LXII.—*The Affinities of some Feebly Basic Substances.*

By John Kerfoot Wood.

Since the enunciation of the theory of electrolytic dissociation, a large amount of work has been done with a view to determining the strengths of acids and bases, these strengths or affinities being proportional to the extent to which the substances are ionised in aqueous solution. In the majority of cases, the desired object has been attained by determining the electrical conductivity of solutions of known strength, but for the so-called very weak acids and bases this method has been inapplicable, owing to the very slight dissociation which obtains in solutions of these substances. For such compounds as these, methods based on the catalysis or saponification of methyl acetate and the inversion of cane sugar have been employed, these methods being termed hydrolytic, because they are applied to substances the salts of which undergo hydrolysis in aqueous solution.

The present paper contains the results obtained in determining the strengths of a number of weak bases, many of which had not been previously examined from this point of view. These bases belong principally to the urea and uric acid series, and as their solutions are exceedingly poor conductors of electricity, the first of the above-mentioned hydrolytic methods was employed, namely, that dependent on the catalysis of methyl acetate.

The theoretical basis of the method has been set forth in an earlier paper, which also contains a full description of the mode of carrying out the determinations so as to secure the greatest possible accuracy (Walker and Wood, this vol., p. 484). In most cases the velocity constant of the solution of the hydrolysed salt was compared with that of a solution of acid and sodium chloride in proportions as nearly as possible the same as those existing between the free acid and the unhydrolysed salt in the former solution. The salts used were the hydrochlorides, and the solutions were prepared by adding to the base under examination sufficient normal acid to form a salt of the type B,HCl, and then diluting until the concentration was that of a $N/10$ solution.

The experiments were carried out at a temperature of 40·2°, because in some cases solutions of greater concentration could be employed than would have been possible at lower temperatures, and, moreover, the experiments were rendered less protracted than they would otherwise have been.

The correctness of the determinations being largely conditioned by

the accuracy of the titrations, special care was taken to avoid error in this respect, a narrow glass tube carefully calibrated and mounted on a millimetre scale being used in place of an ordinary burette. The titrations were read in millimetres, actual volumes not being required for purposes of calculation. The tube was connected in the usual way with a reservoir containing barium hydroxide solution.

The observations are given in full in the case of urea, but with the other bases only the velocities of reaction are stated.

Urea.—Determinations of the hydrolysis of urea hydrochloride have already been made at 25° by Walker (*Zeit. physikal. Chem.*, 1889, **4**, 337), and at 60° by Walker and Aston (Trans., 1895, **67**, 581). The urea, which was dried in a desiccator over H_2SO_4, melted at 130°.

N/10 *Urea Hydrochloride.*

t.	Titre.	*x.*	$A-x$.	*k.*
0°	510·9	0	448·3	—
180	356·4	154·5	293·8	0·001020
202	339·8	171·1	277·2	0·001034
236	318·9	192·0	256·3	0·001029
254	308·5	202·4	245·9	0·001027
∞	62·6	$A=448·3$	—	
			Mean =	0·001027

N/10 Cl (90 *per cent.* HCl, 10 *per cent.* NaCl).

t.	Titre.	*x.*	$A-x$.	*k.*
0°	522·2	0	456·3	—
183	362·5	159·7	296·6	0·001022
204	348·5	173·7	282·6	0·001021
233	327·5	194·7	261·6	0·001037
255	318·0	204·2	252·1	0·001010
∞	65·9	$A=456·3$	—	
			Mean =	0·001022

$$\text{Hydrolysis} = \frac{0·001027}{0·001022} \times 90 = 90·4 \text{ per cent.}$$

Thiourea.—Determinations of the hydrolysis of the hydrochloride of this substance have already been made at different temperatures by Walker (*loc. cit.*) and Walker and Aston (*loc. cit.*).

The preparation used melted at 171°.

N/10 solution of thiourea hydrochloride..... $k=0·001115$.
N/10 Cl solution (96 per cent. HCl, 4 per cent. NaCl) $k=0·001061$.

These figures show that the salt is completely hydrolysed in *N*/10 solution.

Nitroguanidine.—(Compare Jousselin, *Compt. rend.*, 1879, **88**, 814; and Thiele, *Annalen*, 1892, **270**, 15.)

