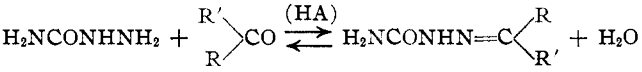
[CONTRIBUTION FROM THE HAVEMEYER CHEMICAL LABORATORY OF COLUMBIA UNIVERSITY]

Semicarbazone Formation, and the Incomplete Dissociation of a Salt of the Ammonium Type

BY PAUL D. BARTLETT[1]

Semicarbazone formation is a reaction of a base with a neutral compound, catalyzed by an acid



$$H_2NCONHNH_2 + \underset{R}{\overset{R'}{>}}CO \underset{\longleftarrow}{\overset{(HA)}{\longrightarrow}} H_2NCONHN{=}C\underset{R'}{\overset{R}{<}} + H_2O$$

The rate of the reaction, in very dilute aqueous solution, is proportional to the concentration[2] of each of these three molecular species. In the absence of unexpected complications, this proportionality should be maintained at least up to a 0.5 M concentration of the catalyst, as in the well-known cases of general acid catalysis.[3]

However, in the case of furfural reacting with semicarbazide under the catalytic influence of acetic acid, the relationship between acid concentration and rate of reaction is a linear one only below 0.05 M acid.[4] Above this value the curve (shown in Fig. 1) flattens off rapidly with increasing acid concentration, until at an acid concentration of 0.42 M the reaction rate constant is only one-fifth of that predicted from the values at the lowest concentrations. These measurements were made in different dilutions of an acetic acid–sodium acetate buffer, the P_H and ionic strength being kept constant. In buffers of the concentration used, the catalytic effect of the hydrogen ion is much less than that of the undissociated acetic acid.

The type of curve which represents this abnormal behavior is just that which would be expected if the salt, semicarbazide acetate, were not completely dissociated in aqueous solution, but existed in an undissociated molecular form in increasing amount with increasing concentration of free acetic acid. If this were the case, the relationship at any P_H between the bimolecular velocity constant k and the acid concentration [HA] should be

$$k = k_h + \frac{b[HA]}{[HA] + K_m} \qquad (1)$$

K_m is the dissociation constant of the salt into molecular acid and molecular base, k_h is the reaction rate due to hydrogen ions, and b is the constant upper limit approached by the second term of the equation.

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(1) National Research Fellow.

(2) Conant and Bartlett, THIS JOURNAL, **54**, 2881 (1932).

(3) A strictly linear relationship between acid concentration and reaction rate was found by Dawson, Hall, and Key [*J. Chem. Soc.*, 2847 (1928)] for the iodine–acetone reaction catalyzed by acetic acid up beyond 0.5 M. Brönsted and Guggenheim [THIS JOURNAL, **49**, 2573 (1927)] measured the rate of the mutarotation of glucose with formic acid up to 0.25 M, also without deviations from the linear relationship.

(4) Conant and Bartlett, Ref. 2, p. 2890.

The constant k_h is a difficult quantity to measure, since this reaction requires buffered solutions in order to yield velocity constants and therefore cannot be run in dilute strong acids. The value of k_h in the present case can be estimated by extrapolation from the first two points on the curve. The value so obtained is 8.8.

In Fig. 1 is shown the curve for Equation (1) when $k_h = 8.8$, $b = 149$ and $k_m = 0.119$. The closeness of fit of this curve supports the hypothesis of incomplete dissociation of the salt.

