Solvent Effect Studies on the Ionization Constants of Phenylmercapto-, Phenylsulfinyl-, and Phenylsulfonylacetic Acids

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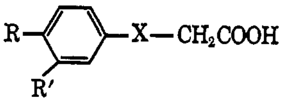
The ionization constants of β-phenylpropionic, phenoxy-, phenylmercapto-, phenylsulfinyl-, and phenylsulfonylacetic acids have been accurately determined in water–ethanol and water–dioxane solvent systems. An inversion of the relative acidities of phenylsulfinyl- and phenylsulfonylacetic acids is observed, the phenylsulfonylacetic acid being the stronger acid of the two in pure water but the weaker acid of the two in highly nonaqueous solvent sytems. This behavior is explained on the basis of conformational and hydrogen-bonding effects.

During the course of a study involving the determination of the ionization constants of a series of acids **1** in water, 50% ethanol–water, and 50% dioxane–water, an unusual p*K* dependence on the solvent composition was observed. The acidity of the phenylsulfonylacetic acid was observed to decrease at a greater rate in progressing to nonaqueous solvent systems than did the acidity of the phenylsulfinylacetic acid. In order to gain an understanding of the factors involved in this p*K* solvent dependence we have carefully determined the ionization constants (see Experimental for details of the method and calculations employed) for the parent acids (R = R′ = H) of **1** in water–ethanol and water–dioxane systems.



1, X = CH_2, O, S, SO, and SO_2

R and R′ represent a single substituent on the aromatic ring

Experimental

Preparation of Materials.—Phenylpropionic acid was obtained from Distillation Products Industries of Eastman Kodak and was recrystallized twice from petroleum ether; m.p. 47.5–49.0°.

Phenoxyacetic acid was also obtained from Distillation Products Industries and was recrystallized from chloroform–petroleum ether; m.p. 98.5–99.5°.

Phenylmercaptoacetic acid was prepared by dissolving thiophenol in an excess of aqueous sodium hydroxide and adding a slight excess of chloroacetic acid. The reaction mixture was heated on a steam bath for 15 min. and acidified with hydrochloric acid, and the free acid was recovered by extraction with ether. Several recrystallizations from petroleum ether gave the pure acid, m.p. 62.5–63.5° (lit.[2] 59–61°).

Phenylsulfinylacetic acid was prepared by oxidation of phenylmercaptoacetic acid employing the method of Leonard and Johnson[3] with sodium metaperiodate in aqueous methanol. Several recrystallizations from chloroform–petroleum ether gave pure acid, m.p. 116–117.5° (lit. 113–115°[4] and 118–119.5°[3]).

Phenylsulfonylacetic acid was prepared by the oxidation of phenylmercaptoacetic acid with hydrogen peroxide in glacial acetic acid on a steam bath for 0.5 hr. The reaction mixture was poured into water and extracted several times with chloroform. The acid was recrystallized from chloroform–petroleum ether; m.p. 113.5–114° (lit.[5] 111.5–112.5°).

Water–ethanol mixtures were prepared from twice-distilled water (from permanganate) and 95% ethanol. The mixtures were standardized by density measurements.[6] The dioxane, used in the preparation of the water–dioxane mixtures, was obtained from Fisher Scientific Co., certified reagent grade, and fractionally distilled from sodium. The mixtures were prepared on a volume per cent basis.

The titrant solutions were prepared by dissolving sodium hydroxide in the solvent system followed by standardization with reagent potassium hydrogen phthalate. The titrant solutions were maintained at 25° and used within 24 hr.

A standard reference aqueous phthalate buffer, pH 4.008, was prepared as described by Bates[7] and used to standardize the working buffer, pH 4.014.

