Effect of Mixtures of Water and Organic Solvents on the Acidities of 5-Membered Heteroaromatic Carboxylic Acids

Chang Kiu Lee* [a], Eun Hee Jeoung [a], and In-Sook Han Lee [b]

[a] Department of Chemistry, Kangwon National University, Chuncheon, 200-701, Korea
[b] Department of Science Education, Kangwon National University, Chuncheon, 200-701, Korea
Received February 16, 1999

pKa values of various 5-membered heterocyclic aromatic carboxylic acids (pKa^s) were determined in solutions of 20.3, 35.2, 50.1, 65.1, and 79.9 weight percent of organic solvents in water. The pKa^s values show good linearity when they are ploted as a function of the dielectric constants of the mixed solvents methanol, ethanol, isopropyl alcohol, and tert-butyl alcohol. On the other hand, the pKa^s values show a poor correlation with the dielectric constants in aqueous acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, and dioxane. The pKa values in pure water and in pure organic solvent could be calculated by extrapolation of the plot of the pKa^s versus percentage of organic solvent. The pKa^s values of 4- and 5-substituted 2-thiophenecarboxylic acids were also determined, and the ρ values are calculated in the same series of the solvents.
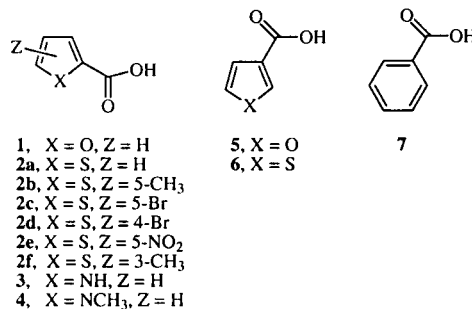
The reactivity of five-membered heterocyclic aromatic compounds containing one heteroatom has been extensively studied. Comprehensive reviews have appeared in literature. The effect of the heterocyclic ring on various kinds of reactions has been examined. The results can be related to either aromaticity of the heterocyclic ring or the inductive effect of the heteroatom [1]. Aromaticity, for example, as a criterion of the characteristics of cyclic compounds having 6π electrons has been discussed in terms of resonance energy, ring current, heat of hydrogenation, etc. However, the reactivity of the heterocycle portion of the heterocyclic compounds cannot be reliably predicted based on such physical properties.

There are numerous reports comparing the reactivities of five-membered heterocycles to those of benzene derivatives so that any correlation could be interpreted as a reference of aromaticity. One of the common strategies is the treatment of substituted five-membered heterocycles as if they are benzene derivatives [2]. For example, 5-substituted 2-furan- and 2-thiophenecarboxylic acids could be considered as benzoic acid derivatives and their pKa values may be used to calculate ρ values. Experimental ρ values which were determined in 80% methyl cellosolve for the thiophenes and the furans are 1.17 and 1.31, respectively, when the identical σ values for the substituents are employed and the ρ value of benzoic acid was 1 [3]. On the other hand, they are slightly different when determined in water and 1.20 for 2-thiophenecarboxylic acid and 1.40 for 2-furoic acid when 1.00 is assigned for benzoic acid [4]. Furthermore, the ρ value for a reaction in which O-H bond of a carboxylic acid is involved is quite different. For example, the ρ value for the reaction of 5-substituted 2-furoic acid with diphenyldiazomethane in ethanol is 1.00 at 15.5° and 0.975 at 24.85° [5].

It seems to be difficult to make a universal correlation for the effects of the substituents as well as the effects of the heteroatoms on the reactivity of the heterocycles because they are dependent on each other. They vary irregularly depending on the ring positions and the reaction conditions. Furthermore, for such heterocycles it may be difficult to find a reaction to which an identical mechanism can be applied [6].

Here we report our results from an extensive measurement of acid dissociation constants of the various 5-membered heterocyclic aromatic acids in mixtures of water and a variety of organic solvents. The main objective of our investigation was to examine the effect of solvents on the dissociation of the heterocyclic carboxylic acids which could be presumed to follow an identical reaction process.

1, X = O, Z = H
2a, X = S, Z = H
2b, X = S, Z = 5-CH$_3$
2c, X = S, Z = 5-Br
2d, X = S, Z = 4-Br
2e, X = S, Z = 5-NO$_2$
2f, X = S, Z = 3-CH$_3$
3, X = NH, Z = H
4, X = NCH$_3$, Z = H
5, X = O
6, X = S
7

Results and Discussion.

