J. Org. Chem. 1991, 56, 1419-1424

Kinetics and Mechanism of Benzaldehyde Girard T Hydrazone Formation

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Received March 26, 1990

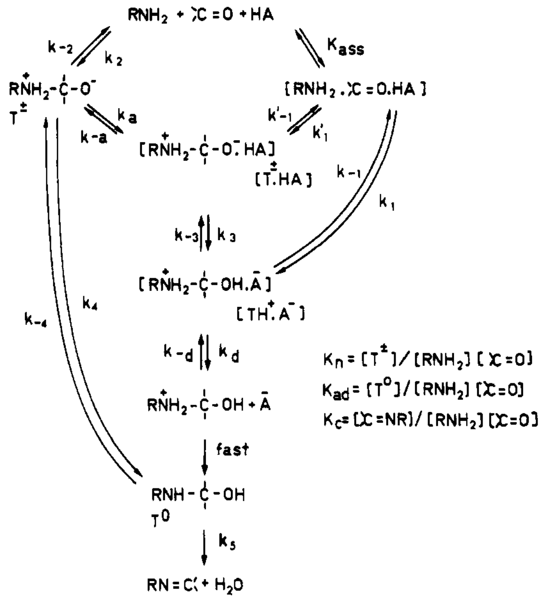
In aqueous solution, Girard T hydrazone formation from para-substituted benzaldehydes does not proceed to completion under the conditions used. The corresponding equilibrium constants were determined and employed to calculate the rate of the reaction at completion. For all the reactions studied, the pH-rate profiles, extrapolated to zero buffer concentration, show one break at pH 4-5, characteristic of a change in the rate-determining step from carbinolamine dehydration to carbinolamine formation upon going from pH 7 to pH 1. The formation of the carbinolamine is subject to catalysis by hydronium ion and by carboxylic acids present in the buffers used to maintain pH. Brønsted α values for this catalysis varied from 0.19 to 0.37. Rate constants for the cyanoacetic, chloroacetic, and formic acid catalyzed formation of carbinolamine from the para-substituted benzaldehydes correlate with σ^+ substituent constants, giving a value of ρ^+ equal to 0.70. Rate constants for the hydronium ion catalyzed formation of the carbinolamine from the same benzaldehydes are, however, insensitive to the substituent effect. These observations lead to the conclusion that the reactions occur by different routes as a function of the catalyst. We suggest a stepwise preassociation mechanism for the reaction catalyzed by carboxylic acids and a concerted preassociation mechanism for that catalyzed by hydronium ion.

The addition of nucleophilic nitrogen reagents to carbonyl compounds occurs in two stages: formation of a carbinolamine intermediate (T^0) and subsequent dehydration of the carbinolamine to yield the imine product.[1,2] Studies of the detailed mechanism of the addition of nitrogen nucleophiles to carbonyl compounds[3-7] have demonstrated the generality of the mechanism outlined in Scheme I. The acid-catalyzed formation of the neutral intermediate carbinolamine (T^0) can occur by at least three separate mechanisms: (1) a diffusion-controlled trapping mechanism in which a free zwitterionic intermediate ($T^\pm$), formed in the initial attack step, undergoes proton transfer to give the neutral intermediate (T^0) in a subsequent step (or steps) that may or may not be kinetically significant (k_2 followed by $K_n k_3 a_H$ or $K_n k_4$); (2) a stepwise preassociation mechanism characterized by preassociation of the carbonyl compound, the nucleophile, and the catalyst to form an encounter complex ($K_{ass.}$) that subsequently gives rise to an associated zwitterionic intermediate ($T^\pm \cdot HA$) (subsequent steps then lead to the neutral intermediate); and (3) a concerted preassociation mechanism in which the carbonyl coupound, the nucleophile, and the catalyst associate to form an encounter complex that converts to the neutral intermediate (T^0) via simultaneous C-N bond formation and proton transfer, without formation of the intermediate ($T^\pm \cdot HA$).

