# EQUILIBRIUM ACIDITIES OF CARBON ACIDS

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Abstract - A scale of absolute equilibrium acidities for organic acids in dimethyl sulfoxide solution is presented, and these acidities are compared with: (a) apparent acidities in solvents of low dielectric constant, (b) absolute acidities in water, and (c) relative acidities in the gas phase. In dimethyl sulfoxide the carbon acid acetophenone is weaker than its oxygen analog, benzoic acid, by almost fourteen orders of magnitude, but the Hammett ρ for acetophenones is only one order of magnitude greater than for benzoic acids. This shows that large changes in the stabilities of ions in side chains may be accompanied by relatively small changes in ρ, and that the success of the Hammett equation rests, in part, on its relative insensitivity to energy changes.

INTRODUCTION

For the past 40 years organic chemists have been using a scale developed by McEwen as a guide to the relative acidities of weak acids and the relative stabilities of anions derived therefrom [1]. Following a method developed by Conant and Wheland in ether [2], McEwen constructed his scale by determining, in a semiquantitative manner, the position of equilibrium in benzene solution between two weak acids, HA and HIn, one of which forms a colored (indicator) anion, In⁻.

$$HA + M^+In^- \xrightarrow{\quad C_6H_6 \quad} M^+A^- + HIn$$
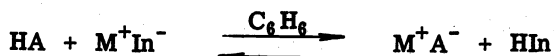
In a solvent of low dielectric constant, such as benzene, the metallic salts, M^+In^- and M^+A^-, exist as ion pairs or ion aggregates, and the relative stabilities of these ion pairs or clusters, as well as the relative acidities of the acids, HA and HIn, determine the position of the equilibrium. In other words, the apparent acidity of HA will depend on the nature of the reference base, M^+In^-, with which it is compared. Another disadvantage of the McEwen scale is that it is based on an arbitrary reference standard, the pK of methanol in methanol, which was taken as 16. The choice is arbitrary because, of course, the acidity of MeOH in benzene, if it could be measured free of ion pair effects, would be far less than that in methanol. The McEwen scale was brought up to date by Cram in 1965 in his MSAD scale by adding "pK's" determined by other investigators using similar methods in ether, cyclohexylamine, and the like [3]. The relative acidities in the McEwen and MSAD scales are not really pK's, of course, since they are not on an absolute scale, and because the values are subject to change, depending on the reference bases chosen. As a result of work carried out in our laboratory during the past five years it is now possible to replace the McEwen and MSAD scales with an absolute acidity scale that is independent of the reference bases used to construct the scale. This absolute equilibrium acidity scale will be presented in this paper and used to examine a number of structure-reactivity relationships.

ABSOLUTE ACIDITY SCALE IN DIMETHYL SULFOXIDE

The absolute equilibrium acidity scale was constructed by adapting the Conant-Wheland-McEwen method to a solvent, dimethyl sulfoxide, which has solvation and dielectric properties such that, in dilute solution, ion pairing is avoided. The scale was anchored on absolute acidities in the 7 to 12 pK range that had been determined by potentiometric and spectroscopic methods. It was expanded to the 12 through 32 pK region by over-lapping of about 20 standard acids having colored anions (indicators) and about 20 standard acids having colorless anions [4]. Two different indicators (or standard acids)

were used for each pK determination. Determinations with different indicators were generally within ±0.05 pK unit of one another, and the overall accuracy in the pK region 7 to 32 is believed to be ∓0.1 pK unit. The method can be applied to any acid within this region that forms an anion that is stable for a matter of minutes. The method has been applied to over 400 compounds of various structural types. A representative list is given in Table 1.

