droxide solution, water, and finally dried over magnesium sulfate and evaporated. The solid material was taken up in hot 95% ethanol once the solution was treated with Norit and filtered. In this way 160 mg. of (+)-1,2,2-triphenylethyl acetate was isolated, m.p. 140°, $[\alpha]^{25}\text{D}$ +26° (dioxane). Still more N-acetyl-1,2,2-triphenylethylamine remained in the alcoholic mother liquors. The identity of the (+)-1,2,2-triphenylethyl acetate was established by deacetylation to (+)-1,2,2-triphenylethanol, followed by oxidation of the carbinol to benzhydryl phenyl ketone. The ketone was oxidized[6] with nitric–acetic acid to α-phenylbenzoin which was oxidized with chromic acid to benzophenone and benzoic acid.[24]

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(24) The preparation of the N-nitrosoacyl-1,2,2-triphenylethylamine and its subsequent thermal decomposition were carried out by Mrs. Joan B. Christie. Further details will be published at a later date.

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[CONTRIBUTION FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY]

Studies on the Mechanism of Oxime and Semicarbazone Formation[1]

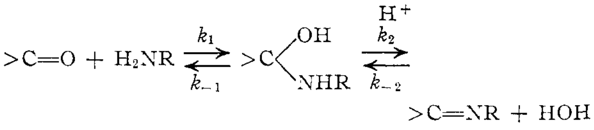
BY WILLIAM P. JENCKS

RECEIVED JUNE 23, 1958

At neutral pH hydroxylamine and semicarbazide react rapidly with a number of aldehydes and ketones to form addition compounds which lack the ultraviolet and infrared absorption of the original carbonyl compound. These addition compounds undergo a slow, acid-catalyzed dehydration to form oxime or semicarbazone. The decrease in the rate of oxime formation at acid pH appears to be due to a transition to a rate-limiting attack of free nitrogen base on the carbonyl compound and is not dependent on general acid catalysis. Dehydration of the addition complex, addition of water to the oxime or semicarbazone and addition of semicarbazide to the carbonyl group are subject to both specific and general acid catalysis, while the addition of the stronger base, hydroxylamine, to the carbonyl group is specific acid-catalyzed to only a small extent.

The classical experiments of Barrett and Lapworth,[2] Olander,[3] Conant and Bartlett,[4] and Westheimer[5] demonstrated that the reactions of carbonyl compounds with such nitrogen bases as hydroxylamine and semicarbazide exhibit striking maxima in their pH–rate profiles. These pH optima have been attributed to the opposing effects of general acid catalysis and the decrease in the concentration of attacking free nitrogen base due to conversion to the conjugate acid at low pH.[4,6]

The observation that hydroxylamine reacts rapidly with p-nitrophenyl esters at neutral pH without significant acid catalysis (to give a mixture of O- and N-substituted products)[7] suggested that in the relatively slow, acid-catalyzed reaction of hydroxylamine with aldehydes and ketones the addition of nitrogen base to the carbonyl group might not be the rate-limiting step. The kinetics of oxime and semicarbazone formation have accordingly been studied by following the changes in the ultraviolet absorption of a number of carbonyl compounds in aqueous solution after the addition of the appropriate nitrogen base. It has been found that at neutral pH the attack of nitrogen base on the carbonyl compound is fast, so that the over-all rate is dependent on the equilibrium concentration of a non-absorbing addition compound and on the rate of its acid-catalyzed dehydration. The pH–rate maxima for oxime formation appear to be the result of a transition to a rate-limiting attack of free nitrogen base on the carbonyl compound at acid pH and are not dependent on general acid catalysis.



$$>C{=}O + H_2NR \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} >C\begin{matrix}OH\\NHR\end{matrix} \underset{k_{-2}}{\overset{H^+\ k_2}{\rightleftharpoons}} >C{=}NR + HOH$$

Experimental

Materials.—Benzaldehyde and furfural were redistilled and stored at −15°; solutions in water, containing 10^{-4} M ethylenediaminetetraacetic acid (EDTA) to retard heavy metal catalyzed decomposition, were made up just before use. Solutions of nitrogen bases were prepared from the solid or from stock solutions of the hydrochloride and were neutralized to the desired pH with NaOH just before use; 10^{-4} M EDTA was added to alkaline solutions. Glass-distilled water was used throughout.

Ultraviolet measurements were made on a Cary model 14 recording spectrophotometer, a Beckman model DU spectrophotometer or a Zeiss model PMQ II spectrophotometer. Infrared spectra were obtained with a Perkin–Elmer model 21 spectrophotometer using calcium fluoride cells. Solutions of hydroxylamine in D_2O were prepared by dissolving $NH_2OH \cdot HCl$ and NaOH in D_2O, evaporating to dryness, making up 4 M solutions in D_2O and neutralizing just before use.

Kinetic measurements were made on Beckman or Zeiss spectrophotometers with jacketed cell compartments through which was circulated water from a thermostat at 25.0 ± 0.1°. Dilute solutions of the reactants were equilibrated in the thermostat before mixing. Readings were taken beginning 10 to 15 seconds after the start of the reaction and continued, usually with about 10 readings, until the reaction had proceeded to completion. All kinetic determinations were carried out with the concentration of nitrogen base greatly in excess of that of the aldehyde or ketone so that pseudo first-order kinetics were obtained. The results were plotted on semi-logarithmic graph paper, the half-times determined graphically, and the first-order rate constants obtained from the formula $k_1 = 0.693/t_{1/2}$. Rates were followed at a wave length, as indicated in the experimental data, suitable for measurement of product appearance or, after the initial rapid drop, of starting material disappearance; in several cases rate constants were determined under both conditions and found to be identical. The pH values reported are the apparent pH as measured with the glass electrode of the Beckman model G pH meter.

