

CLXXVI.—*The Acidic Constants of Some Ureides and Uric Acid Derivatives.*

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DURING the determination of the acidic constants of the methyl derivatives of xanthine (see following paper) results were obtained which appeared to be contrary to those which, on constitutional grounds, might have been expected. It was therefore considered advisable to conduct similar experiments with a number of other imino-compounds, chiefly ureides and derivatives of uric acid, with a view to finding the influence which other groups have on the acidity of the imino-group. The results of these experiments, together with the conclusions drawn from them, form the subject of the present paper.

In the case of some of the substances, the acidity was determined by

the ordinary conductivity method. The water used as solvent was specially distilled, and in no case did its conductivity exceed 1.5×10^{-6} at 25° .

All conductivities given in this paper are expressed in terms of reciprocal ohms.

With the majority of the substances, however, it was impossible to employ the conductivity method owing to the degree of ionisation being very small. In such cases, the dissociation constant was calculated from the velocity of saponification of methyl acetate by the sodium salt of the substance (Shields, *Zeit. physikal. Chem.*, 1893, 12, 167). The acid was dissolved in an equivalent amount of $N/20$ sodium hydroxide and the solution then mixed with one of methyl acetate, the alkali and ester being in equivalent proportions. Portions of the mixture were removed at intervals and titrated with $N/100$ hydrochloric acid, the indicator used being *o*-nitrophenol. From the results obtained the constants were calculated by means of the equation

$$k = \frac{1}{t} \left\{ \frac{e}{e-x} - 1 - 2.302 \log \frac{e}{e-x} \right\},$$

where e represents the initial concentration of the ester and x the portion transformed in the time t . This equation can only be used satisfactorily during the middle portion of the action.

The constant k calculated as above must not be confused with the dissociation constant of the acid. It represents the product of the velocity constant (c) for the saponification of methyl acetate by sodium hydroxide and the hydrolysis constant (h) of the sodium salt of the compound under examination. Experiments on the saponification of methyl acetate by sodium hydroxide have shown that c has the value 11.42 at 25° , so that

$$h = \frac{k}{11.42}.$$

Now $h = \frac{K}{k_a}$, where K is the dissociation constant of water and k_a the dissociation constant of the acid under examination (Arrhenius, *Zeit. physikal. Chem.*, 1890, 5, 17), and at 25° , the temperature at which all the experiments were performed, K has the value 1.2×10^{-14} . The equation finally becomes, therefore,

$$k_a = \frac{11.42 \times 1.2 \times 10^{-14}}{k}.$$

For purposes of illustration the whole of the figures obtained are given in the case of methyluracil; in the case of other substances for which this method was used only the mean values of k and k_a are given.

Methyluracil.—Trübsbach (*Zeit. physikal. Chem.*, 1895, **16**, 711) determined the dissociation constant of this substance by the conductivity method and obtained a result of 4.6×10^{-9} .

The sample used by the author was prepared by Behrend's method (*Annalen*, 1885, **229**, 9).

Saponification Experiment.

25 c.c. *N*/20 solution of sodium methyluracil + 25 c.c. *N*/20 solution of methyl acetate.

Time.	Titre.	<i>k</i> .
0	4.95	—
108	3.70	0.000425
179	3.40	0.000449
208	3.31	0.000447
262	3.20	0.000422
315	3.06	0.000434
	Mean	0.000435

The value of k_a calculated from the above mean value of k is 3.14×10^{-10} ; this number was confirmed by subsequent experiments. The divergence from Trübsbach's result is probably explained by the difficulty of obtaining trustworthy values for the conductivity in the case of very feeble electrolytes.

α-Dimethyluracil, $\text{CO} \left\langle \begin{array}{l} \text{NMe} \cdot \text{CMe} \\ \text{NH} - \text{CO} \end{array} \right\rangle \text{CH}$.—This compound, which melted at 220—230°, was prepared by Behrend and Dietrich's method (*Annalen*, 1899, **309**, 266). The value of k found by the saponification method was 0.00155, corresponding to a dissociation constant of 8.8×10^{-11} .

β-Dimethyluracil, $\text{CO} \left\langle \begin{array}{l} \text{NH} \cdot \text{CMe} \\ \text{NMe} - \text{CO} \end{array} \right\rangle \text{CH}$.—This substance was prepared by Behrend and Dietrich's method (*loc. cit.*); the sample melted at 258°.

$$k = 0.00185; k_a = 7.4 \times 10^{-11}.$$

Hydantoin.—The conductivity of this substance was determined by Trübsbach (*loc. cit.*), but the dissociation constant was not calculated. Using the figure given by him as the conductivity in *N*/128 solution, the calculated dissociation constant was found by the author to be 6.34×10^{-10} .