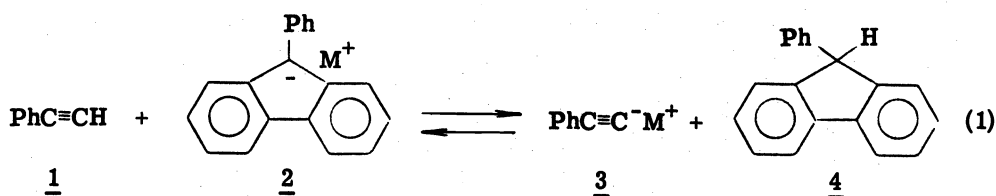TABLE 1. Acidities of organic compounds in dimethyl sulfoxide

Acid	pK	Acid	pK
$PhSO_2CH_2NO_2$	7.1_5	p-$PhCOC_6H_4NH_2$	24.4
$O_2NCH_2CO_2Et$	9.2	$PhCOCH_3$	24.7
9-CO_2Me-fluorene	10.3	CH_3CONH_2	25.5
3-Nitropropene	11.1	Cyclohexanone	26.4
$(PhSO_2)_2CH_2$	12.1	CH_3COCH_3	26.5
$CH_2(COCH_3)_2$	13.4	c-$PrSO_2CF_3$	26.6
$CH_2(CO_2Me)_2$	15.7	$PhCOC_6H_4CH_3$	26.8
CH_3NO_2	17.2	$(H_2N)_2C=O$	26.9_5
$CH_3SO_2NH_2$	17.5	$PhCH_2SOPh$	27.2
9-Ph-fluorene	17.9	$PhC≡CH$	28.8
Cyclopentadiene	18.0	$PhSO_2CH_3$	29.0
Indene	20.1	Xanthene	30.0
p-$NO_2C_6H_4CH_3$	20.5	Ph_3CH	30.6
Indole	20.8	Aniline	30.7
$PhSCH_2CN$	20.8	$(PhS)_2CH_2$	30.8
p-$NO_2C_6H_4NH_2$	21.0	9-Methylanthracene	31.1
$(H_2N)_2C=S$	21.1	$CH_3SO_2CH_3$	31.1
i-$PrSO_2CF_3$	21.8	CH_3CN	31.3
$PhCH_2CN$	21.9	Ph_2CH_2	32.2
Fluorene	22.6	CH_3SOCH_3	35.1
F_3CCH_2OH	22.8	NH_3	~40
$(PhS)_3CH$	22.8	$PhCH_3$	~44
Pyrrole	23.0	$PhSCH_3$	~49
$HCONH_2$	23.5	CH_4	>70

ACIDITIES IN DMSO COMPARED TO THOSE IN OTHER MEDIA

Acidities in solvents of low dielectric constant

Direct comparisons of the pK values given in Table 1 with "pK's" determined in solvents of low dielectric constant, such as benzene (1), ether (2), diglyme (5), 1,2-dimethoxy-ethane (6), cyclohexylamine (CHA) (7), etc. are meaningless, since the latter are all relative to some arbitrary standard, often the pK of 9-phenylfluorene, which has been determined to be 18.5 in mixed aqueous solvents by the H_ method. Nevertheless, there is often surprisingly good agreement between the relative "pK's" determined in these solvents and those determined in DMSO. This agreement has been established only for hydrocarbons, however, and breaks down even with these unless the two hydrocarbons being compared both form anions wherein the negative charge is highly delocalized. Thus, comparison of phenylacetylene with fluorenes gives widely differing results, depending on the solvent. Phenylacetylene forms an anion wherein the negative charge is essentially localized. Its absolute acidity in DMSO is 6 pK units lower than that of fluorene (Table 1). This contrasts sharply with the results in CHA, where the apparent

acidities of phenylacetylene and fluorene are nearly equal (8), or with the results in
ether, where phenylacetylene has an apparent acidity close to that of 9-phenylfluorene (2).
(9-Phenylfluorene has a higher acidity than fluorene by 5 pK units in DMSO--see Table 1.)
These results indicate that the equilibrium shown in equation 1 has been shifted to the
right by 11 powers of ten (equivalent to 15 kcal/mole in ΔG°) by changing the solvent
from DMSO to ether.

$$PhC\equiv CH \quad + \qquad\qquad\qquad \rightleftharpoons \qquad PhC\equiv C^-M^+ \quad + \qquad\qquad\qquad\qquad (1)$$

$$\underline{1} \qquad\qquad\qquad \underline{2} \qquad\qquad\qquad\qquad \underline{3} \qquad\qquad\qquad \underline{4}$$

