

References and Notes

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- From Taft's equation: $pK_a = -0.51\sigma^*$ for $ROOH^9$ and σ^* value of $PhMe-(HOCH_2)C^{11}$ (the σ^* value for $HOCH_2CH_2$ was assumed to be $1/3$ of that for $HOCH_2$), K_7 for **3a** is calculated to be 2.0 times higher than that of $t-BuOOH$. Since the corresponding K_7 value of $t-BuOOH$ is determined to be $2.0 M^{-1}$ in 70% MeOH from UV absorbance (280 nm), the K_7 value of **3a** is then $4.0 M^{-1}$.
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- This was estimated from $k_{obsd} = 4.1 \times 10^{-3} s^{-1}$ for **3a** with 0.36 M KOH in 70% MeOH. That is, $k_8 = 4.1 \times 10^{-3} / (0.36 \times 0.41 \times (1/300)) = 8.3$, where 0.41 is a factor of undissociated **3a** (cf. $K_7 = 4 M^{-1}$) and 1/300 is the molar ratio of **5:3**.
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- Washing with a large amount of aqueous NaCl lowered the yield significantly.
- Authentic 1,2-glycols were prepared by hydrolysis of epoxides; their spectra were identical with the reduction products.

Application of the Hammett Equation to Equilibrium Acidities of Meta- and Para-Substituted Acetophenones

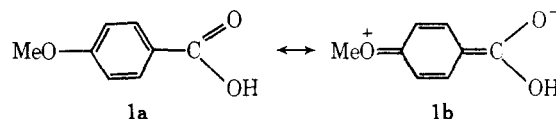
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Equilibrium acidities in dimethyl sulfoxide solution are reported for 23 meta- and para-substituted acetophenones. A plot of the pK values for 14 of these vs. Hammett σ constants gave a linear correlation with $\rho = 3.55 \pm 0.05$ and $r = 0.9990$. The fit of these points to the line appears to be within the experimental error of the measurements. The slightly greater deviations for the remaining nine points can be rationalized. The excellent correlation argues against direct ("through") conjugative effects for $p-Me_2N$, $p-MeO$, and like groups in benzoic acids and acetophenones. Also, for at least 14 substituents solvation effects must be proportional in water and in dimethyl sulfoxide solutions. The absence of direct conjugative effects and solvent effects for most substituents accounts for the general success of the Hammett equation. The close similarity in geometry between the benzoic acids and their carbon analogues, the acetophenones, accounts for the good correlation observed in this particular instance.

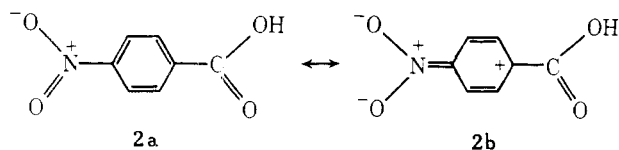
The Hammett equation has proved to be of great utility in physical-organic chemistry¹ and has found application in various other areas of chemistry as well.^{1d} Both kinetic and equilibrium data have been correlated by the equation in many types of benzenoid and heterocyclic systems in all types of media, including the gas phase. Its influence may be judged by the fact that a review of the subject by Jaffe,^{1b} published in 1953, 13 years after the appearance of the first edition of Hammett's classical text,^{1a} has become one of the most cited papers in all of chemistry. The literature in this area has continued to grow at a rapid pace in the ensuing years.¹ Despite its remarkable success, there are a number of problems with the Hammett treatment. In particular, the Hammett σ constants are empirical in nature and do not appear to be "constants" at all in the true sense of the word, since they contain resonance components which vary with the nature of the reactive site. For example, the σ_p constants for substituents having one or more electron pairs on the atom attached to the benzene ring (Me_2N , H_2N , MeO , HO , F , Cl , Br , I , and the like) are believed to be composed of two component parts, an electron-withdrawing polar (inductive) component and an electron-releasing resonance (mesomeric) component. When Me_2N , H_2N , MeO , or HO is substituted into the para position of benzoic acid, the resonance component is dominant, and these substituents are acid weakening. This was accounted for as a direct resonance effect by Ingold in 1933,² as depicted by resonance contributor **1b**, and this interpretation has gained general acceptance.¹



In benzenoid systems where CO_2H has been replaced by some other reactive site, the size of the resonance component varies with the degree of interaction between the two para substituents. When a saturated center intervenes between the benzenoid ring and the reactive site, such as in the arylacetic acids, direct conjugative interactions of type **1b** and **3b** are not possible and the use of σ^n and σ^0 constants has been proposed.¹ When the reactive site is an ion or radical directly attached to the aryl ring, conjugative interactions reach extremes. For cationic sites the use of Brown's σ_p^+ constants (based on rates of formation of cumyl "cations", i.e., ion pairs, in 90% aqueous acetone) is common, whereas for anionic sites σ_p^- constants (based on equilibrium acidities of phenols or anilinium ions in water) are generally used. The degree of direct conjugation of this type is believed to vary with the systems under scrutiny.

