The infrared spectrum of III was taken in chloroform: 2.96(w), 3.37(s), 4.05(w), 5.80(w), 6.05(w), 6.22(w), 6.86 (m), 7.00(w), 7.22(m), 7.42(w), 7.48(w), 8.05–8.30(w), 8.83(w), 9.18(w), 9.53(w), 9.90(w), 10.14(w), 10.50(w), 10.75–10.90(w) μ.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE RICE UNIVERSITY, HOUSTON, TEX.]

On the Solvent Dependence of Substituent Effects on Reactivities

BY C. D. RITCHIE AND E. S. LEWIS

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A solvent dependence of substituent effects on chemical reactivities has been noted in several recent studies. In the cases studied to date, the solvent dependence may be rationalized by assuming that solvents exert a differentiating effect on the direct interactions of substituents and reaction sites. The present study was undertaken to determine if solvent dependences exist in a case where direct interactions of the above type are not possible. For this purpose, we have measured the relative acidities of a series of 4-substituted bicyclo[2,2,2]octane-1-carboxylic acids in a variety of solvents. The linear free energy equations fail to correlate the data in dimethyl sulfoxide and 90% dimethyl sulfoxide. Although electrostatic models also fail to correlate all of the data, we find that Westheimer and Kirkwood's ellipsoidal cavity model does give fair agreement with experiment for the trimethylammonio substituted acid. It does not appear possible at the present time to attribute the solvent dependence of substituent effects to any detailed mechanism. The present results do clearly show, however, that factors other than direct interaction of substituent and reaction site are of importance.

Introduction

Over the past few years, evidence has accumulated which indicates that substituent effects are not generally independent of solvent. Jaffé[1] noted that the Hammett substituent constant for the hydroxyl group appears to be strongly solvent dependent, and attributed this to hydrogen bonding effects. Several workers have noted that the relative effects of alkyl groups on aromatic reactivities are solvent dependent, and have offered a variety of rationalizations for the phenomena.[2]

In attempting to separate polar from resonance effects in aromatic reactivities, Taft[3] found that the contribution of the resonance effects of substituents appears to depend on the solvent.

On other bases, Gutbezahl and Grunwald[4] postulated a solvent dependence for the substituent effect of the nitro group.

For aliphatic reactivities, Romberg and Cruse[5] have reported that trichloroacetic acid is a weaker acid than chloroacetic acid in acetonitrile. Grunwald's[6] *n*-value tabulation also reveals that the relative acidities of aliphatic acids in various ethanol–water mixtures cannot satisfy linear equations. A possible explanation of these solvent dependences may be based on solvent effects on conformations of the acids.[6]

Although other effects have been postulated in rationalizing the above phenomena, clear evidence that solvent dependences exist in the absence of direct interaction of substituent and reaction site has not been offered. In order to provide this evidence, we have measured the relative acidities of a series of 4-substituted bicyclo[2,2,2]octane-1-carboxylic acids in methanol, ethanol, acetone, dimethyl sulfoxide and mixtures of these with water. This series resembles aromatic systems in avoiding conformational problems and the aliphatic systems in avoiding resonance effects.

Methods and Results

The series of acids was prepared following the procedures of Roberts and Moreland.[7] In addition to the acids studied by these authors, we have measured the relative acidities of the carboxyl, carboxylate and trimethylammonio substituted acids. The solvents used were methanol, ethanol, acetone, dimethyl sulfoxide and mixtures of these with water.

An indicator method, using either *p*-nitrophenol or 5-nitrosalicylaldehyde, was employed for all measurements except those in 100% dimethyl sulfoxide. In this solvent, it was necessary to use a potentiometric method, described in detail in the Experimental section. All results are shown in Table I as the equilibrium constant for reaction A.

$$\text{X–C}_8\text{H}_{12}\text{COOH} + p\text{-O}_2\text{NC}_6\text{H}_4\text{O}^- = \text{X–C}_8\text{H}_{12}\text{COO}^- + p\text{-O}_2\text{NC}_6\text{H}_4\text{OH} \quad (\text{A})$$

In those cases where log K is reported as greater than one, 5-nitrosalicylaldehyde was actually used as the indicator. Since there was substantial overlap in the two indicators, it was possible to calculate the constants for reaction A, and these values are reported in the table. Similarly, the overlap between the indicator and potentiometric method with the bromo-, cyano- and carboxy-substituted acids allowed the calculation of the equilibrium constant for reaction A.