Evidently, in ether the ion pair (or aggregate) derived from phenylacetylene,
$PhC\equiv C^-M^+$ (3) is more stable than the corresponding ion pair derived from 9-phenyl-
fluorene (2) by about 15 kcal/mole. We see from this example that measurements of
apparent acidities in solvents of low dielectric constant can give highly misleading
information concerning absolute acidities. On the other hand, comparison of the apparent
equilibrium acidities for a pair of acids in a solvent of low dielectric constant with
absolute equilibrium acidities for the same pair in DMSO can provide valuable information
concerning the relative stabilities of the two ion pairs (or aggregates) in that solvent.
(In DMSO there is little or no ion pairing at low concentrations, i.e., ca. 0.01 M, even
for localized anions, such as $PhC\equiv C^-$, when the counterion is K^+.)
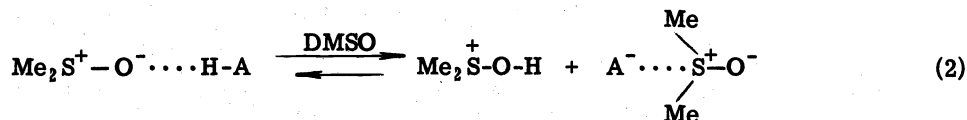
Acidities in water and DMSO

Direct comparisons of equilibrium acidities in water and in DMSO can be made, since
each is on an absolute scale. Examples with inorganic and organic acids are given in
Table 2.

TABLE 2. Acidities in DMSO and in water

Acid	pK (DMSO)[a]	ΔpK[b]
F_3CSO_3H	0.31[c]	large[d]
HBr	0.92[c]	large[d]
$HOSO_2OH$	1.43[c]	large[d]
CH_3SO_3H	1.62[c]	large[d]
9-CN-fluorene	8.4	~-2
F_3CCONH_2	9.7	3.4
PhSH	9.8[e]	3.3
$PhCO_2H$	11.0[e,f]	6.8
$CH_2(CN)_2$	11.1	0.0
$(EtSO_2)_2CH_2$	14.4	2.2
$CH_3SO_2NH_2$	17.5	7.5
Nitrocyclohexane	17.9	8.8
Cyclopentadiene	18.0	~3
Pyrrole	23.0	5.5
$PhCOCH_3$	24.7	~7

[a]From measurements in our laboratory. [b]ΔpK = pK(DMSO) - pK(H_2O).
[c]C. McCallum and A. D. Pethybridge, Electrochem. Acta., 20, 815 (1975).
[d]These acids are completely dissociated in water; H_0 type measurements
indicate pK's ranging from ca -1 for CH_3SO_3H to less than -9 for HBr,
$HOSO_2OH$, and F_3CSO_3H. [e]J. Courtot-Coupez and M. LeDémézet, Bull. Soc.
Chim. (France) [3], 1033 (1969). [f]I. M. Kolthoff, M. K. Chantooni, and
S. Bhowmik, J. Am. Chem. Soc., 90, 23 (1968).

Examination of Table 2 shows that the acidities of strong inorganic acids are leveled in DMSO, just as they are in water. Despite the greater basicity of DMSO, the strong inorganic acids are not completely dissociated in this solvent, as they are in water. This must be due in part to the lower dielectric constant of DMSO (49 at 20° C vs. 80 for H_2O), but the ability of DMSO to stabilize the undissociated acid by acting as a strong H-bond acceptor, as contrasted with its inability to stabilize the conjugate base of the acid by acting as an H-bond donor, is no doubt of greater importance (equation 2).

$$Me_2S^+-O^- \cdots H-A \xrightarrow{\quad DMSO \quad} Me_2\overset{+}{S}-O-H \;+\; A^- \cdots \underset{Me}{\overset{Me}{\underset{|}{\overset{\diagdown}{S}}}}\overset{+}{S}{-}O^- \qquad (2)$$

