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A KINETIC STUDY OF SOME REACTIONS OF DIAZOACETIC ESTER IN BENZENE SOLUTION

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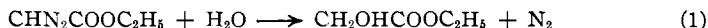
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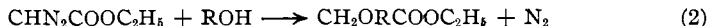
1. Introduction

In the extended theory of acid and basic catalysis¹ the effect of acids in accelerating chemical reactions is looked upon as due to a direct interaction between the molecules reacting and the molecule of the catalyzing acid. In a basic medium like water the catalysis produced by the addition of an acid A may be a compound effect of both A and the hydrogen ion "formed by dissociation." In non-basic media where no protolytic² reaction with acids is possible, acid catalysis ought to be of a simpler character.

With the purpose of broadening the foundation of the extended theory we have in the present investigations studied several reactions of diazoacetic ester in benzene solutions. The reaction of this substance with water in the presence of acids according to the equation

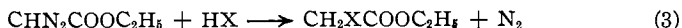


has long been known as an example of hydrogen-ion catalysis, and kinetic measurements of this reaction have been extensively used as a method for determining hydrogen-ion concentration in aqueous solutions. Provided that the solutions are so dilute that salt effects can be neglected, the velocity of reaction (1) is directly proportional to the concentration of "hydrogen ion," which in aqueous solutions is actually H_3O^+ . It has been shown³ that the reaction has a large linear salt effect. Similarly, when various alcohols are used as solvents, the velocity of the reaction



is determined by the concentration of the solvated hydron, though in these media, where the dielectric constant is much less than that of water, primary salt effects are much higher, and are of importance even at low concentrations.¹

In the presence of some acids, *e. g.*, the halogen acids and nitric acid, a side reaction takes place.⁴



The velocity of this reaction is in aqueous solution proportional to the concentrations of both the hydrogen ion and the anion of the acid. Ex-

¹ Brönsted, "Acid and Basic Catalysis," p. 250.

² Brönsted, *Z. angew. Chem.*, **43**, 229 (1930).

³ Brönsted and Duus, *Z. physik. Chem.*, **117**, 299 (1925).

⁴ Bredig and Ripley, *Ber.*, **40**, 4015 (1907).

amination of the data of Bredig and Ripley⁴ and those of Lachs⁵ shows that the salt effect is in this case "exponential" in type, as would be expected for a reaction involving two charged molecules⁶ and that also numerically there is a fair agreement with the theoretical formula for such a reaction.

Thus in water and the alcohols it appears that acid catalysis in the general sense⁷ is at the most very small compared with catalysis by the solvated hydron. Hantzsch⁸ has found an increase of catalytic activity with increasing concentration for the halogen acids in aqueous solution, which he attributes to catalysis by the undissociated molecules. However, in drawing this conclusion, no account has been taken of the fact that the change of acid concentration causes a very considerable change of medium. In fact, if the primary salt effect found at low concentrations³ is assumed to be linear up to the high acid concentrations used by Hantzsch, it is sufficient to account approximately for the increase of catalytic power observed. Furthermore, the reaction of diazoacetic ester with the halogen acids is complex (see equations (1) and (3) above) and the hypothesis of Hantzsch, that the initial stage in the reaction with acid determining the velocity of the reaction is the same in each case, is a pure assumption. Snethlage⁹ considers that his results in ethyl alcohol solution show catalysis by the undissociated picric acid molecule, but this view has been shown to be inconclusive owing to the presence of an unknown, but probably large, secondary salt effect.¹

In aprotic solvents, unable to solvate the free hydrogen ion, acids will not be ionized, and any phenomena of acid catalysis observed must be attributed to acid molecules in general. It is in fact well known that many organic reactions are powerfully catalyzed by solutions of acids in "inert" solvents.¹⁰ The rearrangement of diazoamino compounds in basic solvents, which has been studied extensively by Goldschmidt¹¹ and his co-workers, probably constitutes an example of general acid catalysis, though it is possible to attribute at least a part of the catalysis to ions such as $C_6H_5-NH_3^+$, which in these solvents are nothing more than solvated hydriions. In the case of diazoacetic ester, there will not in general be any possibility

⁵ Lachs, *Z. physik. Chem.*, **73**, 291 (1910).

⁶ Brønsted, "Acid and Basic Catalysis," Chap. IV; *Z. physik. Chem.*, **102**, 169 (1922); **115**, 337 (1925).

⁷ Brønsted, "Acid and Basic Catalysis," Chap. VIII.

⁸ Hantzsch, *Z. physik. Chem.*, **125**, 251 (1927); *Ber.*, **58**, 612 (1925).

⁹ Snethlage, *Z. physik. Chem.*, **85**, 211 (1913).

¹⁰ For example, see Lowry and Magson, *J. Chem. Soc.*, **93**, 117 (1908); Lapworth, *ibid.*, **85**, 30 (1904); Blanksma, *Rec. trav. chim.*, **21**, 366 (1902); **22**, 290 (1903).

¹¹ Goldschmidt and Reinders, *Ber.*, **29**, 1469, 1899 (1896); Goldschmidt, Johnsen and Overwien, *Z. physik. Chem.*, **110**, 251 (1924); Goldschmidt and Overwien, *ibid.*, [A] **134**, 354 (1929); Goldschmidt, *Z. Elektrochem.*, **36**, 662 (1930).

of reaction with the solvent itself in such a case, but it is possible to study the reaction of the ester with the acid added, or with a third substance. Such a study is of interest from two main points of view: (a) the catalytic properties of acid molecules in inert solvents, and (b) the molecular state of carboxylic acids in such solvents.

The only previous work on the kinetics of reactions with diazoacetic ester in non-dissociating solvents is that of Hantzsch¹² with a variety of acids and solvents. These investigations, however, are not of such a character as to permit of any conclusion regarding the nature or mechanism of the reaction. Hantzsch considers that the reactivity of any acid toward diazoacetic ester is a measure of its "strength," but as has been pointed out by v. Halban¹³ this is not allowable, since we are considering a different chemical reaction in each case, and not the same reaction catalyzed by different acids. Even admitting Hantzsch's unproved and improbable assumption that the first step, and that which determines the velocity, is the formation of a diazonium salt, it would not justify the relation proposed between reaction velocity and acid strength in any ordinary sense of this word.

The present investigation deals exclusively with benzene solutions. The reaction of diazoacetic ester has been studied with the following acids: monochloroacetic, dichloroacetic, iodoacetic, nitroacetic, formic, α -bromopropionic, α,β -dibromopropionic and picric.

Measurements have also been made for acid mixtures, and for the rate of reaction of diazoacetic ester with phenol, catalyzed by these acids.

2. Materials

Unless otherwise stated, the products used were of "zur Analyse" grade from Merck or Kahlbaum.