The σ_p constants for substituents in which the atom attached to the benzene ring is part of a multiple bond (NO_2 , CN , $COCH_3$, SO_2CH_3 , etc.) also have polar and resonance components. In this instance both components exert electron-withdrawing effects. Direct resonance interaction between these substituents and the carboxyl group in benzoic acid is not possible, but the presence of the resonance component is indicated by the fact that the effects are larger from

the para position than from the meta position. This is usually accounted for by resonance interaction with the benzene ring resulting in a buildup of positive charge in the para position, which exerts a polar effect on the carboxyl group (and/or the carboxylate ion), as illustrated in valence-bond symbolism by resonance contributor **2b**.³



Aside from the problem of the dual electronic nature of Hammett σ constants, there is also the problem of solvent effects. The primary σ constants are derived from the equilibrium constants for the substituted benzoic acids in water, but in some instances aqueous ethanol has been used for solubility reasons.¹ There is evidence for solvent dependence of σ for charged substituents⁴ and also for a few neutral substituents.^{1,5} Analysis of the thermodynamic data available for meta- and para-substituted benzoic acids shows that the variations in ΔG° are caused as much by variations in ΔS° as by variations in ΔH° .⁶ Indeed, the success of the equation appears to depend essentially on compensation of ΔH_{ext} and ΔS_{ext} parameters, allowing ΔG° to vary linearly with $\Delta H_{\text{int.}}$ ⁶

The development of a method for accurate measurement of equilibrium acidities of very weak acids in dimethyl sulfoxide (Me_2SO) solution has provided us with an alternative method for derivation of Hammett σ constants and allows, therefore, a reexamination of the Hammett relationship. It now becomes possible to derive σ constants in a single medium from equilibrium acidities of meta- and para-substituted acetophenones, the carbon acid analogues of the benzoic acids, or from meta- and para-substituted benzamides, the nitrogen acid analogues of the benzoic acids. We anticipated finding substantial deviations from the Hammett relationship for acetophenones caused by the change from the strongly hydrogen-bonding hydroxylic solvent (H_2O) to the non-hydrogen-bonding dipolar "aprotic" solvent (Me_2SO) and by the change from the carboxyl function, with its high degree of internal resonance energy (RE), to the aceto function wherein resonance is confined to the carbonyl group (compare formulas **3** and **4**).

Most substituents have one or more unshared electron pairs which can interact to varying degrees with the water by hydrogen bonding. Such hydrogen bonding effects are absent in Me_2SO , where solvation is principally by dipole-dipole interactions.

Experimental Results

The equilibrium acidities for 23 meta- and para-substituted acetophenones were determined in dimethyl sulfoxide solution by the indicator method described earlier.⁷ The $\text{p}K$ values and appropriate σ constants are listed in Table I. Of the 23 compounds listed in Table I, 13 compounds with m - and p - CH_3 , m - $\text{N}(\text{CH}_3)_2$, m - and p - OCH_3 , p -Ph, H, m -SPh, m - and

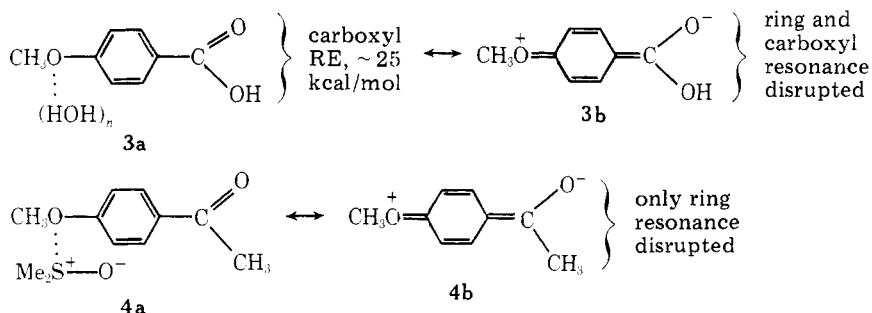
Table I. Equilibrium Acidity Constants for Meta- and Para-Substituted Acetophenones in Dimethyl Sulfoxide Solution