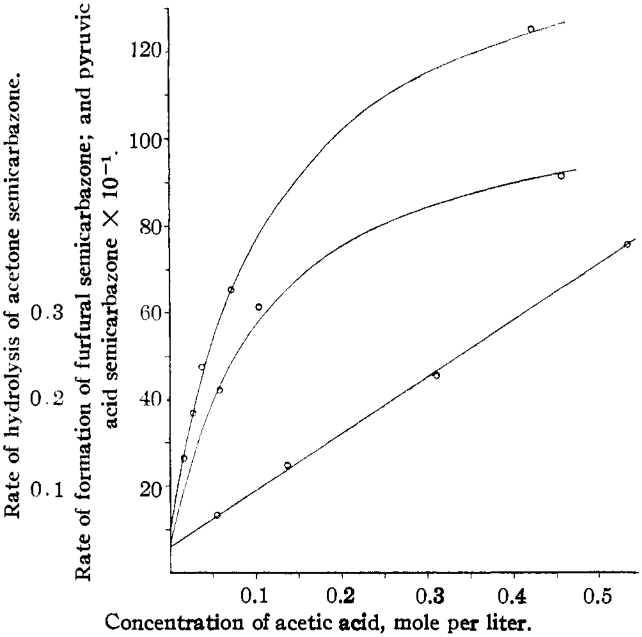

Fig. 1.—Reaction rate as a function of acetic acid concentration at 25°: upper curve, furfural + semicarbazide; middle curve, pyruvic acid + semicarbazide; lower curve, acetone semicarbazone + water.

That this non-linear relationship between reaction rate and catalyst concentration does not occur when semicarbazide is not one of the reactants is shown by the rates of *hydrolysis* of acetone semicarbazone at different concentrations of an acetate buffer of P_H 4.60. Here the rate is a linear function of the acid concentration up past 0.5 M (Fig. 1), as in the case of other acid-catalyzed reactions.

Equation (1) would fit equally well if the incomplete dissociation in question were that of a *furfural acetate.* However, if such a product existed in mobile equilibrium with its dissociation products, with as small a dissociation constant as 0.12, it could be easily prepared by dissolving furfural in glacial acetic acid. There is no noticeable heat effect on mixing these two liquids; and no product can be recovered from the solution except the furfural and acetic acid themselves.

A further evidence that the equilibrium measured concerns the semicarbazide, and not the aldehyde, is offered by three rate measurements on the formation of pyruvic acid semicarbazone in acetate buffers of different concentrations. Application of Equation (1) yields a value of K_m within 10% of that determined from the runs with furfural. If K_m does not vary with the nature of the carbonyl compound involved in the reaction, then the carbonyl compound does not enter into the measured equilibrium. The similarity of the curves of rate against acid concentration is shown in Fig. 1. The constants for the case of pyruvic acid are $k_h = 64$, $b = 1060$ and $K_m = 0.108$.

Since the successes of the Debye–Hückel theory, salts of the ammonium type have been generally regarded as completely dissociated in aqueous solution, and this is believed to be the first case where the dissociation constant of such a salt has been subject to measurement. This is not a favorable case for conductivity methods because of the high degree of "hydrolysis" of the salt. The positive ion of semicarbazide has $pK_A = 3.66$ at 25° at $\mu = 0.08$.[5] Acetic acid has $pK_A = 4.63$ at the same ionic strength.[6] Very closely, then, in any solution of semicarbazide acetate

$$\frac{[H_2NCONHNH_2]\,[CH_3COOH]}{[H_2NCONHNH_3^+]\,[CH_3COO^-]} = 10 \qquad (2)$$

Therefore if the *molecular* dissociation constant

$$K_m = \frac{[H_2NCONHNH_2]\,[CH_3COOH]}{[H_2NCONHNH_3OOCCH_3]} = 0.12$$

then the *ionic* dissociation constant

$$K_i = \frac{[H_2NCONHNH_3^+]\,[CH_3COO^-]}{[H_2NCONHNH_3OOCCH_3]} = 0.012$$

Since semicarbazide is only very slightly soluble in benzene (0.003 g. in 100 cc.), an attempt was made to measure the dissociation of semicarbazide acetate by distribution of acetic acid between benzene and an aqueous solution of semicarbazide acetate. But it was found that the presence of a small amount of acetic acid renders semicarbazide much more soluble in benzene. A molar solution of acetic acid in benzene will dissolve 0.5 g. of semicarbazide per 100 cc., or 160 times as much as pure benzene will dissolve. This disturbance is sufficiently great to render the distribution method unreliable.

Application to Preparation of Semicarbazones.—The incomplete dissociation of semicarbazide acetate has the consequence that the equilibrium reached in the hydrolysis of a semicarbazone, beside being determined by $P_{\rm H}$ in the manner found by Conant and Bartlett,[2] depends also

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(5) Bartlett, THIS JOURNAL, **54**, 2853 (1932). By an error in the manuscript, the correct values 3.68 at 24° and 3.66 at 25° appear interchanged in this paper.

