Organic and Biological Chemistry

Activation Parameters for Semicarbazone Formation[1]

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Abstract: Activation parameters for the attack of semicarbazide on *p*-hydroxybenzaldehyde catalyzed by the hydrated proton, by formic acid, and by the solvent have been evaluated from third-order rate constants measured at each of three temperatures in aqueous solution, ionic strength 0.50. For each catalyst, values of $\Delta H^{\ddagger}$ near 9 kcal/mole have been obtained. Values of $\Delta S^{\ddagger}$ become progressively more negative as the acidity of the catalyst is decreased. Thus, the relative efficiency of these catalysts for the attack of semicarbazide on *p*-hydroxybenzaldehyde is principally a reflection of changes in the entropy of activation. The equilibrium constant for carbinolamine formation from semicarbazide and *p*-chlorobenzaldehyde has been evaluated as a function of temperature and values of $\Delta H°$ of -2.3 kcal/mole and $\Delta S°$ of -5.4 eu obtained. Activation parameters for *p*-chlorobenzaldehyde semicarbazone formation under conditions of rate-determining carbinolamine dehydration and in dilute solutions of semicarbazide in which little of the substrate is converted to the carbinolamine in the preequilibrium reaction were determined: $\Delta H^{\ddagger} = 3.9$ kcal/mole and $\Delta S^{\ddagger} = -22$ eu. From these values and those for *p*-chlorobenzaldehyde carbinolamine formation, activation parameters for the dehydration of this carbinolamine were evaluated: $\Delta H^{\ddagger} = 6.2$ kcal/mole and $\Delta S^{\ddagger} = -16.6$ eu. These latter values are in accord with those obtained directly from the temperature dependence of the rate of *p*-nitrobenzaldehyde semicarbazone formation under conditions of rate-determining carbinolamine decomposition and in solutions of semicarbazide sufficiently concentrated to convert substantially all of the aldehyde to the carbinolamine in a preequilibrium reaction.

Mechanism and catalysis for nucleophilic reactions at the carbonyl carbon atom and for the reverse reaction have been extensively explored in the last few years.[3] A comprehensive summary has been prepared by Jencks.[4] In contrast, little work has been directed toward the evaluation of activation parameters for these reactions in this same time period. There have been a number of studies concerned with activation parameters for semicarbazone and oxime formation carried out some years ago.[5-10] For the most part, these studies require clarification and reinterpretation since (a) they were carried out before it was clearly established that different steps in the reaction sequence were rate determining at different values of pH[3a] and (b) activation parameters were evaluated from second-order rate constants which are pH dependent; therefore, the entropies of activation are themselves pH dependent and not very revealing. A recent evaluation of activation parameters for nitrone formation does not suffer from either of these disadvantages although serious questions about the assignation of rate-determining step can be raised[11] (see below). In an effort to provide a basis for understanding earlier results more clearly and to provide information of a type not yet available in the literature, we have evaluated a rather complete set of activation parameters for semicarbazone formation from benzaldehydes. Activation parameters for the reverse reactions have recently been reported.[12]

Experimental Section

Materials. Carbonyl compounds were obtained commercially and were either redistilled or recrystallized prior to use. Semicarbazide hydrochloride was recrystallized repeatedly from aqueous ethanol; solutions were prepared and neutralized as required just prior to use in kinetic runs or equilibrium constant measurements. Potassium chloride and formic acid were reagent grade and were employed without further purification. Distilled water was used throughout.

Kinetic measurements were carried out spectrophotometrically with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell holder through which water from a thermostated water bath was continuously circulated. Temperature was regulated with the aid of a Bronwill thermostated heater and circulator. Temperatures were measured using a calibrated Beckman thermometer. On repeated occasions, temperatures were measured in the reaction vessels within the cell housing of the spectrophotometer; these were ordinarily within 0.05° of the value for the water bath. All reactions were carried out at an ionic strength of 0.50 maintained with KCl. Reactions were run in aqueous solution containing 3.3% ethanol. Activation parameters were obtained from Arrhenius plots and the appropriate ancillary equations. Slopes of all Arrhenius plots were obtained by unweighted least-squares analysis.