Procedure for the Determination of the Ionization Constants.—A weighed sample of the acid, approximately 80–100 mg., was dissolved in 75.0 ml. of solvent in a thermostated vessel (25.0 ± 0.1°). The ionization constants were determined by potentiometric titrations employing a Beckman Research Model pH meter with a scale readability of ±0.0005 pH and a stated reproducibility of ±0.001 pH unit. The electrodes used were a Beckman asbestos fiber calomel (Beckman No. 39170) and a Beckman No. 41263 glass electrode. The electrodes were standardized before, approximately at the half-neutralization point and at the end of the titration. In the more highly nonaqueous solutions, electrode drift was encountered but was generally less than 0.010 p*K* unit during the titration. The recorded pH readings were accordingly adjusted. Calculations employing nonadjusted and adjusted values usually agreed to within 0.002 p*K* unit. The titrant was added using a 10-ml. microburet with magnifying eye piece or a 10-ml.-capacity Sargent automatic constant-rate buret, Model C. Approximately 20 readings were taken between 10–15 and 60–70% neutralization.

The p*K* values were calculated employing the following equation[8] using ion activities. The hydrogen ion activity was taken

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log \frac{([\text{salt}] + a_{\mathrm{H}^+})}{([\text{acid}] - a_{\mathrm{H}^+})}$$

as the negative antilog of the pH, and the activity coefficient of the undissociated acid was taken as unity (the solubility of the acids in the solvent systems is much greater than the concentrations employed in the titrations). The acid anion activity was calculated at each reading employing the Debye–Huckel equation, the dielectric constants for the ethanol–water system being determined by interpolation of the dielectric constant *vs.* per cent by weight ethanol values tabulated in the International Critical Tables[9] and for water–dioxane mixtures in a similar manner using data of Åkerlöff and Short,[10] and Gillis and Delaunois.[10]

The calculations were carried out with the aid of a Univac 1107 high-speed computer. The pK values, the root mean square deviations, and the number of points included are tabulated in Table I.

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[1] Taken in part from the B.S. Thesis of R. Kent.

[2] D. C. Gregg and C. A. Blood, *J. Org. Chem.*, **16**, 1225 (1951).

[3] N. J. Leonard and C. R. Johnson, *ibid.*, **27**, 282 (1962).

[4] A. Tanager, *Arkiv Kemi Mineral. Geol.*, **24A**, No. 10 (1947).

[5] A. C. Cope, D. E. Morrison, and L. Field, *J. Am. Chem. Soc.*, **72**, 59 (1950).

[6] "Handbook of Chemistry and Physics," 39th Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1957–1958, pp. 1963–1968.

[7] R. G. Bates, *J. Res. Natl. Bur. Std.*, **66A**, 179 (1962).

[8] S. Glasstone, "Textbook of Physical Chemistry," 2nd. Ed., D. Van Nostrand Co., Inc., New York, N. Y., 1946, p. 1003.

[9] "International Critical Tables," Vol. VI, McGraw-Hill Book Co., Inc., New York, N. Y., 1929, p. 101.

[10] G. Åkerlöf and O. A. Short, *J. Am. Chem. Soc.*, **58**, 1241 (1936); J. Gillis and A. Delaunois, *Rec. trav. chim.*, **53**, 186 (1934).