The hydantoin used in the present experiments was prepared by Diels and Heintzel's method (*Ber.*, 1905, **38**, 305); it melted at 216—217°.

$$k = 0.000180; k_a = 7.59 \times 10^{-10}.$$

The value for k_a so determined is in good agreement with that calculated from Trübsbach's conductivity figures.

Allantoin.—This compound was prepared by the action of potassium permanganate on uric acid (Claus, *Ber.*, 1874, 7, 227).

The saponification method was used for the determination of the acidity, but a little uncertainty in the value of the constant was occasioned by the end point of the titration not being quite sharp. The mean values obtained were

$$k = 0.000117 ; k_a = 1.17 \times 10^{-9}.$$

Oxyuracil.—The specimen used for the experiments was prepared by Behrend's method (*Annalen*, 1885, 229, 39).

The quantity of substance available was not sufficient to allow of conductivity determinations being made, whilst the results obtained by the saponification method were not very satisfactory because of the end-point of the titration being indistinct. The mean value of k was found to be 0.0000538, corresponding to a dissociation constant (k_a) of 2.5×10^{-9} .

Parabanic Acid.—This compound was prepared by the action of nitric acid (sp. gr. 1.3) on uric acid. The product was crystallised first from ordinary distilled water and afterwards from the specially distilled water used for conductivity experiments; it was then dried at 100—105°.

Trübsbach (*loc. cit.*) made a series of experiments with this compound, and came to the conclusion that it changes in solution into urea oxalate. Owing to this change taking place, the conductivities obtained for a series of dilutions do not yield a fixed dissociation constant. The dissociation constant calculated from Trübsbach's conductivity for a $N/32$ solution is 3.74×10^{-6} . This number, however, is too high, for, using a solution of equal concentration, the author obtained a value for the conductivity which gave a dissociation constant of 0.75×10^{-6} .

The transformation of the parabanic acid into urea oxalate can be followed in the cell. The results of one experiment of this nature are shown in the following table, the concentration of the solution being $N/32$:

Time in hours.	Value of μ_{32} .	Time in hours.	Value of μ_{32} .
0	2.133	6	6.132
1	2.907	21	11.953
3	4.412	144	30.572

It will be seen that the rate of transformation of the parabanic acid is comparatively slow, so that the quantity which undergoes change during the short period of time necessary to dissolve the acid and raise the temperature of the solution to 25° must be of small dimensions. It follows, therefore, that the number given above for the dissociation constant cannot be much in excess of the true value.

Barbituric Acid.—Trübsbach (*loc. cit.*) found the dissociation constant of this substance to be 9.79×10^{-5} . Hantzsch and Voegelen (*Ber.*, 1902, 35, 1006) determined the conductivity both in aqueous and in aqueous alcoholic solutions, obtaining in the case of the former a value for μ_{64} of 27.06.

The barbituric acid used for the present experiments was prepared by Fischer and Dilthey's method (*Annalen*, 1904, 335, 334) by condensing malonic ester and urea with sodium ethoxide.

The conductivity method yielded a value for k_a of 10.51×10^{-5} , in close agreement with the number obtained by Trübsbach. The saponification method was not available in this instance, because of the action of barbituric acid on indicators.

5-Ethylbarbituric Acid.—This compound was prepared by heating to 100° for two to three hours a mixture of urea, ethylmalonic acid, and phosphoryl chloride (Conrad and Guthzeit, *Ber.*, 1882, 15, 2845). The product obtained was mixed with a small amount of water, the solution filtered off, and the residue repeatedly crystallised, first from ordinary distilled water and then from conductivity water.

A *N*/64 solution was found to have a molecular conductivity of 18.23, corresponding to a value for k_a of 3.83×10^{-5} . Owing to the fact that the solution oxidises in the cell, a series of dilution experiments was not performed.

As with the parent substance, the saponification method was not available, because of the indicators being affected by the acid.

5:5-Dimethylbarbituric Acid.—This compound was prepared by condensing dimethylmalonic ester and urea by means of sodium ethoxide (Fischer and Dilthey, *loc. cit.*). The product was crystallised from conductivity water.

For this substance also the conductivity method was found to be the more suitable. The molecular conductivity of a *N*/64 solution was found to be 0.912, giving a value for k_a of 7.3×10^{-8} .