We used potentiometric titration to determine the acid dissociation constants because it is quite reliable for mixtures of various organic solvents and water [7]. Four protic solvents, methanol (MeOH), ethanol (EtOH), isopropyl alcohol (iPrOH), and tert-butyl alcohol (t-BuOH), were employed for the measurement of the acid dissociation constants. Four aprotic solvents, acetonitrile (AcCN), dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), and dioxane, were used for the same purpose. The dissociation constants were mea-

sured at 20.3, 35.2, 50.1, 65.1, and 79.9 weight percent of each solvent in water. The weight percent of solvent in water was chosen in order to allow comparison with the reported values of benzoic acid (7) in ethanol-water mixed solvent system. Grunwald and Berkowitz reported pKa^s values of 4.77, 5.24, 5.76, 6.10, and 6.79 for 7 in 20.3, 35.2, 50.1, 65.1, and 79.9% of ethanol-water, respectively [8]. We observed pKa^s values of 4.75, 5.25, 5.78, 6.26, and 6.79, which are reasonably close to the reported values for 7 (Table I). Establishing that our methodology correlates with the results in literature we measured the pKa^s values of 7 in mixtures of water and

other organic solvents. The results are listed in Table 1 for 7 as well as for the heteroaromatic carboxylic acids 1-6. With the same weight percent, the pKa^s values generally increase in the order of methanol < ethanol ≈ dimethyl sulfoxide < isopropyl alcohol < tert-butyl alcohol < N,N-dimethylformamide < acetonitrile < dioxane. However, dimethyl sulfoxide and N,N-dimethylformamide show significant deviation from the trend in some cases. The pKa values were generally higher in mixtures of water and aprotic solvents than in mixtures of water and protic solvents. The slopes and the correlation coefficients are listed in Table II.

Table I

pKa^s Values of Aryl Carboxylic Acids in Water-organic Solvents Mixtures at 25°

Compound	%	MeOH	EtOH	iPrOH	t-BuOH	AcCN	DMF	DMSO	Dioxane
1	0 [a]	3.05	2.98	3.02	2.94	2.89	3.45	2.63	2.39
	20.3	3.58	3.59	3.68	3.88	3.81	4.42	3.71	3.97
	35.2	3.93	3.99	4.22	4.35	4.58	4.72	4.32	4.65
	50.1	4.31	4.50	4.66	4.83	5.14	5.25	4.46	5.45
	65.1	4.65	4.94	5.08	5.55	5.79	5.83	5.15	6.48
	79.9	5.09	5.33	5.70	6.32	6.62	6.75	6.60	7.99
	100 [a]	5.56	5.95	6.31	7.02	7.47	7.32	7.06	9.01
2a	0 [a]	3.41	3.33	3.42	3.43	3.30	3.60	2.68	2.65
	20.3	3.95	3.99	4.12	4.29	4.23	4.62	3.94	4.28
	35.2	4.35	4.47	4.76	4.92	4.92	4.93	4.32	4.96
	50.1	4.79	5.00	5.21	5.52	5.62	5.47	4.71	5.79
	65.1	5.14	5.49	5.62	5.93	6.28	6.00	5.56	6.86
	79.9	5.56	5.88	6.35	6.87	6.99	7.10	6.91	8.39
	100 [a]	6.10	6.58	6.99	7.57	7.91	7.64	7.49	9.44
2b	0 [a]	3.73	3.52	3.75	3.73	3.59	3.80	2.89	2.92
	25.3	4.23	4.17	4.45	4.61	4.57	4.70	4.15	4.40
	35.2	4.56	4.74	5.05	5.13	5.03	5.08	4.46	5.22
	50.1	4.90	5.31	5.51	5.63	5.87	5.56	4.97	6.02
	65.1	5.32	5.72	5.97	6.10	6.45	6.21	5.74	7.16
	79.9	5.63	6.22	6.63	7.06	7.17	6.96	7.06	8.59
	100 [a]	6.12	6.93	7.29	7.67	8.03	7.59	7.65	9.78
2c	0 [a]	3.27	3.21	3.16	3.26	3.21	3.51	2.62	2.30
	25.3	3.79	3.82	3.91	4.11	4.06	4.36	3.67	3.82
	35.2	3.98	4.27	4.48	4.62	4.56	4.72	3.93	4.42
	50.1	4.37	4.64	4.87	5.02	5.12	5.24	4.29	5.21
	65.1	4.69	5.10	5.46	5.46	5.65	5.68	4.93	6.31
	79.9	5.10	5.60	6.11	6.48	6.41	6.57	6.08	7.84
	100 [a]	5.50	6.15	6.77	7.00	7.10	7.11	6.53	8.89
2d	0 [a]	3.21	3.18	3.08	3.31	3.12	3.55	2.51	2.26
	25.3	3.71	3.76	3.84	4.05	3.90	4.34	3.60	3.79
	35.2	3.94	4.21	4.27	4.61	4.48	4.62	3.80	4.38
	50.1	4.29	4.50	4.89	5.10	5.00	5.20	4.15	5.02
	65.1	4.63	5.11	5.35	5.59	5.48	5.63	4.82	6.22
	79.9	5.00	5.43	5.95	6.26	6.22	6.33	6.02	7.77
	100 [a]	5.47	6.02	6.63	6.93	6.90	6.89	6.44	8.76
2e	0 [a]	2.94	2.87	2.76	2.80	2.80	3.79	2.51	2.03
	25.3	3.24	3.29	3.40	3.45	3.51	4.25	3.22	3.37
	35.2	3.49	3.54	3.68	3.76	3.80	4.52	3.41	3.65
	50.1	3.67	3.73	3.85	3.95	4.24	5.02	3.65	4.35
	65.1	3.87	4.07	4.37	4.43	4.64	5.31	3.80	4.87
	79.9	4.15	4.43	4.98	5.11	5.32	5.56	4.96	6.62
	100 [a]	4.42	4.75	5.34	5.47	5.79	6.07	5.10	7.43