Table I

Ionization Constants

Solvent[a]	pK	R.m.s. std. dev. (±)	No. of points
Phenylpropionic Acid			
Water	4.708[b]	0.001	19
18.6% ethanol–water	5.022	0.002	23
37.3% ethanol–water	5.577	0.000_5	24
57.3% ethanol–water	6.235	0.001	19
77.7% ethanol–water	6.960	0.000_2	19
20.0% dioxane–water	5.303	0.000_3	19
40.0% dioxane–water	6.160	0.000_4	15
60.0% dioxane–water	7.275	0.002	16
80.0% dioxane–water	8.842[c]	0.000_5	18
Phenoxyacetic Acid			
Water	3.182[d]	0.000_0	19
Water	3.183[e]	0.000_1	19
18.6% ethanol–water	3.472	0.001	22
37.3% ethanol–water	3.997	0.002	21
57.3% ethanol–water	4.614	0.002	19
77.7% ethanol–water	5.338	0.000_1	19
20.0% dioxane–water	3.741	0.000_6	18
40.0% dioxane–water	4.575	0.000_2	16
60.0% dioxane–water	5.661	0.003	16
80.0% dioxane–water	7.180	0.001	16
Phenylmercaptoacetic Acid			
Water	3.566[f]	0.000_4	23
Water	3.568[e]	0.001	15
18.6% ethanol–water	3.908	0.003	27
37.3% ethanol–water	4.460	0.002	21
57.3% ethanol–water	5.095	0.001	19
77.7% ethanol–water	6.020	0.000_4	17
20.0% dioxane–water	4.191	0.002	13
40.0% dioxane–water	5.030	0.000_5	17
60.0% dioxane–water	6.116	0.002	16
80.0% dioxane–water	7.622	0.003	18
Phenylsulfinylacetic Acid			
Water	2.732[g]	0.004	19
18.6% ethanol–water	2.954	0.001	23
37.3% ethanol–water	3.407	0.000_2	19
57.3% ethanol–water	3.973	0.003	19
77.7% ethanol–water	4.650	0.001	18
20.0% dioxane–water	3.184	0.003	20
40.0% dioxane–water	3.905	0.003	15
60.0% dioxane–water	4.915	0.002	17
80.0% dioxane–water	6.241	0.002	16
Phenylsulfonylacetic Acid			
Water	2.513[h]	0.002	19
18.6% ethanol–water	2.882	0.004	16
37.3% ethanol–water	3.345	0.000_0	19
57.3% ethanol–water	3.958	0.002	19
77.7% ethanol–water	4.662	0.001	19
20.0% dioxane–water	3.057	0.002	17
40.0% dioxane–water	3.866	0.004	15
60.0% dioxane–water	4.913	0.000_2	17
80.0% dioxane–water	6.334	0.002	17

[a] Ethanol–water, per cent by weight; dioxane–water, per cent by volume. [b] J. F. J. Dippy and J. E. Page [*J. Chem. Soc.*, 357 (1938)] reported 4.66 (thermodynamic value). [c] The low solubility of sodium hydroxide in 80% dioxane–water required the use of approximately 0.015 *N* concentrations. The sample sizes of the acids were accordingly reduced. [d] W. Ostwald [*Z. physik. Chem.* (Leipzig), **3**, 184 (1889)] reported 3.12. [e] Duplicate run. [f] O. Behagel [*J. prakt. chem.*, **114**, 287 (1926)] reported 3.53, and H. D. Crockford and T. B. Douglas [*J. Am. Chem. Soc.*, **56**, 1472 (1934)] reported 3.56. [g] H. D. Crockford and T. B. Douglas reported 2.66. [h] H. D. Crockford and T. B. Douglas reported 2.64.

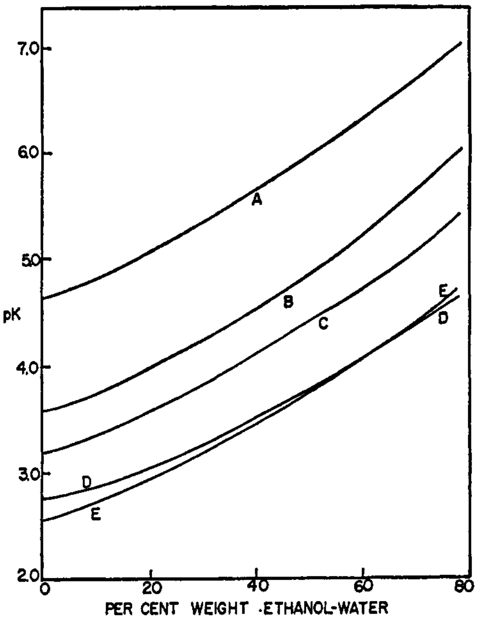

Figure 1.—p*K* solvent dependence for β-phenylpropionic acid (A), phenylmercaptoacetic acid (B), phenoxyacetic acid (C), phenylsulfinylacetic acid (D), and phenylsulfonylacetic acid (E) in ethanol–water.