Changes in the rate-determining step are evidenced by breaks in the pH-rate profile, by breaks in structure-reactivity correlations, by nonlinear plots of rate constants against catalyst concentration, by variation of the Brønsted α exponent for general acid catalysis, and by isotope effects.[3-7]

In this work, we report a study of the kinetics and mechanism of addition of Girard T reagent ($NH_2NHC(O)CH_2N^+(CH_3)_3Cl^-$), a weakly basic nitrogen nucleophile, to para-substituted benzaldehydes. Girard T reagent forms water-soluble hydrazones even with carbonyl compounds of high molecular weight and has been employed to extract carbonyl compounds from mixtures of natural products.[8]

Scheme I



Experimental Section

Materials. All reagents employed were obtained commercially. With the exception of reagent grade inorganic salts, formic acid, and acetic acid, which were used without further purification, the remaining reagents were either redistilled, recrystallized, or sublimed before use. Girard T reagent was recrystallized twice from ethanol. Solutions of Girard T reagent in water were prepared just prior to use. Solutions of the benzaldehydes were prepared in purified ethanol[14] and maintained under a nitrogen atmosphere in the refrigerator for at most 1 week.

pK_a' Determination. The pK_a' (apparent pK_a) of the conjugate acid of Girard T reagent (2.09 ± 0.03) was measured at 25.0 °C in aqueous solution and ionic strength 0.50 (maintained with KCl) by careful partial acidification of nine samples of the reagent with known amounts of standard hydrochloric acid, in accordance with the procedure proposed by Albert and Serjeant.[9] The pH values of these solutions were measured with a glass

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electrode. The glass eletrode was initially calibrated with two blank solutions of the same ionic strength (KCl) containing 0.0100 and 0.001 00 M hydrochloric acid whose pH were taken, respectively, as 2.00 and 3.00. Under such conditions, the measured values of pH refer to hydronium ion concentration rather than to hydronium ion activity. The pK_a' was obtained from the measured values of pH, employing the Henderson–Hasselbalck equation.

Equilibrium Constants. The equilibrium constants for the overall reaction between Girard T reagent and substituted benzaldehydes were determined spectrophotometrically in aqueous solution at ionic strength 0.50 and pH 2, using a Zeiss PMQ II spectrophotometer thermostated at 25.0 °C. The determination of the equilibrium constants was made by preparing 18 solutions containing increasing concentrations of Girard T reagent (2.00×10^{-5} up to 5.00×10^{-2} M) and a constant concentration of the benzaldehyde (5.00×10^{-5} M). The absorptions of the Girard T solution (A_0), of the benzaldehyde solution (A_A), and of the Girard T hydrazone at infinite time (A_∞) were measured and the value of $A_T = A_\infty - A_0$ calculated. At high concentrations of Girard T reagent, the values of A_T approaches the constant value A_P. Representing the concentration of the Girard T reagent present as free base as $[RNH_2]$, the values of the equilibrium constant (K_c) were determined from the slope of plots of $(A_P - A_T)[RNH_2]$ against A_T, employing eq 1.

$$(A_P - A_T)[RNH_2] = 1/K_c(A_T) - A_A/K_c \qquad (1)$$

Kinetic measurements[10,11] were carried out spectrophotometrically at 25.0 °C in aqueous solution and ionic strength 0.50 (KCl) with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder. The final concentration of the ethanol introduced into the reaction mixtures from the aldehyde stock solutions did not exceed 1%. Reaction kinetics were monitored by observing the appearance of the Girard T hydrazones at the appropriate wavelength. The initial concentration of the benzaldehydes was 3.3×10^{-5} M and, in all cases, a sufficient excess of nucleophile reagent was employed such that pseudo-first-order behavior was observed. First-order rate constant (k) were evaluated from slopes of plots of $\log (A_\infty - A_t)$ against time using an appropriate computer program. Under the conditions of these experiments, the addition of Girard T reagent to the benzaldehydes does not proceed to completion, since a plot of k vs $[RNH_2]$, the concentration of Girard T reagent free base, gives a straight line that does not pass through the origin. The observed pseudo-second-order rate constant (k_{obsd}) for the reaction going to completion was calculated by using eq 2, where k is the observed pseudo-first-order rate constant and K_c is the equilibrium constant for the overall reaction.