5:5-Diethylbarbituric Acid.—The method used for the preparation of this compound was similar to that employed for the dimethyl derivative. The sample melted at 187° . After repeated crystallisation from ordinary distilled and conductivity water, the conductivity of a *N*/64 solution was determined. The molecular conductivity was found to be 0.573, giving a value for k_a of 3.7×10^{-8} .

Alloxan.—Trübsbach (*loc. cit.*) also determined the conductivity of this substance, but the dilution experiments performed by him did not give a fixed value for the dissociation constant. The value calculated from the conductivity in *N*/64 solution was 4.11×10^{-5} .

The alloxan used by the author was supplied by Kahlbaum and, after being recrystallised from conductivity water, was dried first in the desiccator and then at 120° . A *N*/64 solution had a molecular

conductivity of 2.156, giving a dissociation constant of 2.32×10^{-7} . The alloxan was found to undergo, in solution, the same kind of change as was noticed with parabanic acid. After five minutes the molecular conductivity rose from 2.156 to 2.466, whilst after fourteen hours it had a value of 11.45. Probably this fact partly accounts for the high value obtained by Trübsbach for the dissociation constant of alloxan.

Succinimide.—The sample used was prepared by the distillation of ammonium succinate.

By means of the saponification method the following values were obtained :

$$k = 0.00453; k_a = 3.02 \times 10^{-11}.$$

Phthalimide.—This substance was supplied by Kahlbaum.

The saponification method could not be used because of the action of the phthalimide on the indicator. A portion of the substance was recrystallised from alcohol and ether and, after drying at 120° , the conductivity of the recrystallised product was determined. The strongest solution which could be prepared had a concentration of $N/256$; the molecular conductivity of this solution was found to be 1.99, giving a dissociation constant of 1.09×10^{-7} . The conductivity of the solution was found to increase either when it was kept in the cell or in a stoppered flask. After standing sixty hours in a closed flask the molecular conductivity had increased to 3.83, whilst after about five days it had risen to 8.1.

Summary of Results.

Substance.	Dissociation constant $\times 10^7$.
Barbituric acid, $\text{CO} \begin{array}{l} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CH}_2$	1051.0
5-Ethylbarbituric acid, $\text{CO} \begin{array}{l} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CHEt}$	383.0
Parabanic acid, $\text{CO} \begin{array}{l} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array}$	7.5
Alloxan, $\text{CO} \begin{array}{l} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CO}$	2.32
Phthalimide, $\text{C}_6\text{H}_4 \begin{array}{l} \text{CO} \\ \text{CO} \end{array} \text{NH}$	1.09
5 : 5-Dimethylbarbituric acid, $\text{CO} \begin{array}{l} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CMe}_2$	0.73
5 : 5-Diethylbarbituric acid, $\text{CO} \begin{array}{l} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CEt}_2$	0.37
Oxyuracil, $\text{CO} \begin{array}{l} \text{NH} \cdot \text{CH}_2 \\ \text{NH} \cdot \text{CO} \end{array} \text{CO}$	0.025

Summary of Results (continued).

Substance.	Dissociation constant $\times 10^7$.
Allantoin, CO $\left\{ \begin{array}{l} \text{NH}\cdot\text{CH}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2 \\ \\ \text{NH}\cdot\text{CO} \\ \\ \text{NH}\cdot\text{CH}_2 \end{array} \right.$	0.0117
Hydantoin, CO $\left\{ \begin{array}{l} \text{NH}\cdot\text{CH}_2 \\ \\ \text{NH}\cdot\text{CO} \end{array} \right.$	0.00759
Methyluracil, CO $\left\{ \begin{array}{l} \text{NH}\cdot\text{CMe} \\ \\ \text{NH}\text{---CO} \end{array} \right. \begin{array}{l} \diagup \\ \diagdown \end{array} \text{CH} \dots\dots\dots$	0.00314
α -Dimethyluracil, CO $\left\{ \begin{array}{l} \text{NMe}\cdot\text{CMe} \\ \\ \text{NH}\text{---CO} \end{array} \right. \begin{array}{l} \diagup \\ \diagdown \end{array} \text{CH} \dots\dots\dots$	0.00088
β -Dimethyluracil, CO $\left\{ \begin{array}{l} \text{NH}\cdot\text{CMe} \\ \\ \text{NMe}\text{---CO} \end{array} \right. \begin{array}{l} \diagup \\ \diagdown \end{array} \text{CH} \dots\dots\dots$	0.00074
Succinimide, $\left\{ \begin{array}{l} \text{CH}_2\cdot\text{CO} \\ \\ \text{CH}_2\cdot\text{CO} \end{array} \right. \text{NH} \dots\dots\dots$	0.000302

Discussion of Results.

