

Secondary Deuterium Isotope Effects for Addition of Nitrogen Nucleophiles to Substituted Benzaldehydes^{1a}

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Abstract: Kinetic secondary deuterium isotope effects, k_D/k_H , for the water-catalyzed addition of semicarbazide to a series of substituted benzaldehydes are near 1.30 and are independent of the nature of the polar substituent; corresponding values for the same reaction catalyzed by the hydrated proton and other acids are near 1.21. Values of k_D/k_H for the water-catalyzed addition of phenylhydrazine to substituted benzaldehydes decrease from 1.28 to 1.16 as the nature of the polar substituent is varied from *p*-methoxy to *p*-nitro. The corresponding values for the same reaction catalyzed by the hydrated proton decrease from 1.21 to 1.13 for the same substituents. These results indicate that the extent of carbon–nitrogen bond formation in the transition state for addition of nucleophiles to the carbonyl group is a function of the reactivity of substrate, nucleophilic reagent, and the strength of the catalyzing acid. The secondary deuterium isotope effect on the equilibrium constant for carbinolamine formation from benzaldehyde and hydroxylamine is near 1.36, larger than the largest of the kinetic effects observed. Under conditions in which carbinolamine dehydration is rate determining, values of k_D/k_H for the overall rate of semicarbazone formation from benzaldehydes decrease from 1.31 to 1.20 as the nature of the polar substituent varies from hydrogen to *p*-nitro. This result demonstrates that the extent of carbon–oxygen bond cleavage in the transition state for carbinolamine dehydration is a function of the nature of the polar substituent of the substrate. Moreover, for those substituents which are not strongly electron withdrawing, the transition state closely resembles the carbinolamine itself.

One of the central questions in physical organic chemistry is the relationship between substrate structure and transition-state structure. This subject has been treated theoretically several times^{2–6} and a number of experimental approaches, including study of linear free energy relationships and isotope effects, have been brought to bear on it. Among these, α -deuterium isotope effects have proved useful indicators of transition-state structures in several cases.⁷ For example, measurement of the α -deuterium isotope effects for the hydrolysis of acetals and orthoformates revealed a marked change in the degree of carbon–oxygen bond cleavage in the transition state as a function of substrate structure, clarifying structure–reactivity relationships for these hydrolyses.⁸

Simple carbonyl addition reactions provide one of the most versatile settings in which to study the relationship between substrate and transition-state structure.

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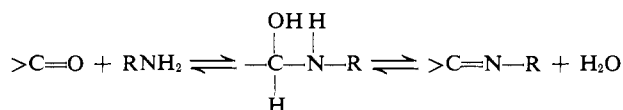
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For example, the addition of amines to carbonyl compounds proceeds with rate-determining attack of the nucleophilic reagent under acidic conditions and with rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions.^{9,10}



Consequently, through appropriate choice of experimental conditions, one can probe the transition-state structure for both steps employing a single set of compounds.

As a specific set of reactants, substituted benzaldehydes have been chosen as the carbonyl component and semicarbazide and phenylhydrazine as amines. This provides for study of the effect of variation in reactivity of both substrate and nucleophile on transition-state structure. Moreover, with these reactants, the addition step exhibits a pH-independent reaction as well as specific and general acid catalysis.^{11,12} Consequently, the strength of the acid catalyst is an additional variable whose effect on transition-state

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structure may be probed. This manuscript reports the results of a study of α -deuterium isotope effects for these reactions as a function of the structure of carbonyl component, amine, and acid catalyst. A preliminary report has been published.¹³

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Glass-distilled water was used throughout. Hydroxylamine hydrochloride, semicarbazide hydrochloride, and phenylhydrazine were recrystallized prior to use. Benzaldehyde- α - d_1 ,¹⁴ 3-bromobenzaldehyde- α - d_1 ,¹⁵ 4-methoxybenzaldehyde- α - d_1 ,⁸ and 4-nitrobenzaldehyde- α - d_1 ⁸ were prepared as previously described. Deuterium analyses were performed with a Varian A-60 magnetic resonance spectrometer. The pmr spectra of neat samples of all deuterated compounds indicated an isotopic purity of at least 98% for each.

Kinetics. All reactions were monitored spectrophotometrically employing a Zeiss PMQ II spectrophotometer. Reactions involving semicarbazide were carried out in aqueous solution; those involving phenylhydrazine in 20% aqueous ethanol. All runs were carried out at $25.0 \pm 0.5^\circ$. Temperature variation during those kinetic measurements for determination of a specific isotope effect did not vary more than 0.02° and was monitored as previously described.⁸

Values of pH were recorded with a Radiometer PHM 4c meter equipped with a glass electrode. Values of pH were recorded at the temperature of the kinetic runs.

