

4. The effect of substitution on the oxidizing power of a hydroquinone-quinone system has been shown.

5. The results thus obtained have been compared with the electrochemical data in the form of oxidation-reduction potentials.

MINNEAPOLIS, MINNESOTA

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

A QUANTITATIVE STUDY OF SEMICARBAZONE FORMATION

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RECEIVED FEBRUARY 10, 1932

PUBLISHED JULY 6, 1932

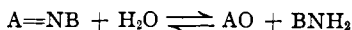
The interaction between ketones or aldehydes and such substances as phenylhydrazine and hydroxylamine has been the subject of numerous investigations in which the rate of the reaction has been measured. Most of these studies, however, were carried out before the use of the hydrogen electrode had enabled the chemist to define with precision the acidity of his solutions.¹ In recent years it has become apparent that in all these reactions one is dealing with a reversible reaction in which the acidity of the medium plays an important role in determining both the rate of the reaction and the final equilibrium which is reached. The early work of Acree and of Lapworth considered the influence of these factors to the extent that was possible at that time. The recent work of Ölander on the formation of acetoxime is the most complete study of this type of reaction from the modern viewpoint. This work will be referred to again in connection with our own measurements.

We have undertaken to study semicarbazone formation by a variety of carbonyl compounds in aqueous buffer solutions. Our results show the conditions which control the equilibrium in this reaction and the factors which influence the rate of the process. It seems probable that the fundamental principles which we believe we have elucidated can be applied to other similar reactions such as phenylhydrazone and oxime formation; these reactions, therefore, will be briefly discussed in the appropriate place in this paper. We shall first present our own results which are concerned with the equilibrium, then the kinetic study and finally a discussion of the influence of the structure of the carbonyl compound on both the composition of the equilibrium mixture and the rate at which this equilibrium is reached.

¹ The following references are among the most important: (a) Acree and Johnson, *Am. Chem. J.*, **38**, 308 (1907); Acree, *ibid.*, **39**, 300 (1908); (b) Barrett and Lapworth, *J. Chem. Soc.*, 93, 85 (1908); (c) Ölander, *Z. physik. Chem.*, **129**, 1 (1927); (d) Bodfors, *ibid.*, **109**, 223 (1924); (e) Petrenko-Kritschenko and co-workers, *Ann.*, **341**, 150 (1905); *Ber.*, **34**, 1702 (1901); **39**, 1452 (1906); (f) Stewart, *J. Chem. Soc.*, **87**, 410 (1905); (g) Grassi, *Gazz. chim. ital.*, **38**, II, 32 (1908); *ibid.*, **40**, II, 139 (1910); (h) Michael, *THIS JOURNAL*, **41**, 393 (1919); (i) Ardagh and Williams, *THIS JOURNAL*, **47**, 2976, 2983 (1925).

I. Equilibrium Measurements

The reaction between a carbonyl compound AO and a carbonyl reagent such as semicarbazide, phenylhydrazine or hydroxylamine BNH_2 is a reversible reaction; it is convenient to regard this reaction as an hydrolysis of the condensation product and write the reaction:



The reagent, BNH_2 , is a base whose conjugate acid is BNH_3^+ and the condensation product is similarly related to the acid $\text{A}=\text{NBH}^+$. We may write for the two acid-base equilibria the following equations in which the concentrations are denoted by the square brackets; these are the limiting laws holding in very dilute solution, and the relationships we shall derive with their use are subject to this same limitation. The probable error introduced by assuming their validity in solutions containing considerable salt will be discussed later.

$$K_R = \frac{[\text{BNH}_2][\text{H}^+]}{[\text{BNH}_3^+]} \quad (1)$$

$$K_C = \frac{[\text{ANB}][\text{H}^+]}{[\text{ANBH}^+]} \quad (2)$$

For the reversible formation of the condensation product $\text{A} = \text{NB}$ we may define a constant which corresponds to the equilibrium in a solution so strongly acid that no appreciable quantity of the reagent or condensation product is uncombined with a proton. This is the limiting hydrolysis in acid solutions

$$K_{\infty A} = \frac{[\text{AO}][\text{BNH}_3^+]}{[\text{ANBH}^+]} \quad (3)$$

If there are no appreciable quantities of intermediate compounds (such as the hypothetical direct addition product of the reagent and carbonyl compound) we may write for the hydrolysis of the condensation product in a solution of any acidity the equation (where K is a constant only at constant acidity).

$$K = \frac{[\text{AO}]([\text{BNH}_3^+] + [\text{BNH}_2])}{[\text{ANB}] + [\text{ANBH}^+]} \quad (4)$$

Substituting values of $[\text{BNH}_2]$ and $[\text{ANB}]$ from equations 1 and 2 into 4, we find the following relation between K , $K_{\infty A}$, K_R and K_C (equation 5)

$$K = K_{\infty A} \frac{[\text{H}^+] + K_R}{[\text{H}^+] + K_C} \quad (5)$$

When $[\text{H}^+]$ is small compared to K_R and K_C , we have the limiting value of K for the case where the solution is so weakly acid that no appreciable quantity of the reagent or condensation product is combined with a proton. This limiting value will be denoted as $K_{\infty B}$

$$K_{\infty B} = K_{\infty A} \frac{K_R}{K_C} \quad (6)$$

It is clear that the ratio of the equilibrium constants in very acid and basic solutions is a function of the difference in acid strength of the ions BNH_3^+

and ANBH^+ . Expressed logarithmically $pK_{\infty B} - pK_{\infty A} = pK_R - pK_C$. It is interesting to note that when the hydrolysis constant (K) is midway between its limiting values, $[\text{H}^+] = K_C$ or $pH = pK_C$; that the inflection of the $pH:K$ curve must occur at this point can be shown by differentiation of equation 5.

The data we have obtained on the equilibrium involving the hydrolysis of acetone semicarbazone illustrates the application of the equations we have just developed. The data are summarized in Table I and shown graphically in Fig. 1. The experimental procedure consisted in dissolving the semicarbazone in an aqueous buffer solution containing in some cases a definite quantity of acetone to suppress the hydrolysis, and removing samples from time to time and titrating with iodine at a pH of about 7 obtained by using a concentrated phosphate buffer solution. This method of determining semi-

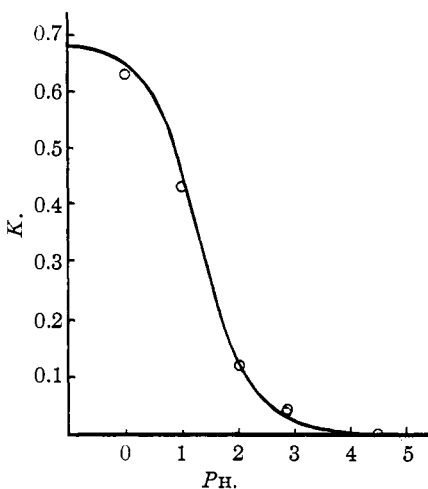


Fig. 1.—Variation of hydrolysis constant of acetone semicarbazone with pH at 25° .