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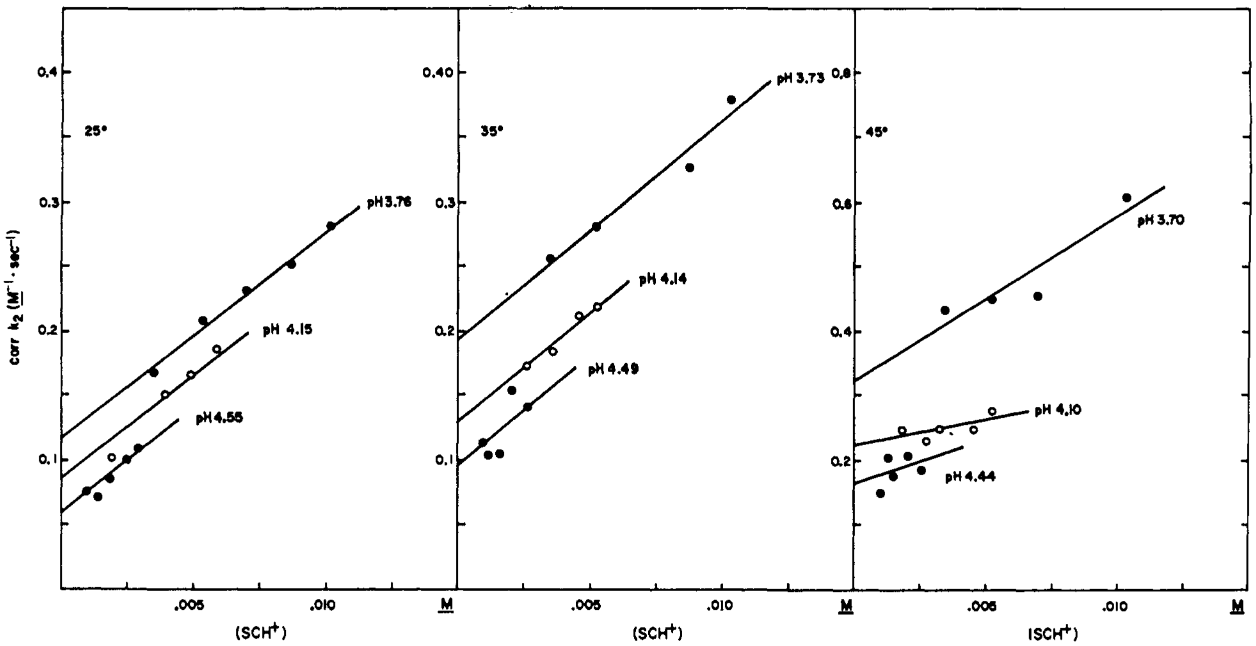


Figure 1. Second-order rate constants for *p*-hydroxybenzaldehyde semicarbazone formation corrected to constant values of pH (see text) plotted against the concentration of the conjugate acid of semicarbazide. At 25 and 35°, the slopes at each value of pH are those calculated by least-squares treatment for the data under the most acidic conditions. At 45°, the slopes were calculated for each set of data independently.

All kinetic runs were carried out in the presence of semicarbazide present in sufficient excess so that first-order kinetics were obtained throughout the course of each run. First-order rate constants were obtained as usual by determination of half-times from semilogarithmic plots of ($OD_\infty - OD_t$) against time and the expression $k_{obsd} = 0.693/t_{1/2}$. Evaluation of higher order rate constants is not completely trivial, and we discuss each case in turn. For the reaction of *p*-hydroxybenzaldehyde with semicarbazide under mildly acidic conditions, in which attack of the amine on the carbonyl compound is the rate-determining step, second-order rate constants were obtained by dividing first-order constants by the concentration of semicarbazide in the free base form. Calculation of third-order rate constants was accomplished essentially as previously described.[3d] These reactions have a rate law of the following form: $k_{obsd} = k_0(RNH_2) + k_{H^+}(RNH_2)(H^+) + k_{SCH^+}(RNH_2)(RNH_3^+)$ or $k_2 = k_0 + k_H(H^+) + k_{SCH^+}(RNH_3^+)$ in which k_0, k_{H^+}, and k_{SCH^+} are the third-order rate constants for catalysis by solvent, the hydrated proton, and the conjugate acid of semicarbazide, respectively.[3d] Hence, the data are treated by first plotting the calculated second-order rate constants against the concentration of the protonated semicarbazide. The slopes of such plots are measures of k_{SCH^+} and the intercepts are equal to $k_0 + k_{H^+}(H^+)$. Such plots are indicated in Figure 1. For the data at 25 and 35° in which substantial catalysis was observed at all values of pH, the least-squares slopes were evaluated from the data at the most acidic values of pH employed. These should be the most accurate determinations of k_{SCH^+} since the greatest range of catalyst concentration is obtained under these conditions. Then, applying these least-squares slopes to the data at higher values of pH, least-squares intercepts were evaluated. At 45°, rather little catalysis was observed, and the intercepts were obtained at each value of pH from independent least-squares calculations. No attempt was made to evaluate k_{SCH^+} at this temperature. Third-order rate constants for the solvent and hydrated proton-catalyzed reactions were evaluated from the intercept and slope, respectively, of a plot of these intercepts against the activity of hydrogen ion as determined with the glass electrode. These rate constants were then slightly refined as follows. Usually five kinetic runs were made for each value of pH at each temperature. The actual values of pH for these solutions varied by as much as ±0.03 pH unit from the mean value. Since the procedure just described yields third-order rate constants for the reactions catalyzed by the hydrated proton, it is possible to return to the original data and correct all the second-order rate constants to a constant pH by adding or subtracting, as appropriate, the quantity $k_{H^+}(\Delta H^+)$ in which (ΔH^+) is the difference between the average (H^+) for the group of runs under consideration and the value of (H^+) for each particular run. These corrections are quite small, usually less than 5%. Then, employing the corrected values of the second-order rate constants, refined third-order constants were obtained by repeating the analysis just described.

The reaction of *p*-chlorobenzaldehyde with semicarbazide in neutral or mildly alkaline solutions, conditions in which decomposition of the carbinolamine intermediate is the rate-determining step, has a rate law which is third order over-all: first-order in aldehyde, amine, and the hydrated proton.[3a,b] The third-order rate constant is given by $[k_{obsd}/(RNH_2)(H^+)][1 + K(RNH_2)]$, the term $[1 + K(RNH_2)]$ correcting for the fact that appreciable fractions of the carbonyl compound may be converted to the carbinolamine in a preequilibrium reaction. In this expression, K is the equilibrium constant for carbinolamine formation. Since this quantity was measured at each temperature employed, third-order rate constants could be calculated directly employing the above expression.