Measurement of Equilibrium Constants. Secondary deuterium isotope effects for the addition of hydrogen cyanide to 4-methoxybenzaldehyde and for the addition of hydroxylamine to benzaldehyde were determined. Individual equilibrium constants were determined from the extent of decrease of optical density at the wavelength maximum of the aldehyde, 250 nm for benzaldehyde and 283 nm for 4-methoxybenzaldehyde, as a function of the concentration of the nucleophilic reagent. All measurements were made in 1-cm glass-stoppered quartz cells in which solutions were maintained at $25.0 \pm 0.03^\circ$. All solutions were prepared immediately prior to use and contained 10^{-4} M EDTA. The aldehydes employed were distilled under nitrogen on a Nestor-Faust spinning band column and were stored in the dark under nitrogen at -40° .

Each absorbance value used in calculation of an equilibrium constant was the average of seven consecutive observations. The average standard error in any absorbance value was 0.0004 OD unit and was independent of the absorbance in the range 0.100–1.400. Measurement of optical density changes for the addition of hydroxylamine to benzaldehyde was complicated by the slow dehydration of the addition product to the oxime.¹⁶ In this case, the absorbance values at t_0 were the least-squares y intercepts of linear plots of absorbance against time. The average standard error in these extrapolated absorbance values was 0.0004, for absorbances between 0.400 and 0.600. Several techniques were employed to introduce precisely known values of aldehyde and nucleophile solutions into the cells. These are described below.

The procedure used to determine the isotope effect on cyanohydrin formation typifies the basic approach. Explicitly, the procedure was as follows. Stock solutions of cyanide, aldehyde, and aldehyde- $1-d$ in glass-distilled water containing 10^{-4} M EDTA were prepared. The cyanide solution was 0.0734 ± 0.006 M in each of potassium cyanide, hydrogen cyanide, and potassium chloride. The 4-methoxybenzaldehyde and 4-methoxybenzaldehyde- $1-d$ solutions were prepared to contain roughly 10^{-4} M aldehyde. Five glass-stoppered 1-cm cells were tared (error = 0.0001 g), and long disposable pipets were used to introduce 1.40 ± 0.10 -ml portions of distilled water into cells 1, 3, and 5, and of the stock cyanide solution into cells 2 and 4. Then the absorbances (OD_1^0 , OD_2^0 , ..., OD_5^0) were measured (standard error = ± 0.0004) and the cells reweighed. With care not to contact the surfaces of the solutions already present, 1.00 ± 0.10 -ml portions of the aldehyde solution were placed in cells 1 and 2, of the aldehyde- $1-d$ solution in cells 3 and 4, and of the stock cyanide solution in cell 5 with the disposable

pipets. After inverting each cell 14 times to effect mixing and then allowing 7 min for thermal equilibration in the cell block, the new absorbances (OD_1^1 , OD_2^1 , ..., OD_5^1) were measured and the cells were reweighed.

The equilibrium constants for aldehyde or aldehyde- $1-d$ were calculated in the following way. The volume of any solution was assumed to be directly proportional to its weight. The initial volumes were designated as V_1^1 , V_2^1 , ..., V_5^1 , the second volumes as V_1^2 , V_2^2 , ..., V_5^2 , and the total volumes as V_1^3 , V_2^3 , ..., V_5^3 . The absorbance of the stock aldehyde solution was $OD_1 = (OD_1^1 - OD_1^0)(V_1^3/V_1^2)$. The absorbance that would have been obtained in the aldehyde-cyanide solution had the cyanide been absent is $OD_2 = OD_1 V_2^2/V_2^3$. The absorbance of the stock cyanide solution is $OD_3 = (OD_3^1 - OD_3^0)V_3^3/V_3^2$, so the initial absorbance of cell 2 in the absence of cyanide would have been $OD_4 = OD_2^0 - OD_3$ and the final absorbance in the absence of any cyanide contribution would have been $OD_5 = OD_2^1 - (OD_3 V_2^1/V_2^3)$. The true absorbance of free aldehyde in the cyanide-aldehyde solution is $OD_6 = OD_5 - OD_4$. The concentration of hydrogen cyanide in this solution with respect to its concentration in the stock solution, C_0 , is $C_1 = C_0(V_2^1/V_2^3)$. The equilibrium constant is then $K_{eq}^H = (OD_2 - OD_6)/(OD_6 C_1)$. Each of the absorbance values used in these equations was the average of seven observations; common absorbance values were $OD_1^0 = 0.067$, $OD_1^1 = 1.019$, $OD_2^0 = 0.172$, $OD_2^1 = 0.486$, $OD_3^0 = 0.042$, $OD_3^1 = 0.154$. Repeating these calculations with the data for cells 3 and 4 gave the equilibrium constant for aldehyde- $1-d$. The absorbance of the stock cyanide solution, OD_3 , changed between each run, increasing from 0.071 during run 1 to 0.183 during run 4.