At least four measurements of each equilibrium constant were made, using different ratios of indicator salt to acid. These measurements generally gave agreement within 10% of the mean value. When the equilibrium constant was very different from unity, deviations as large as 20% were ob-

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(1) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(2) C. C. Price and D. C. Lincoln, *J. Am. Chem. Soc.*, **73**, 5836 (1951); E. Berliner, M. C. Beckett, E. A. Blommers and B. Newman, *ibid.*, **74**, 4940 (1952); V. J. Shiner and C. J. Verbanic, *ibid.*, **79**, 369 (1957).

(3) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960), and earlier papers cited there.

(4) B. Gutbezahl and E. Grunwald, *J. Am. Chem. Soc.*, **75**, 559 (1953).

(5) E. Romberg and K. Cruse, *Z. Elektrochem.*, **63**, 404 (1959).

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

(7) J. D. Roberts and W. T. Moreland, *ibid.*, **75**, 637 (1953); **75**, 2167 (1953).

TABLE I

SUBSTITUENT AND SOLVENT EFFECTS ON THE CARBOXYLIC ACID–p-NITROPHENOXIDE ION EQUILIBRIUM

$\log (K/K_{p-\mathrm{NO_2Phenol}})$

Solvent	Substituent							
	H	OH	CO_2Et	COOH[a]	Br	CN	COO^-[b,c]	$N(CH_3)_3^+$[c]
MeOH	0.85	1.16	1.20	1.14	1.43	1.54	−0.50	2.37
90% MeOH	1.02	1.31	1.40	1.45	1.62	1.68	− .37	2.50
75% MeOH	0.94	1.33	1.37	1.37	1.56	1.87	− .25	2.20
50% MeOH	1.29	1.78	1.60	1.76	1.77	2.06	.39	1.97
EtOH	0.54	0.81	0.91	0.73	1.23	1.32	− .72	2.44
90% EtOH	.66	0.88	1.07	0.79	1.25	1.50	− .41	2.56
75% EtOH	.89	1.13	1.35	1.04	1.36	1.63	.17	2.42
50% EtOH	.97	1.21	1.45	1.12	1.56	1.51	.52	1.81
DMSO[e]	−1.95	−1.88	−1.22	−1.46	−1.04	−1.08	−3.41	−0.74
90% DMSO	−1.18	−1.03	−0.79	−0.69	−0.23	−0.23	..	0.15
75% DMSO	−0.25	0.06	0.22	0.23	0.73	0.63	..	1.07
50% DMSO	0.80	0.91	1.19	1.10	1.57	..	0.27	2.00
Acetone	−1.63	−1.31	−1.18	−0.63	−0.69	−0.56	..	1.39
90% Acetone	0.02	0.40	0.52	0.22	0.78	1.00	..	1.96
Substit. const.[d]	0.00	0.28	0.30	..	0.45	0.58	..	..

[a] A statistical correction of −log 2 has been applied to allow for the fact that there are two acid groups present. [b] A statistical correction of +log 2 has been applied. [c] Corrections for ionic strength have been made by the Debye–Hückel approximation. [d] σ-values from ref. 7. [e] Dimethyl sulfoxide.

served. The measurement of the equilibrium constant for the carboxylate substituted acid was especially difficult, and values differing by as much as a factor of two were observed. In the 50% aqueous solvents, the equilibrium was far to the right, and very small deviations of the indicator salts from Beer's law at low concentrations added to the possible error.