The specimen used was prepared by Jousselin's method:

0·0340 gave 15·3 c.c. moist nitrogen at 8° and 755 mm. N = 53·71.

$CH_4O_2N_4$ requires N = 53·84 per cent.

Owing to its slight solubility, the hydrochloride was employed in *N*/25 solution:

N/25 solution of nitroguanidine hydrochloride..... $k = 0{\cdot}0004290$.
N/25 Cl solution (95 per cent. HCl, 5 per cent. NaCl). $k = 0{\cdot}0004180$.
Hydrolysis = 97·5 per cent.

It has been stated in the previous paper (Walker and Wood, *loc. cit.*) that when the dilution of the solution varies, the hydrolysis of a solution in which the base and acid are in equivalent quantities is regulated by the equation

$$\frac{x^2}{(1-x)v} = c,$$

where x = amount of hydrolysed salt, $(1-x)$ the unhydrolysed portion, v the volume, in litres, containing one gram-molecule of the substance, and c a constant.

Applying this equation to the case of nitroguanidine, it is found that a *N*/10 solution of the hydrochloride would be hydrolysed to the extent of 94 per cent.

Glycocyamine.—A specimen of this substance was prepared from glycine and guanidine carbonate by the method described by Nencki and Sieber (*J. pr. Chem.*, 1878, [ii], **17**, 747):

0·0520 gave 15·75 c.c. moist nitrogen at 13·5° and 757 mm. N = 35·62.

$C_3H_7O_2N_3$ requires N = 35·9 per cent.

N/10 solution of glycocyamine hydrochloride ..... $k = 0{\cdot}0001266$.
N/10 Cl solution (10 per cent. HCl, 90 per cent. NaCl). $k = 0{\cdot}0001149$.
Hydrolysis = 11 per cent.

Acetoguanamine,

$$C(CH_3)\lessdot\begin{matrix}N\text{—}C(NH)\\ NH\cdot C(NH)\end{matrix}\gtrdot NH \quad \text{or} \quad C(CH_3)\lessdot\begin{matrix}N\cdot C(NH_2)\\ N{:}C(NH_2)\end{matrix}\gtrdot N.$$

—This substance, which was prepared by heating dry guanidine acetate at 230°, melted at 265°:

N/10 solution of acetoguanamine hydrochloride..... $k = 0{\cdot}0001160$.
N/10 Cl solution (10 per cent. HCl, 90 per cent. NaCl). $k = 0{\cdot}0001180$.
Hydrolysis = 9·8 per cent.

Biuret.—The sample employed, when recrystallised from alcohol and dried at 110°, melted at 189—190°:

$N/10$ solution of biuret hydrochloride..... $k = 0{\cdot}001140$.
$N/10$ Cl solution (96 per cent. HCl, 4 per cent. NaCl). $k = 0{\cdot}001082$.

These figures show that the biuret hydrochloride is completely hydrolysed in $N/10$ solution :

$N/4$ solution of biuret hydrochloride..... $k = 0{\cdot}002850$.
$N/4$ Cl solution (90 per cent. HCl, 10 per cent. NaCl). $k = 0{\cdot}002595$.
$N/4$ Hydrolysis in $N/4$ solution $= 98{\cdot}8$ per cent.

Semicarbazide.—In this case the solution was prepared by dissolving the hydrochloride itself. The specimen employed after recrystallisation from alcohol melted at 174° :

$N/10$ solution of semicarbazide hydrochloride ..... $k = 0{\cdot}0001225$.
$N/10$ Cl solution (10 per cent. HCl, 90 per cent. NaCl) $k = 0{\cdot}0001177$.
Hydrolysis $= 10{\cdot}4$ per cent.

Acetonesemicarbazone.—The specimen was prepared in the usual way and melted at 184° :

$N/10$ solution of acetonesemicarbazone hydrochloride. $k = 0{\cdot}0002948$.
$N/10$ Cl solution (30 per cent. HCl, 70 per cent. NaCl). $k = 0{\cdot}0003284$.
Hydrolysis $= 26{\cdot}9$ per cent.

Creatine.—The preparation used was analysed, with the following result :

0·0460 gave 12·75 c.c. moist nitrogen at 17·5° and 760 mm. N = 32·09.
$C_4H_9O_2N_3$ requires N = 32·06 per cent.

