the acetates of glucose, cellobiose and cellotriose has been developed.

2. Identity period measurements and calculations of these built-up crystals have been obtained.

3. Speculations upon the spacings of these compounds in relation to the cellulose molecule have been presented.

RECEIVED MAY 24, 1934

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Semicarbazone Formation in Sixty Per Cent. Methyl Cellosolve[1]

BY FRANK H. WESTHEIMER[2]

In a recent paper Conant and Bartlett[3] determined the kinetics and equilibria of semicarbazone formation in aqueous solution. They found that the bimolecular addition

$$R_1R_2CO + NH_2NHCONH_2 \rightleftharpoons R_1R_2COHNHNHCONH_2$$

is the rate determining step, while the dehydration

$$R_1R_2COHNHNHCONH_2 \rightleftharpoons R_1R_2C{=}NNHCONH_2 + H_2O$$

follows instantaneously. The reaction is acid catalyzed and the dependence of the rate of condensation on acidity was, in two cases, worked out. The present study was undertaken to determine the changes caused by operating in a semi-aqueous solvent. The one chosen was a mixture of sixty per cent. by volume of methyl cellosolve and forty per cent. of water.

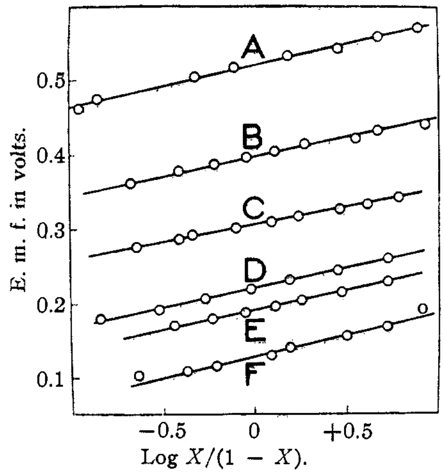

Fig. 1.—A, tributylamine-HCl; B, *p*-nitrophenol-NaOH; C, acetic acid-NaOH; D, dimethylaniline-HCl; E, monochloroacetic acid-NaOH; F, dichloroacetic acid-NaOH.

Since the reaction in water is dependent upon acidity, it was necessary to know the comparative acidities of various buffer solutions in the new solvent. The first part of this paper deals, then, with hydrogen ion determinations, the second with the kinetics of semicarbazone formation, in sixty per cent. methyl cellosolve.

Acidities

The acidities were measured by electrometric titration. This method, as generally applied, measures the e. m. f. set up between an aqueous calomel cell and the buffer solution in question in the particular non-aqueous or semi-aqueous solvent used.[4] That this method is not subject to error due to the mixed solvent junction has recently been established by Halford.[5]

The antimony electrode so successfully employed by Halford in his butyl carbitol-water mixture was chosen for this work. The results of the titrations gave a series of buffers covering a larger range of acidities than that needed in the kinetic work. Figure 1 is a graph of the titrations, where the e. m. f. is plotted against log $X/(1-X)$ (X is the fraction of the acid neutralized). All the curves have practically the same

TABLE I

STRENGTH OF ACIDS, COMPARED TO ACETIC ACID, IN 60% METHYL CELLOSOLVE

Acid	ΔpK Water[6]	60% Methyl cellosolve
Chloroacetic	−1.9	−2.2
Dichloroacetic	−3.5	−3.5
p-Nitrophenol	2.5	1.6
Semicarbazonium ion	−1.1	−2.4
Tributylammonium ion	5.2	3.9
Dimethylanilinium ion	0.3	−1.7

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(1) Trade name for glycol monomethyl ether.

(2) John Harvard Fellow, 1933–1934.

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

(4) (a) Hall and Conant, *ibid.*, **49**, 3047 (1927); (b) Conant and Hall, *ibid.*, **49**, 3062 (1927); (c) Hall and Werner, *ibid.*, **50**, 2367 (1928); (d) Conant and Werner, *ibid.*, **52**, 4436 (1930); (e) Halford, *ibid.*, **53**, 2944 (1931); (f) Bright and Briscoe, *J. Phys. Chem.*, **37**, 787 (1933).

(5) Halford, THIS JOURNAL, **55**, 2272 (1933).

