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Acidities of Benzyltetrahydrothiophenium Halides in Water. A Simple Method of Estimation

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The pK_a values of benzyltetrahydrothiophenium halides **1a-f** in water have been estimated by measuring the absorbances of the solution in aqueous hydroxide ion solution. Assuming that the ratios of the activity coefficients remains close to unity, the absorbance of the solution can be expressed as $A/[SH]_o=(\varepsilon_{SH}+\varepsilon_{S^-}K[OH^-])/(1+K[OH^-])$, where A, $[SH]_o$, K, ε_{SH}, and ε_{S^-} are the absorbance of the solution, the initial concentration of **1a-f**, the equilibrium constant, and the extinction coefficients for SH and S^-, respectively. The ε_{S^-} and K values that best fit with this equation were calculated by a nonlinear regression analysis with a large number of absorbance data determined at different $[OH^-]$ and $[SH]_o$. The pK_a values of the SH were then calculated with the relationship $K_a=-\log K+14$. The validity of this method has been demonstrated by the excellent agreements between the experimental and literature pK_a values of three organic acids. The pK_a values of **1a-f** estimated by this method are in the range of 12.5-15.3 and correlate well with the Hammett equation. The large negative deviation for the pK_a values of **1e** and **1f** from the Hammett plot has been attributed to the extra hydrogen bonding between the phenyl group and water molecules attracted by the hydrophilic substituents.

Introduction

Accurate determination of equilibrium solution acidities becomes difficult when one approaches within about 4 to 5 pK_a units of the solvent because of leveling effects. Although Hammett H^- acidity function has allowed the aqueous acidity scale, which has a practical pK_a range of 0-12, to be extended upward by about 12 pK_a units by employing co-solvents and strong bases, it has certain limitations.[1~5]

In connection with other work, we had to determine the pK_a values of benzyltetrahydrothiophenium halides in water.[6] However, the acidity could not be determined by the acidity function because of the limited solubility of the compounds in the mixed solvents and the short wavelength of the absorption maxima, which renders the accurate measurements of the absorbances difficult except in water. Therefore, it was necessary to estimate the pK_a values in water directly.

For equilibrium between benzyltetrahydrothiophenium halide (SH) and hydroxide in water,

$$SH+OH^- \rightleftarrows S^- + H_2O \quad (1)$$

$$K=[S^-]/[SH][OH^-] \quad (2)$$

Substituting the relationship $A=\varepsilon_{SH}[SH]+\varepsilon_{S^-}[S^-]$ and $[SH]_o=[SH]+[S^-]$ into the equation,

$$A/[SH]_o=(\varepsilon_{SH}+\varepsilon_{S^-}K[OH^-])/(1+K[OH^-]) \quad (3)$$

$$pK_a=-\log K+14 \quad (4)$$

where A and $[SH]_o$ are the total absorbance of the solution and the initial concentration of the benzyltetrahydrothiophenium halide, respectively.[8] In this equation all of the variables except for ε_{S^-} and K can be determined accurately. Therefore, if sufficient number of A at different $[OH^-]$ and $[SH]_o$ is accumulated, both ε_{S^-} and K values that best fit with Eq. (3) can be calculated with a nonlinear regression analysis. The pK_a values of the SH can then be calculated with Eq. (4). We now report that the equilibrium acidity of benzyltetrahydrothiophenium halides **1a-f** in water can be estimated simply by measuring the absorbances of the solution.

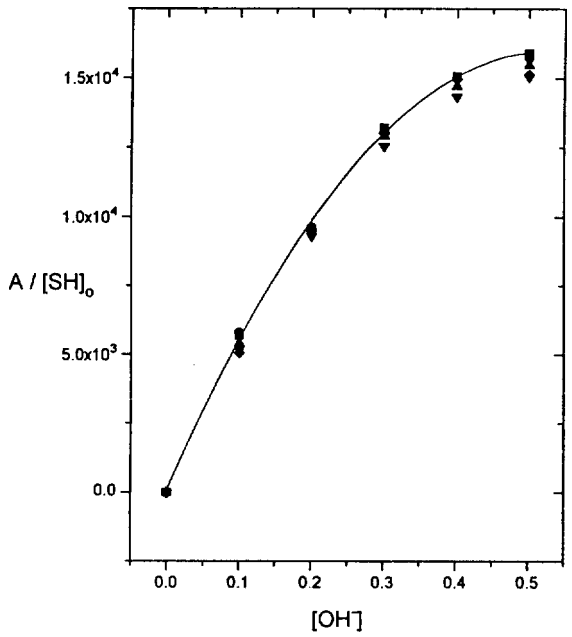


Figure 1. Computer fitted graph of the absorbance data for equilibrium between *p*-nitrobenzyl cyanide and OH^- in H_2O at 430 nm (μ=1.0 M).

