[Contribution from the Department of Chemistry of the University of California.]

THE NATURE OF THE CATALYSIS IN THE CONVERSION OF THE CINCHONA ALKALOIDS INTO THEIR TOXINES.

(ON CATALYSES WITH WEAK ACIDS, VIII.[1])

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1. Introduction.—The phenomena of catalysis are of continuous interest to investigators, partly because of the almost limitless variety of reactions involved and partly because of the element of mystery which in most instances shrouds the nature of the catalyst's action. Attention has been directed particularly to catalyses in homogeneous solutions, of which none have been more thoroughly studied than those involving the action of hydrogen and hydroxyl ions. In the majority of these cases the relation of the reaction velocity to the concentration of the ion has been established with precision. Thus, in the inversion of cane sugar and the hydrolysis of esters in the presence of acids, the speed of the reaction in dilute solutions is shown to be strictly proportional to the concentration of the hydrogen ion.[2] This law, however, does not hold under changed conditions. In more concentrated aqueous solutions, for example, as has been shown by Ostwald,[3] deviations occur and the reaction rate is no longer found to be directly proportional to the concentration of the hydrogen ion. Another apparent deviation in the law is found in the presence of foreign substances, such as neutral salts. The variations in reaction velocity induced by such salts have been the subject of study by a number of investigators[4] and numerous theories have been advanced to account for such variations. One of the most reasonable of these assumes that the salt modifies the dissociating capacity of the new solvent, but the question may be raised in what way this modification is effected. It has been suggested that the variation in reaction velocity is some function of the concentration of the undissociated neutral salt. That there is a direct relation between such variation and the *total* concentration of neutral salt in the case of the transformations of

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[1] Biddle, *Science*, **32**, 486 (1910); *Ber.*, **45**, 526, 2832 (1912); This Journal, **34**, 500 (1912); **35**, 273 (1913); **36**, 84 (1914); Biddle and Rosenstein, *Ibid.*, **35**, 418 (1913); Biddle and Brauer, *Ibid.*, **37**, 2065 (1915); Biddle and Butzbach, *Ibid.*, **37**, 2082 (1915).

[2] Arrhenius, *Z. physik. Chem.*, 4, 244 (1889), and others.

[3] *J. prakt. Chem.*, [2] **31**, 307 (1885).

[4] Arrhenius, *Z. physik. Chem.*, 1, 110 (1881); 4, 237 (1889); **31**, 197 (1899); Euler, *Ibid.*, **32**, 348 (1900); Spohr, *J. prakt. Chem.*, [2] **33**, 270 (1886); Stieglitz, *Am. Chem. J.*, **32**, 224 (1904); **34**, 1689 (1905); **39**, 177, 596, 720 (1908); This Journal, **34**, 1689 (1912); Acree, *Am. Chem. J.*, **38**, 259, 489 (1907); **39**, 226 (1908); **41**, 474 (1909); Kellogg, This Journal, **31**, 403, 886, 889 (1909); **35**, 396 (1913); Biddle, *Ibid.*, **36**, 84 (1914); Biddle and Porter, *Ibid.*, **37**, 1571 (1915), and others.

crystal violet has already been pointed out,[1] but whether this extends in this instance to the undissociated salt is a mooted question.

The role of an undissociated molecule, particularly that of a nonionized electrolyte in a homogeneous chemical reaction, has within the last few years been the subject of much speculation and of numerous investigations.[2] The results obtained have shown that a reaction velocity is often modified and in some cases almost completely determined by the concentration of an undissociated complex. Indeed, as Acree[3] has suggested, "in all reactions we should consider the possibility of the direct transformation of both ions and nonionized substances."

Data, however, are meager, which afford unequivocal evidence that an undissociated ionogen can functionate in aqueous solution as a catalytic agent with the definiteness shown by the hydrogen ion in dilute solutions. It is, consequently, a matter of the greatest interest to secure examples of such catalysis and to establish their existence by mathematical evidence based upon sufficiently comprehensive experimental data.

In the extraordinary conversion of the cinchona alkaloids into their toxines in the presence of organic acids is presented a case of catalysis which affords just such an example. And this proves of additional interest in that it applies, as previously indicated,[4] not to cinchonine and cinchonidine alone, but also to the other members of the cinchona group, such as quinine and quinidine. In 1912 the writer[5] called attention to the probability that in this catalysis the rate of the reaction is a direct function of the molecular concentration of the free acid. Measurements of the reaction rate in the case of cinchonine were later made by Biddle and Rosenstein[6] for two concentrations of acetic acid, and under the conditions of the experiment the rate appeared to be a linear function of the concentration of the acid in excess of the diacetate. In order, however, that the part played in this catalysis by both hydrogen ion and organic acid might be fully established, it became necessary to work out a method for estimating with fair accuracy the concentration of hydrogen ion and of undissociated organic acid in each solution studied. This has been done and the extensive data presented in the two preceding papers fully

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[1] Biddle and Porter, THIS JOURNAL, 37, 1588 (1915).

[2] Goldschmidt, *Z. physik. Chem.*, 29, 118 (1899); 70, 629 (1910); 81, 30 (1912); *Z. Electrochem.*, 17, 684 (1911); Acree and co-workers, *Am. Chem. J.*, 49, 345 (1913), and numerous earlier papers there referred to; Stieglitz and co-workers, THIS JOURNAL, 35, 1774 (1913), and numerous earlier papers there cited; Bredig, *Z. Electrochem.*, 18, 535 (1912); Snethlage, *Ibid.*, p. 539; Biddle and co-workers, *Loc. cit.*

[3] *Am. Chem. J.*, 48, 352 (1912).

[4] Biddle and Rosenstein, THIS JOURNAL, 35, 419 (1913).

[5] *Ber.*, 45, 2835 (1912).

[6] *Loc. cit.*

examined with the result, as will appear in the following pages, that the influence upon the reaction rate, both of the concentration of the hydrogen ion and of that of the undissociated organic acid, has been completely established. It will be shown, indeed, that the specific rate of the reaction with respect to the alkaloid is directly proportional to the concentration of the univalent alkaloid ion and is a direct linear function of the concentration of the undissociated organic acid. Furthermore, the specific catalytic action of three organic acids has been measured as well as the specific variation in speed due to stereoisomerism in the case of cinchonine and cinchonidine.

The results, in addition to their affording a mathematical solution of this remarkable catalysis, are doubly significant in that they fully establish the fact that an undissociated molecule can act as a direct catalytic agent in a homogeneous solution.

2. **The Concentration of the H$^+$ Ion.**—Since the H$^+$ ion inhibits the rate of conversion of a cinchona alkaloid into its toxine, a study of the nature of this retardation, as well as that of the positive catalyzing influence of the organic acid, necessitates a determination of the concentration of this ion or of the function of the ion responsible for the inhibiting action. Of the methods which have been employed for direct measurement of the H$^+$ ion, a colorimetric one such as that of Salm[1] suggests itself, but this is inferior in point of accuracy to that of the hydrogen electrode which has been used to advantage by a number of investigators.[2] In the study of this catalysis, however, any method of direct measurement is objectionable partly on account of the detail work involved and partly on account of the experimental errors necessarily associated with such measurements. It seemed wiser, consequently, to reduce the determination to a calculation based upon a knowledge of the dissociation constants of the different substances present. While in such a calcula-

TABLE I.

[3]Nonionized cinchonine, Cin. $H_2(OH)_2$ = p
[3]Univalent cinchonine ion, Cin. HOH^+ = q
Bivalent cinchonine ion, Cin. H_2^{++} = r
Nonionized organic acid, HAc = S
Ion of organic acid, Ac^- = t
Hydroxyl ion, OH^- = u
Hydrogen ion, H^+ = x
Chloride ion, Cl^- = c
Total cinchonine = Cin.
Total organic acid = Ac

TABLE II.[4]

$$(p)k_1 = (q)(u) \tag{1}$$
$$(q)k_2 = (r)(u) \tag{2}$$
$$(S)k_3 = (x)(t) \tag{3}$$
$$(x) + (q) + 2(r) = (t) + (c) \tag{4}$$
$$(p) + (q) + (r) = (\text{Cin.}) \tag{5}$$
$$(S) + (t) = (\text{Ac}) \tag{6}$$
$$(x)(u) = k_w \tag{7}$$

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[1] *Z. physik. Chem.*, 57, 471 (1906).

[2] Loomis and Acree, *Am. Chem. J.*, 46, 585, 621 (1911); Hildebrand, THIS JOURNAL, 35, 847 (1913), and others.