Substituent	Registry no.	$\text{p}K_{\text{obsd}}^a$	σ^b	$\text{p}K_{\text{calcd}}^g$	$\Delta \text{p}K^h$
p - $\text{N}(\text{CH}_3)_2$	2124-31-4	27.48	-0.83	27.56	-0.08
p - OCH_3	100-06-1	25.70	-0.27	25.56	0.14
m - $\text{N}(\text{CH}_3)_2$	18992-80-8	25.32	-0.21	25.35	-0.03
p - CH_3	122-00-9	25.19	-0.17	25.21	-0.2
m - CH_3	585-74-0	24.95	-0.07	24.85	0.10
p -Ph	92-91-1	24.51	-0.01	24.64	-0.13
H	98-86-2	24.70	0.0	24.60	0.10
p -F	403-42-9	24.45	0.06	24.39	0.06
p -SPh	10169-55-8	24.11	0.075 ^d	24.33	-0.22
m - OCH_3	586-37-8	24.52	0.12	24.17	0.35
m -SPh	26388-18-1	23.65	0.18 ^e	23.96	-0.31
p -Br	99-90-1	23.81	0.23	23.78	0.03
p -Cl	99-91-2	23.78	0.23	23.78	0.00
m -F	455-36-7	23.45	0.34	23.39	0.06
m -Cl	99-02-5	23.18	0.37	23.28	-0.10
m -Br	2142-63-4	23.19	0.39	23.21	-0.02
m - CF_3	349-76-8	22.76	0.43	23.06	-0.30
p -SOPh	65085-80-5	23.18 ^c	0.47 ^d	22.92	0.26
m -SOPh	65085-81-6	22.97	0.52 ^e	22.74	0.23
p - CF_3	709-63-7	22.69	0.54	22.67	0.02
m - SO_2Ph	65085-82-7	22.32	0.62 ^f	22.39	-0.07
p -CN	1443-80-7	22.04	0.66	22.24	-0.20
p - SO_2Ph	65085-83-8	22.12	0.71 ^f	22.07	0.05

^a ± 0.05 unit, not statistically corrected. ^b Values from data in water or 50% ethanol-water were compiled by D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958), unless otherwise noted. ^c ± 0.11 unit. ^d L. Litvenenko, *Izv. Akad. Nauk*, 1653 (1962). ^e H. Szmant and G. Suld, *J. Am. Chem. Soc.*, **78**, 3400 (1956). ^f O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 65 (1966). ^g Calculated from $\text{p}K = -3.57\sigma + 24.60$. ^h $\text{p}K_{\text{obsd}} - \text{p}K_{\text{calcd}}$.

p -SOPh, m - and p - CF_3 , and m - SO_2Ph substituents were measured several times against two or more indicators. For these compounds the values listed in Table I were determined by averaging the results for each indicator separately and then averaging the averages against the several indicators. Substituted acetophenones of acidity equal to or greater than p -bromoacetophenone showed a tendency toward lower $\text{p}K$ values in successive points of a multiple point run. This suggests interference from a slow reaction of the enolate ions of some kind. The nature of this reaction was not investigated. This tendency appeared to increase with the electron-withdrawing ability of the substituents. For the m - and p - CF_3 and p -CN substituted acetophenones, the $\text{p}K$ was determined by extrapolating the absorbance back to the time of mixing. (The correction was small.)

For the other ten compounds whose $\text{p}K$ values are listed in Table I, p - $\text{N}(\text{CH}_3)_2$, m - and p -F, m - and p -Cl, m - and p -Br, p -SPh, p - SO_2Ph , and p -CN, the values in Table I are averages of at least three runs against only one indicator. In each case the compound or its anion had a significant absorbance in the useful range of the alternative available indicator or under-



