found (a) that the dissociation constants of meta derivatives of phenoxyacetic acid can be calculated from those of the corresponding derivatives of benzoic acid by Hammett's equations, (b) that similarly calculated constants for para derivatives are slightly low, when the substituent resonates strongly with the aromatic nucleus, and (c) that similarly calculated constants for all ortho derivatives are too high.

These observations have been explained on the basis of the difference in the types of resonance existing in phenoxyacetic and benzoic acids.

The bromo and iodo phenoxyacetic acids were found to be anomalously weak. It has been pointed out that these anomalies cannot be adequately explained by inductive, resonance, and polarizability effects alone.

BERKELEY, CALIF. RECEIVED MARCH 22, 1943

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY OF WESTERN RESERVE UNIVERSITY]

A Simple Approximate Relation between Successive Dissociation Constants of Symmetrical Inorganic Oxygen Acids

BY TERRELL L. HILL

It is well known[1-6] that, in the absence of interactions between groups, the successive dissociation constants of a symmetrical acid containing n equivalent acidic groups[7] (n being the *maximum* number of equivalent proton positions—see below) are related by the expression

$$K_j = (n - j + 1)K^0/j \quad j = 1, 2, \ldots, n \qquad (1)$$

where K^0 is a constant. Thus

$$K_j/K_{j+1} = (j + 1)(n - j + 1)/j(n - j), \quad j = 1, 2, \ldots, n - 1 \qquad (2)$$

We may call this a zero-th approximation, and it certainly leads to results far from the truth, having neglected the important effects of charges in the molecules, dipole–proton interactions and resonance.

If we consider acids in which resonance and dipole–proton interactions[8] may be neglected, and use as a model[5] an acid B in which there is an atom A (the single center of symmetry), with a (formal) charge[8] z, and about which atom there are distributed n equivalent OH groups, then a treatment of the electrostatic interaction of approximately the same order of refinement as that of Kossiakoff and Harker[5] and of Kirkwood and Westheimer[9] leads, as a first approximation, to

$$K_j/K_{j+1} = (j + 1)(n - j + 1)\alpha/j(n - j), \quad \alpha = e^{\epsilon^2/DkTr}, \quad j = 1, 2, \ldots, n - 1 \qquad (3)$$

and

$$\frac{(n-1)K_1}{2nK_2} = \frac{2(n-2)K_2}{3(n-1)K_3} = \frac{3(n-3)K_3}{4(n-2)K_4} = \cdots = \frac{(n-1)K_{n-1}}{2nK_n} \qquad (4)$$

where ϵ is the protonic charge, D is an effective dielectric constant[9] and r is the distance between a negatively charged oxygen and a dissociable proton (both D and r are assumed the same, in this first approximation, for B and the ions of B). It is probably not worth while to give the derivation of equation 3 in detail since the general procedure is not new.

Equation 4 does not provide a method for predicting dissociation constants of such generality as other methods,[4,5] but it has the advantage of involving only a very simple calculation where it is applicable. That is, here we calculate a dissociation constant from two other known constants of the same acid series (*e. g.*, H_3PO_4, $H_2PO_4^-$, etc.). Other methods allow the calculation of any constant after certain general parameters are adjusted (which adjustment is itself done by making use of measured dissociation constants).

Although equation 4 is restricted to symmetrical[7] acids in which, as a first approximation, resonance can be neglected, it is more general than might appear at first glance. That is, it includes

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(1) E. Q. Adams, THIS JOURNAL, **38**, 1503 (1916).

(2) H. S. Simms, *ibid.*, **48**, 1239 (1926).

(3) A. L. von Muralt, *ibid.*, **52**, 3518 (1930).

(4) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1941.

(5) A. Kossiakoff and D. Harker, THIS JOURNAL, **60**, 2047 (1938).

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

(7) Although this does not exclude acids of the type H_4O^{++}, NH_4^+, etc., only oxygen acids will be considered here. A treatment similar to the one to be mentioned below leads to an analogous result for symmetrical hydrogen acids, but the corresponding simple model which must be employed is apparently not adequate in this case.

(8) The effects of dipole–proton interactions normally cancel in taking ratios between successive dissociation constants, since the same interaction is present in all acids of the series. The same is true of a charge on the central atom of the acid.

(9) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).

