to the support of any one of these hypotheses, nevertheless the facts established demonstrate rather clearly that the final solution of the problem is to be sought in a specific effect of the non-ionized portion of the salt rather than in some function of the ions produced. To this extent our results are in accord with the recent work of A. A. Noyes, E. W. Washburn, J. Walker, and others, who attribute various abnormal effects of electrolytes to the non-ionized side of the equilibrium equation, rather than to the ions. In a recent contribution, published after this work was completed, Stieglitz[1] is inclined to take the same point of view as a basis for the discussion of the salt effect in hydrolysis phenomena among the imido ethers.

It is to be regretted that lack of time, as well as the inherent experimental difficulties, prevented any measurements of the concentration of the hydroxyl and hydrogen ions in the solutions employed and of the degree of hydrolysis of the salts present. Such measurement would have had an important bearing upon the problem, especially in connection with the hypothesis of Euler, namely, that at higher salt concentrations water is much more ionized than in dilute solutions, the increase in the concentrations of its ions increasing the velocity of hydrolysis.

If we admit that the hydrolysis of the ester is largely controlled by the concentration of the salt molecules, the cause of the maximum observed in these experiments finds an easy explanation. Not only does the concentration of the molecules increase as the total concentration rises, but the difficulty of meeting (*i. e.*, the viscosity) varies as well. Plate XV shows this very clearly. The observed maximum is, then, the resultant of two oppositly directed tendencies. On the one hand is the acceleration produced by the salt molecules which increases with concentration. On the other hand is the resistance offered to the meeting between the ester and the water with which it reacts; and when the viscosity becomes sufficiently great, the catalytic effect of the salt begins to diminish.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA.]

THE RATE OF CONVERSION OF CINCHONINE TO CINCHOTOXINE.

(ON CATALYSES WITH WEAK ACIDS, IV.)[2]

BY H. C. BIDDLE AND LUDWIG ROSENSTEIN.

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Introduction.—The nature of the change of certain of the vegetable alkaloids to their toxic isomers has been the subject of recent investigations by Biddle[2] and later by Rabe.[3] It has been shown by the former that weak

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[1] THIS JOURNAL, 34, 1687.

[2] Biddle, *Science*, 32, 486 (1910); *Ber.*, 45, 526, 2832 (1912); THIS JOURNAL, 34, 500 (1912); 35, 273 (1913).

[3] Rabe, *Ber.*, 43, 3300 (1910); 45, 2927 (1912).

acids have a peculiar catalyzing influence on the reaction, and furthermore, within certain limits it appears that the weaker the acid employed the more rapidly does the reaction proceed. Besides this catalyzing influence of the weak acids, attention has been called to the retarding influence of strong acids—an influence quite as strongly characterized as the catalysis. Biddle found, for example, that in solutions of cinchonine made acid only with hydrochloric acid there was practically no reaction; while in solutions containing hydrochloric and acetic acids 4% of the possible conversion was effected in forty-eight hours. In pure acetic acid, however, the reaction after twenty-four hours was complete. In the case of acetic acid it has been shown that the speed of the conversion is a function of the concentration of the undissociated acid.[1]

The present investigation[2] had for its purpose the development of a quantitative method, more exact than the ether extraction method[3] for studying this change of the alkaloids to their toxic isomers, and the application of this method to the particular case of the conversion of cinchonine to cinchotoxine by means of acetic acid. It was planned to determin the kinetic law for this reaction; for a knowledge of the rate of a reaction and of the factors on which the rate depends makes it possible to tell with some degree of certainty not only what molecular species are involved in the reaction, but also in what quantity each is concerned.

Methods of Analysis.—The first step in the investigation was the development of methods for the analysis of solutions containing salts of cinchonine and of cinchotoxine. Two methods have proved useful, a gravimetric one and the polarimetric method.

