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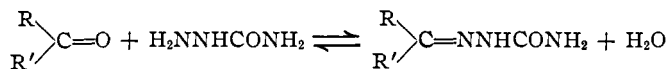
## IODIMETRIC TITRATION OF SEMICARBAZIDE<sup>1</sup>

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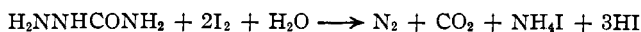
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The reaction of compounds containing the carbonyl group with nitrogen bases such as phenylhydrazine, semicarbazide and hydroxylamine, is one of the most general reactions of organic chemistry. A convenient and exact titration method for one of these nitrogen reagents therefore opens an important type reaction to quantitative study. Perhaps the most favorable case of this reaction for investigation is the formation of semicarbazones



This is so because the semicarbazones crystallize well and are conveniently water-soluble, also because semicarbazide is not rapidly autoxidized. The present paper describes a titration method for semicarbazide which has been applied to the study of rates and equilibria in semicarbazone formation.<sup>1a</sup>

Dilute aqueous semicarbazide has been found to react quantitatively with iodine in the proportion of four atoms of iodine to one molecule of semicarbazide. The reaction, which is attended by effervescence except at high dilution, is probably as follows



In this reaction semicarbazide is analogous to phenylhydrazine,<sup>2</sup> which reacts with iodine in the same proportion, and behaves differently from hydroxylamine, whose iodine equivalent varies with the concentration.<sup>3</sup>

Phenylhydrazine is inconvenient for reaction velocity studies because it and some of the phenylhydrazones are readily oxidized by the air. Just as semicarbazide is more stable in air than phenylhydrazine, so it is less rapidly attacked by iodine. Phenylhydrazine hydrochloride can be titrated with iodine, but the reaction between iodine and semicarbazide hydrochloride is very slow. Some rough tests were therefore made of the rate of this reaction in buffer solutions of different *P<sub>H</sub>* values, in order to determine the necessary conditions for quantitative reaction within the time of a titration.

**Reaction Rate as a Function of *P<sub>H</sub>*.**—Small samples of iodine and semi-

<sup>1</sup> From a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at Harvard University in 1931.

<sup>1a</sup> Conant and Bartlett, *THIS JOURNAL*, **54**, 2881 (1932).

<sup>2</sup> E. Meyer, *J. prakt. Chem.*, [2] **36**, 115 (1887).

<sup>3</sup> Ölander, *Z. physik. Chem.*, **129**, 1 (1927).

carbazine hydrochloride were added in equivalent amounts to 20 cc. of 0.5 *M* buffer solutions diluted to 70 cc., kept in a thermostat at  $25.00 \pm 0.01^\circ$ . Titrations were made with thiosulfate at short intervals. In all cases it was provisionally assumed that throughout the reaction one molecule of semicarbazide had disappeared for each four atoms of iodine which had reacted. The reciprocal of the semicarbazide concentration, calculated on this basis, increased linearly with time, showing that the reaction rate is controlled by a bimolecular step. Consistent results are obtained by the formulation

$$-dx/dt = kx \cdot 2x = 2kx^2$$

where  $t$  is the time in minutes,  $x$  is the concentration of semicarbazide and  $2x$  is the concentration of iodine in moles per liter. The values of  $k$  are computed from the experimental data by the integrated form

$$2k = \frac{1}{t} \left[ \frac{1}{x} - \frac{1}{x_0} \right]$$

$x_0$  being the initial concentration of the semicarbazide.

Table I gives the experimental data and the values of  $k$  for these runs at  $25^\circ$ . In these,  $x_0$  is 0.000238, so that  $1/x_0$  is 4200. The iodine solution used was 0.0336 *N* (0.0168 *M*). The figures in the column headed "Iodine" refer to the amount of iodine found in the reacting solution at the time of titration, expressed in cc. of stock solution.

