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Acidities and Hydrogen Bonding of Phenols in Dimethyl Sulfoxide

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Equilibrium acidities and homohydrogen-bonding constants are reported for phenol and seven substituted phenols in dimethyl sulfoxide solution. A Hammett plot gave $\rho = 5.3$, which is 2.5 times larger than that in water but 2.7 times smaller than that in the gas phase. The ρ is similar in size to values obtained in other dipolar nonhydroxylic ("aprotic") solvents. Hydrogen bonding of phenol to phenoxide ion (eq 1) is stronger by 6.1 kcal/mol than hydrogen bonding between phenol and Me_2SO. The homohydrogen-bonding constants for these phenols remain essentially constant (log K_{hb} = 3.2–3.4) over a pK_a range of 4.5 units.

Phenols and benzoic acids have historically been the most studied organic acids. The substituted acids ionize in a convenient range in water, and the effects of substituents on their acidities were responsible for the original concept of free energy relationships.[1-3] Many well-established ideas about charge dispersal through induction and resonance are based on these two acid classes. More recently their acidities in other solvents and in the gas phase have been instrumental in understanding medium effects on chemical properties and reactions.[4,5] Because dipolar nonhydroxylic ("aprotic") solvents lack the ability to stabilize anions through hydrogen bonding, the properties of ions in these solvents are often intermediate between those in water and the gase phase. Thus they form an important bridge between these two extremes. The lack of anion solvation in dipolar nonhydroxylic solvents can lead to the formation of hydrogen-bonded species (eq 1). This "homohydrogen bonding" complicates the measurement of the acidities of oxygen acids in these solvents.

$$\mathrm{PhO^- + PhOH \overset{K_{hb}}{\rightleftharpoons} PhO^- \cdots HOPh} \qquad (1)$$

Kolthoff has measured acidities in Me_2SO of 22, mostly di- or trisubstituted, phenols.[6] Arnett has measured the enthalpies of ionization (ΔH_i) of 13 monosubstituted phenols in Me_2SO.[7] From Hammett plots of these data two different slopes (ρ) have been derived: 4.3 from the free energies and 5.3 from the enthalpies. This difference suggested that there might be an interesting entropy effect on the ionization of phenols. This would be in contrast with the ionization of a variety of other weak acids in Me_2SO, for which the entropies of ionization are constant and near zero.[7c] However, it would be similar to the situation in water, where entropy changes dominate enthalpy changes in determining phenol acidities.[8]

Table I. Measured pK_a Values for Phenol vs. Various Indicators in Me_2SO at 25 °C

indicator[a] (pK_a)	pK_a	log K_{hb} (L^{-1} mol^{-1})
PFH (17.9)	18.04 ± 0.01	3.45 ± 0.01
PFH (17.9)	18.04 ± 0.01	3.45 ± 0.02
2PhSO$_2$FH (18.1)	18.07 ± 0.00	3.43 ± 0.01
2PhSO$_2$FH (18.1)	17.99 ± 0.02	3.18 ± 0.05
CNAH (18.9)	17.96 ± 0.02	3.27 ± 0.05
ISFH (16.9)	18.06 ± 0.05	3.39 ± 0.06

[a] PFH = 9-phenylfluorene; 2PhSO$_2$FH = 2-(phenylsulfonyl)fluorene; CNAH = 2-nitro-4-chloroaniline; ISFH = 9-(isopropylthio)fluorene.

Because of these differences we considered it worthwhile to measure the acidities of some phenols in Me_2SO. It has been shown that substituents which stabilize negative charge by resonance interactions (e.g., p-NO_2) can have differing degrees of stabilization depending on the acid family and the solvent. Therefore we have chosen seven substituents that stabilize or destabilize primarily by a polar (inductive) interaction. They are well behaved in free energy relations and are therefore excellent substituents for examining the effects of the medium on the acidities. In this paper we report pK_a values and homohydrogen-bonding constants (K_{hb}) for eight phenols in Me_2SO.

Results

The overlapping indicator method that we have used to measure the acidities and homohydrogen-bonding constants of phenols incorporates modifications of our previously described method.[9] This method involves setting up equilibrium 2 between an indicator acid (H–In) with

$$\mathrm{In^- + H{-}A \rightleftharpoons H{-}In + A^-} \qquad (2)$$

a known pK_a and the acid of interest by adding increments of the latter acid to a solution of the former and its anion.