The second-order rate constant for decomposition of the carbinolamine derived from *p*-nitrobenzaldehyde and semicarbazide was evaluated from the observed first-order rate constant for *p*-nitrobenzaldehyde semicarbazone formation under neutral or slightly alkaline conditions and in the presence of sufficient semicarbazide to convert substantially all of the carbonyl compound to the carbinolamine in a preequilibrium reaction, from the measured hydrogen ion activity, and from the expression $k_2 = k_{obsd}/(H^+)\alpha$, in which α is the fraction of aldehyde present as carbinolamine.[3b] Values of α were obtained from the known semicarbazide concentrations and the equilibrium constant for *p*-nitrobenzaldehyde carbinolamine formation in 25% ethanol measured by Anderson and Jencks.[3b] Use of this equilibrium constant cannot introduce significant errors into the data since, in all cases, values of α were greater than 0.9.

Equilibrium Constant Measurements. The equilibrium constant for formation of carbinolamine from *p*-chlorobenzaldehyde and semicarbazide was evaluated from the slopes of plots of $[OD_0 - OD]/(RNH_2)$ against OD in which OD_0 is the optical density at 259 mμ of the aldehyde alone and OD is the value observed at this wavelength in the presence of various concentrations of semicarbazide. This somewhat indirect approach was employed since it avoids the necessity of a direct determination of the end point at infinite semicarbazide concentration. Justification for this procedure is straightforward: if OD_0 is the optical density of the aldehyde alone and if OD_∞ is that at infinite concentration of semicarbazide in which all the aldehyde exists as carbinolamine, then it is clear that the actual optical density is given by

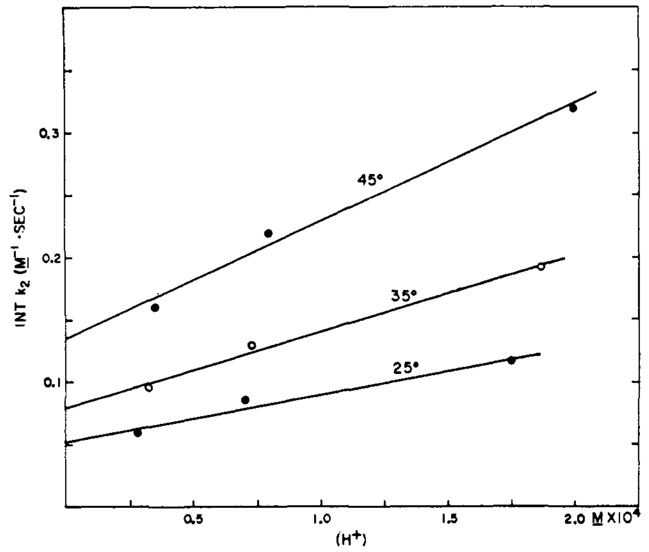


Figure 2. Second-order rate constants for *p*-hydroxybenzaldehyde semicarbazone formation corrected for catalysis by the conjugate acid of semicarbazide (*i.e.*, the intercepts from the plots in Figure 1) plotted against the activity of hydrogen ion for each of three temperatures.

$$OD = f_{ald}(OD_0) + f_{ca}(OD_\infty) \quad (1)$$

in which f_{ald} is the fraction of total substrate which exists as aldehyde and f_{ca} is that fraction which exists as carbinolamine. Introducing the equilibrium constant for carbinolamine formation, K, eq 1 takes the form

$$OD = \{1/[1 + K(RNH_2)]\}(OD_0) + \{K(RNH_2)/[1 + K(RNH_2)]\}(OD_\infty) \quad (2)$$

Rearranging, we obtain

$$(OD_0 - OD)/(RNH_2) = K(OD) - K(OD_\infty) \quad (3)$$

Equation 3 forms the basis for the graphical determination of K described above. Values of optical density were determined immediately following the addition of semicarbazide to the aldehyde. Under the conditions of these experiments, extrapolation of the optical densities to zero time to correct for decomposition of the carbinolamine proved unnecessary.

The value of pK_a for the conjugate acid of semicarbazide at 25° and ionic strength 0.50 to 3.65 was confirmed.[3d] The value at this ionic strength and at 35° was determined to be 3.60 as previously described.[3d] The value at 45° was evaluated as 3.55 from the temperature dependence established by the measurements noted above.

Values of pH were determined with a Radiometer PHM 4c pH meter and a glass electrode. All values of pH were determined at the temperature appropriate to the particular experiment through the use of a thermostated water bath with which the solutions were equilibrated prior to and during the measurement.

Results

First-, second-, and corrected second-order rate constants (see Experimental Section) for the attack of semicarbazide on *p*-hydroxybenzaldehyde in aqueous solution, ionic strength 0.50, at three values of pH at each of three temperatures are collected in Table I. The dependence of the corrected second-order rate constants on the concentration of the conjugate acid of semicarbazide is shown graphically in Figure 1. The slopes and intercepts of these plots were obtained as described in the Experimental Section. From the slopes at 25 and 35°, values of the catalytic rate constant for the conjugate acid of semicarbazide, k_{SCH^+}, were evaluated. The intercepts of plots in Figure 1 have been plotted against the activity of the hydrated proton in Figure 2. The slopes of these plots are equal to the catalytic constants for the hydrated proton, k_{H^+}, and the intercepts, when divided by the molar concentration of water, 55, yield the catalytic constants for water, k_0.