The procedure was repeated four times with the original stock cyanide and aldehyde solutions. The results are shown in Table I.

Table I

Run	K_{eq}^H	K_{eq}^D	k_{eq}^D/K_{eq}^H
1	39.1173	49.8372	1.2741
2	39.0120	49.7837	1.2761
3	39.5426	50.6030	1.2797
*4	36.0341	50.1034	*1.3903
		Mean = 1.2766, error = 0.0028	

K_{eq}^H in run 4 deviates substantially from the others and it is statistically reasonable to disregard this run. The mean isotope effect from the three remaining runs = 1.277, standard error = 0.003. The absorbance of the aldehyde solution (or the aldehyde- $1-d$ solution) was calculated from the equation $OD_1 = (OD_1^1 - OD_1^0)(V_1^3/V_1^2)$, and as such its standard error is an indication of the precision inherent in this procedure for measuring the isotope effect, for the equilibrium constants are functions of several absorbances that are similar to OD_1 . Since values of OD_1 decrease with time, the standard error in OD_1 was taken to be the average of the residuals in a least-squares plot of OD_1 against time. Including the more extensive data from the other isotope effect determinations (eight plots correlating 54 independent values of OD_1) the average standard error in OD_1 was 0.18%. This error is a little larger than that predicted by the observed standard errors in the absorbance and weight readings, which was 0.12%. Based on the standard error in OD_1 , liberal and conservative estimates of the random error in the equilibrium constants are 0.50 and 1.00%, respectively. The observed standard error in K_{eq}^H and K_{eq}^D was 0.71 and 0.74%, respectively.

The relatively fast dehydration of the adduct of benzaldehyde with hydroxylamine required that t_0 be known with some precision. To slow this reaction, 70.0% aqueous dioxane was chosen as the solvent. The stock hydroxylamine solution was 0.260 M (error = 0.001) in hydroxylamine and contained sufficient Tris to neutralize the hydroxylamine hydrochloride and to bring the pH to 7.71 ± 0.02 . The approach was in essence the same as that described for the cyanide equilibria, but utilized disposable pipets to effect mixing as well as to introduce the solutions to the cells. One pair of glass-stoppered 1-cm cells was tared, 1.4 ± 0.1 -ml portions of 70.0% aqueous dioxane were introduced, and the absorbances measured. OD_1^0 and OD_2^0 for cells 1 and 2, respectively. Another pair of glass-stoppered cells, designated 3 and 4, that contained 2.00 ± 0.10 -ml samples of the hydroxylamine solution, was tared and placed in the holder to warm to 25° . Then 20.0 μ l of 10^{-3} M solutions of aldehyde and aldehyde- $1-d$ in 70% aqueous dioxane were

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placed in cells 1 and 2, and these cells were reweighed. The absorbance of cell 1 was measured, OD_1^1 and then, with a disposable pipet, 1.00 ± 0.10 ml of the stock hydroxylamine solution was taken from cell 3 and was introduced with some force into cell 1. This achieved more than 80% mixing in a 3-sec interval. To complete the process this mixture was then sucked into and forced from the disposable pipet three times over a period of 20 sec, taking care to draw somewhat more solution each time to effectively rinse the pipet. After a delay of 60 sec from t_0 the absorbance, OD_1^2 , was followed for 3 min at 10-sec intervals. The change in OD_1^2 was linear over this period, increasing about 0.005 optical density unit per sec. This procedure was then repeated for aldehyde-*l-d*; the order aldehyde-aldehyde-*l-d* was reversed in the following run, as usual, to obviate systematic errors. During the procedure a fifth cell containing solvent and some stock nucleophile solution was used as described earlier to provide corrections for certain absorbances.