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(1) Publication #14 of the Graduate Department of Biochemistry, Brandeis University. Presented at the 134th National Meeting of the American Chemical Society in Chicago, September, 1958.

(2) E. Barrett and A. Lapworth, *J. Chem. Soc.*, **93**, 85 (1908); *cf.* also S. F. Acree and J. M. Johnson, *Am. Chem. J.*, **38**, 308 (1907); D. G. Knorre and N. M. Emanuel, *Doklady Akad. Sci. S.S.S.R.*, **91**, 1163 (1953) (*C. A.*, **49**, 12936 (1955)).

(3) A. Olander, *Z. physik. Chem.*, **129**, 1 (1927).

(4) J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 2881 (1932).

(5) F. Westheimer, *ibid.*, **56**, 1962 (1934).

(6) L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, p. 331.

(7) W. P. Jencks, THIS JOURNAL, **80**, 4581 (1958); **80**, 4585 (1958).

Results

In Fig. 1 are shown spectra of dilute aqueous solutions of furfural at neutral *p*H obtained with a rapid scanning spectrophotometer (A) before, (B) 30 to 90 seconds after and (C) two hours after the addition of hydroxylamine, O-methylhydroxylamine or semicarbazide. In each case there is an initial decrease in the furfural absorption which is proportional to the amount of base added and which increases in the order semicarbazide < O-methylhydroxylamine < hydroxylamine. This is followed by the slow appearance of the characteristic absorption of the oxime or semicarbazone over a two-hour period. Similar spectral changes were observed with benzaldehyde and pyruvate on addition of the same nitrogen bases.

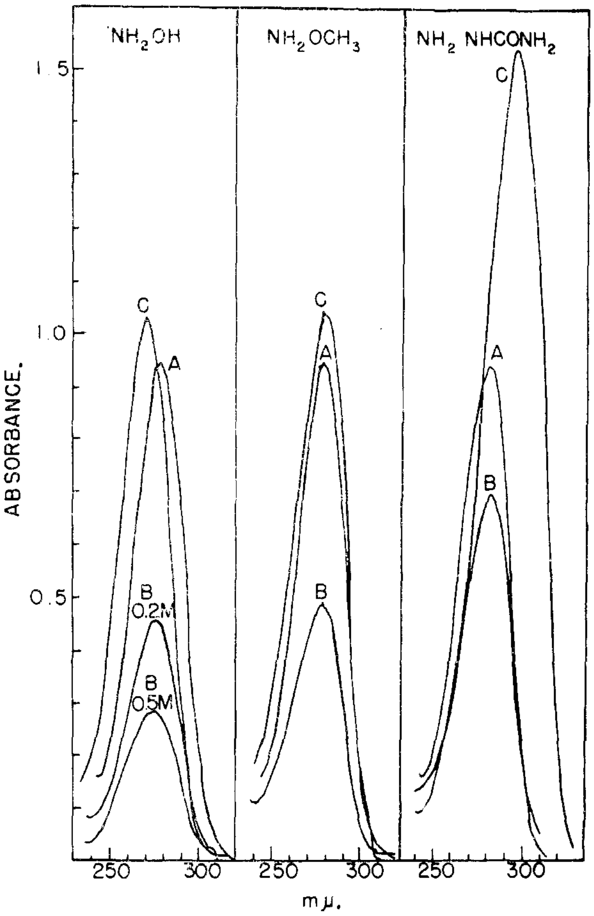

Fig. 1.—Spectra of furfural in water: (A) before, (B) 30–90 seconds after and (C) two hours after addition of the indicated nitrogen base. The base was neutralized to *p*H 7.2–7.4 and added to a final concentration of 0.5 *M* except as indicated. Samples containing base were read against a blank containing the same concentration of base.

The absorption maxima of the final products of the reaction of furfural and benzaldehyde correspond to those of α-furfuraldoxime (in water) and α-benzaldoxime (in 25% ethanol) at 271 and 252 mμ, respectively, and not to those of the β-isomers at 267 and 245 mμ; in the case of furfural the same product was observed over the entire range of *p*H investigated (*cf.* ref. 8).

The initial decrease in absorption on mixing carbonyl compound and nitrogen base indicates that a compound other than the final product is formed from these reactants. This is assigned the carbinolamine, $R_2C(OH)NHR$, structure by analogy with known addition compounds of hydroxylamine, semicarbazide and ammonia with carbonyl compounds which contain strongly electron-withdrawing groups.[9,10] Molecular or charge transfer complexes appear unlikely on chemical grounds and in view of the fact that no change in the carbonyl absorption of pyruvate was found in 0.2 *M* N-dimethylhydroxylamine or 0.2 *M* trimethylamine.

Equilibrium constants for addition compound formation were obtained for a number of carbonyl compounds and nitrogen bases by measuring the carbonyl absorption at short intervals after the addition of 4 or more different concentrations of nitrogen base and estimating the extent of the initial drop in absorption by extrapolation to zero time (Table I). As the further formation of oxime or semicarbazone is slow at neutral or slightly alkaline *p*H, the extrapolation was small for all compounds examined except acetone and cyclohexanone. These two compounds react rapidly even at *p*H 8 and required extrapolation amounting to 15–30% of the total absorption; the equilibrium constants for these compounds, which are the average of some 20 determinations, are accordingly less accurate than those for the other compounds examined. Measurements at high base concentration and extrapolation to infinite base concentration indicated that the absorption of the addition compounds is negligible at the wave length used for determination of the equilibrium constant except for pyruvate-hydroxylamine, pyruvate-O-methylhydroxylamine and pyruvate–semicarbazide which showed 5, 7 and 8%, respectively, of the original absorption at 320 mμ.