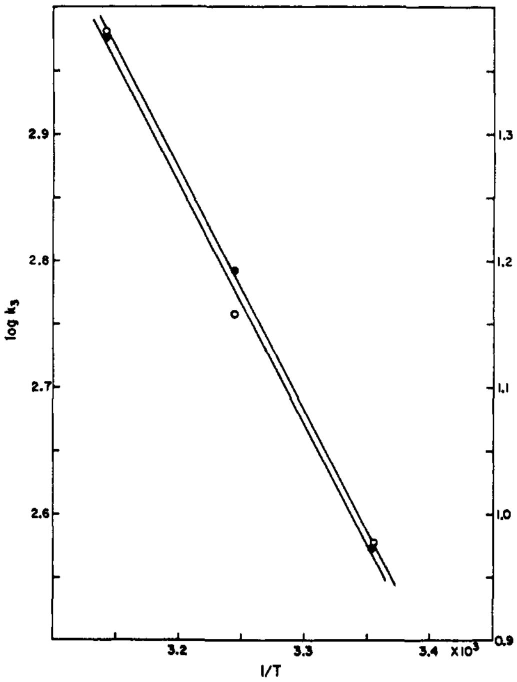


Figure 3. Arrhenius plots for *p*-hydroxybenzaldehyde semicarbazone formation catalyzed by the hydrated proton, ● and left ordinate, and by solvent, ○ and right ordinate. The points in this plot are taken from the data of Table III.

First- and second-order rate constants for the attack of semicarbazide on *p*-hydroxybenzaldehyde under similar conditions are presented as a function of formic acid concentration at two values of pH and at each of three temperatures in Table II. The third-order rate constants for the formic acid catalyzed reactions were evaluated from a least-squares analysis of a plot of second-order rate constants against the concentration of undissociated formic acid for each set of data. Values for each temperature were obtained by averaging the third-order rate constants for the two values of pH at that temperature.

In Table III, the third-order rate constants for catalysis of this reaction by solvent, by the hydrated proton, by the conjugate acid of semicarbazide, and by formic acid are collected and presented as a function of temperature. All values at 25° are in excellent agreement with those previously obtained for these reactions except that for the reaction catalyzed by the hydrated proton for which a value of 567 M^{-2} sec^{-1} was previously reported.[3d]

Enthalpies of activation have been derived from least-squares analysis of Arrhenius plots constructed from data of Table III and the relationship $\Delta H^{\ddagger} = E_a - RT$. Values are tabulated in Table IV. The Arrhenius plots for k_{H^+} and k_0 are shown in Figure 3. These plots are satisfactory though not particularly precise. That for catalysis by formic acid, k_{HCOOH}, is not so satisfactory and less reliance may be placed in the derived values. The complicated analysis required to derive the third-order rate constants for the water and

Table I. First- and Second-Order Rate Constants for Attack of Semicarbazide on *p*-Hydroxybenzaldehyde in 3.3% Aqueous Ethanol as a Function of Temperature

Temp, °C	pH	Semicarbazide, M		k_{obsd}, sec^{-1}	k_2, M^{-1} sec^{-1}	k_2(cor),[a] M^{-1} sec^{-1}
		Total	Free base			
25	4.20	0.008	0.00611	0.000608	0.0995	0.101
	4.15	0.016	0.01209	0.001814	0.1501	0.150
	4.15	0.020	0.01520	0.002509	0.1650	0.165
	4.15	0.024	0.01824	0.003372	0.1849	0.185
	4.55	0.008	0.00709	0.000528	0.0745	0.075
	4.60	0.012	0.01076	0.000742	0.0691	0.071
	4.56	0.016	0.01422	0.001195	0.0840	0.084
	4.53	0.020	0.01762	0.001783	0.1012	0.100
	4.54	0.024	0.02119	0.002384	0.1125	0.112
	3.76	0.008	0.00450	0.00075	0.1667	0.167
	3.76	0.012	0.00672	0.00139	0.2068	0.207
	3.76	0.016	0.00903	0.00209	0.2308	0.231
	3.76	0.020	0.01126	0.00284	0.2520	0.252
	3.77	0.024	0.01365	0.00381	0.2793	0.281
35	4.14	0.012	0.00931	0.00162	0.174	0.174
	4.14	0.016	0.01242	0.00231	0.186	0.186
	4.12	0.020	0.01536	0.00333	0.217	0.214
	4.15	0.024	0.01872	0.00399	0.219	0.220
	4.49	0.008	0.00709	0.00081	0.114	0.114
	4.56	0.012	0.01082	0.00111	0.100	0.104
	4.59	0.016	0.01441	0.00143	0.099	0.105
	4.45	0.020	0.01794	0.00284	0.158	0.156
	4.51	0.024	0.02139	0.00302	0.141	0.142
	3.74	0.008	0.00451	0.00116	0.258	0.257
	3.73	0.012	0.00672	0.00189	0.282	0.282
	3.73	0.020	0.01126	0.00369	0.328	0.328
	3.73	0.024	0.01365	0.00521	0.381	0.381
45	4.01	0.008	0.00595	0.00165	0.277	0.257
	4.10	0.012	0.00935	0.00215	0.230	0.230
	4.10	0.016	0.01248	0.00311	0.249	0.249
	4.18	0.020	0.0162	0.00359	0.221	0.235
	4.14	0.024	0.0191	0.00505	0.264	0.271
	4.44	0.008	0.00712	0.00106	0.149	0.149
	4.46	0.012	0.01078	0.00222	0.206	0.208
	4.44	0.016	0.01425	0.00252	0.177	0.177
	4.36	0.020	0.01735	0.00396	0.228	0.219
	4.46	0.024	0.02139	0.00383	0.179	0.181
	3.69	0.008	0.00448	0.00195	0.435	0.434
	3.70	0.012	0.00672	0.00303	0.451	0.451
	3.71	0.016	0.00897	0.00419	0.467	0.468
	3.70	0.024	0.01342	0.00829	0.617	0.617