Table I (continued)

pKa^s Values of Aryl Carboxylic Acids in Water-organic Solvents Mixtures at 25°

Compound	%	MeOH	EtOH	iPrOH	t-BuOH	AcCN	DMF	DMSO	Dioxane
2f	0 [a]	4.12	3.93	4.16	4.23	4.12	4.06	3.38	3.36
	25.3	4.63	4.59	4.85	5.04	4.98	5.04	4.55	4.94
	35.2	4.98	5.20	5.55	5.58	5.66	5.40	4.97	5.53
	50.1	5.40	5.82	6.03	6.16	6.30	6.06	5.47	6.38
	65.1	5.82	6.27	6.55	6.62	6.89	6.53	6.15	7.55
	79.9	6.09	6.72	7.12	7.38	7.59	7.52	7.44	9.09
	100 [a]	6.64	7.50	7.87	8.07	8.44	8.15	8.04	10.21
3	0 [a]	4.34	4.37	4.25	4.26	4.42	4.50	3.65	3.62
	20.3	4.96	4.98	5.10	5.20	5.30	5.27	4.92	5.31
	35.2	5.35	5.55	5.60	5.74	5.89	5.67	5.36	5.87
	50.1	5.63	6.28	6.40	6.22	6.48	6.21	5.86	6.49
	65.1	6.32	6.71	6.78	6.76	7.08	6.83	6.66	7.80
	79.9	6.60	6.98	7.54	7.79	7.82	[b]	8.00	9.31
	100 [a]	7.19	7.83	8.31	8.42	8.60	8.00	8.66	10.28
4	0 [a]	4.58	4.68	4.67	4.66	4.56	4.70	3.98	3.78
	20.3	5.22	5.28	5.52	5.55	5.56	5.51	5.22	5.33
	35.2	5.63	6.03	5.97	6.15	6.36	5.95	5.66	6.27
	50.1	6.08	6.66	6.53	6.68	6.95	6.48	6.16	7.26
	65.1	6.36	7.30	7.27	7.26	7.62	7.17	6.96	8.22
	79.9	7.05	7.45	8.00	8.15	8.38	[b]	8.24	9.76
	100 [a]	7.54	7.90	8.19	9.75	9.36	8.39	8.90	10.90
5	0 [a]	4.00	3.74	3.85	3.85	3.81	3.88	3.20	3.12
	20.3	4.50	4.40	4.57	4.67	4.79	4.86	4.42	4.70
	35.2	4.79	4.88	5.14	5.12	5.23	5.19	4.80	5.40
	50.1	5.17	5.44	5.62	5.67	6.05	5.79	5.18	6.24
	65.1	5.54	5.82	6.15	6.18	6.64	6.34	6.00	7.34
	79.9	5.88	6.38	6.73	6.91	7.37	7.28	7.30	8.74
	100 [a]	6.35	7.02	7.43	7.56	8.21	7.90	7.87	9.84
6	0 [a]	4.13	3.93	4.05	4.10	4.04	3.94	3.38	3.29
	20.3	4.63	4.55	4.75	4.88	4.94	4.94	4.53	4.89
	35.2	4.94	5.07	5.34	5.36	5.56	5.34	4.96	5.60
	50.1	5.32	5.62	5.80	5.87	6.21	5.89	5.38	6.36
	65.1	5.70	5.94	6.30	6.34	6.91	6.54	6.07	7.41
	79.9	6.03	6.50	6.90	7.08	7.54	7.47	7.37	8.97
	100 [a]	6.52	7.12	7.58	7.71	8.37	8.12	7.93	9.98
7	0 [a]	4.15	4.06	4.12	4.29	4.11	4.42	3.47	3.47
	20.3	4.71	4.75	4.87	5.03	5.00	5.16	4.64	5.11
	35.2	5.07	5.25	5.54	5.84	5.72	5.43	5.06	5.62
	50.1	5.50	5.78	6.03	6.25	6.34	6.05	5.57	6.62
	65.1	5.89	6.26	6.54	6.97	6.95	6.58	6.21	7.77
	79.9	6.29	6.79	7.22	7.48	7.70	[b]	7.54	9.14
	100 [a]	6.82	7.47	7.95	8.33	8.56	7.68	8.46	10.26

[a] Calculated from the plot of pKa^s as a function of percentage of organic solvents. [b] It was not able to be determined.