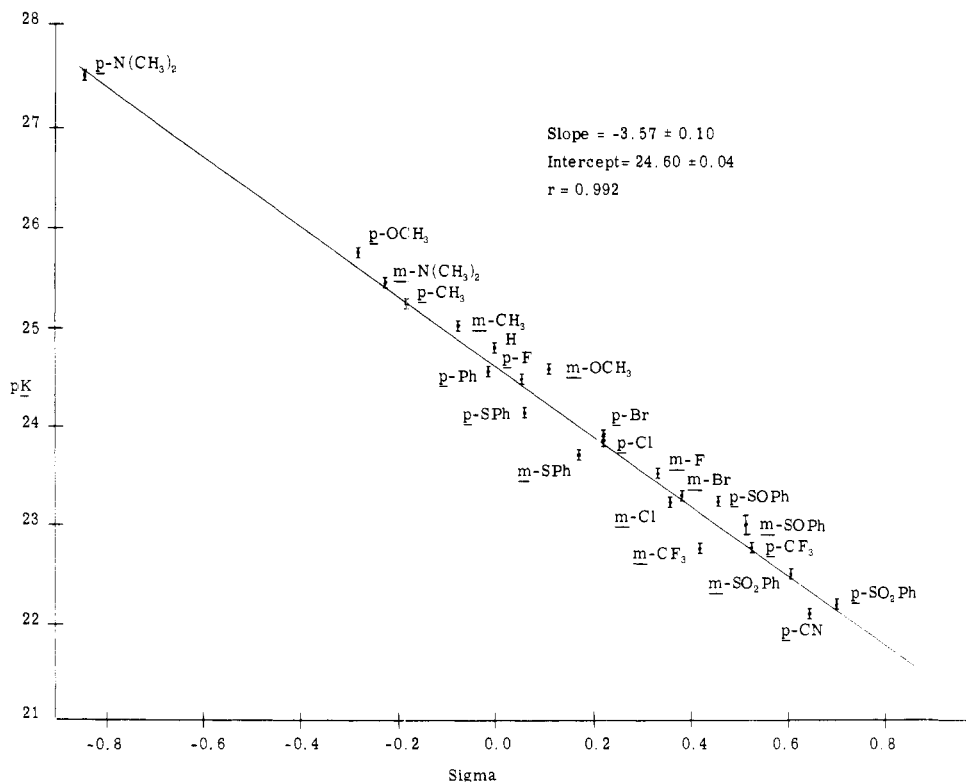


Figure 1. Plot of pK values for meta- and para-substituted acetophenones in dimethyl sulfoxide solution vs. Hammett σ constants.

went an apparent reaction with the indicator. The anions of p - $N(\text{CH}_3)_2$, p -Ph, m - and p -SOPh, m - and p - SO_2Ph , m - and p - CF_3 and p -CN substituted acetophenones were all visibly yellowish in color. The absorbance of the anions of p -Ph, m - and p -SOPh, and m - and p - CF_3 was, however, negligible at the concentrations used for pK determination (ca. 10^{-2} – 10^{-3} M) at the wavelength of the appropriate indicators. The anion of the p - $N(\text{CH}_3)_2$ substituted acetophenone had an absorbance of slightly over 0.1 unit at the concentrations used for pK determination in the useful range (ca. 622 nm) of 9-phenylxanthene. The absorbance of the anions of m - and p - SO_2Ph and p -CN tailed out too far to measure against fluorene at ca. 525 nm, and p - SO_2Ph and p -CN could not even be measured against 3-methylfluorene at ca. 540 nm. The absorbance of these anions was, however, low enough (<0.1 unit) to be compensated for at 572 nm in measurement against 9-methylfluorene. In addition p - N,N -dimethylaminoacetophenone could not be measured against 9-phenylxanthene, and m - and p -SPh substituted acetophenones could not be measured against 1,3,3-triphenylpropene because of apparent reactions with the indicator. The apparent reactions resulted in unsteady, rapidly falling then rising, or immediately rising absorbances. The m - and p -SOPh substituted acetophenones when measured against fluorene showed absorbances which fell rapidly, leveled off, and then rose slowly. The absorbance as it leveled off was used to calculate the pK values. The halo-substituted acetophenones also showed an apparent reaction with fluorene in which the absorbance fell, leveled off, and then rose. In all cases except p -fluoroacetophenone the rise in absorbance was slow enough that the pK could be based on the level absorbance value.

The color of the halo-substituted acetophenone pK solutions all appeared to change from the yellow of the fluorenyl anion to a very intense dark reddish purple in a period of ca. 0.5 h to several hours. To investigate this change a sample of p -bromoacetophenone was treated with 1 equiv of fluorene in Me_2SO containing 1 equiv of $\text{CH}_3\text{SOCH}_2\text{-K}^+$ for several days under an inert atmosphere. After quenching and con-

centration of the ether extracts, the residue consisted of $\sim 70\%$ unchanged acetophenone and fluorene and 25% p -(9-fluorenyl)acetophenone by NMR analysis.

For each of these ten compounds a single acceptable indicator was available and at least three separate experiments exhibited reproducible results with an average deviation from the mean of less than 0.04 unit.

For all of the compounds in Table I measured against two or more indicators, the averages against each indicator deviated from the final average by 0.05 unit or less with the exception of p -benzenesulfinylacetophenone, which had a mean deviation of 0.11 unit for three indicators. As stated above the pK values of those compounds measured against one indicator showed deviations 0.04 unit or less from their average values. The uncertainty in the pK values listed in Table I is therefore taken as 0.05 unit for all compounds except p -benzenesulfinylacetophenone, which is taken as 0.11 unit.