No correction for liquid–liquid junction potentials has been made, and the p*K* values in ethanol–water and dioxane–water should be regarded only as relative p*K* values.

Discussion

The p*K* values reported in Table I were calculated employing ionic activities and not ionic concentrations. The difference between the two modes of calculations is significant, in particular when the more sensitive methods of pH determination are employed. The p*K* calculated for phenylmercaptoacetic acid without employing ionic activities is 3.535 ± 0.001 in contrast to the average value of 3.567 calculated using ionic activities derived by the Debye–Hückel approximation. The reproducibility from one determination to another is within the stated limits of the instrument employed in the determinations.

The p*K* values determined in this study are plotted *vs.* solvent composition in Figures 1 and 2. It is interesting to note that in both ethanol–water and dioxane–water solvent systems the phenylsulfonylacetic acid is a stronger acid than phenylsulfinylacetic acid in the lower per cent region, but the reverse is true in the highly nonaqueous solvent systems. It is perhaps more instructive to consider the actual Δp*K* values on progressing from one solvent system to another. These values are tabulated in Table II.

From the data presented it is difficult to decide which, if any, of the acids show anomalous behavior. In fact, from the data presented in Table II it might appear that the phenylsulfinylacetic acid behaves abnormally.

In an attempt to resolve this problem, some correlation between the change in p*K* value with change in solvent, or a simple p*K* relationship, was desired. Grunwald and Berkowitz[11] have proposed the equation

$$\Delta pK = pK_A - pK_A^W = \log f_H + \log (f_A/f_{HA})$$

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

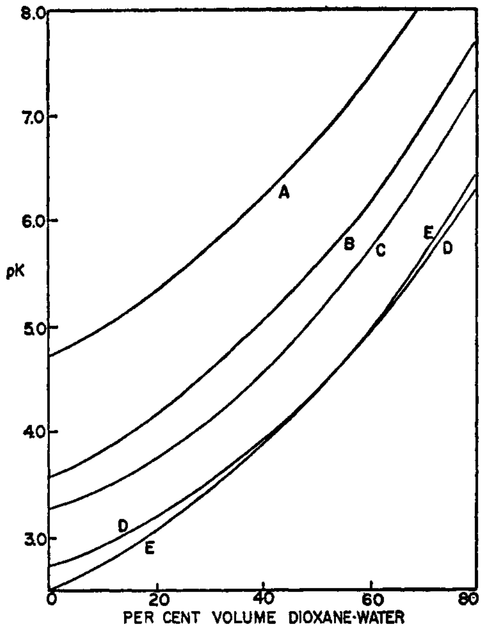

Figure 2.—pK solvent dependence for β-phenylpropionic acid (A), phenylmercaptoacetic acid (B), phenoxyacetic acid (C), phenylsulfinylacetic acid (D), and phenylsulfonylacetic acid (E) in dioxane–water.

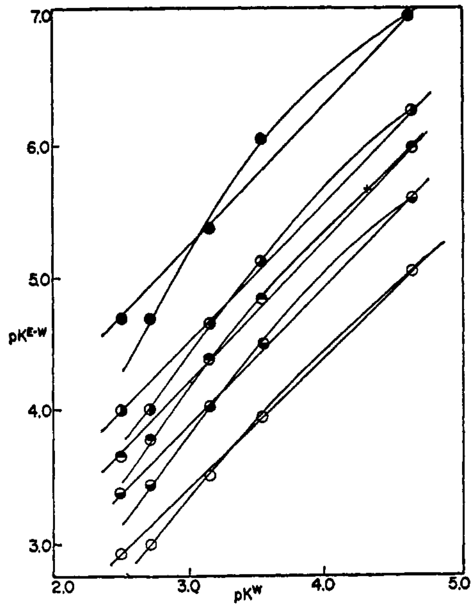

Figure 3.—Plot of pK^{H_2O} *vs.* pK in 18.6 (○), 37.3 (◒), 50.0 (◓), 57.3 (◑), and 77.7% (●) ethanol–water (x represents the pK of benzoic acid taken from other data in our laboratories).

to describe the change in ionization constant of an acid in going from water to another solvent system. Log f_H is a function of solvent only and log (f_A/f_{HA}) must be in part a function of the structure of the acid and possibly of the solvent. These authors observed that ΔpK values increased with increased ethanol content, but that the magnitudes of the increases were characteristic of individual acids. The lack of a meaningful interpretation of the terms in the equation above with respect to the behavior of a series of acids does not lend assistance to the solving of the present problem.