TABLE I

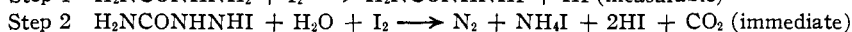
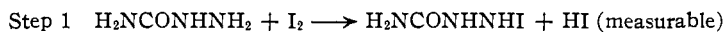
RATE OF REACTION OF IODINE WITH SEMICARBAZIDE AT $25.00 \pm .01^\circ$					
$P_H$	Minutes	Iodine	$1/x$	$(1/x - 1/x_0)$	$k$
1.48	0.93	1.63	5610	1410	750
	3.23	1.01	9055	4855	750
	4.25	0.89	10300	6100	720
	6.02	.70	13065	8865	730
2.02	0.30	1.68	5450	1250	2080
	.98	1.17	7810	3610	1840
	1.47	0.86	10640	6440	2190
	1.95	.70	13060	8860	2270
2.45	0.37	1.11	8240	4040	5410
	.63	0.86	10640	6440	5100
	1.25	.50	18300	14100	5640
	1.68	.39	23450	19250	5720
3.01	0.16	0.75	12200	8000	25000
	.27	.52	17600	13400	24800

At  $P_H$  3 the reaction has become almost too fast to measure, but the rates can be followed into solutions of higher  $P_H$  values by measurements at  $0^\circ$ . In these runs (summarized in Table II)  $x_0 = 0.000184$  and  $1/x_0 = 5435$ .

TABLE II

RATE OF REACTION OF IODINE WITH SEMICARBAZIDE AT 0.1 M ± 0.1°					
$P_H$	Minutes	Iodine	$1/x$	$(1/x - 1/x_0)$	$k$
3.01	1.02	1.63	7900	2465	1200
	2.00	1.01	11110	5675	1310
	3.12	0.89	13620	8185	1410
	3.97	.70	15320	9885	1230
3.57	0.48	1.19	10430	4995	5200
	.96	0.78	15920	10485	5450
	1.21	.68	18245	12810	5290
	1.76	.59	21000	15565	(4430)
	1.88	.50	24810	19375	5150
5.01	0.18	.68	18250	12815	35600
	.44	.38	32700	27265	31000
7.08	.10	.25	49600	44400	180000
	.15	.23	54000	48800	248000

The chemical interpretation of a measurable first step followed by an immediate second step may be as follows



The dependence of the reaction rate upon the  $P_H$  would also be explained if, according to this picture, it is the free, non-ionized form of semicarbazide which reacts. We should then expect the rate constant to be proportional to the fraction of the semicarbazide which is present in the non-ionized form at the  $P_H$  of the reaction. This is shown to be true up to  $P_H$  5 by dividing each value of  $k$  by that fraction, which we define as

$$F = \frac{(\text{H}_2\text{NCONHNH}_2)}{(\text{NH}_2\text{CONHNH}_2) + (\text{H}_2\text{NCONHNH}_3^+)}$$

Substituting the values for the semicarbazide positive ion (see below)  $pK_A = 3.68$  at  $25^\circ$  and  $4.40$  at  $0^\circ$ , in the equation

$$pK_A - P_H = \log \frac{(\text{H}_2\text{NCONHNH}_3^+)}{(\text{H}_2\text{NCONHNH}_2)} = \log (1/F - 1)$$

we find values of  $F$  as shown in Table III.

Within the accuracy of the rate determinations, the corrected velocity constant  $k/F$  is independent of  $P_H$  up to  $P_H$  5. This constancy through a set of buffer solutions involving different acids at different concentrations demonstrates the absence at these  $P_H$  values of any considerable catalysis by either acidic or basic substances in the buffers. On the other hand, rough as the measurements at  $P_H$  7 are, they show clearly that there is an increase of about five-fold over the value of  $k/F$  in the other buffers at  $0^\circ$ . This is probably due to an independent hypiodite reaction, analogous to the replacement of amide hydrogen by halogen, and yielding the same product as Step 1.