Water is a unique solvent in being capable of forming strong H-bonds when acting in either a donor or acceptor capacity. Its ability to act as a strong H-bond donor, whereas DMSO cannot, accounts for the much greater acidity in water of acids that dissociate to given anions in which the negative charge can be delocalized to oxygen (sulfonic acids, sulfonamides, carboxylic acids, nitroalkanes, ketones, etc.). This effect can also be used to explain the greater acidity in water of acids in which the negative charge resides on nitrogen or sulfur (Table 2). For acids dissociating to give anions in which the negative charge resides to an appreciable extent on carbon, H-bonding is much weaker. For such acids stabilization of the anion by the (stronger) dipole and polarizability properties of DMSO may balance the superior H-bonding properties of water. As a result, hydrocarbons, sulfones, sulfoxides, nitriles, and the like may be nearly as acidic in DMSO as in water, or more so (Table 2).

Acidities in the gas phase and in DMSO

Substituent effects in m- and p-substituted benzoic acids are severely attenuated in water or DMSO, relative to the gas phase. (The Hammett ρ's are 1.0, 2.5, and ~10, respectively.) This suggests that very strong, specific solvation forces are being exerted at the carboxylic acid group in solution and that the polar and resonance effects of the ring substituents are small by comparison. On the other hand, in several series of carbon acids, such as $CH_2(CN)_2$, $PhCH_2CN$, CH_3CN, a plot of relative gas phase acidities versus relative DMSO acidities is roughly linear with a slope near one. It would appear that, when the negative charge is distributed over a substantial part of the anion, as is true for $CH(CN)_2^-$, $PhCHCN^-$, and CH_2CN^- anions, solvation by DMSO is nonspecific and relatively constant (9). In such instances the structural effects on relative acidities in DMSO approach those in the gas phase in size. Additional correlations of this type have been made between enthalpies of deprotonation of weak acids (which are linearly related to DMSO acidities) and gas phase acidities (10).
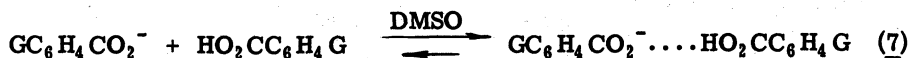
REMOTE SUBSTITUENT EFFECTS

Hammett correlations

There are literally thousands of successful correlations between the effects of m- and p-substituents on the equilibrium acidities of benzoic acids in water (or 50% EtOH-H_2O) and equilibrium or rate data in other like-substituted benzene systems. The success of these Hammett relationships is remarkable when one considers that the sigma "constants" derived from equilibrium data in water are being related to rate, as well as equilibrium data, for reactions carried out in all types of solvents, as well as in the gas phase. In an earlier section we observed large differences in the abilities of water and DMSO in stabilizing anions (Table 2). We know, for example, that in water benzoate ions and acetophenone enolate ions are strongly H-bonded, whereas in DMSO they are not. The difference in solvent stabilization, as judged by pK differences (Table 2) is of the order of 10 kcal/mole. In addition, we can expect differences in solvation of H-bond acceptor groups, G, when such groups (e.g., MeO, Me_2N, C=O, S=O, NO_2, etc.) are present in the m- or p-positions of the benzene rings in such anions. These solvation effects in H_2O and DMSO are illustrated in structures 5 and 6.

5

6
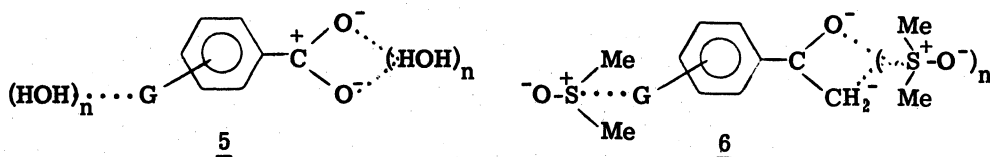
The importance of H-bonding effects in stabilizing anions is demonstrated further by the observation that the anions of oxygen acids, such as carboxylic acids, phenols, and alcohols, interact with their conjugate acids to form complexes (e.g. $\underline{7}$), even in dilute DMSO solution (11).