Experiments in which the disappearance of the carbonyl band was measured by infrared spectroscopy of deuterium oxide solutions gave similar results. On mixing equal volumes of 0.5 *M* furfural and 2.0 *M* hydroxylamine at *p*H 7.6 the carbonyl absorbance at 5.99 μ dropped immediately to 29% of the original value (calculated from equilibrium constant in water, 21%) and then disappeared slowly in an approximately first-order reaction with a half-time of 2.8 minutes. In a similar experiment with sodium pyruvate at *p*H 7.2 the drop in carbonyl absorption at 5.85 μ was complete at the time of the first reading 30 seconds after mixing (calculated disappearance 98%) and a slow formation of oxime (half-time 2.3 minutes) was followed by measuring the increase in absorption at 7.15 μ.

In the neutral *p*H range the rate of dehydration of addition compound to form oxime or semicarbazone is proportional to the amount of complex present and to the concentration of hydrogen ion (Fig. 2). The data for the reactions of acetone and furfural with hydroxylamine cover the range of *p*H in which hydroxylamine is converted to its conjugate acid, so that the fraction of the carbonyl compound present as the addition compound, which is proportional to the concentration of free hydroxylamine, varied from 0.00066 to 0.016 and from 0.0077 to 0.41 for acetone and furfural, respectively. Some deviation from linearity is noted in the case of furfural as the *p*H is lowered below 5 (see below). Although individual experiments were carried out at constant *p*H and with a large excess of nitrogen base so that pseudo first-order kinetics were obtained, the first-order rate constants in dilute solution increase with the concentration of nitrogen base and of hydrogen ion so that the over-all reaction is third order. However, at a higher concentration of base, in which most of the carbonyl compound is present as the addition compound, the rate at a given *p*H becomes independent of the concentration of nitrogen base and approaches over-all first-order kinetics; this is the case, for example, for pyruvate which is 74–95% in the form of the addition compound in 0.05 to 0.30 *M* hydroxylamine (Fig. 2, solid triangles). The rate constants for oxime formation from the addition compound, summarized in Table I, increase in the order furfural < pyruvate < benzaldehyde < acetone < cyclohexanone. The rate constants for dehydration of the semicarbazide addition compounds of pyruvate and furfural are almost identical to those of the corresponding hydroxylamine compounds.

The rate of oxime formation from pyruvate, furfural and acetone in the neutral *p*H region is increased by phosphate buffer (Fig. 3). This acceleration is greater at *p*H 6.7 than at *p*H 7.6, suggesting that in this *p*H region these reactions are subject to general acid catalysis by $H_2PO_4^-$ ion as well as to specific acid catalysis. Acceleration by buffer of the

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(8) O. L. Brady and R. F. Goldstein, *J. Chem. Soc.*, 1959 (1927).

(9) P. K. Chang and T. L. V. Ulbricht, THIS JOURNAL, **80**, 976 (1958); A. Kling, *Compt. rend.*, **148**, 569 (1909); G. Knopfer, *Monatsh.*, **32**, 768 (1911); A. Hantzsch, *Ber.*, **25**, 701 (1892).

(10) Compounds which exist predominantly in the hydrated form in aqueous solution were not studied in this investigation.

TABLE I

EQUILIBRIA OF ADDITION COMPOUND FORMATION AND RATES OF PRODUCT FORMATION FROM CARBONYL COMPOUNDS AND NITROGEN BASES AT 25.0°

>C=O	RNH_2, *M*	*p*H[a]	Ionic strength[b]	Wave length, mμ	*K*, l. mole^{-1}	k_2,[c] l. mole^{-1} min.$^{-1}$
Pyruvate	NH_2OH 0.033–0.133	6.8	0.3	320, 240	57	4.0×10^6
Benzaldehyde	NH_2OH 0.05–0.30	7.4	0.3	250	11.3	7.0×10^6
Furfural	NH_2OH 0.25–0.61	6.9	3.2	277, 260	5.2	2.2×10^6
Cyclohexanone	NH_2OH 0.067–0.67	7.6	3.2	260	6.5	1.5×10^8
Acetone	NH_2OH 0.4–3.2	7.7[d]	3.2	270	1.0	0.91×10^8
Pyruvate	NH_2OCH_3 0.033–0.133	6.5[d]	0.3	320, 240	35	8.0×10^5
Pyruvate	NH_2NH_2[e] 0.033–0.133	8.3	0.3	320	24	1.8×10^8[f]
Pyruvate	$NH_2NHCONH_2$ 0.067–0.67	6.5[d]	0.3	335	10	4.8×10^6
Furfural	$NH_2NHCONH_2$ 0.27–0.67	6.4[d]	0.67	293, 277	1.1	2.0×10^6

[a] Apparent *p*H measured with the glass electrode. [b] Ionic strength maintained constant in all runs by addition of NaCl. [c] $k_2 = k_{obs}/[H^+]$ (fraction as addition compound). [d] In 0.01 *M* phosphate buffer. [e] At low hydrazine concentration a further slow reaction is observed, presumably the formation of dipyruvic acid hydrazide (azine). [f] This rate constant is not independent of *p*H due to the contribution of a non-acid-catalyzed dehydration which becomes significant at high *p*H.