$N/10$ solution of creatine hydrochloride ..... $k = 0{\cdot}0001404$.
$N/10$ Cl solution (13·4 per cent. HCl, 86·6 per cent. NaCl). $k = 0{\cdot}0001524$.
Hydrolysis $= 12{\cdot}35$ per cent.

Creatinine.—A specimen of this base was kindly supplied by Prof. E. W. Reid, F.R.S. :

$N/10$ solution of creatinine hydrochloride ..... $k = 0{\cdot}00009795$.
$N/10$ Cl solution (10 per cent. HCl, 90 per cent. NaCl). $k = 0{\cdot}0001093$.
Hydrolysis $= 8{\cdot}96$ per cent.

Caffeine.—The specimen which was analysed melted at 234° :

0·1717 gave 41·8 c.c. moist nitrogen at 11° and 759·5 mm. N = 28·84.
$C_8H_{10}O_2N_4$ requires N = 28·87 per cent.

Before preparing the solution the caffeine was heated at 130° in order to expel any water of crystallisation :

$N/10$ solution of caffeine hydrochloride ..... $k = 0{\cdot}001015$.
$N/10$ Cl solution (90 per cent. HCl, 10 per cent. NaCl). $k = 0{\cdot}001025$.
Hydrolysis $= 89{\cdot}7$ per cent.

6-Aminocaffeine, $\begin{matrix}N(CH_3)\cdot C(NH_2):C\cdot N(CH_3)\\ CO\text{—}N(CH_3)\text{—}C\text{=}\!\!=N\end{matrix}\!\!>CO$.—This compound is precipitated by water from its solution in hydrochloric acid, and it has therefore been supposed to be a weaker base than caffeine, which is not liberated in this manner. As will be shown later, this precipitation of aminocaffeine cannot be taken as an indication that it is a very weak base.

The sample used was prepared by Fischer's method (*Annalen*, 1882, **215**, 253):

0·0356 gave 10·4 c.c. moist nitrogen at 13° and 757 mm. N = 34·21.
$C_8H_{11}O_2N_5$ requires N = 33·49 per cent.

On attempting to prepare a solution of the hydrochloride in the usual way, it was found to be impossible, owing to the very slight solubility of the base, to obtain a solution of sufficient concentration for conducting the experiments.

An approximate idea of the strength of a base can, however, be obtained by comparing its solubility in water with the solubilities in acid solutions of known strength.

The solubilities were determined by treating a known weight of the base with a definite volume of the solvent, the mixture being left in the thermostat for a day or two and vigorously agitated at intervals. The residue was then collected, thoroughly drained, and dried at 100°, the solubility being calculated from the weight of the undissolved base.

The following results were obtained:

100 c.c. H_2O dissolved 0·128 gram aminocaffeine.
100 c.c. *N*/20 HCl dissolved 0·192 gram aminocaffeine.
100 c.c. *N*/10 „ „ 0·307 „ „

It has been shown by Walker (*loc. cit.*) that the hydrolysis equilibrium is governed by the law:

$$\frac{\text{Free base} \times \text{free acid}}{\text{Salt}} = C(\text{a constant}).$$

The data obtained in the solubility determinations indicate that, in the solution of aminocaffeine in *N*/10 hydrochloric acid, the concentrations of the acid, aminocaffeine and aminocaffeine hydrochloride are respectively 0·09043-, 0·006125-, and 0·009567-normal. These figures show that the value of *C* is 0·0579, and since this constant has the same value for all systems containing the acid, aminocaffeine, and aminocaffeine hydrochloride, it is possible to calculate the amount of free base, that is, to ascertain the amount of hydrolysis, in a system containing equivalent amounts of aminocaffeine and hydrochloric

acid. The result calculated for the hydrolysis in a decinormal solution is 52·4 per cent. From the solubility of aminocaffeine in the $N/20$ acid a somewhat higher value is obtained. It may be considered therefore that the hydrolysis of aminocaffeine hydrochloride in decinormal solution is approximately 55 per cent. 6-Aminocaffeine therefore is a stronger base than caffeine; the precipitation produced on diluting the solution in hydrochloric acid is simply due to the slight solubility of the base in water, and is not to be regarded as giving any indication of the relative strength of the base.