The acetophenone pK values were plotted against the best available Hammett σ constants. For the most part these are "primary" values derived from the acidities of benzoic acids in water. The slope of the line, as determined by least-squares regression analysis, is -3.57 ± 0.10 with an intercept of 24.60 ± 0.04 . The correlation coefficient is 0.992 (see Figure 1).

Since ketones sometimes undergo reactions in basic media, an experiment was performed to determine if the acetophenone could be recovered unchanged after equilibration under pK conditions. Acetophenone, 106 mg, was mixed with a small molar excess of 1,3,3-triphenylpropene and its anion for 5 min under pK measurement conditions. The mixture took on the expected deep red color of the triphenylpropenyl anion. The mixture was then quenched with water and extracted with ether. Evaporation of the ether left a mixture of acetophenone and the 1,3,3 and 1,1,3 isomers of triphenylpropene in a 20:80 ratio, as shown by NMR. The mixture was separated by chromatography and analyzed by TLC and NMR. In this way 95 mg of acetophenone was recovered, representing a 90% recovery of the original amount as compared to a 93% recovery in an identical blank experiment omitting only the base.

Discussion

Correlation of Acetophenone Acidities with Hammett σ Constants. The correlation of the acetophenone acidities in Me₂SO with those of the benzoic acids in water (as represented by Hammett σ values) was found to be much better than we anticipated. The standard deviation from the line of ± 0.1 pK unit (see Experimental Results section) is, however, outside the error in the measurements (± 0.05 pK unit). The deviations of the various observed pK values from the calculated pK values are shown as ΔpK in Table I. The ΔpK values for 14 of the 23 compounds are ± 0.10 unit or less. Of the remaining nine compounds, the points for *p*-OMe and *p*-Ph deviate by +0.14 and -0.13 unit, respectively, while those for *m*-OMe, *m*- and *p*-SPh, *m*-CF₃, *m*- and *p*-SOPh, and *p*-CN show deviations of ± 0.20 to ± 0.35 unit. The uncertainty in the calculated pK can be determined from the partial differential of the Hammett equation and the uncertainties in the slope and intercept. For the nine points with ΔpK of 0.13 unit or more, the sum of the uncertainty in the observed pK and the calculated pK is less than the ΔpK and in most cases less than half of ΔpK . If these nine points are omitted, and the remaining 14 points fitted by least-squares regression, the slope is -3.55 ± 0.05 with an intercept of 24.60 ± 0.02 and a correlation coefficient, *r*, of 0.9990. While the slope and intercept are unchanged, this new line represents a 50% reduction in the uncertainty of both slope and intercept and a 100% improvement in the correlation coefficient.

A new set of σ constants (σ_D) may be calculated using this new line and the pK values for the nine deviant points. The σ_D values for these points differ from the literature σ values by 0.04 to 0.10 unit (Table II). The excellent correlation observed for acidities of benzoic acids in water vs. acetophenones in Me₂SO for 14 of 23 substituents makes it seem likely that the differences in (calculated) σ_D values and literature σ values may be due to specific solvation effects or experimental error in the literature or observed values. The σ_D value of 0.27 for *m*-SPh derived herein for σ is in much better accord with Hammett correlations that we have obtained for acidities in Me₂SO in the ArCH₂CN and ArCH₂SO₂Ph carbon acid series⁸ than is the lower literature value (0.18). We believe, therefore, that the literature value is suspect. On the other hand, the data from the ArCH₂CN and ArCH₂SO₂Ph series, and also for the aniline series,⁹ are in better agreement with the original σ value for *m*-CF₃ than the one derived herein. We conclude, therefore, that the *m*-F₃CC₆H₄COCH₃ pK value is suspect. There are, indeed, experimental reasons to question the accuracy of this value, as well as that for *p*-CNC₆H₄COCH₃ (see the Experimental Results section). The rather strong deviation observed for the *m*-OMe point has been observed also for acidities of ArCH₂CN, ArCH₂SO₂Ph, and ArNH₂ in Me₂SO.^{8,9} In each of these series, as well as in the fluorene series,¹⁰ use of the σ_D of 0.02 for *m*-OMe derived herein will bring the point much closer to the Hammett line than will the normal σ of 0.12 or even the value of 0.06 suggested by Taft^{5a} for use in organic solvents. Here it seems likely that a solvent effect may be responsible. Hydrogen bonding to oxygen in the aqueous medium may enhance the electron-withdrawing properties of the methoxyl group and thereby increase its apparent σ constant. A similar effect would be expected for other functions capable of strong H bonding. An effect of this kind would account for the appreciably larger σ constants derived for *m*- and *p*-PhSO substituents in water than in Me₂SO (0.06 and 0.07 unit larger, respectively). The smaller value for *m*-PhSO in Me₂SO gives a better fit for this point in the 2-substituted fluorene series.¹⁰

