

159. Dissociation Constant, Solubility, and the pH Value of the Solvent.

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The relationship between the dissociation constant of a sparingly soluble acid (or basic) substance, its solubility, and the pH value of the solvent is stated. This relationship is tested and confirmed by measurement of the solubilities of an amphoteric substance (the drug, "sulphadiazine") in buffer solutions ranging from pH 1 to pH 8. The procedure is suggested as convenient for determining the dissociation constant of a substance too insoluble to be dealt with by the usual methods.

If HA is a sparingly soluble, acid substance, ionising according to $HA \rightleftharpoons H^+ + A'$, its thermodynamic dissociation constant (K_a) is given by

$$K_a = \{H^+\}\{A'\}/\{HA\} = \{H^+\}[A']f_{A'}/[HA]f_{HA} \dots \dots \dots (1)$$

(where [] represents a concentration, { } an activity, and f an activity coefficient), and its total solubility (S) by

$$S = [HA] + [A'] \dots \dots \dots (2)$$

At a sufficiently high hydrogen-ion concentration, S falls practically to $S^\circ (= [HA])$. Combining (1) and (2), we have

$$S = S^\circ + S^\circ K_a f_{HA} / \{H^+\} f_{A'} \dots \dots \dots (3)$$

or, rearranging, taking common logarithms, and putting $-\log \{H^+\} = \text{pH}$ and $-\log K_a = \text{p}K_a$,

$$\log (S/S^\circ - 1) = \text{pH} - (\text{p}K_a + \log f_{A'}/f_{HA}) = \text{pH} - \text{p}K'_a \dots \dots \dots (4)$$

$K'_a (= \{H^+\}[A']/[HA])$ is Bronsted's acidity constant (*Chem. Rev.*, 1928, 5, 293). When $\log (f_{A'}/f_{HA})$ is ignored, equation (4) leads to $\text{p}K'_a$ rather than to $\text{p}K_a$. The former is not a true constant, and the difference between them cannot be unambiguously stated, as it involves the individual ion activity coefficient $f_{A'}$; but, under conditions of constant and low ionic strength, $\log (f_{A'}/f_{HA})$ will also be approximately constant and fairly small; and it can be estimated with the help of the arbitrary assumptions that have in any case to be accepted when attempting to standardise the pH scale in terms of hydrogen ion activity (cf. Clark, "The Determination of Hydrogen Ions," Chap. XXIII; Dole, "The Glass Electrode," Chap. XVII).

With or without activity corrections, calculations equivalent to (3) have often been made in deducing the acid dissociation constants of amphoteric oxides from their enhanced solubilities in caustic alkali solutions (e.g., by Goldschmidt and Eckhardt, *Z. physikal. Chem.*, 1906, 56, 385; Berl and Austerweil, *Z. Elektrochem.*,

1907, 13, 165; Glasstone, J., 1921, 119, 1697; Johnson and Leland, *J. Amer. Chem. Soc.*, 1938, 60, 1439; cf. also Britton, *Ann. Reports*, 1943, 40, 43).

In the present work, equation (4), which was needed in an investigation of the solubilities of sulphonamides in buffer solutions of various pH values, has been tested and found satisfactory; a plot of $\log(S/S^\circ - 1)$ against pH followed a straight line of unit slope, intercepting the pH axis at pK'_a . Furthermore, the procedure adopted is suggested as convenient for determining the dissociation constant of an acid too insoluble to be dealt with by the usual methods. The acid should be capable of being estimated in presence of the buffer solution, its S° should not be immeasurably small, and its alkali salt should be relatively highly soluble.