Discussion

Statistical Evaluation of Data.—Roberts[7] first used the bicyclooctane acids to show the existence of linear free energy relationships in the aliphatic series. The apparent acidities in 50% ethanol were used to define substituent constants for the hydrogen, cyano, bromo, carbethoxy and hydroxyl substituents. These constants were shown by Taft[8] to be virtually the same as the values obtained from ester hydrolyses in the aliphatic series.

We have used the constants defined by Roberts to fit the data of Table I to the equation

$$\log K/K_0 = \sigma'\rho \qquad (1)$$

The parameters obtained by standard least squares treatment of the data are shown in Table II.

Plots of the data are shown in Figs. 1–4.

Also shown in Table II are the substituent "constants" for the two charged groups studied. It has often been noted that charged substituents fail to obey linear free energy relationships, and our data confirm this conclusion.

More surprising is the fact that the linear free energy equation fails in the solvents dimethyl sulfoxide and 90% dimethyl sulfoxide.[9] There is no basis for attributing the poor fit to a varying solvation of some particular substituents, although such speculation is tempting.

TABLE II

LINEAR FREE ENERGY RELATIONSHIP APPLIED TO THE ACIDITIES OF THE 4-SUBSTITUTED BICYCLO[2,2,2]OCTANE-1-CARBOXYLIC ACIDS

Solvent	ρ	$\log K_0$	s[a]	r[b]	$s\rho$[c]	$\sigma_{\mathrm{NMe_3^+}}$	$\sigma_{\mathrm{COO^-}}$
MeOH	1.22	0.85	0.075	1.00	0.17	1.25	−1.11
90% MeOH	1.21	1.01	.089	0.96	.21	1.23	−1.15
75% MeOH	1.53	0.92	.095	.97	.22	0.84	−0.78
50% MeOH	1.22	1.31	.088	.96	.20	0.54	− .75
EtOH	1.44	0.50	.036	1.00	.08	1.34	− .85
90% EtOH	1.46	.61	.098	0.97	.23	1.34	− .70
75% EtOH	1.23	.88	.10	.95	.23	1.25	− .58
50% EtOH[d]	1.01	1.02	.12	.91	.28	0.78	− .49
DMSO[e]	1.72	−1.99	.29	.83	.66	.73	− .85
90% DMSO	1.88	−1.30	.21	.91	.48	.77	....
75% DMSO	1.74	−0.28	.17	.93	.39	.78	....
50% DMSO	1.59	0.71	.20	.88	.47	.81	−0.26
Acetone	1.99	−1.71	.14	.96	.33	1.56	....
90% acetone	1.70	0.00	.052	.99	.12	1.18	....

[a] Standard deviation; *cf.* ref. 1. [b] Correlation coefficient, ref. 1. [c] Standard deviation in ρ, ref. 1. [d] Roberts used this reaction as standard, assigning $\rho = 1.45$; *cf.* ref. 7. [e] Dimethyl sulfoxide.

In all of the other solvents, with the exception of the 50% aqueous solvents and 75% dimethyl sulfoxide, the fit of the data is satisfactory, and the standard deviations are about those expected from the estimate of experimental error. In the 50% aqueous solvents, the deviations are probably due to the experimental difficulties mentioned earlier.

Plots of $\log K_0$ *vs.* Y^{-6} for the aqueous alcohol solvents are not linear. Gutbezahl and Grunwald[4] have given reasons for not expecting p-nitroaniline to obey the $\mathbf{m}Y_0$ correlation, and these same considerations apply in the case of p-nitrophenol. The failure of this correlation is therefore not surprising. The uncertainty in the ρ_- values listed in Table II prevents any conclusions regarding the correlation of ρ and Y_-.