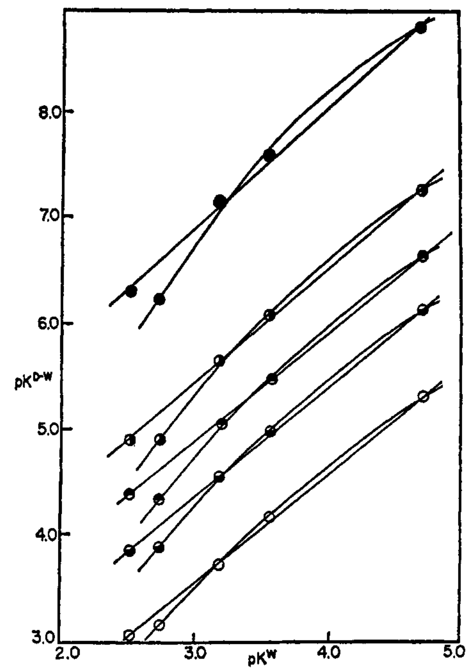

Figure 4.—Plot of pK^{H_2O} *vs.* pK in 20 (○), 40 (◒), 50 (◓), 60 (◑), and 80% (●) by volume dioxane–water.

TABLE II

ΔpK VALUES FOR $C_6H_5XCH_2COOH$ WITH CHANGE IN SOLVENT COMPOSITION

Solvent system	ΔpK — X — CH$_2$	O	S	SO	SO$_2$
Dioxane–water, %					
0–20	0.59	0.56	0.62	0.45	0.55
20–40	0.86	0.84	0.84	0.72	0.81
40–60	1.12	1.08	1.09	1.01	1.04
60–80	1.56	1.52	1.50	1.32	1.42
0–80	4.13	4.00	4.06	3.51	3.82
Ethanol–water, %					
0–18.6	0.31	0.29	0.34	0.22	0.37
18.6–37.3	0.58	0.53	0.55	0.46	0.47
37.3–57.3	0.66	0.61	0.64	0.56	0.60
57.3–77.7	0.72	0.73	0.92	0.68	0.70
0–77.7	2.25	2.16	2.45	1.92	2.15

A variety of functions were plotted in an effort to derive some meaningful correlation. Only one plot has proved to be of value. Figures 3 and 4 show the plots of $pK_A^{H_2O}$ *vs.* the pK_A in the other solvent systems. For any one given solvent system a series of five points result which can be correlated in two entirely different manners. In all cases four of the points, excluding the phenylsulfinylacetic acid point, yield a very reasonable straight line with slopes very close to unity. Also, in all cases four points, excluding the phenylsulfonylacetic acid point, yield a curved line with increasing curvature as the organic solvent composition is increased.

Distinction between these two alternatives was made in the following fashion. We have determined the pK values for 14 *meta-* and *para*-substituted phenylmercapto-, phenylsulfinyl-, and phenylsulfonylacetic acids in 50% dioxane–water.[12] If the straight-line correlation is correct, the slope of the line of plots of $pK_A^{H_2O}$ *vs.* pK_A in the substituted phenylmercapto-, phenylsulfinyl-, and phenylsulfonylacetic acid series