$$k_{obsd} = k/([RNH_2] + 1/K_c) \qquad (2)$$

The pH was maintained constant by using carboxylic acid–carboxylate buffers. At high concentrations of the buffers used, the dehydration step (which is subject to hydronium ion catalysis, but not significantly catalyzed by carboxylic acid) becomes partially rate limiting.[3,12] Employing eq 3, k_{obsd} was corrected for the contribution of the dehydration step ($K_{ad}k_5$), to obtain k_{ad}, the rate constant for the addition step.[12]

$$k_{ad} = k_{obsd}/(1 - k_{obsd}/K_{ad}k_5a_{H^+}) \qquad (3)$$

Rate constants for catalysis by carboxylic acids, $k_{cat.}$, were obtained from the slopes of plots of k_{ad} against free carboxylic acid concentration. The extrapolation to zero carboxylic acid concentration gives $k_{ad}°$, the rate constant for the addition step catalyzed by hydronium ion plus water. We then calculated the value of $k_{overall}$, at zero buffer concentration, using eq 4.

$$k_{overall} = k_{ad}°/(1 + k_{ad}°/K_{ad}k_5a_{H^+}) \qquad (4)$$

For p-nitrobenzaldehyde, corrections were also made for the equilibrium constants and rates of formation and dehydration of the corresponding carbinolamines[15] and for hydration of the aldehyde.[13]

Table I. Equilibrium and Kinetic Constants for the Reaction of Girard T Reagent with Substituted Benzaldehydes (XC_6H_4CHO)[a]

X	K_c, 10^4 M	k_1, $M^{-2}\ s^{-1}$	K_nk_4, $M^{-1}\ s^{-1}$	$K_{ad}k_5$, $M^{-2}\ s^{-1}$
p-nitro	9.40	1400	1.60	4500
p-chloro	1.41	550	0.70	5600
p-bromo	1.80	950	0.50	4300
p-fluoro	0.90	600	0.28	3300
hydrogen	1.00	700	0.50	4500
p-phenyl	1.33	980	0.30	5000
p-methyl	0.68	880	0.22	5200
p-methoxy	0.39	850	0.05	2500

[a] In water at 25.0 °C and ionic strength 0.5 (KCl). K_c, equilibrium constants for the overall reaction; K_n, equilibrium constants for formation of zwitterionic intermediate; K_{ad}, equilibrium constant for the formation of neutral carbinolamine intermediate; k_1, observed rate constant for carbinolamine formation catalyzed by hydronium ion; K_nk_4, observed rate constant for uncatalyzed carbinolamine formation; $K_{ad}k_5$, observed rate constant for the carbinolamine dehydration catalyzed by hydronium ion. See Scheme I.

The observed pH–rate profile may be fit by a steady-state rate law[3,4] *having* the form of eqs 5 and 6, where $k_{obsd}°$ is the observed

$$k_{obsd}° = k_{ad}°K_{ad}k_5a_{H^+}/(k_{ad}° + K_{ad}k_5a_{H^+}) \qquad (5)$$

$$k_{ad}° = k_1a_{H^+} + K_nk_4 \qquad (6)$$

second-order rate constant for overall reaction, extrapolated to zero buffer concentration, $k_{ad}°$ is the apparent rate constant for the addition step at zero buffer concentration, $K_{ad}k_5$ is the observed rate constant when the dehydration step is rate determining, and K_nk_4 is the observed rate constant of uncatalyzed carbinolamine formation, with $K_n = k_2/k_{-2}$ being the equilibrium constant for formation of the zwitterionic intermediate ($T^{\pm}$) from the reactants.

Results

The reaction between Girard T reagent and substituted benzaldehydes is reversivel due to the low nucleophilicity of the Girard T reagent since the reaction is not complete under the conditions employed in this work. We determined the corresponding values of the equilibrium constants for the overall reaction (K_c), which are given in Table I.