Table II

Slopes [a] and Correlation Coefficients (in Parenthesis) for the Plots of pKa^s versus Percent of Organic Solvents in Water

Compound	MeOH	EtOH	iPrOH	t-BuOH	AcCN	DMF	DMSO	Dioxane
1	2.51	2.97	3.29	4.08	4.58	3.87	4.43	6.61
	(0.999)	(0.999)	(0.998)	(0.993)	(0.998)	(0.982)	(0.945)	(0.986)
2a	2.69	3.25	3.57	4.14	4.61	4.04	4.81	6.79
	(1.000)	(0.999)	(0.995)	(0.993)	(1.000)	(0.974)	(0.960)	(0.988)
3	2.85	3.46	4.06	4.15	4.18	3.50	5.00	6.66
	(0.990)	(0.987)	(0.995)	(0.986)	(0.999)	(0.996)	(0.971)	(0.976)
4	2.96	3.22	3.51	4.09	4.79	3.69	4.92	7.11
	(0.998)	(1.000)	(0.999)	(1.000)	(0.998)	(0.994)	(0.973)	(0.989)

Table II (continued)

Slopes [a] and Correlation Coefficients (in Parenthesis) for the Plots of pKa^s versus Percent of Organic Solvents in Water

Compound	MeOH	EtOH	iPrOH	t-BuOH	AcCN	DMF	DMSO	Dioxane
5	2.35	3.29	3.57	3.72	4.41	4.02	4.67	6.72
	(0.999)	(0.999)	(1.000)	(0.996)	(0.997)	(0.985)	(0.961)	(0.990)
6	2.39	3.20	3.53	3.61	4.33	4.18	4.55	6.69
	(0.999)	(0.997)	(0.999)	(0.996)	(0.999)	(0.988)	(0.966)	(0.985)
7	2.67	3.41	3.82	4.04	4.45	3.26	4.66	6.79
	(1.000)	(1.000)	(0.998)	(0.990)	(0.999)	(0.990)	(0.969)	(0.989)

[a] Times 10^2.

As shown in Table II the slope of the plot is the smallest in methanol-water and the largest in dioxane-water. This may be due to the drastic change in the dielectric constant (ε) of the medium as the content of water varies in the dioxane-water mixtures although the magnititude of the change in slope is not directly proportional to the change in ε. For example, the $\Delta\varepsilon$ between 20.3% methanol-water and 79.9% methanol-water is 29.6; whereas it is 45.5 for dioxane-water mixtures.

For comparison we examined the dependence of the pKa^s values of 1-7 on the dielectric constants of the solvent mixture. As shown in Figure 1 the pKa^s values of 7 determined by the present method show excellent linearity ($r = 0.997$) with the dielectric constants in the range of ε 18-70 in the protic solvents-water mixtures. However, a very scattered plot was observed in the mixtures of water and the aprotic solvents (Figure 1, $r = 0.943$). Similarly, the plots for heterocyclic analogues 1-6 show good linearity in the protic solvents although their correlations are slightly lower than that of 7 ($r = 0.972$-0.994) as shown in the Table III. By extrapolating the plots similar to the Figure 1 the pKa values of the 5-membered heteroaromatic carboxylic acids in water (pKa^w) are calculated and listed in Table III.

The pKa^s values in Table I are in reasonable agreement with the literature values obtained from mixtures of ethanol, tert-butyl alcohol, and dimethyl sulfoxide [9]. The pKa^s values do not show linearity as the contents weight percent of organic solvent become very small (less than 10%). Therefore, the pKa^w values calculated by

extrapolation of the plots of pKa^s versus percentage of organic solvent are a little lower than the actual values obtained from water (Table I). On the other hand, the calculated pKa^w values by extrapolating the plots of pKa^s versus ε (see Figure 1) are slightly higher when the values from the aprotic solvent-water mixture were used and slightly lower in cases of the protic solvent-water mixture
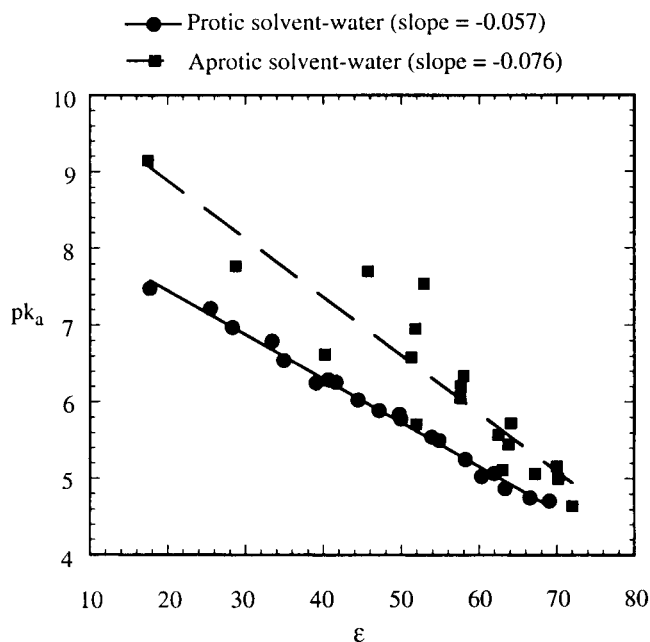

Figure 1. Plots of pKa of benzoic acid as a function of ε of the mixtures of protic solvent-water (circle) and aprotic solvent-water (rectangle) at 25°.

