl,5-CF_3	6.18	6.15	0.03	7.11	0.97
38	3,6-Cl_2,5-CF_3	4.83	4.98	−0.15	6.15	0.97
39	3-Cl,6-NO_2	5.77	6.10	−0.33	7.07	0.97
40	3-CH_3	9.25	9.54	−0.29	9.95	1.24
41	3-NO_2	7.23	7.08	0.15	8.18	2.52
42	3-NO_2,5-CF_3	4.83	4.73	0.10	6.25	2.52
43	3-CF_3	6.85	6.56	0.29	7.73	2.40
44	5-Br,6-Cl,3-CF_3	4.11	4.13	−0.02	5.73	2.40
45	6-Cl,3-CF_3	5.16	5.26	−0.10	6.66	2.40

a) Parameters were from Ref. 9. b) Calculated by use of Eq. 2.

Table 3. Observed and Calculated pK_A Values and Substituent Parameter of Series III Compounds[a]

No.	Compound	pK_A^m Obsd	Calcd[b]	Dev.	pK_A^e	$-E_s(S)$
48	3-Br,4-CF_3	6.38	6.36	0.02	7.26	2.78
49	3-Cl,4-CH_3	10.14	10.19	−0.05	10.58	1.20
50	3-Cl,4-CF_3	6.18	6.28	−0.10	7.11	2.33
51	3-Cl,4-SO_2Me	5.36	5.21	0.15	6.16	2.57
52	3-Cl,4-SO_2NEt_2	6.17	6.31	−0.14	7.57	5.09
53	3-I,4-CF_3	6.72	6.76	−0.04	7.72	3.36
54	3-OBu(*i*),4-CF_3	8.06	7.97	0.09	8.53	1.32
55	3-OEt,4-CF_3	7.94	7.97	−0.03	8.53	1.32
56	3-OPr(*n*),4-CF_3	7.97	7.92	0.05	8.48	1.32
57	3,5-Cl_2,4-CH_3	9.53	9.30	0.23	9.94	2.41
58	4-COOEt	8.84	9.02	−0.18	9.30	0

a) Parameters were from Ref. 9. b) Calculated by use of Eq. 3.

F is the ratio of variances between observed and calculated values.

Series II:

$$pK_A^m = 1.216pK_A^e + 0.238E_s^{\text{ortho}} - 2.273 \qquad (2)$$
$$(0.072) \qquad (0.099) \qquad (0.602)$$
$$n = 22,\ s = 0.172,\ r = 0.994,\ \text{and}\ F_{2,19} = 802.8$$

Series III:

$$pK_A^m = 1.084pK_A^e - 0.152E_s^{\text{m}}\cdot E_s^{\text{p}} - 1.085 \qquad (3)$$
$$(0.084) \qquad (0.081) \qquad (0.807)$$
$$n = 11,\ s = 0.129,\ r = 0.997,\ \text{and}\ F_{2,8} = 679.8$$

From Eqs. 1, 2, and 3, we found that the variations in $\log K_A^m$ values correspond to those of the $\log K_A^e$ values in almost a one-to-one relationship be separating the contribution from the steric effect in each series of compounds. It demonstrated that the electronic effects of substituents are similar in the two systems.

The positive signs of the steric terms in Eqs. 1 and 2 suggest that the bulkier the *ortho* substituent was, the higher the dissociation constant was in the micellar system. In the micellar environment, the surfactant molecules are arranged in a highly ordered manner owing to their mutual hydrophobic interaction. The shape of a solute molecule such as branching and coplanarity affects greatly the stability of the molecule in the ordered lipid bilayer membrane.[16,17] Therefore, the result of relief of steric congestion in these compounds is expected to be more significant in the micellar system than that in the 50% EtOH–water system. This is because the surfactant molecules may force the crowded distorted tetrahedral structure of the neutral form to take a coplanar conformation to decrease the disturbance of the ordered lipid arrangement and to increase the steric congestion around the –NH moiety. The positive coefficient of the steric effect terms in Eqs. 1 and 2 reflected the relief of the increased steric congestion. In the compounds of Series I, only the $E_s(S)^{\text{ortho}}$ term was significant. As shown previously, the smaller *ortho* substituents are forced "inside" the molecular bend and interact with A ring substituents to a greater extent than did the larger ones.[9] Comparing the coefficient of each term of the best regression equation deduced from $\log K_A^m$ and $\log K_A^e$ by parameter analyses, it was found that the ratio, $\log K_A^m/\log K_A^e$ of the electronic, the $E_s(L)^{\text{ortho}}$, and $E_s(S)^{\text{ortho}}$ terms were 1.08, 1.74, and 2.24, respectively. Apparently, the proximity steric term especially the less bulky ones show more important effect on the dissociation of this series of diarylamines in the micellar system than that in the 50% EtOH–water system.