Benzene was allowed to stand for periods ranging from two weeks to several months over phosphorus pentoxide, and was finally refluxed and distilled over fresh phosphorus pentoxide in an all-glass apparatus. It was stored in a container protected by mercury seals and phosphorus pentoxide tubes, and when making up a solution only dried air came in contact with the solution and the stock of benzene. All solutions when made were kept in a desiccator.

Monochloroacetic acid was recrystallized from pure benzene, and dried in vacuo over sulfuric acid.

Dichloroacetic acid was redistilled, and the fraction boiling at 191–192.5° was used.

α,β -Dibromopropionic acid was recrystallized from ligroin, and dried in vacuo over sulfuric acid.

α -Bromopropionic acid was purified by partial freezing, and dried in vacuo over sulfuric acid.

¹² Hantzsch, *Z. Elektrochem.*, **24**, 201 (1918); **29**, 221 (1923); **30**, 194 (1926); *Z. physik. Chem.*, **125**, 251 (1927).

¹³ V. Halban, *Z. Elektrochem.*, **29**, 434 (1923).

Iodoacetic acid was prepared by the method of Abderhalden and Guggenheim.¹⁴ It was recrystallized from a mixture of one volume of benzene and six volumes of ligroin, and dried in vacuo over sulfuric acid. The acid and its solutions were kept in the dark.

Nitroacetic acid was prepared according to the directions given by Steinkopf¹⁵ and Pedersen.¹⁶ It was recrystallized from chloroform. Only freshly made samples were used.

Formic and picric acids were used without further purification.

Phenol was dried in vacuo over sulfuric acid and kept in the dark.

A test of the purity of the acids was afforded by titration of the stock solutions, which were prepared from weighed amounts of acid. The figures thus obtained corresponded to a purity of 99% or better.

Diazoacetic ester was prepared from a 20% alcoholic solution. The alcohol was removed by standing in a vacuum desiccator over sulfuric acid until the weight had fallen to 5% of its original value. The purity of the product thus obtained was tested by measuring the volume of nitrogen evolved when a weighed amount of the ester reacted in a *N*/20 aqueous solution of perchloric acid. The values obtained for various samples ranged between 97.8 and 99.1% purity. A further check on the purity, which also served as a test of the simple nature of the reaction between diazoacetic ester and monochloroacetic acid, was as follows. A weighed amount of ester was allowed to react with a known excess of monochloroacetic acid in benzene at room temperature. After standing for some weeks (it being known from kinetic measurements that this period corresponded to practically complete reaction), the solution was poured into water and the residual monochloroacetic acid immediately titrated with alkali. The values obtained for the amount of acid which had reacted were 95-98% of the values calculated from the weight of ester taken.

The ester was not kept as such, but was immediately dissolved in pure benzene to give a stock solution about *N*/10 volume normally. These solutions were perfectly stable over long periods, as was shown by the fact that the volume of nitrogen obtained from a given amount of solution remained appreciably constant for at least several months.

3. Measurements

The reactions were followed by measuring the pressure of the nitrogen evolved in a closed system. The apparatus used is shown in Fig. 1. The reacting solution (volume 20 cc.) was contained in the flask A (volume 40 cc.) which was in a thermostat at $15 \pm 0.01^\circ$. The flask was shaken to and fro mechanically with an amplitude of about 2 cm., and the rate of shaking was maintained constant by a centrifugal regulator. It was connected by the flexible glass tubing B to the mercury manometer C. The reaction flask was closed by an unlubricated ground cap D, sealed with mercury, and the vacuum side of the manometer by a mercury seal E. At F was a porous plug of gypsum, as described by Prytz.¹⁷ The tube G served to introduce mercury into the manometer, and was afterward sealed off.

The method of carrying out an experiment was as follows. The required

¹⁴ Abderhalden and Guggenheim, *Ber.*, **41**, 2853 (1908).

¹⁵ Steinkopf, *ibid.*, **42**, 3925 (1909).

¹⁶ Pedersen, *Trans. Faraday Soc.*, **23**, 316 (1927).

¹⁷ Prytz, *Det. kgl. danske Videnskab. Selskab. Forh.*, 293 (1904).

acid solution was introduced into A by means of pipets protected by calcium chloride tubes, standard solutions of known strength being employed. The diazoacetic ester solution was introduced by a small pipet, D immediately closed, the shaking started, and the apparatus evacuated through H for two to four minutes with a good water suction pump, the taps J and K being open. (On account of the high vapor pressure of benzene, the use of a better pump is unnecessary at this stage.) J and K were then closed and the mercury caused to rise in the manometer by introducing a little air through F. This was effected by pushing a small plug of cotton wool (which contains sufficient air entangled) through the mercury above F, and pressing it upon the upper surface of the gypsum. J and K were then opened, and the right-hand side of the manometer evacuated with a Cenco Hyvac oil-pump. Finally, J was closed and mercury allowed to rise in the seal E by admitting a little air through K.

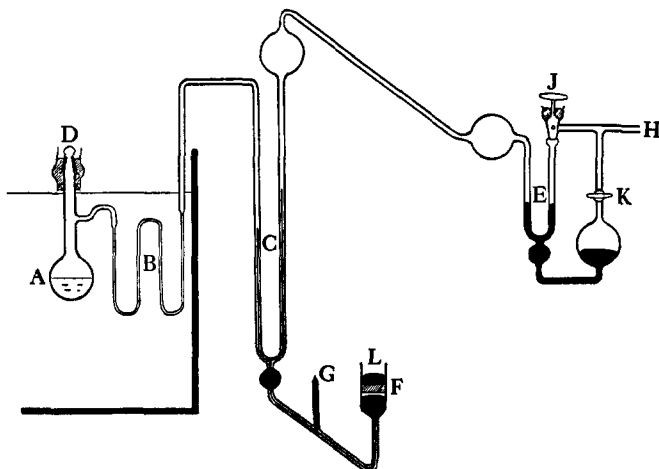


Fig. 1.

The apparatuses were mounted in pairs on a common shaking mechanism. The pressure was measured at intervals by reading the heights in the two manometer limbs, correct to 0.01 cm., using small lenses. The total pressure change for the reaction of 0.0002 gram molecule of ester was about 48 mm. of mercury.

The chief possibility of a systematic error in the results lies in the presence of dissolved gases in the benzene solutions which are probably not completely removed by the short period of evacuation employed. This probably accounts for an occasional irregularity observed in the first few readings, but a steady state appeared to be rapidly reached. A longer period of evacuation is inadvisable, owing to the possibility of appreciable alteration in the concentration of the solutions by the evaporation of

benzene. The mutual concordance of the results obtained with periods of evacuation varying from two to four minutes shows that no appreciable error from this source is present. Since the vapor pressure of benzene at 15° changes by about 3 mm. for 1° temperature change, temperature fluctuations of more than 0.03° will affect the manometer reading. A control of $\pm 0.01^\circ$ is therefore adequate.