The great diversity of the results contained in the preceding table is very striking; the first-mentioned compound is an acid six times as strong as acetic acid, whilst the last substance, succinimide, only possesses one-quarter of the acidity of phenol. A closer examination will show that the substances forming the table can be divided into four groups, as follows:

(1) Barbituric acid and 5-ethylbarbituric acid, both of which have dissociation constants greatly in excess of the others.

(2) Parabanic acid, alloxan, 5:5-dimethylbarbituric acid and 5:5-diethylbarbituric acid.

(3) Oxyuracil, allantoin, hydantoin, methyluracil, α -dimethyluracil, and β -dimethyluracil, all of which have dissociation constants much lower than those possessed by the members of group (2).

(4) The simple imides, phthalimide and succinimide.

Reserving until later a consideration of group (1), a comparison of the constitution of the members of groups (2) and (3) will show that in all cases the members of the former class contain the grouping $\text{CO} \left\{ \begin{array}{l} \text{NH}\cdot\text{CO}\cdot \\ | \\ \text{NH}\cdot\text{CO}\cdot \end{array} \right.$, whereas in no member of the latter class is this grouping present. In the presence of this grouping we have a probable explanation of the greater acidity possessed by members of the second compared with that possessed by members of the third group. Each of the imino-groups contained in the above-mentioned grouping, being connected with two carbonyl groups, will be possessed of acidic properties, whereas in substances of the third class there is only one

such imino-group, the other not being attached to two carbonyl groups and having accordingly much feebler acid properties. It is well known that in the case of certain dibasic carboxylic acids, for example, succinic acid, the two carboxyl groups mutually reinforce each other and thus give rise to a dissociation constant which is of greater magnitude than would have been the case in the absence of such stereochemical influence. It appears extremely probable that in substances which contain two acidic imino-groups there will be a similar mutual reinforcement, and consequently such substances will have higher dissociation constants than substances of a similar type which only contain one such group.

The results given by the three methyluracils are in accordance with what might have been expected on constitutional grounds. The introduction of a methyl group in place of hydrogen generally causes a lowering in the acidic constant, and it will be observed that both the dimethyluracils possess smaller dissociation constants than the mono-methyluracil. A comparison of the formulæ of the isomeric dimethyluracils,



shows that in the α -compound the imino-group is united to two carbonyl groups, whereas in the β -derivative it is only attached to one carbonyl group, the other nitrogen valency being satisfied by union with an unsaturated carbon atom. It would naturally be expected that the α -compound would have the greater acidity and this is confirmed by the results obtained for the two isomerides.

With regard to the two simple imides which form group four, the results obtained are also in agreement with those anticipated, phthalimide being much stronger than succinimide, just as phthalic acid is stronger than succinic acid.

Of the various results obtained none are more interesting than those given by barbituric and 5-ethylbarbituric acids. Both substances are seen to be stronger acids than acetic acid, and both can be estimated by titration with alkalis, using the ordinary indicators. The dissociation constants of these substances are, in fact, more comparable with those of the carboxylic acids than with those of the imides. Hantzsch and Voegelen (*loc. cit.*) have classed barbituric acid as a pseudo-acid. Provided that no change other than one of a tautomeric nature occurred on solution, the positive hydrogen ion of barbituric acid would be derived either from one of the imino-groups or from the methylene group. All the available evidence goes to support the latter view. In the first place, as previously mentioned, the dissociation constant is much greater than those of imino-compounds in general. The 5:5-dialkyl acids

contain the same two imino-groups as the original barbituric acid, and if the positive ion were derived from one of these groups, the substituted acids should be nearly as strong as the parent substance, but as is seen from the table this is by no means the case, the dissociation constant of barbituric acid being more than one thousand times as great as those of the dialkylbarbituric acids. If further proof were needed that the hydrogen ion is derived from the methylene group, it is found in the result given by 5-ethylbarbituric acid. In this substance there is still one of the hydrogen atoms of the methylene group unsubstituted, and the result is that the dissociation constant of this substance is nearly as great as that of barbituric acid. Although it may be taken as proved that the acidity of barbituric and ethylbarbituric acids is primarily due to the presence of the methylene group, no explanation of the fact can as yet be given. It does not appear to be due simply to the presence of the grouping $\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot$, for other substances which contain the same grouping, for example, malonic ester and acetoacetic ester, are almost devoid of acid properties.

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