TABLE III  
 VELOCITY CONSTANTS REFERRED TO FREE SEMICARBAZIDE

Temp.	$P_H$	$(pK_A - P_H)$	$(1/F - 1)$	$1/F$	$k$	$k/F$
25°	1.48	2.20	159	160	740	118000
	2.02	1.66	45.7	46.7	2090	98000
	2.45	1.23	17.0	18.0	5470	99000
	3.01	0.67	4.68	5.68	24900	141000
Average at 25°						115000
0°	3.01	1.39	24.6	25.6	1290	38000
	3.57	0.83	6.76	7.76	5270	41000
	5.01	-.61	0.246	1.25	33300	42000
	7.08	-2.68	.002	1.00	214000	214000
Average at 0° (omitting $P_H$ 7.08)						39000

**Conditions of Titration.**—This acceleration makes the reaction an acceptable titration method at  $P_H$  7. Using the procedure described below, 99.9% of the semicarbazide present reacts with iodine in three seconds.

Experiments on the rate of reaction of iodine with semicarbazones will be described in a later communication.<sup>1a</sup> In no case is this reaction rapid enough to be a significant source of error when titrating semicarbazide in the presence of semicarbazones.

On the basis of this study, the following procedure is employed in titrating semicarbazide with iodine. To 20 cc. of a 0.5  $M$  phosphate buffer of  $P_H$  7 (or, in the case of reactions taking place in acid solutions, the calculated amount of di-sodium phosphate to bring the  $P_H$  of the resulting solution to 7) enough 0.02  $M$  iodine is added from a buret to provide a 2.5-cc. excess. A sample of the reacting solution is then added from a pipet and the excess of iodine is titrated back with thiosulfate.

**Basicity of Semicarbazide.**—The basicity of semicarbazide, expressed in terms of the acid dissociation constant  $K_A$  of the ion  $H_2NCONHNH_3^+$ , was determined at 24° (room temperature) and at 0° by potentiometric titration of semicarbazide hydrochloride with standard sodium hydroxide. The value of  $pK_A$ , the negative logarithm of  $K_A$ , was taken as equal to the  $P_H$  at the point of half neutralization on the curves shown in Fig. 1. The semicarbazide hydrochloride was tenth normal, and the ionic strength at the midpoint was 0.079. The values found for  $pK_A$  were 3.66 at 24° and 4.40 at 0°. Such values, of course, involve the magnitude of the activity coefficient of the semicarbazide positive ion ( $\gamma$ ) and are therefore not the same at all ionic strengths. The quantity determined experimentally is

$$pK_A = P_H - \log \frac{(H_2NCONHNH_2)}{(H_2NCONHNH_3^+)} = pK - \log \gamma$$

If the approximate limiting equation held for the relation between  $\gamma$  and ionic strength at high dilutions

$$-\log \gamma = 0.5 \sqrt{\mu}$$

the value of  $-\log \gamma$  at  $\mu = 0.079$  would be 0.14, and the value of  $pK$  (infinite dilution) would be 3.52 at 24° and 4.26 at 0°. The experimentally determined values for  $pK_A$  were used in all the calculations, since semicarbazide was worked with in solutions of  $\mu = 0.08$  and higher.  $pK_A$  at 25° was computed from its values at room temperature and 0° by applying the integrated form of the van't Hoff formula. This yields the value 3.68 for  $pK_A$  at 25° and  $\mu = 0.079$ .

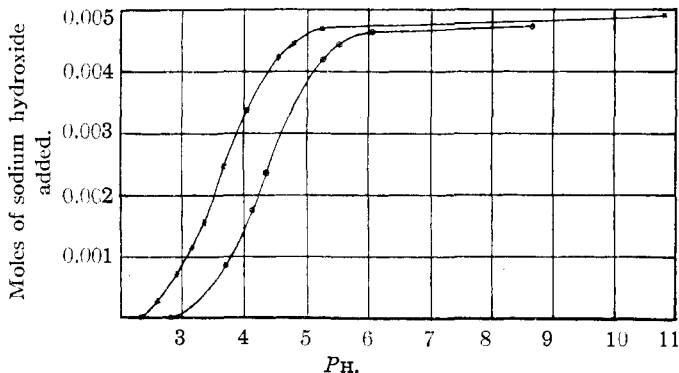


Fig. 1.—Titration of semicarbazide with sodium hydroxide: Crosses, 24°, Circles, 0°.