[3] The nonionized cinchonine is represented as being in the form of the hydroxide.

[4] Symbols express concentrations in mols per liter.

tion certain assumptions must be made which are not rigidly correct, these are of minor effect upon the comparative results obtained. If in an aqueous solution containing cinchonine, hydrochloric acid and an organic acid, we consider that there is neither cinchonine salt nor hydrochloric acid in an undissociated condition, equilibrium will exist between the substances and the ions given under Table I, and the various relations of these substances and their ions may be formulated in the seven equations given under Table II, in which in all cases as elsewhere in this paper concentrations are expressed in mols per liter.

From Equations 1, 2, 5 and 7.

$$(q) = \frac{(\text{Cin.})}{1 + \frac{k_w}{k_1(x)} + \frac{k_2(x)}{k_w}} \qquad (a)$$

and,

$$(r) = \frac{(\text{Cin.})}{1 + \frac{k_w}{k_2(x)} + \frac{k_w^2}{k_1k_2(x)^2}} \qquad (b)$$

From Equations 3 and 6

$$(t) = \frac{k_3(\text{Ac})}{k_3 + (x)}. \qquad (c)$$

Substituting in Equation 4 the values of q, r and t from Equations a, b and c, we have,

$$(c) = (x) - \frac{k_3(\text{Ac})}{k_3 + (x)} + \frac{(\text{Cin.})}{1 + \frac{k_w}{k_1(x)} + \frac{k_2(x)}{k_w}} + \frac{2\ (\text{Cin.})}{1 + \frac{k_w}{k_2(x)} + \frac{k_w^2}{k_1k_2(x)^2}} \qquad (d)$$

which may be expressed in the general equation:

$$(c) = (x) + (\text{Cin.}) - \frac{k_3(\text{Ac})}{k_3 + (x)} + \frac{(\text{Cin.})\left(\frac{k_1k_2(x)^2}{k_w^2} - 1\right)}{1 + \frac{k_1(x)}{k_w} + \frac{k_1k_2(x)^2}{k_w^2}} \qquad (e)$$

In the absence of hydrochloric acid, this equation takes the form,

$$(\text{Ac}) = \left[(x) + (\text{Cin.}) + \frac{(\text{Cin.})\left(\frac{k_1k_2(x)^2}{k_w^2} - 1\right)}{1 + \frac{k_1(x)}{k_w} + \frac{k_1k_2(x)^2}{k_w^2}}\right]\left[\frac{k_3 + (x)}{k_3}\right]. \qquad (f)$$

An equation is thus obtained in which, in solutions of known concentrations with respect to the cinchonine, hydrochloric acid and the organic acid, the concentration of the hydrogen ion is expressed in terms of the dissociation constant of the organic acid (k_3), the first and second dissociation constants of cinchonine (k_1 and k_2), and the ionization product of water (k_w).

In applying this general equation for calculating the concentration of H^+ ion, it became necessary to determine the values of k_1, k_2, k_3 and k_w at 100°, the temperature at which the catalysis was studied.

The value of k_w at 100° as determined by A. A. Noyes[1] is 48×10^{-14}. The value of the dissociation constant of acetic acid (k_3) at this temperature as calculated by the same investigator[2] from conductivity measurements is 1.11×10^{-5}. The corresponding dissociation constants for formic and propionic acids at 100° have not as yet been experimentally determined. Since the heats of neutralization of the three organic acids named, as determined by Thomsen[3] at 18–20°, closely approach a common value, it was assumed that the ratio of the dissociation constant at 100° to that at a temperature such as 18°, or $K_{100°}/K_{18°}$, would be practically constant in the case of the three acids. If the dissociation constants of formic,[4] acetic[5] and propionic[6] acids at 18° are, respectively, 2.14×10^{-4}, 1.82×10^{-5} and 1.4×10^{-5}, the calculated value of this constant at 100° for formic acid will be 1.31×10^{-4} and for propionic acid at the same temperature will be 0.86×10^{-5}. These values which cannot vary much from the true values were used in the calculations made later in this paper.

The so-called first and second dissociation constants of cinchonine, k_1 and k_2, have been measured by Veley[7] who obtains at 15° the values, $k_1 = 1.63 \times 10^{-7}$ and $k_2 = 3.3 \times 10^{-10}$. The measurement of the first constant was based on the determination of the quantity of sodium hydroxide contained in a hydrolyzed aqueous solution of borax which is required to produce an initial precipitation of alkaloid from an aqueous solution of the hydrochloride and is open to question as to its accuracy. By a conductivity method, another investigator[8] obtains at 18° the value, $k_1 = 1.2 \times 10^{-6}$, which is probably more nearly correct. Veley based his determination of the second dissociation constant on measuring colorimetrically the degree of hydrolysis of cinchonine dihydrochloride in an aqueous solution of known concentration, methyl orange being used as indicator. The same method was later employed by Barratt[9] in measuring the second dissociation constant of quinine. From an applica-

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[1] Noyes, Kato and Sosman, THIS JOURNAL, **32**, 159 (1910).

[2] Noyes, *Ibid.*, **30**, 335 (1908).

[3] *Thermochemistry*, pp. 93–95 (1908).

[4] Salm, *Z. physik. Chem.*, **63**, 83 (1908); Ostwald, *Ibid.*, **3**, 170 (1889).

[5] Noyes, THIS JOURNAL, **30**, 335 (1908).

[6] Barmwater, *J. physik. Chem.*, **45**, 557 (1903); **56**, 225 (1906).

[7] *J. Chem. Soc.*, **93**, 2114 (1908); **95**, 758 (1909).

[8] Mauz, Dis. Tübingen (1904).

[9] Barratt, *Z. Elektrochem.*, **16**, 130 (1910).

tion of the method in this laboratory[1] the values of k_2 for cinchonine and cinchonidine at a temperature of 15–18° were found to be, respectively, 0.597×10^{-10} and 0.509×10^{-10}, or practically identical within the limits of experimental error. At a temperature of 100°, cinchonine by the same method gave $k_2 = 1.11 \times 10^{-9}$, the value used for both cinchonine and cinchonidine in the calculations appearing later in this paper.

The value of the first dissociation constant, k_1, at 100° was not determined, since, as can readily be shown, this constant may be ignored in the calculations made. If for example, k_1 at 100° has a value of not less than 10^{-6}, an assumption which may be safely made as the actual value is doubtless considerably above this, then for all concentrations of hydrogen ion even down to one of the three lowest measured (8.3×10^{-6}) the final fraction in the general equation (*e*) may be simplified so that this equation becomes,

$$(c) = (x) + (\text{Cin.}) - \frac{k_3(\text{Ac})}{k_3 + (x)} + \frac{k_2(\text{Cin.})(x)}{k_w + k_2(x)}, \qquad (g)$$

or, in the absence of hydrochloric acid,

$$(\text{Ac}) = \left[(x) + (\text{Cin.}) + \frac{k_2(\text{Cin.})(x)}{k_w + k_2(x)}\right]\left[\frac{k_3 + (x)}{k_3}\right]. \qquad (h)$$

The error introduced by this simplification of the equation is negligible in all concentrations of hydrogen ion calculated, except possibly the three lowest. If, for example, k_1 equals the minimum value of 10^{-6}, the concentration of H^+ ion calculated as 8.0×10^{-6} by Equation *h* will be slightly over 10% too low; and the concentration calculated as 1.06×10^{-5} will be 7% too low. The value calculated as 3.06×10^{-5} H^+ ion will, however, be only slightly over 1% too low and with increasing concentrations, the possible error soon reduces to a fraction of a per cent. Since these results represent the maximum error possible under these conditions, the simplified equations (*g* and *h*) were employed in the calculations of H^+ ion presented in this paper.

3. The Concentrations of the Undissociated Organic Acid and of the Univalent and Bivalent Cinchonine Ions.—The concentration of the H^+ ion having been fixed, that of the undissociated organic acid is readily obtained. By combining Equations 3 and 6, Table II, there is derived the following general equation for calculating this value:

$$(\text{S}) = \frac{(\text{Ac})(x)}{(x) + k_3} \qquad (i)$$

The concentration of the H^+ ion affords also a ready means of calculating the concentrations of univalent and bivalent cinchonine ions As has already been pointed out, from the experimental determination of k_2,

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[1] From unpublished work in this laboratory.

$$\frac{(\text{Cin. H}_2^{++}) \times (\text{OH}^-)}{(\text{Cin. H}^+)} = 1.11 \times 10^{-9}.$$

Since in water at 100°, $(\text{H}^+) \times (\text{OH}^-) = 48 \times 10^{-14}$, the foregoing equation may be expressed as,

$$\frac{(\text{Cin. H}_2^{++})}{(\text{Cin. H}^+)} = \frac{(\text{H}^+)}{4.32 \times 10^{-4}},$$

or

$$\frac{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}{(\text{Cin. H}^+)} = \frac{4.32 \times 10^{-4} + (\text{H}^+)}{4.32 \times 10^{-4}},$$

whence,

$$\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})} = \frac{1}{1 + 2.315 \times 10^3\,(\text{H}^+)}, \qquad (j)$$

an equation which gives the ratio of univalent cinchonine ion to the total cinchonine in terms of the concentration of the H^+ ion.