(6) Cohn, Heyroth and Menkin, *ibid.*, **50**, 696 (1928).

upon the concentration of undissociated acid in acetate, and probably in varying degree also in other buffers. If we neglect the reaction due to hydrogen ion, which is a small fraction of k in strong buffer solutions, we may write the approximate equations

$$k' = c[\mathrm{HA}] \tag{3}$$

which defines c, the specific catalytic constant of the acid HA in the hydrolysis of the semicarbazone, and

$$k = \frac{b[\mathrm{HA}]}{[\mathrm{HA}] + K_\mathrm{m}} \tag{4}$$

then the equilibrium constant K for the hydrolysis is given approximately by

$$K = \frac{c}{b}(K_\mathrm{m} + [\mathrm{HA}]) \tag{5}$$

Therefore in preparing semicarbazones in the usual manner, from semicarbazide hydrochloride and sodium acetate, the yield is diminished if the acetic acid concentration is allowed to rise much above the value of K_m, or 0.12. When the acid is at this concentration, the rate of formation of the semicarbazone is, by Equation (1), at more than half its maximum value for that buffer, so that any advantage of having more acid present is more than offset by unfavorable effects on the equilibrium.

Theoretical Part

Derivation of Equation (1).—At a constant P_H a constant fraction of the semicarbazide present is in the free-base form. Dividing the observed velocity constants by this fraction gives these constants referred to the free-base form. The constants appearing in the tables have been so corrected. We may then, for simplicity, assume that the solution contains only the form $H_2NCONHNH_2$ (represented SH_2) in equilibrium with acetic acid (HA) and the undissociated salt (SH_3A). The dissociation constant of the latter is defined as

$$K_\mathrm{m} = [\mathrm{SH_2}]\,[\mathrm{HA}]/[\mathrm{SH_3A}] \text{ whence}$$
$$[\mathrm{SH_3A}] = [\mathrm{SH_2}]\,[\mathrm{HA}]/K_\mathrm{m}$$

Assuming that SH_3A is unreactive, the velocity constant due to HA as a catalyst, $(k - k_\mathrm{h})$, will be proportional to the fraction

$$[\mathrm{SH_2}]/([\mathrm{SH_2}] + [\mathrm{SH_3A}])$$

and to [HA]. Since HA in this work is a buffering acid, and its concentration is large compared to that of SH_3A, we may write

$$k - k_\mathrm{h} = a\,\frac{[\mathrm{SH_2}]\,[\mathrm{HA}]}{[\mathrm{SH_2}] + [\mathrm{SH_3A}]}$$

where a is a proportionality constant. Substituting from above for $[SH_3A]$, we have

$$k - k_\mathrm{h} = a\,\frac{[\mathrm{SH_2}]\,[\mathrm{HA}]}{[\mathrm{SH_2}](1 + [\mathrm{HA}]/K_\mathrm{m})} = \frac{aK_\mathrm{m}\,[\mathrm{HA}]}{K_\mathrm{m} + [\mathrm{HA}]}$$

Defining $b = aK_m$

$$k - k_h = \frac{b[\mathrm{HA}]}{[\mathrm{HA}] + K_m} \qquad (1)$$

For the purpose of fitting to data, Equation (1) is thrown into the form

$$b - \frac{k}{[\mathrm{HA}]} K_m = k - k_h$$

and the unknowns b and K_m are determined by the solution of normal equations formed from the several observations.

The Temperature Coefficient.—One of the unusual characteristics of the semicarbazone reaction is its very low temperature coefficient which, in the case of acetone reacting with semicarbazide in a phosphate buffer of *P*H 7, corresponds to a heat of activation of only 2500 calories. It has seemed plausible to regard this reaction as between one of the molecular species involved and a binary complex in equilibrium with the other two. If this complex were formed with evolution of heat, its greater dissociation at the higher temperatures would work to counteract its increased reaction rate in formation of the final product, thus explaining the low over-all temperature coefficient of the reaction.