The equilibrium constant for hydrazone formation from Girard T reagent and para-substituted benzaldehydes is increased by electron-withdrawing substituents on the aldehyde. The Hammett[16] plot for hydrazone formation gives $\rho = +1.23$ ($100r^2 = 94.9$; CL = 99.9%). The stabilization of the hydrazone (>C=N—) relative to the benzaldehyde (>C=O) by substituents that decrease the electron density is consistent with the fact that nitrogen is less electronegative than oxygen. A similar observation has been made by Anderson and Jencks for the formation of semicarbazones of para-substituted benzaldehydes.[17,18]

Figure 1 presents the pH–rate profiles for Girard T hydrazone formation with p-nitro-, p-bromo-, p-methoxy-,

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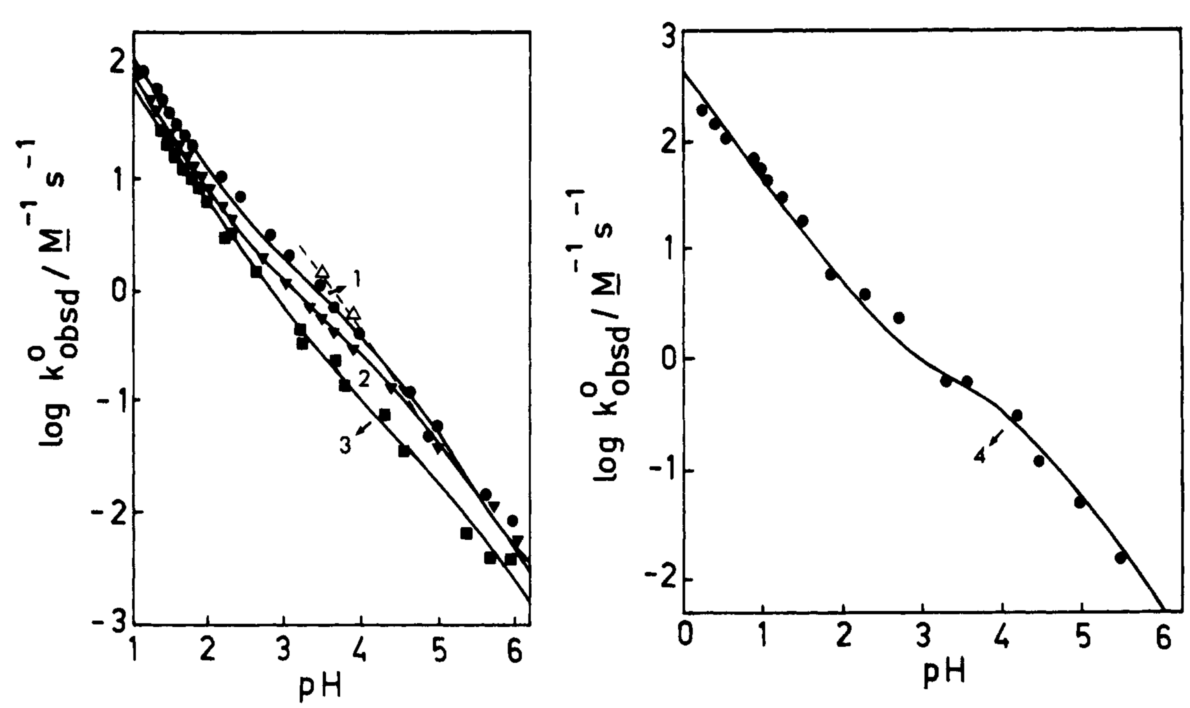

Figure 1. Dependence of the observed second-order rate constants on pH for the reactions of Girard T reagent free base with *p*-nitro- (1), *p*-bromo- (2), *p*-methoxy- (3), and *p*-chlorobenzaldehyde (4) extrapolated to zero concentration of general acid catalysts. The open symbols (△) and the broken line indicate the rate constants for the dehydration step at high pH or higher buffer concentration. The solid curves are theoretical profiles for the overall reactions rate, $k_{obsd}{}^o$, at zero buffer concentration, calculated from eqs 5 and 6 by using the rate constant of Table I.