Application of Electrostatic Models.—Obviously, no single electrostatic model will correlate all of the data of Table I, since these models predict linear free energy relationships.[10] More noteworthy is the fact that no simple relationship exists between

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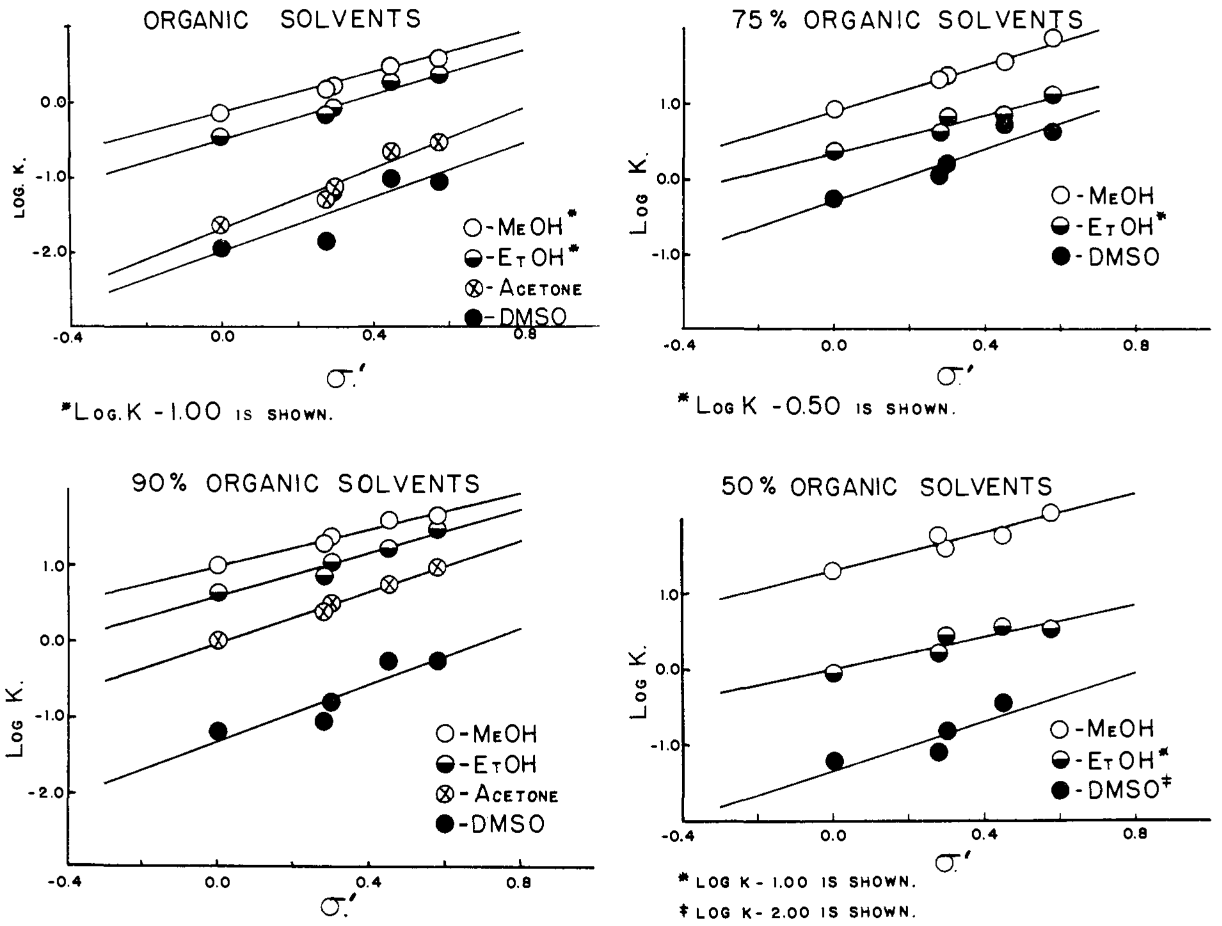
(8) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956.

(9) The failure is based on Jaffé's criteria (*cf.* ref. 1) that correlations having correlation coefficients less than 0.9 or standard deviations greater than 0.2, in this range of ρ-values, are considered to violate the linear equation. In the present case, failure could just as well be based on visual inspection of Figs. 1–4.