The calculations were, in brief, as follows. The volumes were corrected to reflect their different densities, in the usual manner. These volumes were defined as: V_1 = the volume of solution present when OD_1^1 was determined; V_2 = the volume of stock nucleophile solution that was transferred to cell 1 from cell 3; $V_3 = V_1 + V_2$, the effective volume of the resulting "reaction" solution (that is, not taking account of the part of this solution that remained in the disposable pipet when it was thrown away). The aldehyde concentration in the reaction solution before any adduct was formed was $OD_2 = (OD_1^1 - OD_1^0)(V_1/V_3)$. The nucleophile concentration in the reaction solution was $C_1 = C_0(V_2/V_3)$, where C_0 was its concentration in the stock solution. This concentration C_1 contributed an absorbance $OD_3 = OD_3(C_1/C_0)$, in which the absorbance of the stock nucleophile solution is OD_3 as defined and discussed earlier, to that of the reaction solution. The concentration of free aldehyde in the reaction solution was proportional to $OD_6 = OD_1^2 - OD_1^0 - OD_3$. The equilibrium constant was then $K = (OD_2 - OD_6)/(OD_6C_1)$. Each of the absorbance values used in these equations was the average of seven observations; common absorbance values were: $OD_1^0 = 0.072$, $OD_1^1 = 1.408$, $OD_1^2 = 0.431$. Repeating these calculations with the data for cells 2 and 4 gave the equilibrium constant for aldehyde-*l-d*. The absorbance of the stock hydroxylamine solution, $OD_3 = 0.114$, remained essentially constant with time.

The procedure was repeated seven times with the original stock hydroxylamine and aldehyde solutions. The results are shown in Table II. The mean isotope effect = 1.360, standard error =

Table II

Run	K_{eq}^H	K_{eq}^D	K_{eq}^D/K_{eq}^H
1	6.6123	8.9764	1.357
2	6.7947	9.1561	1.348
3	6.7770	9.2744	1.368
4	6.9337	9.4040	1.356
5	6.8210	9.0664	1.329
6	6.3577	8.9147	1.402
7	6.2340	8.4746	1.359
			Mean = 1.360, error = 0.021

0.021. The standard errors in the data were comparable to those described for the cyanide equilibria, so the standard error in the isotope effect was predicted as before to be 1.00–2.00%. This prediction is, in this instance, in agreement with the observed standard error, 1.54%. The nature of the procedure caused the ratio of adduct/free aldehyde to vary over the range 0.605–0.914; over this narrow range no discernable trend occurred in the isotope effect for K_{eq} .

Note that the method just described for determination of the deuterium isotope effect on the equilibrium constant for addition of cyanide and hydroxylamine to benzaldehydes assumes that the adducts do not absorb light appreciably at the wavelengths employed for the determination. This assumption is difficult to check directly for the systems studied although it is certainly reasonable. The principal danger is possible contamination of the aldehydes with the corresponding benzoic acids, readily formed by air oxidation. Were both protio and deuterio substrates so contaminated, it would result in a measured isotope effect slightly smaller than the true one. Since the isotope effects are large, this seems unlikely. Were only one aldehyde contaminated by 10% benzoic acid, the measured effect might be either too small or too large but not by more than 0.02 in either direction.

Results

The experimentally determined α -deuterium isotope effects on equilibrium constants for addition of hydrogen cyanide and hydroxylamine to, respectively, 4-methoxybenzaldehyde and benzaldehyde are summarized in Table III.

Table III. α -Deuterium Isotope Effects on the Equilibrium Constants for Addition of Hydrogen Cyanide and Hydroxylamine to Benzaldehydes in Aqueous Solutions at 25.00°

Substrate	Nucleophile	K_{eq}^D/K_{eq}^H
4-Methoxybenzaldehyde	Hydrogen cyanide	1.276 ± 0.002^a
Benzaldehyde	Hydroxylamine	1.360 ± 0.020^b

^a Standard deviation of the mean of three determinations.

^b Standard deviation of the mean of seven determinations.

Measurement of isotope effects for individual rate constants for addition of amines to benzaldehydes is complicated by difficulties in achieving experimental conditions in which just one rate constant dominates the kinetics. In efforts to measure isotope effects for the water catalyzed and specific acid catalyzed attack reaction, there are two principal dangers: first, the rate of the acid-catalyzed reaction may contribute significantly when it is desired to study the water-catalyzed reaction and *vice versa*; and, second, the rate of the dehydration reaction may significantly influence the overall reaction rate.¹⁷ For studies of isotope effects on the dehydration reaction, the only important problem is the possible importance of the contribution of the attack reaction to the overall rate. Reaction conditions were chosen to minimize these dangers although there generally exists no set of conditions in which they can be eliminated. Conditions employed for each measurement, together with calculated estimates, based on rate constants previously determined,^{11,12} of the relative contributions of various processes are collected in Table IV. Values of rate constants necessary for these calculations for the reaction of 3-bromobenzaldehyde were estimated from the Hammett constant for this substituent and rate constants for reactions of other benzaldehydes.¹¹

The measured α -deuterium isotope effects for the various rate constants for benzaldehyde semicarbazone or phenylhydrazone formation are collected in Tables V and VI.