and *p*-chlorobenzaldehyde. The data were corrected for the influence of the equilibrium and of dehydration and were extrapolated to zero buffer concentration, as described in the Experimental Section. Note that for all the benzaldehydes studied, the pH–rate profiles for Girard T hydrazone formation show a single break between pH 4 and 5, characteristic of the transition from rate-determining carbinolamine formation to carbinolamine dehydration as the pH is increased. Although the break for Girard T hydrazone formation from para-substituted benzaldeyde is small, the occurence of a change in the rate-determining step in this pH region is confirmed by the nonlinearity of a plot of the second-order rate constant against formate buffer concentration. Figure 2 shows this dependence for the reaction of the nucleophile with *p*-bromobenzaldehyde at pH 3.45. This is a result of a transition from a rate-limiting step subject to buffer catalysis to one that is not buffer catalyzed as the buffer concentration is increased.[4] The limiting rate constant at high buffer concentration, determined from the intercept of a double reciprocal plot[4,19] of observed rate constants at pH 3.45 against concentration of general acid catalyst, is in good agreement wih that calculated for the dehydration step (Figure 1, broken line) from the rate constants observed at higher pH. No other break[3,4] is observed below pH 1.5, the pH–rate profiles having been extended down to pH near zero (*p*-chlorobenzaldehyde, Figure 1).

The pH–rate profiles for the reaction of Girard T reagent with benzaldehydes and with *p*-fluoro-, *p*-methyl-, and *p*-phenylbenzaldehyde are similar to those shown in Figure 1. The values of the rate constants of k_1, K_nk_4, and $K_{ad}k_5$, defined in Scheme I, are presented in Table I.

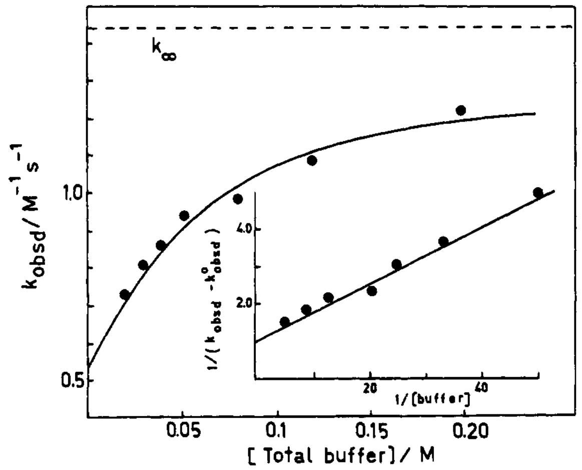

Figure 2. Experimental determination of the limiting rate constant, $K_{ad}k_5a_H$, for the dehydration of the carbinolamine derived from *p*-bromobenzaldehyde and Girard T reagent in the presence of formic acid/sodium formate buffer, pH = 3.34, ionic strength 0.50 (KCl). The broken line represents the limiting rate constant at high buffer concentration determined from a double reciprocal plot (inset) of the experimental data. The values of rate constants are 0.52 and 1.44 M^{-1} s^{-1} at zero buffer concentration and high buffer concentration, respectively.

Substitution of these values into equs 3 and 4 gives the theoretical pH–rate profiles indicated by the solid lines of Figure 1, which are in good agreement with the experimental points.

In the pH region where the formation of the intermediate T^0 is rate-determining, the reaction of Girard T reagent with the benzaldehydes is subject to general acid catalysis by the buffers employed to maintain constant pH. On the other hand, the dehydration of the intermediate T^0 is not subject to general acid catalysis. Measurement of the catalytic effect as a function of the ratio of acidic and basic forms of the buffers established that the catalysis is, within experimental error, of the general acid type

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Table II. Catalytic Constants for the Effect of Chloroacetic Acid (pK_a' = 2.72) on the Reactions of Girard T Reagent with Substituted Benzaldehydes (XC_6H_4CHO)[a]

X	pH	$k_{cat.}$, M^{-2} s^{-1}	$k_{cat.}$(av),[b] M^{-2} s^{-1}
p-nitro	2.19	2.2×10^2	
	3.40	1.8×10^2	2.0×10^2
p-chloro	2.35	8.7×10	
	2.75	7.4×10	
	3.35	7.8×10	8.0×10
p-methyl	2.20	5.1×10	
	2.68	4.4×10	
	3.28	4.5×10	4.7×10
p-methoxy	2.15	1.7×10	
	2.72	2.0×10	
	3.28	1.6×10	1.8×10

[a] In water at 25.0 °C, ionic strength 0.50 M (KCl). [b] Average value.