The gravimetric method is based on the difference in the strength of the two difficultly soluble bases, cinchonine and cinchotoxine. Cinchonine is a base much weaker than ammonia, while cinchotoxine is considerably stronger. For this reason cinchotoxine, although somewhat difficultly soluble in water, will dissolve in a solution of ammonium nitrate or any other ammonium salt with the liberation of free ammonia. The solubility of cinchonine, on the other hand, is not much affected by ammonium salts. When a solution containing salts of both of the alkaloids and of ammonia is made alkaline with ammonia, the cinchonine alone is precipitated. The free base may then be collected on a Gooch filter, dried at 100° C. and weighed. To test this method, analyses were made on known mixtures of cinchonine and cinchotoxine salts in solution. The solutions were nearly saturated with ammonium nitrate before being made alkaline

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

[2] This study is one of a number of investigations begun in this laboratory seven months ago along similar lines with regard to the conversion of cinchonine and cinchonidine to cinchotoxine, and of quinine and quinidine to quinotoxine in the presence of acids of varying dissociation constants.—H. C. BIDDLE.

[3] Biddle, THIS JOURNAL, **34**, 500 (1912).

with ammonia. The precipitates were in each case allowed to settle twelve hours before filtering. In Table I are given the results of four such analyses.

TABLE I.

Volume of solution. Cc.	Gms. cinchonine taken.	Gms. cinchotoxine taken.	Gms. cinchonine found.
350	0.182	0.192	0.182
350	0.182	0.384	0.179
350	0.457	0.096	0.446
350	0.457	0.384	0.459

The method is accurate to approximately 2%. The manipulation, while not difficult, is not as convenient, nor is the method as accurate, as the one next to be described. For these reasons the second method was used in preference to the first. However, two determinations of the specific reaction rate were made by the first method.

The second method of analysis is based upon the fact that the rotatory power of solutions of cinchonine salts is much greater than that of cinchotoxine salts.[1] The change in the rotatory power of a solution of cinchonine salt is then a measure of the extent to which conversion to cinchotoxine has taken place. But the rotatory power is a function, not only of the concentrations of optically active substances in the solution, but also of the nature of the solvent. The experiments were planned to be carried out in solutions 3.0 molal and 1.5 molal with respect to free acetic acid, and so the rotation of solutions of cinchonine and cinchotoxine in both these strengths of acid was determined. The instrument used in all of the determinations was a Franz Schmidt and Haensch quartz wedge saccharimeter. The source of light was a Welsbach burner. A bichromate cell was used as a light filter. In Table II are given the rotations determined with a one decimeter tube in terms of the arbitrary readings of the instrument.[2] Column 1 gives the concentration of cinchonine diacetate in mols per liter, column 2 the concentration of cinchotoxine diacetate, column 3 the concentration of free acetic acid, and column 4 the corrected readings of the instrument. Each of the figures in column 4 is a mean of six settings.

TABLE II.

Expt. No.	1. Concentration of cinchonine.	2. Concentration of cinchotoxine.	3. Concentration of acetic acid.	4. Readings.
1..........	0.10 m.	0.00	1.5 m.	20.90
2..........	0.00 m.	0.10	1.5 m.	2.08
3..........	0.05 m.	0.05	1.5 m.	11.36
4..........	0.10 m.	0.00	3.0 m.	21.06
5..........	0.00 m.	0.10	3.0 m.	2.70

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[1] See Landolt, "The Optical Rotation of Organic Substances," 2nd ed., pp. 500, 680, 687.

[2] The instrument readings are per cent. sugar.

Experiments No. 4 and 5 in this table show that the rotatory power of a solution of the alkaloid in 3.0 molal acid is slightly greater than that of a solution in 1.5 molal acetic acid. The reading in the case of No. 3 shows that the rotatory power of the solution 0.05 m. with respect to both cinchonine and cinchotoxine is a mean of the rotatory power of the 0.10 m. cinchonine and 0.10 m. cinchotoxine solutions, that is, the rotatory power is a linear function of the composition of the solution.

Experimental Details.—To determin the rate of the reaction with respect to the cinchonine and the acetic acid, 0.10 molal solutions of the alkaloid in acetic acid were kept at a constant temperature of 99.6° (±0.1°) during the course of the experiments. The flask in which the reaction took place was hung in a well-insulated thermostat through which steam from a small boiler passed continuously at atmospheric pressure. The reaction flask was provided with a condenser to prevent any change of concentration due to evaporation, a stirrer to maintain uniform temperature, a syphon, and a thermometer graduated in tenths of a degree. At different time intervals samples were removed by means of the syphon and the reaction stopped by immediately chilling the sample in an ice bath. The sample was then analyzed, either gravimetrically or by means of the polarimeter.