(6) The aqueous values for the acids are taken from the "I. C. T." The value for the semicarbazonium ion was determined by Conant and Bartlett. The *pK* of dimethylanilinium ion and tributylammonium ion were taken from Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

slope; the close approach of the experimental points to straight lines testifies to the success of the titrations. In Table I the difference in *p*K between the acids listed and acetic acid are given, both for water and for 60% methyl cellosolve. For the latter solvent, the average value of the slope of the lines in the graph, 54 millivolts per *p*K unit, is used.

Experimental

Cells and Electrodes.—The cells and electrodes were of the same type as those employed by Halford.[4e] Two electrodes in the same solution usually agreed within two millivolts; the end-points were sharp.

Procedure.—A given acid of known concentration (about 0.1 *N*) was titrated with sodium hydroxide, and the potential of the cell measured three minutes after each addition of base. After the base had been added, the e. m. f. of the cell quickly became constant, and remained so for about ten minutes. After this, a drift, similar to that noted by workers with the antimony electrode in water solution, set in.[7] To minimize and standardize the salt effect, all solutions were made 0.1 *M* in lithium chloride. A half neutralized solution of acetic acid was taken as standard, and only differences in potential between a given acid solution and this buffer were considered. Successive values of the potential difference between two solutions varied by 8 millivolts or less. All measurements were made at 25 ± 1°. The solutions were slowly stirred throughout the measurements.

Kinetics.—The technique for the kinetic measurements discussed later in this paper was the same as that used by Conant and Bartlett.[8] The iodimetric titration[8] for determining the amount of semicarbazide proved reliable when the 10-cc. samples removed for analysis were first diluted with 100 cc. of water containing enough secondary sodium phosphate to bring the *p*H up to 7. The temperature was controlled by a thermostat to 25.1 ± 0.1°. In order that the salt effect should be small and should correspond with the titrations, all solutions were brought to an ionic strength of 0.2 with lithium chloride.

Blanks were run to prove that the time was insufficient for the reaction between chloroacetic acid and sodium thiosulfate to interfere with the analysis, nor did the reaction between chloroacetic acid and semicarbazide advance appreciably. The chloroacetate buffers were made up fresh from time to time to guard against hydrolysis. Hydrolysis constants were determined in the manner used by Conant and Bartlett. When they were large enough to be significant, these constants were incorporated in the rate equation.

Materials.—Methyl cellosolve, obtained from the Carbide and Carbon Company was treated with silver oxide and sodium carbonate to remove aldehydes, and was then carefully fractionated. Since some samples contained considerable aldehyde, each batch of material was tested by means of a blank with semicarbazide, it being required that the titer of the latter remain constant over the period of the velocity determinations. Eastman semicarbazide hydrochloride was repeatedly recrystallized from dilute alcohol until it titrated 99.5–100% pure with standard iodine. It melted at 177°. Monochloroacetic acid, recrystallized from benzene, melted at 62°, *o*-nitrobenzaldehyde, recrystallized from water, at 43–44°, *p*-nitrophenol at 114°. All other organic chemicals were distilled, either at normal or diminished pressure, except the butylamine. This was a sample from du Pont marked "mixed butyl amines, about 80% tributyl amine."

Experimental Results

The following is a table of hydrolysis constants. With the exception of citronellal, the constants for the aldehydes considered were less than 10^{-5}.

TABLE II

HYDROLYSIS CONSTANTS OF SEMICARBAZONES

Carbonyl compound	60% Methyl cellosolve Acetate buffer $E = 0.340$ v.	Monochloroacetate buffer $E = 0.192$ v.	Water *p*H 7
Acetone	4.3×10^{-4}	8.5×10^{-4}	3.24×10^{-3}
Diethyl ketone	2.9×10^{-3}	6.5×10^{-3}	2.14×10^{-3}
Cyclohexanone	3.5×10^{-4}	5.5×10^{-4}	1.26×10^{-2}
Pinacolone		1.9×10^{-3}	
Acetophenone		3.4×10^{-4}	
Citronellal	3.4×10^{-5}		

In the kinetic work, furfural and acetone (the same compounds used by Conant and Bartlett) were condensed with semicarbazide in acetate, monochloroacetate and dichloroacetate buffers, and with two differing buffer molalites. The biomolecular constants show an average deviation from the mean of 8%. In the acetate buffers the reaction is approximately bimolecular. A two-fold variation in the concentration of both reactants varied the velocity constant of a condensation of acetone with semicarbazide from 8.4 to 9.1. A furfural run in a 0.2 *M* acetate buffer gave the following successive values for the condensation constant: 1.62, 1.71, 1.58, 1.57. However, in more acid solutions (chloroacetate buffers) a two-fold increase in concentration changed the velocity constant of the condensation of furfural with semicarbazide from 16.2 to 12.2. In these solutions there was also a decided drift toward lower values of the constant as the run progressed. An example of successive values of an acetone constant are as follows: 12.6, 10.7, 9.0, 9.8, 8.2, 8.8.