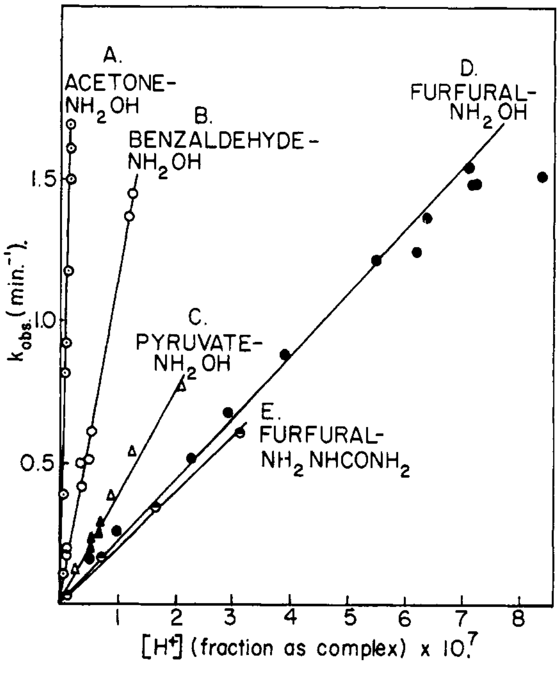

Fig. 2.—Rate of oxime or semicarbazone formation as a function of the concentration of hydrogen ion and of addition complex: A, acetone 0.0005 *M*, NH_2OH 0.0167 *M*, μ = 0.12, *p*H 7.2–4.6, 220 mμ; B, benzaldehyde 0.00005 *M*, NH_2OH 0.1 *M*, μ = 0.3, 25% ethanol, *p*H 7.6–6.5, 250 mμ; C, pyruvate 0.0005 *M*, μ = 0.3, 240 mμ; Δ, NH_2OH 0.1 *M*, *p*H 7.5-6.6; ▲, 0.05–0.3 *M*, *p*H 7.2; D, furfural 0.000055 *M*, NH_2OH 0.133 *M*, μ = 0.67, *p*H 6.9–4.0, 260 mμ; E, furfural 0.000028 *M*, $NH_2NHCONH_2$ 0.167 *M*, 0.01 *M* phosphate buffer, μ = 0.67, *p*H 7.1–5.7, 293 mμ. The fraction of the carbonyl compound in the form of the addition compound was calculated from the equilibrium constant and the concentration of free base present at each *p*H.

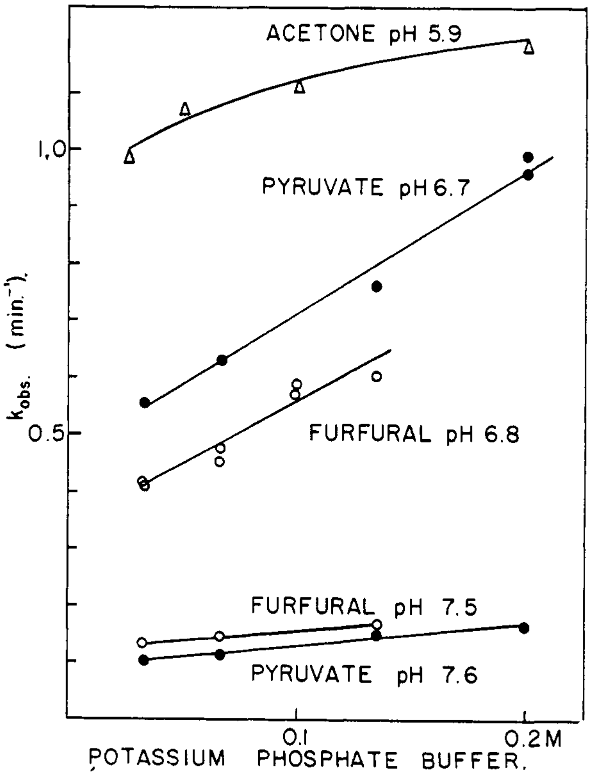

Fig. 3.—General acid catalysis of oxime formation by phosphate buffer: Δ, 0.0133 *M* total hydroxylamine, 0.00067 *M* acetone, ionic strength maintained at 0.5 with NaCl, measured at 220 mμ; ●, 0.2 *M* hydroxylamine, 0.0005 *M* pyruvate, ionic strength maintained at 0.6 with KCl, 240 mμ; ○, 0.5 *M* hydroxylamine, 0.000055 *M* furfural, ionic strength maintained at 0.4 with KCl, 270 mμ.