One is therefore on the lookout for a complex in equilibrium with any two of the reactants in semicarbazone formation. With the discovery that molecular semicarbazide acetate exists in equilibrium with semicarbazide

TABLE I

RATE OF FORMATION OF FURFURAL SEMICARBAZONE AT 25.00 ± 0.01° AS A FUNCTION OF ACETIC ACID CONCENTRATION (DATA OF CONANT AND BARTLETT)

Fit of the equation $k = 8.8 + \frac{149[\mathrm{HA}]}{[\mathrm{HA}] + 0.119}$

[HA]	(k − 8.8) calcd.	k(calcd.)	k(obs.)	Deviation, %
0.0173	18.9	27.7	26.4	4.9
.0273	27.8	36.6	37.0	1.1
.0395	37.1	45.9	47.4	3.2
.0718	56.0	64.8	65.3	0.8
.424	116.1	124.9	125.4	0.4
			Average	2.1

The observed constants of Conant and Bartlett have been divided by 0.85, to be expressed in terms of pure SH_2 rather than a mixture of SH_2 and SH_3^+.

TABLE II

RATE OF FORMATION OF PYRUVIC ACID SEMICARBAZONE AT 25.00 ± 0.01° AS A FUNCTION OF ACETIC ACID CONCENTRATION

Fit of the equation $k = 64 + \frac{1060[\mathrm{HA}]}{[\mathrm{HA}] + 0.108}$

[HA]	(k − 64) calcd.	k (calcd.)	k (obs.)	Deviation, %
0.0585	372	436	420	3.8
.104	520	584	613	4.4
.457	857	921	915	0.6
			Average	2.9

TABLE III

RATE OF FORMATION OF FURFURAL SEMICARBAZONE AT 0.1 ± 0.1° AS A FUNCTION OF ACETIC ACID CONCENTRATION

Fit of the equation $k = 5.5 + \frac{84[\text{HA}]}{[\text{HA}] + 0.115}$

[HA]	(k − 5.5) calcd.	k (calcd.)	k (obs.)	Deviation, %
0.0259	15.5	21.0	22.1	5.0
.0568	27.8	33.3	31.6	5.4
.100	39.2	44.7	44.2	1.1
.148	47.3	52.8	49.9	5.8
.248	57.5	63.0	65.3	3.5
.405	65.6	71.1	72.6	2.1
			Average	3.8

and acetic acid, the hypothesis that this may be the desired intermediate, however improbable, deserves consideration.

Semicarbazide acetate is ruled out as the kind of intermediate sought, by the fact that K_m, determined from a set of buffer-dilution rate measurements with furfural at 0°, has the same value within the experimental accuracy as at 25°. It will be noticed, however, that on account of the constant ratio between $[\text{HA}][\text{SH}_2]$ and $[\text{SH}_3\text{A}]$, Equation (1) would apply equally well if SH_3A were the reactive form and SH_2 and HA were inactive.

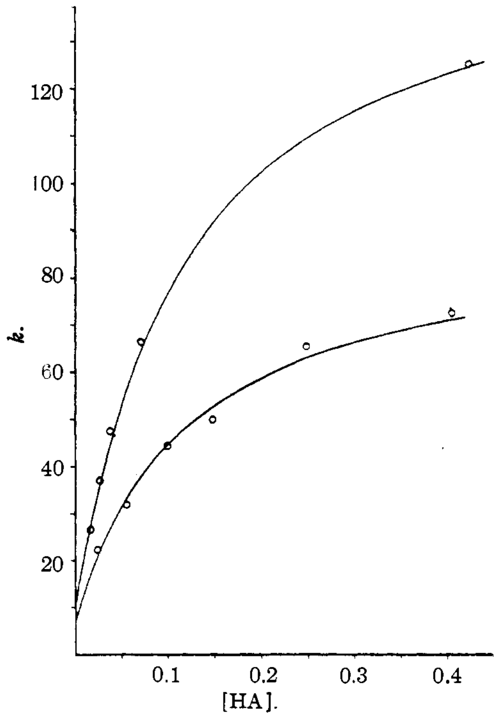

Fig. 2.—Rate of formation of furfural semicarbazone as a function of acetic acid concentration: upper curve, 25°; lower curve, 0°.