TABLE I

HYDROLYSIS OF ACETONE SEMICARBAZONE AT $25.00 \pm 0.01^\circ$

For the composition of the buffer solutions employed, see Table VIII.

pH of buffer	Initial concn. of semicarbazone, moles $\times 10^{-3}$ per liter	Initial concn. of acetone, moles per liter	0.2304 N iodine for 10.14-cc. sample, cc.	Concn. of semicarbazide at equilibrium, moles $\times 10^{-3}$ per liter	K	K_C (by equation 7)
0	2.45	0.270	3.33			
			3.33	1.72	0.633	0.0443
1.00	2.73	.257	3.34			
			3.33	1.72	.435	.0416
			3.26			
2.02	2.63	.303	1.48			
			1.53	0.076	.122	.0532
2.84	3.76	.0752	2.10			
			2.26	1.29	.0379	(- .0451)
			2.27			
2.87	2.73	.257	0.81			
			.72	0.39	.0426	(- .0314)
			.76			
4.50	2.63	0	3.34	1.72	.00324
			3.33			

carbazine has recently been published.² The chief sources of error in the determination of the hydrolysis constant are the slowness with which final equilibrium is reached and the appreciable decomposition of semicarbazide into hydrazine and hydrazodicarbamide. This decomposition slowly displaces the equilibrium in such a way as to increase the iodine equivalent of the solution. The two sources of error thus work in opposite directions, and where the rate of hydrolysis was such that equilibrium was reached in a few hours, the results are more reliable than in those cases where several days were required. Several samples were always taken from the reaction mixture and titrated at successive times sufficiently far apart to ensure equilibrium being reached.

In the case of acetone semicarbazone the limiting hydrolysis on the weakly acid side is sufficient so that the value of $K_{\infty B}$ can be measured experimentally and is clearly the value of K obtained at PH values of 4, 5 and 7 (0.0032–0.0034). With this value and the dissociation constant of semicarbazide $K_R = 0.000219$, one can obtain the value of K_C from each value of K by combining equations 5 and 6 to yield 7. The values thus

$$K_C = \frac{[H^+]}{\frac{K_{\infty B}}{K K_R} ([H^+] + K_R) - 1} \quad (7)$$

obtained (last column of Table I) were satisfactory except with the two citrate buffer solutions, in which case impossible negative values were obtained. The curve in Fig. 1 is drawn with the constants $K_R = 0.000219$, $K_{\infty B} = 0.0032$ and $K_C = 0.0463$ which yield $K_{\infty A} = 0.69$. The agreement is all that can be expected considering the experimental difficulties and the uncertainties involved in applying equations developed for very dilute solutions to those containing considerable salt.³ It will be noted that the acid limit of hydrolysis is very nearly reached in 1.2 M hydrochloric acid, so that with acetone semicarbazone the whole curve can be realized experimentally.

In the case of the semicarbazones of aromatic aldehydes the hydrolysis is so slight in the more basic solutions that no direct measure of $K_{\infty B}$ is possible. Portions of the $PH : K$ curve lying in the more acid regions can be estimated from values of K obtained at different PH values. Since two unknown constants, K_C and $K_{\infty A}$ (or $K_{\infty B}$ if one desires), are involved, the best curve through the experimental points can be obtained by a trial and error graphical method. It was found more convenient, however,

² Paul D. Bartlett, *THIS JOURNAL*, **54**, 2853 (1932).

³ The buffer solutions employed (see Table VIII) varied in ionic strength from 0.045 to 1.28; the value of K_R taken corresponds to an ionic strength of 0.08. The errors introduced by the effect of changing ionic strength and individual ion effects on the values of K_R , K , K_C and $K_{\infty B}$ have been neglected. It is doubtful in the present case whether the equilibrium measurements are of sufficient precision to warrant a consideration of these factors.

to determine the most probable values of the two constants by an application of the method of least squares.

The observational equations were in the form $aK_{\infty A} + bK_C = q$ and by the theory of normal equations the most probable values of the two constants were obtained by solving the equations

$$\Sigma(aa) K_A + \Sigma(ab) K_C = \Sigma(aq) \text{ and } \Sigma(ab) K_{\infty A} + \Sigma(bb) K_C = \Sigma(bq)$$

The values thus calculated are given in Table II for the semicarbazones of furfural, acetaldehyde and benzaldehyde. In the case of the first compound, equilibrium was approached from the side of the aldehyde and semicarbazide; with the other two the same procedure was used as with acetone semicarbazone. In Table II are recorded the observed values of K (the hydrolysis constant) at the different P_H values and the value of K calculated with the aid of K_C and $K_{\infty A}$ determined as just described. A comparison of the observed and calculated values of K shows that equation 4 is a satisfactory formulation of the hydrolysis equilibrium in these cases. It is evident that the limit of acid hydrolysis ($K_{\infty A}$) should be nearly reached at a P_H value of 0. With furfural semicarbazone, however, absurd values of K , some 200 times too large, were obtained with a 1.2 M solution of hydrochloric acid. It seems that some side reactions were involved in this strong acid solution.

TABLE II
HYDROLYSIS OF SEMICARBAZONES AT DIFFERENT P_H VALUES AT 25.00 \pm 0.01°

P_H	Furfural		Semicarbazones of				Pyruvic acid	
	$K \times 10^4$ obs.	$K \times 10^4$ calcd.	Acetaldehyde $K \times 10^4$ obs.	Benzaldehyde $K \times 10^4$ calcd.	Benzaldehyde $K \times 10^4$ obs.	Benzaldehyde $K \times 10^4$ calcd.	$K \times 10^4$ obs.	$K \times 10^4$ calcd.
-0.01	72000							
1.00	9.37	9.12	45	44	7.6	7.6	2.95	3.06
2.02	2.10	2.65	9.3	8.5	1.34	1.24	0.69	0.55
2.44	1.13	1.20						
2.88	0.56	0.51			0.23	0.21	.18	.19
2.93	.40	.43						
3.24	.32	.27						
3.40	.20	.21						
3.95	.15	.11	0.27	0.32				
4.00							.089	.069
7.00			.29	.21			.051	.051

Constants used for calculating K are given in Table IIa.

