at 140°. As little as 0.1% of the *para* compound could be detected in the presence of the *ortho*.

Complete analysis was accomplished by using the packed column to obtain the ratio of benzyltrifluoromethylcarbinol to *o*-(2-hydroxy-3,3,3-trifluoropropyl)phenyltrifluoromethylcarbinol. The peak corresponding to the *o*-tolyltrifluoromethylcarbinol (possibly admixed with the *para* isomer) was collected and analyzed on the capillary column. No trace of the *para* isomer was detected.

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Some Aspects of Mechanism and Catalysis for Carbonyl Addition Reactions[1]

Luciano do Amaral,[2] W. A. Sandstrom, and E. H. Cordes

Contribution No. 1352 from the Department of Chemistry, Indiana University, Bloomington, Indiana. *Received May 8, 1965*

Abstract: Benzaldehyde phenylhydrazone formation, like oxime, semicarbazone, and benzylideneaniline formation, occurs with rate-determining nucleophilic reagent attack under acidic conditions and with rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions. The Brønsted α value for general acid catalysis of the attack of phenylhydrazine on benzaldehyde is 0.20. The addition of urea to acetaldehyde exhibits both acid- and base-catalyzed reactions. This reaction too is subject to general acid catalysis which, in this case, is characterized by a Brønsted α value of 0.45. These values of α, together with several previously determined, are linearly related to the values of $\mathrm{p}K_a$ for the conjugate acids of the nucleophilic reagents. First-order rate constants for the hydrolysis, in slightly basic solution, of a series of benzylideneanilines substituted in the aniline moiety decrease slightly with increasing electron-withdrawing capacity of the polar substituent. The reaction of methoxyamine with a similar series of substituted benzylideneanilines is dependent on acid catalysis. Third-order rate constants for these reactions also decrease slightly with increasing electron-withdrawing capacity of the polar substituent.

This article reports the results of three lines of investigation relevant to mechanism and catalysis for carbonyl addition reactions. These studies include (i) examination of the variation in susceptibility to general acid catalysis as a function of the basicity of the attacking nucleophilic reagent, (ii) kinetic investigation of structure–reactivity correlations for the hydrolysis of a series of benzylideneanilines substituted in the aniline moiety, and (iii) elucidation of structure–reactivity correlations for the methoxyaminolysis of the same series of benzylideneanilines.

Previous studies have revealed that the attack of relatively weak nucleophilic reagents such as water,[3-8] thiourea,[9-11] semicarbazide,[12,13] aniline,[14] and phenylhydrazine[15] on carbonyl compounds is subject to general acid catalysis. In contrast, corresponding reactions involving stronger nucleophilic reagents such as hydroxylamine,[16] cyanide,[17] *t*-butylamine,[18] and sulfite[19,20] exhibit little or no catalysis of this type.[21] Consideration of multiple structure–reactivity correlations for general acid catalysis of carbonyl addition reactions reveals that the Brønsted α values, which are measures of susceptibility to catalysis of this type, should be linearly related to the $\mathrm{p}K_a$ of the conjugate acid of the nucleophilic reagent.[13,21] In an effort to examine more closely the validity of this conclusion and, in so doing, to gain further understanding of the variation in susceptibility to general acid–base catalysis as a function of reactivity, Brønsted α values for the attack of phenylhydrazine and urea on suitable carbonyl compounds have been determined.

Several studies of substituent effects on rates of Schiff base hydrolysis reveal that such effects may be reasonably complex. Early work is difficult to interpret since the nature of the rate-determining step at the values of pH employed is uncertain.[22,23] It is now clear that the pH–rate profiles for Schiff base hydrolysis are quite complex and that the observed structure–reactivity correlations are a sensitive function of the pH at which the reactions are studied.[14,18,24,25] Considerable attention has been devoted to the nature of the pH-independent reaction which is commonly observed

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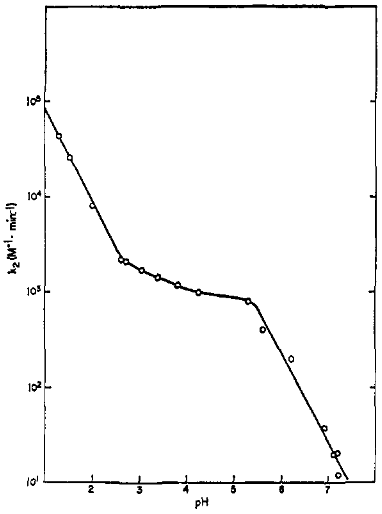

Figure 1. Logarithms of second-order rate constants for benzaldehyde phenylhydrazone formation in 20% ethanol at 25° and ionic strength 0.50 plotted as a function of pH. All points are extrapolated to zero buffer concentrations. Cyanoacetate, chloroacetate, methoxyacetate, β-bromopropionate, acetate, and phosphate buffers were employed in the appropriate ranges of pH.

in alkaline solution. This reaction may be either the attack of water on the unprotonated substrate or the attack of hydroxide ion on the protonated substrate, a kinetically indistinguishable alternative. The pertinent Hammett ρ values for the rates of hydrolysis of benzylideneanilines and benzylidene-1,1-dimethylethylamines substituted in the carbonyl component are slightly negative strongly suggesting that the latter alternative is correct.[14,18] Reeves has recently extended these findings to a series of aniline-substituted Schiff bases derived from *p*-trimethylammonium benzaldehyde and has obtained concordant results.[26] We report here the results of a similar study employing Schiff bases derived from benzaldehyde itself.

The direct interconversion of Schiff bases, transaldimination reactions, has received some kinetic study.[27-29] The best evidence available at this time suggests that attack is the rate-determining step for the reaction of weakly basic amines with Schiff bases derived from strongly basic amines.[29] In an effort to corroborate this conclusion, substituent effects on the rate of methoxyaminolysis of a series of substituted benzylideneanilines have been examined.

Experimental Section

Materials. Substituted benzylideneanilines were synthesized from benzaldehyde and the appropriate anilines according to the methods of Roe and Montgomery:[30] benzylideneaniline, mp 51-53° (lit.[30] mp 52°); N-benzylidene-*p*-methylaniline, mp 29-30° (lit.[30] mp 29-30°); N-benzylidene-*p*-chloroaniline, mp 62-63° (lit.[30] mp 62-63°); N-benzylidene-*p*-methoxyaniline, mp 70-71° (lit.[30] mp 70-71°); N-benzylidene-*p*-nitroaniline, mp 114-116° (lit.[30] mp 117-119°); N-benzylidene-*m*-nitroaniline, mp 72-74° (lit.[31] mp 72-73°); and N-benzylidene-*m*-chloroaniline, bp 165° (4 mm), mp 37-39° (lit.[32] mp 37-39°). All other reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts and acetaldehyde, were either redistilled or recrystallized before use. Solutions of nitrogen bases were prepared just prior to use.