The dependence on acidity and molality of buffer solutions of the rate of condensation of acetone and of furfural with semicarbazide is shown in Figs. 2 and 3. For comparison, the corresponding graphs in aqueous solution, taken from the data in Bartlett's thesis,[9] are placed

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[7] Robinson and Britton, *J. Chem. Soc.*, 458 (1931).

[8] Bartlett, THIS JOURNAL, **54**, 2853 (1932).

[9] Bartlett, "Dissertation," Harvard University, 1931.

above those representing the work in 60% methyl cellosolve. Since there is no absolute means of comparing acidities in different solvents half neutralized solutions of acetic acid have been placed on the same abscissa. It is at once obvious that the curves in methyl cellosolve solution, while very similar to the aqueous ones, are displaced into the acid region. Also, while Conant and Bartlett[3] found that, with respect to any particular condensation and any particular buffer, the rate varied linearly with the buffer molality, at least when this latter had values of 0.1 or less, this situation does not obtain here, as is shown by the varying distance apart of the curves for the 0.05 and 0.2 M buffers. With substances other than furfural and acetone, no such extensive study was made, and the rates were determined only in the most basic 0.05 M acetate buffer, and at the maximum (as indicated by the furfural and acetone curves) in 0.2 M chloroacetate buffers. The table of the rate constants appears below. Since the values for aqueous solution determined by Conant and Bartlett depend linearly on molality, the absolute values of the ratio A/C are accidental.

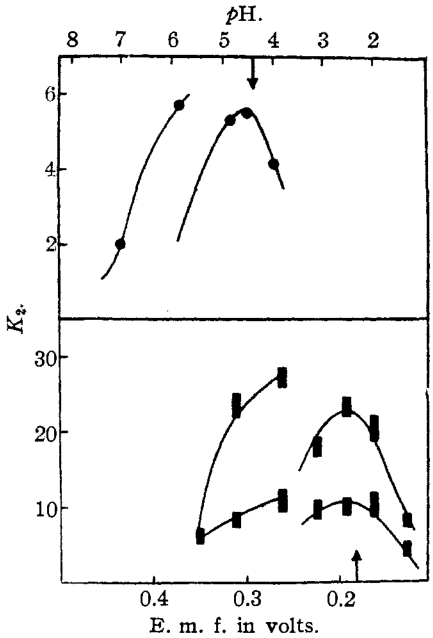

Fig. 2.—Condensation velocity of acetone and semicarbazide: above, in water solution at 0.1°, 0.045 M buffers (from Bartlett's data); below, in 60% methyl cellosolve at 25.1°, upper curves, 0.2 M buffers, lower curves, 0.05 M buffers.

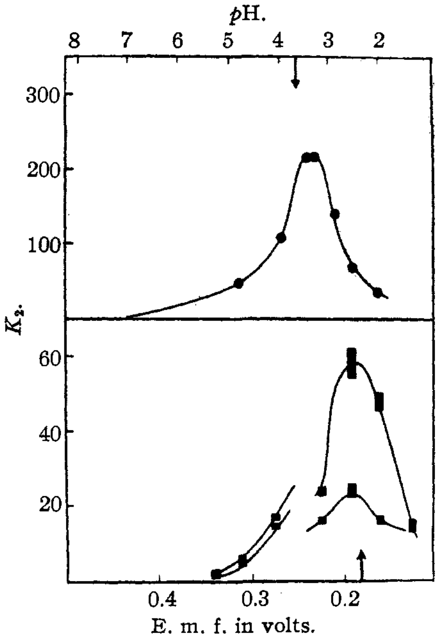

Fig. 3.—Condensation velocity of furfural and semicarbazide: above, in water solution at 25.0°, 0.5 M buffers (from Bartlett's data); below, in 60% methyl cellosolve at 25.1°, upper curves, 0.2 M buffers, lower curves, 0.05 M buffers.