Theobromine.—The specimen employed was analysed:

0·0794 gave 21·7 c.c. moist nitrogen at 13° and 743 mm. N = 31·42.
$C_7H_8O_2N_4$ requires N = 31·11 per cent.

In this case also the hydrolysis of the hydrochloride was ascertained by the solubility method, which has already been employed by Theodor Paul (*Arch. Pharm.*, 1901, **239**, 48) in determining this constant at 18°.

The following solubilities were obtained at 40·2°:

100 c.c. distilled H_2O	dissolved	0·060	gram	theobromine
100 c.c. $N/20$ HCl	,,	0·074	,,	,,
100 c.c. $N/10$ HCl	,,	0·0925	,,	,,

From the figures representing the solubility in H_2O and in $N/10$ HCl, the hydrolysis of theobromine hydrochloride in decinormal solution is calculated to be 71·7 per cent., whereas the value obtained from the $N/20$ solution is 74·1. The hydrolysis in a decinormal solution of theobromine hydrochloride is therefore approximately 73 per cent.

Guanine.—The purity of the specimen was ascertained by analysis:

0·1184 gave 47·0 c.c. moist nitrogen at 14° and 755·5 mm. N = 46·20.
$C_5H_5ON_5$ requires N = 46·35 per cent.

The solubility method was also employed in this case:

100 c.c. distilled water	dissolved	0·0039	gram	guanine
100 c.c. $N/10$ HCl	,,	0·0975	,,	,,
100 c.c. $N/20$ HCl	,,	0·194	,,	,,

The calculated hydrolysis in a decinormal solution of guanine hydrochloride is 17·9 per cent.

Xanthine.—The base used was prepared by the action of nitrous acid on guanine:

0·1646 gave 52·2 c.c. moist nitrogen at 16° and 756 mm. N = 36·62.
$C_5H_4O_2N_4$ requires N = 36·84 per cent.

The solubility method was employed:

100 c.c. distilled water dissolved 0·0183 gram xanthine.
100 c.c. $N/10$ HCl ,, 0·0210 ,, ,,

The calculated hydrolysis in a decinormal solution of xanthine hydrochloride is 88·5 per cent.

Acetoxime.—Walker (*loc. cit.*) has shown that at 25° acetoxime is a stronger base than urea, and a similar result was obtained at the higher temperature employed in the present series of experiments. The sample used was prepared in the usual manner and melted at 61°:

$N/10$ solution of acetoxime hydrochloride ..... $k = 0·0003751$.
$N/10$ Cl solution (35 per cent. HCl, 65 per cent. NaCl) $k = 0·0003823$.
Hydrolysis = 34·35 per cent.

Acetamide.—Previous experiments with this substance have been made by Walker (*loc. cit.*), and Walker and Aston (*loc. cit.*). The methyl acetate method employed in the former series of experiments showed acetamide to be slightly weaker than urea; in the other determinations, the method based on the inversion of cane sugar was used, and gave numbers showing urea to be the weaker base. The present experiments give a result in agreement with that previously obtained by the use of the methyl acetate method. The specimen employed melted at 82°:

$N/10$ solution of acetamide hydrochloride ..... $k = 0·001035$.
$N/10$ Cl solution (90 per cent. HCl, 10 per cent. NaCl) $k = 0·001020$.
Hydrolysis = 91·3 per cent.

Benzamide.—M. p. 130°:

$N/10$ solution of benzamide hydrochloride..... $k = 0·001106$.
$N/10$ Cl solution (94 per cent. HCl, 6 per cent. NaCl) $k = 0·001038$.

These figures indicate that benzamide hydrochloride is completely hydrolysed in decinormal solution.

Acetanilide.—M. p. 115°. The hydrolysis was determined in a $N/20$ solution owing to the sparing solubility of the substance, and from the result obtained the value for a $N/10$ solution calculated, as in the case of nitroguanidine:

$N/20$ solution of acetanilide hydrochloride ..... $k = 0·0005215$.
$N/20$ Cl solution (92 per cent. HCl, 8 per cent. NaCl) $k = 0·0005112$.
Hydrolysis: Found = 93·8 per cent.
Calculated for $N/10$ solution = 88·9 ,,

Propionitrile.—B. p. 96—97°. This substance has been shown to

possess feeble basic properties by Walker, and by Walker and Aston:

$N/10$ solution of propionitrile hydrochloride ..... $k = 0{\cdot}001088$.
$N/10$ Cl solution (95 per cent. HCl, 5 per cent. NaCl) $k = 0{\cdot}001062$.
Hydrolysis = 97·3 per cent.