Kinetic measurements were carried out spectrophotometrically at 25° with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder as previously described.[16,33] The reactions of benzaldehyde with phenylhydrazine and hydroxylamine were followed by observing the appearance of the product at 340 and 265 mμ with an initial concentration of aldehyde of 3.3×10^{-5} and 10^{-4} M, respectively. The addition of urea to acetaldehyde was followed by observing the disappearance of aldehyde at 265 mμ with an initial aldehyde concentration of 0.07 M. The hydrolysis and methoxyaminolysis of the substituted benzylideneanilines were followed by observing the disappearance of the Schiff bases at or near their absorption maxima. In all cases, the reactions were initiated by the addition of $^1/_{30}$ volume of the substrate dissolved in ethanol or acetonitrile. Thus, the reaction mixtures contained about 3% organic solvent. Second-order rate constants were evaluated from the slopes of plots of first-order rate constants against the concentration of the nucleophilic reagent. Third-order rate constants were similarly evaluated from the slopes of plots of second-order rate constants against the concentration of catalyst. Values of pH were recorded with a Radiometer Model PHM 4c pH meter. All kinetic and equilibrium experiments were carried out at an ionic strength of 0.50, maintained with KCl.

Measurement of the equilibrium constant for the addition of urea to acetaldehyde was accomplished spectrophotometrically at 265 mμ and 25° according to the method of Bloch-Chaude.[22]

Product Analysis. The products of the addition of hydroxylamine and phenylhydrazine to benzaldehyde were identified as the oxime and phenylhydrazone, respectively, from their characteristic ultraviolet spectra. Similarly, the products of the reaction of water and methoxyamine with the N-benzylideneanilines were identified as the free aldehydes and the corresponding O-methyl oximes from their ultraviolet spectra. The identification of the product from the reaction of urea with acetaldehyde poses special problems. The expected reaction product, ethylolurea, is insufficiently stable to permit direct isolation from aqueous solution and, in addition, cannot be identified spectrophotometrically. The proton magnetic resonance spectrum of acetaldehyde in the presence of 2 M urea in deuterium oxide solution is similar to that of acetaldehyde hydrate, consistent with and support for ethylolurea formation. Aqueous solutions of 0.07 M acetaldehyde in the presence of 5 M urea exhibit no light absorption above 240 mμ over the pH range 2-12. Furthermore, the characterisitics of the reaction leave little doubt that ethylolurea formation is the rate-determining step for this reaction and, in addition, that ethylolurea is the quantitatively most important reaction product. These include the observation that the reaction between acetaldehyde and urea in neutral or acidic solution is kinetically first order in each reactant. Furthermore, equilibrium constant data reveal that, except under quite acidic conditions, the reaction between urea and acetaldehyde involves one molecule of each reactant. Finally, Ogata, *et al*, have concluded, from studies of both the addition of urea to acetaldehyde and of the decomposition of ethylidenediurea, that ethylolurea formation is the rate-determining step.[34]

Results

In Figure 1, the logarithm of second-order rate constants for benzaldehyde phenylhydrazone formation in 20% ethanol at 25° and ionic strength 0.50 are plotted as a function of pH. All points have been extrapolated to zero buffer concentration (see below). The shape of this curve is similar to that previously observed for benzaldehyde semicarbazone and benzylideneaniline formation and for benzophenone phenylhydrazone formation[35] and may be interpreted in a similar fashion.[13,14] (See Discussion.) Under condi-

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tions in which phenylhydrazine attack is rate determining, second-order rate constants are a sensitive function of the nature and concentration of the buffer employed for maintenance of constant pH. Variation of such second-order rate constants with the concentration of several carboxylic acid buffers is indicated in Table I. Studies of buffer catalysis conducted with varying ratios of carboxylic acid to carboxylate ion revealed that the buffer catalysis is of the general acid type. No evidence for general base catalysis was obtained. These results are concordant with previously established catalytic patterns for closely related reactions.[13,14] The catalytic constants for several carboxylic acids, derived from the data of Table I, are collected in Table II. Fitting of the catalytic constants for the carboxylic acids to a single straight line in a Brønsted plot by least-squares analysis yields an α value of 0.20 for this reaction. No statistical corrections have been made. Catalytic constants for the hydrated proton and water have been evaluated from the data in Figure 1 and are included in Table II. The former constant falls near the line in the Brønsted plot determined by the carboxylic acids while the latter value falls somewhat below this line. In addition, catalysis by the conjugate acid of phenylhydrazine was evident in that first-order rate constants below pH 5 increased more rapidly than the concentration of phenylhydrazine. Plots of second-order rate constants against the concentration of the conjugate acid of phenylhydrazine yields a catalytic constant for this acid (Table II). This catalytic constant falls near the line in the Brønsted plot.

Table I. Variation of Second-Order Rate Constants for Attack of Phenylhydrazine on Benzaldehyde in 20% Ethanol at 25° as a Function of the Concentration of Several Carboxylic Acid Buffers[a]

Total buffer concn, *M*	Cyanoacetic acid (50% base)	Chloroacetic acid (50% base)	Methoxyacetic acid (20% base)	Formic acid (20% base)	β-Bromopropionic acid (10% base)	Acetic acid (10% base)
0.10	0.63	0.42	0.86	0.54	0.53	0.48
0.20	1.05	0.69	1.41	0.94	0.94	0.79
0.30	1.47	1.01	2.03	1.29	2.14	1.17
0.40	1.90	1.18	2.50	1.64	2.15	1.57
0.50	2.17	1.97	3.03	1.93	2.71	1.66

[a] Rate constants have the units of M^{-2} min^{-1} and have been multiplied by 10^{-4}.