In Fig. 2 the curves of catalyst concentration *vs.* rate of reaction in formation of furfural semicarbazone at 25 and at 0° are shown. Extrapolation of the data at 0° yields a k_h of about 14, and direct application of the three-constant equation (1) gives a value of 8.3. It may be that the hydrogen-ion catalyzed reaction has a zero or negative temperature coefficient (Kilpatrick and Kilpatrick[7] have shown that the heat of activation of the mutarotation of glucose varies by as much as 1700 calories with different catalysts). But in

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(7) Kilpatrick and Kilpatrick, THIS JOURNAL, **53**, 3698 (1931).

this case, in view of the limited accuracy of extrapolation from the data, it seems more legitimate to estimate k_h at 0° by ascribing the same fraction of the catalysis at a given concentration to the hydrogen ion as at 25°. This has been done, and the value $k_h = 5.5$ is used in the calculations. This reaction should prove rewarding to more accurate physico-chemical study.

The constants obtained at 0° are $k_h = 5.5$, $b = 84$ and $K_m = 0.115$. The fit of the equation to the data is shown in Table III.

Question of the Reaction Path.—This reaction brings out clearly a fact inherent in all acid and basic catalysis. Consistent results have been obtained from the first by treating the reaction as if it were between the uncharged, basic form of semicarbazide and the ketone or aldehyde, catalyzed by the uncharged acetic acid. However, in any solution containing both a base B and an acid HA, on account of the equilibria

$$B + H^+ \rightleftharpoons BH^+ \text{ and}$$
$$A^- + H^+ \rightleftharpoons HA$$

there is, independent of P_H, a constant ratio

$$[B][HA]/[BH^+][A^-]$$

a relationship of which Equation (2) is the expression in the present case. It follows that any formulation of a reaction as an acid catalysis of any base, however weak, can be replaced by a formulation of the same reaction as a basic catalysis of the *conjugate acid* of the substrate. Semicarbazone formation might equally well be described as a reaction of the ion $H_2NCONHNH_3^+$, catalyzed by the acetate ion. None of the kinetic methods at our disposal will distinguish between the possible reaction paths.

If the temperature coefficient of this reaction had first been measured in acid solution, or if the basic catalysis interpretation had been applied, the heat of activation would have had the not unusual value of 14,100 calories, instead of the 3100 calculated from the rates at 0.100 *M* acid, in Tables I and III. This follows from the change in the relative acidity constants of the semicarbazide ion and acetic acid with the temperature, from which the heat value

$$H_2NCONHNH_2 + CH_3COOH \longrightarrow H_2NCONHNH_3^+ + CH_3COO^-;$$
$$\Delta H = -11{,}000 \text{ calories}$$

is obtained. Thus, the *pair of ions* $H_2NCONHNH_3^+$ and CH_3COO^- fulfil the thermodynamic criterion for an "intermediate" in the reaction, but this fact does not advance our knowledge of the mechanism.

Experimental Part

The velocity measurements on the hydrolysis of acetone semicarbazone and the formation of furfural and pyruvic acid semicarbazones were carried out in the manner previously described. Three acetate buffer solutions were used,[2] in varying dilutions.

Use	[HA]	[NaA]	P_H
Pyruvic acid runs	0.475	0.302	4.39
Furfural runs	.515	.515	4.59
Acetone semicarbazone runs	.467	.467	4.60

The ionic strength in these runs was not held constant, since the salt effect in the reaction is slight. However, this necessitates corrections in the more dilute solutions for the fact that the pK_A for semicarbazide ion changes with ionic strength in the opposite direction to the pK_A of acetic acid. pK_A for semicarbazide ion was taken as 4.40 above $\mu = 0.08$ at 0°, and was assumed below $\mu = 0.08$ to be equal to $4.26 + {}^1/_2 \sqrt{\mu}$.

For the runs at 25°, a thermostat regulated within 0.01° was used, and for the runs at 0°, an ice-bath.

The concentration of semicarbazide was determined by titration at P_H 7 with 0.02 N iodine. Five titrations were made during the course of a velocity run. The mean deviation of the constants in any one run was from 0.6 to 3.8%. The condensation velocity constants were corrected by dividing each by the fraction of the semicarbazide in the free-base form at the P_H of the reaction.