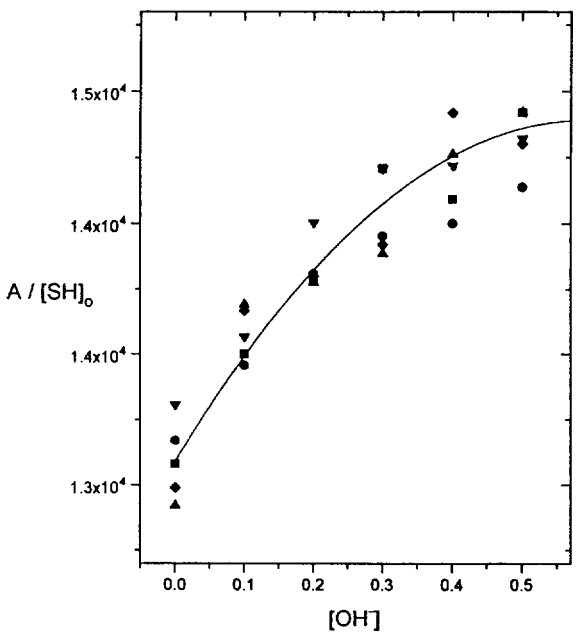
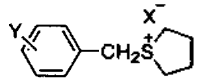
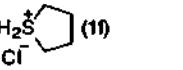


Figure 2. Computer fitted graph of the absorbance data for equilibrium between *p*-hydroxymethylbenzyltetrahydrothiophenium bromide **1e** and OH^- in H_2O at 225 nm (μ=1.0 M).



Y = H (**1a**), *p*-Cl (**1b**), *m*-Cl (**1c**), *m*-NO_2 (**1d**)
p-CH_2OH (**1e**), *m*-  (**1f**)

Results and Discussion

Benzyltetrahydrothiophenium halides **1a-f** were synthesized in high yields by refluxing the solution of appropriately substituted benzyl halides with tetrahydrothiophene in methanol by the literature method.[9] The spectral data for all of the compounds were consistent with the proposed structures.

To qualitatively assess the acidities of the benzylic C-H bonds, the hydrogen-deuterium exchange experiments were conducted by dissolving the compounds in an nmr tube containing (0.5-1.0)×10^{-2} M of OD^- in D_2O and taking the nmr spectra. In all cases, the signals at δ 4.3-4.6 corresponding to the benzylic protons of **1a-f** disappeared immediately, indicating that they are reasonably acidic.

The validity of this method was checked by measuring the acidities of three organic acids with known pK_a values. The absorbances of the solution containing SH in aqueous NaOH were measured at different $[OH^-]$ and $[SH]_o$. The concentration of the acids were varied in 1.00×10^{-5} M increments between 1.00×10^{-5} M and 5.00×10^{-5} M. The hydroxide ion concentration was chosen depending upon the acidity of the organic acids to minimize the error involved in the measurements by shifting the equilibrium in Eq. (1) toward S^- to an optimal extent and thus maximizing the total changes in the absorbance. The base concentrations used to determine the pK_a values of malononitrile and other organic acids were 1.0-5.0×10^{-3} M and 0.1-0.5 M, respec-

Table 1. Values of ε_{S^-}, K, and pK_a for equilibrium between several organic acids and OH^- in H_2O at 25.0 ℃

Compounds[a]	λ, nm	ε_{SH}[b]	ε_{S^-}[b]	K[b]	pK_a^{exp}[b]	pK_a^{lit}
malononitrile[c]	225	3,930± 10	26,900± 570	506± 4	11.3± 0.1	11.1[d]
			27,300[e]			
	227	3,750± 50	24,000± 700	564± 1		
			25,500[e]			
p-nitrobenzyl-cyanide[f]	420	0.0	26,700± 30	2.71± 0.03	13.6± 0.1	13.4[g]
			28,900[g]			
	430	0.0	28,200± 100	2.61± 0.02		
4-amino-3-nitro-pyridine[c]	360	3700± 20	13,300± 70	0.040± 0.001	15.6± 0.1	15.9[h]
	400	1130± 40	11,700± 150	0.020± 0.001		