Note that all isotope effects were measured at sufficiently high ratios of amine to aldehyde to generate satisfactory pseudo-first-order kinetics. Isotope effects for acid-catalyzed carbinolamine dehydration were measured at values of pH sufficiently high so that the rate of the attack reaction contributed not more than 6% to the overall rate. In addition, these isotope effects were measured at concentrations of semicarbazide sufficiently low so that not more than 5%, and generally much less, of the carbonyl substrate was converted to carbinolamine in a rapid preequilibrium step as judged on the basis of the equilibrium constants measured by Anderson and Jencks.¹⁸ The equilibrium constant for carbinolamine formation from benzalde-

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Table IV. Experimental Conditions for Measurement of α -Deuterium Isotope Effects for Individual Rate Constants for Reaction of Semicarbazide and Phenylhydrazine with Substituted Benzaldehydes

Nucleophile	Rate constant ^a	Substituent ^b	(Amine) _{total} / (aldehyde)	pH	$k_{H^+}(H^+)/$ $k_{H_2O}^c$	$v_{attack}/$ $v_{dehydration}^d$
Semicarbazide	$k_{H^+}^e$	4-OCH ₃	100	2.0	92	0.068
		H	112	2.07	180	0.009
		3-Br	11.2	2.10	40	0.040
	k_o^f	4-OCH ₃	75	5.0	0.09	0.081
		H	10.4	4.90	0.025	0.37
		3-Br	9.5	4.30	0.20	0.24
	k_{deh}^g	H	40	6.61		20
		3-Br	130	6.97		37
		4-NO ₂	45	6.00		24
Phenylhydrazine	$k_{H^+}^e$	4-OCH ₃	100	2.0	18	0.0024
		H	131	2.15	10	0.004
		4-NO ₂	15	2.14	100	0.0067
	k_o^f	4-OCH ₃	100	5.0	0.018	0.13
		H	36	4.54	0.031	0.12
		4-NO ₂	14	4.84	0.15	1.04
	k_{deh}^g	H	24	6.63		16

^a For which the α -deuterium isotope effect is being measured. ^b In the carbonyl substrate. ^c The relative contribution of the acid-catalyzed and water-catalyzed reactions to the overall rate of carbinolamine formation under the conditions of the measurement. ^d The ratio of the overall rate of carbinolamine formation, $[k_{H^+}(H^+) + k_{H_2O}](RNH_2)$, to the rate of carbinolamine dehydration, $k_{deh}(H^+)$ (carbinolamine), under the conditions of the measurement. ^e Third-order rate constant for acid-catalyzed attack of nucleophilic reagent on the substrate. ^f Second-order rate constant for pH-independent attack of nucleophilic reagent on the substrate. ^g Third-order rate constant for acid-catalyzed carbinolamine dehydration.

Table V. Kinetic α -Deuterium Isotope Effects for the Addition of Semicarbazide and Phenylhydrazine to Substituted Benzaldehydes at 25.00°^a

Catalyst	Semicarbazide			
	4-Methoxy ^b	Hydrogen ^b	3-Bromo ^b	4-Nitro ^b
H ₃ O ⁺	1.216 ± 0.006	1.207 ± 0.007	1.218 ± 0.004	
H ₂ O	1.310 ± 0.004	1.312 ± 0.004	1.288 ± 0.004	
Acetic acid		1.228 ± 0.009		
(CH ₃) ₃ N ⁺ OH		1.226 ± 0.008		
	Phenylhydrazine			
H ₃ O ⁺	1.208 ± 0.010	1.218 ± 0.007		1.126 ± 0.007
H ₂ O	1.276 ± 0.011	1.218 ± 0.011		1.163 ± 0.006

^a Errors are given as the standard deviation of the mean of three determinations. ^b Substituents in the benzaldehyde substrate.