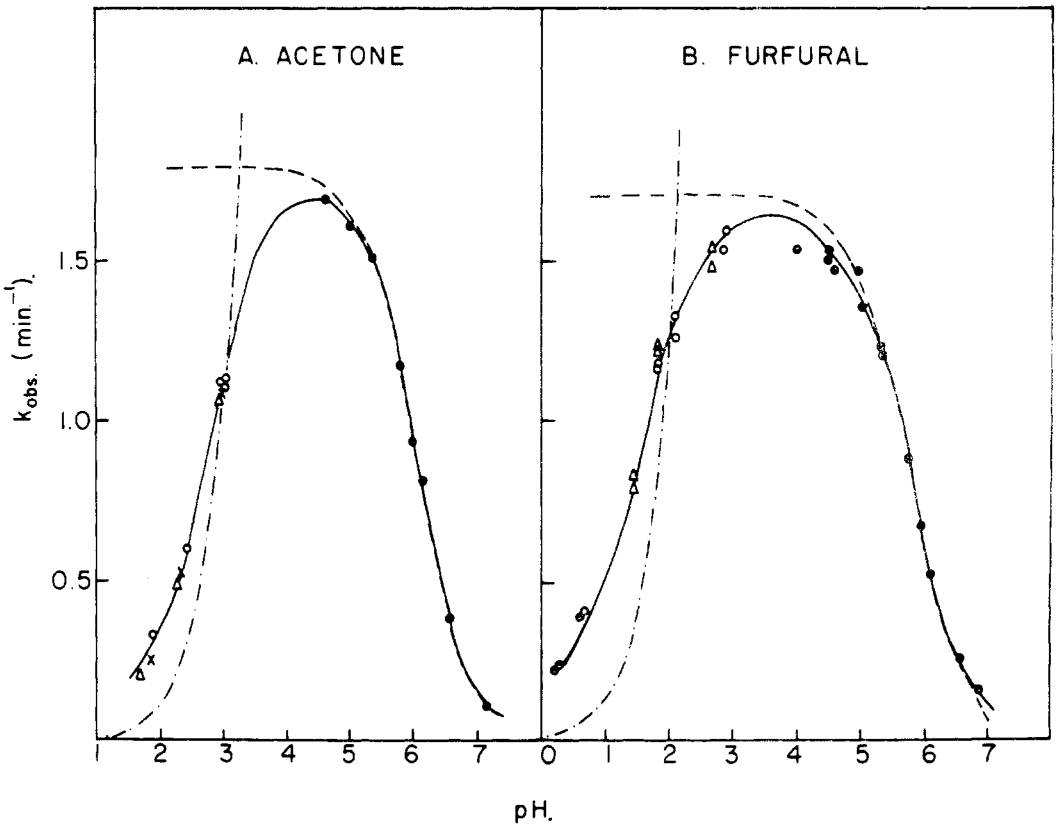

Fig. 4.—Rates of reaction of hydroxylamine with acetone and furfural as a function of *p*H: ●, no added buffer; ○, ×, △, 0.025, 0.05, 0.10 *M* potassium phosphate buffer, respectively; ◓, in dilute HCl; - - -, calculated for rate-limiting acid-catalyzed dehydration of addition complex; - · · · -, calculated for rate-limiting addition of free hydroxylamine to the carbonyl group. A. Acetone–hydroxylamine: total hydroxylamine 0.0167 *M*, acetone 0.0005 *M*, ionic strength maintained at 0.32 with NaCl, measured at 220 mμ; calculated curves from $k_{obs.} = (1.08 \times 10^8)$ [H$^+$] (fraction as complex) and from $k_{obs.} = 6.8 \times 10^4$ [NH_2OH]; concentration of addition compound calculated from the equilibrium constant and the concentration of free hydroxylamine. B. Furfural–hydroxylamine: total hydroxylamine 0.134 *M*, furfural 0.000055 *M*, ionic strength maintained at 0.67 with NaCl, measured at 260 mμ; calculated curves from $k_{obs.} = 2.2 \times 10^6$[H$^+$] (fraction as addition compound) and from $k_{obs.} = 9 \times 10^4$[NH_2OH].

rate of oxime formation from *d*-carvone has been shown previously by Stempel and Schaffel.[11]

As the *p*H is lowered to a point at which the rate of acid-catalyzed dehydration of addition compound is fast and the concentration of nitrogen base becomes small because of conversion to its conjugate acid, the rates of oxime and semicarbazone formation no longer follow the above relationships. For the reactions of hydroxylamine with acetone and furfural (Fig. 4) the rate begins to fall off below *p*H 5 and at low *p*H appears to approach a small and constant value; this represents the *p*H-independent reaction observed by Barrett and Lapworth even in strong acid[2] which may be due to a specific acid-catalyzed addition of free hydroxylamine. In the same figure are shown the calculated rates for a rate-limiting acid-catalyzed dehydration of addition compound and for a rate-limiting attack of hydroxylamine as the free base on the carbonyl group. The former curve agrees closely with the experimental results in the region near neutrality and, although some deviation is observed because of the *p*H-independent reaction, the latter predicts the decrease in rate observed at more acid *p*H.[12] Although individual runs followed pseudo first-order kinetics in the presence of excess hydroxylamine, the increase of the first-order rate constants with increasing free hydroxylamine concentration indicates that the over-all reaction in this *p*H region is second order. These data and the known equilibrium constant for acetoxime formation[3,4] permit an approximate calculation of the rate and equilibrium constants for all of the steps of the acetone–hydroxylamine reaction except the base-catalyzed reaction[2] (Table II).

In contrast to its effect at neutral *p*H, variation of the phosphate buffer concentration at acid *p*H does not significantly alter the rate (Fig. 4). This indicates that general acid catalysis by buffer is not responsible for the *p*H-rate maxima and provides further support for a change in the rate-limiting step of the reaction at acid *p*H. General acid catalysis by hydroxylammonium ion also does not account for the rate maxima, since such catalysis would lead to a maximum at the pK_a of hydroxylamine[6] and to a rate which would be more than first-order in respect to hydroxylamine.

The reaction of semicarbazide with furfural shows a similar decrease from the predicted rate at acid *p*H, but in this case the reaction is complicated by both general[4] and specific acid catalysis. Second-order rate constants for semicarbazone formation, obtained by dividing the observed pseudo first-order rate constant by the concentration of free semicarbazide, are plotted logarithmically in Fig. 5 as a function of *p*H. From *p*H 5.7 to 7.1 the rate is directly proportional to hydrogen ion concentration and the second-order rate constant does not depend on the concentration of semicarbazide.[13] Below this *p*H the rate falls below that expected from extrapolation of the results at higher *p*H. The second-order rate constants become increasingly de-

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[11] G. H. Stempel and G. S. Schaffel, THIS JOURNAL, **66**, 1158 (1944).

[12] Complete conversion of the addition product to its conjugate acid would lead to a constant rate and not to the observed decrease in rate at more acid *p*H.