In a similar manner, the ratio of the bivalent cinchonine ion to the total cinchonine may be derived and expressed as follows:

$$\frac{(\text{Cin. H}_2^{++})}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})} = \frac{2.315 \times 10^3(\text{H}^+)}{1 + 2.315 \times 10^3(\text{H}^+)} \qquad (k)$$

4. Tabulation of Results.—From the data presented in the foregoing papers on the rates of conversion of cinchonine and of cinchonidine to cinchotoxine,[1] were calculated the concentrations of H^+ ion, of nonionized organic acid and the value for $\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}$, according to the general equations (*g* or *h*, *i* and *j*). In the results which are given in Tables III to VII inclusive, K_2 is the rate of conversion; in all cases the concentrations of acid, of H^+ ion and of nonionized organic acid are in mols per liter, and the values under $\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$ are the ratio of the univalent cinchonine ion to the total cinchonine in the solution.

TABLE III.—CINCHONINE, 0.25 MOLAL.

No.	Acetic acid.	K_2.	H^+.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$.	Acetic acid nonionized.
1	0.50	0.0192	1.06×10^{-5}	0.976	0.244
2	0.75	0.0327	2.07×10^{-5}	0.957	0.490
3	1.00	0.0434	3.05×10^{-5}	0.934	0.733
4	1.25	0.0566	4.03×10^{-5}	0.915	0.980
5	1.50	0.0721	5.15×10^{-5}	0.896	1.230
6	2.00	0.0901	6.70×10^{-5}	0.867	1.715
7	2.50	0.1112	8.43×10^{-5}	0.838	2.210

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[1] Biddle and Brauer, THIS JOURNAL, 37, 2065 (1915); Biddle and Butzbach, *Ibid.*, 37, 2082 (1915).

TABLE IV.—CINCHONINE, 0.01 MOLAL.

No.	Acetic acid.	Hydrochloric acid.	K_2.	H^+.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$.	Acetic acid non-ionized.
1......	0.05	...	0.0058	3.99×10^{-5}	0.915	0.0391
2......	0.10	...	0.0089	8.40×10^{-5}	0.839	0.0883
3......	0.15	...	0.0127	1.24×10^{-4}	0.779	0.138
4......	0.20	...	0.0162	1.61×10^{-4}	0.729	0.187
5......	0.40	...	0.0256	2.98×10^{-4}	0.593	0.386
6......	0.80	...	0.0347	5.40×10^{-4}	0.445	0.784
7......	0.5	0.010	0.0163	7.70×10^{-4}	0.360	0.493
8......	0.5	0.015	0.0114	1.83×10^{-3}	0.240	0.495
9......	0.5	0.020	0.0056	3.05×10^{-3}	0.125	0.497

TABLE V.—CINCHONINE, 0.1 MOLAL.

No.	Acetic acid.	Hydrochloric acid.	K_2.	H^+.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}^{2++}}$.	Acetic acid non-ionized.
1	0.15	...	0.00565	5.30×10^{-6}	0.988	0.0485
2	0.175	...	0.00712	8.00×10^{-6}	0.985	0.0734
3	0.20	...	0.0094	1.06×10^{-5}	0.976	0.0977
4	0.40	...	0.0239	3.06×10^{-5}	0.937	0.294
5	0.80	...	0.0448	6.73×10^{-5}	0.868	0.688
6	1.00	...	0.0566	8.45×10^{-5}	0.837	0.884
7	1.70	...	0.0796	1.40×10^{-4}	0.756	1.574
8	2.00	...	0.0901	1.63×10^{-4}	0.729	1.870
9	3.20	...	0.1351	2.49×10^{-4}	0.636	3.075
10	4.00	...	0.1486	3.03×10^{-4}	0.590	3.870
11	8.00	...	0.2229	5.56×10^{-4}	0.438	7.850
12	1.00	0.100	0.0389	2.74×10^{-4}	0.613	0.962
13	1.00	0.125	0.0321	4.30×10^{-4}	0.501	0.975
14	1.00	0.150	0.0227	7.60×10^{-4}	0.362	0.986
15	1.00	0.175	0.0140	1.70×10^{-3}	0.203	0.994
16	1.00	0.200	0.0044	7.20×10^{-3}	0.057	0.998
17	1.00	0.210	0.0021	1.37×10^{-2}	0.031	0.999
18	1.00	0.220	0.0015	2.22×10^{-2}	0.019	1.000
19	1.00	0.230	0.0011	3.17×10^{-2}	0.014	1.000
20	0.5	0.15	0.0136	6.05×10^{-4}	0.418	0.491
21	0.5	0.25	0.00035	5.09×10^{-2}	0.0085	0.500
22[1]	0.1	0.09	0.0076	7.30×10^{-5}	0.859	0.0868
23[1]	0.2	0.09	0.0115	1.12×10^{-4}	0.796	0.182
24[1]	0.4	0.09	0.0216	1.66×10^{-4}	0.724	0.374
25[1]	0.8	0.09	0.0339	2.53×10^{-4}	0.632	0.767
26[1]	1.6	0.09	0.0548	4.00×10^{-4}	0.520	1.552
27	0.1	0.20	0.00066	6.40×10^{-3}	0.0634	0.0999
28	0.2	0.20	0.0010	6.45×10^{-3}	0.0630	0.199
29	0.4	0.20	0.0017	6.70×10^{-3}	0.0607	0.399
30	0.8	0.20	0.0030	6.94×10^{-3}	0.0587	0.799
31	2.0	0.20	0.0068	7.90×10^{-3}	0.052	1.995
32	2.0	0.30	0.0000	1.01×10^{-1}	0.0043	2.000

[1] In the experiments whose results are recorded under 22 to 26 inclusive, the concentration of the cinchonine was 0.09 molal.

TABLE VI.—CINCHONINE, 0.1 MOLAL.

No.	Propionic acid.	Formic acid.	Hydrochloric acid.	K_2.	H^+.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$.	Organic acid non-ionized.
1	0.20	...	...	0.0117	8.30×10^{-6}	0.985	0.0985
2	0.40	...	...	0.0296	2.40×10^{-5}	0.949	0.294
3	0.80	...	...	0.0611	5.33×10^{-5}	0.890	0.690
4	1.20	...	...	0.0760	8.10×10^{-5}	0.844	1.085
5	..	0.2	...	0.0062	9.20×10^{-5}	0.825	0.0826
6	..	0.4	...	0.0121	2.51×10^{-4}	0.634	0.263
7	..	0.8	...	0.0165	5.40×10^{-4}	0.445	0.644
8	..	...	0.15	0.00163	4.25×10^{-4}	0.505	..
9	..	...	0.175	0.00077	1.205×10^{-3}	0.264	..
10	..	...	0.20	0.0003	6.46×10^{-3}	0.063	..
11	..	...	0.25	0.0001	5.08×10^{-2}	0.0085	..
12	..	...	0.40	0.0000	......	..	..

TABLE VII.—CINCHONIDINE, 0.1 MOLAL.