TABLE IIa
SUMMARY OF HYDROLYSIS CONSTANTS OF DIFFERENT SEMICARBAZONES AT 25.00 \pm 0.01°

Semicarbazone of	K_C	Acid limit $K_{\infty A}$	Basic limit $K_{\infty B} \times 10^3$	pK_C	$pK_{\infty A}$	$pK_{\infty B}$
Furfural	0.036	0.0012	0.0076	1.44	2.92	5.42
Acetaldehyde	.078	.0076	.021	1.10	2.12	4.68
Benzaldehyde	.111	.0015	.0030	0.96	2.82	5.52
Pyruvic acid	.258	.0010	.0051	.59	3.00	5.29
Acetone	.046	.69	3.24	1.33	0.16	2.49

Pyruvic Acid Semicarbazone.—In the case of pyruvic acid we have an interesting example of a carbonyl compound which also enters into an acid-base equilibrium, so that the behavior of its semicarbazone would be expected to differ from that of a semicarbazone of an ordinary ketone or aldehyde. The limiting basic hydrolysis equilibrium is one between neutral semicarbazide, the negative ion of pyruvic acid and the negative ion of the semicarbazone.

The results are included in Table II, the value of K_A for pyruvic acid being taken as 0.0056.⁴ It seems most reasonable to attribute the value of K_C to the compound HPNBH^+ , regarding the uncharged form of pyruvic acid semicarbazone as the molecular form $\text{CH}_3\text{C}(\text{COOH})=\text{NNHCONH}_2$, and not an "inner-salt" form. The hydrolysis of pyruvic acid semicarbazone increases with acidity more slowly than the hydrolysis of the other semicarbazones. This is due to the tendency of the semicarbazone $\text{CH}_3\text{C}(\text{COO}^-)=\text{NNHCONH}_2$ to take on a hydrogen ion at the carboxyl group, which occurs in approximately the same P_H range as the taking of a hydrogen ion by the free semicarbazide. In their effects upon hydrolysis constant these two changes work against each other. Therefore pyruvic acid is well adapted for regenerating ketones and aldehydes from their semicarbazones and similar derivatives, working either in acid solutions (as with 10% neutralized pyruvic acid) or with the sodium salt of pyruvic acid in neutral solution. The low limiting value of the hydrolysis constant which is more like that of an aldehyde semicarbazone than a ketone semicarbazone is, of course, of fundamental importance in this connection. Such a use of pyruvic acid has been suggested by Grassi, and by Sidgwick.^{1g,5}

We may now consider briefly the equilibria which are concerned with the hydrolysis (or formation) of oximes and phenylhydrazones. If we may make the same assumption as in the case of semicarbazone formation that there are no appreciable quantities of intermediates in the equilibrium mixture, the equations developed above should apply directly to the hydrolysis of these other condensation products. The only adequate data available to test this point seem to be those of Ölander on the equilibria in acetoxime formation in buffer solutions from P_H 1.22 to 5.27. We have calculated from Ölander's values of $1/K$ (since he expressed his equilibrium constant in the inverse form from our equation), the most probable values of K_C and $K_{\infty A}$ taking his value of K_R for hydroxylamine as 8.05×10^{-7} . The following table (Table III) shows that except at the extreme end of his range, the agreement between $1/K$ calculated, and observed, is excellent, showing the applicability of equation 5 to the hydrolysis of oximes.

The acid dissociation constant of the acetoxime ion $(\text{CH}_3)_2\text{C}=\text{NH}^+\text{OH}$ by this computation is 0.012 or $pK_C = 1.92$; from the values in the litera-

⁴ Hantzsch and Miolati, *Z. physik. Chem.*, **10**, 1 (1892).

⁵ Sidgwick, "Organic Chemistry of Nitrogen," Oxford, 1910, p. 247.

TABLE III
 HYDROLYSIS OF ACETOXIME AT 20.0° (DATA OF ÖLANDER)

pH	Equilibrium constant		Deviation, %	pH	Equilibrium constant		Deviation, %
	$1/K$ obs.	$1/K$ calcd.			$1/K$ obs.	$1/K$ calcd.	
1.22	54.1	85	+57	3.15	1428	1286	-10
1.70	103.0	114	+11	3.41	2500	2273	-9.1
1.74	106.8	118	+10.5	3.50	3060	2780	-9.1
2.15	203.4	192.6	-5.3	3.80	5120	5453	+6.5
2.18	215.2	201.3	-6.5	4.25	16250	15207	-6.4
2.58	475.5	396.9	-16.5	4.86	55700	57729	+3.6
2.65	560	455.1	-18.9	5.27	71000	139088	+96

The calculated values of K were obtained using equation 5 and the values: $K_{\infty A} = 14 \times 10^{-3}$; $K_R = 8.05 \times 10^{-7}$; $K_C = 12 \times 10^{-3}$.

ture it appears⁶ that K_B (the old basic dissociation constant) is about 6×10^{-13} ; this corresponds to pK for the acid ion of 1.78 in good agreement with our value. It is clear from an inspection of the values given in Table IIa for the dissociation constant of the acid ion of the semicarbazone (pK_C) that they differ not more than half a pK unit from a mean value of 1.1. It is not certain that this variation really represents differences in the acid-base equilibria of the condensation product as some of the errors of the equilibrium measurements are reflected in these constants. The acetoxime ion appears to be a weaker acid than the corresponding semicarbazone ion by about one pK unit (*i. e.*, acetoxime is a somewhat stronger base); however, the closeness of the two acid constants shows that the acid dissociation of the ion $R_2C=NH^+B$ is not very dependent on the nature of B .

It is interesting to compare the common carbonyl reagents in regard to the hydrolysis of their condensation products with acetone, and the effect of changing hydrogen-ion concentration on the equilibrium. In Table IV are collected values for $pK_{\infty B}$ for acetoxime (Ölander's data), acetone phenylhydrazone (some preliminary unpublished data) and acetone semicarbazone, the values of pK for the acid dissociation constant of the reagent BNH_3^+ (pK_R) and for the condensation product (pK_C); the value of $pK_{\infty A}$ was calculated by equation 6. If one assumes that pK_C for a phenylhydrazone is the same as for a semicarbazone, $pK_{\infty A}$ for phenylhydrazine would be -1.1.