Table III

Calculated pKa^w Values of Heterocyclic Carboxylic Acids from the Slopes and Intercepts of the Plots of the pKa^s as a Function of Dielectric Constant (ε) of the Mixed Solvents at 25° (Method A) and as a Function of the pKa^s of Benzoic Acid, with That of Benzoic Acid Set as 4.21 (Method B)

Compound	Method A			Method B			
	Protic (r)	Aprotic (r)	Ave	Protic (r)	Aprotic (r)	Ave	Literature
1	2.97 (0.991)	3.56 (0.858)	3.28	3.08 (0.991)	3.31 (0.988)	3.19	3.16
2a	3.38 (0.994)	3.72 (0.924)	3.55	3.48 (0.993)	3.52 (0.996)	3.50	3.53
3	4.34 (0.972)	4.75 (0.925)	4.55	4.46 (0.976)	4.46 (0.993)	4.46	4.45
4	4.66 (0.990)	4.98 (0.879)	4.82	4.77 (0.992)	4.69 (0.996)	4.73	-
5	3.87 (0.984)	4.19 (0.889)	4.03	3.97 (0.989)	3.94 (0.998)	3.95	3.95
6	4.05 (0.988)	4.34 (0.891)	4.20	4.15 (0.992)	4.09 (0.998)	4.12	4.10
7	4.09 (0.997)	4.43 (0.906)	4.26	-	-	-	4.21

(Table III). Furthermore, the average values of the pKa^w from the protic and aprotic solvents in Table III are reasonably close to the literature values.

Another notable phenomenon is that the C-2 carboxylic acids show large differences in calculated pKa^w values (0.12-0.19) in the protic solvent-water mixtures from the literature values although their correlation coefficients are good (r = 0.990-0.994) except for **3** (r = 0.972). But the C-3 carboxylic acids show a slightly scattered correlation (r = 0.984-0.988) in the protic solvents whereas the differences between the calculated and the reported pKa^w values are small (ΔpKa^w = 0.05-0.08). On the other hand, the calculated pKa^w values in the aprotic solvent-water mixtures in Table III have much poorer correlation coefficients (r = 0.858-0.925) regardless of the position of COOH in the rings.

The effect of solvent on the ring of a heterocyclic carboxylic acid may be compared with the effect of the phenyl ring of benzoic acid. The plots of the pKa^s of **1-6** versus the pKa^s of **7** in the four protic solvent-water mixtures and in the four aprotic solvent-water mixtures show excellent correlations, as shown in Figure 2. The differences between the slopes of the plots of pKa^s of benzoic acid versus those of the heteroaromatic carboxylic acids and **1**, which is the theoretical value, are listed in Table IV. Correlations are excellent in both protic and aprotic solvents. If the pKa^w of **7** is set as 4.21, those of **1-6** can be calculated from the plots. The values are listed in Table III. The average values are very close to those reported in the literature.

boxylic acid is expected to be that of benzoic acid. The order of **1** and **2a** are consistent with the well-known order of the aromaticity indices [10], but a similar analogy may not be applied to 2-pyrrolecarboxylic acid (**3**) which behaves differently in the protic and aprotic solvent-water mixtures.
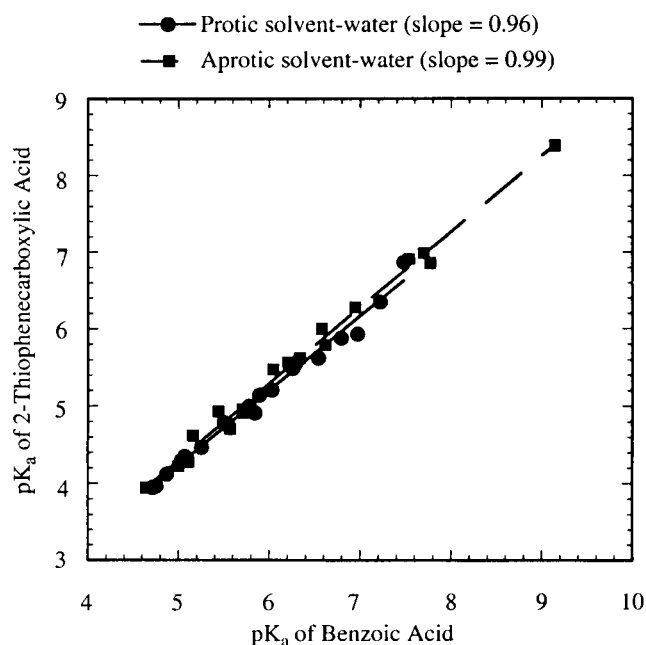
—●— Protic solvent-water (slope = 0.96)
—■— Aprotic solvent-water (slope = 0.99)

Figure 2. Plots of pKa^s of 2-thiophenecarboxylic acid versus those of benzoic acid in the mixtures of protic solvent-water (circle) and aprotic solvent-water (rectangle) at 25°.