We conclude that the Hammett σ constants derived from benzoic acids in water are applicable with remarkable precision for most acetophenones in Me₂SO. The exceptions noted

Table II. Differences in σ Values Derived in Water for Benzoic Acids and in Dimethyl Sulfoxide for Acetophenones

Substituent	σ^a	σ_D^b	$\sigma - \sigma_D$
<i>p</i> -OMe	-0.27	-0.31	0.04
<i>p</i> -Ph	-0.01	0.03	-0.04
<i>p</i> -SPh	0.075	0.14	-0.065
<i>m</i> -OMe	0.12	0.02	0.10
<i>m</i> -SPh	0.18	0.27	-0.09
<i>m</i> -CF ₃	0.43	0.52	-0.09
<i>p</i> -SOPh	0.47	0.40	0.07
<i>m</i> -SOPh	0.52	0.46	0.06
<i>p</i> -CN	0.66	0.72	-0.06

^a Derived from benzoic acids in water. ^b Derived from acetophenones in dimethyl sulfoxide.

are *m*- and *p*-OCH₃, *m*- and *p*-SOPh, and *m*- and *p*-SPh. These σ_D values may be useful in other aprotic media also.

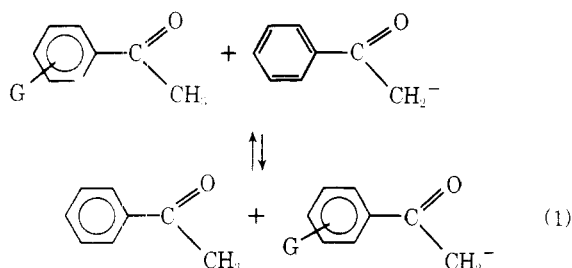
Comparison with Acidity Data in Other Solvents. No direct comparison can be made between the absolute pK of acetophenone in Me₂SO with the values of 19 in benzene solvent¹¹ or 19.1 in polyether solvent,¹² since the latter "pKs" are "ion pair pKs", and are based on an arbitrary reference standard.¹³ It is of interest to note, however, that in benzene acetophenone appears to be a *stronger* acid than fluorene by about six powers of 10, whereas in Me₂SO it is a *weaker* acid than fluorene by about two powers of 10.

A pK for acetophenone in aqueous medium of 19.2 was estimated by Bell from kinetic data.¹⁴ Another kinetic approach places the pK several units lower (~ 16).¹⁵ The latter value indicates that the acidity of acetophenone in water is about 7-8 units higher than that in Me₂SO, which is comparable to the difference in acidity for nitroalkanes in H₂O vs. Me₂SO (6-9 pK units¹⁶).

In H₂O-Me₂SO mixtures containing about 60% Me₂SO, the apparent pK of acetophenone is 21.5, i.e., about 4.5 pK units above that in water and about 3.2 pK units below that in 100% Me₂SO.^{17,18} For 9-substituted fluorenes apparent relative acidities as determined by the *H*₋ method were found to be contracted compared to those in Me₂SO. This is probably due to high apparent pK values in the more aqueous medium arising from the fact that fluorenes have lower acidities in water than in Me₂SO.⁷ On the other hand, acetophenones have higher acidities in the more aqueous medium, and the apparent pK values in this region will be low, which would be expected to lead to an expanded scale in the H₂O-Me₂SO medium. This is what is observed.¹⁷ For example, the ΔpK for *p*-cyanoacetophenone and acetophenone is 3.1 units in the H₂O-Me₂SO medium, as compared to 2.7 units in Me₂SO. For a series of para-substituted acetophenones (CN, Br, Cl, H, and Me), a roughly linear Hammett correlation was observed in the mixed H₂O-Me₂SO medium with $\rho = 4.6$,¹⁷ as compared to our value of 3.55. The *p*-OMe and *p*-NMe₂ points deviated badly from this line, the compounds being much more acidic than predicted. As a consequence, ΔpK between *p*-NMe₂ and *p*-CN substituted acetophenones is considerably smaller in the H₂O-Me₂SO medium (4.2 units) than in Me₂SO (5.5 units).¹⁹

Solvation, Conjugative, and Geometric Effects. In the introduction we showed that because of appreciable differences in solvation in H₂O vs. Me₂SO, and because of appreciable differences in the conjugative abilities of the aceto and carboxyl functions, that a poor fit with the Hammett equation when applied to acetophenones in Me₂SO would not be surprising. Instead, the correlation between the acidities of meta- and para-substituted benzoic acids in water and the acidities of corresponding acetophenones in Me₂SO appears to be as good or better than is usually achieved with as many as 14