TABLE IV

A COMPARISON OF THE CONSTANTS INVOLVED IN THE EQUILIBRIUM BETWEEN ACETONE AND THREE COMMON CARBONYL REAGENTS

Reagent	pK_R	pK_C	$pK_R - pK_C$	$pK_{\infty B}$ (at 25°)	$pK_{\infty A}$
Hydroxylamine	6.09 (at 20°)	1.92	4.2	6.03	1.8
Phenylhydrazine	5.21 (at 15°)	2.76	...
Semicarbazide	3.66 (at 25°)	1.33	2.3	2.49	0.16

⁶ Scudder, "Electrical Conductivity and Ionization Constants of Organic Compounds," New York, 1914.

It is clear from the values of $pK_{\infty B}$ and $pK_{\infty A}$ that the oximes are much less hydrolyzed than the phenylhydrazones or the semicarbazones and that the difference between the classes of compounds is more pronounced in weakly acid solutions than in strongly acid solutions.

The hydrolysis constant of acetone semicarbazone was determined at P_H 7 at 0° —the value of $K_{\infty B}$ thus obtained was 0.00073 as compared with 0.00324 at 25° . A substitution of these values in the usual integrated form of the Van't Hoff equation yields $\Delta H_{298} = +9700$ cal. for the hydrolysis of acetone semicarbazone to acetone and free semicarbazide in very dilute aqueous solution. ΔF_{298} for the same process is $-1365 \log 0.00324 = +3400$ cal., from which $T\Delta S$ equals 6300 cal. or $\Delta S = 21.1$ E. U.

II. Kinetic Measurements

It has been known for some time that the rate of reaction of ketones and aldehydes with reagents of the type BNH_2 is a function of the acidity of the medium. Acree and Johnson showed that oxime formation was catalyzed by acids and Barrett and Lapworth, working on the formation of acetone and acetaldehyde oximes, found an optimum concentration of acid, above and below which the velocity decreased sharply. Ölander investigated this phenomenon with more care and put forward a hypothesis, accounting for it as purely an effect of hydrogen ion activity. The work of Brönsted has shown that in many reactions it is not solely the hydrogen ion (H_2OH^+) which is the catalyst but that other acids present in the solution⁷ may be effective in increasing the rate of the reaction. In general with those reactions which are subject to acid catalysis, the rate is proportional to the concentration of each species of acid present and a constant characteristic for the acid in question. These catalytic constants roughly parallel the acid dissociation constants of the acid, and for this reason if one is using a series of buffer solutions of about the same concentrations true acid catalysis may be overlooked and erroneously believed to be merely hydrogen ion catalysis. To determine whether or not the rates were solely a function of the P_H of the buffer solution or whether catalytic effects were at work, we measured the rate of formation of furfural semicarbazone in an acetate buffer of constant P_H but varying concentration of acetic acid and acetate ions.

Measurement of Velocity Constants.—It has been customary, apparently, in studies of this type of bimolecular reaction, to introduce the two reactants in exactly equal concentrations. This simplifies the mathematical treatment if the reaction is irreversible, but for reversible reactions it makes the treatment unnecessarily difficult. The logarithmic integration of the differential equation for such a process is not suitable for exact

⁷ Brönsted, *Chem. Rev.*, 5, 231-338 (1928); Brönsted and Guggenheim, *This Journal*, 49, 2554 (1927).

computation in those cases where the reaction is almost irreversible. However, by maintaining a difference in concentration of the two reactants, it is possible to determine the velocity constants in both directions in a reversible reaction, from a single run and by a single equation with which it is easy to compute. There are three constants which must be known: the difference in concentration of the two reactants (called c in these formulations), the equilibrium constant K and either the initial concentration of a reactant or its concentration at equilibrium (one of these can be derived from the other). These are expressed by x_0 and x_e , respectively.

For a reversible bimolecular reaction in which a single molecule of product is formed by combination of one molecule of each reactant, where the concentrations of the reactants are x and $(x + c)$, respectively, and the equilibrium constant for the reverse reaction $K = k_1/k_2 =$ the ratio of the backward to the forward rate

$$-dx/dt = k_2x(x + c) - k_1(x_0 - x)$$

where x_0 is the initial concentration of x ; or

$$k_2dt = \frac{-dx}{x(x + c) - K(x_0 - x)}$$

The integrated equation takes on the final form

$$k_2t = \frac{2.303}{(2x_e + c + K)} \log \frac{x + (x_e + c + K)}{x - x_e} + C$$

Since the quantities in parentheses are all made up of constants known or measured in the course of the reaction, this equation reduces for a special run to a very simple form in which, especially with a calculating machine, the values of x can be rapidly and easily substituted. It is equally easy to determine k_1 directly from the original equation, or to find it as the product Kk_2 .

The integration constant is evaluated if desired by taking x_0 as one of the values of x . In certain cases in this work, x_0 is known with certainty (for example, in all runs at room temperature when the PH is 7 or less) and in these cases the integration constant is incorporated in the logarithmic formula. At 0° , where the coefficients of expansion were not allowed for in calculating the molarity, and in the alkaline buffers, where addition of semicarbazide was followed by some immediate decomposition by dissolved air, the first determined value of x was sometimes more reliable than the calculated x_0 . In these cases the integration constant was not determined, but was canceled out in taking the differences of the logarithms.

It will be seen that this equation reduces to the equation for an irreversible reaction in the special case where x_e and K are equal to zero, for it becomes

$$k_2t = \frac{2.302}{c} \log \frac{x + c}{x} + C$$

This form was used for reactions in which x_e and K were too small to affect the value of the logarithm.

The concentration of reactants was usually chosen which would give not more than 80% reaction in five minutes. The usual velocity run included five titrations, covering about 80% reaction. Whenever there was a measurable equilibrium, the reversible-reaction formula was used in calculating the constants.

The most careful measurements were those in which the sampling was done at one-minute intervals. The 250-cc. glass-stoppered flask containing 200 cc. of buffer solution and 5 cc. of standard furfural solution (previously added from a pipet) and the bottle of standard semicarbazide hydrochloride were brought to temperature in the thermostat. Just before starting the run, the flask was removed and dried, and its stopper, on the inside of which a small inverted weighing bottle was sealed with de Khotinsky cement, was removed and inverted; 5 cc. of the semicarbazide hydrochloride solution was pipetted into the little bottle and at the moment of starting the run the stopper was inserted into the flask and the whole vigorously shaken, resulting in practically instantaneous mixing, as the timing was begun. The flask was replaced in the thermostat, and samples were taken at the stated intervals and added to successive flasks containing a measured amount of iodine, and enough disodium phosphate to bring the P_H of the mixture to 7. Immediately after addition of a reaction sample, the excess of iodine was destroyed by thiosulfate from a pipet. After the five minutes, the excess thiosulfate in each flask was titrated with iodine.