Table II. Catalytic Constants of Several Acids for the Attack of Phenylhydrazine on Benzaldehyde in 20% Ethanol at 25° and Ionic Strength 0.50

Catalyst	pK_a	pH	Concn range, *M*	k_3, M^{-2} min^{-1}
H_3O^+	−1.74	1–2.5	...	9.0×10^5
Cyanoacetic acid	2.45	2.61	0.1–0.5	9.5×10^4
Chloroacetic acid	2.90	2.95	0.1–0.5	5.9×10^4
Methoxyacetic acid	3.55	2.72	0.1–0.5	6.5×10^4
Formic acid	3.75	3.22	0.1–0.5	5.0×10^4
β-Bromopropionic acid	4.00	3.34	0.1–0.5	5.4×10^4
Acetic acid	4.76	3.63	0.1–0.5	3.2×10^4
Phenylhydrazinium ion	5.20	5.37	0.1–0.5	2.6×10^4
Water	15.74	...	44	22

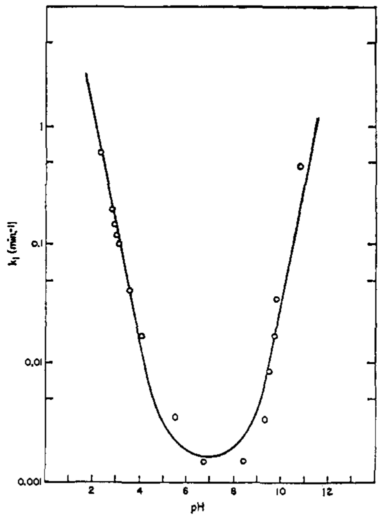

Figure 2. Logarithms of first-order rate constants for the disappearance of acetaldehyde in the presence of 0.50 *M* urea in aqueous solution at 25° and ionic strength 0.50 plotted as a function of pH. Points on the acid side of the rate minimum have been extrapolated to zero buffer concentration. Cyanoacetate, chloroacetate, formate, acetate, phosphate, and carbonate buffers were employed in the appropriate ranges of pH.

At values of pH above 5, in which decomposition of the carbinolamine intermediate is rate determining, little or no general acid–base catalysis was observed for benzaldehyde phenylhydrazone formation. Such catalysis has been observed, in contrast, for benzophenone phenylhydrazone formation.[35] Second-order rate constants for this reaction at pH 7.18 did not detectably increase with increasing imidazole concentration from 0.20 to 1.0 *M*; while those at pH 6.93 increased from 43 to 72 M^{-1} min^{-1} as the concentration of total phosphate increased from 0.01 to 0.20 *M*. It is unclear whether this small rate increase reflects general acid–base catalysis or is a special salt effect.

In Figure 2, logarithms of first-order rate constants extrapolated to zero buffer concentration for the reaction of 0.50 *M* urea with acetaldehyde in aqueous solution at 25° and ionic strength 0.50 are plotted as a function of pH. This reaction clearly exhibits both acid- and base-catalyzed reactions. The first-order rate constants near the minimum of this curve, pH 6.8, are considerably larger than those expected on the basis of the sum of the rate constants due to the acid- and base-catalyzed reactions suggesting the existence of a modest uncatalyzed reaction as well. Under the conditions of these experiments, the addition of urea to acetaldehyde does not proceed to completion. All points indicated in Figure 2 were measured at a urea concentration of 0.50 *M* and, therefore, are directly comparable although they have not been corrected to account for the failure of the reaction to go to completion or for the hydration of acetaldehyde. Under acidic conditions, the first-order rate constants were found to depend linearly on urea concentration when they were corrected, employing the measured equilibrium constant (see below), to conditions of complete reaction. In contrast, under alkaline conditions (pH 9.80) the corrected first-order rate constants for acetaldehyde disappearance increased only from 0.015 to 0.032 min^{-1} as the concentration of urea was increased from 0.1 to 0.5 *M* urea. No initial immediate loss of acetaldehyde absorption was detected indicating that preequilibrium formation of an acetaldehyde adduct does not occur. We are unable to account for the failure of the base-catalyzed reaction to exhibit second-order kinetics.

Under acidic conditions, the addition of urea to acetaldehyde is subject to general acid catalysis (Table III). In Table IV, catalytic constants for several acids, derived from the data in Table III and Figure 2, as catalysts for this reaction are collected. The catalytic constants for the carboxylic acids are well correlated by a single straight line in a Brønsted plot with a slope of 0.45. No statistical corrections have been made. The catalytic constant for the hydrated proton falls near the line in the Brønsted plot determined by the carboxylic acids. The catalytic constants in Table IV have been derived from second-order rate constants which have not been corrected for the failure of the reaction to go to completion or for the hydration of acetaldehyde. The derived α value is, of course, not affected by such corrections. No evidence for general base catalysis by the carboxylate anions was found.

Table III. Variation in Second-Order Rate Constants for the Attack of Urea on Acetaldehyde in Aqueous Solution at 25° as a Function of the Concentration of Several Carboxylic Acid Buffers[a]

Total concn, *M*	Cyanoacetic acid (80% base)	Chloroacetic acid (50% base)	Formic acid (20% base)	Acetic acid (20% base)
0.1	3.70	5.34	2.92	0.49
0.2	4.62	6.98	3.70	0.77
0.3	5.38	7.92	4.12	1.02
0.4	6.16	9.24	4.74	1.21
0.5	6.94	9.88	5.54	1.43

[a] Rate constants are in units of M^{-2} min^{-1} and have been multiplied by 10. The rate constants have not been corrected to account for the fact that the reaction does not proceed to completion under these conditions or for the hydration of acetaldehyde. Urea concentration 0.5 *M*.

Table IV. Catalytic Constants of Several Acids for the Attack of Urea on Acetaldehyde in Aqueous Solution at 25° and Ionic Strength 0.50[a]

Catalyst	pK_a	pH	Concn range, *M*	k_3, M^{-2} min^{-1}
H_3O^+	−1.74	2–4	. . .	300
Cyanoacetic acid	2.45	2.91	0.1–0.5	3.0
Chloroacetic acid	2.90	2.75	0.1–0.5	1.9
Formic acid	3.75	3.03	0.1–0.5	0.76
Acetic acid	4.76	4.06	0.1–0.5	0.26

[a] All reactions were carried out at a total urea concentration of 0.50 *M*. The rate constants have not been corrected to account for the fact that the reaction does not proceed to completion under these conditions or for the hydration of acetaldehyde.