The $E_s^m\cdot E_s^p$ term in Eq. 3 was defined to indicate the buttressing steric effects of *para* and *meta* to *ortho* substituents on the twist of the two nitro groups.[9] The nitro groups of the neutral form of this series of compounds were assumed to be twisted the A ring plane less in the micellar system than in EtOH–water system, because the surfactant molecules would force the nitro groups and the whole molecules to take a coplanar conformation as discussed above. Therefore, the difference of the buttressing steric effects between the neutral and the ionized forms would be decreased in the micellar system. The negative coefficient of the $E_s^m\cdot E_s^p$ term reflected the less sensitivity of the buttressing steric effects in the micellar than those in the 50% EtOH–water systems.

In the comparison analyses, compounds **40**—**42** in

Series II and compound **58** in Series III were also included, which were excluded in the analysis of $\log K_{\mathrm{A}}^{\mathrm{e}}$ because of intramolecular hydrogen bonds. Equations 2 and 3 were confirmed in almost the same quality of the correlation and regression coefficients of each term as those obtained without the outliers, respectively (data not shown). The results suggest that the contribution of the formation of the intramolecular hydrogen bond to stabilize the neutral form of the outliers is similar in both $\mathrm{C_{12}E_8}$ micellar and 50% EtOH–water systems.

The $\log K_{\mathrm{A}}^{\mathrm{m}}$ value of each compound is generally larger than its $\log K_{\mathrm{A}}^{\mathrm{e}}$ value, as shown in Tables 1, 2, and 3 and exhibited by the negative constant terms in Eqs. 1, 2, and 3. Considering that the dielectric constant of the miceller interfacial region of $\mathrm{C_{12}E_8}$ (ca. 28) is lower than that of the 50% EtOH–water mixture (ca. 52[18]), these results seem to be peculiar in terms of the electrostatic theory of the medium effects on acid dissociation.[19] These results suggest that some specific and/or nonspecific interactions between diarylamines and their environment in the micellar system may affect the acid–base dissociation equilibrium. The "solvent" effects of the micellar interfacial region on the acid dissociation constants of diarylamines were examined below using various organic solvents and organic solvent–water mixtures as a simple model.

2) Solvent Effects on the Acid Dissociation Constant of Compound 37. The variations in the $\mathrm{p}K_{\mathrm{A}}$ value of compound **37** in various organic solvent (MeOH, EtOH, dioxane, and DMSO/water) mixtures with different water contents are shown in Fig. 1. The $\mathrm{p}K_{\mathrm{A}}$ value decreased with the increase in the content of organic solvents, in other words, with the decrease in the dielectric constant of the medium. According to the simple electrostatic theory of medium effect on acid dissociation, the relationship between the $\mathrm{p}K_{\mathrm{A}}$ and the dielectric constant of the medium is shown by Eq. 4,[19,20] predicting that the higher the dielectric constant of the medium, the lower is the $\mathrm{p}K_{\mathrm{A}}$ value of a neutral acid in that medium.

$$\mathrm{p}K_{\mathrm{A}(2)} = \mathrm{p}K_{\mathrm{A}(1)} + \mathrm{const.}(1/\varepsilon_2 - 1/\varepsilon_1) \qquad (4)$$

The relationships shown in Fig. 1 do not conform to the simple electrostatic theory. These results suggest that some solute–solvent interactions other than the electrostatic effect of the media are of primary importance in the acid dissociation equilibrium of compound **37**.