(10) J. Hine, *J. Am. Chem. Soc.*, **82**, 4877 (1960).



*Log. K - 1.00 is shown.

*Log K - 0.50 is shown.

* Log K - 1.00 is shown.

‡ Log K - 2.00 is shown.

Figs. 1–4.—Linear free energy plots of relative acidities of the 4-substituted bicyclo[2,2,2]octane-1-carboxylic acids in various solvents.

log K_0 values and dielectric constant. Log K_0 in acetone, the solvent with the lowest dielectric constant, is most similar to log K_0 in dimethylsulfoxide, the solvent with the highest dielectric constant. It is interesting that these two solvents are structurally similar.

The differences in log K for the hydrogen and trimethylammonio substituted acids are, however, nearly linearly related to the dielectric constant of the solvent. We have treated this difference by two models. First, we have used the simple Bjerrum[11] model, calculating the distance between charge and proton from Pauling's covalent radii.[12] Next we used the Westheimer and Kirkwood model of an ellipsoidal cavity.[13] The dimensions of the cavity were calculated on the following bases: The distance between the charge and the proton was calculated using the assumption that the proton is located 1.45 Å. from the carboxyl carbon on the extension of the bond between that carbon and the bridgehead carbon to which it is bonded.[13] The distance of the surface of the cavity from the charge, along the major axis, was taken as the distance of the farthest hydrogen, of one of the methyl groups, from the nitrogen. The charge and the proton were placed at the foci.

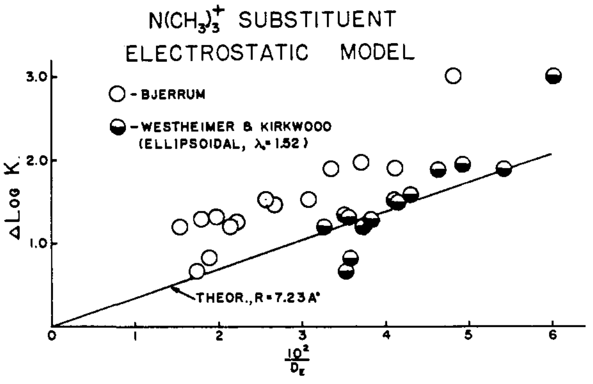


Fig. 5.—Comparison of experimental and theoretical relative acidities of the hydrogen and trimethylammonio substituted acids.

Although this model probably brings the solvent too close to the nitrogen, this is compensated to some extent by having the solvent too far from the proton.

Figure 5 shows the agreement between the calculated and observed data. The agreement for the Westheimer and Kirkwood model is certainly all that could be hoped for. Better agreement

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(11) N. Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923).

(12) L. Pauling, "The Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1948.

(13) F. H. Westheimer and J. G. Kirkwood, *J. Chem. Phys.*, **6**, 513 (1938).

could be obtained by using different models in different solvents,[14] but the increased number of adjustable parameters makes the procedure of doubtful value.

Conclusions.—The present data clearly show that solvent dependences of substituent effects are not entirely due to direct interaction of substituent and reaction site.

The observed failure of the linear free energy equation could be ascribed to either of two effects. A specific interaction between the solvent and substituent could alter the effect of the substituent, in which case other reaction series in the same solvent would show the same alterations in reactivity. That is, they would obey a linear free energy relationship using the substituent constants characteristic of the particular solvent.

The second possibility is that the deviations are caused by a general breakdown in the relationship such that substituent constants would not be independent of the reaction series.

Unfortunately, the present data do not allow a choice between these possibilities. It is clear that further work can make a distinction.

Experimental

Preparation of Materials.—The 4-H, NH_2, CN, CO_2Et, CO_2H, Br and OH substituted bicyclo[2,2,2]octane-1-carboxylic acids were prepared by the procedures of Roberts and Moreland.[7] The 4-trimethylammonium bromide substituted acid was prepared by the treatment of the amino acid with excess methyl iodide and sodium carbonate in methanol. The resulting ester, which showed no N–H stretch in the infrared, was hydrolyzed with 48% hydrogen bromide, the excess of which was removed by vacuum distillation. The residue was the nearly pure quaternary bromide. *Anal.* Calcd. for $C_{12}H_{22}NO_2Br$: C, 49.3; H, 7.5. Found: C, 49.0; H, 7.0; inorganic residue, 1.7. The error introduced by this contamination does not influence the results perceptibly unless it is a strong polyfunctional acid or base.