[a] [compd]=(1.00-5.00)×10^{-5} M. [b] Average and standard deviation calculated from the data for two or more runs except otherwise noted. [c] $[OH^-]$=(1.00-5.00)×10^{-3} M. [d] Ref. 13. [e] Determined by adding $CH_2(CN)_2$ to 0.5 M NaOH(aq). [f] $[OH^-]$=0.1-0.5 M. [g] Ref. 14. [h] Ref. 4.

Table 2. Calculated Values of ε_{S^-}, K, and pK_a for equilibrium between $XC_6H_4CH_2S^+(CH_2)_4Cl^-$ and OH^- in H_2O at 25.0 °C

X	λ, nm	ε_{SH}[a]	ε_{S^-}[a]	K[a]	pK_a[b]
H	220	8760± 30	33610± 450	0.064± 0.002	15.3± 0.2
	230	5590± 40	26310± 10	0.030± 0.001	
p-Cl	215	7570± 130	34310± 290	0.25± 0.01	14.6± 0.1
	220	10620± 240	28070± 300	0.20± 0.01	
m-Cl	225	6720± 50	10270± 700	1.15± 0.05	13.8± 0.1
	245	300± 10	3200± 290	2.00± 0.11	
m-NO_2	230	3920± 10	5040± 30	24.0± 0.1	12.5± 0.1
	250	5590± 10	9650± 20	36.2± 0.2	
p-CH_2OH	225	12970± 80	19870± 170	1.1± 0.1	13.7± 0.2
	230	10070± 40	15320± 630	4.0± 0.1	
	240	2540± 40	6280± 110	0.9± 0.05	
m-$CH_2S^+(CH_2)_4$	220	10050± 170	11570± 220	16.8± 0.7	13.1± 0.3
	225	8220± 80	9720± 100	3.02± 0.04	
	230	4490± 90	6320± 220	5.0± 0.3	

[a]Average and standard deviation calculated from the absorbance data with Eq. (2) using the nonlinear regression analysis. [b]Average and standard deviation calculated from the K values with Eq. (3).

tively. In all cases, the ionic strength was maintained to 1.0 M with KCl. Figure 1 shows a computer fitted graph for the data for *p*-nitrobenzyl cyanide with Eq. (3). The correlations between the experimental and calculated data were excellent for all three organic acids. The calculated values of pK_a and ε_{S^-} are compared with the experimental data in Table 1. They are in excellent agreement with each other, demonstrating the reliability of this method.

The pK_a values of **1a-f** were estimated by the same procedure. The OH^- concentration was varied between 0.1 and 0.5 M. The changes in the absorbances were in the range of 0.01-0.08, apparently due to the low acidity of SH and the small differences in the ε_S and ε_{S^-} values. However, the differences are within the range of accurate measurement with our spectrophotometer.

Figure 2 shows the computer fitted graph for the data for **1f** with Eq. (3). The correlation between the calculated and the experimental data is not as good as that in Figure 1, probably because of the much smaller change in the absorbances. However, a reasonable correlation could be obtained when the total change in the absorbance was greater than 0.01. The ε_{SH}, ε_{S^-}, K, and pK_a values for **1a-f** calculated at different wavelength are summarized in Table 2.

The influence of aryl substituents upon the pK_a values could be correlated with Hammett equation by the use of σ values (Figure 3). The correlation is excellent, but the data for **1e** and **1f** show large negative deviations. The Hammett ρ value calculated without these data is -4.0 ± 0.2. The value is very similar to -4.07 for the diphenylamines and somewhat less negative than -5.2 for aminopyridines, aminopyrimidines, aminotriazines, and anilines, and amino substituted heterocycles.[4,5] Considering that the carbanion is a poorer hydrogen bonding acceptor than amide, the result appears somewhat surprising. The modest ρ value for **1a-d** may be attributed to the presence of the sulfonium halide moiety adjacent to the carbanion, which may attract the water molecules closer to the latter so that it can be solvated more efficiently. This would predict that the carbanion should be less susceptible to the change in the electron-withdrawing ability of the aryl substituent, as observed.