Dimethylpyrone.—(Compare Collie, Trans., 1899, **75**, 710). Earlier experiments conducted at 35° showed that the basic strength was about equal to that of urea (Walker, *Ber.*, 1901, **34**, 4115). The present determinations, made with dimethylpyrone hydrochloride kindly supplied by Prof. J. Norman Collie, F.R.S., show it to be a somewhat stronger base than urea:

$N/10$ solution of dimethylpyrone hydrochloride ..... $k = 0{\cdot}0009033$.
$N/10$ Cl solution (86 per cent. HCl, 14 per cent. NaCl) $k = 0{\cdot}0009142$.
Hydrolysis = 85 per cent.

Cyneol is another non-nitrogenous substance, which unites with acids to form salts. A sample was obtained from oil of Cajeput by the method described by Wallach and Brass (*Annalen*, 1884, **225**, 294). Owing to the slight solubility in water, the catalytic method could not be employed, whilst the value obtained by the solubility method can only be regarded as a rough approximation, because there is no accurate method for estimating cyneol. The method adopted was to mix known volumes of cyneol and water, or hydrochloric acid, and, after leaving the mixture for a day or two in the thermostat, observing the final volumes; it was found that:

100 c.c. distilled water dissolved about 0·63 gram cyneol.
100 c.c. N-HCl ,, ,, 0·79 ,,

As calculated from these solubilities, the hydrolysis in a decinormal solution would be about 98 per cent.

Calculation of Dissociation Constants.

It was shown by Arrhenius (*Zeit. physikal. Chem.*, 1881, **5**, 17) that the following equation holds for a system containing free acid, free base, and salt:

$$\frac{k_1}{k_2} = \frac{v(1-x)}{x^2},$$

where v = volume of solution, which would contain 1 gram-molecule of salt.
x = the amount of hydrolysis calculated on 1 gram of salt.
k_1 = the affinity constant of the base.
k_2 = the affinity constant of water.

By means of this equation, therefore, it is possible to calculate the dissociation constants of the bases, the salts of which have been examined. The value of this constant for water is ascertained from Kohlrausch and Heydweiller's results (*Zeit. physikal. Chem.*, 1894, **14**, 317); the amount of dissociation at 40·2° is $1{\cdot}775 \times 10^{-7}$, giving a dissociation constant of $1{\cdot}775^2 \times 10^{-14}$.

The hydrolysis of the hydrochlorides of the bases in decinormal solution and the calculated dissociation constants are given in the following table:

Base.	Percentage hydrolysis of hydrochloride in decinormal solution.	Dissociation constant of base at 40·2°.
Creatinine	8·9	$3\ 57 \times 10^{-11}$
Acetoguanamine	9·8	$2{\cdot}96 \times 10^{-11}$
Semicarbazide	10·4	$2{\cdot}61 \times 10^{-11}$
Glycocyamine	11·0	$2{\cdot}32 \times 10^{-11}$
Creatine	12·3	$1{\cdot}81 \times 10^{-11}$
Guanine	17·9	$0{\cdot}807 \times 10^{-11}$
Acetonesemicarbazone	26·9	$0{\cdot}318 \times 10^{-11}$
Acetoxime	34·3	$0{\cdot}175 \times 10^{-11}$
6-Aminocaffeine	55·0	$0{\cdot}047 \times 10^{-11}$
Theobromine	73·0	$0{\cdot}016 \times 10^{-11}$
Dimethylpyrone	85·0	* $0{\cdot}0065 \times 10^{-11}$
Xanthine	88·5	$0{\cdot}0046 \times 10^{-11}$
Acetanilide	88·9	$0{\cdot}0044 \times 10^{-11}$
Caffeine	89·7	$0{\cdot}0040 \times 10^{-11}$
Urea	90·4	$0{\cdot}0037 \times 10^{-11}$
Acetamide	91·3	$0{\cdot}0033 \times 10^{-11}$
Nitroguanidine	94·0	$0{\cdot}0021 \times 10^{-11}$

* Walden (*Ber.*, 1901, **34**, 4197), working at another temperature and employing a different method, has obtained a value for the dissociation constant of dimethylpyrone of the same order of magnitude as that given above.