$$GC_6H_4CO_2^- + HO_2CC_6H_4G \quad \xrightleftharpoons{\text{DMSO}} \quad GC_6H_4CO_2^-\ldots\ldots HO_2CC_6H_4G \quad (\underline{7})$$

Acetophenone, the carbon analog of benzoic acid, is a weaker acid than benzoic acid in DMSO by nearly 14 pK units. (The acidity of benzoic acid in water is higher still by another 6.8 pK units.) One might then expect the acidities of acetophenones in DMSO to be much more sensitive to aryl substituent effects than is true for benzoic acids in water (or DMSO). Also, considerable variation in substituent effects between the two systems would be expected because of the variation of solvation of the individual substituents (compare 5, 6, and $\underline{7}$). In other words, according to this reasoning, the ρ value for acidities of acetophenones in DMSO should be large compared to that for benzoic acids in water (or DMSO), and correlation with Hammett σ constants should be poor. Instead, we find (12) that ρ for acetophenones is not particularly large ($\rho = 3.60$, as compared to 2.5 for benzoic acids in DMSO) and that the Hammett plot is good ($\underline{r} = 0.992$). We conclude that the negative charge in enolate ion side chain of 6 is so strongly stabilized by DMSO molecules that the negative charge in the benzene ring remains relatively small. For this reason the acidities of acetophenones in DMSO are surprisingly insensitive to changes in the polar nature of G, and even less sensitive to changes in solvation of G. Some idea of the magnitude of the solvation effects stabilizing the enolate ions (6) can be obtained from estimates of the single ion solvation enthalpies in going from the gas phase to water or DMSO solutions. For chloride ion these are 86.8 and 81.7 kcal/mole, respectively (13). Judging from these data, the energies of solvation of the enolate ions (6) in DMSO are large, although not as large as the energies of solvation of the benzoate ions (5) in water. These large solvation forces will be concentrated in each instance around the negatively charged atoms in the side chain. Stabilization of the CO_2^- and $COCH_2^-$ functions by the polar effect of G in 5 or 6 turns out to be small compared to these large solvation effects. For example, the acidifying effect on benzoic acid in water by the "powerful" p-CN group amounts to only 0.9 kcal/mole; the acidifying effect of p-CN on acetophenone in DMSO amounts to 3.7 kcal/mole. It is understandable, then, why the even smaller changes in solvent stabilizing (or destabilizing) effects on G caused by a change in solvent from H_2O to DMSO are not noticeable. We see that even though the $PhCOCH_2^-$ ion in DMSO is less stable by ca. 19 kcal/mole than is the $PhCO_2^-$ ion in water (judging from pK data) the solvation forces on the enolate ion function are still so large that stabilization by the polar effect of m- or p-G remains small by comparison. This must be a general phenomenon, and we conclude that one of the reasons for the remarkable success of the Hammett equation is that the small differences in the electrostatic effects of meta and para substituents are generally submerged in a large sea of solvent effects operating at the reaction site. The result is to level out differences in substituent effects, making the Hammett equation a relatively insensitive probe for changes occurring at the reaction site. When acidities of carbon acid systems in which the charge in the anion is on a carbon atom directly attached to the ring, as in $ArCH_2EWG$, are examined in DMSO, the sensitivity to substituent effects is found to increase by ca. 2 orders of magnitude. For example, ρ for the $ArCH_2CN$ system in DMSO is 5.5 (14) as compared to 3.6 for $ArCOCH_3$. The negative charge in the $ArCHCN^-$ ions apparently still remains largely in the side chain, however, and the leveling effect of the solvent is still enormous. It is only when the electron-withdrawing group (EWG) is replaced by hydrogen, i.e., in m- and p-substituted toluenes, $GC_6H_4CH_3$, that the negative charge becomes extensively delocalized into the benzene ring. Now solvation by DMSO changes from specific to general, and the full force of the electrostatic effect of G is brought into play. The result is an increase in ρ by 10 orders of magnitude for $ArCH_3$, relative to $ArCH_2CN$. It seems likely that the ρ observed for the acidities of toluenes in DMSO solution ($\rho \cong 15$) will rival that for the gas phase acidities.

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