TABLE I

Acid, $n = 3$	Number	K Observed	K Calculated	Reference[a]
$H(HO)_3P^+$	K_1		2.0×10^2	
$H(HO)_2PO$	K_2	6.3×10^{-2}		BC
$H(HO)PO_2^-$	K_3	2.0×10^{-5}		BC
$CH_3CHClCH_2(HO)_3As^+$	K_1		6.3	
$CH_3CHClCH_2(HO)_2AsO$	K_2	1.6×10^{-4}		BC
$CH_3CHClCH_2(HO)AsO_2^-$	K_3	4.0×10^{-9}		BC
$(HO)_3S^+$	K_1		2.0×10^3	
$(HO)_2SO$	K_2	1.6×10^{-2}		BC
$HOSO_2^-$	K_3	1.3×10^{-7}		BC
$(HO)_3Se^+$	K_1		2.5×10^2	
$(HO)_2SeO$	K_2	3.2×10^{-3}		BC
$HOSeO_2^-$	K_3	4.0×10^{-8}		BC
$(HO)_3Te^+$	K_1		5.0×10^2	
$(HO)_2TeO$	K_2	3.2×10^{-3}		BC
$HOTeO_2^-$	K_3	2.0×10^{-8}		BC
$n = 4$				
$(HO)_4P^+$	K_1		7.8×10^2	
$(HO)_3PO$	K_2	$7.5 \times 10^{-3}(1)$	$\alpha_{(1)}(K_2, K_3) = 5.4 \times 10^4$	L, KH
		$7.9 \times 10^{-3}(2)$	$\alpha_{(2)}(K_2, K_3) = 2.7 \times 10^4$	BC
$(HO)_2PO_2^-$	K_3	$6.2 \times 10^{-8}(1)$	$\alpha_{(1)}(K_3, K_4) = 2.3 \times 10^4$	L, KH
		$1.3 \times 10^{-7}(2)$	$\alpha_{(2)}(K_3, K_4) = 4.9 \times 10^4$	BC
$HOPO_3^=$	K_4	$10^{-12}(1, 2)$		L, KH, BC
$(HO)_4As^+$	K_1		1.6×10^2	
$(HO)_3AsO$	K_2	4.0×10^{-3}	$\alpha(K_2, K_3) = 1.8 \times 10^4$	BC
$(HO)_2AsO_2^-$	K_3	1.0×10^{-7}	$\alpha(K_3, K_4) = 1.2 \times 10^4$	KH
$HOAsO_3^=$	K_4	3.2×10^{-12}[b]		BC
$n = 6$				
$(HO)_6Te$	K_1	6.3×10^{-7}		BC
$(HO)_5TeO^-$	K_2	4.0×10^{-11}		KH
$(HO)_4TeO_2^=$	K_3		3.3×10^{-15}	
$(HO)_6I^+$	K_1		6.8×10^2	
$(HO)_5IO$	K_2	2.3×10^{-2}		L
$(HO)_4IO_2^-$	K_3	10^{-6}		L
$(HO)_3IO_3^=$	K_4		4.6×10^{-11}	

[a] References: L, Latimer, "The Oxidation States of the Elements and Their Potentials in Aqueous Solutions"; BC, footnote 4; KH, footnote 5. [b] This is the value given in the most recent source (BC). The value $pK = 9.2$ (KH) has been ignored since the present method, and those of Kossiakoff and Harker and of Branch and Calvin all predict a value closer to the given one.

acids such as $P(OH)_4^+$ and $I(OH)_6^+$, and therefore the acids H_3PO_4 and H_5IO_6, etc., and allows an approximation of dissociation constants in these cases.[10] In other words, we need not be confined to initially neutral acids. Most positively charged acids of the type mentioned above and later in the paper will, of course, be very highly dissociated in aqueous solution, but they may be important in other solvents.[10,13] Equation 4 may, therefore, prove to be of value in connection with such solvents (the equation is not restricted as to solvent).

It should be emphasized that the constants in equation 4 are not necessarily numbered in the customary fashion (see Table I). For example, K_2, K_3 and K_4 are the usual first, second and third dissociation constants of phosphoric acid, while K_1 is the dissociation constant of $P(OH)_4^+$.

It will be observed that dropping the numerical coefficients in equation 4 would not introduce a

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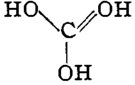
[10] The resonating ion  would be the corresponding positive ion of H_2CO_3. Aided by this resonance, $C(OH)_3^+$ should not be altogether ignorable even in aqueous solutions. Since CO_2 rather than H_2CO_3 is predominant in water we should, perhaps, consider CO_2 here rather than H_2CO_3.[11] Then $O{=}C{=}OH^+$ (and $C(OH)_2^{++}$ to a very slight extent) would be the positive ion. In this connection it may be mentioned that many carboxylic acids as well as nitric acid have been found[12] to exhibit basic properties in the solvent sulfuric acid. The positive ions formed are analogous to those discussed above.

[11] The author is indebted to Professor I. M. Kolthoff for this suggestion.

[12] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 45-48.