It will be observed that the result obtained for the dissociation constant of urea is different from that previously given (Walker and Wood, this vol., p. 490), where the value is put down as $0{\cdot}0015 \times 10^{-11}$. The discrepancy is due to the difference in temperature in the two cases, the experiments described in the earlier paper being conducted at 25°.

In addition to the bases mentioned in the table, the hydrochlorides of propionitrile, benzamide, cyneol, thiourea, and biuret were investigated and found to be more or less completely hydrolysed in decinormal solution. No attempt was made to calculate the dissociation constants of these bases, because no reliance can be placed on this coefficient when the amount of hydrolysis is greater than 95 per cent. Between 95 and 100 per cent. an error of 1 per cent. in

the hydrolysis is magnified to one of 50 or 100 per cent. in the dissociation constant.

As indicated in the following table, the calculated dissociation constants become more reliable when the hydrolysis is less:

Hydrolysis.	Dissociation constant.	Change in hydrolysis.	Change in dissociation constant.
10 per cent.	$2{\cdot}55 \times 10^{-11}$	10 per cent.	9·0 per cent.
11 ,,	$2{\cdot}32 \times 10^{-11}$		
25 ,,	$0{\cdot}378 \times 10^{-11}$	4 ,,	9·5 ,,
26 ,,	$0{\cdot}345 \times 10^{-11}$		
90 ,,	$0{\cdot}0039 \times 10^{-11}$	1·1 ,,	12·8 ,,
91 ,,	$0{\cdot}0034 \times 10^{-11}$		

Discussion of Results.

Five of the bases investigated, namely, guanine, xanthine, caffeine, 6-aminocaffeine, and theobromine, belong to the same series of compounds, and taking into account the general effects on the basic strength of a compound, caused by the introduction of amino- and methyl groups, it might be expected that the order of basic strength would be guanine, 6-aminocaffeine, caffeine, theobromine, and xanthine, guanine being the strongest base in the series.

A review of the results already given will show that this order is not strictly followed, the actual arrangement being guanine, 6-aminocaffeine, theobromine, xanthine, caffeine. The position occupied by caffeine is one to occasion surprise, but it has been confirmed by repeated experiments. Of these five substances, caffeine is the only one to which the methyl acetate method was applied, but the anomalous position of the base is not explicable on the grounds of differences in the methods of determination.

Solubility experiments made with caffeine showed that 100 c.c. of distilled water or $N/10$ HCl dissolve 4·463 or 4·755 grams of caffeine respectively. These solubilities give a hydrolysis of 86·1 per cent., a value which, whilst slightly below that found by the other method, is far too high to allow of caffeine taking a position between 6-aminocaffeine and theobromine. The result may possibly be explained by some singularity in the nature of caffeine, and the great difference between the solubility of this base and that of the other members of the series seems to support this view.

In the case of the urea and guanidine derivatives, perhaps the most surprising result is that given by biuret. Since ammonia is evolved in the course of its production from urea, it might be expected that

biuret would be slightly less basic than the parent substance. The results show, however, that biuret is practically devoid of basic attributes, a fact which could scarcely have been predicted from a consideration of the formula of the compound.

Another interesting result, obtained with nitroguanidine, illustrates the highly negative character of the nitro-group, for whereas guanidine has been shown by Bredig (*Inaug. Dissert. Leipzig*) to be a very strong base, the nitro-compound is a weaker base than urea.

The guanidine derivatives, glycocyamine, creatine, and creatinine, are all weaker than guanidine and stronger than nitroguanidine.

Semicarbazide approximates in strength to these guanidine derivatives, and, as might be expected, is a much stronger base than urea.

Although the experiments have only been conducted at one temperature, it is scarcely probable that the order of affinity would be in any way changed if similar determinations were made at other temperatures. In the case of acetoxime, urea, acetamide, propionitrile, and thiourea, the order of basic strength at 40·2° is the same as that found by Walker with the same substances at 25°.

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