The first set of experiments was carried out in solutions 1.5 molal with respect to free acetic acid and 0.10 molal with respect to cinchonine diacetate. The next set was made with solutions 3.0 molal with respect to acetic acid and again 0.10 molal with respect to cinchonine diacetate. An experiment was also performed with a solution 3.0 molal with respect to the acid, 0.10 molal with respect to the alkaloid, and containing an amount of sodium acetate sufficient to reduce the concentration of hydrogen ion to the same amount as in the 1.5 molal acetic acid.

If the reaction is a monomolecular one with respect to the alkaloid, that is, if the rate is directly proportional to the concentration of cinchonine in the solution, then the rate of the reaction for any particular strength of the catalyzer is expressed by the equation

$$—d(c)/dt = \mathrm{K}(c)$$

where c is the concentration of alkaloid at the time t, and K is the specific reaction rate. The value of K will depend upon the concentration of free acetic acid and of hydrogen ion in the solution. On integration this equation gives for the value of the specific reaction rate

$$\mathrm{K}_1 = 1/t \log c_0/c_1 \qquad (1)$$

where K_1 is the specific reaction rate, t is the time, c_0 is the concentration of alkaloid at the beginning of the experiment, c_1 is its concentration after the time t, and log is the logarithm to the base 10. Or, if instead of calculating K from the time when the reaction began, the calculation is made during different time intervals,

$$K_2 = 1/t_2 - t_1 \log c_1/c_2 \qquad (2)$$

where c_1 is the concentration after the time t_1, and c_2 is the concentration after the time t_2. It has been shown that the rotatory power of solutions of cinchonine and cinchotoxine salts is a linear function of their composition and, therefore, the rotatory power may be used directly in the formulae for the specific reaction rate. Replacing concentrations by polarimeter readings, formula (1) becomes

$$K_1 = 1/t \log \alpha_0 - \alpha_\infty / \alpha_1 - \alpha_\infty \qquad (3)$$

and formula (2) becomes

$$K_2 = 1/t_2 - t_1 \log \alpha_1 - \alpha_\infty / \alpha_2 - \alpha_\infty \qquad (4)$$

In these formulae, α_0 is the instrument reading for 0.10 molal cinchonine diacetate, α_1 and α_2 the readings for the solution after the time intervals t_1 and t_2, and α_∞ the reading for 0.10 molal cinchotoxine diacetate.

If the catalysis is one which is monomolecular with respect to the catalyzer, then its specific reaction rate will be directly proportional to the concentration of the catalyzer, provided the reaction does not proceed at an appreciable rate when the catalyzer is absent. If, on the other hand, the reaction does proceed at a measurable rate even when none of the catalyzer is present, then the specific reaction rate will not be directly proportional to the concentration of the catalyzer but will be a linear function thereof, provided other conditions in the solution, such as the concentration of hydrogen ion, are the same.

Results of the Experiments.—The following tables summarize the results of all the experiments. Tables III and IV give the results of two experiments carried out by means of the gravimetric method above outlined. In column 1 is given the time in minutes from the beginning of the experiment, that is, from the time at which the cinchonine was introduced. Column 2 gives the concentration of cinchonine in mols per liter found by analysis; column 3 gives the value of K_1, calculated by equation (1); and column 4 the value of K_2, calculated by equation (2).

TABLE III.

Concentration of cinchonine diacetate	0.10 molal
Concentration of free acetic acid	3.0 molal
Temperature	99.6° (± 0.1° C.)

1. Time.	2. Concen. of cinchonine found.	3. K_1.	4. K_2.
0 min.	[0.1000]	...	...
10 "	0.0934	0.00298	0.00298
30 "	0.0868	0.00205	0.00158
50 "	0.0794	0.00200	0.00193
100 "	0.0644	0.00191	0.00183
160 "	0.0461	0.00209	0.00239
	Mean,	0.00221	0.00214

TABLE IV.

Concentration of cinchonine diacetate.................. 0.10 molal
Concentration of free acetic acid...................... 1.50 molal
Temperature.. 99.6° (± 0.1° C.)