a) Hydrogen-Bonded and Proton-Transfer Complexes: The UV/vis spectra of compound **37** were measured with various contents of DMSO in $\mathrm{CHCl_3}$ as shown in Fig. 2. The inset in Fig. 2 shows the relationship of the absorbance at 335, 345, and 480 nm to the volume percent of DMSO. The intensity of the band observed at 335 nm in $\mathrm{CHCl_3}$ was decreased with the progressive addition of DMSO, a hydrogen-bond acceptor, to the $\mathrm{CHCl_3}$ solution of compound **37**, until the DMSO content reached ca. 50% (v/v). In this concentration range of DMSO, the absorption band at 480 nm was not observed. In the inset of Fig. 2, the absorption at 345 nm measured below 50% DMSO is not for the independent band but just for the shoulder of the band at 335 nm. Considering the steric congestion around the NH group of compound **37**, this "steric hin-

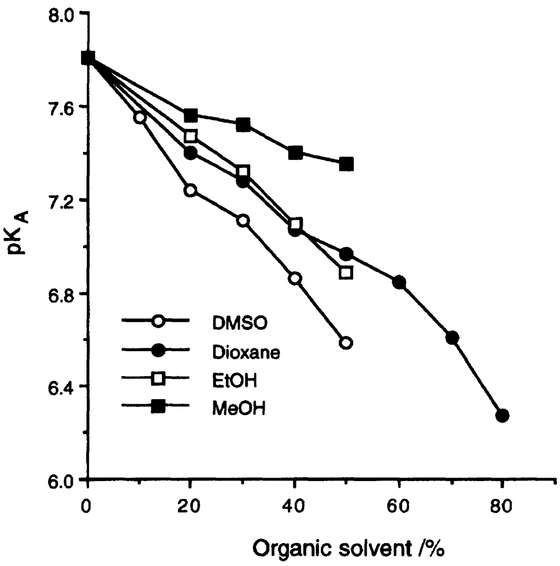

Fig. 1. The $\mathrm{p}K_{\mathrm{A}}$ value of compound **37** in various organic solvent–water mixtures with different contents of the organic solvent.

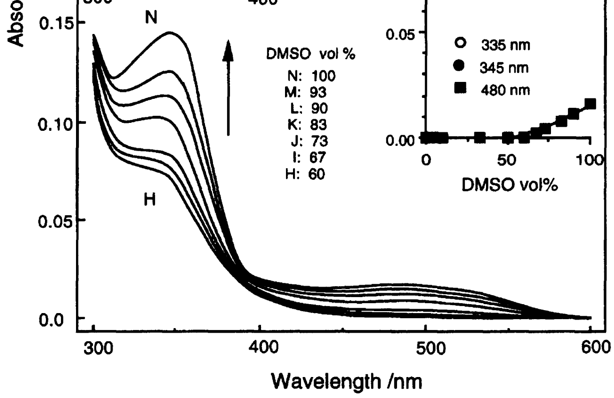

Fig. 2. The UV/vis spectra of compound **37** (18 μM) in $\mathrm{CHCl_3}$ in the absence (curve A) and in the presence of DMSO (curve B through N). The volume percentage of DMSO was shown in the figure. The inset shows the variations in the absorption intensities at the peak regions.