4. Calculation of Velocity Constants

All concentrations are expressed as gram formula weights per liter of solution at 15°. The concentration of ester present in most experiments was 0.0075–0.011 *N*. In a few experiments with acid concentrations less than 0.1 *N*, the ester concentration was about 0.005 *N*, and in the experiments with the two most dilute solutions of dichloroacetic acid, about 0.0025 *N*. Thus the ester concentration was in no case more than 8% of that of the other reactant, and in most cases considerably less, so that the course of an experiment may be expected to follow fairly closely the monomolecular law. This was in fact found to be the case, and all velocity constants given have been calculated by the method of Guggenheim.¹⁸ In three experiments with monochloroacetic acid, an end-point was measured experimentally and used to calculate the constants in the usual manner. The same values were obtained as by Guggenheim's method. The number of readings taken in one experiment was 40–60. In calculating the constant decadic logarithms were used, *i. e.*, the constants given in the tables are'

$$k_1 = \frac{d \log_{10} c}{dt}$$

the unit of time being the minute.

5. Results for Carboxylic Acids

The acids which were studied over a large range of concentrations were monochloroacetic, dichloroacetic, α,β -dibromopropionic and α -bromopropionic. Most experiments employed benzene purified as described above, but a few, marked *, were made with Merck's benzene "zur Analyse," which had not been further treated. No difference was detectable between the two sets of results.

Since the concentration of acid never changed by more than 8% during the course of the experiment, and usually by much less, we have taken the monomolecular velocity constant (k_1) to refer to the mean of the initial and final concentrations of acid (c).

It is at once obvious from the figures that in no case is the reaction velocity even approximately proportional to the concentration of acid. As may be seen from Figs. 2 and 3, the velocity in the range of concentrations considered is more nearly proportional to the square of the concentra-

¹⁸ Guggenheim, *Phil. Mag.*, [2] 7, 538 (1926).

TABLE II
 EXPERIMENTAL DATA

	α	β
Monochloroacetic	1.20×10^{-2}	4.5×10^{-4}
α, β -Dibromopropionic	2.35×10^{-2}	5.2×10^{-3}
α -Bromopropionic	1.58×10^{-3}	1.75×10^{-4}
Dichloroacetic	3.34	8.4×10^{-2}

action velocity of amylenes with various carboxylic acids in both amylenes and benzene solutions is also proportional to the square of the acid concentration. They explain this relation by assuming that the velocity is proportional to the concentration of double molecules, which are in equilibrium with a much greater concentration of single molecules. It is doubtful whether this view is correct for amylenes solutions and it is certainly untenable both for the benzene solutions employed by Nernst and Hohmann, and for those studied in the present work, since cryoscopic molecular weight determinations show the acids to be present almost entirely as double molecules at the concentrations concerned.²⁰ We must therefore conclude that the reaction with diazoacetic ester (and probably also with amylenes) is kinetically of the second order with respect to the double molecules, which may thus be said to catalyze their own reaction. This conception is further supported by the results given later for the reaction of mixtures of acids.

Goldschmidt has previously found²¹ that the reaction of carboxylic acids with aniline to give anilides in aniline solution is of the second order with respect to the acid, and has termed these reactions "autocatalytic." In the case of aniline as a solvent the state of affairs may be more complex than in benzene solutions, owing to the formation of the anilinium ion,

²⁰ See, e. g., Tollens, *Ber.*, **48**, 489 (1915); Celincev and Kozlov, *J. Russ. Phys.-Chem. Soc.* [Sect. chim.], **46**, 718 (1916); Walden, *Bl. Acad. Petrograd.*, **6**, Ser. 8, 1161 (1914); Rabinowitsch, *Z. physik. Chem.*, **132**, 83 (1928).

²¹ Goldschmidt and Wachs, *ibid.*, **24**, 353 (1898); Goldschmidt and Bräuer, *Ber.*, **39**, 97 (1906).

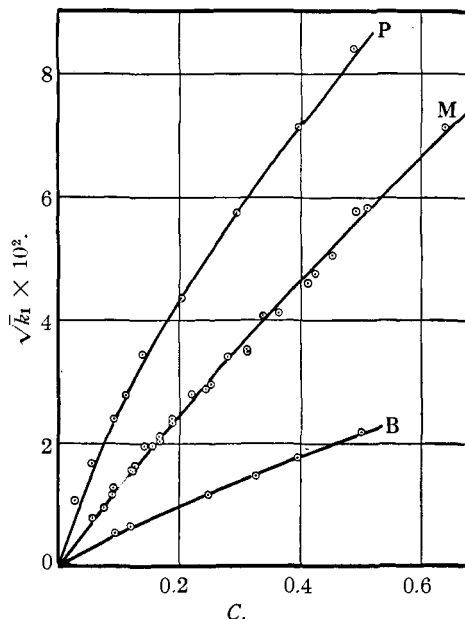


Fig. 2.—B, α -bromopropionic acid; M, monochloroacetic acid; P, α, β -dibromopropionic acid.

which may have catalytic properties. The same applies to the self-esterification of di- and trichloroacetic acids in alcohol solution, which has also been found by Goldschmidt²² to be a second order reaction, though in this case it seems probable that the catalytic agent is the acid molecule itself, since the addition of di- and trichloroacetates causes but little diminution in catalytic power.

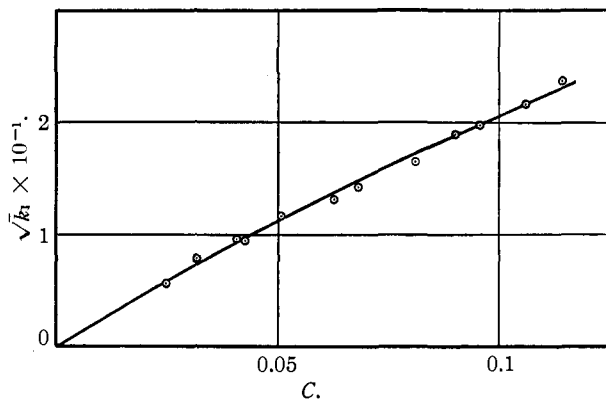


Fig. 3.—Dichloroacetic acid.