Two determinations of the basicity of semicarbazide are reported in the literature. Wood<sup>4</sup> reported  $K_B$  at 40.2° to be  $2.6 \times 10^{-11}$ , from studies of the hydrolysis of methyl acetate. Veley,<sup>5</sup> using methyl orange and a colorimeter, reported this constant to be  $9.1 \times 10^{-9}$  at 15°. The  $pK_A$  values corresponding to these are 2.90 and 6.25, respectively. Thus Wood's catalytic constant is in reasonable agreement with the present potentiometric results, while the work of Veley is not substantiated.

### Experimental

The iodine-potassium iodide solution was standardized against weighed potassium bromate by comparing both with the thiosulfate solution on the same day. The iodine was 0.03365 *N*.

Semicarbazide hydrochloride from the Eastman Kodak Co. was recrystallized from alcohol-water. Its tenth normal solution was standardized by potentiometric titration with standard sodium hydroxide.

In the potentiometric titrations, a saturated calomel half-cell was used which had been standardized at the beginning of the run against a tenth normal calomel half-cell, whose single potential of 0.3377 volt at 24° was

<sup>4</sup> Wood, *J. Chem. Soc.*, **83**, 568-578 (1903).

<sup>5</sup> Veley, *ibid.*, **93**, 652-666 (1908).

in turn checked by measuring its e. m. f. against a  $M/20$  solution of potassium hydrogen phthalate of assumed  $P_H$  3.974.<sup>6</sup>

The buffer solutions were composed approximately as follows

$P_H$	Acid	Concentration	Salt	Concentration
1.48	$H_3PO_4$	0.295	Mono-sodium	0.205
2.02	$H_3PO_4$	.155	Mono-sodium	.345
2.45	$H_3PO_4$	.425	Mono-sodium	.075
3.01	Citric	.25	Mono-sodium	.25
3.57	Citric	.08	Mono-sodium	.42
5.01	Acetic	.17	Sodium	.33
7.08	$NaH_2PO_4$	.06	Di-sodium	.14

In measuring the rates of reaction at  $25^\circ$ , the following procedure was used. In each of a series of Erlenmeyer flasks were put 20 cc. of the appropriate buffer solution, 50 cc. of distilled water, and 5 cc. of a prepared iodine solution containing 2.18 cc. of the standard iodine. This was the amount calculated to react with 2.02 cc. of 0.00909  $M$  semicarbazide hydrochloride, which was added to the flask from a pipet when the flasks had come to temperature in the thermostat. The several samples were thus identical and the excess iodine in the different flasks was titrated after suitable lengths of time. The time was measured to 0.01 minute with a stop watch.

In measuring the rate at  $0^\circ$  a similar procedure was used except that the total concentration of diluted reacting solution was in this case 100 cc., and the volumes of semicarbazide hydrochloride and of iodine solutions were, respectively, 2.02 and 2.39 cc. The reaction mixtures were kept in an ice-bath.

### Summary

1. Semicarbazide reacts quantitatively, one molecule with four atoms of iodine.
2. The reaction is bimolecular; its rate is proportional to the non-ionized fraction of the semicarbazide up to  $P_H$  5, but is considerably accelerated at  $P_H$  7.
3. At  $P_H$  7 the reaction is rapid enough to provide a suitable titration method for semicarbazide.
4. The basicity of semicarbazide has been determined by potentiometric titration at 0 and at  $24^\circ$ .

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<sup>6</sup> Clark, "Determination of Hydrogen Ions," Williams and Wilkins Co., Baltimore, Md.