Reagent grade methanol, ethanol and acetone were used without further purification. Dimethyl sulfoxide was purified by several fractional freezings just before use; it then gave no reaction with *p*-nitrophenol or potassium *p*-nitrophenoxide.

The potassium salts of *p*-nitrophenol and 5-nitrosalicylaldehyde were obtained by neutralization of an ethanolic solution of the phenol with concentrated aqueous potassium hydroxide. The salts were recrystallized twice from water and dried in a vacuum desiccator. Further recrystallizations did not change the absorption spectra. Titration with standard hydrochloric acid gave the following assays: potassium *p*-nitrophenoxide, 95.3%; potassium salt of 5-nitrosalicyladehyde, 98.5%. Neither assay was improved by further recrystallization, and these values were used in the calculation of the concentrations of these substances.

Eastman Kodak Co. quinhydrone and reagent grade potassium chloride were used without further purification for the potentiometric studies.

The aqueous solvent mixtures were made by adding known volumes of water to a known volume of the organic solvent. Thus, "90%" means 9 volumes of the organic solvent plus one volume of water.

Equilibrium Measurements.—Solutions of the indicator salts were prepared in each solvent and adherence to Beer's law over the concentration range studied was demonstrated. Very small deviations from Beer's law were observed in the 50% alcohol solvents at very low concentrations. The indicator acids were not significantly ionized at the concentrations employed.

In a typical experiment, *ca.* 3 mg. of the carboxylic acid (accurately weighed on a Cahn electrobalance) was placed in a 10-ml. volumetric flask and diluted to the mark with solvent. The indicator salt was dissolved in a separate portion of the solvent to give a concentration about ten times as great as that of the acid solution. Two ml. of the acid solution was placed in a 0.10-mm. path length cell, and 0.100-ml. portions of the indicator solution were successively added to the cell. The absorbance of the solution at the absorption maximum of the indicator salt was determined after each addition. The equilibrium constant then was calculated knowing the extinction coefficient of the indicator anion and the amounts present.

Both potassium *p*-nitrophenoxide and potassium 5-nitrosalicylaldehyde were used for the measurements in the methanol, ethanol and 50% dimethyl sulfoxide solvents. Overlap was established with at least three acids in each of the solvents, *p*-nitrophenoxide was used in the acetone and other dimethyl sulfoxide solvents.

In 100% dimethyl sulfoxide, no satisfactory indicator could be found, so a potentiometric method with the following cell was used:

Pt	K salt of H subst. acid H subst. acid Quinhydrone Dimethyl sulfoxide Satd. KCl	Satd. KCl in dimethyl sulfoxide	K salt of X subst. acid X subst. acid Quinhydrone Dimethyl sulfoxide Satd. KCl	Pt

The potential was measured with a *p*H meter. The difference in acidities then can be derived by the approximate equations

$$E = 0.0591\,(\log a_{\mathrm{H}^+}{}^1 - \log a_{\mathrm{H}^+}{}^2)$$

and

$$\log a_{\mathrm{H}^+} = \log K_a + \log \frac{(\mathrm{RCOOH})}{(\mathrm{RCOO}^-)}$$

The overlap between the potentiometric method and the potassium *p*-nitrophenoxide indicator method allowed the calculation of the equilibrium constants. The relative values obtained by the two methods for the Br, CN and COOH substituted acids were in perfect agreement.

Acknowledgments.—We gratefully acknowledge the generous support of this work by the Robert A. Welch Foundation.

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[14] C. Tanford, *J. Am. Chem. Soc.*, **79**, 5348 (1957).