No.	Acetic acid.	Formic acid.	Hydrochloric acid.	K_2.	H^+.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$.	Organic acid non-ionized.
1	0.2	...	..	0.0078	1.06×10^{-5}	0.976	0.0977
2	0.3	...	..	0.0125	2.06×10^{-5}	0.956	0.195
3	0.4	...	..	0.0180	3.06×10^{-5}	0.937	0.294
4	0.5	...	..	0.0238	4.00×10^{-5}	0.915	0.391
5	0.8	...	..	0.0370	6.73×10^{-5}	0.868	0.688
6	1.5	...	..	0.0586	1.25×10^{-4}	0.775	1.378
7	3.0	...	..	0.1053	2.35×10^{-4}	0.648	2.860
8[1]	0.2	...	0.09	0.0098	1.12×10^{-4}	0.796	0.182
9[1]	0.3	...	0.09	0.0138	1.40×10^{-4}	0.755	0.278
10[1]	0.4	...	0.09	0.0170	1.66×10^{-4}	0.724	0.374
11[1]	0.8	...	0.09	0.0275	2.53×10^{-4}	0.632	0.767
12[1]	1.5	...	0.09	0.0418	3.81×10^{-4}	0.531	1.456
13	0.2	...	0.2	0.0008	6.45×10^{-3}	0.0630	0.199
14	0.3	...	0.2	0.0012	6.57×10^{-3}	0.0617	0.299
15	0.5	...	0.2	0.0018	6.78×10^{-3}	0.0600	0.499
16	0.8	...	0.2	0.0027	6.94×10^{-3}	0.0587	0.799
17	1.5	...	0.2	0.0044	7.53×10^{-3}	0.0543	1.499
18	0.8	...	0.3	0.0000	....	..	..
19	...	0.2	..	0.0050	9.20×10^{-5}	0.825	0.0826
20	...	0.3	..	0.0076	1.72×10^{-4}	0.715	0.170
21	...	0.4	..	0.0095	2.51×10^{-4}	0.634	0.26;
22	...	0.5	..	0.0113	3.25×10^{-4}	0.570	0.356

5. Relation between the Speed of the Reaction and the Concentration of H^+ Ion.—If,—from Table V in those experiments in which the concentration of the acetic acid is 1.0 molal and the concentration of H^+ ion is varied by the introduction of increasing quantities of hydrochloric acid (Table V, 12–19),—the concentration of H^+ ion is plotted against the reaction velocities, we obtain the curve (I) given in Fig. 1. If now the speed of the

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[1] In the experiments whose results are recorded under 8 to 12 inclusive, the concentration of the cinchonidine was 0.09 molal.

reaction were directly proportional to the total organic acid present, this curve, the concentration of organic acid being constant, would represent the influence of H^+ ion upon the reaction velocity. That the reaction velocity is not directly proportional to the concentration of the *total* organic acid, appears from a consideration of the rates of conversion of cinchonine into cinchotoxine already presented.[1] The reaction velocity appears rather to be a function of the concentration of the undissociated acid as has previously been pointed out[2] and if a linear function, then the specific reaction rate, K, may for a given concentration of H^+ ion be expressed by the equation,

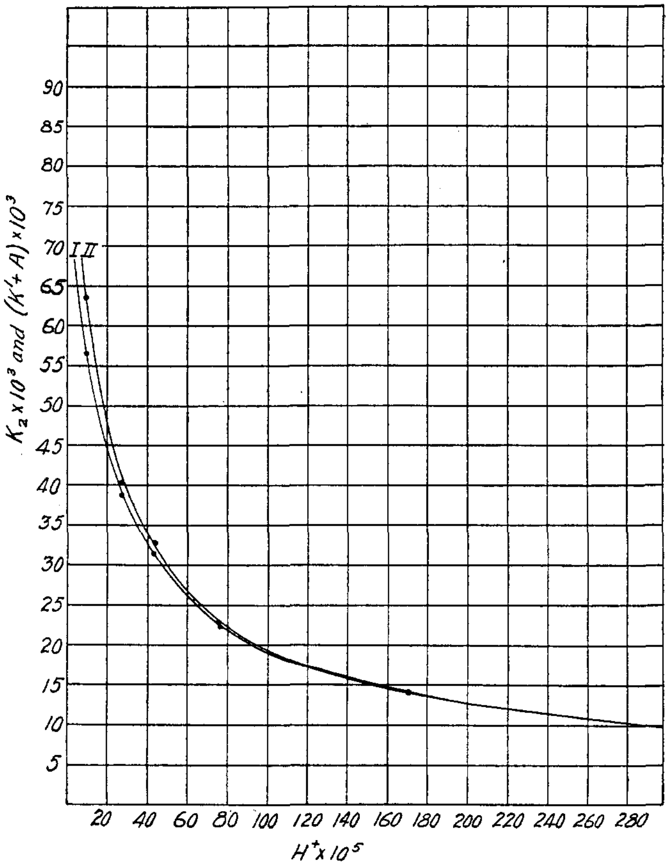

Fig. 1.

$$K = K' + AC', \qquad (l)$$

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[1] Biddle and Brauer, *Loc. cit.*

[2] Biddle, *Ber.*, 45, 2832 (1912).

where K' and A are constants and C' is the concentration of the undissociated organic acid in mols per liter.[1]

If now the values of K' are known for the various concentrations of H^+ ion studied, the value $K' + A$ is the reaction rate at molal concentration of the *undissociated* organic acid. This rate, plotted against the concentration of H^+ ion, should give a graph expressing the interrelation of these two values freed from other influences. The values of K' at varying concentrations of H^+ ion, may be obtained from a study of the conversion of cinchonine in the presence of hydrochloric acid alone. The rate of conversion in the presence of this acid is small and if we assume that the hydrochloric acid itself has no positive catalytic effect, as indicated below, then the rates at varying concentration of H^+ ion are in this case really the values of K' at these concentrations. As shown in Fig. 2 (Section 6) these rates of conversion, or the values of K', are to be considered as a linear function of $\frac{\text{Cin. }H^+}{\text{Cin. }H^+ + \text{Cin. }H_2^{++}}$. Introducing in Table VIII the values of K' as obtained from Fig. 2, we derive the corresponding values of $K' + A$, in which the concentration of undissociated organic acid is constant. Graph II in Fig. 1 results from the plotting of $K' + A$ against the concentration of H^+ ion. It will be observed that the curve obtained, except in the lower concentrations of H^+ ion, coincides with that resulting from the use of the original reaction velocities, K_2.

TABLE VIII.

Cinchonine, 0.1 molal. Acetic acid, 1.0 molal.

No.	Hydrochloric acid.	H^+.	K_2.	K'.	$K_2 - K'$.	A.	$K' + A$.
1	...	8.45×10^{-5}	0.0566	0.00270	0.0539	0.0610	0.0637
2	0.100	2.74×10^{-4}	0.0389	0.00197	0.0369	0.0384	0.0404
3	0.125	4.30×10^{-4}	0.0321	0.00161	0.0305	0.0313	0.0329
4	0.150	7.60×10^{-4}	0.0227	0.00117	0.0215	0.0218	0.0230
5	0.175	1.70×10^{-3}	0.0140	0.00064	0.0134	0.0135	0.0141
6	0.200	7.20×10^{-3}	0.0044	0.00018	0.0042	0.0042	0.0044
7	0.210	1.37×10^{-2}	0.0021	0.00009	0.00201	0.00201	0.0021
8	0.220	2.22×10^{-2}	0.0015	0.00006	0.00144	0.00144	0.0015
9	0.230	3.17×10^{-2}	0.0011	0.00004	0.00106	0.00106	0.0011

6. Relation of the Speed of the Reaction to the Concentration of the Univalent Cinchonine Ion.—If in those experiments in which the total acetic acid is of uniform concentration (1.0 molal), a comparison is made between the specific reaction rates (K_2) and the concentrations of the univalent cinchonine ion (Cin. H^+), a remarkable relationship is discovered. A cursory inspection of the two sets of values in Table IX leads to the conclusion that the reaction velocity is in all probability directly proportional to the concentration of the univalent cinchonine

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[1] Biddle and Rosenstein, THIS JOURNAL, 35, 425 (1913).

ion. In order, however, that a study of the matter may be made under conditions of equal concentration with respect to the undissociated organic acid, it becomes necessary to compare with the concentrations of Cin. H^+ ion, not the values of $K_2 = K' + AC'$, but those of $K_2 = K' + A$, in which C' has been reduced to unity. Assuming that the specific reaction rate is proportional to the concentration of the univalent cinchonine ion, then in the equation, $K_2 = K' + AC'$, (K') and (AC') will each be linear functions of this concentration. If, now, in the conversion of cinchonine into cinchotoxine in the presence of hydrochloric acid, this acid is considered to have no positive catalyzing influence, a conclusion which is reached from a consideration of the specific reaction rate in the presence of this acid alone, then in this case, $K_2 = K'$, and the values of K' at varying concentrations of H^+ ion are obtained by plotting the rates (K_2) against the values of $\frac{\text{Cin. } H^+}{\text{Cin. } H^+ + \text{Cin. } H_2^{++}}$, as shown in Fig. 2.