TABLE V

RATE OF FORMATION OF FURFURAL SEMICARBAZONE IN ACETATE BUFFERS OF VARYING CONCENTRATION BUT CONSTANT IONIC STRENGTH

P_H , 4.4; Temp., $25.0 \pm 0.01^\circ$; μ , 0.694

Total concn. of acetate ion plus acetic acid, moles per liter	0.0302	0.0477	0.0691	0.1257	0.742 ^a	0.742 ^a
Constant of rate of semicarbazone formation k_2	22.5	31.5	40.4	55.6	102.9	108.4

^a The ionic strength here was 0.74.

The ionic strength of the solutions dilute in acetate was made up by the addition of potassium chloride. The ratio of acetate ion to acetic acid throughout was 1.7. Two experiments at a molarity of 0.069 with an ionic strength of 0.069 gave values of k_2 of 36.6 and 37.9, showing that a large change of ionic strength had little effect on the rate. To illustrate the method of measuring k_2 , some typical data are given in Table Va.

The results summarized in Table V clearly show that at essentially constant P_H (and ionic strength) the rate of furfural semicarbazone formation may be increased five-fold by a change in concentration of the acetate

TABLE Va

DATA ILLUSTRATING METHOD OF MEASUREMENT OF CONDENSATION RATE BETWEEN FURFURAL AND SEMICARBAZIDE

pH, 4.42; total molarity of acetate + acetic acid, 0.0302; ionic strength, 0.694; temperature, 25.00 ± 0.01°; initial concentration of semicarbazide (x_0), 0.0001811 *M*; initial concentration of furfural ($x_0 + c$), 0.0002332; $c = 0.0000521$.

Minutes	Cc. of 0.0209- <i>N</i> iodine for 20.48-cc. sample	x	k
3.33	3.48	0.0001823	..
14.50	3.23	.0001691	21.3
21.25	3.10	.0001624	23.2
29.75	2.99	.0001566	22.4
37.50	2.87	.0001502	23.2
			Average 22.5

$$kt = 44195 \log \frac{0.7767x + 0.0000405}{x}$$

ion and acetic acid. The increase in rate with increase in concentration is nearly linear up to a molarity of about 0.13; in higher concentrations the increase of concentration produces a less effect. From these results it seemed probable that we were dealing with a reaction between the free semicarbazide (BNH_2) and the carbonyl compound, the reaction being subject to acid catalysis by the acetic acid molecules; as will be shown later, we could obtain no evidence that the reaction was subject to basic catalysis in aqueous solutions. Further evidence was obtained by studying the rate of formation of acetone semicarbazone at 0° in acetate and phosphate buffer solutions. The results are shown graphically in Fig. 2. Since the hydrolysis constant of acetone semicarbazone is high, k_2 was determined indirectly by measurements of the equilibrium constant and of the velocity of hydrolysis of the semicarbazone.

A test of the applicability of Brönsted's theory to semicarbazone formation is afforded by the results shown in Fig. 2. From the relationship $pK - pH = \log ([\text{BNH}_3^+]/[\text{BNH}_2])$ and the value of pK at 0° for semicarbazide acid ion (4.40),² the fraction of total semicarbazide present as free base may be calculated. The reaction velocity constant referred to free semicarbazide (k_2°) is obviously the ob-

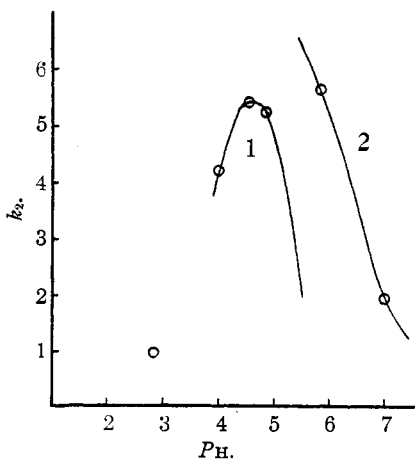


Fig. 2.—Velocity of condensation of acetone and semicarbazide at 0° in 0.045 *M* buffer solutions; curve 1, acetate buffers; curve 2, phosphate buffers.

served velocity constant (k_2) divided by this fraction; this value is given in the fourth column of Table VI.

TABLE VI
SUMMARY OF DETERMINATIONS OF CONDENSATION VELOCITY OF ACETONE AND SEMI-CARBAZIDE AT $0.1 \pm 0.1^\circ$

P_H	C_A	k_2	k_2°	$k_A = k_2^\circ/C_A$	
2.84	0.0226	1.13	42.2	...	Citric acid buffer
4.00	.0363	4.25	14.9	410	Acetic acid buffers
4.52	.0233	5.43	9.55	406	
4.84	.0157	5.30	7.05	450	
5.84	.0350	5.70	5.90	169	Phosphate buffers
7.00	.0146	2.02	2.02	138	

In the second column of the same table is given the molar concentration of acid in each of the buffers; according to Brönsted's theory the value of k_2° should be proportional to this concentration since in general $k_2^\circ = \Sigma C_A k_A$ where C_A and k_A are the concentrations and specific catalytic constants for all the species of acids involved. The last column in Table VI shows that the value of k_A for acetic acid is $420 \pm 5\%$ and for $H_2PO_4^-$, $150 \pm 10\%$. These facts show clearly that the formation of acetone semicarbazone is a reaction involving acetone and free semicarbazide subject to acid catalysis. (No attempt was made to calculate a value for the citric acid buffer since it is difficult to identify the molecular species of acid present in this case.)