If the partial conversion of double molecules into single molecules leads to an increase in reaction velocity, we have a qualitative explanation of the form of equation (4), though it is impossible at present to give a fully quantitative interpretation. In the presence of two species of acid molecules there are theoretically four possible catalytic reactions, two of which are practically indistinguishable. On this basis of classical kinetics we should expect the total velocity to be given by an equation of the type

$$k_1 = a_1[(HA)_2]^2 + a_2[HA]^2 + a_3[\bar{HA}][(HA)_2] \quad (5)$$

where a_1 , a_2 and a_3 are constants. For small concentrations of such molecules and values of a_1 , a_2 and a_3 of the same order of magnitude the member containing a_2 would tend to vanish. The experimental accuracy is however not sufficient to make the equation thus appearing distinguishable from equation (4). It is possible that the lack of agreement with equation (4) shown by the two most dilute solutions of α, β -dibromopropionic acid is due to the fact that a considerable fraction of the acid is present as single molecules. (Cryoscopic measurements show²⁰ that this acid is much less completely associated than monochloroacetic acid at the same concentrations.)

If the equilibrium between double and single molecules can be expressed by the simple mass law equation

$$\frac{[HA]^2}{[(HA)_2]} = K \quad (6)$$

²² Goldschmidt, *Ber.*, **29**, 2212 (1896); *Z. Elektrochem.*, **15**, 4 (1909); cf. also Michael and Wolgast, *Ber.*, **42**, 3161 (1909); Kailan, *Monatsh.*, **29**, 805 (1908).

we have for nearly complete association

$$[\text{HA}] = \sqrt{\frac{Kc}{2}} \quad [(\text{HA})_2] = \frac{c}{2}$$

and equation (6) becomes

$$k_1 = \frac{a_1}{4} c^2 + \frac{a_2}{2} Kc + \frac{a_3}{2} \sqrt{\frac{K}{2}} c^{3/2} \quad (7)$$

What evidence there is, however, goes to show that equation (6) does not hold for carboxylic acids in inert solvents: in other words that the mass action law is not strictly applicable for such solutions. Previous attempts to calculate an association "constant" have not been successful²³ and calculations on the basis of the cryoscopic data of Peterson and Rodebush²⁴ for very dilute benzene solutions of acetic acid give no constant value for K in equation (7). The results of partition experiments are often quoted as evidence for a simple mass law equilibrium between single and double molecules but it has been found by Szyszkowski²⁵ that the presence of hydrated molecules invalidates the usual treatment of these results, and it has been recently shown²⁶ that Szyszkowski's method of correcting this treatment is based on false assumptions.

There is, however, nothing very surprising in the failure of such solutions to obey the gas laws. It seems to be the general view that such deviations are principally confined to ionic solutions, where they are caused by interionic forces. It is necessary, however, also to take into consideration the interaction of dipole fields, which in solvents of low dielectric constant are considerable and can lead to departures from simple behavior in just the same manner as interionic forces. In the case of a dipole gas, the magnitude of this effect has been evaluated quantitatively by Falkenhagen²⁷ and shown to agree with experiment for several gases. In benzene solution one would expect the double molecule to be more "normal" than the single molecule and thus the constant K to increase with increasing dilution. Recent work of Briegleb,²⁸ however, seems to show that not only the single carboxylic acid molecules, but also the double ones, have fairly large dipole moments, which introduces some uncertainty in the above conclusion.

Side by side with this departure from simple thermodynamic behavior, we must also anticipate a kinetic "dipole effect" (analogously to kinetic salt effect), so that the constants a_1 , a_2 and a_3 of equation (6) are probably not strictly constant over a large range of concentrations. An example

²³ Trautz and Moschel, *Z. anorg. Chem.*, **155**, 13 (1926); Brown and Bury, *J. Phys. Chem.*, **30**, 694 (1926).

²⁴ Peterson and Rodebush, *ibid.*, **30**, 694 (1926).

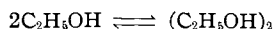
²⁵ Szyszkowski, *Z. phys. Chem.*, **131**, 180 (1927).

²⁶ Bell, *ibid.*, [A] **150**, 20 (1930).

²⁷ Falkenhagen, *Physik. Z.*, **23**, 887 (1922).

²⁸ Briegleb, *Z. physik. Chem.*, [B] **10**, 205 (1930).

of this type of effect is afforded by the results of Bugarsky²⁹ on the velocity of the reaction between alcohol and bromine in inert solvents. Bugarsky interprets the abnormalities observed by assuming an equilibrium between double and single alcohol molecules governed by the mass, only the double molecules reacting with bromine. Apart from the improbability of the last assumption, cryoscopic measurements show that the activity coefficient of alcohol in inert solvents changes in a manner which cannot be explained by the simple equilibrium



and it seems more reasonable to consider such solutions as containing only single molecules, which show an abnormal thermodynamic behavior owing to the strong inter-dipole forces. Bugarsky's results then appear as a consequence of the corresponding kinetic abnormality of these molecules.

These considerations of deviations from simple behavior leave unaffected the main conclusions, *i. e.*, (a) that the reaction is mainly a second order reaction involving two double molecules, and (b) that the values of α in equation (4) and Table II represent at least approximately the specific reaction velocities of the double molecules.

It may be noted that the values of α increase in the same order as the electrolytic dissociation constants in water.

6. Results for Picric Acid

These results are given separately in Table III, since they differ fundamentally from those for the carboxylic acids.

TABLE III
RESULTS FOR PICRIC ACID

c	0.068	0.083	0.104	0.136
$k_1 \times 10^6$	2.93	3.68	5.33	6.60

Owing to the limited solubility of picric acid, it was not possible to study more concentrated solutions. The results are plotted in Fig. 4, from which it is seen that the reaction velocity is directly proportional to the concentration, not to its square. Picric acid also differs from the carboxylic acids in not forming double molecules, but it is strange that such a strong acid should not show "self-catalysis," particularly as it will be shown later that it is capable of catalyzing the reactions of monochloroacetic acid and of phenol with the ester. It is of course possible that a catalyzed reaction is present with picric acid alone, but is obscured by a faster non-catalyzed reaction.

7. Results for Mixtures of Acids

If two different acids are present together in the same solution, we have the added possibility of what one may term a cross-catalysis, *i. e.*, that each

²⁹ Bugarsky, *Z. physik. Chem.*, 71, 705 (1910).

acid may catalyze the reaction of the other. Thus if the molecules of each acid remain unchanged by mixing, we should expect a total reaction velocity greater than the sum of velocities for the two acids when present separately at the same concentrations. Actually we must anticipate, in the case of the carboxylic acids, the formation of a new species of complex double molecules (cf. Szyszkowski's results on the solubility of mixtures of acids in benzene).²⁵ Since the number of possible catalytic reactions is thus still further increased, this will in general give rise to a further increase of reaction velocity, though it may in some cases give a decrease if the two acids concerned have very widely differing reactivities, but are present in comparable amounts.