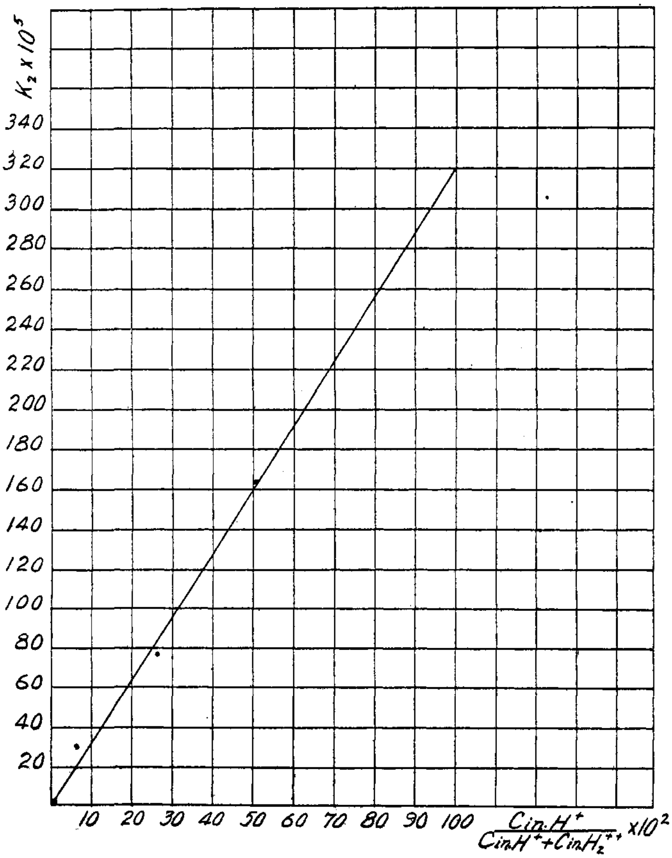

Fig. 2.

TABLE IX.

Cinchonine, 0.10 molal.

No.	Acetic acid.	Hydrochloric acid.	K_2.	$K' + A$.	Cin. H^+.	$\frac{\text{Cin. } H^+}{K' + A}$.
1	0.20	...	0.0094	0.0673	0.0976	1.45
2	1.00	...	0.0566	0.0637	0.0837	1.31
3	1.00	0.100	0.0389	0.0404	0.0613	1.52
4	1.00	0.125	0.0321	0.0329	0.0501	1.52
5	1.00	0.150	0.0227	0.0230	0.0362	1.57
6	1.00	0.175	0.0140	0.0141	0.0203	1.44
7	1.00	0.200	0.0044	0.0044	0.0057	1.30
8	1.00	0.210	0.0021	0.0021	0.00306	1.46
9	1.00	0.220	0.0015	0.0015	0.00191	1.33
10	1.00	0.230	0.0011	0.0011	0.00137	1.25[1]
					Mean,	1.433

In Table IX, as in Table VIII, the values under $K' + A$ (obtained from $K' + A = K' + 1/C'(K_2 - K')$) represent the specific reaction rate at constant concentration with respect to the undissociated organic acid. The ratio of the concentration of the univalent cinchonine ion to this rate, $\frac{(\text{Cin. } H^+)}{K' + A}$, is seen to be practically constant in solutions of uniform concentration with respect to the alkaloid.

From these considerations the conclusion must be drawn that, in solutions of uniform concentration with respect to the alkaloid, the speed of the conversion of cinchonine into cinchotoxine at constant concentrations of the undissociated catalyzing acid is directly proportional to the concentration of the univalent cinchonine ion.

As has been pointed out in the previous papers, if the reaction is monomolecular with respect to the alkaloid, then the rate of the reaction for any particular strength of the catalyzer is expressed by the equation:

$$-\frac{d(C)}{dt} = K_2(C)$$

where C is the concentration of the alkaloid at the time t and K_2 is the specific reaction rate. Since, however, the speed of the conversion under the conditions given is directly proportional not to the concentration of the cinchonine, but to that of the univalent cinchonine ion, this equation takes the form,

$$-\frac{d(C)}{dt} = K_0 \frac{(\text{Cin. } H^+)}{(\text{Cin. } H^+) + (\text{Cin. } H_2^{++})} (C),$$

in which $\frac{(\text{Cin. } H^+)}{(\text{Cin. } H^+) + (\text{Cin. } H_2^{++})}$ represents the fraction of the alkaloid in the form of the univalent ion. Now the value of this fraction, is determined by the concentration of the H^+ ion. In any particular solution,

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[1] Omitted in calculating mean value, since K_2 at higher concentrations of H^+ ion is open to much larger experimental error.

consequently, in which the concentration of the H^+ ion is assumed to remain unchanged throughout the reaction, the value of this fraction must be constant.

It follows, therefore, that in the values of the specific reaction rate as previously calculated from the experimental data, in any particular case,

$$K_2 = K_o \frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}$$

where K_o is the specific reaction rate which would be observed under the conditions of the experiment in case all of the cinchonine, at any moment, were in the form of the univalent cinchonine ion.

7. **Relation of the Speed of the Reaction to the Concentration of the Undissociated Organic Acid.**—The specific reaction rate of the conversion of cinchonine to cinchotoxine was determined by Biddle and Rosenstein for two concentrations of acetic acid. In these two instances the reaction velocity was apparently a linear function of the concentration of the organic acid above the diacetate. It was at the time assumed that this concentration represented that of the undissociated acid, an assumption whose error did not appear in the high concentrations employed, but is clearly seen from the data already given in the present paper. The assumption made, however, in the paper referred to and in a previous paper, that the speed of the reaction is a direct function of the concentration of the undissociated organic acid has proved correct.

In the equation, $K_2 = K' + AC'$, it has been shown in the cases considered (Table IX) that $(K' + A) \propto (\text{Cin. H}^+)$, or taking the mean value of 1.433 for the ratio, $\frac{(\text{Cin. H}^+)}{K' + A}$, then $K' + A = 0.697\ (\text{Cin. H}^+)$. This expressed in terms of the ratio of the univalent cinchonine ion to the total cinchonine present gives, since we are working with 0.1 molal cinchonine, the equation,

$$K' + A = 0.0697 \frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}.$$

If now all the cinchonine were converted into the univalent ion, $K' + A$ would become constant, $K_o' + A_o$. Under these conditions,

$$(K' + A) \frac{(\text{Cin. H}^+)+(\text{Cin. H}_2^{++})}{(\text{Cin. H}^+)} = K_o' + A_o = 0.0697. \quad (m)$$

The value, $K_o' + A_o$, is obviously the specific reaction rate of 0.1 molal cinchonine in acetic acid under conditions under which the concentration of the univalent ion is 0.1 molal and that of the undissociated organic acid is 1.0 molal. From this value, which may be termed the *absolute reaction rate* in the case of 0.1 molal cinchonine in the presence of acetic acid,

$$A_o = 0.0697 - K_o' = 0.0665 \qquad (n)$$

since from Fig. 2 the value of $K_o' = 0.0032$.

The relation of A_o to K_2 will be seen from the general equation,

$$K_2 = K' + AC' = (K_o' + A_oC') \frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}, \qquad (o)$$

in which K' and A are the constants in the equation, $K_2 = K' + AC'$, at any constant concentration of univalent cinchonine ion and K_o' and A_o are the corresponding constants under conditions under which all the cinchonine is in the form of the univalent ion.

From the above equation,

$$A_o = 1/C'\left[K_2 \frac{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}{(\text{Cin H}^+).} - K_o'\right]. \qquad (p)$$

Since, in the absence of the catalyzing organic acid,

$$K_o' = K' \frac{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}{(\text{Cin. H}^+)},$$

the last equation may also be written,

$$A_o = 1/C'(K_2 - K') \frac{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}{(\text{Cin. H}^+)}. \qquad (q)$$

The value of K' for any value of univalent cinchonine ion may be obtained from the graph, Fig. 2, or calculated directly from the equation,

$$K' = K_o' \frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}. \qquad (r)$$

From these considerations it will be clear that the constancy of the value A_o, as derived from experiments of widely divergent concentrations of organic acid and of H^+ ion, is conditioned upon the correctness of the assumptions that the rate of this conversion is a linear function of the concentration of the undissociated organic acid and is also directly proportional to the concentration of the univalent cinchonine ion. The validity of the assumption with respect to the organic acid will naturally be tested most rigorously in the case of low concentrations of the undissociated acid in which case any error in the assumption must lead to widely divergent values of A_o.