Since in general the specific catalytic constants of a series of acids parallel the dissociation constants,⁷ it is evident that as one passes from a set of buffers composed of the monobasic phosphate ion to one composed of acetic acid and then to those containing still stronger acids the value of k_A would increase. Furthermore, in a given set of buffers C_A , the concentration of the acid component, increases with decreasing P_H values. These two effects by themselves would cause an increase in the rate of semicarbazone formation with increasing acidity. However, this effect is counteracted by increasing removal of free semicarbazide by the formation of the ion $NH_2CONHNH_3^+$ as soon as one approaches a P_H value near the pK value of the semicarbazide ion. The result of these two opposing factors would obviously lead to a maximum in the P_H versus k_2 curve for semicarbazone formation. It would be clearly accidental, however, if such a curve were a smooth continuous curve; indeed, it is not as shown by Fig. 2. It would be easy, however, to assume that there was such a smooth curve showing a maximum if a limited number of buffer solutions of approximately the same concentration were employed. This is shown by the results we obtained early in the work using furfural at 25° . These measurements are summarized in Fig. 3; the values of k_2 and K were measured directly as explained above. There is a maximum value

of k_2 at P_H 3.13, but the curve is not regular. Ölander obtained a similar maximum in studying acetoxime formation but explained it by an entirely different mechanism. As his measurements were made before Brönsted's work had shown the importance of general acid catalysis, he made no experiments to determine whether or not the P_H value of the solution alone determined the rate. We believe that these results of Ölander's indicate that oxime formation like semicarbazone formation is a reaction between the free base and the carbonyl compound catalyzed by the acid component of the buffer.

The temperature coefficient of the reaction between acetone and semicarbazide was determined at P_H 7 (phosphate buffer molarity of 0.049) by measuring the rate at $0.1 \pm 0.1^\circ$, and $25.00 \pm 0.01^\circ$. The values for k_2 were 2.02 ± 0.06 and 2.95 ± 0.06 , respectively; these values in the usual Arrhenius equation yield a value for the heat of activation of 2500 cal. \pm 240 cal. This, combined with the value of ΔH for the hydrolysis of acetone semicarbazone given above (9700), gives the heat of activation of the hydrolysis reaction as 12,200 cal.

This latter value is about what one might expect for a reaction of this sort, but the very small heat of activation of semicarbazone formation is very unusual. The facts concerning acid catalysis, however, show that the rate of the reaction is dependent on the concentration of three substances, namely, the carbonyl compound, the reagent and the acid. It seems probable that in reality we have a bimolecular reaction between one of the reactants and a complex of the other two. The low temperature coefficient of the reaction would be accounted for by the fact that the equilibrium involving the complex would be shifted toward dissociation by increased temperature. This shift would diminish the concentration of the reactant in the rate-determining step and lower the velocity. This effect would offset to a considerable extent the usual increase in rate of a reaction with increase in temperature. According to this view, then, the value of the heat of activation of the reaction in question does not correspond to any real reaction but is complicated by including the heat of dissociation of a complex.

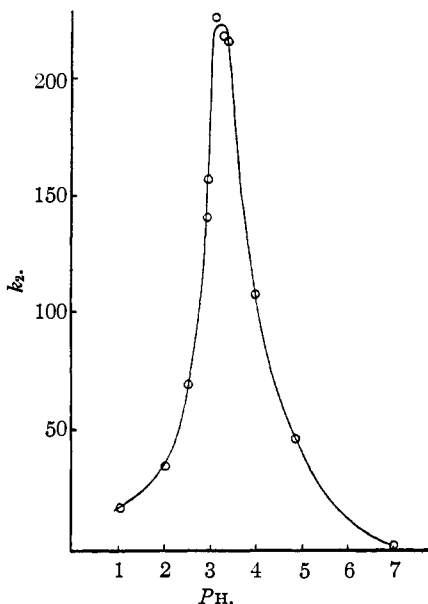


Fig. 3.—Condensation velocity of furfural and semicarbazide in 0.5 *M* phosphate, citrate and acetate buffers.

We have not been able to obtain any clear evidence of basic catalysis of semicarbazone formation. For study in a borate buffer of *PH* 9.11 and a dibasic-tribasic phosphate buffer of *PH* 11.01, the most reactive carbonyl compound, acetaldehyde, was chosen. This aldehyde, which condenses with semicarbazide with a velocity constant of about 360 in a 0.1 *M* phosphate buffer at *PH* 7, showed a constant of 9.2 in the *PH* 9 buffer and a constant of 1.42 at *PH* 11. Evidently the rate at neutrality was almost entirely due to catalysis by the H_2PO_4^- ion. Certainly there is no basic catalysis evident by the $\text{PO}_4^{=}$ ion in 0.25 *M* solution. To avoid using acetaldehyde, with its tendency to polymerize in strongly basic solutions, cyclohexanone was condensed with semicarbazide in the *PH* 11 buffer, and in 0.1 *N* and 1 *N* sodium hydroxide solution, carrying the *PH* almost up to 14. The constants, which were not very satisfactory for the slower reactions, were: at *PH* = 11.0, $k_2 = 0.27 \pm 0.06$; 0.1 *N* NaOH, $k_2 = 0.22 \pm 0.03$; 1 *N* NaOH, $k_2 = 1.61 \pm 0.05$. There appears to be about a five-fold increase in velocity on passing from 0.1 *N* sodium hydroxide to 1 *N*, which is perhaps too large a difference to be caused by a solvent effect; but since the velocity in normal sodium hydroxide is less than one-twentieth of that in our *PH* 7 buffer (with 0.03 *M* monobasic sodium phosphate functioning as an acid catalyst), it would appear that, if there is any basic catalysis of semicarbazone formation, it is exceedingly small in aqueous solutions.

On the other hand, the accelerating effect of strong alkali on oxime formation appears well-established. It was first noticed by Auwers in 1889 and is commonly used in the preparation of the slowly forming oximes of highly substituted ketones. According to the work of Barrett and Lapworth^{1b} the velocity of formation of acetoxime increases linearly with the quantity of alkali present, up to an alkali concentration of about 0.025 *N*, which was as high as their experiments were carried. Acree and Johnson put forward the hypothesis that this accelerating effect of alkali on oxime formation was due to formation of the negative ion of hydroxylamine, which had a greater reactivity than the neutral form. If such is the case, we should expect the accelerating effect of alkali on the formation of semicarbazones to be much less pronounced than in the case of oximes, or perhaps not to appear at all in ordinary aqueous solutions, since free semicarbazide shows no acid ionization.

III. The Effect of the Structure of the Carbonyl Compound on the Equilibrium and the Rate

From the work reported in the two previous sections of this paper it is clear that a comparison of rates and equilibria with a variety of carbonyl compounds and the same nitrogen base should be made (a) under conditions where all the nitrogen base and all the condensation product are in

the free-base form, and (b) with a definite concentration of a known catalyst present. This concentration of catalyst should not much exceed 0.1 M and should not be more than about 100 times the concentration of the reactants. These conditions will be fulfilled for semicarbazone formation if we choose a phosphate buffer of concentration 0.1 M or 0.2 M and with a value of P_H 7, since the concentration of the catalyst (primary phosphate ion) in a 0.2 M buffer of this P_H is only 0.06 M , and since here more than 0.999 of the semicarbazide is in the form of the free base.