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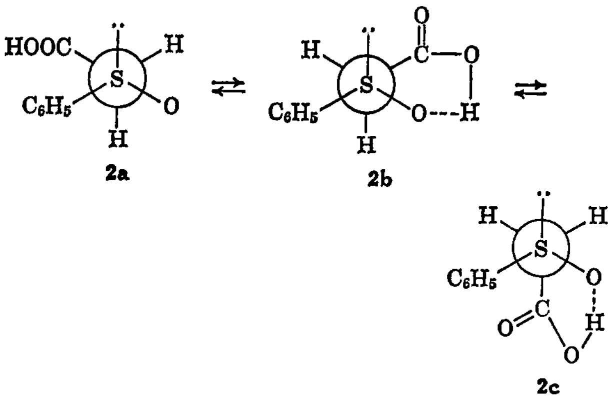
[12] D. J. Pasto, D. McMillan, and T. Murphy, *J. Org. Chem.* **30**, 2688 (1965).

should also be near unity as they represent very small portions of the larger scale plots. If, however, the curved-line correlation is correct, the slope of the line from the plots of the substituted acids series should approximate the slopes of the curved line at the positions corresponding to the parent acids.

This latter alternative was, in fact, found to be the case. The pK values of the parent acids were calculated by interpolation from Figure 1. The slopes at the positions of the parent acids on the corresponding curved line were found to be 1.3 for phenylmercaptoacetic acid, 1.7 for phenylsulfinylacetic acid, and 1.8 (by extrapolation of the curved line) for phenylsulfonylacetic acid. Corresponding values from the individual plots of the substituted acids series were found to be 1.4 for the phenylmercaptoacetic acid series, 1.9 for the phenylsulfinylacetic acid series, and 1.95 for phenylsulfonylacetic acid series. The correspondence of the slope values indicates that the curved-line correlation may be the more correct correlation and that phenylsulfonylacetic acid behaves abnormally on progressing to more concentrated ethanol and dioxane solutions.

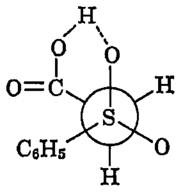
One might be led to expect that the greater inductive effect of the sulfonyl group would make the sulfonylacetic acid a stronger acid than the sulfinylacetic acid regardless of the solvent system. However, in both acids we have the possibility of intramolecular hydrogen bonding between the carboxyl hydrogen and the oxygen bonded to sulfur. In such cases the removal of water from the immediate solvation sphere of the highly polar sulfur–oxygen bond and the carboxyl group should increase the extent of intramolecular hydrogen bonding thus causing a greater reduction in the acidity of that acid relative to a nonintramolecularly hydrogen-bonded carboxyl group on progressing to poor solvating solvents. The presence of such intramolecular hydrogen bonding should therefore result in an anomalous behavior when compared with other acids, in which such hydrogen bonding does not exist.

It would therefore appear that intramolecular hydrogen bonding exists in the sulfonylacetic acid but not in the sulfinylacetic acid. This can be rationalized on the basis of a preferred conformation for phenylsulfinylacetic acid in which intramolecular hydrogen bonding is not possible. The three major conformations for phenylsulfinylacetic acid may be represented as **2a**, **2b**, and **2c**. Intramolecular hydrogen bonding may exist in conformers **2b** and **2c** but not in conformer **2a**. The presence of hydrogen bonding in **2b** and **2c** would favor these conformers over **2a**. Conformer **2b** would be preferred over **2c** on the basis of steric considerations. Conformer **2a**, however, would be expected to be more favorable owing to the opposition of the dipoles, particularly in the anion, existing in the carboxyl and SO groups. The observed pK behavior of phenylsulfinylacetic acid would indicate that conformer **2a** is the preferred conformation for the acid.

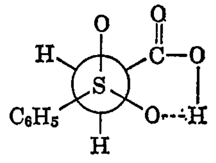


2a **2b** **2c**

In contrast, phenylsulfonylacetic acid is *not* capable of existing in a conformation in which intramolecular hydrogen bonding is not possible. Conformers **3a** and **3b** may be used to represent phenylsulfonylacetic acid. The possible existence of intramolecular hydrogen bonding in all conformations should lead to a greater decrease in acidity in poorer solvating solvents leading to an anomalous behavior.



3a



3b