Table IV

Deviation of the Slope from the Value of 1 for the Plots of pKa^{Het} as a Function of pKa^{Ph}

Compound	MeOH (r)	EtOH (r)	iPrOH (r)	t-BuOH (r)	AcCN (r)	DMF (r)	DMSO (r)	Dioxane (r)
1	-0.061 (0.999)	-0.130 (0.999)	-0.140 (1.000)	-0.003 (0.986)	0.031 (0.999)	-0.025 (0.999)	-0.033 (0.992)	-0.023 (0.999)
2a	0.007 (0.999)	-0.050 (0.998)	-0.065 (0.999)	0.011 (0.985)	0.037 (1.000)	-0.043 (0.999)	0.041 (0.998)	0.002 (0.999)
3	0.067 (0.989)	0.014 (0.987)	0.060 (0.994)	0.015 (0.978)	-0.061 (0.999)	0.063 (0.997)	0.071 (0.998)	-0.009 (0.996)
4	0.110 (0.997)	-0.057 (1.000)	-0.082 (0.989)	0.003 (0.995)	0.079 (0.999)	0.121 (0.995)	0.051 (0.989)	0.047 (0.999)
5	-0.118 (1.000)	-0.037 (0.999)	-0.067 (0.997)	-0.093 (0.987)	-0.011 (0.995)	0.031 (1.000)	0.008 (0.998)	-0.011 (1.000)
6	-0.106 (1.000)	-0.062 (0.998)	-0.078 (1.000)	-0.119 (0.988)	-0.028 (1.000)	0.091 (0.997)	-0.020 (0.999)	-0.014 (0.998)

It is worth pointing out that the magnitudes of the slopes increase in the order of **6** (0.88) < **5** (0.89) < **1** (0.90) < **4** (0.95) < **2a** (0.96) < **3** (0.99) in the protic solvent-water mixtures. On the other hand, the order is different in the aprotic solvent-water mixtures: **1** (0.94) < **3** (0.98) ≈ **5** (0.98) ≈ **6** (0.98) < **2a** (0.99) < **4** (1.04). The narrower range in the value of the slopes, the closer they are to unity, the more the behavior of the acid dissociation of the heterocyclic car-

There should be several factors which may affect the pKa^s value in aqueous mixtures. One of them may be the capability of forming hydrogen bonds between the protic solvent and the solute. It seems apparent that the stablization of the carboxylate ion comes from the solvation of the ion, mostly by water molecules. Solvation by protic solvents may also contribute to the stronger acidity of the carboxylic acid but the effect may not be as strong as that for water.

The effects of acetonitrile and N,N-dimethylformamide are quite different from each other although they have close dielectric constants, 37.5 for acetonitrile and 36.5 for N,N-dimethylformamide. The slopes in Table II are 5-39% larger in acetonitrile, indicating that the pKa^s becomes more sensitive as the content of acetonitrile increases. Furthermore, the pKa^s of 1 and 2a are notably larger in 20.3%-N,N-dimethylformamide than those in acetonitrile of the same composition. This may be explained by the N,N-dimethylformamide-water association as follows:
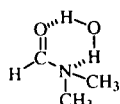
A similar kind of hetero-intermolecular hydrogen bonding is known with N,N-dimethylformamide [11]. This, along with the smaller pKa^s values in the protic solvent may mean that the major factor affecting the acidity in the heterocyclic carboxylic acids is the hydrogen bonding by water or alcohol.

2-Pyrrolecarboxylic acid (3) and its 1-methyl derivative (4) show a very non-uniform trend in pKa^s. According to Siegel et al, the degree of the partial positive charge on

the carbonyl carbon is the key factor in determining the acid strength of the carboxylic acid [12]. The pyrrole molecule is known to act either as a proton donor forming NH-π or NH-X hydrogen bonds, or as a proton acceptor to form π-NH hydrogen bonds [13]. If hydrogen bonding such as I with water is feasible the magnitude of $δ^+$ charge on the carbonyl carbon will be greatly enhanced. Other types of hydrogen bonding such as II and III are also feasible in protic solvent and in aprotic solvent-water mixture when water content is high. Therefore, interaction between the N-methyl group and the solvent may affect the magnitude of +I effect of the methyl group. The difference in the slope of 3 and 4 is the largest in acetonitrile-water (0.61×10^{-2}) and the smallest in *tert*-butyl alcohol-water (0.06×10^{-2}). Although we cannot explain the exact nature of such interaction, it is conceivable that the hydrogen bonding is least effective in *tert*-butyl alcohol and the hydrophobic interaction between the methyl groups may be the major contributor to the non-uniform increase of pKa^s of 4.