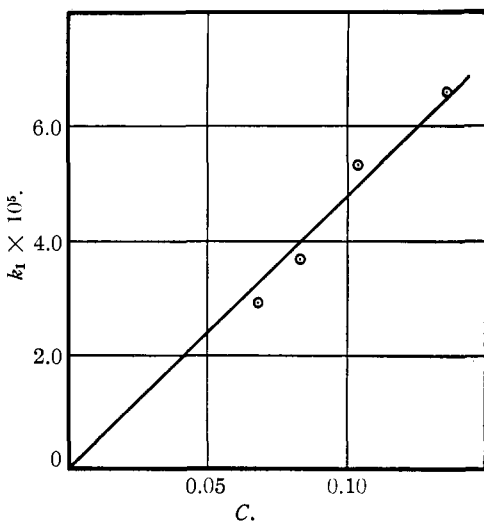


Fig. 4.—Picric acid.

The experimental results for acid mixtures are given in Table IV. As for single acids, the concentrations given are the mean of the initial and final concentrations, the latter differing at the most by a few per cent.

TABLE IV

c_A, c_B = concentrations of the two acids
 k_1 = observed velocity constant for the mixture
 k_A, k_B = velocity constants for the two acids when present singly at concentrations c_A and c_B , calculated from equation (4) and Table II.

$$p = k_1 - k_A - k_B$$

$$n = 100 p / (k_A + k_B)$$

(a) Dichloroacetic acid (A) + monochloroacetic acid (B)

c_A	c_B	$k_1 \times 10^3$	$k_A \times 10^3$	$k_B \times 10^3$	$p \times 10^3$	n
0.0407	0.114	7.13	8.46	0.21	-1.44	-16.6
.0411	.190	7.48	8.63	.54	-1.69	-18.5
.0409	.337	7.92	8.57	1.56	-2.21	-21.9

(b) α, β -Dibromopropionic acid (A) + α -bromopropionic acid (B)

c_A	c_B	$k_1 \times 10^3$	$k_A \times 10^3$	$k_B \times 10^3$	$p \times 10^3$	n
0.151	0.203	0.1315	0.1220	0.0100	-0.5	≈ 0.0
.151	.320	.1362	.1220	.0218	-7.6	-5.3

(c) Dichloroacetic acid (A) + α, β -dibromopropionic acid (B)

c_A	c_B	$k_1 \times 10^3$	$k_A \times 10^3$	$k_B \times 10^3$	$p \times 10^3$	n
0.0418	0.289	12.6	8.88	4.70	-0.94	-6.9
.0412	.155	9.28	9.03	1.25	-1.00	-9.7

TABLE IV (Concluded)

(d) α,β -Dibromopropionic acid (A) + monochloroacetic acid (B)							
c_A	c_B	c_{ACB}	$k_1 \times 10^3$	$k_A \times 10^3$	$k_B \times 10^3$	$p \times 10^3$	n
0.0457	0.240	0.0110	1.32	0.189	0.850	0.284	27.3
.0925	.240	.0222	2.11	0.566	.850	.699	49.5
.153	.241	.0369	2.96	1.25	.858	.852	39.0
.229	.151	.0347	3.45	2.24	.360	.850	32.6
(e) Dichloroacetic acid (A) + α -bromopropionic acid (B)							
c_A	c_B	$k_1 \times 10^3$	$k_A \times 10^3$	$k_B \times 10^3$	$p \times 10^3$	n	
0.0409	0.00973	8.14	8.99	0.00	-0.85	-9.5	
.0409	.0195	6.66	8.99	.01	-2.24	-24.8	
.0409	.0389	6.18	8.99	.02	-2.83	-31.4	
.0409	.0973	4.68	8.99	.04	-4.35	-48.1	
.0409	.176	4.81	8.99	.08	-4.26	-47.1	
.0409	.353	4.58	8.99	.26	-4.67	-50.4	
(f) Monochloroacetic acid (A) + α -bromopropionic acid (B)							
c_A	c_B	c_{ACB}	$k_1 \times 10^4$	$k_A \times 10^4$	$k_B \times 10^4$	$p \times 10^4$	n
0.243	0.0931	0.0226	9.65	8.13	0.30	1.22	14.7
.243	.142	.0345	10.4	8.13	0.57	1.73	19.9
.243	.246	.0598	12.5	8.13	1.39	3.03	31.8
.243	.352	.0855	15.9	8.13	2.58	5.21	48.7
(g) Monochloroacetic acid (A) + picric acid (B)							
c_A	c_B	c_{ACB}	$k_1 \times 10^4$	$k_A \times 10^4$	$k_B \times 10^4$	$p \times 10^4$	
0.169	0.0331	0.0056	5.18	4.19	0.16	0.83	
.169	.0510	.0086	5.73	4.19	.24	1.30	
.169	.0795	.0134	6.80	4.19	.38	2.23	
.169	.0980	.0166	7.20	4.19	.47	2.54	
.169	.112	.0190	8.44	4.19	.53	3.72	
.298	.0220	.00652	13.52	11.96	.16	1.46	
.298	.0379	.0113	14.10	11.96	.18	1.96	
.298	.0604	.0180	15.56	11.96	.29	3.31	
.298	.0696	.0207	15.66	11.96	.33	3.37	
.298	.0950	.0284	17.38	11.96	.45	4.97	

For the three acid pairs (d), (f) and (g) an increase of velocity is found, and it is seen from Figs. 5 and 6 that this increase is roughly proportional to the product of the acid concentrations, as would be expected if the effects of cross-association can be neglected. For the acid pairs (a) and (e) the effect is a reduction. For this last pair, dichloroacetic and α -bromopropionic acids, the dichloroacetic acid concentration was the same in each experiment, and in Fig. 7 the percentage reduction is plotted against the concentration of α -bromopropionic acid. It is seen that at high concentrations the reduction tends to a constant value. Since the velocity attributable to the reaction of the α -bromopropionic acid is only a small fraction of the total velocity, this constant value can be interpreted as corresponding to a total conversion of dichloroacetic acid molecules into

complex double molecules. For the acid pairs (b) and (c), the effect observed is small, and is probably compounded of both the above influences.

8. Acid Catalysis in the Reaction of Alcohol and Phenol

When the two acids react simultaneously with diazoacetic ester, it is impossible from measurements of the nitrogen evolved to deduce the velocities of the separate reactions involved. Such measurements cannot therefore be used to compare the catalytic activities of different acids for the same reaction. This may however be possible if we can find a suitable substance of low acidity whose reaction with the ester is catalyzed by acids. The catalyzing acid will itself react simultaneously but this can be corrected for on the assumption that its reaction velocity is unaffected by the presence of the second substance.