The equilibrium constant for addition of urea to acetaldehyde was measured spectrophotometrically at 25° in the presence of 0.05 *M* formate buffer, 50% base, and in the presence of a 0.02 *M* bicarbonate–carbonate buffer, 30% base. In both instances the data were well correlated by a formulation involving the addition of the single molecule of urea, strongly suggesting the formation of ethylolurea under these conditions. In both experiments a value of K_{eq} = (ethylolurea)/(urea)·(acetaldehyde)$_T$ of 1.3 M^{-1} was obtained. Similar measurements at pH 2 indicated that, under these conditions, more than one molecule of urea added to acetaldehyde suggesting the formation, in part, of ethylidenediurea.

In the course of completion of the present study, a study similar in many respects appeared.[34] Ogata, *et al.*, found that the addition of acetaldehyde to urea yielded small quantities of ethylidenediurea as isolable product. On the basis of kinetic studies of the addition of urea to acetaldehyde and of the decomposition of ethylidenediurea, these workers concluded, in harmony with the results indicated above, that ethylolurea formation is rate determining for the addition reaction. The kinetic results obtained by Ogata, *et al.*, are basically in accord with those presented above. Of particular note is the finding of a Brønsted α value for general acid catalysis of ethylolurea formation of 0.46.

The kinetics of benzaldehyde oxime formation in aqueous solution at 25° and ionic strength 0.50 were studied in the pH range 1 to 7 (Table V). The second-order rate constants increase linearly with hydrogen ion activity over the pH range 2 to 7. Under more acidic conditions, the third-order rate constants were less than those predicted on the basis of data obtained at higher values of pH (Table V). This behavior suggests that dehydration of the carbinolamine intermediate is rate determining at pH values greater than 2 and that a transition to rate-determining hydroxylamine attack occurs near this pH. The third-order rate constant for benzaldehyde oxime formation in the region of rate-determining carbinolamine decomposition, $k_3 = k_{obsd}/(NH_2OH)(H^+)$, is 6×10^{-7} M^{-2} min^{-1}. This rate law is, of course, valid only for dilute solutions of hydroxylamine in which no appreciable fraction of the benzaldehyde is converted to the carbinolamine in a pre-

Table V. Rate Constants for the Formation of Benzaldehyde Oxime in Aqueous Solution at 25° as a Function of pH

pH	$(NH_2OH)_{free\ base}$, *M*	k_{obsd}, min^{-1}	k_3,[a] M^{-2} min^{-1}
1.0	1.07×10^{-7}	0.139	1.3×10^{7}
2.0	1.07×10^{-6}	0.415	3.9×10^{7}
3.05	1.18×10^{-5}	0.574	5.5×10^{7}
3.65	4.37×10^{-5}	0.598	6.1×10^{7}
4.39	2.56×10^{-4}	0.613	5.9×10^{7}
5.54	2.71×10^{-3}	0.488	6.2×10^{7}
6.54	7.88×10^{-3}	0.221	6.2×10^{7}

[a] $k_3 = k_{obsd}/(H^+)(NH_2OH)$.

Table VI. First-Order Rate Constants for the Hydrolysis of Several Benzylideneanilines in Basic Aqueous Solution at 25° and Ionic Strength 0.50

Substrate	k_{obsd}, min^{-1} pH 10.0	pH 10.56
N-Benzylidene-*p*-methoxyaniline	0.012	0.012
N-Benzylidene-*p*-methylaniline	0.014	0.012
N-Benzylidene-*p*-chloroaniline	0.0065	0.0064
N-Benzylidene-*m*-chloroaniline	0.0034	0.0028
N-Benzylidene-*m*-nitroaniline	0.0025	0.0024
N-Benzylidene-*p*-nitroaniline	0.0053	0.0067

Table VII. Second- and Third-Order Rate Constants for the Methoxyaminolysis of N-Benzylidene-Substituted Anilines in Aqueous Solution at 25° and Ionic Strength 0.50

	k_2, M^{-1} min^{-1} at pH								k_3, M^{-2} min^{-1}
Substituent	8.98	9.01	9.41	9.48	9.97	10.02	10.31	10.43	
p-Methoxy		57.3	21.8		6.9		2.66		5.7×10^{10}
p-Methyl		80.3	31.2		7.9		4.0		8.0×10^{10}
Unsubstituted	52.5			19.0		7.2		2.1	5.6×10^{10}
p-Chloro		29.8	13.8		3.15		2.0		3.3×10^{10}
m-Chloro		28.4	11.5		3.0			1.31	2.9×10^{10}
m-Nitro		11.8	4.6		1.7			0.54	1.3×10^{10}
p-Nitro		14.7	6.7		2.25			1.0	1.9×10^{10}

equilibrium reaction. This condition was fulfilled at the concentration of hydroxylamine employed as judged from the equilibrium constant for addition of hydroxylamine to benzaldehyde measured by Jencks.[16] General acid–base catalysis of benzaldehyde oxime formation was not detected with certainty. Second-order rate constants for this reaction at pH 4.61 did not increase with concentration of an acetate buffer from 0.1 to 0.5 *M*. At pH 6.55, second-order rate constants for benzaldehyde oxime formation increased from 24 to 33 M^{-1} min^{-1} as the concentration of a phosphate buffer was increased from 0.01 to 0.1 *M*. In 70% ethanol at an ionic strength of 0.10 and an apparent pH of 6.14, second-order rate constants for this reaction did not increase with increase in the concentration of an acetate buffer from 0.04 to 0.26 *M*.

First-order rate constants for the hydrolysis of a series of N-benzylideneanilines substituted in the aniline moiety are collected in Table VI. All reactions were conducted at 25° and ionic strength 0.50. Rate constants measured at pH 10.00 are similar to those measured at pH 10.56 indicating that the observed values are pH independent. Similar pH-independent reactions have been observed in slightly basic solution for a number of Schiff bases.[14,18,26] The rate constants of Table VI fall near a single straight line when plotted against the Hammett σ constants with the exception of that for the *p*-nitro derivative which falls about threefold above this line. Neglecting the point for the *p*-nitro derivative, one obtains a ρ value of -0.8 for this reaction.