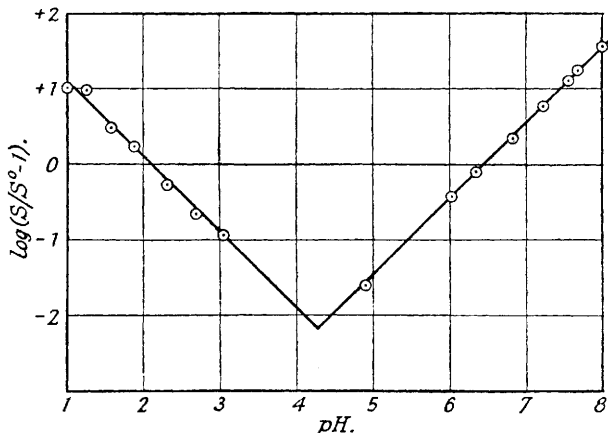
With obvious modifications, the treatment can be applied to a sparingly soluble base (B, giving the ion BH^+) for which

$$\log(S/S^\circ - 1) = \left. \begin{aligned} & (pK_w - pK_b - \log f_{BH^+}/f_B) - pH \\ & = (pK_w - pK'_b) - pH \end{aligned} \right\} \dots \dots \dots (5)$$

The measurements described here were made on 2-sulphanilamidopyrimidine ("sulphadiazine") (I), an amphoteric compound illustrating both acid and basic effects.

EXPERIMENTAL.

All measurements were made at 25.0°. The sulphadiazine, m. p. 256°, was obtained by recrystallising a commercial specimen from water. Buffer solutions were prepared by adding sodium hydroxide to a solution of two weak acids chosen so as to give an approximately uniform buffering capacity over a range of pH (cf. the universal buffer mixtures of Prideaux and Ward, J., 1924, 125, 426, and others), diluting, and in each case adding the appropriate quantity of *N*-sodium chloride to maintain the ionic strength at 0.1M. For the pH range 2—5, the mixed acid solution contained 0.0375M-phosphoric acid + 0.0375M-acetic acid; for the range 6—9, 0.0375M-phosphoric acid + 0.00938M-sodium tetraborate (*i.e.*, equivalent to 0.0188M- H_2PO_4 + 0.0188M- NaH_2PO_4 + 0.0375M- HBO_2); after dilution, the final total concentration of each acid was 0.0268M. For pH's below 2, a mixture of hydrochloric acid and sodium chloride was used. The buffer solutions were saturated by shaking them vigorously with an excess of solid sulphadiazine for at least 3 hours—a period found to be amply sufficient with this compound. They were then quickly filtered. The sulphadiazine concentration was estimated by the method of Bratton and Marshall (*J. Biol. Chem.*, 1939, 128, 537), and the pH values were measured with the glass electrode, which was standardised in terms of the buffer solutions recommended by Hitchcock and Taylor (*J. Amer. Chem. Soc.*, 1937, 59, 1812).



Plot of solubility function, $\log(S/S^\circ - 1)$, against pH for sulphadiazine at 25°.

The pH must be measured after saturation, as its value is somewhat altered by dissolution of the sulphadiazine (cf. the method for determining the isoelectric point of an ampholyte described by Michaelis, *Biochem. Z.*, 1912, 47, 251). It can easily be shown that under the optimum buffering conditions obtaining in an equimolar mixture of a weak acid and its salt (each *C* molar), the change in pH caused by saturation with an acid or basic compound of very low solubility (*S* molar) is given approximately by

$$\Delta pH = \log [1 + 2(S - S^\circ)/C] \approx 2(S - S^\circ)/2.3C \dots \dots \dots (6)$$

In practice the change will tend to be rather larger than this (since the buffering capacity is not usually optimum), and increasingly so as *S* rises.

Results are shown in the table. The solubility passes through a minimum in the neighbourhood of pH 4.3, in accordance with a well-known principle (cf. Michaelis and Davidsohn, *Biochem. Z.*, 1910, 30, 142). Before equation (4) can be applied, S° must be known. For an acid solute this may be found with all necessary accuracy by making a

Solubility of sulphadiazine at various pH values.