In Table X are brought together the values of A_o as calculated by Equation *p* for all the cases studied containing acetic acid in which the concentration of the cinchonine was 0.1 molal. The series presents a range of concentration of H^+ ion varying from 5.3×10^{-6} to 1.01×10^{-1} and of concentration of undissociated organic acid varying from 0.0485 molal to 7.85 molal. In all cases, as is seen, A_o is practically a constant within the limits of experimental error and errors introduced by unavoidable assumptions in the calculations. The mean value of A_o as obtained from the thirty-one determinations agrees, as will be seen, with the mean value already derived under (*n*) from nine determinations in Table IX.

Under $K' + AC'$ are given the values for K_2 as calculated from the equation.

$$K_2 = K' + AC' = (K'_o + A_oC')\ \frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})} =$$

$$(0.0032 + 0.0665\ C')\ \frac{(\text{Cin}\cdot\text{H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})},$$

in which the mean value of $A_o = 0.0665$ is employed. The agreement of the calculated values $K' + AC'$ with the measured speeds K_2, as is seen, is fully within the limits of experimental error.

Table X.

Cinchonine, 0.10 molal.

No.	Acetic acid.	Hydrochloric acid.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$.	A_o.	$K' + AC'$. (K_2, calculated.)	K_2 (observed).
1	0.15	...	0.988	0.0522	0.00634	0.00565
2	0.175	...	0.985	0.0550	0.00795	0.00712
3	0.20	...	0.976	0.0655	0.00945	0.0094
4	0.40	...	0.937	0.0738	0.0213	0.0239
5	0.80	...	0.868	0.0790	0.0425	0.0448
6	1.00	...	0.837	0.0731	0.0519	0.0566
7	1.70	...	0.756	0.0645	0.0816	0.0796
8	2.00	...	0.729	0.0645	0.0928	0.0901
9	3.20	...	0.636	0.0680	0.1320	0.1351
10	4.00	...	0.590	0.0644	0.1540	0.1486
11	8.00	...	0.438	0.0650	0.2290	0.2229
12	1.00	0.100	0.613	0.0627	0.0411	0.0389
13	1.00	0.125	0.501	0.0624	0.0342	0.0321
14	1.00	0.150	0.362	0.0601	0.0249	0.0227
15	1.00	0.175	0.203	0.0667	0.0141	0.0140
16	1.00	0.200	0.057	0.0742	0.0040	0.0044
17	1.00	0.210	0.0306	0.0655	0.00204	0.0021
18	1.00	0.220	0.0191	0.0754	0.00123	0.0015
19	1.00	0.230	0.0137	0.0773	0.00096	0.0011
20	0.5	0.15	0.418	0.0622	0.0150	0.0136
21	0.5	0.25	0.0085	0.0760	0.0003	0.00035
22	0.1	0.09	0.859	0.0654	0.0077	0.0076
23	0.2	0.09	0.796	0.0620	0.0121	0.0115
24	0.4	0.09	0.724	0.0711	0.0202	0.0216
25	0.8	0.09	0.632	0.0640	0.0342	0.0339
26	1.6	0.09	0.520	0.0655	0.0554	0.0548
27	0.1	0.20	0.063	0.0761	0.00062	0.00066
28	0.2	0.20	0.063	0.0640	0.00103	0.0010
29	0.4	0.20	0.061	0.0622	0.0018	0.0017
30	0.8	0.20	0.059	0.0600	0.0033	0.0030
31	2.0	0.20	0.052	0.0640	0.0071	0.0068
32	2.0	0.30	0.0043	..	...	0.0000
			Mean,	0.0665		

Closer agreement apart from experimental error could scarcely be expected in view of the fact that small errors are necessarily introduced into the calculation by ignoring such conditions as the presence of undissociated cinchonine salt and of undissociated hydrochloric acid, such conditions also as the slight alteration in concentration of H^+ ion due to the change of cinchonine to cinchotoxine of slightly different basicity, and such also as the fact that with increasing concentration of organic acid the dissociation constant of the acid itself changes. At constant concentration with respect to the cinchonine, however, the errors introduced by these factors must, from the very nature of the case, be so small as to be negligible[1] with reference to any serious effect upon the final results. It is, consequently, conclusively established that *the rate of conversion of cinchonine into cinchotoxine under the conditions given is directly proportional to the concentration of the univalent cinchonine ion and is a linear function of the concentration of the undissociated organic acid.*

8. The Specific Catalytic Action of Different Organic Acids.—Since the absolute reaction rate, A_0, for acetic acid represents the specific reaction rate for one mol of undissociated organic acid, this value when determined for different organic acids affords a comparison of the specific catalytic action of these acids under like conditions. In Table XI are given the calculated values of A_0 and of $K' + AC'$ for formic and propionic acids. As is seen, the same general principles obtain as are found in the case of acetic acid. The mean value of A_0 for formic acid equals 0.0550, that for propionic acid 0.0901, and as already shown that for acetic acid is 0.0665. The specific catalytic action of the acid would seem then to increase with acids of decreasing dissociation constant.

TABLE XI.

Cinchonine, 0.1 molal.

No.	Formic acid.	Propionic acid.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}^{2++}}$.	A_0.	$K' + AC'$. (K_2, calculated.)	K_2 (observed).
1........	0.2	...	0.825	0.0524	0.00642	0.0062
2........	0.4	...	0.634	0.0605	0.0113	0.0121
3........	0.8	...	0.445	0.0527	0.0173	0.0165
4........	...	0.2	0.985	0.0885	0.0119	0.0117
5........	...	0.4	0.949	0.0960	0.0280	0.0296
6........	...	0.8	0.890	0.0952	0.0580	0.0611
7........	...	1.2	0.844	0.0818	0.0846	0.0760

Formic acid, A_0 = 0.0550
Acetic acid, A_0 = 0.0665
Propionic acid, A_0 = 0.0901

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[1] This assumption would, of course, be incorrect if the undissociated cinchonine salts varied greatly in solutions of constant initial concentration with respect to the cinchonine and if at the same time the reaction rate were largely influenced by the concentration of such undissociated salt. As indicated later in this article, these factors will be considered in a subsequent paper.

A curious relation, probably accidental, is noted in comparing the ratio of these values in the case of any two acids with the corresponding ratio of the molecular weights of the two acids. As is shown in Table XII, the ratio is practically identical in the two cases.

TABLE XII.

	A_0/A_0.	M. W./M. W.
Propionic/Acetic	1.35	1.23
Acetic/Formic	1.21	1.3
Propionic/Formic	1.64	1.61

9. **The Effect upon the Reaction Rate of Varying the Concentration of the Cinchonine.**—If the reaction in the conversion of cinchonine into cinchotoxine is monomolecular with respect to the alkaloid, the specific reaction rate K_2, should be independent of the *initial* concentration of the cinchonine. It is of interest, consequently, to determine the value of A_0 (the absolute reaction rate of an organic acid) for the two other concentrations of cinchonine studied, *viz.*, 0.25 and 0.01 molal. A general consideration of the specific reaction rates (K_2), measured in the case of 0.25, 0.1, and 0.01 molal cinchonine, leads one to infer that there is a general decrease in speed with increasing initial concentration of cinchonine. This inference is substantiated in comparing the values of A_0.

TABLE XIII.

Cinchonine, 0.25 molal.

No.	Acetic acid.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$.	A_0.	K′ + AC′. (K_2, calculated.)	K_2 (observed).
1	0.50	0.976	0.0676	0.0178	0.0192
2	0.75	0.957	0.0633	0.0319	0.0327
3	1.00	0.934	0.0590	0.0450	0.0434
4	1.25	0.915	0.0600	0.0580	0.0566
5	1.50	0.896	0.0628	0.0706	0.0721
6	2.00	0.867	0.0588	0.0939	0.0901
7	2.50	0.838	0.0587	0.1169	0.1112
		Mean,	0.0615		

TABLE XIV.

Cinchonine, 0.01 molal.