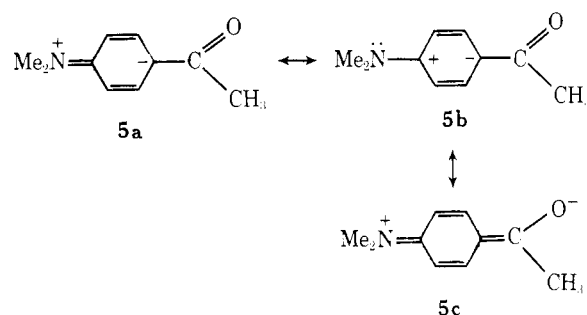
substituents. Furthermore, the deviations observed for most of the remaining nine substituents studied are not far outside of experimental error. This remarkable correlation indicates that the large differences in solvation effects of H₂O vs. Me₂SO on acetophenone and benzoic acid, as revealed by the large differences in acidities of these parent acids in the two media,⁷ are unimportant. Either the solvation effects remain constant as meta and para substituents are introduced or the solvation effects vary in a proportional manner with substitution in the two media. The substantial changes in ΔS° of ionization with substitution for the benzoic acids in water indicate that solvation is changing in this medium. Presumably, the changes in ΔS° are complemented by changes in ΔH_{int} .⁶ In Me₂SO a roughly linear correlation between enthalpies of deprotonation of a variety of weak acids by CH₃SOCH₂-K⁺ and equilibrium acidities has been observed to hold over a range of about 20 powers of 10.²⁰ The slope of this line indicates that ΔS° is often zero in Me₂SO.²⁰ Pitzer has pointed out that ΔS_{int} for a reaction of the type shown in eq 1 is nearly zero.²¹ If ΔS° for



this reaction is close to zero, as the ΔH° vs. ΔG° correlation suggests, this would mean that in Me₂SO ΔS_{ext} , as well as ΔS_{int} , remains essentially constant with meta and para substitution. In this instance the change in substituent effects must correspond to a change in ΔH_{int} . Since Kolthoff and Chantooni have observed that ρ for phenols remains essentially constant in Me₂SO, CH₃CN, and HCONMe₂ solvents, despite a change of over 10 pK units in acidities in these solvents,²² this is no doubt true also in other dipolar aprotic solvents. From these results it would appear that, in protic solvents and dipolar aprotic solvents, solvation effects vary in a proportional manner with meta and para substitution and that this accounts for the ability of the Hammett equation to accommodate data in all types of media. Another reason for the success of the Hammett equation apparently lies in the relative unimportance of direct ("through") conjugative effects.

The close correspondence in effects for *p*-F, *p*-Ph, *p*-Me, *p*-MeO, and *p*-NMe₂ substituents on benzoic acids in water and acetophenones in Me₂SO argues against major contributions from direct conjugative interactions such as those depicted by formulas 1b, 3b, 4b, and 5c. "Through conjugation" of this type would be expected to be much more important for acetophenones than for benzoic acids, and this is not observed.²³ These functions are obviously engaged in an electron-releasing resonance interaction involving the benzene ring, but evidently this does not include the carboxyl or carbonyl function to any appreciable degree. Instead, the negative charge generated next to the CO₂H or COCH₃ function by this interaction must operate primarily by an electrostatic effect. This can be depicted in valence-bond symbolism by resonance contributors such as 5a and 5b. [Resonance contributor 5c is of minor importance because (a) a high degree of charge separation is required and (b) the aromaticity of the benzene ring is lost.] Resonance of this type will stabilize the undissociated acid and will destabilize the corresponding anion. Both effects are acid weakening.

Direct conjugation of the type depicted by 3b (or 5c) is no longer possible when a methylene group is interposed between