[13] Experiments in this *p*H range were carried out in 0.01 *M* phosphate buffer; consequently the rates shown are approximately 4% greater than the uncatalyzed rates because of buffer catalysis.

TABLE II

APPARENT RATE AND EQUILIBRIUM CONSTANTS FOR THE REACTION OF ACETONE AND HYDROXYLAMINE[b]

K_{overall}	$= [A]/[B][C]$	1.06×10^{6}[a]
K_1	$= [D]/[B][C]$	1.0
K_2	$= [A]/[D] = K/K_1$	1.06×10^{6}
k_1;	$v_1 = k_1[C][B]$	6×10^{4}
k_{1a};	$v_{1a} = k_{1a}[C][B][H^+]$	1×10^{7}
k_{-1}	$= k_1/K_1$	6×10^{4}
k_{-1a}	$= k_{1a}/K_1$	1×10^{7}
k_2;	$v_2 = k_2[D][H^+]$	0.91×10^{8}
k_{-2}	$= k_2/K_2$	86

[a] See references 3 and 4. [b] A = $(CH_3)_2C{=}NOH$, B = $(CH_3)_2C{=}O$, C = NH_2OH, D = $(CH_3)_2C(OH)NHOH$.

pendent on the semicarbazide concentration with decreasing *p*H, indicating general acid catalysis by the conjugate acid of semicarbazide, and after extrapolation to zero semicarbazide concentration the rates still increase with the hydrogen ion concentration, indicating that the reaction is also subject to specific acid catalysis.

Discussion

Since the rate-limiting step of oxime and semicarbazone formation at neutral *p*H is the acid-catalyzed dehydration of the carbinolamine addition compound, the over-all rate of these reactions at low reactant concentration is dependent on the equilibrium concentration of addition compound and on the rate of its dehydration, while at high reactant concentration, with most of the carbonyl compound in the form of the addition compound, the rate at a given *p*H is first-order and dependent only on the rate of dehydration. Thus the more rapid rate of oxime formation from pyruvate than from furfural in dilute solution is due principally to the more favorable equilibrium constant for formation of the pyruvate–hydroxylamine addition compound, while the rapid formation of acetoxime is a consequence of a rapid dehydration which more than compensates for the low equilibrium concentration of addition compound. Under these circumstances it is not surprising that the over-all rates of semicarbazone formation in a series of aldehydes and ketones show no correlation with the equilibrium constants for formation of other addition compounds.[14] The equilibrium constants given in Table I for formation of hydroxylamine addition compounds, although obtained under somewhat different conditions, increase in the order acetone < cyclohexanone ~ furfural ~ benzaldehyde < pyruvate, which generally parallels the equilibrium constants for the addition of cyanide[15] and bisulfite[16] and the rate constants for the addition of hydride ion to these compounds.[17] The relatively favorable equilibrium constant for the cyclohexanone addition compound compared to acetone is presumably due to the transition from an sp_2 to a less strained sp_3 hybridization of the carbonyl carbon atom in the former compound on addition compound formation[17,18] and the low equilibrium constants for the addition compounds of the aldehydes, furfural and benzaldehyde, which are only slightly greater than for simple ketones are presumably the result of the loss of conjugation of the carbonyl group with the aromatic ring of these compounds on addition compound formation.[15,19] It should be noted that the oxime reaction is not symmetrical with respect to the rates of formation of addition compound from carbonyl compound and from oxime since only the latter step is significantly acid-catalyzed. Thus, although the equilibrium constants are not favored, the relatively rapid dehydration of the acetone and cyclohexanone addition compounds may be ascribed to stabilization by the electron-donating alkyl groups of a transition state which resembles the immediate product of the reaction $\overset{H^+}{>C{=}N{-}}$, and not the final product, $>C{=}N{-}$.

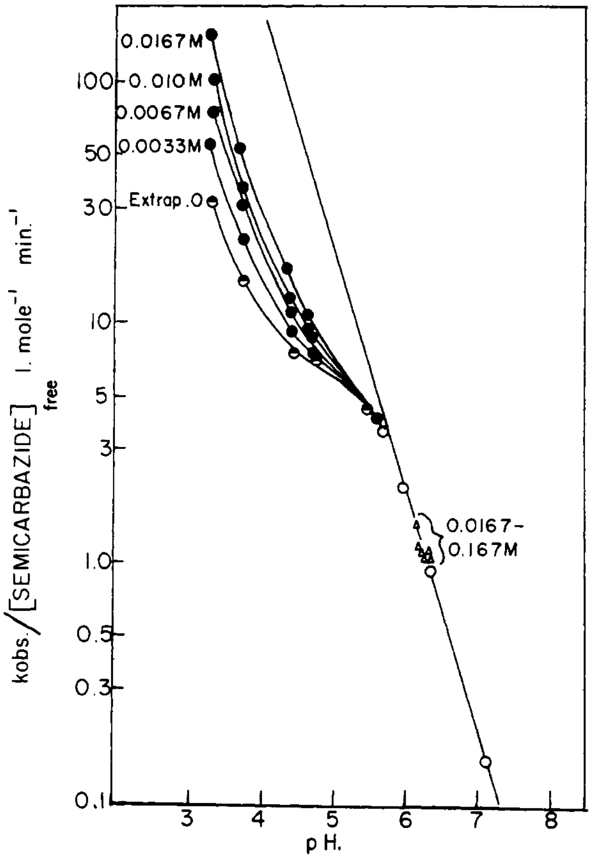

Fig. 5.—Furfural semicarbazone formation as a function of *p*H: ○, 0.167 *M* semicarbazide, 0.01 *M* phosphate buffer; ▲, 0.0167–0.167 *M* semicarbazide, 0.01 *M* phosphate buffer; ●, semicarbazide buffer; ◓, extrapolated to zero semicarbazide concentration; furfural 0.000028 *M*, ionic strength 0.67, measured at 293 mμ.