The slope in Table IV may reflect the sensitivity of the heterocyclic ring toward solvent comparable to that of the phenyl ring; the closer to unity, the greater the similarity of solvent-solute interaction of the heterocycles to phenyl

Table V

Calculated pKa^w Values of Substituted Thiophenecarboxylic Acids from the Plots of Observed pKa^s as a Function of Percent of Organic Solvents

Compound	MeOH (r)	EtOH (r)	iPrOH (r)	t-BuOH (r)	AcCN (r)	DMF (r)	DMSO (r)	Dioxane (r)
2a	3.41 (1.000)	3.33 (0.999)	3.42 (0.995)	3.43 (0.993)	3.30 (1.000)	3.60 (0.974)	2.68 (0.960)	2.46 (0.988)
2b	3.73 (0.999)	3.52 (0.998)	3.75 (0.998)	3.73 (0.988)	3.59 (0.997)	3.80 (0.991)	2.89 (0.964)	2.81 (0.991)
2c	3.27 (0.994)	3.21 (0.999)	3.16 (0.997)	3.26 (0.979)	3.21 (0.997)	3.51 (0.985)	2.62 (0.956)	2.18 (0.983)
2d	3.21 (0.997)	3.18 (0.995)	3.08 (0.998)	3.31 (0.998)	3.12 (0.997)	3.55 (0.991)	2.51 (0.946)	2.14 (0.977)
2e	2.94 (0.997)	2.87 (0.992)	2.76 (0.973)	2.80 (0.973)	2.80 (0.989)	2.79 (0.993)	2.51 (0.898)	1.98 (0.948)
2f	4.12 (0.998)	3.93 (0.997)	4.16 (0.998)	4.23 (0.997)	4.12 (1.000)	4.06 (0.985)	3.38 (0.971)	3.23 (0.984)

Table VI

Calculated ρ Values of Substituted Thiophenecarboxylic Acids from the Plots of Observed pKa^s as a Function of σ Values

%	MeOH (r)	EtOH (r)	iPrOH (r)	t-BuOH (r)	AcCN (r)	DMF (r)	DMSO (r)	Dioxane (r)
20.3	0.975 (0.989)	0.880 (0.991)	1.031 (0.984)	1.137 (0.986)	1.048 (0.983)	0.489 (0.932)	0.954 (0.994)	1.063 (0.989)
35.2	1.111 (0.992)	1.195 (0.987)	1.409 (0.997)	1.395 (0.984)	1.307 (0.995)	0.589 (0.940)	1.132 (0.992)	1.595 (0.993)
50.1	1.116 (0.992)	1.618 (0.998)	1.666 (0.980)	1.759 (0.973)	1.710 (0.999)	0.573 (0.980)	1.381 (0.993)	1.748 (0.997)
65.1	1.524 (0.997)	1.687 (0.983)	1.581 (0.974)	1.716 (0.969)	1.951 (0.998)	0.950 (0.985)	2.212 (0.980)	1.910 (0.997)
79.0	1.526 (0.982)	1.813 (0.989)	1.677 (0.984)	2.049 (0.987)	1.983 (0.999)	1.607 (0.977)	2.149 (0.996)	2.040 (0.991)

I   II   III
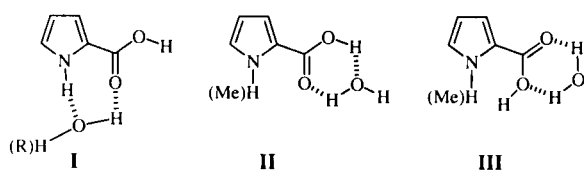
derivatives. The correlations are excellent except in a few cases of *tert*-butyl alcohol. If we pay attention to the medium, most heterocycles behave with more or less similarity to phenyl in dioxane-water mixture showing 0.2-4.7% deviation from unity. Solvation of the carboxylate ion by dioxane should be minimal. The ionization is assisted merely by water in that mixture. Therefore, it may be natural that the amount of water present may determine the magnitude of the effect on the stability of the carboxylate ion. A 2-thienyl ring may be considered to be most like the phenyl ring in dioxane-water, whereas 2-furyl and 1-methyl-2-pyrrolyl rings may behave like a phenyl ring in *tert*-butyl alcohol-water. A 3-furyl ring, on the other hand, is most like a phenyl ring in dimethyl sulfoxide. The slope of 3-thienyl ring plot shows a noticeable deviation (1.4-11.9%) from unity.

In order to examine the effect of substituent on pKa^s we measured the pKa^ss of **2b-2f** in the same medium used for **2a**, and the results are listed in Table I. The pKa^w values calculated by extrapolation are listed in Table V. The correlations are excellent except for **2e**. Dimethyl sulfoxide gave the poorest correlation coefficients for all the acids (r = 0.898-0.971). The values from *N,N*-dimethylformamide appear to be quite different from the actual values for **2a-f**. Abnormality in *N,N*-dimethylformamide is known [14].