[13] Arlman (*Rec. trav chim.*, **56**, 919 (1937); **58**, 871 (1939)) has shown the existence of the ions $P(OH)_4^+$ and $Se(OH)_3^+$ in nitromethane by electrolysis and conductivity experiments.

large error. This is the basis for the approximate rule that successive dissociation constants of a given acid of the type being discussed here fall at equal intervals along a pK scale.

In Table I are listed a few acids together with those values of their dissociation constants which have been given in the most recent compilation. From these values and equation 4, other dissociation constants have been calculated and are included in the table. Only in the cases of phosphoric and arsenic acids is it possible to compare observed and calculated values, since these are the only ones with three measured dissociation constants. This comparison is made by calculating the value of the constant α from K_2 and K_3, and from K_3 and K_4. Two recent sets of dissociation constants for phosphoric acid, not differing a great deal, have been employed. The agreement for each set is quite satisfactory, and the two sets give the same average value: $\alpha = 3.8 \times 10^4$. The calculated value of K_1 was obtained using this average value of α and $K_2 = 7.7 \times 10^{-3}$. The agreement between the two values of α for arsenic acid is better than for phosphoric acid. Evidence for the validity of equation 4 as a good approximation is not limited, however, to these two examples, for the success of the general methods of Branch and Calvin and of Kossiakoff and Harker must also be considered as evidence. As a matter of fact, equation 4 may readily be derived from the fundamental equation[14] (for water as solvent) used by Branch and Calvin.

The calculated dissociation constants of $H(HO)_3P^+$, $(HO)_3S^+$, $(HO)_3Se^+$, $(HO)_3Te^+$, $(HO)_4P^+$, $(HO)_4As^+$ and $(HO)_6I^+$ (all of the same order of magnitude) predict the expected virtually complete ionization into the uncharged molecule and hydrogen ion, in the solvent water. The acid $CH_3CHClCH_2(HO)_3As^+$ is, on the other hand, a somewhat less strong acid.

Further constants of $(HO)_6Te$ and of $(HO)_6I^+$ could have been calculated, but the "extrapolation" from two experimental constants certainly become less valid for more "distant" constants.

The author is indebted to Professor I. M. Kolthoff for his interest and helpful comments.

Summary

A simple equation is obtained which makes it possible, when two or more dissociation constants are known, to predict other unmeasured dissociation constants of symmetrical inorganic oxygen acids. A few examples are given, including some acids which are positively charged. The relationship of this equation to other methods is pointed out. The equation is not restricted as to solvent.

(14) Equation 7, p. 204.

CLEVELAND, OHIO RECEIVED APRIL 26, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE DENVER CHEMICAL MANUFACTURING CO.]

The Interaction of Amides with Amines: A General Method of Acylation[1]

BY ALEXANDER GALAT AND GERTRUDE ELION

Various authors have observed the formation of substituted amides when aromatic amines are heated with amides.[2,3,4,5,6] More recently, good yields have been reported for the preparation of disubstituted ureas by the reaction between carbamide and aromatic amines.[7a] and poorer yields with aliphatic amines.[7b] In addition, monosubstituted ureas have been prepared by the treatment of primary amines with nitrourea.[8]

The latest work on this subject, dealing with the interaction of amides and aniline,[9] indicates that yields are generally poor and that, with certain amides, *e. g.*, *i*-butyramide, the reaction does not take place at all. There is no indication in the literature of the application of this reaction to the aliphatic series, probably because the lower aliphatic amines are too volatile, while the higher ones have not been generally available until recently.

Hoffman[10] discovered that acetamide reacted satisfactorily with the hydrochloride of an amine, namely, hydroxylammonium chloride

$$CH_3CONH_2 + HONH_3Cl \longrightarrow NH_4Cl + CH_3CONHOH$$

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(1) Original manuscript received September 13, 1939.

(2) Fleischer, *Ber.*, **9**, 995 (1876).

(3) Kelbe, *ibid.*, **16**, 1199 (1883).

(4) Just, *ibid.*, **19**, 1202 (1886).

(5) Freund and Goldsmith, *ibid.*, **21**, 2461 (1888).

(6) Hirst and Cohen, *J. Chem. Soc.*, **67**, 830 (1895).

(7) (a) Davis and Underwood, THIS JOURNAL, **44**, 2595 (1922); (b) Davis and Blanchard, *ibid.*, **45**, 1816 (1923).

(8) Davis and Blanchard, *ibid.*, **51**, 1790, 1801, 1806 (1929).

(9) Hurd, Dull and Martin, *ibid.*, **54**, 1974 (1932).

(10) Hoffman, *Ber.*, **22**, 2855 (1889).