[a] Second-order rate constants corrected to constant pH as described in the text. The following values of pH have been chosen for the individual sets of data reading from the top down: 4.15, 4.55, 3.76, 4.14, 4.49, 3.73, 4.10, 4.44, and 3.70.

Table II. Formic Acid Catalysis of the Attack of Semicarbazide on *p*-Hydroxybenzaldehyde in 3.3% Aqueous Ethanol as a Function of Temperature

Temp, °C	pH	Formic acid,[a] M	Semicarbazide,[b] M	k_{obsd}, sec^{-1}	k_2, M^{-1} sec^{-1}
25	3.85	0.004428	0.00613	0.00123	0.200
	3.87	0.008624	0.00624	0.00138	0.221
	3.87	0.017248	0.00624	0.00156	0.250
	3.85	0.022140	0.00613	0.00208	0.339
	3.87	0.025872	0.00624	0.00231	0.371
	3.45	0.013300	0.00387	0.00172	0.445
	3.48	0.02604	0.00403	0.00194	0.502
	3.45	0.03330	0.00387	0.00250	0.646
	3.45	0.03996	0.00387	0.00270	0.699
35	3.91	0.00409	0.00645	0.00195	0.302
	3.87	0.01295	0.00624	0.00291	0.466
	3.95	0.02073	0.00666	0.00358	0.537
	3.90	0.02488	0.00640	0.00392	0.613
	3.52	0.00635	0.00454	0.00231	0.508
	3.51	0.01280	0.00448	0.00270	0.602
	3.48	0.01967	0.00431	0.00335	0.777
	3.44	0.02706	0.00409	0.00391	0.955
	3.50	0.03226	0.00442	0.00462	1.043
45	3.80	0.00489	0.00640	0.00195	0.304
	3.78	0.00998	0.00627	0.00286	0.457
	3.75	0.01540	0.00613	0.00356	0.580
	3.74	0.02088	0.00605	0.00375	0.621
	3.73	0.02625	0.00602	0.00490	0.806
	3.49	0.00658	0.00466	0.00264	0.570
	3.46	0.01351	0.00446	0.00393	0.881
	3.45	0.02037	0.00443	0.00424	0.956
	3.43	0.02758	0.00433	0.00452	1.036
	3.43	0.03440	0.00431	0.00522	1.211
	3.42	0.04157	0.00426	0.00677	1.588

[a] Of the undissociated acid. [b] Of the free base.

Table III. Temperature Dependence of Catalytic Constants for Attack of Semicarbazide on *p*-Hydroxybenzaldehyde in 3.3% Aqueous Ethanol

Temp, °C	k_{H^+}, M^{-2} sec^{-1}	$k_{\text{H}_2\text{O}}$, M^{-2} sec^{-1}	k_{HCOOH}, M^{-2} sec^{-1}	k_{SCH^+}, M^{-2} sec^{-1}
298.17	375	0.00095	8.75	16
308.18	620	0.00144	18.75	17
318.18	947	0.00240	23.50	. .

Table IV. Activation Parameters for Catalysis of the Attack of Semicarbazide on *p*-Hydroxybenzaldehyde

Catalyst	$\Delta G^{\ddagger}$, kcal/mole	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu
Hydrated proton	13.7	8.8	−16.5
Water	21.7	8.7	−43.4
Formic acid	16.2	8.7	−25.1
Protonated semicarbazide	15.9	<8	<−26

hydrated proton reactions, due to the complexity of the rate laws, makes measurements of these quantities to an accuracy greater than ±10% difficult. Consequently, it is possible that the derived enthalpies of activation for these reactions are in error by as much as 2 kcal/mole. Insufficient data were collected for evaluation of activation parameters for the semicarbazide cation promoted reaction but, judging from the data at just two temperatures, it seems reasonable to conclude that $\Delta H^{\ddagger}$ for this reaction is less than that for the formic acid catalyzed case. Since the values of $\Delta G^{\ddagger}$ are about the same for these two cases, it follows that $\Delta S^{\ddagger}$ must be more negative for the reaction catalyzed by the conjugate acid of semicarbazide. The most striking aspect of these data is that the enthalpies of activation are reasonably independent of the nature of the catalyst.