No.	Acetic acid.	Hydrochloric acid.	$\frac{\text{Cin. H}^+}{\text{Cin. H}^+ + \text{Cin. H}_2^{++}}$.	A_0.	K′ + AC′. (K_2, calculated.)	K_2 (observed).
1	0.05	...	0.915	0.0805	0.0062	0.0058
2	0.10	...	0.839	0.0840	0.0094	0.0089
3	0.15	...	0.779	0.0955	0.0118	0.0127
4	0.20	...	0.729	0.1015	0.0147	0.0162
5	0.40	...	0.593	0.1033	0.0228	0.0256
6	0.80	...	0.445	0.0955	0.0332	0.0347
7	0.50	0.010	0.360	0.0860	0.0173	0.0163
8	0.50	0.015	0.240	0.0895	0.0116	0.0114
9	0.50	0.020	0.125	0.0842	0.0061	0.0056
			Mean,	0.0911		

In Tables XIII and XIV the values of A_0 and of $K' + AC'$ have been calculated for the various measurements made in solutions containing 0.25 and 0.01 molal cinchonine. In these calculations, as in those previously determined, it is assumed that $K_0' = 0.0032$. On considering the values obtained it is evident that for a given concentration of cinchonine A_0 as before approaches a constant. The mean constant resulting, however, varies with the concentration of the alkaloid. Thus, for solutions containing, respectively, 0.25, 0.1 and 0.01 molal cinchonine, the mean values of A_0 are 0.0615, 0.0665 and 0.0911.

In seeking some explanation of these deviations of the values of A_0 from constancy, one naturally raises the question as to whether similar variations have been observed in such catalyses as the inversion of cane sugar. The question must be answered in the affirmative; for, as Ostwald[1] has shown, the rate of inversion is strictly proportional to the concentration of the H^+ ions *only* when the solutions are *dilute*, since at higher concentrations deviations occur. The variations in the values of A_0 are, consequently, not abnormal.

The actual cause of these deviations is more difficult to determine. Certain factors, may however, be noted. In the determination of the concentration of H^+ ion, upon which all subsequent calculations in this paper depend, no account has been taken of the existence in the solution of nonionized cinchonine salt. That such salt exists can not be questioned. The concentration of undissociated salt, though probably small, may be assumed not to vary greatly in solutions of constant concentration with respect to the alkaloid, but to increase in solutions of increasing concentration with respect to the cinchonine. The general effect of this factor might not be noticeable in solutions of constant concentration with respect to the alkaloid, but would probably lead to an apparent decrease in the value of A_0 in solutions of increasing concentration with respect to this substance, unless the undissociated salt exerted an effect upon the reaction velocity exceeding that of the univalent cinchonine ion. As is seen, the deviations in the values of A_0 for the three concentrations of cinchonine studied are in the direction which would naturally be expected from the presence of undissociated cinchonine salt. It is of interest to note that if the variations in the value of A_0 could be attributed *solely* to the varying proportion of undissociated salt, these might serve as a basis for calculating in any case the amount of alkaloid in the form of such salt.

Another factor which the calculation of necessity ignores is the effect upon the reaction rate of the varying total concentration of the salt, in other words, the salt effect. The "neutral salt effect," which in other cases

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[1] *J. prakt. Chem.*, [2] 31, 307 (1885).

of catalysis has been the subject of numerous investigations,[1] would in different concentrations of cinchonine salt naturally affect the value of A_0. The whole question of the salt effect, however, is involved with that of the undissociated salt which, as will be shown later in this paper, must be taken into consideration in a complete interpretation of the mechanism of the reaction.

An interesting attempt has been made by Rosanoff[2] to account in general for unexpected variations in catalytic reaction rates due to changes in concentration. He divides catalyzers into two classes, direct and indirect. The former are assumed to take part in the reaction, but not to appear in the stoichiometric equation; the latter "without taking any part in the reaction are regarded as influencing its velocity by affecting the particular conditions upon which the mechanism of the given reaction may depend." Under this classification as he has noted, "all substances are indirect catalyzers of *all* reactions." It is too early as yet, however, to determine just what value is to be assigned to the general equation which he has developed.

10. The Specific Reaction Rate of the Stereoisomeric Cinchonidine.—In studying the exact catalytic action of organic acids upon the isomeric cinchonidine, it becomes necessary, as in the case of cinchonine, to determine the values of the dissociation constants of the alkaloid. As has already been shown earlier in this paper, the values of the second dissociation constant, k_2, are practically identical in the case of the two alkaloids. As to the first dissociation constant, k_1, the results obtained by Veley[3] indicate but slight difference in the two cases. While, as has already been pointed out the accuracy of Veley's method is open to question, it may at least be safely concluded that the difference between the values of k_1 in the two alkaloids, if at all existent, must be small. In determining the concentration of H^+ ion, consequently, the dissociation constant k_1, as has already been pointed out, may be neglected as was done in the case of cinchonine. The data presented in Table VII were calculated accordingly in the same way as those given in the preceding tables.

In the preceding paper[4] attention was called to the fact that the mean ratio between the specific reaction rates of cinchonidine and cinchonine under like conditions is that of 1 : 1.21+. The significance of this ratio becomes apparent, if the first and second dissociation constants, k_1 and k_2, of the two alkaloids possess for all practical purposes identical values. Then, the concentration of H^+ ion and that of undissociated organic acid

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[1] See references in introduction of this paper.

[2] THIS JOURNAL, 35, 173, 248 (1913).

[3] *J. Chem. Soc.*, 95, 758 (1909).

[4] Biddle and Butzbach, THIS JOURNAL, 37, 2082 (1915).

will remain unchanged under like conditions whether the solution contains cinchonine or cinchonidine and any constant difference in speed of conversion must be explained on the basis of stereoisomeric difference existing between the two alkaloids.

In Table XV is presented a study of all the reaction rates given in Table VII. The values under K′ + AC′ were calculated from the equation,

$$K' + AC' = (K'_0 + A_0C')\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})} =$$

$$(0.0032 + 0.0665\ C')\ \frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2^{++})}.$$

They represent, consequently, the specific reaction rates for *cinchonine* under the conditions given and serve as a basis of comparison with the experimental values of K_2 for cinchonidine under like conditions.

TABLE XV.

Cinchonidine, 0.1 molal.

No.	Normality of organic acid. *Acetic acid.*	Normality of hydrochloric acid.	K_2 (observed cinchonidine).	$K' + AC'$, (K_2, calculated, cinchonine.)	$\frac{K' + AC'}{K_2}$.	A_0' (cinchonidine).	A_0'' (cinchonine).
1......	0.2	..	0.0078	0.0095	1.21	0.0550	0.0665
2......	0.3	..	0.0125	0.0155	1.24	0.0535	0.0646
3......	0.4	..	0.0180	0.0213	1.18	0.0563	0.0680
4......	0.5	..	0.0238	0.0267	1.12	0.0596	0.0725
5......	0.8	..	0.0370	0.0425	1.15	0.0580	0.0704
6......	1.5	..	0.0586	0.0735	1.25	0.0531	0.0644
7......	3.0	..	0.1053	0.1251	1.19	0.0560	0.0677
8[1].....	0.2	0.09	0.0098	0.0121	1.24	0.0529	0.0644
9[1].....	0.3	0.09	0.0138	0.0164	1.19	0.0563	0.0682
10[1].....	0.4	0.09	0.0170	0.0202	1.19	0.0557	0.0676
11[1].....	0.8	0.09	0.0275	0.0342	1.24	0.0531	0.0644
12[1].....	1.5	0.09	0.0418	0.0531	1.27	0.0521	0.0630
13......	0.2	0.2	0.0008	0.0010	1.25	0.0505	0.0615
14......	0.3	0.2	0.0012	0.0014	1.17	0.0560	0.0680
15......	0.5	0.2	0.0018	0.0022	1.22	0.0548	0.0666
16......	0.8	0.2	0.0027	0.0033	1.22	0.0543	0.0657
17......	1.5	0.2	0.0044	0.0056	1.27	0.0523	0.0634
	Formic acid.				Mean,	0.0547	0.0663
18......	0.2	..	0.0050	0.0064	1.28	0.0414	0.0500
19......	0.3	..	0.0076	0.0090	1.18	0.0469	0.0566
20......	0.4	..	0.0095	0.0113	1.19	0.0470	0.0570
21......	0.5	..	0.0113	0.0130	1.15	0.0482	0.0585
				Mean,	1.21	0.0459	0.0555

The ratio between these two values, or $\frac{K' + AC'}{K_2}$, should be identical with that previously obtained, *viz.*, 1 : 1.21+. As will be noted the re-

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[1] The concentration of the cinchonidine in these experiments was 0.09 molal.

sulting mean value of all the ratios is, $\frac{K' + AC'}{K_2} = 1.21$, a value which is practically identical with that previously given. The general specific reaction rate of cinchonine is, consequently, 1.21 times that of cinchonidine under the same experimental conditions. In view of the values obtained for the first and second dissociation constants of the two alkaloids this difference in rate of conversion must be ascribed, as already pointed out, to the stereoisomeric difference between cinchonine and cinchonidine.