In addition to the methods outlined above for measuring equilibrium and rate constants, another method was introduced for convenient determination of the rate of hydrolysis of a semicarbazone. This method is applicable in certain cases only, and depends upon the stability of the semicarbazone toward iodine. If iodine does not attack a semicarbazone directly, hydrolysis may be carried on in a solution containing iodine, and the continuous removal of the semicarbazide by the iodine makes the hydrolysis kinetically irreversible and easily subject to treatment by the simple monomolecular formula.

The constancy of the values of k calculated from any such hydrolysis run where only a slight excess of iodine is present constitutes a sufficient criterion of the stability of the semicarbazone; for if iodine participates in the rate-controlling reaction, the "monomolecular constants" will decrease with time, and be proportional to the concentration of iodine remaining.

The logarithm of the semicarbazone concentration was plotted against the time for the several semicarbazones measured. The method was applied only to those semicarbazones for which such a plot resulted in a straight line; these were acetone, acetaldehyde and cyclohexanone semicarbazones. With the last two, the rate of hydrolysis could be measured more accurately than the rate of formation, so that this was a very useful method in these cases.

An account of the determination of the hydrolysis velocity of acetone semicarbazone will illustrate the method. The dry semicarbazone was weighed and a solution of it in water made up to be about 0.01 M . This was kept overnight and then for a few hours in the thermostat; 5-cc. portions of this solution were then introduced into flasks containing 7 cc. of iodine and 20 cc. of a 0.2 M phosphate buffer of P_H 7.02. The time from addition of this sample to the iodine, to reaching the end-point with thiosulfate was taken with a stop watch. At any time a new point on any part of the curve could be taken. In another run 50 cc. of 0.1 M buffer (P_H 7.08) was used instead of 20 cc. of the 0.2 M buffer. This made a buffer concentration of 0.0794 instead of 0.125 and a semicarbazone concentration of 0.00082 instead of 0.001568. The two values for k_1 found are 0.0214 and 0.0152. Corrected to a concentration of catalyst of 0.06 M (buffer concentration of exactly 0.1 M) these yield the constants 0.017 and 0.019.

The average of these values, divided by the rate of formation of acetone semicarbazone at the same concentration of buffer, $(2.95/0.049 \times 0.100 = 6.0)$, gives a value for the equilibrium constant of 0.0030 as compared with 0.00324 from the measurements of equilibrium as a function of P_H (Table I).

In preparing to study the other semicarbazones, blanks were run in each case to test for any reaction between iodine and the ketone or aldehyde itself. In all these cases it was found that there was no reaction rapid enough to be a source of error. Acetaldehyde, for example, reacted forty times more slowly with iodine at P_H 7 than the semicarbazone.

The final results of the comparative study of eight different aldehydes and ketones are given in Table VII.

TABLE VII
COMPARISON OF EQUILIBRIA AND RATES OF SEMICARBAZONE FORMATION OF A VARIETY OF KETONES AND ALDEHYDES

At $25 \pm 0.01^\circ$ in $0.07 M Na_2HPO_4 + 0.03 M NaH_2PO_4$

Semicarbazone of:	$K_{\infty B} \times 10^5$ Hydrolysis constant of semicarbazone	$pK_{\infty B}$	Velocity constants formation = k	hydrolysis $k_1 \times 10^5$
Acetaldehyde	2.9	4.5	(361)	1040
Benzaldehyde	(0.30)	5.5	2.05	(0.62)
Furfural	(0.76)	5.1	0.73	(0.55)
Trimethylacetaldehyde	1.85	4.7	20	(37)
Pyruvic acid	0.51	5.3	7.37	(3.8)
Acetone	324	2.5	6.02	1800
Cyclohexanone	214	2.7	(36)	7600
Pinacolone	1260	1.9	0.068	(86)

In this table the figures which were not determined directly, but were computed from other data at hand, are enclosed in parentheses. The values of $K_{\infty B}$ for benzaldehyde and furfural were calculated by equations 5 and 6 from values of K at different P_H values. Values of k_2 for acetaldehyde and cyclohexanone were calculated from $K_{\infty B}$ and k_1 and the reverse procedure was used in calculating k_1 for the four bracketed values.

A consideration of Table VII brings out a number of points of interest. In the first place it is clear that there is no apparent relation between the speed of formation of the semicarbazone and its stability as measured by the hydrolysis constant $K_{\infty B}$. Thus the rates of formation of the semicarbazones of benzaldehyde, pyruvic acid, trimethylacetaldehyde and acetone are within a power of ten but the hydrolysis constants show a divergence of a thousand-fold between the extremes, and the most rapidly reacting of the four (trimethylacetaldehyde) is about in the middle of the series from the point of view of the extent of hydrolysis of the semicarbazones. Considering first the relation between structure and rate of semicarbazone formation, acetaldehyde is found at the top of the list, with its

trimethyl substitution product about a tenth as reactive, but some ten times more reactive than benzaldehyde or furfural. The latter is the least reactive of all the aldehydes and differs from acetaldehyde by nearly a thousand-fold. Of the ketones, cyclohexanone is the most reactive, as would have been expected from previous work, acetone and pyruvic acid essentially equal and about a sixth as rapid in semicarbazone formation as the cyclic ketone. The large drop in reactivity caused by substitution of three methyl groups (0.068 for pinacolone compared with 6.0 for acetone) is in accord with a large variety of qualitative and quantitative facts of organic chemistry. It is interesting that the change in reactivity produced by the substitution of three methyl groups in the alpha position is much less in the case of the aldehyde than with the ketone ($361/20 = 18$, compared with $6.0/0.06 = 100$). A comparison of benzaldehyde, furfural, acetone and trimethylacetaldehyde gives very little support to the idea that the rate of carbonyl reactions is determined solely by so-called "steric effects." If the comparison is sufficiently restricted, however, as, for example, between acetaldehyde and its trimethyl derivative, the concept of steric hindrance is in accord with the facts.