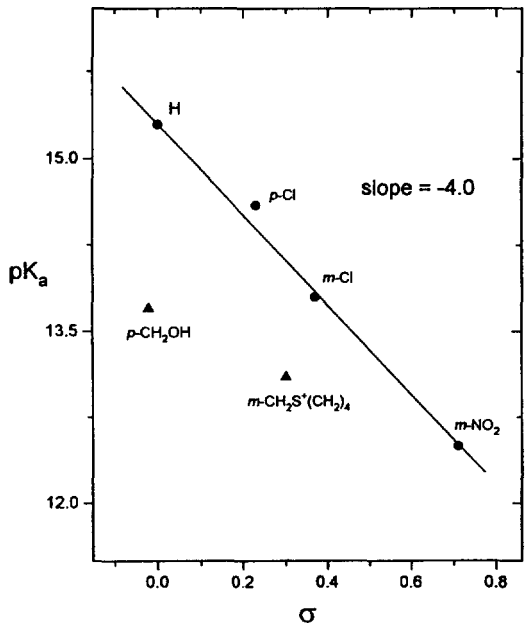


Figure 3. Hammett plot for the acidity of substituted benzyltetrahydrothiophenium halide **1a-f** in H_2O (μ=1.0 M).

It is interesting to note that the compounds with hydrophilic substituents **1e** and **1f** show negative deviations from the Hammett plot. The deviation is larger for **1e** which has more hydrophilic substituent, indicating that hydrogen bonding ability might be the reason. One plausible explanation for the deviation may be that the hydrophilic substituents may provide extra stabilization for the carbanion by increasing the number of water molecules available for the hydrogen bonding with the carbanion. However, the substituents appear too far away from the carbanion for such interaction to be effective. Alternatively, the water molecules surround-

Table 3. The absorbance data for equilibrium between *p*-hydroxymethylbenzyltetrahydrothiophenium bromide and OH in H_2O determined at 230 nm

$[OH^-]^a$	Abs when $[SH]_o$ is				
	1.00×10^{-5b}	2.00×10^{-5b}	3.00×10^{-5b}	4.00×10^{-5b}	5.00×10^{-5b}
0	0.105	0.200	0.302	0.411	0.507
0.100	0.110	0.222	0.316	0.413	0.511
0.200	0.111	0.220	0.319	0.421	0.515
0.300	0.111	0.232	0.321	0.429	0.525
0.400	0.112	0.230	0.331	0.445	0.551
0.500	0.118	0.234	0.340	0.477	0.563

[a]Initial concentration of OH^- ion, M. [b]Initial concentration of SH, M.

ing the hydrophilic substituent may form hydrogen bonds with the π cloud of the aromatic rings to withdraw some of the electron density, which would in turn stabilize the carbanion and increase the acidity. It has been demonstrated that benzene can form hydrogen bonds with water with the binding energy of >1.78 kcal/mol.[10] Therefore, if the substituents attract more water molecules toward the phenyl ring than the hydrophobic one does, this could provide enough stabilization energy for the carbanions to decrease their pK_a values lower than expected from the Hammett plot.

In conclusion, we have estimated the relative pK_a values of very weak acids by the use of a spectrophotometer and a computer calculation. This method can easily be extended to determine the acidity of other acids in other solvents as long as there is an appreciable change in the UV absorption arising from the change in the conjugate acid-base composition. However, it should be emphasized that the errors involved in this estimation is significant and the estimated pK_a values should be used only when the relative acidities of structually related compounds are compared.

Experimental Section

Materials. Reagent grade KCl and NaOH were used without further purification. The NaOH solution was prepared by dissolving reagent grade NaOH in distilled water and titrated with a standard solution of HCl(aq).

4-Amino-3-nitropyridine, *p*-nitrobenzyl cyanide, and *p*-bromomethybenzyl alcohol were prepared by the literature methods.[4,12,13] Reagent grade malononitrile was recrystalized from EtOH.