Table VI. α -Deuterium Isotope Effects for Specific Acid Catalyzed Carbinolamine Dehydration for the Reaction of Semicarbazide and Phenylhydrazine with Substituted Benzaldehydes at 25.00°^{a,b}

Nucleophilic reagent	Substrate		
	Hydrogen	3-Bromo	4-Nitro
Semicarbazide	1.311 ± 0.008	1.271 ± 0.010	1.196 ± 0.003
Phenylhydrazine	1.268 ± 0.004		

^a Errors are given as the standard deviation of the mean of three determinations. ^b Isotope effects refer to overall rates for carbinolamine dehydration, not to the rate constant for dehydration itself.

hyde and phenylhydrazine is not known. However, concentrations of phenylhydrazine lower than those previously observed to yield kinetics first order in nucleophile under conditions of rate-determining dehydration were employed throughout.¹² Consequently, the secondary deuterium isotope effects for acid-catalyzed carbinolamine dehydration are not appreciably compromised in any way.

Isotope effects for acid-catalyzed attack of amines on the benzaldehydes could generally be measured under conditions in which neither the rate of the water-catalyzed reaction nor the rate of carbinolamine dehydration contributed significantly to the overall rate. In two cases, the attack of phenylhydrazine on benz-

aldehyde and the attack of semicarbazide on 4-methoxybenzaldehyde, these reactions did contribute respectively about 10 and 7% to the overall rate. Since isotope effects for acid-catalyzed attack are somewhat smaller than for the other reactions (Tables V and VI), the recorded values in these two cases may be slightly too high, possibly by as much as 0.02.

The isotope effects for the water-catalyzed attack of amines on benzaldehydes appear to be the most severely compromised since, under the experimental conditions employed (Table IV), the rate of carbinolamine dehydration frequently contributed substantially to the overall rate. Fortunately, this does not result in a significant error in the isotope effects since those for the water-catalyzed attack and acid-catalyzed dehydration are very nearly identical (Tables V and VI). To the extent, usually small, that the acid-catalyzed attack contributed to the overall rate, the recorded values for the water-catalyzed reaction may be slightly too small. Throughout, the maximum concentration of nucleophile employed was 0.004 M; consequently general acid catalysis by the conjugate acid of the nucleophile was negligible.

For the attack of semicarbazide on benzaldehyde, efforts were made to measure the α -deuterium isotope effect for the general acid catalyzed reaction employing acetic acid and the conjugate acid of trimethylamine

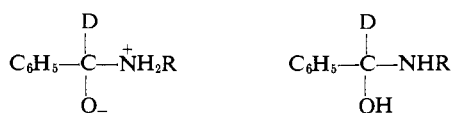
N-oxide as catalysts. In the former case, the reaction was carried out at pH 3.34 in the presence of 0.10 *M* total acetic acid. Calculations based on rate constants previously measured¹¹ reveal that, under these conditions, 84% of the rate of the attack reaction is due to the acetic acid catalyzed pathway and the remainder is about equally divided between the specific acid and water-catalyzed reactions. The ratio of the rate of carbinolamine dehydration to nucleophile attack is 17. Consequently, these conditions suffice to provide for a reasonably accurate measurement of the isotope effect acetic acid catalyzed reaction; the value is included in Table V. In the latter case, the isotope effect was measured at pH 3.30 in the presence of 0.10 *M* total trimethylamine *N*-oxide. Under these conditions, catalysis by the conjugate acid of trimethylamine *N*-oxide accounts for about 83% of the total rate of the attack reaction and the ratio of the rate of dehydration to attack is 19.¹¹ These conditions, thus, provide for a realistic determination of the α -deuterium isotope effect for catalysis by this acid and the value determined has also been included in Table V.

Discussion

Equilibrium Constant for Carbinolamine Formation.

Secondary deuterium isotope effects for carbinolamine formation from benzaldehyde and hydroxylamine and for addition of hydrogen cyanide to 4-methoxybenzaldehyde (Table III) are in the direction expected by analogy with carbonium ion solvolyses, $>C^+D + OX^- \rightarrow >C^+ - D + OX^-$, $k_H/k_D = 1.23$,⁷ but are significantly larger, probably because the stretching force constant associated with the aldehyde C-H bond is low compared to that for other C(sp²) bonds. The observation that the isotope effect for addition of the nitrogen nucleophile is greater than that for the carbon one accords with theoretical expectations.⁷

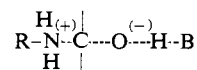
The isotope effect on the equilibrium constant for carbinolamine formation serves to provide a basis for the interpretation of *kinetic* isotope effects for the same reaction in terms of the degree of carbon-nitrogen bond formation in the transition state. That is, the isotope effect should increase from unity to 1.36 ± 0.02 as carbon-nitrogen bond formation becomes increasingly complete. This conclusion is based on the reasonable assumption that there is little or no difference in the isotope fractionation factors between