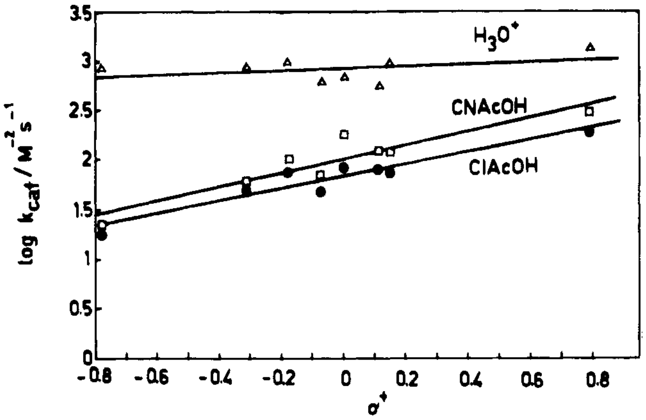

Figure 3. Dependence of log $k_{cat.}$ on σ^+ for carbinolamine formation catalyzed by hydronium ion (△), cyanoacetic acid (□), and chloroacetic acid (●). Reaction of Girard T reagent and para-substituted benzaldehydes at 25 °C and ionic strength 0.5 (KCl). The slopes of the lines (ρ^+) are hydronium ion (H_3O^+) +0.11, cyanoacetic acid (CNAcOH) +).71, chloroacetic acid (ClAcOH) +0.65.

(Table II). The catalytic rate constants, $k_{cat.}$, for the carbinolamine formation (Table III) were obtained after correction of the observed rate constants for the contribuition from the buffer-independent dehydration step, as described in the Experimental Section. The Brønsted plots for general acid catalysis of carbinolamine formation are shown in Figure 4 and the α values are given in Table IV.

Figure 3 shows Hammett plots of the rate constants for the catalyzed formation of carbinolamines from Girard T reagent and para-substituted benzaldehydes (σ_p^+, ref 23). When the catalyst is hydronium ion, ρ^+ = 0.11 (insignificant). When the catalyst is cyanoacetic acid, ρ^+ = 0.71 (without phenyl, $100r^2$ = 95.5 and CL = 99.9%). Employing chloroacetic acid, ρ^+ = 0.65 (without phenyl, $100r^2$ = 98.0 and CL = 99.9%).

When the catalyst is formic acid, ρ^+ = 0.70 (without unsubstituted benzaldehyde ($100r^2$ = 91.2 and CL = 99.9%). The catalysis by cyanoacetic acid gave a value of ρ_R^+ = 0.91 (without methyl, $100r^2$ = 98.0, CL = 99.9%) when correlated against σ_R^+ (ref 23).

Discussion

Addition reactions of nitrogen nucleophiles to the carbonyl group ordinarily proceed by a two-step mechanism involving formation of a carbinolamine intermediate, T^0, followed by its dehydration to the observed product, an imine. For many of these reactions, a break is observed in the pH-rate profile with decreasing pH.[1,10,21] This is a consequence of a change in the rate-determining step from dehydration to formation of the carbinolamine when the acid-catalyzed dehydration step becomes faster than the uncatalyzed formation of the intermediate. The pH-rate profiles for Girard T hydrazone formation from benzaldehydes (Figure 1) exhibit a break at pH ~4, corresponding to this change in rate-determining step.

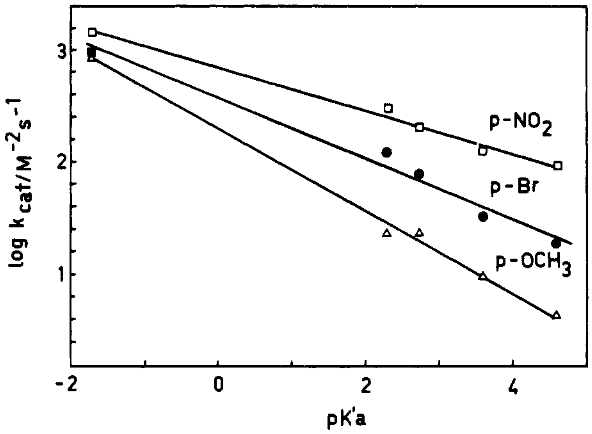

Figure 4. Brønsted plots for general acid catalysis of carbinolamine formation from Girard T reagent and substituted benzaldehydes by hydronium ion and carboxylic acids. Acid catalysts are identified in Tables I and III. The slopes of the lines (α) are 0.19 for *p*-nitro- (□), 0.29 for *p*-bromo- (●), and 0.37 for *p*-methoxybenzaldehyde (△) (see Table IV).