Equilibrium constants for the addition of semicarbazide to *p*-chlorobenzaldehyde to form the carbinolamine have been evaluated at three temperatures from the change in optical density at 259 mμ as a function of the concentration of semicarbazide as detailed in the Experimental Section. The data are presented in Table V and plots of $(\text{OD}_0 - \text{OD})/(\text{RNH}_2)$ against OD are shown in Figure 4. Equilibrium constants were evaluated from the least-squares slopes of these plots. These equilibrium constants together with the derived thermodynamic parameters are collected in Table VI.

Table V. Data for Evaluation of Equilibrium Constants for Addition of Semicarbazide to *p*-Chlorobenzaldehyde at Various Temperatures[a]

Semicarbazide, M	Optical density[b] at temperatures, °K 298.17	308.07	318.22
0.00	0.774	0.539	0.630
0.06			0.566
0.12		0.419	0.515
0.18	0.515	0.381	0.475
0.24	0.470	0.350	0.445
0.30	0.433	0.324	0.423
0.36	0.404	0.305	
0.42	0.374	0.295	0.382
0.48	0.355		

[a] Reaction mixtures contain 0.01 M phosphate buffer, pH 7.9, ionic strength 0.50. [b] 259 mμ.

Table VI. Equilibrium Constants and Thermodynamic Parameters for Carbinolamine Formation from *p*-Chlorobenzaldehyde and Semicarbazide in 3.3% Aqueous Ethanol

Temp, °K	K,[a] M^{-1}	$\Delta G°$, kcal/mole	$\Delta H°$, kcal/mole	$\Delta S°$, eu
298.17	3.48	−0.74	−2.3	−5.4
308.07	3.20			
318.22	2.72			

[a] K = (carbinolamine)/(aldehyde)(amine).

Table VII. Rate Constants for *p*-Chlorobenzaldehyde Semicarbazone Formation in the Region of Rate-Determining Carbinolamine Dehydration as a Function of Temperature

Temp, °K	Semicarbazide, M	pH	$k_{obsd} \times 10^3$, sec^{-1}	$k_3{}^a \times 10^{-5}$, M^{-2} sec^{-1}
298.25	0.01	6.18	0.915	1.413
	0.02	6.20	1.747	1.470
	0.03	6.20	2.438	1.455
	0.04	6.19	3.652	1.592
	0.01	6.33	0.612	1.356
	0.02	6.30	1.396	1.489
	0.03	6.34	1.737	1.417
	0.04	6.29	2.84	1.578
	0.01	6.58	0.371	1.458
	0.02	6.63	0.596	1.359
	0.03	6.60	0.989	1.450
			Av	1.458
308.17	0.01	6.15	1.261	1.838
	0.02	6.18	2.087	1.681
	0.03	6.16	2.772	1.843
	0.04	6.20	4.05	1.805
	0.01	6.37	0.760	1.859
	0.02	6.38	1.398	1.773
	0.03	6.39	2.098	1.985
	0.04	6.37	2.678	1.760
	0.04	6.72	1.346	1.967
	0.06	6.70	2.044	2.044
	0.08	6.70	2.612	2.055
			Av	1.883
318.14	0.01	6.24	1.187	2.134
	0.02	6.25	2.344	2.197
	0.03	6.26	3.227	2.116
	0.04	6.25	4.320	2.128
	0.01	6.30	1.175	2.407
	0.02	6.31	1.998	2.132
	0.03	6.32	2.737	2.051
	0.04	6.30	4.081	2.276
	0.02	6.70	0.911	2.352
	0.04	6.69	1.620	2.197
	0.06	6.70	2.411	2.312
			Av	2.209

[a] $k_3 = [k_{obsd}/(H^+)(RNH_2)][1 + K(RNH_2)]$ in which (RNH_2) is the concentration of semicarbazide free base and K is the equilibrium constant for formation of the carbinolamine.

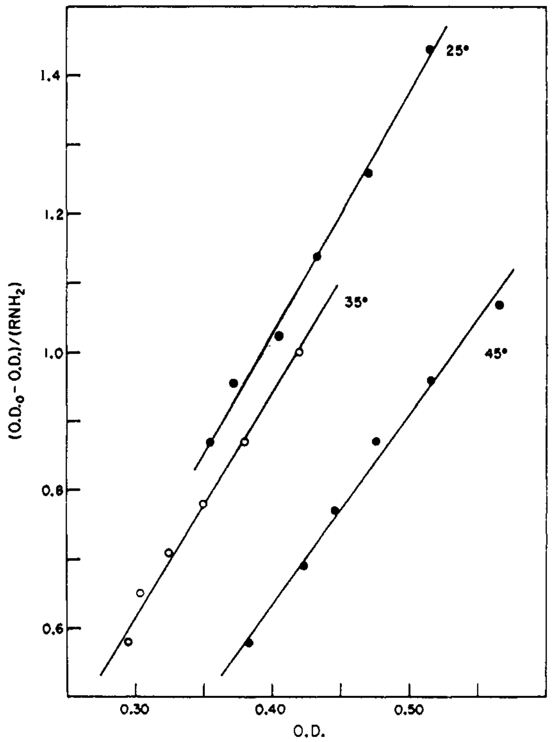


Figure 4. Change in optical density at2 59 mμ divided by the concentration of semicarbazide free base plotted against the observed optical density at this wavelength for the addition of increasing concentrations of semicarbazide to *p*-chlorobenzaldehyde at pH 7.9. The slopes of these lines are equal to the equilibrium constants for carbinolamine formation.