The isotope effect for carbinolamine formation is also useful as a guide to the extent of carbon-oxygen bond cleavage in the transition state for carbinolamine dehydration. Specifically, the isotope effect must vary from 1.36 ± 0.02 to some minimum value as cleavage of the carbon-oxygen bond becomes increasingly complete. This minimum value is the isotope effect for formation of the iminium ion product. This value has not been measured but may be approximately calculated from the isotope effect of carbinolamine formation and the maximum kinetic isotope effect for the attack of oxygen nucleophiles on protonated imines,

$k_D/k_H = 1.22$.¹⁹ The calculated value $(k_D/k_H)_{\text{overall}} = 1.11$.

Rate Constants for Carbinolamine Formation. The α -deuterium isotope effects for acid-catalyzed and water-catalyzed attack of semicarbazide on benzaldehydes are independent of the nature of the polar substituent in the aldehyde moiety (Table V). That is, within the accuracy of the measurements, the extent of carbon-nitrogen bond formation in the transition state is independent of the reactivity of the substrate. In accord with this conclusion, there is no detectable change in the Brønsted α value for general acid catalysis of the same series of reactions.¹¹ However, the isotope effects for the water-catalyzed reaction are significantly larger than those for both specific and general acid catalyzed routes; thus, the transition state for the former reaction occurs further along the reaction coordinate than do those for the latter ones. This finding accords with predictions of the Hammond postulate² and confirms a suggestion made earlier on the basis of differences in values of ρ^+ for the water-catalyzed and acid-catalyzed reactions.¹¹ Of particular note are the absolute values of the α -deuterium isotope effects: those for the water-catalyzed reaction approach, but do not attain, the value of 1.36 ± 0.02 which corresponds to complete formation of the carbon-nitrogen bond. The simplest interpretation is that this bond is nearly fully formed in the transition state for the water-catalyzed reaction. However, it ought to be explicitly recognized that it is not possible to unequivocally eliminate the possibility of complete C-N bond formation in the transition state. Thus, the conclusion that the kinetic isotope effects are smaller than the equilibrium one requires that the following assumptions hold: (i) the difference in charge distribution between the dipolar intermediate and the uncharged one does not appreciably affect the isotope effect; (ii) semicarbazide and hydroxylamine addition to carbonyl compounds yields the same isotope effect for the equilibrium constant for addition; and (iii) the contribution from acid-catalyzed attack does not appreciably lower the measured isotope effect for the water reaction (see Table IV). Although these assumptions appear reliable, the small difference in isotope effect on which the case for incomplete C-N bond formation rests requires that final judgment be withheld on this point. For the acid-catalyzed reactions it appears certain that substantial, but not complete, C-N bond formation has occurred in the transition state. Since Brønsted α values for general acid catalysis of semicarbazone formation are quite small,^{11,17} these findings indicate that the extent of proton transfer from catalyst to substrate does not parallel the extent of bond formation between amine and carbonyl group.

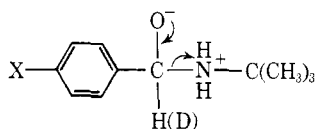


In contrast to the behavior observed for semicarbazide, the α -deuterium isotope effects for addition of phenylhydrazine to benzaldehydes do vary as a function of the nature of the polar substituent: for both

(19) J. Archila, H. Bull, C. Lagenaar, and E. H. Cordes, *J. Org. Chem.*, **36**, 1345 (1971).

acid-catalyzed and water-catalyzed reactions, the transition state is reached progressively earlier as the substrate reactivity increases. This behavior accords with theoretical expectations.²⁻⁶ It is not clear why the extent of carbon–nitrogen bond formation in the transition state should be more sensitive to the nature of substrate reactivity for the addition of phenylhydrazine than for that of semicarbazide. As in the case of semicarbazide addition, the isotope effects tend to be smaller for the acid-catalyzed reaction than for the water-catalyzed one. In all cases, there is substantial carbon–nitrogen bond formation in the transition state.