Second-order rate constants for the methoxyaminolysis a of series of benzylideneanilines substituted in the aniline moiety are collected in Table VII. All reactions were conducted at 25° and ionic strength 0.50. Each second-order rate constant was evaluated from first-order rate constants measured at at least three concentrations of methoxyamine. In all cases, the first-order rate constants were observed to depend linearly on the concentration of methoxyamine. As indicated in Table VII, each second-order rate constant was measured at four values of pH. In all cases, the second-order rate constants are linearly related to the activity of hydrated protons. Thus the over-all rate expression for the methoxyaminolysis reaction is $v = k_3(\text{>=N—})\cdot(\text{RNH}_2)(\text{H}^+) = k_3'(\text{>=NH}^+\text{—})(\text{RNH}_2)$. Third-order rate constants, k_3, derived from plots of second-order rate constants against (H$^+$), are also collected in Table VII. These rate constants are reasonably well correlated by a single straight line when plotted against the Hammett σ constants having a slope, ρ, of -0.90. The point for the *p*-methoxy derivative falls somewhat below this line while that for the *p*-nitro derivative falls somewhat above.

Discussion

A. Catalysis for Carbonyl Addition Reactions. The pH–rate profile for the formation of benzaldehyde phenylhydrazone is similar to those for benzaldehyde semicarbazone and benzylideneaniline formation[13,14,16] and for benzophenone phenylhydrazone formation.[35] These results have been interpreted in terms of rate-determining attack of the nucleophilic reagent under acidic conditions with a transition to rate-determining decomposition of the carbinolamine intermediate under neutral or basic conditions.[13,14,16] A similar conclusion appears warranted in the present case as well. Oxime formation involving certain quite reactive carbonyl compounds also occurs with a transition in rate-determining step.[16] Results presented herein, together with those of Jencks,[16] strongly suggest that benzaldehyde oxime formation behaves similarly although the transition in rate-determining step occurs at relatively low values of pH. An authoritative review of the mechanisms for carbonyl addition reactions of the type considered here has been prepared by Jencks.[21]

The pH–rate profile for the addition of urea to acetaldehyde, involving catalysis by both the hydrated proton and by hydroxide ion,[34] is qualitatively similar to those for the addition of urea to formaldehyde[36,37] and for the addition of thiourea to formaldehyde.[10] The reaction in dilute acid almost certainly proceeds with rate-determining attack of urea and apparently yields largely ethylolurea. Some evidence for the formation of considerable ethylidenediurea in more strongly acidic (pH 2) media has been obtained.[34] As noted above, ethylidenediurea is the only isolable reaction product, and evidence for formation of both ethylolurea and ethylidenediurea in acidic solution has been obtained by Ogata, *et al.*[34] As noted in the Results, the base-catalyzed addition of urea to acetaldehyde was not first-order urea concentration; the explanation for which is unclear.

Catalytic constants for general acid catalysis of the attack of a series of nucleophilic reagents on carbonyl compounds may be correlated by a series of two Brønsted (or one Brønsted and one Swain–Scott) relationships. One series yields the various values of α for general acid catalysis (one α for each of the nucleophilic reagents) and the other series yields the various values of β for nucleophilic attack (one β for each of the general acid catalysts). Theoretical considerations of cases involving multiple structure–reactivity correlations have revealed that the several parameters characterizing the reactions are interdependent and that simple

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(36) G. A. Crowe, Jr., and C. C. Lynch, *J. Am. Chem. Soc.*, 71, 3731 (1949).

(37) L. Bettelheim and J. Ledwall, *Svensk Kem. Tid.*, 60, 208 (1948).

Table VIII. Brønsted α Values for General Acid Catalysis of the Attack of Nucleophilic Reagents on the Carbonyl Carbon Atom

No.	Nucleophilic reagent	pK_a[a]	Substrate	Solvent	α	Ref
1	*t*-Butylamine	10.4	Benzaldehydes	Water	Near zero	18
2	Phenylhydrazine	5.2	Benzaldehyde	20% ethanol	0.20	This work
3	Aniline	4.6	*p*-Chlorobenzaldehyde	Water	0.25	14
4	Semicarbazide	3.65	Benzaldehydes	Water	0.25	13
5	Urea	0.2	Acetaldehyde	Water	0.45	This work, 34
6	Water	−1.74	Acetaldehyde	Water	0.54	5
7	Thiourea	−1.0	Formaldehyde	Water	0.27	10
8	Water	−1.74	*sym*-Dichloroacetone	95% dioxane	0.27	6

[a] Of the conjugate acid.

quantitative expressions describing these interdependencies may be written.[13,21,38] In the particular case at hand, these expressions are

$$\frac{\alpha_2 - \alpha_1}{\mathrm{p}K_{a1}{}^{\mathrm{N}} - \mathrm{p}K_{a2}{}^{\mathrm{N}}} = C = \frac{\beta_2 - \beta_1}{\mathrm{p}K_{a2}{}^{\mathrm{A}} - \mathrm{p}K_{a1}{}^{\mathrm{A}}} \qquad (1)$$

In eq 1, values of α and β are the appropriate Brønsted coefficients, p$K_a{}^{\mathrm{N}}$ refers to the pK_a of the conjugate acid of the nucleophilic reagent and p$K_a{}^{\mathrm{A}}$ refers to the pK_a of the general acid catalyst. Equation 1 may be regarded as a quantitative statement of the considerations of Hammond,[39] Leffler,[40] and Swain and Thornton.[41] Data are now at hand for a test of the left-hand side of eq 1 and are collected in Table VIII. Taking the data for phenylhydrazine as standards, a plot of $\Delta\alpha$ *vs.* Δp$K_a{}^{\mathrm{N}}$ has been constructed and is indicated in Figure 3. Of the eight measured values of α, five are well correlated by the single straight line in this plot, a sixth is consistent with this line, and two are aberrant.

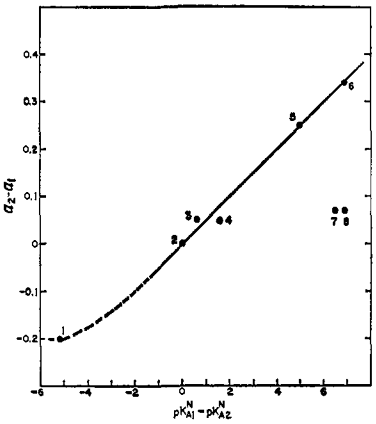
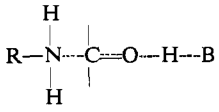


Figure 3. Variation in the Brønsted α value for general acid catalysis for the attack of nucleophilic reagents on the carbonyl carbon atom as a function of the pK_a of the conjugate acid of the nucleophilic reagent. The numbers correspond to the numbers of the reactions listed in Table VIII.