In the addition of more basic nitrogen nucleophiles, phenylhydrazine[24,26] (pK_a' = 5.30), methoxyamine[4] (pK_a' = 4.73), and semicarbazide[3] (pK_a' = 3.86) to benzaldehydes, a second break is observed as the pH is decreased further. This break becomes apparent near pH 1.5, corresponding to a change in the rate-determining step from hydronium ion catalyzed to uncatalyzed carbinolamine formation. In this step an uncatalyzed attack of the nucleophile occurs to form a highly unstable zwitterionic intermediate, $T^{\pm}$. As a result of the two breaks, five regions are observed[3] in the pH-rate profile. These regions correspond to significant contributions from the following rate-determining processes in order of decreasing pH: (5) hydronium ion catalyzed dehydration ($K_{ad}k_5$) of the neutral carbinolamine T^0, (4) water-mediated proton transfer (K_nk_4) between the nitrogen and oxygen atoms of $T^{\pm}$, (e) diffusion-controlled proton transfer (K_nk_3) from the hydronium ion to $T^{\pm}$, (2) uncatalyzed attack (k_2 of the nucleophile on the carbonyl group, (1) hydronium ion catalyzed attack (k_1) of the nitrogen nucleophile (see the rate constants in Scheme I).

This second break in the pH-rate profile near pH 1.5 is not observed in the addition of less basic nitrogen nucleophiles such as acethydrazide[5b] (pK_a' = 3.44), thiosemicarbazide[12] (pK_a' = 1.88), and Girard T reagent (pK_a' = 2.09). The hydronium ion catalyzed formation of the carbinolamine from these nucleophiles and *p*-chlorobenzaldehyde proceed via a preassociation mechanism (see Scheme I) rather than via a pathway that involves free $T^{\pm}$. The preassociation[5,27] can be either concerted, with no

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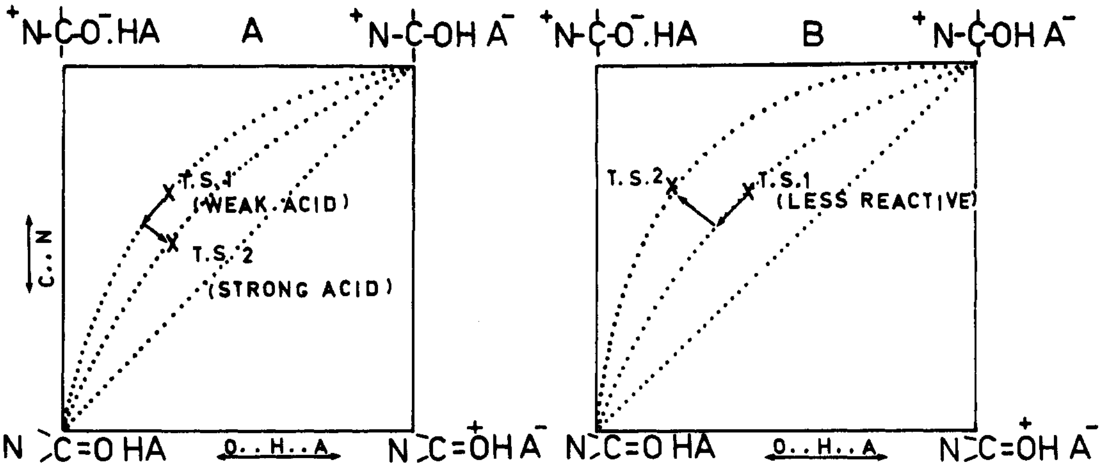


Figure 5. Schematic reaction coordinate diagram for the addition of a weak nucleophile to a carbonyl group, catalyzed by a general acid (HA) with proton transfer along the horizontal coordinate defined by α and formation and cleavage of the C–N bond along the vertical coordinate, with a preferred diagonal pathway. The energy contour lines are omitted. The transition state is at x. (A) Change in the position of the transition state (perpendicular to the reaction coordinate) upon increasing the acidity of the catalyst. (B) Change in the position of the transition state upon changing the reactivyity of the carbonyl compound.