Price and Hammett have shown that the differences in the rates of semicarbazone formation from a group of carbonyl compounds in phosphate buffer at *p*H 7 are due largely to differences in the entropy of activation, and suggested that these differences were due to differences in restriction of

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(14) *Cf.* ref. 6, p. 211.

(15) A. Lapworth and R. H. F. Manske, *J. Chem. Soc.*, 2533 (1928); 1976 (1930).

(16) M. A. Gubareva, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 2259 (1947); (*C. A.*, **42**, 4820 (1948)).

(17) H. C. Brown, O. H. Wheeler and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957); H. C. Brown and K. Ichikawa, *ibid.*, **1**, 221 (1957).

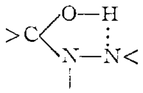
(18) H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951).

(19) *Cf.* also J. W. Baker, *J. Chem. Soc.*, 191 (1942); 1089 (1949); 2831 (1952), for further discussion of the effects of structure on cyanohydrin equilibria.

free movement in the transition state.[20] As they pointed out, these differences include the effect of phosphate catalysis, and it now appears that they can be further divided into effects on the equilibrium constant for addition compound formation and on the rate of acid-catalyzed dehydration; exact interpretation of these effects and of similar data from other laboratories[21] must therefore await the determination of the differences in the energy and entropy of the individual reaction steps. Similarly, the recently described lack of correlation of the rates of semicarbazone[22] and Schiff base[23] formation in a series of substituted benzaldehydes with Hammett's substituent constants, σ, may be accounted for, as was already suggested as a possibility by these workers,[22,23] by the two-step course of these reactions.

The alkali-catalyzed reaction of hydroxylamine with acetone described by Barrett and Lapworth[2] has generally been attributed to a reaction of the H_2NO^- anion, but it has not been clear how the attack of this anion should lead to oxime formation. It now appears that hydroxide ion catalysis of this reaction represents a base-catalyzed dehydration of addition compound, or, in the reverse reaction, an attack of hydroxide ion on acetoxime.

The over-all rates of reaction of hydroxylamine and semicarbazide with the same carbonyl compound are very similar, although the basicity of hydroxylamine is 300 *times* greater than that of semicarbazide and its nucleophilic strength would be expected to be greater by a similar factor. The nucleophilic strength, however, governs only the *rate* of attack of these compounds on the carbonyl group, while the over-all rate of reaction at neutral *p*H depends on the rate of dehydration, which is similar in both cases, and on the equilibrium constant for the formation of addition compound, which depends on the relative affinities of the nitrogen atom for hydrogen and for the carbonyl carbon atom. From the equilibrium constants for the formation of pyruvate addition compounds, this relative affinity appears to vary over only a sixfold range from semicarbazide (pK_a 3.7)[4] to methoxyamine (pK_a 4.6)[24] to hydroxylamine (pK_a 6.0)[24] to hydrazine (pK_a 7.9).[25] Not all nitrogen bases with a replaceable hydrogen atom will form addition compounds, however, since no decrease in the absorption of pyruvate at 320 mμ was found in 2 *M* piperidine or 1 *M* imidazole, suggesting that the affinity of the nitrogen atom of these compounds for the carbonyl group is much less. The affinity of the oxygen atom of water for the carbonyl carbon atom is also small since all of the compounds examined exist in the carbonyl form rather than as the hydrate in aqueous solution. A possible explanation for the abnormal affinity of semicarbazide, hydrazine and hydroxylamine for the carbonyl group is that the addition compounds may be stabilized by hydrogen bonding of the hydroxyl hydrogen to the α-nitrogen or oxygen atom of the base in a manner similar to that postulated for stabilization of the transition state in the unusually rapid attack of hydroxylamine on the carbonyl group of activated acyl compounds.[7]



The unfavorable equilibrium constants for the addition of water to acetoxime (Table II) and to furfural and pyruvate semicarbazones, calculated from the known equilibrium constants of the over-all reaction and of addition compound formation (Table III), also reflect the relatively low affinity of the water oxygen for carbon as well as the relatively low susceptibility of the weakly electronegative >C=N— group to addition reactions.

TABLE III

APPARENT RATE AND EQUILIBRIUM CONSTANTS FOR THE REACTIONS OF FURFURAL AND PYRUVATE WITH SEMICARBAZIDE

	$K_{overall}$[a]	K_1	K_2[b]	k_{-2}[c]
Furfural	1.32×10^5	1.1	1.2×10^5	16.7
Pyruvate	1.96×10^5	10	1.96×10^4	245

[a] [>C=NR]/[>C=O][H_2NR] from ref. 4. [b] [>C=NR]/[>C(OH)NHR]; from $K_{overall}/K_1$. [c] $v_{-2} = k_{-2}$ [>C=NR] [H^+] from k_2/K_2.

At acid *p*H the rates of oxime and semicarbazone formation are less than those calculated for a rate-limiting acid-catalyzed dehydration of addition compound. This is interpreted as a transition to a rate-limiting addition of free nitrogen base to the carbonyl group under conditions in which the rate of acid-catalyzed dehydration is very fast and, in the case of hydroxylamine, the concentration of nitrogen base is lowered by conversion to its conjugate acid. With the weakly basic semicarbazide molecule, which would be expected to react relatively slowly with carbonyl compounds, this transition occurs at a higher *p*H than with the more basic hydroxylamine. Moreover, the addition of semicarbazide is subject to both general and specific acid catalysis, as might be expected for a weak nucleophile,[26] while acid catalysis is of minor importance for the addition of the stronger base, hydroxylamine. The addition of the still weaker base, water, to the relatively unreactive >C=N— group appears to be completely dependent on acid catalysis, since the reverse of this reaction, dehydration of the addition complex, requires acid catalysis and must pass through the same transition state.