On the basis of the five points through which the line is drawn, a value of C (eq 1) of +0.05 is calculated. The derived value of C is independent of the choice of standard, provided data from reactions 1, 7, and 8 are not employed for this purpose. Questions concerning the validity of attempts to correlate the α values with basicity of the nucleophilic reagents employing different substrates may certainly be raised. Ideally, all of the studies should be accomplished employing the same carbonyl compound. However, previous results indicate that α for general acid catalysis of semicarbazone formation does not vary significantly as the substrate is varied from *p*-nitrobenzaldehyde to acetophenone, a change in reactivity of about two orders of magnitude.[13] We make the tentative assumption that independence of α of reactivity of the carbonyl compound extends to acetaldehyde as well. Deviation from this independence for extremely reactive carbonyl compounds may account for the failure of the α values for attack of thiourea on formaldehyde and for attack of water on *sym*-dichloroacetone to be correlated by eq 1. Correlation of the latter value with the remainder of the data is questionable in any event since it was obtained in a largely nonaqueous solvent.

Values of α provide a measure of the degree of proton transfer in the transition state (or the degree of stretching of the X–H bond being broken if the proton transfer follows the formation of other covalent bonds). Measurement of the variation in Brønsted coefficients with appropriately chosen structural parameters may yield information concerning variation in transition state structures with substrate reactivity provided the reaction mechanism is known. For example, arguments previously developed[13] suggest that the transition state for general acid catalyzed attack of nucleophilic reagents on the carbonyl carbon atom proceeds with true general acid catalysis (transition state I) rather than with the kinetically indistinguishable alternative involving specific acid–general base catalysis (transition state II). To the extent that variation in the degree of proton transfer in the transition state, as measured by changes in the magnitude of α, reflects alteration in the structure of the transition state as a whole, results presented in Table VIII indicate that the transition state is reached progressively earlier as the nucleophilicity of RNH_2 is increased. Thus the variation in Brønsted α values for these reactions is precisely that expected on the basis of the considerations of Hammond[38] and Leffler[39] and transition state I.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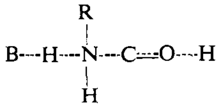
II

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(38) S. I. Miller, *J. Am. Chem. Soc.*, **81**, 101 (1959).

(39) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(40) J. E. Leffler, *Science*, **117**, 340 (1953).

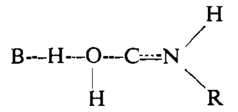
(41) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **84**, 817 (1962).

In a recent communication, Swain and Worosz have argued that transition state I is the correct formulation for these reactions based on somewhat different considerations.[42] Employing data of the type included in Table VIII and reasoning from the "reacting bond rule"[41] and the "solvation rule,"[43] these workers suggest that the decrease in α with increasing nucleophilicity requires transition state I. Although this conclusion can certainly be rationalized in terms of these rules, we feel that there exists some uncertainty as to the proper way of applying them to reactions of this type and, indeed, we are inclined to the point of view that a perfectly strict application leads to the opposite conclusion.

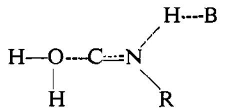
The earlier conclusion that transition state I is correct is based on the argument that the calculated second-order rate constant for the attack of semicarbazide on protonated *p*-nitrobenzaldehyde (transition state II) is greater than that for a diffusion-controlled reaction.[13] Swain and Worosz have dismissed this conclusion on the basis that the protonated aldehyde need not be an intermediate along the reaction path.[42] Although Jencks has clearly recognized this point and has dealt with it briefly,[21] perhaps a closer look at this problem is in order. We note first that transition state II consists of four basic components: a proton, an aldehyde, a nucleophilic reagent, and a basic catalyst. It is exceedingly likely if not certain that this transition state would be formed in a bimolecular reaction preceeded by at least two preequilibrium reactions. In the second place, those preequilibrium associations which involve covalent bond formation between aldehyde and nucleophile have been considered and excluded on a variety of grounds.[13,21] Two general pathways to transition state II remain. That pathway, which we have considered and continue to consider the more likely of the two, which involves preequilibrium formation of the protonated aldehyde has been excluded on the basis noted above. The alternative must involve a preequilibrium (noncovalent) association between aldehyde and nucleophilic reagent (which may or may not be associated with the catalyst) if it is to avoid the intermediacy of the protonated aldehyde. Weak interactions between tertiary amines and carbonyl compounds have been noted.[44,45] However, such interactions are so weak, as evidenced by the fact that even with the reactive substrate methyl ethyl ketone and with the strongly basic amine trimethylamine and in the nonpolar solvent heptane, no interaction can be observed,[44] that the equilibrium constant for association of weakly basic semicarbazide with the unreactive substrate *p*-nitrobenzaldehyde in the highly polar solvent water must be vanishingly small! Furthermore, such association, if it does occur, would not necessarily result in a marked increase in basicity of the carbonyl oxygen atom. Thus, alternative routes to transition state II seem even less likely than that explicitly discussed previously, and that line of argument continues to be the strongest evidence favoring transition state I.

As indicated by previous studies[16,32] and confirmed and extended herein, dehydration of the carbinolamines formed from carbonyl compounds and hydroxylamine, phenylhydrazine, and semicarbazide is, with one exception, at best weakly susceptible to general acid catalysis. Powers and Westheimer have observed such catalysis for benzophenone phenylhydrazone formation.[35] Minimum values of α for general acid catalyzed decomposition of carbinolamines derived from weakly basic amines may be calculated. Assuming that a 10% increase in observed rate constants with increasing imidazole buffer concentration for benzaldehyde phenylhydrazone formation at pH 7.18 might have been overlooked, a maximum catalytic constant for imidazolium ion of 2.0 M^{-2} min^{-1} may be calculated. This value, together with that for the hydrated proton (Figure 1) of 2×10^8 M^{-2} min^{-1}, yields a minimum α for this reaction of 0.9. Similarly, assuming that the 10% increase in observed rate constants with increasing concentration of an acetate buffer for benzaldehyde oxime formation at pH 4.61 might have been overlooked, a maximum value of the catalytic constant for acetic acid of 800 M^{-2} min^{-1} may be calculated. This value together with that for a hydrated proton of 6.7×10^7 M^{-2} min^{-1} yields a minimum α value for this reaction of 0.8. These values are distinctly larger than that for general acid catalyzed decomposition of carbinolamines derived from strongly basic amines. This conclusion follows from the fact that the observed β value for general base catalyzed attack of water on benzhydrylidenedimethylammonium ion (the reverse reaction) is 0.27.[29] Since α for general acid catalyzed carbinolamine decomposition is just $1 - \beta$, it follows that a value of 0.73 is appropriate for this reaction. The increasing α values with decreasing amine basicity for general acid catalyzed carbinolamine decomposition may be employed as a test of the "reacting bond rule" and the "solvation rule" provided the structure of the transition state is known.