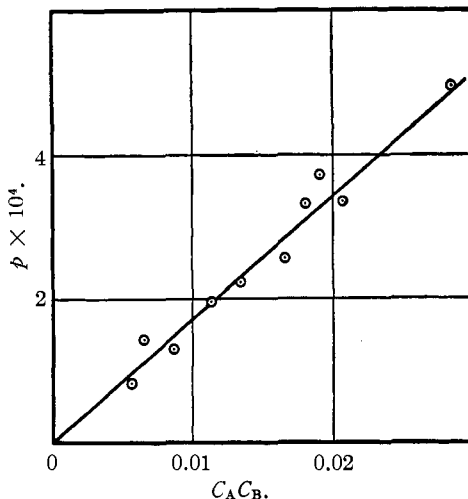
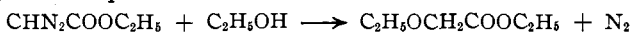


Fig. 5.—Monochloroacetic + picric acids.

The first substance tried was ethyl alcohol, which is known to react according to the equation



which reaction is catalyzed by solvated hydrogen ions in aqueous and alcoholic solutions. Experiments in benzene solution with mixtures of mono-

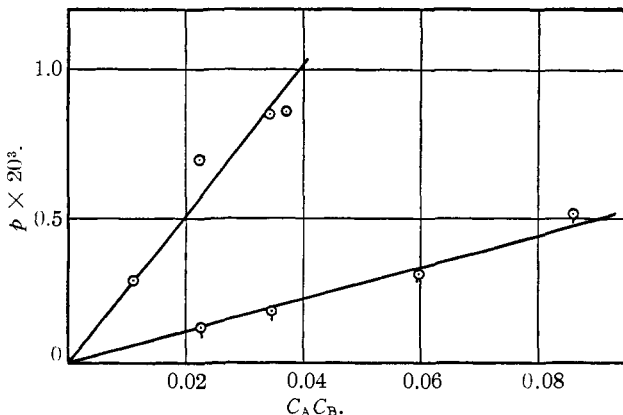


Fig. 6.—○, α, β -Dibromopropionic + monochloroacetic acids;
 ◻, monochloroacetic + α -bromopropionic acids.

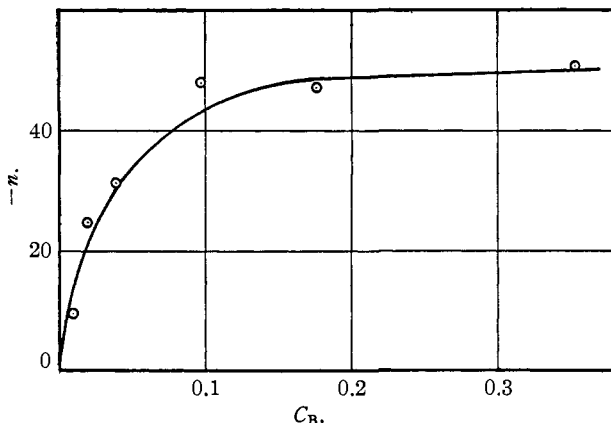
chloroacetic acid and alcohol showed, however, that alcohol caused a very large decrease in velocity instead of the expected increase. The figures given in Table V were obtained.

TABLE V

c_1 = concentration of monochloroacetic acid; c_2 = concentration of alcohol

c_1	0.220	0.220	0.220
c_2	0	0.685	1.10
$k_1 \times 10^5$	67.0	2.6	1.3

There is thus present some complicating effect, possibly due to association of the alcohol and acid molecules.

Fig. 7.—Dichloroacetic + α -bromopropionic acids.

A few experiments were also carried out to test whether the presence of small quantities of water would have any appreciable effect on the results obtained (Table VI).

TABLE VI

c_1 = concentration of acid; c_2 = concentration of water; k_1' = velocity constant in absence of water

Monochloroacetic Acid			
c_1	c_2	$k_1 \times 10^4$	$k_1' \times 10^4$
0.141	0.043	3.92	3.03
.184	.056	5.70	5.50
Dichloroacetic Acid			
c_1	c_2	$k_1 \times 10^4$	$k_1' \times 10^4$
0.0524	0.043	95.4	135

It is seen that the effect is sometimes positive and sometimes negative, but that it is small enough to exclude any uncertainty in the experimental results due to the presence of traces of water.

With benzene solutions of picric acid, however, the addition of alcohol gives rise to an increase in velocity, which must be attributed to the re-

action of alcohol with the ester. The results are given in Table VII, the concentrations being as usual the mean of the initial and final values.

TABLE VII

c_A = concentration of picric acid; c_B = concentration of alcohol; k_1 = observed velocity constant; k_A = velocity constant for picric acid alone; $p = k_1 - k_A$

c_A	c_B	$k_1 \times 10^4$	$k_A \times 10^4$	$p \times 10^4$	$c_A c_B$
0.0495	0.685	1.94	0.24	1.70	0.0344
.070	.685	2.70	.33	2.37	.0480
.105	.685	3.80	.50	3.30	.0719
.140	.685	5.60	.67	4.93	.0960
.140	1.03	8.40	.67	7.73	.144

It is seen from Fig. 8 that p is directly proportional to $c_A c_B$, which is what we should expect for the catalyzed reaction of the alcohol. A single experiment with picric acid + butyl alcohol gave an increase almost identical with that for ethyl alcohol.

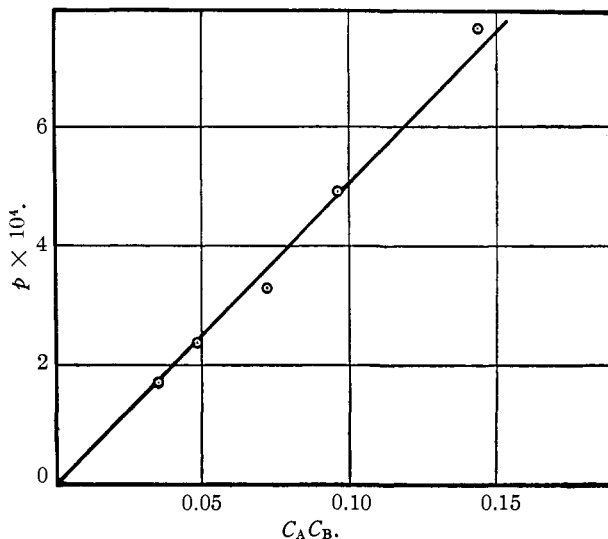
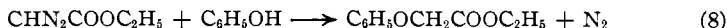
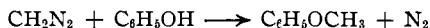


Fig. 8.—Picric acid + ethyl alcohol.

The addition of phenol was next tried, and was found to give an increase of velocity with all the acids studied. This increase we attribute to the reaction



catalyzed by the acid present. We have not been able to find any reference to the formation of phenoxyacetic ethyl ester by this reaction, but the corresponding reaction of diazomethane



takes place readily. Since phenoxyacetic ester is a liquid boiling at 250° , and will be accompanied by the products of reaction of the acid itself (which are not reported in Beilstein, but which probably have similar

boiling points), we have not attempted to isolate the products of reaction. The chief evidence that the increase of velocity is due to reaction (8) is afforded by the kinetic measurements themselves.