drance" was even enhanced with the access of DMSO molecules to the amino hydrogen to form the hydrogen-bonded complex (**I**).[21,22] The formation of the hydrogen-bonded complex (**I**) may induce variations in the conformation of the two nitro groups on the benzene ring moiety as well as in the dihedral angle between the benzene and pyridine rings, resulting in distortions of the resonance structure and consequently the decrease in the absorption at 335 nm (Chart 2). By further additions of DMSO, the peaks at 345 and 480 nm attributed to the anionic form of compound **37** appeared and increased progressively (Fig. 2). In Fig. 2, the absorption at 335 nm measured above 50% DMSO is not for the band assigned to the neutral form of compound **37** but just for the shoulder of the band at 345 nm. The appearance of the absorption band in the 480 nm region clearly suggests the formation of a proton-transfer (ion-pair) complex (**II**). Scott and his collaborators[23] have observed tautomeric equilibria between hydrogen-bonded and proton-transfer complexes of nitrophenols in the presence of Lewis bases similar to that observed here. They indicated that there is a range of solvent polarities or dielectric constant conditions which favor the formation of the proton-transfer complex over the formation of a hydrogen-bonded complex. The polarity for the appearance of proton-transfer between compound **37** and DMSO in $CHCl_3$ seems to be at the concentration of about 50% DMSO. Similar tautomeric equilibria of compound **37** were also observed with MeOH–$CHCl_3$ and EtOH–$CHCl_3$ systems (data not shown). The proton-transfer complexes were observed over 20 and 7% MeOH and EtOH, respectively. With dioxane in $CHCl_3$, the formation of a hydrogen-bonded complex between compound **37** and dioxane was detected, but the proton-transfer complex was not observed. This is probably due to the dielectric constant of dioxane (2.2) which is much lower than those of DMSO (46.5), EtOH (24.6), and MeOH (32.7).

^{1}H NMR spectroscopic studies of compound **37** in $CDCl_3$ with various contents of DMSO-d_6 were also performed (Fig. 3). Addition of DMSO-d_6 induced a steep increase in the chemical shift of the amino proton until the DMSO-$d_6$content reach about 50% (v/v). This result suggests the formation of a hydrogen-bonded complex (**I**). Further addition of DMSO-d_6 exceeding 50% affected the chemical shift of the amino proton less sensitively and the signal became broader than that below 50%. These changes in the resonance signal of the amino proton at a higher content of DMSO-d_6 (>50%) might be due to the formation of a proton-transfer complex. The possibility of the formation of the proton-transfer complex in the concentration region higher than about 50% DMSO is consistent with the results observed by the UV/vis spectroscopic measurements.

$$\mathrm{RH} + n\mathrm{B} \rightleftharpoons \underset{\text{(I)}}{\mathrm{R-H\cdots B}_n} \rightleftharpoons \underset{\text{(II)}}{\mathrm{R^-\cdots H^+ - B}_n}$$

Chart 2.

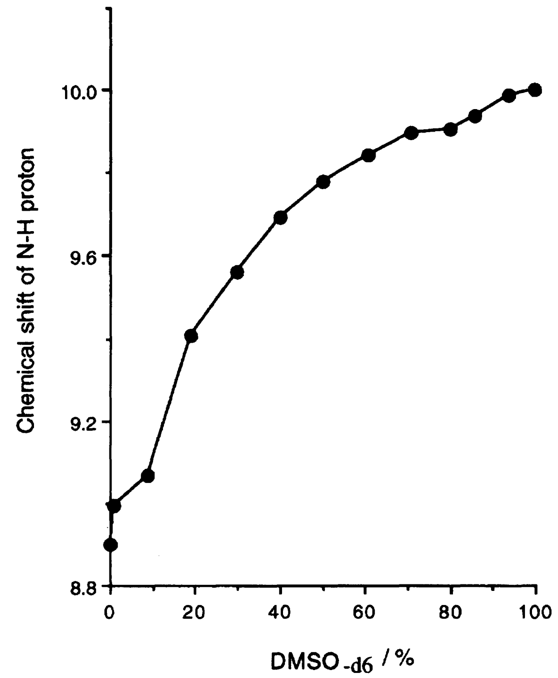

Fig. 3. The chemical shift of amino proton of compound **37** (0.04 M) varied with the concentration of DMSO-d_6 in $CDCl_3$.

The results of the UV/vis and NMR spectroscopic studies indicated that DMSO and also EtOH and MeOH could weaken the N–H bond of the amino group of compound **37** by forming hydrogen-bonded and proton-transfer complexes. Since these solvents are stronger hydrogen-bond acceptors than water, the formation of those kind of complexes is expected to favor the acid dissociation of compound **37** in these aqueous organic mixture solvents compared to that in water. It means that the capacity of hydrogen-bond acceptability of a solvent or solvent mixture could be a significant factor governing the dissociation of the diarylamines.