TABLE IV

DATA TO ILLUSTRATE DETERMINATION OF VELOCITY CONSTANTS FURFURAL + SEMICARBAZIDE AT 0.1 ± 0.1°

49.8 cc. buffer, 100 cc. water, 4.96 cc. each of 0.1604 M furfural and 0.0919 M semicarbazide hydrochloride. $y_0 = 0.00499$ (furfural); $x_0 = 0.00285$ ($[SH_2] + [SH_3^+]$); $[HA] + 0.148$; $P_H = 4.59$

$$kt = 1005 \log_{10} \frac{x + 0.002238}{x - 0.000055} + C$$

Minutes	Sample, cc.	Iodine, cc.	x	Fraction	Log	k	Dev.	%
1.15	10	4.57	0.00228	2.026	0.3066			
5.71	10	2.66	.1326	2.804	.4478	31.1	0.7	
10.72	10	1.65	.823	3.985	.6004	30.7	.3	
15.28	10	1.17	.583	5.345	.7279	29.8	.6	
20.12	10	.81	.405	7.55	.8779	30.1	.3	
210+	20	0.27			Average	30.4	.5	1.6
		.18	whence equilibrium $K = 0.00004$					
		.23						
		.20						

The solubility of semicarbazide in benzene, with and without acetic acid, was determined by extracting aliquot portions of the saturated benzene solution with 0.1 N hydrochloric acid, and titrating the extract, after bringing to P_H 7 with 0.02 N iodine: 2 cc. of saturated semicarbazide in benzene required 0.22 cc. of iodine; 2 cc. of saturated semicarbazide in 1 N benzene–acetic acid took 29.0 cc. of iodine solution, at 25°.

The data for hydrolysis rate of acetone semicarbazone as a function of catalyst concentration are given in Table V.

TABLE V

RATE OF HYDROLYSIS OF ACETONE SEMICARBAZONE AT 25°, AS A FUNCTION OF ACETIC ACID CONCENTRATION, P_H 4.60

[HA]	k	No. of detns.	Mean deviation, %
0.0550	0.0672	5	1.6
.1375	.124	3	3.2
.311	.226	5	3.1
.535	.379	2	0.8

The author is appreciative of the helpful interest shown in this work by Drs. D. A. MacInnes, Theodore Shedlovsky, and A. S. Brown, and by Professor V. K. La Mer; and is especially indebted to Professor J. M. Nelson for the hospitality of his laboratory, where this work was carried out.

Summary

1. Evidence is found that semicarbazide acetate, a salt of the ammonium type, is incompletely dissociated in aqueous solution, from the dependence of the rate of semicarbazone formation on acetic acid concentration.

2. The dissociation constant of this salt into molecules has the approximate value 0.12, both at 25 and at 0°.

3. Consequences of this new equilibrium effect, for semicarbazone preparation and for the mechanism of the reaction are discussed.

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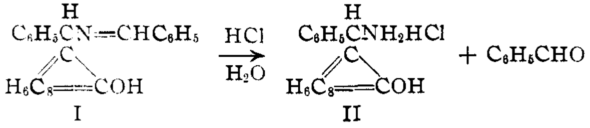
The Betti Condensation. Effect of Substituents on the Stability and Optical Rotation of the Resulting Amines

BY FRANCIS EARL RAY AND WILLIAM A. MOOMAW

In 1900 Mario Betti first reported the condensation of benzaldehyde, ammonia and β-naphthol to give a Schiff base, I. On hydrolysis with hydrochloric acid phenyl-β-naphtholaminomethane hydrochloride and benzaldehyde resulted,[1] II.



The reaction was extended by the use of primary amines instead of ammonia, and quite recently Littman and Brode[2] have further extended the application to secondary amines.

Betti[3] in a study of optical rotation has condensed his amine with sub-

(1) Betti, *Gazz. chim. ital.*, **30**, II, 310 (1900); **31**, I, 386 (1901).

(2) Littman and Brode, THIS JOURNAL, **52**, 1655 (1930).

(3) Betti, *Gazz. chim. ital.*, **36**, II, 392 (1906); **37**, I, 63 (1907); **46**, I, 200 (1916); **50**, II, 276 (1920).