Preliminary experiments showed that phenol alone gave no measurable reaction with diazoacetic ester in benzene solution. The most extensive experiments were carried out with monochloroacetic acid, and are given in Table VIII. The concentrations of both phenol and acid are the mean of initial and final concentrations differing by, at the most, a few per cent.

TABLE VIII

c_A = concentration of acid; c_B = concentration of phenol; k_1 = observed velocity constant; k_A = calculated velocity constant for acid alone; $p = k_1 - k_A$

Monochloroacetic Acid (A) + Phenol (B)					
c_A	c_B	$k_1 \times 10^4$	$k_A \times 10^4$	$p \times 10^4$	$c_A c_B$
0.216	0.085	7.90	6.57	1.33	0.0184
.0778	.426	2.02	0.96	1.06	.0331
.0930	.426	3.02	1.46	1.56	.0396
.217	.256	9.50	6.60	2.90	.0555
.155	.426	6.21	3.46	2.75	.0660
.217	.426	10.90	6.70	4.20	.0924
.218	.597	12.90	6.63	6.27	.130
.312	.426	19.65	12.76	6.89	.133

It is seen from Fig. 9 that the velocity of the catalyzed reaction can be represented by the equation

$$p = l c_A c_B \quad (9)$$

where "l" is a constant. For the same reasons as those given in section

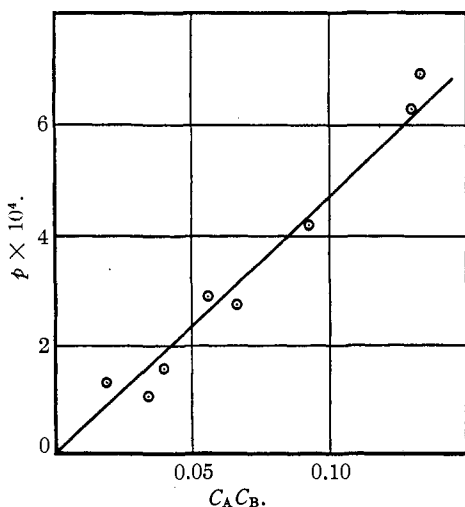


Fig. 9.—Monochloroacetic acid + phenol.

(5), we must conclude that "l" is at least approximately the catalytic constant for the double monochloroacetic molecule. "Medium effects" and effects due to the presence of single molecules cannot be detected within the limits of accuracy obtained. A single experiment with *o*-chlorophenol + monochloroacetic acid gave a value of p only slightly greater than with phenol.

We have not tested equation (9) extensively for any other acids, but have preferred to carry out a few experiments for a number of different acids, and to calculate the values of "l" assuming equation (9) to hold. Even if the

values so obtained are only provisional, a comparison for acids of widely varying strength is of great interest. Table IX contains such results, the notation being the same as that employed in Table VIII.

For α,β -dibromopropionic acid the values of k_A are obtained from the curve in Fig. 2. For iodoacetic and formic acids these values were obtained by carrying out an experiment without phenol. For these two acids approximate values have been calculated for the specific reaction velocities of the double molecules α by assuming that

$$k_A = \alpha c_A^2 \quad (10)$$

TABLE IX

Iodoacetic Acid (A) + Phenol (B)					
c_A	c_B	$k_1 \times 10^5$	$k_A \times 10^5$	$p \times 10^5$	$c_A c_B$
0.173	0.256	12.20	5.9	6.30	0.0444
.173	.426	14.7	5.9	8.8	.0737
.181	.426	21.3	6.5	14.8	.0772
		$\alpha = 2.0 \times 10^{-3}$	$l = 1.4 \times 10^{-3}$		
Formic Acid (A) + Phenol (B)					
c_A	c_B	$k_1 \times 10^5$	$k_A \times 10^5$	$p \times 10^5$	$c_A c_B$
0.208	0.426	15.8	3.20	13.6	0.089
.240	.426	18.9	4.12	17.8	.102
.259	.426	27.6	7.80	19.8	.110
.320	.426	27.3	7.30	20.0	.136
		$\alpha = 8.0 \times 10^{-3}$	$l = 1.6 \times 10^{-3}$		
α,β -Dibromopropionic Acid (A) + Phenol (B)					
c_A	c_B	$k_1 \times 10^5$	$k_A \times 10^5$	$p \times 10^5$	$c_A c_B$
0.0588	0.426	38.0	28.2	10	0.0250
.0944	.426	111	60.8	50	.0403
.146	.426	161	117	54	.0622
		$l = 8.5 \times 10^{-3}$			
Picric Acid (A) + Phenol (B)					
c_A	c_B	$k_1 \times 10^5$	$k_A \times 10^5$	$p \times 10^5$	$c_A c_B$
0.0704	0.426	5.50	3.43	2.07	0.0301
.106	.426	9.03	5.04	3.99	.0452
		$l = 8.4 \times 10^{-4}$			

With dichloroacetic acid it was found that the addition of phenol to solutions of 0.05–0.1 normality caused no measurable change of velocity. However, by decreasing the acid concentration greatly, while keeping the phenol concentration fairly high, the phenol reaction became the predominant one, as was shown by the fact that the course of these reactions was strictly monomolecular, in spite of the fact that the acid concentration was smaller than that of the ester. Experiments were carried out with constant acid concentration and varying phenol concentration, and the total reaction velocity plotted against $c_A c_B$. The slope of the best straight line thus obtained was taken as the catalytic constant.

A similar procedure was adopted for nitroacetic acid, which is too little soluble in benzene to measure at high concentrations (Table X).

TABLE X
Dichloroacetic Acid (A) + Phenol (B)

c_A	c_B	$k_1 \times 10^5$	$c_A c_B \times 10^4$
0.00204	0.171	9.1	3.49
.00204	.256	10.6	5.22
.00204	.342	11.1	6.99
.00204	.426	12.3	8.70

$$l = 1.0 \times 10^{-1}$$

Nitroacetic Acid (A) + Phenol (B)

c_A	c_B	$k_1 \times 10^5$	$c_A c_B \times 10^4$
0.00720	0.171	11.3	1.23
.00720	.256	13.5	1.84
.00720	.256	17.5	1.84
.00720	.341	16.3	2.46
.00720	.426	25.2	3.07
.00720	.426	18.8	3.07

$$l = 5.8 \times 10^{-2}$$

In Table XI are collected for each acid the values of α , the specific reactivity of the double molecules, l , the catalytic constant, and K_d , the electrolytic dissociation constant in aqueous solution. Unless a reference is given, the values of this last constant are taken from Landolt-Börnstein "Tabellen" (5th Auflage and Erster Ergänzungsband). The values of α marked * are only approximate, being taken from Table IX and equation (10).