1. Time.	2. Concen. of cinchonine found.	3. K_1.	4. K_2.
0 min.	[0.1000]	...	...
35 "	0.0908	0.00120	0.00120
55 "	0.0854	0.00124	0.00131
75 "	0.0793	0.00134	0.00163
185 "	0.0617	0.00113	0.00099
245 "	0.0499	0.00123	0.00154
	Mean,	0.00123	0.00135

Tables V, VI, VII, and VIII give the results of the experiments made with the aid of the polarimeter. In each case column 1 gives the time in minutes from the beginning of the experiment, column 2 the observed rotation in terms of the arbitrary readings of the instrument, column 3 the values of K_1[1] calculated by equation (3), and column 4 the values of K_2 calculated by equation (4).

TABLE V.

Concentration of cinchonine diacetate.................. 0.10 molal
Concentration of free acetic acid...................... 1.50 molal
Temperature.. 99.6° (± 0.1° C.)

1. Time.	2. Polarimeter readings.	3. K_1.	4. K_2.
19 min.	19.43	...	...
39 "	18.50	0.00120	0.00120
149 "	13.80	0.00131	0.00133
199 "	12.10	0.00133	0.00136
259 "	10.65	0.00132	0.00113
328 "	9.05	0.00132	0.00130
	Mean,	0.00130	0.00126

TABLE VI.

Concentration of cinchonine diacetate.................. 0.10 molal
Concentration of free acetic acid...................... 1.50 molal
Temperature.. 99.6° (± 0.1° C.)

1. Time.	2. Polarimeter readings.	3. K_1.	4. K_2.
22 min.	19.46	...	...
42 "	18.40	0.00136	0.00136
62 "	17.34	0.00142	0.00146
82 "	16.36	0.00142	0.00144
287 "	9.70	0.00135	0.00133
327 "	8.96	0.00132	0.00111
	Mean,	0.00137	0.00134

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[1] These values of K_1 are calculated from the time at which the first polarimeter reading was taken instead of from the time at which the alkaloid was introduced.

TABLE VII.

Concentration of cinchonine diacetate.................. 0.10 molal
Concentration of free acetic acid...................... 3.0 molal
Temperature.. 99.6° (± 0.1° C.)

1. Time.	2. Polarimeter readings.	3. K_1.	4. K_2.
15 min.	19.61	...	...
37 "	17.84	0.00219	0.00219
60 "	16.33	0.00208	0.00199
80 "	15.07	0.00209	0.00210
150 "	11.77	0.00200	0.00193
195 "	9.82	0.00208	0.00234
	Mean,	0.00209	0.00211

TABLE VIII.

Concentration of cinchonine diacetate.................. 0.10 molal
Concentration of free acetic acid...................... 3.0 molal
Temperature.. 99.6° (± 0.1° C.)

1. Time.	2. Polarimeter readings.	3. K_1.	4. K_2.
15 min.	19.80	....	....
35 "	18.12	0.00224	0.00224
55 "	16.80	0.00209	0.00195
75 "	15.58	0.00197	0.00197
95 "	12.03	0.00191	0.00248
	Mean,	0.00205	0.00216

An experiment was also performed to determin the effect of the addition of sodium acetate on the rate of the reaction. The sodium acetate was added in such amount as to reduce the concentration of hydrogen ion in the solution to about one-half its original value. Table IX gives the result of this experiment.

TABLE IX.

Concentration of cinchonine diacetate.................. 0.10 molal
Concentration of free acetic acid...................... 3.0 molal
Concentration of sodium acetate........................ 0.133 molal
Temperature.. 99.6° (± 0.1° C.)

1. Time.	2. Polarimeter readings.	3. K_1.	4. K_2.
42 min.	17.06	0.00214	0.00214
62 "	15.64	0.00219	0.00226
83 "	14.37	0.00218	0.00214
167 "	10.28	0.00221	0.00224
	Mean,	0.00218	0.00219

Discussion of the Results.—The values of the specific reaction rate K_1 or K_2 are fairly constant in all the experiments. The fact that these values show no systematic variation justifies the assumption that the reaction is of the first order with respect to the alkaloid salt, that is, that only one molecule of the alkaloid salt is involved in the reaction.