The ρ values were calculated for each mixture of solvents using typical Hammett σ values [15] and the results are listed in Table VI. The ρ values generally increase as the contents of organic solvent increase, although they do not show any linearity to the percentage of the solvent. However, the abnormality in *N,N*-dimethylformamide appears to be remarkable in that the ρ values are about half of the values calculated for other solvent mixtures of the same percentage. One exception is the case with 79.9% *N,N*-dimethylformamide. Correlation coefficients are generally poor in *N,N*-dimethylformamide, ranging 0.932-0.985. Furthermore, the value of 50.1% *N,N*-dimethylformamide is smaller (0.573) than that of 35.2% (0.589). It is also notable that the ρ values are slightly less than 1 in cases of 20% mixtures of methanol, ethanol, and dimethyl sulfoxide.

EXPERIMENTAL

Materials.

The carboxylic acids **1-7** were purchased from the Aldrich Chemical Co. and used without purification. Organic solvents

were all spectral grade. Water was deionized first and then distilled twice using a glass distillation apparatus.

Preparation of Solutions.

The aqueous solvent mixture was prepared by weighing a predetermined weight of organic solvent and then water was added to make 100 g of solution. The acid solution was prepared in a 50 ml-volumetric flask by dissolving an appropriate amount of the acid with the solvent mixture so that the final concentration was 10^{-2} M. Sonication for a few minutes was applied to ensure complete dissolution. Standard sodium hydroxide solution was prepared with the corresponding solvent mixture by similar manner and was titrated with potassium biphthalate.

Measurement of pKa^s.

The pKa^s values were determined electrometrically with a potentiometer (Metrom 686 Titroprocessor) attached with a combination electrode. It was calibrated with pH buffers at pH 4.00 and pH 7.00. The solvent correction was determined by measuring the pH values of four perchloric acid solutions of known concentration between 10^{-2} M and 10^{-4} M in the corresponding solvent mixture.

The values of pKa^s of heterocyclic carboxylic acids are determined with sodium hydroxide solution (10^{-2} - 10^{-3} M) as a titrant from the pH at the midpoint (50% neutralization) of the titration. The activity coefficient ($\gamma_\pm$) is obtained from the Debye-Hückel equation, given in the following equation:

$$\log \gamma_\pm = \frac{AZ_i^2 I^{1/2}}{1 + BaI^{1/2}}$$

Z_i is ionic charge. Parameter A and B were calculated by taking the dielectric constant for the corresponding solvent which is obtained by linear interpolation of the reported values for the corresponding solvents. The parameter a is related to ion size or hydrated diameter. The size of the corresponding solvent may be regarded to be close to that of tetrapropylammonium ion and the value of a is taken as 8 x 10^{-8} cm.

REFERENCES AND NOTES

[1]   M. J. Cook and A. R. Katritzky, *Adv. Heterocyclic Chem.*, **17**, 255 (1974).
[2]   H. H. Jaffe and H. L. Jones, *Adv. Heterocyclic Chem.*, **3**, 209 (1964).
[3]   O. Exner and W. Simon, *Coll. Czech Chem. Commun.*, **29**, 2016 (1964).
[4]   F. Fringuelli, G. Marino, and A. Taticchi, *J. Chem. Soc. Perkin Trans. II*, 1738 (1972).
[5]   W. K. Kwok, R. A. More O'ferrall, and S. I. Miller, *Tetrahedron*, **20**, 1913 (1964).
[6]   F. Fringuelli, G. Marino, and G. Savelli, *Tetrahedron Letters*, **25**, 5815 (1969).
[7]   A. Albert and E. P. Serjeant, The Determination of Ionization Constants, 3rd Ed., Chapman and Hall, New York, 1984, pp 40-64.

[8]   E. Grunwald and B. J. Berkowitz, *J. Am. Chem. Soc.*, **73**, 4939 (1951).

[9]   A. J. Hoefnagel and B. M. Wepster, *J. Chem. Soc. Perkin Trans. II* , 977 (1989).

[10]   M. J. Cook and A. R. Katritzky, *Adv. Heterocyclic Chem.*, **17**, 255 (1974).

[11]   C. Reichardt, Solvents and Solvent Effects in Organic Chemistry, VCH, New York, 1988, p 14.

[12]   M. R. F. Siegel, A. Streitwieser, Jr. and T. D. Thomas, *J. Am. Chem. Soc.*, **110**, 8022 (1988).

[13]   R. A. Jones and G. P. Bean, The Chemistry of Pyrroles, Academic Press, New York, 1977, p 440.

[14]   L. P. Hammett, Physical Organic Chemistry, 2nd Ed., McGraw-Hill, New York, 1970, p 233.

[15]   F. Ruff and I. G. Csizmadia, Organic Reactions Equilibria, Kinetics and Mechanism; Elsevier: Amsterdam, 1994, p 164.