In the conversion of cinchonine into cinchotoxine (see Equation *o*)

$$K_2 = (K_o' + A_oC')\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})}.$$

In the presence of acetic acid this becomes,

$$K_2 = (0.0032 + 0.0665\ C')\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})},$$

and in the presence of formic acid (see Table XI)

$$K_2 = (0.0032 + 0.0550\,C')\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})}.$$

In the conversion of cinchonidine into cinchotoxine, the general equation naturally becomes,

$$K_2 = \frac{1}{1.21}(K'_o + A_oC')\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})}. \qquad (s)$$

In the presence of acetic acid this leads to,

$$K_2 = (0.00264 + 0.0550\ C')\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})},$$

and in the presence of formic, to

$$K_2 = (0.00264 + 0.0455\ C')\frac{(\text{Cin. H}^+)}{(\text{Cin. H}^=) + (\text{Cin. H}_2{}^{++})}.$$

In the case of cinchonidine, then, $K_o' = 0.00264$, for acetic acid $A_o = 0.0550$ and for formic acid $A_o = 0.0455$.

Under A_o' (cinchonidine), Table XV, the values for the absolute reaction rate for cinchonidine have been calculated from the equation,

$$A_o' = 1/C'(K_2 \times \frac{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})}{(\text{Cin. H}^+)} - 0.00264).$$

Under A_o'' (cinchonine), the corresponding values for cinchonine have been calculated from the equation,

$$A_o'' = 1/C'(1.21 \times K_2 \times \frac{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})}{(\text{Cin. H}^+)} - 0.0032).$$

As was of course to be expected, the mean values obtained for A_o' and A_o'' correspond with those already given, as is shown in Table XVI.

TABLE XVI.

	A_0' (acetic).	A_0' (formic).	A_0'' (acetic).	A_0'' (formic).
From Table XV.	0.0547	0.0459	0.0563	0.0555
Previously given	0.0550	0.0455	0.0665	0.0550

11. Discussion of the Nature of the Reaction.—In the study of the catalysis of the cinchonà alkaloids in the presence of organic acids, the puzzling question that remains to be answered is that regarding the mechanism of the reaction. That the positive catalyzing influence is not a matter of decreasing concentration of H^+ ion, but is a definite linear function of the concentration of the undissociated acid, has been clearly shown in the preceding pages. This catalytic action has been observed in the case of all such common organic acids as lactic, citric, tartaric, malic, formic, acetic and propionic. What, it must be asked, is the specific role of the organic acid in the mechanism of the reaction? While the data obtained as yet are insufficient fully to *answer* this question, there is one property of an organic acid which leads to a tentative suggestion and that is the readiness with which such an acid yields an acid amide when heated with ammonia, or a primary or secondary amine. It is conceivable that the tendency to form an acetyl or other acyl derivative of cinchotoxine as an intermediate product is a factor contributing to the conversion of the tertiary cinchona alkaloid into a toxine containing a secondary nitrogen atom. Such an acyl derivative, however, if formed, apparently occurs as an intermediate and not a final product, since in all cases examined titration accounted for the total organic acid present.

A reaction favoring the hypothesis advanced is the readiness with which the alkyl halides of the cinchona alkaloids are converted into toxines. Thus, cinchonine methyl iodide on treatment with potassium hydroxide readily yields methylcinchotoxine.[1] Of additional interest in this connection is the influence of the concentration of acetic acid upon the familiar reaction, the conversion of aniline into acetanilide. As shown by Tobias[2] the amount of acetanilide formed in a given time at a constant temperature is dependent upon the concentration of the acetic acid present. A further study of reactions of this type is being continued in this laboratory.

It may be noted finally that any attempt adequately to determine the mechanism of the reaction discussed in this paper must take into consideration all the factors possibly involved. Thus, for example, the mathematical proof given does not necessarily exclude the possibility that partially ionized cinchonine salt, *i. e.*, intermediate ions of the type

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[1] Claus and Müller, *Ber.*, **13**, 2290 (1880); Miller and Rhoda, *Ibid.*, **27**, 1280 (1894); *Ibid.*, **28**, 1066 (1895).

[2] *Ibid.*, **15**, 2868 (1882).

Cin. $\frac{\text{HAc}}{\text{H}^+}$, may not take some part in the reaction. Furthermore, as has already been pointed out, from the nature of the case no account has been taken in the calculation of the role played by the totally undissociated alkaloid salt unquestionably present in the solution. In view of the general simultaneous action of ions and undissociated ionogens so ably investigated by Goldschmidt, Acree, Stieglitz and others,[1] a complete mathematical and theoretical interpretation of the reaction must needs, consequently, take into consideration the influence upon the reaction both of the partially and of the completely nonionized alkaloid salt. Such consideration will doubtless largely explain the deviations in reaction rate occasioned by varying initial concentration of the alkaloid. The influence of these and other factors upon the specific reaction rate, both in the case of the cinchona alkaloids and in that of the less involved acetylation of an amine such as aniline, will be made the subject of a subsequent paper.

In conclusion I take this opportunity of expressing my appreciation to Prof. Joel Hillebrand and Dr. L. Q. Adams for a number of helpful suggestions, and my indebtedness to M. J. Gavin for the experimental work in determining the second dissociation constant of cinchonine and of cinchonidine.

Summary.

1. The concentration of H^+ ion in a solution of a cinchona alkaloid containing acids of varying concentration may be calculated with sufficient accuracy to determine the effect of different concentrations of the ion upon the rate of the conversion of the alkaloid into its toxin.

2. The graph obtained by plotting the specific reaction rates against the concentrations of H^+ ion, for solutions of constant concentration with respect to the undissociated organic acid, is a regular curve in which the specific reaction rates change the more rapidly the lower the concentration of the H^+ ion.

3. The specific reaction rate at constant concentration of catalyzing acid in solutions of constant concentration with respect to the alkaloid is directly proportional to the concentration of the univalent cinchonine or cinchonidine ion, *i. e.*, $K_2 \propto (\text{Cin. H}^+)$.

4. The specific reaction rate at constant concentration of the univalent cinchonine or cinchonidine ion is a linear function of the concentration of the undissociated organic acid, *i. e.*, $K_2 = K' + AC'$. This result is particularly significant in that it fully establishes the fact that an undissociated molecule (in this case an un-ionized electrolyte) in homogeneous solution can act as a direct catalytic agent and that through a wide range of concentration (in the case of acetic acid, the law was

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[1] *Loc. cit.*

confirmed for concentrations of undissociated acid varying from 0.0485 molal to 7.85 molal).

The relations set forth under 3 and 4 are conveniently expressed in the general equation,

$$K_2 = (K_o' + A_oC') \frac{(\text{Cin. H}^+)}{(\text{Cin. H}^+) + (\text{Cin. H}_2{}^{++})},$$

which enables us to extend the application also to varying concentrations of the alkaloid.

5. The specific catalytic action of the three organic acids, formic, acetic and propionic, increases in the order of the acids named. Indeed, the absolute reaction rate for an organic acid, A_o, appears to be directly proportional to the molecular weights of the particular acids concerned—a relationship, however, which is probably accidental.

6. The specific reaction rate, which on theoretical grounds should under like conditions be independent of the initial concentration of the cinchonine or cinchonidine, is found slowly to decrease with increasing concentration of the alkaloid. In view of similar variations in rate of reaction under similar conditions in the case of such catalyses as the inversion of cane sugar and the hydrolysis of esters, these deviations from constancy in the case of the cinchona alkaloids are not to be regarded as abnormal.

7. The specific reaction rates of the two isomeric alkaloids under like conditions bear to each other a constant ratio, whose mean value is, cinchonidine to cinchonine, 1 : 1.21. This difference in rate of conversion is apparently to be attributed solely to the stereoisomeric difference existing between the two alkaloids.

8. A tentative suggestion as to the mechanism of the reaction involved in the conversion of the cinchona alkaloids into their toxins is offered on the basis of the readiness with which organic acids yield acyl derivatives with primary and secondary amines.

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AN APPARATUS FOR THE STUDY OF REACTIONS BETWEEN GASES AND LIQUIDS.

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The apparatus here described has been devised and used for the study of catalytic hydrogenation, but may serve for the study of any reaction in which a gas is to be brought into intimate contact with a liquid under constant conditions. The problem is to introduce a high speed stirrer, inlet and outlet tubes, and, possibly, a sampling tube through a comparatively small stopper and to render the whole gas tight for both increased and reduced pressure. The apparatus is shown in the sketch in section, Fig. 1.