At the two concentrations of acetic acid which were investigated the ratio of the concentrations of hydrogen ion was approximately 2 to 1, and larger in the stronger solution. As hydrogen ion tends to retard this reaction its influence might come into consideration in the above cases even though the concentration of hydrogen ion is very small. This point was determined experimentally by the determination of the rate in the solution of 3.0 molal acetic acid containing 0.10 mols per liter of cinchonine diacetate and 0.133 mols per liter of sodium acetate, this amount being sufficient to reduce the concentration of hydrogen ion to approximately the value it had in the 1.5 molal acetic acid containing 0.10 mols of cinchonine diacetate per liter. (See Table IX.) The mean value of the constant determined in this last experiment is not markedly different from the constants determined without the addition of sodium acetate. The retarding effect, then, of the hydrogen ion at these small concentrations is very slight.

The average of all the values of K_2 determined in the solutions 1.5 molal with respect to free acetic acid is 0.00132; the average of the values of K_2 determined in the solutions 3.0 molal with respect to free acetic acid is 0.00215. So that the rate of the reaction is evidently not directly proportional to the concentration of free acetic acid in the solution, for if it were, the value of the constant at the higher concentration would be 0.00264. Nor is the rate proportional to the concentration of acetate ion, for in that case the constant determined with sodium acetate added to the solution would be considerably greater than the constant determined without this addition.

As has been previously mentioned, Biddle found that the rate of the reaction is some function of the undissociated acid in the solution, and if it be assumed that this function is a linear one, that is, that the specific reaction rate may be expressed by the equation

$$K = K' + Ac_1 \qquad (5)$$

where K is the specific reaction rate at the concentration, c_1, of free acetic acid, and K' and A are constants, then the two values of the specific reaction rate determined make it possible to calculate the values of the constants in the above equation. Such a calculation leads to the figures

$$K' = 0.00049 \quad A = 0.00055.$$

The value of K', that is, of the specific reaction rate for pure cinchonine diacetate with no excess of acetic acid has been determined experimentally and found to be 0.00041,[1] a figure in fairly good agreement with the one above

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[1] Private communication from unpublished paper of Mr. O. L. Brauer on the study of this catalysis.

given. Then the assumption made that the rate of catalysis is a linear function of the concentration of undissociated acid appears to be justified, and, as was pointed out previously, the significance of this fact is that the catalysis is monomolecular with respect to the undissociated acid present in the solution.

The rate of the reaction when the concentration of hydrogen ion in the solution is very small may then be represented by the differential equation

$$-d(c)/dt = \mathrm{K}(c)$$

where c is the concentration of cinchonine salt in the solution at any time. Or, substituting for K its value given in equation (5),

$$-d(c)/dt = (\mathrm{K}' + \mathrm{A}c_1)(c)$$

This equation is evidently not a complete expression for the kinetic law of the reaction, for it does not include the retarding effect of hydrogen ion. It does, however, indicate that the reaction of the conversion of cinchonine to cinchotoxine is made up of at least two reactions going on simultaneously; one of these reactions proceeding without the aid of a weak acid, and the other involving the weak acid. It is hoped that future work will make it possible to determin this law completely.

Summary.

1. The specific reaction rate for the change of cinchonine to cinchotoxine by the catalytic action of acetic acid in large excess has been determined for two concentrations of acetic acid.

2. The reaction has been found to be monomolecular with respect to the alkaloid, and the catalysis has been found to be monomolecular with respect to undissociated acetic acid.

3. It has been found that acetate ion has little or no effect on the speed of the reaction.

4. At low concentrations of hydrogen ion the retarding effect of this substance has been found to be very small.

BERKELEY, CAL.

[CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY.]

HYDRAZONES OF OXY-ALDEHYDES AND KETONES; ALKALI-INSOLUBLE NAPHTHOLS.[1]

BY H. A. TORREY AND C. M. BREWSTER.

Received January 21, 1913.

In an earlier paper of the series on phenols insoluble in alkalies, H. B. Kipper and one of us[2] pointed out that in the compounds they had studied

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[1] This research was suggested by the late Professor H. A. Torrey, and the experimental work was done under his direction, but the writing of the paper was deprived of the benefit of his supervision by his too early death.—C. L. JACKSON.

[2] THIS JOURNAL, 30, 841 (1908); see also *Ibid.*, 29, 77 (1907).