b) Solvation Energy of Compound 37: The variations in the pK_A value of an acidic compound in two solvents are related to the Gibbs free energy of transfer of all components involved in the dissociation equilibrium from one solvent to the other. Taking the case of the variation in the pK_A value upon transfer from water(W) to DMSO–water (D), this relation can be described as Eq. 5,[24)]

$$\Delta \mathrm{p}K_{\mathrm{A(D \leftarrow W)}} = \log {}^{\mathrm{W}}\gamma^{\mathrm{D}}_{(\mathrm{R}^-)} + \log {}^{\mathrm{W}}\gamma^{\mathrm{D}}_{(\mathrm{H}^+)} - \log {}^{\mathrm{W}}\gamma^{\mathrm{D}}_{\mathrm{HR}} \quad (5)$$

where ${}^{\mathrm{W}}\gamma^{\mathrm{D}}_{(\mathrm{R}^-)}$, ${}^{\mathrm{W}}\gamma^{\mathrm{D}}_{\mathrm{HR}}$, and ${}^{\mathrm{W}}\gamma^{\mathrm{D}}_{(\mathrm{H}^+)}$ are the solvent activity coefficients for the transfer of the anionic and neutral forms of compound **37** and the oxonium ion, respectively, from water (W) to DMSO–water mixtures (D), the activity coefficient of solutes in water being taken as the reference. The $\log {}^{\mathrm{W}}\gamma^{\mathrm{D}}_{(\mathrm{R}^-)}$ and $\log {}^{\mathrm{W}}\gamma^{\mathrm{D}}_{\mathrm{HR}}$ were achieved by measurement of the partition of compound

Table 4. pK_A Values, Partition Coefficient, and Solvent Activity Coefficients for Transfer of Compound **37** Acid and Its Anion Form Water to DMSO–Water Mixtures ($^{W}\gamma^{D}$)

DMSO%	pK_A	$\log {}^{W}\gamma^{D}_{HR}$	$\log {}^{W}\gamma^{D}_{(R^-)}$	$\log {}^{W}\gamma^{D}{}_{(H^+)}$ a)	$\log {}^{H}P^{D}{}_{HR}$ b)	$\log {}^{H}P^{D}{}_{(R^-)}$ c)
0	7.81				4.32±0.03	0.34±0.02
10	7.55	−0.30	−0.82	−0.48	4.02±0.03	−0.48±0.02
20	7.24	−0.58	−1.39	−0.80	3.74±0.03	−1.05±0.03
30	7.11	−0.89	−2.40	−1.20	3.43±0.02	−2.06±0.02

a) From Ref. 25. b) $\mathrm{Log}\,{}^{H}P_{HR}$ for DMSO 0% was directly measured with the system of heptane and water. Otherwise, the values were $\log {}^{H}P_{HR}$ with heptane and DMSO–water mixtures. c) $\mathrm{Log}\,{}^{H}P_{(R^-)}$ for DMSO 0% was directly measured with the system of heptane and water. Otherwise, the values were $\log {}^{H}P_{(R^-)}$ with heptane and DMSO–water mixtures.

37 between heptane (H) and various compositions of DMSO–water (D) mixtures, following the procedure of Bernasconi and Bunnell.[24] The partition coefficient of the neutral form of compound **37** (RH) in a system of heptane (H)–water (W) or a heptane (H)–DMSO–water mixture (D) is defined as the ratio of the equilibrium concentration of compound **37** (C_{HR}) distributed in the two phases of solvents as shown by Eq. 6 or 7.

$$P_{HR(H/W)} = {}^{H}C_{HR}/{}^{W}C_{HR} \tag{6}$$

$$P_{HR(H/D)} = {}^{H}C_{HR}/{}^{D}C_{HR} \tag{7}$$

The partition coefficient between the composition of the DMSO–water mixture and water is then given by the following equation,

$$P_{HR(D/W)} = P_{HR(H/W)}/P_{HR(H/D)} \tag{8}$$

while the solvent activity coefficient for the transfer from water to the composition of DMSO–water mixture is the inverse of $P_{HR(D/W)}$ (Eq. 9).

$${}^{W}\gamma^{D}_{HR} = 1/[P_{HR(D/W)}] = P_{HR(H/D)}/P_{HR(H/W)} \tag{9}$$

In a similar manner, the solvent activity coefficient for the anionic form (R^-) is given by Eq. 10.