The concentration of the indicator anion is measured spectrophotometrically and the equilibrium constant determined from that, the base strength, and the amounts of the two acids added to the solution. For most phenols and other oxygen acids the results vary within each run, between runs, and with different indicators because of the interference of equilibrium 1. We have modified our data treatment to take this into account by fitting the two equilibrium constants to the data using a general least-squares computer program. The equations and procedure are available as supplementary material. A second method

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Table II. Phenol Acidities in Me_2SO at 25 °C

substituent	σ^a	pK_a^b	$\log K_{hb}$ $(L^{-1}\ mol^{-1})^b$
H	0	18.03 ± 0.04, 16.4^c	3.36 ± 0.11
p-CH_3	-0.170	18.86 ± 0.05	3.39 ± 0.03
m-CH_3	-0.069	18.23 ± 0.01	3.36 ± 0.06
p-Cl	0.227	16.74 ± 0.03	3.37 ± 0.05
m-F	0.337	15.88 ± 0.07	3.33 ± 0.08
m-Cl	0.373	15.83 ± 0.05	3.29 ± 0.04
m-CN	0.56	14.76 ± 0.05	3.18 ± 0.04
m-NO_2	0.710	14.39 ± 0.12, 13.75^c	3.34 ± 0.12

[a] Hammett σ values as derived from the acidity of benzoic acids.[11] [b] The error limits given here are the standard deviations between runs. The absolute errors in pK values are approximately ±0.1. [c] Reference 6.

Table III. Hammett ρ's of Organic Acid Systems in Me_2SO

parent acid	pK_a	ρ^a	ref
$PhCH(CN)_2$	4.2	4.1	12
PhSH	10.3	4.4	28
$PhCO_2H$	11.0	2.4	13
$PhCH_2NO_2$	12.3	2.7	12
PhOH	18.0	5.3	this work
$PhCH_2COCH_3$	19.8	4.7	30
$PhCH_2CN$	21.9	5.5	12
$PhCH_2SO_2Ph$	23.4	5.1	14
$PhCOCH_3$	24.7	3.6	15
$PhCH_2SO_2CH_3$	25.4	5.1	16
$PhCHPh_2$	30.6	5.7	29
$PhNH_2$	30.7	5.7	17
$PhCH_2Ph$	32.1	5.7	12

[a] These ρ values were derived by using different numbers and types of substituents and should be considered as approximate.

of obtaining the pK_a is to use the normally calculated pK_a at the point where $[HA] = [A^-]$. At this point the homohydrogen bonding equilibrium, since it involves HA and A^- in a 1:1 ratio, does not disturb the value of $[A^-]/[HA] = 1$ used in calculating the equilibrium constant for equilibrium 2. The pK_as calculated by this method agree well with those calculated by the general least-squares method. We have used the latter method because it does not required that $[HA] = [A^-]$ during the run.

The results for phenol are shown in Table I. The agreement between different runs using different indicators is excellent. There are several other possible equilibria in these solutions. Formation of higher order hydrogen-bonded species $[A(HA)_2^-, AH(A^-)_2$, etc.] is possible at higher concentrations but is insignificant at our working concentrations ($1\text{–}10 \times 10^{-3}$ M) in Me_2SO.[6] The indicator acids and their anions are very poor hydrogen-bond donors and acceptors, respectively, and are not involved in any such equilibria. Finally we have excluded the possibility of ion pairing (K^+ is the counterion) by adding increments of an Me_2SO solution of KI and observing no change in the indicator anion concentration other than that due to the effect of dilution. This has recently been shown to be an effective means of detecting and quantifying ion pairing.[10]

The acidities and hydrogen-bonding constants for eight phenols are shown in Table II.

Discussion

Acidities in Me_2SO. The substituents in Table II interact with the charged oxygen atom almost exclusively by induction. Because of this effect they usually act consistently in free energy relationships. That is, the substituent effects on the ionization of benzoic acids in water, the Hammett σ's, correlate in a good linear fashion with the substituent effects on a variety of other equilibria and reaction rates. In the case of the phenols reported here the Hammett plot is excellent, giving a slope (ρ) of 5.3 with an R^2 of 0.991. As reported in Table II the acidities of phenol and m-nitrophenol have been measured before. These values, obtained by potentiometric titration, are 1.6 and 0.5 units lower than our values. Differences of this order and direction have been found for other acids measured by potentiometric and overlapping indicator techniques in the region above $pK_a = 14$.[9] It appears that slow electrode response for weak acids makes the potentiometric method unreliable at high pK_a values.[4] Values obtained by the two techniques agree very well for stronger acids. The Hammett ρ for these two and other (mostly di- and trisubstituted) phenols was reported as 4.29.[6] Because of our carefully selected substituents and the problems of the potentiometric technique, we believe our value of 5.3 is a more accurate one.