The value for 25° is in agreement with a value of 4.14 M^{-1} measured in 25% ethanol and at ionic strength 0.32.[3b] The $\Delta H°$ for carbinolamine formation is considered to be accurate to within ± 1.5 kcal/mole.

In Table VII, first- and third-order rate constants for formation of *p*-chlorobenzaldehyde semicarbazone under conditions of rate-determining carbinolamine dehydration at three temperatures are collected. The value at 25° is in excellent agreement with a value previously determined at this temperature and in 25% ethanol, ionic strength 0.32.[3b] For each temperature, data were collected for three or four concentrations of semicarbazide at each of three values of pH. Dilute solutions of semicarbazide were employed throughout so that only a small fraction of the carbonyl compound was converted to the carbinolamine in a preequilibrium reaction. Small corrections for the conversion that did occur were made employing the measured equilibrium constants at each of the temperatures as indicated in Table VI. Activation parameters for the over-all third-order reaction were calculated from these data and are collected in Table VIII. Enthalpies of activation are considered accurate to within ± 1.5 kcal/mole.

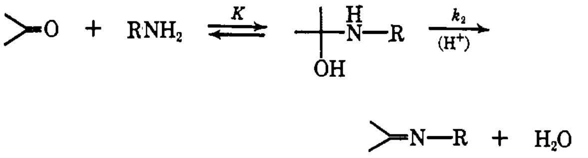
Knowledge of the activation parameters for the over-all third-order reaction in the region of rate-determining *p*-chlorobenzaldehyde carbinolamine dehydration and of the standard enthalpy and entropy changes for formation of the *p*-chlorobenzaldehyde carbinolamine permits a calculation of the activation parameters for the decomposition of the carbinolamine. This reaction is second-order: first-order in carbinolamine and first-order in protons. The second-order rate constant is given by $k_2 = k_3/K$ (eq 4). Hence, the activation

Table VIII. Activation Parameters Associated with Semicarbazone Formation under Conditions of Rate-Determining Carbinolamine Dehydration[a]

Substrate	$\Delta G_3^{\ddagger}$, kcal/mole	$\Delta H_3^{\ddagger}$, kcal/mole	$\Delta S_3^{\ddagger}$, eu	$\Delta G_2^{\ddagger}$, kcal/mole	$\Delta H_2^{\ddagger}$, kcal/mole	$\Delta S_2^{\ddagger}$, eu
p-Chlorobenzaldehyde	10.45	3.9	−22	11.19	6.2	−16.6
p-Nitrobenzaldehyde	...	...	...	12.15	8.9	−10.7

[a] Parameters with the subscript 3 were calculated from over-all third-order rate constants in the region of rate-determining carbinolamine dehydration; those with a subscript 2 were calculated from second-order rate constants for dehydration of the carbinolamine.

parameters associated with k_2 are given by $\Delta H_2^{\ddagger} = \Delta H_3^{\ddagger} - \Delta H°$ and $\Delta S_2^{\ddagger} = \Delta S_3^{\ddagger} - \Delta S°$. These have been calculated from the data of Tables VI and VII and are included in Table VIII.



(4)

First- and second-order rate constants for formation of *p*-nitrobenzaldehyde semicarbazone under conditions of rate-determining carbinolamine dehydration and at three temperatures are collected in Table IX. These experiments were run under conditions in which more than 90% of the aldehyde was converted to the carbinolamine in a preequilibrium reaction judging from the equilibrium constants for this reaction previously published.[3b] This equilibrium constant was employed to correct the second-order rate constants to those that would have been obtained had complete conversion to the carbinolamine been achieved (see Experimental Section). At each temperature, at least four separate runs were performed. From the average values for the second-order rate constants at each temperature, activation parameters were calculated. These are included in Table VIII. The second-order rate constant obtained at 25° is in accord with a previously reported value.[3b]

Table IX. Rate Constants for *p*-Nitrobenzaldehyde Semicarbazone Formation under Conditions of Rate-Determining Carbinolamine Dehydration as a Function of Temperature in 3.3% Aqueous Ethanol

Temp, °K	Semicarbazide, *M*	pH	$k_{obsd} \times 10^4$, sec^{-1}	α^a	k_2,[b] M^{-1} sec^{-1}
298.74	0.3	6.89	0.780	0.92	6.59×10^3
	0.3	7.43	0.252	0.92	7.36×10^3
	0.4	6.90	0.785	0.94	6.63×10^3
	0.4	7.44	0.238	0.94	7.02×10^3
				Av	6.90×10^3
308.04	0.3	6.88	1.28	0.92	1.05×10^4
	0.3	7.45	0.378	0.92	1.15×10^4
	0.4	6.92	1.24	0.94	1.10×10^4
	0.4	7.45	0.437	0.94	1.33×10^4
				Av	1.16×10^4
317.74	0.3	6.89	1.88	0.92	1.58×10^4
	0.3	7.11	1.26	0.92	1.77×10^4
	0.3	7.24	1.04	0.92	1.97×10^4
	0.4	7.01	1.57	0.94	1.72×10^4
	0.4	7.31	0.93	0.94	2.02×10^4
				Av	1.81×10^4

[a] The fraction of aldehyde present as the carbinolamine. [b] $k_2 = k_{obsd}/(H^+)\alpha$.