Although the analogous reactions of phenylhydrazine with carbonyl compounds could not be studied by ultraviolet spectroscopy, data in the literature strongly suggest that these reactions also proceed with the slow dehydration of an intermediate addition compound. Such a formulation was

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(26) Acid catalysis of the addition of a free nitrogen base to the carbonyl group is kinetically indistinguishable from an uncatalyzed addition of the conjugate acid of the base (*cf.* ref. 3); as pointed out by Lapworth in 1908,[2] the latter mechanism is very unlikely on chemical grounds because of the inability of the $R\overset{+}{N}H_3$ group to act as a nucleophilic reagent.

proposed by Bodforss,[27] following a suggestion by Wieland,[28] to explain the rapid fall in phenylhydrazine concentration and the slow formation of colored phenylhydrazone which was observed on mixing phenylhydrazine and *m*-nitrobenzaldehyde. Phenylhydrazone formation was found to follow monomolecular kinetics, as would be expected if the aldehyde were almost completely converted to addition compound in an initial fast reaction. In the analogous reaction with acetophenone, bimolecular kinetics was observed at low phenylhydrazine concentration, as would be expected if the concentration of addition compound in equilibrium with starting materials were low. Similar shifts from first- to second-order kinetics, depending on the concentration of nitrogen base and the equilibrium constant for addition compound formation, are described above (*cf.* Fig. 2) and account for the varying order of reaction described by other workers for phenylhydrazine reactions.[29]

The acid and alkaline hydrolysis of esters and amides has been shown by Bender to be accompanied in many cases by incorporation of O^{18} from water into unreacted ester or amide, suggesting that an intermediate addition product has some stability in these reactions.[30] The even greater importance of a tetrahedral addition product in these reactions of aldehydes and ketones suggests that rate-acceleration by enzymes and other catalysts of the reactions of a number of carbonyl compounds may be due to an acceleration of the decomposition of addition compounds rather than to acceleration of the addition of a nucleophilic reagent to the carbonyl group.

Acknowledgments.—The author is greatly indebted to the National Science Foundation, the National Cancer Institute of the National Institutes of Health (Grant C-3975) and the Lilly Research Laboratories for financial support, to Mrs. Reba Chakrabarti, Miss Marion Hyatt and Miss Joan Carriuolo for technical assistance in various phases of this investigation, and to Dr. Henry Linschitz for helpful discussions on kinetic problems.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Rearrangements of Aryl Sulfones. II. The Synthesis and Rearrangement of Several *o*-Methyldiaryl Sulfones to *o*-Benzylbenzenesulfinic Acids[1]

BY WILLIAM E. TRUCE AND WILLIAM J. RAY, JR.

RECEIVED JUNE 2, 1958

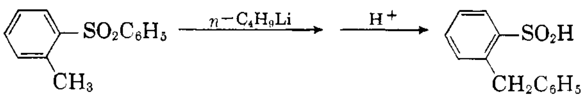
The synthesis and *n*-butyllithium-induced rearrangement of phenyl *o*-tolyl sulfone and some of its methylated homologs to the corresponding substituted *o*-benzylbenzenesulfinic acids is reported.

The synthesis of phenyl *o*-tolyl sulfone by the Friedel–Crafts reaction of *o*-toluenesulfonyl chloride with benzene is reported in the literature.[2] We have also carried out this reaction obtaining results similar to those described. Because of the difficulty in preparing sizable amounts of the sulfonyl chloride completely free of the *para* isomer, however, an alternate procedure was investigated. This involved treatment of *o*-tolyllithium with phenyl disulfide according to the method of Burton and Davey.[3] Oxidation of the product gave phenyl *o*-tolyl sulfone in good over-all yield. The sulfone prepared in this manner was identical to that prepared by the Friedel–Crafts reaction.

The preparation of phenyl 2,4-xylyl sulfone is also described in the literature.[4] The reported reaction of 2,4-dimethylbenzenesulfonyl fluoride with phenylmagnesium bromide, however, seemed less attractive than the Friedel–Crafts reaction of the corresponding sulfonyl chloride with benzene; hence, the latter preparation was used.

Phenyl 2,6-xylyl sulfone was prepared in good yield *via* the sulfide in a reaction sequence similar to that used to prepare phenyl *o*-tolyl sulfone. In the preparation of this sulfide, however, the reaction of 2,6-dimethylphenyllithium with benzenesulfenyl chloride[5] instead of phenyl disulfide was employed.

The reaction of solutions of these sulfones in refluxing ether with a 5% excess of *n*-butyllithium gave the corresponding *o*-benzylbenzenesulfinic acids, *e.g.*



Both mesityl sulfone and phenyl 2,6-xylyl sulfone rearranged almost completely, while phenyl *o*-tolyl sulfone and phenyl 2,4-xylyl sulfones gave only a 65–70% conversion to the corresponding sulfinic acids, most of the remainder being recovered as starting sulfone on hydrolysis. These low conversions might be the result of a reaction concurrent with rearrangement whereby the common intermediate, I, is used up. This is doubtful,

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[1] Abstracted from W. J. R.'s Ph.D. Thesis.

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[5] Sulfenyl chlorides may be used to good advantage in place of disulfides in such preparations where a product free of the starting disulfide is desired. This is unnecessary, however, if the sulfide is to be oxidized to the sulfone.