TABLE XI
VALUES OF CONSTANTS

Acid	α	l	$\log_{10} l$	K_d	$\log_{10} K_d$
Formic	8.0×10^{-3} *	1.6×10^{-3}	$\bar{3}.204$	1.77×10^{-4}	$\bar{4}.248$ ³⁰
Iodoacetic	2.0×10^{-3} *	1.4×10^{-3}	$\bar{3}.146$	7.5×10^{-4}	$\bar{4}.875$
α -Bromopropionic	1.58×10^{-3}	1.08×10^{-3}	$\bar{3}.033$
Monochloroacetic	1.20×10^{-2}	4.7×10^{-3}	$\bar{3}.672$	1.41×10^{-3}	$\bar{3}.149$ ³¹
α, β -Dibromopropionic	2.35×10^{-2}	8.5×10^{-3}	$\bar{3}.929$	6.7×10^{-3}	$\bar{3}.826$
Nitroacetic	5.8×10^{-2}	$\bar{2}.763$	2.1×10^{-2}	$\bar{2}.322$ ³²
Dichloroacetic (Picric)	3.34	1.0×10^{-1}	$\bar{1}.000$	5×10^{-2}	$\bar{2}.700$
	8.4×10^{-4}	...	1.6×10^{-1}

It appears from Fig. 10 that there is an approximate agreement with the reaction previously derived³³

$$l = G_1 K_d^2 \quad (11)$$

³⁰ Harned and Owen, THIS JOURNAL, 52, 5079 (1930).

³¹ Grove, *ibid.*, 52, 1405 (1930).

³² Pedersen, *Trans. Faraday Soc.*, 23, 316 (1927).

³³ Brönsted, *Chem. Rev.*, 5, 312 (1928).

which has been shown to hold in aqueous solution in several cases.³⁴ In this case the exponent x has the value approximately unity. It must be remarked that while the catalytic constants refer to double acid molecules, the dissociation constants refer to single ones. This may explain why the catalytic value for picric acid (which exists as single molecules in benzene solutions) is very much lower than that predicted from equation (11), though we should expect the catalytic constants of the single carboxylic acid molecules to be still higher than those of the double ones. It is more probable that the abnormality of picric acid in this respect is connected with the fact that in a solvent of low dielectric constant the influence of the rest of the acid molecule will be much greater than in water, and thus equation (11) may only hold for acids of the same chemical type. It may be significant in this connection that for the carboxylic acids, the widest deviations are shown by formic and α,β -dibromopropionic acids, while the four substituted acetic acids show good mutual agreement.

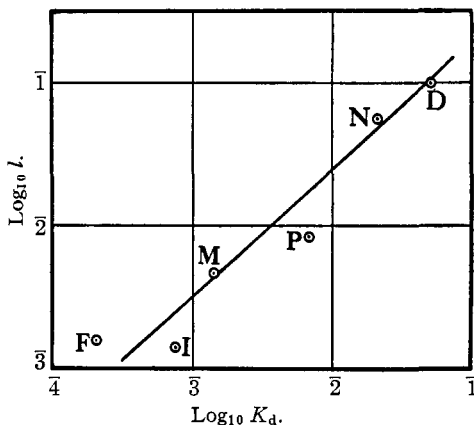


Fig. 10.—F, Formic; I, iodoacetic; M, monochloroacetic; P, α,β -dibromopropionic; N, nitroacetic; D, dichloroacetic.

According to modern views of the acid-base function, the cation of a weak base such as pyridine is also an acid, and we should anticipate that such ions would show catalysis in the reaction of phenol with diazoacetic ester. It was found, however, that a 0.0225 *N* solution of pyridinium trichloroacetate showed no measurable catalytic effect. It is possible that this represents an extreme case of the influence of electric type in solvents of low dielectric constant.

Summary

1. This paper contains a kinetic study of the reaction of diazoacetic ethyl ester with several substances in benzene solution. The reactions were followed by measuring the pressure of the nitrogen evolved.

2. In solutions of one or more carboxylic acids, the reaction consists of the replacement of the N_2 group by an acid molecule. The velocity of the reactions was found to be expressible by the equation

$$k_1 = \alpha c^2 + \beta c$$

³⁴ Brønsted and Pedersen, *Z. physik. Chem.*, **108**, 13 (1924); Brønsted and Duus, *ibid.*, **117**, 229 (1925); Brønsted and Guggenheim, *THIS JOURNAL*, **49**, 2554 (1927); Brønsted and Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

c being the concentration of the acid, and α and β constants characteristic for the individual acids. The velocity increases with increasing acid strength.

This empirical equation is compatible with the assumption that the addition of an acid molecule is catalyzed by the presence of acid molecules of the same or different kind, taking into account the progressive dissociation of double acid molecules into single molecules as the dilution increases. The reaction can be considered as a case of general acid catalysis.

3. The velocity of addition of picric acid is directly proportional to its concentration.

4. The velocity of addition of phenol to diazoacetic ester is strongly catalyzed by the presence of carboxylic acids, the catalytic effect increasing with increasing acid strength. The equation

$$l = GK^x$$

which has previously been shown to hold true for general acid catalysis in aqueous solution also applies approximately in the presence case, the exponent x having the limiting value of unity. Picric acid is much less active than required by the above equation.

COPENHAGEN, DENMARK

[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, HARVARD MEDICAL SCHOOL]

THE DETERMINATION OF CALCIUM BY ALKALIMETRIC TITRATION. I

BY CYRUS H. FISKE AND ELLIOTT T. ADAMS

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Among the possible volumetric methods for the determination of small amounts of calcium, after precipitation as the oxalate, alkalimetric titration of the oxide should have certain definite advantages over oxidation with permanganate, which is now used almost exclusively for this purpose. The end-point in the titration of pure calcium oxide is so sharp that, if no errors are introduced in the precipitation and washing of the calcium oxalate or in its subsequent conversion to the oxide, a method based upon this principle should be accurate to 0.002 mg. of calcium. The permanganate titration method, on the other hand, according to the most extensive investigation so far published,¹ is subject to an error of 0.006–0.008 mg. in the analysis of samples containing between 0.2 and 0.5 mg. of calcium.

Of the various objections that have been raised against the determination of small amounts of calcium by permanganate oxidation of the oxalate precipitate, only two appear to be of much importance. These are (1) the fact that the precipitate must be washed with water (or dilute ammonia), in which its solubility is appreciable, and (2) the mechanical loss involved in centrifuging the calcium oxalate, which except perhaps in

¹ Van Slyke and Sendroy, *J. Biol. Chem.*, **84**, 217 (1929).