Discussion

Semicarbazone formation from benzaldehydes proceeds *via* the formation of a carbinolamine intermediate as indicated in eq 4. Under acidic conditions, the formation of the carbinolamine is the rate-determining step while in neutral or alkaline solutions, acid-catalyzed dehydration of the carbinolamine is rate determining.[3a,b,d] Carbinolamine formation from aromatic aldehydes and semicarbazide is markedly subject to general acid catalysis while decomposition of such species is rather insensitive to catalysis of this type.[3a,b,d]

Activation parameters for the attack of semicarbazide on *p*-hydroxybenzaldehyde, collected in Table IV, suggest the tentative generalization that the relative efficiencies of different catalysts for this reaction reflect principally changes in the entropy of activation. Thus, within the error of experimental measurement, enthalpies of activation for catalysis by the hydrated proton, water, and formic acid are equal while the entropies of activation become progressively more negative as the efficiency of the catalyst decreases. The force of this generalization is weakened by two factors. First, the catalysts are structurally dissimilar and, hence, the activation parameters may contain quite variant contributions from solvation factors and the like. Second, it is possible that the catalytic mechanisms may differ from catalyst to catalyst; earlier work does suggest, however, that water and the hydrated proton, like formic acid, act as general acid catalysts.[3c,d] Ideally, one should evaluate activation parameters for structurally similar general acid catalysts such as a series of substituted acetic acids. However, in systems as complicated as this one, evaluation of such parameters for these catalysts with sufficient accuracy to permit meaningful conclusions to be drawn would prove a challenging task. Some agreement has been reached, on the basis of different considerations, that the transition state for general acid catalyzed carbonyl addition reactions involves hydrogen-bond formation between the acid catalyst and the carbonyl oxygen atom.[3d,13,14] In terms of such a transition state, it would seem likely that increasing the strength of the acid catalyst should reduce the enthalpy of activation. However, it is well known that differences in the ionization of carboxylic acids and phenols show up largely in the entropy terms; perhaps the current observations are, in part, a reflection of similar behavior for reactions involving only partial proton transfer.

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The similarity of enthalpies of activation for general acid catalyzed and solvent-catalyzed attack of semicarbazide on *p*-hydroxybenzaldehyde is in marked contrast to behavior noted in reactions involving nucleophilic attack at acyl carbon. A particularly nice example has been discovered by Bruice and Benkovic for the reaction of hydrazine with phenyl acetates.[15] In this system, enthalpies of activation decrease markedly from the solvent-catalyzed to the general base catalyzed to the general acid catalyzed reaction. At the same time, the entropies of activation become increasingly negative so that the over-all rate constants do not vary greatly as a function of the type of catalysis involved. Similar results have been obtained for the aminolysis of thiol esters[16] and alkylaminolysis of phenyl acetate.[17] This clear difference in behavior may reflect different mechanisms of catalysis, distinct roles for solvent in the two types of reaction, or simply the difference in charge type of the catalyst.

The thermodynamic quantities for the addition of semicarbazide to *p*-chlorobenzaldehyde are similar to those for the addition of water to monochloroacetone.[18] The hydration of more reaction carbonyl compounds exhibits substantially more negative values of $\Delta H°$ and $\Delta S°$ [18] as does the addition of cyanide ion to acetone in water.[19] The modest loss of entropy in carbinolamine formation presumably reflects the loss of translational freedom of the molecule of amine.

A number of early determinations of activation parameters for carbonyl addition reactions, including oxime formation,[7,8,10] semicarbazone formation,[5,6,9] and thiosemicarbazone formation,[9] were carried out under conditions in which one would expect carbinolamine dehydration to be the rate-determining step. Typically, small values for the enthalpies of activation and very large negative values for the entropies of activation were observed. These results are in accord with those noted here (Table VIII). Appreciation of this point requires the observation that most previous activation parameters were calculated from second-order, pH-dependent rate constants while we have made such calculations on the basis of third-order, pH-independent rate constants. If we recalculate our values on the basis of second-order rate constants at, for example, pH 7, we obtain a value of $\Delta S^{\ddagger}$ near -54 eu, a value similar to those previously published. Recent studies of activation parameters for nitrone formation in a region of acid catalysis have revealed values which are similar to those obtained in this study.[11] However, the conclusion of these workers that carbinolamine formation is the rate-determining step in this region must be abandoned both in light of what has been generally established about the kinetics and mechanism for carbonyl addition reactions[4] and in light of recent studies of nitrone formation by Reimann and Jencks.[3i] The activation parameters obtained are almost certainly those for acid-catalyzed, rate-determining carbinolamine dehydration.

Values of entropies of activation for acid-catalyzed carbinolamine decomposition (not those for the overall reaction in the region of rate-determining carbinolamine dehydration which are discussed above) near -11 to -16 eu as indicated in Table VIII are surprising. These reactions are certainly unimolecular decompositions of the carbinolamine conjugate acids. Nucleophilic attack of solvent on the carbinolamines would, in fact, simply regenerate the same carbinolamine. Unimolecular acid-catalyzed reactions usually exhibit entropies of activation near zero, although exceptions are known.[20] This reaction must be added to those known to exhibit anomalous entropies of activation. Perhaps the substantial negative entropy of activation reflects loss of rotational degrees of freedom associated with the developing carbon–nitrogen double bond.

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