Hammett ρ's are a measure of the sensitivity of the chemical system to stabilization or destabilization of charge in the anion by substituents relative to the acidities of benzoic acids in water ($\rho = 1$). As such they are dependent on both the system and the medium. Phenol acidities have been measured in many solvents and in the gas phase, and these will be compared in the next section. The acidities of a variety of arene oxygen, nitrogen, and carbon acids have now been measured in one solvent, Me_2SO. The results are summarized in Table III. Such variety is not possible in hydroxylic solvents because of the acidity limits imposed by the solvents themselves. The ρ values are remarkably constant (5.1–5.7) for those acids where the negative charge in the anion is concentrated primarily on the atom next to the phenyl ring, except for the most acidic compounds, i.e., thiophenols (4.4) and phenylmalononitriles (4.1). A correlation between parent acid pK_a and ρ might have been expected, but there is none. The ρ values are significantly smaller for those acids where the charge is predominantly on an atom β or γ to the phenyl ring, as would be expected.

Medium Effects on Acidities. Solvent effects on the acidities of organic acids have been much studied and, with the advent of mass spectrometric methods for measuring ionic equilibria in the gas phase, acidities in the absence of solvent have added to our knowledge in this area. The absolute magnitude of solvent effects on acidity are very large, as shown by the free energy of ionization of phenol in the gas phase (343 kcal mol^{-1}) vs. aqueous solution (13.6 kcal mol^{-1}) in Table IV. Most of this difference is due to the solvation of the proton, but anion solvation energies can be quite large also.[8] In addition to these very large absolute effects, relative acidities can change drastically from medium to medium. For instance the equilibrium

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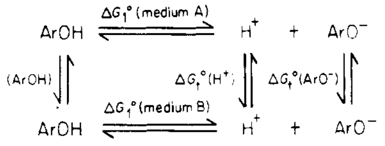
Table IV. Relative Acidities, Free Energies of Ionization, and Enthalpies of Ionization of Phenols in H_2O, Me_2SO, and the Gas Phase[a]

	H_2O[b]			Me_2SO			gas phase[e]
substituent	ΔpK	$\delta \Delta G^\circ_i$	$\delta \Delta H^\circ_i$	ΔpK[c]	$\delta \Delta G^\circ_i$[c]	$\delta \Delta H^\circ_i$[d]	$\delta \Delta G^\circ_i$
H	0	0	0	0	0	0	0
(absolute)	(9.98)	(13.60)	(5.48)	(18.03)	(24.58)	(24)	(343.4)
p-CH_3	0.31	0.42	0.0	0.83	1.13	1.7	1.1,[f] 1.3,[g] 1.2[h]
m-CH_3	0.13	0.18	0.0	0.20	0.27	0.1	0.4,[f] 0.4,[g] 0.5[h]
p-Cl	−0.54	−0.74	0.20	−1.29	−1.76	−1.5	−5.9,[f] −6.6,[g] −2.9[h]
m-F	−0.68	−0.93	−0.12	−2.15	−2.93	−2.4	−5.3,[f] −5.8,[g] −4.8[h]
m-Cl	−0.85	−1.16	−0.3	−2.20	−3.00	−2.8	−7.1,[f] −7.9,[g] −6.1[h]
m-CN	−1.40	−1.91	−0.44	−3.27	−4.46		−13,[f] −14.3[g]
m-NO_2	−1.61	−2.20	−0.6	−3.64	−4.96		−14.4,[f] −15.9[g]

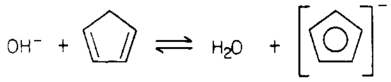
[a] Free energies and enthalpies are in kcal mol^{-1}. In order to calculate absolute values, add those shown to the absolute value for phenol itself. [b] Reference 8. [c] This work. [d] Reference 7. [e] $\delta \Delta H^\circ_i \approx \delta \Delta G^\circ_i$ for phenols in the gas phase.[22] [f] Reference 21. [g] Reference 22. [h] Reference 23.