TABLE III

RATES OF SEMICARBAZONE FORMATION

Carbonyl compound	A. 0.05 M acetate buffer	B. 0.02 M monochloroacetate buffer	C. Water pH 7, 0.1 M buffer	Ratio B/A	Ratio A/C
Furfural	1.62	58.3	0.73	36	2.2
Benzaldehyde	5.1	145	2.05	28	2.5
o-Nitrobenzaldehyde	1.61	78		48	
Cinnamic aldehyde	6.8	66.5		9.8	
Butyric aldehyde	113	fast			
Heptaldehyde	68	fast			
Citronellal	31.6	fast			
Acetone	5.92	23.2	6.02	3.9	0.98
Diethyl ketone	1.7	11.1		6.5	
Pinacolone	0.41	1.48	0.068	3.6	6.0
Acetophenone	.33	2.8		8.5	
Cyclohexanone	24.9	fast	36		0.69

Discussion of Results

Before these facts can be interpreted intelligently, it is necessary to review the theory advanced by Conant and Bartlett to explain the results in aqueous solution. They assumed that reaction takes place between neutral semicarbazide molecules and the aldehyde or ketone in question, and that the condensation is catalyzed by acid molecules. Under these conditions, decreasing *p*H would increase the rate, since a more acid buffer would either contain more of a given acid, or else be composed of a stronger acid. This, of course, allows for discontinuities in the *p*H–rate graph whenever a change in the acid constituting the buffer occurs. However, when the *p*H falls to the *pK* of the semicarbazonium ion, free semicarbazide would be converted into the ammonium type ion, and the rate would decrease, despite increasing acidity, due to the waning concentration of one of the reactants. This theory requires that the maximum rate should occur at the *pK* of the semicarbazonium ion; and that this prediction was amply verified at two different temperatures may be seen by inspecting the uppermost curves in Figs. 2 and 3 where the arrows indicate the *pK* of the semicarbazonium ion.

In the methyl cellosolve–water mixture, as can be seen from Table I, the *pK* of the semicarbazonium ion is displaced, with respect to a half-neutralized solution of acetic acid, a unit and a third into the acid region, yet here again, as shown by the arrows in the lower curves in Figs. 2 and 3, the maximum occurs exactly at the *pK* of the semicarbazonium ion.

Inspection of Table III at once reveals the fact that the "relative reactivities" of the various carbonyl compounds studied is not the same in the acetate as in the chloroacetate buffer. In fact, while the acetone rate is four times as large as that of *o*-nitrobenzaldehyde in the more basic solution, at the maximum the aldehyde rate is three times greater than that of the ketone. A still more striking example is recorded by Conant and Bartlett in water solution, where the ratio of the rate of condensation with semicarbazide of furfural to the rate of condensation of acetone, increases, from *p*H 7 to the maximum rates recorded, by a factor of 55. Further, if the most basic acetate buffer in 60% methyl cellosolve is analogous to *p*H 7 in water, then the last column in Table III indicates that we can expect changes in relative rate, due to a change of solvent, of as much as a power of ten. It becomes at once apparent, then, that, unless a definite acidity and a definite solvent are specified, "relative reactivities" of carbonyl compounds, measured by the rate of condensation with the ammonia bases in solution, can be considered accurate only within several powers of ten. This does not, in any way, mean that there are not differences between carbonyl compounds in activity. Butyric aldehyde is under all conditions faster than acetophenone, corresponding to the organic chemist's qualitative ideas on the subject. The data do indicate, however, that any numbers assigned to this difference are all but meaningless.

The author wishes to thank Dr. James B. Conant, who suggested this problem, and whose assistance during its progress was invaluable.

Summary

1. The acidities of buffer solutions in 60% methyl cellosolve have been measured by electrometric titration with the antimony electrode.

2. The rate of condensation of semicarbazide with some aldehydes and ketones has been measured in these buffers.

3. These rates have been compared with those obtained in aqueous solution by Conant and Bartlett. Their theory of the mechanism of the reaction has, in general, been verified.

4. The implications raised by the fact that the dependence of reaction rate on acidity varies among carbonyl compounds, as they concern the question of "relative reactivity," have been discussed.

CAMBRIDGE, MASS. RECEIVED MAY 25, 1934