General base catalysis for attack of water on *protonated* benzylidene-1,1-dimethylethylamines (the microscopic reverse of carbinolamine dehydration) has been considered to proceed *via* transition state III on the basis of the argument that the kinetically indistinguishable alternative transition state IV did not represent a *catalytic* pathway since hydrogen bonding to the imino nitrogen atom should stabilize the ground state more than the transition state.[18] The case for transition state III has been markedly strengthened by the observation of general base catalysis for hydrolysis of benzhydrylidenedimethylammonium ion,[29] a substrate which contains no imino hydrogen atom to which a hydrogen bond might be formed. Swain, *et al.*, have taken exception to conclusions based on anthropomorphic arguments in general and to transition state III in particular.[43] Arguing that the small β value for general base catalysis of benzylidene-1,1-dimethylethylamine hydrolysis (near 0.25) indicates that the transition state is close to reactants, the conclusion is drawn that the imino hydrogen is more acidic than the hydrogens of



III



IV

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[42] C. G. Swain and J. C. Worosz, *Tetrahedron Letters*, 3199 (1965).

[43] C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, 87, 1553 (1965).

[44] O. H. Wheeler and E. M. Levy, *Can. J. Chem.*, 37, 1727 (1959).

[45] B. Becker and A. W. Davidson, *J. Am. Chem. Soc.*, 85, 159 (1963).

water in the transition state and, hence, that transition state IV is of lower energy than transition state III. In the case of benzhydrylidenedimethylammonium ion hydrolysis, transition state IV is modified to provide a solvation role for the base catalyst rather than one involving hydrogen bond formation. We disagree with these conclusions and defend transition state III for both of these reactions on the following basis. (i) Values of Brønsted coefficients provide only a measure of the extent of proton transfer in the transition state and may not reflect the degree of formation or cleavage of covalent bonds to carbon in the transition state; (ii) the arguments of Swain, *et al.*, deal only with change in energy of that part of the transition state which involves hydrogen transfer, neglecting the change in energy of the remainder of the structure; (iii) the fact that the values of β for hydrolysis of protonated benzylidene-1,1-dimethylethylamines and of benzhydrylidenedimethylammonium ion are very nearly equal receives a natural explanation in terms of transition state III, in which the catalysts play identical roles in the two reactions, but must be dismissed as coincidental for transition state IV, in which the catalysts play quite distinct roles for the two reactions; (iv) the catalytic constant for imidazole as catalyst for the attack of water on benzhydrylidenedimethylammonium ion falls near the line in a Bronsted plot established by carboxylate anions.[46] This is the expected result in terms of transition state III. In the other case, one would certainly expect that anions would be more effective in solvating the cationic center than uncharged molecules such as imidazole. In view of these considerations, particularly point (iv), we conclude that transition state III is correct for these two cases and very probably is correct for reactions of this type in general. This conclusion is inconsistent with the solvation rule provided that β is a good measure of transition state structure.

If transition state III is accepted, the use of the "reacting bond" and "solvation" rules predicts that with increasing electron donation in the amine moiety the B–H bond should shorten. That is, values of α for general acid catalyzed carbinolamine decomposition should decrease with increasing basicity of the nucleophilic reagent in accord with the experimental results. Thus, the variation in β with structural alteration seems consistent with the rules although the magnitude of β does not.

While, as noted above, we consider the available evidence to strongly support transition state III for general acid catalyzed carbinolamine dehydration, the basis for our previous conclusion that transition state IV does not represent a catalytic pathway must be reexamined. Swain, *et al.*, have argued, on the basis of the very limited direct association of most acid–base pairs in dilute aqueous solution, that the ground states of the reactants for these reactions will be little stabilized by hydrogen bond formation.[43] The very existence of general acid–base catalysis indicates that transition states are so stabilized, a fact which has been rationalized by the assumption that highly polarizable electron clouds in the transition state may be capable of formation of abnormally strong hydrogen bonds.[43] If these conclusions are correct, the reaction pathway occurring *via* transition state IV must be considered to be catalytic. Alternatively it seems possible that stabilization of both ground and transition states may involve hydrogen bond formation between substrate and catalyst through intervening water molecules.[47] If this is the case, one might expect quite appreciable stabilization of ground states through interaction with the catalyst and the reaction path involving transition state IV might or might not be catalytic.

While we are certainly aware that reaction rates depend only on energy differences between ground and transition state, we do not agree that anthropomorphic arguments are "entirely unsound."[43] The considerations of Hammond,[39] Leffler,[40] and of Hine and Bayer[48] suggest that transition state energies are linear functions of ground-state and product-state energies. Thus the most favorable reaction pathway will be that which avoids the formation of unstable starting materials (structures present in vanishingly small concentrations), unstable intermediates, or unstable products. Anthropomorphic arguments attempt to answer the question of how to arrange the various components of the transition state to avoid formation of unstable species. For example, on the above basis transition state III is a better transition state than IV since III avoids formation of unstable intermediates or products while IV involves the formation of an unstable product. Anthropomorphic arguments, then, involve comparisons of relative energies of possible transition states rather than comparisons of transition state energies with energies of standard state concentrations of the separated components of the transition state. The former procedure, as well as the latter, seems to us to be quite legitimate.

B. Schiff Base Hydrolysis. Several lines of evidence strongly suggest that the pH-independent reaction under basic conditions commonly observed for Schiff base hydrolysis is, as initially suggested by Willi,[24] the attack of hydroxide ion on the protonated substrate rather than the attack of water on the free base form of the substrate. First, the *observed* second-order rate constant for attack of hydroxide ion on benzhydrylidenedimethylammonium ion is similar to that *calculated* for the attack of hydroxide ion on the conjugate acid of benzhydrylidenemethylamine.[29] Second, electron-withdrawing polar substituents in the aldehyde component of benzylideneanilines and benzylidene-1,1-dimethylethylamines decrease the rate of hydrolysis of these substrates.[13] Third, electron-withdrawing polar substituents in the aniline moiety of Schiff bases derived from *p*-trimethylammonium benzaldehyde decrease the rates of hydrolysis of these substrates.[26] The results reported above extend observations on the influence of polar substituents on Schiff base hydrolysis to aniline-substituted N-benzylideneanilines and are in complete accord with the above findings.