Scheme I



$$\Delta G^\circ{}_i(A) - \Delta G^3{}_i(B) = \Delta G^\circ{}_t(ArOH) - \Delta G^\circ{}_t(H^+) - \Delta G_t(ArO^-)$$

constants for eq 3 are 10^{-1} in water,[19] 10^{13} in Me_2SO,[20] and 10^{25} in the gas phase.[5]

 (3)

In contrast, within a single family of compounds such as the phenols, the effects of solvation are similar, and the acidities correlate well in various media. The absolute acidity of phenol and the relative acidity of seven substituted phenols in water, dimethyl sulfoxide, and the gas phase are shown in Table IV. By comparing the three columns of ΔG_i°, it can be seen that the range of acidities is quite different. In water the total range for these seven phenols is only 2.62 kcal mol^{-1}, while in dimethyl sulfoxide it is 6.09 kcal mol^{-1} and in the gas phase it is 17.0 kcal mol^{-1}. This increase in acidity range parallels the increase in the absolute values of the free energies of ionization from 13.60 to 24.58 to 343.4 kcal mol^{-1} in the three media. The differences in acidities in various media can be divided into three terms, as shown in Scheme I. Most of the difference between the acidities in the gas phase and solution is due to the large solvation energy of the proton ($\Delta G_t^\circ(H^+$,gas phase to $H_2O) = -260.5$ kcal mol^{-1} and $\Delta G_t^\circ(H^+$,gas phase to $Me_2SO) = -265.0$ kcal mol^{-1}).[24,25] Although the remaining terms are smaller, they are solely responsible for the differences in the relative acidities of the phenols, since the proton term is a constant for every phenol.

The linear correlation of the acidities of the phenols in Me_2SO plotted against those in H_2O is excellent, with a slope of 2.4 and an R^2 of 0.990. The correlation of the gas-phase acidities with those in Me_2SO is good. For the three sets of gas-phase studies the slopes are 2.6 (R^2 = 0.944),[21] 2.8 (R^2 = 0.944),[22] and 1.7 (R^2 = 0.973).[23] Using all of the data, the overall slope is 2.6 (R^2 = 0.915). The correlation with the gas-phase data is poorer than with the aqueous solution data, but this may be the result of the larger experimental errors in the former. The sensitivity to substituent effects of the phenol acidities increases in the order $H_2O < Me_2SO <$ gas phase. From these data it is not possible to separate this trend into differential solvation of the phenols or their anions. Arnett has done this for the heats of ionization, however, and he finds that the major effect is in the anion solvation.[7b] This is likely to be true for the free energies of ionization also. Less stable anions are more solvated in Me_2SO and are solvated even more strongly in water than the more stable ions. This follows the general rule that localized charges are better solvated than delocalized charges.[18]

The relative acidities of various phenols are similar in the dipolar nonhydroxylic solvents Me_2SO,[6] dimethylformamide,[6] acetonitrile,[6] and *N*-methylpyrollidinone (NMP).[26] For example, a plot of pK_a values for several phenols in Me_2SO vs. NMP is linear (R^2 = 0.9998) over a range of 17.4 units with a slope of 0.91.[26] This shows that once the capability of hydrogen bonding is removed, anion solvation is similar for these solvents.

Enthalpies and Entropies of Ionization. As mentioned in the introduction, previous acidity (free energy of ionization) and enthalpy of ionization measurements on phenols in Me_2SO showed different sensitivities to substituent effects, the Hammett ρ's being 4.3 and 5.3, respectively. However, most of the phenols in the former study were those known to behave poorly in free energy relationships, being either polysubstituted or substituted in the para position by resonance-stabilizing groups. In addition, there were only two phenols studied by both methods. The phenols in this study give a ρ value of 5.3, equal to that for the enthalpy study. A plot of ΔG_i° vs. ΔH_i° for six phenols in Me_2SO gives a slope of 1.01 with R^2 = 0.973. Therefore there is no systematic differential entropy effect on the ionization of phenols in Me_2SO, which distinguishes them from other families of acids.[7c] This consistency between free energies and enthalpies of ionization differs from the behavior of phenols in water. Much of the acidity differences in aqueous solution is due to differential entropies of ionization.[8] Undoubtedly the difference between the two solvents is due to the much more ordered structure of water and the changes in this

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structure on ionization of the phenols.