Comparison of α -deuterium isotope effects for corresponding reactions of semicarbazide and phenylhydrazine reveals that those for the former are consistently larger than those for the latter. That is, there is decreasing carbon–nitrogen bond formation in the transition state with increasing reactivity of the attacking amine, as expected.² This conclusion rests on the assumption that the maximum value of the isotope effect for addition of semicarbazide and phenylhydrazine to benzaldehydes is the same, an assumption expected to be quite reliable. This conclusion is corroborated by measurements of the α -deuterium isotope effects for hydrolysis of 3-bromo- and unsubstituted benzylidene-1,1-dimethylethylamines²⁰ in the



region of rate-determining carbinolamine decomposition: $k_D/k_H = 1.021 \pm 0.007$ and 1.037 ± 0.005 , respectively.^{21,22}

In the reverse direction, this corresponds to the uncatalyzed (or water-catalyzed) addition of a strongly basic amine to benzaldehydes and the estimated isotope effects for the forward reaction²² are smaller than those observed for the same substrates with phenylhydrazine as the nucleophilic reagent. These results also accord with the observation that the values of the Brønsted exponent for general acid catalysis of nucleophilic attack of amines on benzaldehydes¹² and anilines on formaldehyde²³ decrease with increasing amine reactivity.

Rate Constants for Carbinolamine Dehydration.

α -Deuterium isotope effects for acid-catalyzed dehydration of the carbinolamines derived from a series of benzaldehydes and semicarbazide are large and decrease with increasing electron-withdrawing capacity

(20) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963).

(21) H. G. Bull, unpublished observations.

(22) The limits on the isotope effects corresponding to no and complete cleavage of the carbon–nitrogen bond are not precisely defined. The minimum upper limit, for no bond cleavage, is 1.22, the maximum isotope effect observed for the rate of attack of oxygen nucleophiles on the Schiff base.¹⁹ An approximate lower limit, for complete bond cleavage, is provided by the inverse of the isotope effect for the overall reaction in the forward direction: $1/1.11 = 0.90$ (*vide supra*). Consequently, the observed secondary deuterium isotope effects correspond to values of k_D/k_H near 1.14–1.16 in the forward direction.

(23) W. R. Abrams, Ph.D. Thesis, University of Pennsylvania, 1971.

of the polar substituent (Table VI). Note that the isotope effects refer to overall rates of carbinolamine dehydration, the product of the equilibrium constant for carbinolamine formation and the rate constant for dehydration, and not to the rate constant for dehydration only. Thus large isotope effects correspond to transition states which resemble the carbinolamine. Particularly for those carbinolamines derived from benzaldehyde and 3-bromobenzaldehyde, rather little carbon–oxygen bond cleavage has occurred in the transition state. Consequently, the transition state must have the bulk of the positive charge concentrated on oxygen and rather little on nitrogen. Jencks and coworkers have established that Brønsted α values for general acid catalyzed carbinolamine decomposition are large.^{17,24} This finding both accords with the suggestion of a substantial positive charge on carbinolamine oxygen in the transition state and provides another example of the lack of parallelism in extent of proton transfer from catalyst to substrate and the extent of covalent bond cleavage at carbon in the transition state. The trend in isotope effects, and hence in transition-state structure, is precisely that expected on the basis of the Hammond postulate.²

The isotope effect for the decomposition of the carbinolamine derived from benzaldehyde and phenylhydrazine is distinctly smaller than that for the same reaction involving semicarbazide. Thus, the transition state appears to be reached later for carbinolamines derived from more basic amines. However, this conclusion is compromised by the observation that secondary deuterium isotope effects for the attack of water on the conjugate acids of benzylidene-1,1-dimethylethylamines, the microscopic reverse of acid-catalyzed dehydration of carbinolamines formed from addition of *tert*-butylamine to benzaldehydes, are very large, indicating complete or nearly complete carbon–oxygen bond formation in the transition state.¹⁹ This requires little or no carbon–oxygen bond stretching in dehydration of the carbinolamine from this basic amine, in apparent conflict with the conclusion based on the data for semicarbazone and phenylhydrazone formation only. On the basis of the Hammond postulate,² one would expect the transition state to be reached increasingly early with increasing amine basicity. This accords with the findings of Sayer, *et al.*, who have determined that values of α for general acid catalyzed decomposition of carbinolamines derived from hydrazines increase with decreasing basicity of the parent amine.²⁴ As noted earlier, the extent of proton transfer in the transition state is not proportional to the extent of bond formation or cleavage at carbon; yet one might expect these two components of the reaction coordinate to change in parallel ways as a function of substrate structure. Final judgment concerning details of the relationship between transition state and amine structures for carbinolamine dehydration must await further experimentation.

(24) J. M. Sayer, M. Peskin, and W. P. Jencks, *J. Amer. Chem. Soc.*, **95**, 4277 (1973).