C. Methoxyaminolysis of Benzylideneanilines. The strong (or complete) dependence of the reaction of methoxyamine with N-benzylideneanilines on acid catalysis corroborates previous findings concerning transaldimination reactions.[29] Several indirect lines of evidence suggest that attack of the nucleophilic reagent is the rate-determining step for the reaction of weakly

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[46] K. Koehler and E. H. Cordes, unpublished experiment.

[47] See E. Grunwald and S. Meiboom, *J. Am. Chem. Soc.*, **85**, 2047 (1963), and references therein.

[48] J. Hine and R. P. Bayer, *ibid.*, **84**, 1989 (1962).

basic amines with Schiff bases derived from strongly basic amines.[29] The principal goal of the present studies was to provide additional evidence for this conclusion. Methoxyamine ($pK_a = 4.60$) is about as basic as aniline ($pK_a = 4.58$). Thus, by varying the nature of the polar substituent in the aniline moiety of N-benzylideneanilines, one may make the resident amine either more or less basic than the attacking amine, methoxyamine. Provided that the relative basicities of the resident and attacking amine is the only important factor in determining the behavior of the *gem*-diamine intermediates, one expects that the attack of methoxyamine on those substrates possessing electron-donating substituents will be rate determining and that decomposition of the tetrahedral intermediate will be rate determining for those substrates possessing electron-withdrawing substituents. Thus a transition in rate-determining step with variation in polar substituent is expected for the methoxyaminolysis of N-benzylideneanilines, and it was hoped that such behavior would manifest itself in the form of a break in the Hammett plot. Such is not the case. Either no transition in rate-determining step occurred or else the effect of polar substituents on the rate constants is the same in both cases. Inasmuch as previous work suggests that the latter alternative is not unlikely,[29] and since the assumption that basicity alone determines the rate-determining step is certainly oversimplified, no grounds exist for distinguishing between these alternatives.

Acknowledgment. We are indebted to Professors William P. Jencks, C. Gardner Swain, Edward Thornton, and Richard Schowen for helpful comments concerning certain aspects of this work.

Conformational Mobility and Optical Rotation Effects of Aromatic Nuclei[1]

James H. Brewster and J. George Buta[2]

Contribution from the Department of Chemistry, Purdue University, Lafayette, Indiana. 47907.

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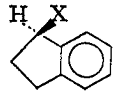
Abstract: A series of 1-substituted indans has been prepared in known absolute configuration. Multiple Cotton effects are shown in the region 250–275 mμ, corresponding in fine structure to the ^1L_b absorptions bands, notably when the 1 substituent has a positive charge or can hydrogen bond to the nucleus. The dispersion curves of the indans are essentially enantiomeric to those of the corresponding α-phenylethyl compounds of the same absolute configuration; the open-chain compounds show much smaller Cotton effects. These results indicate that conformational mobility has a significant effect on the optical rotation properties of aromatic compounds.

Desiring to gain some insight into the effect of conformational mobility of the phenyl group upon the optical rotation properties of aromatic compounds, we have prepared a series of 1-substituted indans (Ia–h), in the absolute configuration shown, for comparison with the corresponding open-chain compounds (II). As may be seen from the figures, many, but not all, of these compounds show multiple rotation anomalies in the region of the ^1L_b transition[3] of the aromatic ring. These are similar to, but in several cases larger than, apparently authentic anomalies which have recently been reported for other aromatic compounds.[4] We believe that we have taken the precautions necessary[5] to ensure that these anomalies are real and not artifacts.



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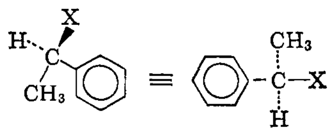

II

a, X = CO_2H
b, X = CO_2Na
c, X = NH_2
d, X = NH_3Cl
e, X = $N(CH_3)_3I$
f, X = OH
g, X = CH_2OH
h, X = CH_3

The substituted indans were all prepared from (R[6])-(+)-1-indancarboxylic acid[7] (Ia) by standard synthetic

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(1) A Useful Model of Optical Activity. VII. Part VI: J. H. Brewster and J. E. Privett, *J. Am. Chem. Soc.*, **88**, 1419 (1966).

(2) We wish to express our appreciation to the Purdue Research Foundation and the Eli Lilly Co. for grants in support of this research and to the National Science Foundation for Grant GP1688 for purchase of the spectropolarimeter.

(3) J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).

(4) (a) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960); (b) I. P. Dirkx and Th. J. DeBoer, *Rec. Trav. Chim.*, **83**, 535 (1964); (c) K. S. Brown, Jr., and C. Djerassi, *J. Am. Chem. Soc.*, 86, 2456 (1964); (d) T. M. Hooker, Jr., and C. Tanford, *ibid.*, 86, 4989 (1964); (e) L. Verbit, *ibid.*, **87**, 1617 (1965); (f) A. Moscowitz, A. Rosenberg, and A. E. Hansen, *ibid.*, **87**, 1813 (1965); (g) A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes, and M. J. Vernengo, *J. Chem. Soc.*, 2239 (1965); (h) A. Yogev and Y. Mazur, *Chem. Commun.*, 388 (1965).

(5) A Bendix-Ericsson Polaromatic-60 recording spectropolarimeter with a 250-w xenon light source was used. Concentrations were chosen so that transmission did not drop below 40% in the spectral regions of interest. Under these conditions further dilution did not alter the shape of the dispersion curve, enantiomers gave mirror image curves, and racemic substances gave zero rotation; see I. P. Dirkx, P. J. vander Haak, and F. J. L. Sixma, *Anal. Chem.*, **36**, 1988 (1964), and C. Djerassi, E. Lund, E. Bunnenberg, and J. C. Sheehan, *J. Org. Chem.*, **26**, 4509 (1961), for discussions of some factors which produce false anomalies in strongly absorbing solutions.

(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); R. S. Cahn, *J. Chem. Educ.*, 41, 116 (1964).

(7) A. Fredga, *Chem. Ber.*, **89**, 322 (1956), has assigned the *R* configuration to (+)-Ia by the method of quasiracemates. W. G. Dauben and P. Baumann, *Tetrahedron Letters*, 565 (1961), have assigned the *R*