$${}^{W}\gamma^{D}_{(R^-)} = 1/[P_{(R^-)(D/W)}] = P_{(R^-)(H/D)}/P_{(R^-)(H/W)} \tag{10}$$

From the measured $\log P_{RH}$ and $\log P_{(R^-)}$ values, $\log {}^{W}\gamma^{D}_{HR}$ and $\log {}^{W}\gamma^{D}_{(R^-)}$ values are calculated and summarized in Table 4 along with $\log {}^{W}\gamma^{D}_{(H^+)}$ values from Wells.[25] The negative solvent activities mean better solvation and greater stability. For such a "large" and hydrophobic molecule as compound **37** as the neutral form, solvation with DMSO has been shown to be substantially superior over that by water.[23] In fact, the neutral form of compound **37** is stabilized more in the solvent mixtures of higher DMSO contents, as reflected by the increase in the negative $\log {}^{W}\gamma^{D}_{RH}$ values with the increase in DMSO content in the solvent mixtures.

The anionic form of compound **37** was more stable in the solvent mixtures of higher DMSO contents. This fact is in contrast to cases for the anionic form of "simple" acidic compounds such as phenol and nitromethane.[24] For the anionic species of these "simple" acids, the negative charge mainly localized on the oxygen or carbon atoms is much better solvated by water in the form of a hydrogen bond, which achieves the maximum effectiveness towards localized charge, than by DMSO.[26] In the anionic form of compound **37**, the negative charge of which is highly delocalized because of the existence of a number of electron-withdrawing substituents, the hydrogen bond with water molecules may no longer be effective, while the solvation by the polarizable solvent DMSO could become the dominant factor (the polarizabilities of DMSO and water in terms of "α" defined by Miller[27] are 7.97 and 1.45 respectively). That is, the dispersion interaction of the largely delocalized (or dispersed) charge of the anionic species with polarizable DMSO might be the major factor governing the stability of the anionic form in a DMSO–water mixture. On the contrary, a hydrogen bond with the amino nitrogen would concentrate the negative charge. This effect does not favor charge delocalization. The precise argument based on Eq. 5 could not be possible because the pK_A values in DMSO–water mixtures were not corrected for pH-meter readings and the $\log {}^{W}\gamma^{D}_{(H^+)}$ values were determined under different conditions. However, the variations in the pK_A value shown in Fig. 1 are reasonable because the $\log {}^{W}\gamma^{D}_{(R^-)}$ values are more negative than those of the $\log {}^{W}\gamma^{D}_{RH}$ values obtained for the same content of DMSO of DMSO–water mixtures and the negative $\log {}^{W}\gamma^{D}_{(H^+)}$ values are also negative. Similar effects of the large charge delocalization (or dispersion) on the acid dissociation in DMSO–water mixtures have been reported with 9-substituted fluorene,[24] 2,2′,4,4′-tetranitrodiphenylmethane,[28] and picric aicd.[26,29] In analogy with a DMSO–water mixture, the dispersion force may contribute significantly to the stabilization of the anionic form of compound **37** in mixtures of water and water-miscible organic solvents such as MeOH, EtOH, and dioxane because the polarizabilities of MeOH, EtOH, and dioxane in terms of "α" defined by Miller[27] are higher (3.23, 4.94, and 8.60, respectively) than that of water (1.45).

As shown above, the pK_A^m value of each compound was smaller in the micellar interfacial region with a dielectric constant (ca. 28) lower than that in the 50% EtOH–water mixture (ca. 52). This was due to contributions of some specific and/or nonspecific solute–solvent interactions such as hydrogen bonding and dispersion between compound **37** and surfactant molecules. Compound **37** may be in the poly(oxyethylene) and glycol headgroups region of the micelle. The physicochemical properties of the interfacial region as a "solvent" are expected to be similar to those of structurally related dioxane having ether and methanol having hydroxyl moieties. Therefore, the solute-solvent interactions similar to those described above may also be important factors in determining the log K_A values of the test compounds in the micellar system.

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