Homohydrogen Bonding. From our measured equilibrium constants for homohydrogen bonding (Table II) it is clear that this interaction is strong and remarkably constant for these eight phenols. Since the "free" phenol in eq 1 is actually hydrogen bonded to the solvent, a more realistic equilibrium is eq 4. Expressed this way, $\Delta G° =$

$$PhO^- + PhOH\cdots OSMe_2 \rightleftharpoons PhO^-\cdots HOPh + Me_2SO \quad (4)$$

6.1 kcal/mol, or the hydrogen bond between phenol and its conjugate base is favored by 6.1 kcal/mol over the hydrogen bond between phenol and Me_2SO. The latter bond strength has been measured: $\Delta H° = 6.9, 7.21$ kcal/mol.[27] Although we cannot quantitatively combine these values because of the unknown entropy of reaction 4, it is clear that the phenol–phenoxide bond is quite strong.

The values of the homohydrogen-bonding constants for substituted phenols are functions of bond-donating and -accepting ability. As the acidities of the phenols increase, the hydrogen bond donating ability increases, but the accepting ability of the conjugate base decreases.[6,13] For the eight phenols of this study these two factors compensate for each other so that the equilibrium constants are the same for all of them.

Experimental Section

The phenols were all commercially available and were purified by distillation and/or crystallization until they were pure by VPC or TLC. The preparation and purification of the indicators have been previously described. Spectrophotometric grade Me_2SO, a gift from Crown Zellerbach, Camas WA, was purified by distillation from sodium amide,[9] and potassium dimsyl was prepared by using potassium hydride.[20] The experimental details of the indicator method have been described.[9,20] For the present compounds 5–10 titration points were used to calculate the pK_a and K_{hb} by a general least-squares curve-fitting procedure (see supplementary material).

Acknowledgment. Some of the acidity measurements were made by Mark E. Stark. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation. We thank Professors E. M. Arnett and R. W. Taft for helpful comments.

Registry No. Me_2SO, 67-68-5; PhOH, 108-95-2; *p*-methylphenol, 106-44-5; *m*-methylphenol, 108-39-4; *p*-chlorophenol, 106-48-9; *m*-fluorophenol, 372-20-3; *m*-chlorophenol, 108-43-0; *m*-cyanophenol, 873-62-1; *m*-nitrophenol, 554-84-7.

Supplementary Material Available: Equations for and a fuller description of the two procedures used to work up the data from the overlapping indicator method of measuring pK_a and K_{hb} and Table V, a numerical comparison of the two methods for phenol (9 pages). Ordering information is given on any current masthead page.

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Notes

Sulfazecin Analogues. Preparation of 4-(Fluoromethyl)-1-sulfo-2-azetidinone Derivatives

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The recent discoveries of sulfazecins[1] and monobactams[2] from bacteria have stimulated considerable interest in the synthesis of 1-sulfo-2-azetidinones.[3] In the course of our studies on the synthesis of sulfazecin analogues, we planned to introduce a fluorine atom into the methyl group at the 4β-position, because the 4β-methyl-1-sulfo-2-azetidinone derivative was reported to have a potent antibacterial activity especially against Gram-negative strains[4] and the electron-withdrawing property of the fluorine atom would increase the chemical reactivity of the β-lactam ring that might be correlated with the biological activity.[5]

In this paper, we describe a facile synthesis of the 4-(fluoromethyl)-1-sulfo-2-azetidinone derivatives[6] starting with commercially available 2-fluoroethanol. 2-Fluoroethanol was converted, without isolation of intermediates, in a one-pot procedure into β-lactam 1 (see Scheme I). Thus, Swern oxidation[7] of 2-fluoroethanol with oxalyl chloride and dimethyl sulfoxide followed by treatment with 2,4-dimethoxybenzylamine gave an imine. The resulting methylene chloride solution of the imine was used for the cycloaddition reaction with phthalimidoacetyl chloride in the presence of triethylamine to give β-lactam 1 (31.6% yield from 2-fluoroethanol). The IR spectrum of 1 showed an absorption band at 1760 cm^{-1} attributable to a β-lactam,

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† Deceased.

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