the benzene ring and the acidic site, as in the arylacetic acids. Nevertheless, Dippy showed many years ago that a *p*-MeO substituent is acid weakening, not only in the benzoic acid series but also in the phenylacetic, β -phenylpropionic, and cinnamic acid series.²⁴ This is true also in carbon acids of the type ArCH₂G, where G is an electron-withdrawing group.⁸ This acid weakening effect is clearly a property of a methoxy group attached to a benzene ring, irrespective of the type of acidic site attached in the para position. It can be properly represented as in 5a or 5b; contributors of type 5c can be ignored. It follows that attempts to derive precise σ constants lacking a resonance component (σ^0 or σ^n) from data taken from *p*-MeOC₆H₄CH₂CO₂H and like systems are doomed to failure. The relative importance of contributors 5a and 5b is uncertain. The similar size of the orbitals on first-row elements permits better overlap between carbon and first than second row elements, allowing representation 5a to be used to account for the larger electron-releasing effects from first-row elements (e.g., CH₃O > CH₃S).^{1f} On the other hand, 5b requires less separation of charge, as compared to 5a, and 5b allows maintenance of the aromaticity of the benzene ring (6 π electrons), whereas 5a does not. Furthermore, there is reason to believe that the surprisingly large electron-releasing effect of fluorine, as compared to other halogens, is dictated primarily by a high internal energy caused by the high concentration of unshared electrons on this small (first-row) element.²⁵ Similar effects may be operative to a greater or lesser extent for OMe and NMe₂ functions. Polarization of the benzene ring, as in 5b, provides a means of lowering this energy, at the same time stabilizing the carbonyl function (C=O \leftrightarrow C⁺-O⁻).

Another factor contributing to the excellent Hammett correlation observed between the acidities of the acetophenones and benzoic acids is the close correspondence in geometry between the two systems (compare 3 and 4). Part of the transmission of the electronic effects of substituents to the acidic site must be relayed through the molecular cavity, including the solvent. (In aliphatic systems there is evidence that this is the major mode of transmission, σ bonds, and even isolated π bonds, playing minor roles.²⁶) The degree of transmission will depend on the medium, as well as the nature and geometry of the substrate. For example, ρ increases from 1.0 to ~ 2.5 to ~ 10 for benzoic acids as the medium is changed from water to Me₂SO to the gas phase, and ρ increases from ~ 2.5 to 3.5 as the substrate is changed from benzoic acids in Me₂SO to acetophenones in Me₂SO. One of the major causes of the latter increase is probably the concentration of charge on the single oxygen atom in the enolate ions derived from the acetophenones, as compared to a distribution of charge equally over two oxygen atoms in the benzoate ions. In substrates such as ArCH₂CO₂H, ArCH=CHCO₂H, ArOH, ArCH₂CN, etc., the geometric relationship between the individual meta and para substituents and the acidic site has changed, and we cannot expect Hammett σ constants derived for benzoic acids to fit precisely. When one atom intervenes between the benzene ring and the acidic site, as in the acetophenones (and benzoic acids), the present study shows that

solvent and direct conjugative effects can be ignored, leaving differences in the nature and geometry of the substrate as the principal variables. If the acidic site is moved closer to the ring, as in phenols, enhanced interactions are encountered. These will be discussed in the next paper in this series.

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Substituent Effects and Additivity in the Carbon-13 Nuclear Magnetic Resonance Spectra of Chlorinated Naphthalenes and Their Chlorinated Naphthol Metabolites

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Carbon-13 and proton nuclear magnetic resonance spectra were obtained for 12 chlorinated naphthalenes and six chlorinated naphthols, some of which are metabolites of the naphthalenes. The validity of the use of additivity of chlorine and hydroxyl substituent effects to predict ^{13}C chemical shifts in these compounds was examined. Deviations from the additivity predictions resulted from peri and ortho substituent interactions, both steric and hydrogen bonding. Despite these deviations, additive substituent parameters could be used to assign ^{13}C spectra correctly and to distinguish uniquely between similar isomers.

Polychlorinated naphthalenes are widely used industrially as complex mixtures of chlorinated naphthalene isomers. Because of the large volume and wide distribution of their use, the potential human exposure to these compounds is great. Characterization of the metabolites and elucidation of the metabolic pathways for chlorinated naphthalenes have been the focus of several investigations in the past few years. Recent work has shown that some individual chlorinated naphthalene isomers are metabolized to chlorinated naphthols.^{1,2}

Our interest centered on the identification and characterization of the individual chlorinated naphthalenes and their known and potential metabolites. We were particularly interested in those characteristics which might influence the metabolism or toxicity of these compounds. For example, their

steric properties may influence the rate at which hydroxylation takes place. Intramolecular hydrogen bonding in the metabolites may affect the relative rates of excretion and hence the relative toxicities.

Several studies of substituent effects on the ^{13}C shieldings of aromatic compounds have appeared in the literature. Substituent effects in monosubstituted benzenes³ and halobenzenes^{4,5} have been examined. Carbon-13 NMR substituent effects in 4-substituted biphenyls,⁶ 4,4'-disubstituted biphenyls,⁷ and polychlorinated biphenyls^{7,8} have also been studied. Substituent effects on the ^{13}C shieldings of methyl-naphthalenes,^{9,10} halonaphthalenes,^{11,12} and some other naphthalenes^{13,14} have been reported. Kitching et al.¹⁵ have analyzed ^{13}C chemical shift data for a large number of 1- and