Turning now to the equilibrium constants, we find all the ketones (except pyruvic acid) falling into one class and the aldehydes into another. Within the ketone class the variation in $K_{\infty B}$ is only three-fold, the most highly substituted ketone being the most completely hydrolyzed. The variation among the aldehydes in $K_{\infty B}$ is ten-fold, but the difference between the least hydrolyzed ketone semicarbazone (always excepting pyruvic acid) and the most hydrolyzed aldehyde semicarbazone is 100-fold. Pyruvic acid behaves like an aldehyde in respect to the hydrolysis constant of the semicarbazone. It would appear that the carbonyl compounds, as far as the energy relationships are concerned, show a rather simple relationship between structure and semicarbazone formation, the equilibrium constant being determined by the same sort of factors which determine the dissociation constants of acids. For convenience these factors may be termed the polarity or negativity of the attached groups.

Using the dissociation constants of the acid XCOOH, as a measure of the negativity of the group X, we have the following series, the groups being arranged in order of decreasing negativity (the values of pK_A for the acids are given in parentheses): COOH (2.8), H (3.7), C₆H₅ (4.2), CH₃ (4.7), (CH₃)₃C (5.0). Now turning to a comparison of the extent of hydrolysis of the semicarbazones formed from carbonyl compounds of the type XCOCH₃, we find the following order for the group X (the values of $pK_{\infty B}$ are given in parentheses): COOH (5.3), H (4.5), CH₃ (2.5), (CH₃)₃C (1.9). The two series coincide not only qualitatively but semi-quantitatively, the most hydrolyzed semicarbazone corresponding to the weakest negative group. If we compare the values of pK_B for semicar-

bazones derived from compounds of the type $XCHO$, we find that the value for benzaldehyde is greater than for acetaldehyde, as would be predicted, but that trimethylacetaldehyde is out of place. This discrepancy we do not feel is serious in view of the uncertainty of the interpretation of small differences in pK values.

We are aware that some of our conclusions in regard to the relation between structure and rate of reaction are contradictory to earlier measurements which have been much quoted. It would take far too much space to discuss all the earlier work but with the exceptions previously noted we feel that the previous work is unreliable because of the then unknown factors affecting both equilibrium and rates and a failure to distinguish between equilibria and rates in the measurements themselves. Furthermore, we have devised a few qualitative experiments which demonstrate the correctness of some of the conclusions summarized in Table VII.

A comparison of semicarbazone formation of cyclohexanone and furfural is of interest. The differences in rate are in favor of the former by a factor of about 50; the hydrolysis of the aldehyde semicarbazone, however, is only $1/300$ of that of the ketone. As a result, if one mole of semicarbazide and one mole each of cyclohexanone and furfural are allowed to react, practically the entire *final* product is furfural semicarbazone. Because of the differences in the rates of reaction, however, the *initial* product in such an experiment is almost wholly cyclohexanone semicarbazone. The effects of differences of rate and equilibrium constants on the nature of the product can be shown very simply by allowing semicarbazide to react with a mixture of cyclohexanone and furfural in alcoholic solution and isolating the semicarbazone after a few seconds and after a few hours. Because of the solubility of cyclohexanone semicarbazone in water, it is necessary to precipitate the product by pouring a sample of the mixture into a saturated ammonium sulfate solution in which the cyclohexanone semicarbazone is almost insoluble. In such an experiment starting with 0.01 mole each of semicarbazide hydrochloride, furfural, and cyclohexanone and 0.05 mole of potassium acetate in 50% alcohol, a sample precipitated after twenty seconds yielded a product melting at 165° (identified as cyclohexanone semicarbazone by mixed melting point); after two and one-half hours a similar precipitate melted at 190° and was identified as furfural semicarbazone. In a comparison of acetone and furfural, it is impossible to isolate the ketone semicarbazone by precipitation as it is too soluble. The delayed precipitation of furfural semicarbazone from a reaction mixture containing one mole of acetone (and saturated with furfural semicarbazone) was however striking proof of the correctness of the results shown in Table VII, where k_2 for acetone is nearly ten times greater than that of furfural. Two exactly parallel experiments were performed using an aqueous solution of semicarbazide hydrochloride (0.01 mole) and potassium acetate (0.05 mole) in

20 cc. of water saturated with furfural semicarbazone. In one flask a mixture of 0.01 mole each of acetone and furfural was introduced, in the other 0.01 mole of furfural alone. In the first flask the precipitate after one minute was 0.25 g., in the other 1.20; the filtrate from these precipitates yielded, after standing for twelve hours, 1.00 g. and 0.20 g. of additional furfural semicarbazone.

TABLE VIII

COMPOSITION OF BUFFER SOLUTIONS				
P_H	Acid	Concentration	Salt	Concentration
-0.01	HCl	1.284		
0.50	HCl	...		
1.00	H ₃ PO ₄	0.455	NaH ₂ PO ₄	0.045
1.48	H ₃ PO ₄	.295	NaH ₂ PO ₄	.205
2.02	H ₃ PO ₄	.155	NaH ₂ PO ₄	.345
2.45	H ₃ PO ₄	.425	NaH ₂ PO ₄	.075
2.84	Citric	.25	Sodium citrate	.25
2.87	Citric	.25	(Monobasic)	.25
3.40	Citric	.085	Sodium citrate	.415
3.95	Acetic	.40	Sodium acetate	.10
4.00	Acetic	.40	Sodium acetate	.10
4.52	Acetic	.26	Sodium acetate	.24
4.84	Acetic	.175	Sodium acetate	.325
5.84	NaH ₂ PO ₄	.39	Na ₂ HPO ₄	.11
7.00	NaH ₂ PO ₄	.06	Na ₂ HPO ₄	.14
7.02	NaH ₂ PO ₄	.06	Na ₂ HPO ₄	.14
9.11	Boric	.28	Sodium borate	.22
11.01	Na ₂ HPO ₄	.25	Na ₃ PO ₄	.25

The buffers of other P_H 's in the neighborhood of 3, not listed here, were prepared from these buffers by adding different amounts of acid or base, account being taken of the changes in concentration in the values reported for μ .

Summary

A quantitative study has been made of the factors affecting the equilibria and rates of semicarbazone formation. The extent of hydrolysis of a given semicarbazone is a function of the acidity of the solution, which may be expressed by an equation which has been derived. The results obtained correspond to this equation. The formation of semicarbazones has been found to be subject to general acid catalysis and a fairly satisfactory formulation has been developed in terms of the effect of acidity on the amount of semicarbazide reacting and acid catalysis. The equilibria and rates of semicarbazone formation for a variety of ketones and aldehydes have been measured under strictly comparable conditions. Certain relations between structure and equilibria and rates of semicarbazone formation have been pointed out.