| | | | | | | | | | | | | | | | |
|------------------------|------|------|------|------|------|------|------|------------------|------|------|------|------|------|------|------|
| pH (at saturn.) | 1.00 | 1.26 | 1.55 | 1.89 | 2.31 | 2.69 | 3.06 | 4.89 | 6.01 | 6.35 | 6.82 | 7.23 | 7.56 | 7.67 | 8.00 |
| <i>S</i> (mg./100 ml.) | 68 | 66 | 25.2 | 16.5 | 9.3 | 7.5 | 6.9 | 6.3 ₃ | 8.5 | 11.1 | 19.4 | 43.5 | 86 | 114 | 229 |

solubility measurement at a pH sufficiently below pK'_a . Alternatively, or if for any reason (such as amphoteric behaviour) this is not possible, *S* may be plotted against $1/\{H^+\}$, whence, according to (3), extrapolation to $1/\{H^+\} = 0$ gives S° . Application of the latter procedure to the solubilities measured at pH 4.89, 6.01, and 6.35 leads to a value of 6.16 mg./100 ml.; $\log(S/S^\circ - 1)$ can then be plotted against pH as in the figure. The points do not deviate sig-

nificantly from the straight lines drawn to have unit slopes. The line of positive slope intersects the axis at pH 6.45, equal to pK'_a ; that of negative slope at pH 2.1, corresponding to $pK'_b = 14.0 - 2.1 = 11.9$.

Bell and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 2906) recorded $pK_a = 6.48$ and $pK_b = 12.0$ (the temperature being 25°; private communication), but these values were presumably obtained by empirical adjustment of values found for 50% aqueous alcohol; pK_a and pK_b have therefore been redetermined at 25.0° by potentiometric titration in water, the general details having been described previously (J., 1940, 855). Difficulty arises from the low solubility of sulphadiazine in water (about 0.00025M). Best results were achieved with solutions prepared by warming a weighed amount of the compound with water containing rather more than 1 equiv. of hydrochloric acid. The acid does not materially increase the solubility, owing to the extreme weakness of the base; but supersaturated solutions (about 0.0005M) resulted on cooling, and by titrating these with sodium hydroxide both basic and acidic ranges of the sulphadiazine could be studied. From several determinations under slightly different conditions pK_a was found to be 6.56 ± 0.06 .

With a base so weak as sulphadiazine, and at such high dilutions, the potentiometric titration method is hardly within the range of its practical applicability in aqueous solution. The chance of error is very unsymmetrical, and the average value calculated for pK_b , 11.5, is therefore best regarded as a lower limit. The solubility method is many times more accurate here.

To bring these data into strict comparability with those derived from the figure, $\log(f_{A'}/f_{HA})$ must be added to pK_a , and the analogous term $\log(f_{B'}/f_{HB})$ to pK_b . Under the conditions employed f_{HA} will not differ appreciably from unity; as already explained, $f_{A'}$ (or f_{HB}) cannot be unequivocally known, but, if it is assumed to be equal to the mean ion activity coefficient for a typical uni-univalent electrolyte at ionic strength 0.1 (cf. Guggenheim, *J. Physical Chem.*, 1930, **34**, 1764), it may be about 0.75. Accordingly $pK'_a = pK_a - 0.12$, and $pK'_b = pK_b - 0.12$. A more direct comparison was made by carrying out potentiometric titrations in the presence of 0.1M-sodium chloride, giving $pK'_a = 6.40 \pm 0.06$ and $pK'_b \approx 11.5$ (a lower limit again). The agreement between the dissociation constants, both acid and basic, found by the two methods is therefore well within experimental error.

The treatment given applies to a monobasic acid or monoacid base. If, as the pH changes, a second acid or basic group becomes active, then the plot of $\log(S/S^\circ - 1)$ against pH will deviate from the original line of unit slope and converge upon one of slope 2, intersecting the pH axis at $\frac{1}{2}(pK'_1 + pK'_2)$. The sulphadiazine molecule possesses more than one potentially basic group; but a solubility determination at a pH so low as 1.0 (made in 0.15N-hydrochloric acid, and therefore not at the ionic strength of 0.1 obtaining in the other determinations) shows no significant deviation from the straight line. The effect can, however, be clearly detected in MacDowell and Johnston's data (*J. Amer. Chem. Soc.*, 1936, **58**, 2009) for the solubility of copper oxide in concentrated alkali solutions.

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