Benzyltetrahydrothiophenium halides **1a-f** were synthesized by refluxing corresponding benzyl halides with tetrahydrothiophene in MeOH as reported in the literature.[7] After removing the solvent by evaporation, the products were precipitated by adding cold acetone and then washed several times with cold acetone. Due to the lack of a distinct functional group and the hygroscopic nature of the compounds, they could not be identified by IR and elemental analysis. However, the nmr spectra of the compounds were consistent with the proposed structures. The yields (%), melting point (℃), and nmr data (ppm) of the compounds are as follows. $C_6H_5CH_2S^+(CH_2)_4Cl^-$ (**1a**): yield 82; mp 64-65; ^1H NMR (D_2O) δ 2.05-2.15 (m, 4H), 3.20-3.40 (m, 4H), 4.30 (s, 2H), 7.32 (s, 5H). *p*-$ClC_6H_4CH_2S^+(CH_2)_4Cl^-$ (**1b**): yield 86; mp 176-178; ^1H NMR (D_2O) δ 2.05-2.20 (m, 4H), 3.15-3.38 (m, 4H), 4.30 (s, 2H), 7.25-7.40 (m, 4H). *m*-$ClC_6H_4CH_2S^+(CH_2)_4Cl^-$ (**1c**): yield 74; mp 105; ^1H NMR (D_2O) δ 2.05-2.25 (m, 4H), 3.20-3.45 (m, 4H), 4.33 (s, 2H), 7.20-7.40 (m, 4H). *p*-$ClC_6H_4CH_2S^+(CH_2)_4Cl^-$ (**1c**): yield 86; mp 176-178; ^1H NMR (D_2O) δ 2.05-2.18 (m, 4H), 3.20-3.40 (m, 4H), 4.30 (s, 2H), 7.30-7.40 (m, 4H). *m*-$O_2NC_6H_4CH_2S^+(CH_2)_4Br^-$ (**1d**): yield 88; mp 103; ^1H NMR (D_2O) δ 2.13-2.35 (m, 4H), 3.30-3.51 (m, 4H), 4.52 (s, 2H), 7.6 (t, 1H), 7.80 (d, 1H), 8.20 (d, 1H), 8.30 (d, 1H). *p*-$HOCH_2C_6H_4CH_2S^+(CH_2)_4Br^-$ (**1e**): yield 54; mp 109-111; ^1H NMR (D_2O) δ 2.23-2.32 (m, 4H), 3.30-3.60 (m, 4H), 4.50 (s, 2H), 4.70 (s, 2H), 7.52 (s, 4H). *m*-$Cl^-S^+(CH_2)_4CH_2C_6H_4CH_2S^+(CH_2)_4Cl^-$ (**1f**): yield 58; mp 70; ^1H NMR (D_2O) δ 2.25-2.40 (m, 4H), 3.40-3.61 (m, 4H), 4.58 (s, 2H), 7.65-7.75 (m, 4H).

Hydrogen-Deuterium Exchange Experiment. The hydrogen-deuterium exchange experiments were conducted by dissolving small amounts of **1a-f** in $(0.5\text{-}1.0)\times10^{-2}$ M of OD^- in D_2O. The nmr spectra taken immediately after preparing the samples indicated that the signals at δ 4.3-4.6 corresponding to the benzylic protons of **1a-f** disappeared completely, indicating that all of the C-H bonds are reasonably acidic.

Determination of the pK_a values. 3.0 μL of 1.0×10^{-2} M solution of **1a-f** in distilled water was added to a 3.0 mL of aqueous NaOH solution in a cuvette maintained at 25.0 ℃. The absorbance was measured at two or more wavelengths with Varian 3E UV-VIS spectrophotometer which has photometric accuracy of ± 0.003 at 1 Abs. The concentration of the organic acid was increased in 1.0×10^{-5} M increments until the concentration of **1a-f** reached 5.0×10^{-5} M by adding the solution with a micro syringe to the cuvette. The absorbance was measured after each addition. The same procedure was repeated at five different base concentrations. The base concentrations used to determine the pK_a values of malononitrile and other organic acids were $1.0\text{-}5.0\times10^{-3}$ and 0.1-0.5 M, respectively. In all cases, the ionic strength was maintained to 1.0 M with KCl. A typical absorbance data for equilibrium between **1e** and OH^- is shown in Table 3. Utilizing the absorbance data, ε'_{SH}, and the $[OH^-]$, the K and ε_{S^-} values that best fit with eq 3 have been calculated with the NLSFIT function in the GENPLOT program, which is a nonlinear square fitting routine based on the gradient search and function linearization method.[15] The K values were inserted to Eq. (3) to calculate the pK_a values.

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