Table III. Rate Constants[b] for General Acid Catalysis of the Reaction of Girard T Reagent with Substituted Benzaldehydes (XC_66H_4CHO)[a]

	$k_{cat.}$(av), M^{-2} s^{-1}				
X	cyanoacetic acid $pK_a' = 2.29$	chloroacetic acid $pK_a' = 2.72$	formic acid $pK_a' = 3.59$	β-bromopropionic acid $pK_a' = 3.83$	acetic acid $pK_a' = 4.60$
p-nitro	3.0×10^2	2.0×10^2	1.3×10^2		9.1×10
p-chloro	1.2×10^2	8.0×10	5.3×10	4.1×10	
p-bromo	1.2×10^2	7.5×10	2.3×10		1.9×10
p-fluoro	6.9×10	4.8×10	2.3×10	2.5×10	1.1×10
hydrogen	1.8×10^2	8.5×10	8.1×10	5.1×10	
p-phenyl	1.0×10^2	7.6×10	3.6×10	4.4×10	2.2×10
p-methyl	6.0×10	4.7×10	2.2×10	2.3×10	1.2×10
p-methoxy	2.3×10	1.8×10	9.7		4.3

[a] In water at 25.0 °C, ionic strength 0.5 (KCl). [b] Catalytic constant based on free-acid concentration. $pK_a' = pK_a$ – correction. The pK_a values[22] of the carboxylic acids were corrected to ionic strength 0.50 (KCl) according to Serjeant.[9] The values of rate constants catalyzed by hydronium ion (k_1) are given in Table I and the pK_a' value is –1.72.

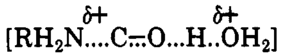
Table IV. Brønsted α Values for the General Acid Catalyzed Carbinolamine Formation from Girard T Reagent and Substituted Benzaldehydes (XC_6H_4CHO)[a]

X	α	s_α	n	s_{est}	r	$100r^2$	F	CL, %
p-nitro	0.19	0.04	5	0.05	0.995	99.0	292	99.9
p-chloro	0.20	0.05	5	0.07	0.990	98.0	153	99.5
p-bromo	0.27	0.07	5	0.10	0.991	98.2	168	99.5
p-fluoro	0.27	0.04	6	0.08	0.993	98.6	277	99.9
hydrogen	0.19	0.09	5	0.12	0.971	94.4	50.1	99.0
p-phenyl	0.26	0.03	6	0.06	0.996	99.2	523	99.9
p-methyl	0.29	0.02	6	0.04	0.999	99.8	1713	99.9
p-methoxy	0.37	0.04	5	0.06	0.998	99.6	978	99.9

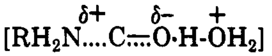
[a] n, number of points; s, standard error; r, correlation coefficient; $100r^2$, percent of data accounted for by the regression equation; F, test for significance of correlation; CL, confidence levels.

intermediate, or stepwise with an intermediate ($T^{\pm}$·HA).

The values of the rate constants for hydronium ion catalyzed formation of the carbinolamine from Girard T and para-substituted benzaldehydes are insensitive to polar substituents on the aldehyde (Figure 3). This is evidence for the "concerted" pathway with transition state 1 in which the formation of both bonds occurs simultaneously and the effects of the substituents are comparable, whereas the pathway involving the intermediate $T^{\pm}$ has essentially the same sensitivity to substituents as equilibrium addition of the nucleophiles (ρ near 1.8).[28] Let us compare the values of ρ^+ for hydronium ion catalyzed carbinolamine formation with weakly basic nitrogen nucleophiles to those for the more basic nucleophile methoxyamine ($pK_a' = 4.73$). The ρ^+ values for Girard T reagent and 2-methyl-3-thiosemicarbazide[19] ($pK_a' = 1.2$), 0.11 and 0.17, respectively, are much smaller than that of $\rho^+ = 1.2$ for methoxyamine, at low acidity (pH 2–4 where $K_n k_3$ dominates), but are similar to the values of $\rho^+ = 0.1$ for the "concerted" reactions of methoxyamine[4] expected at high acidity (pH <1 where k_1 dominates).


$$[RH_2\overset{\delta+}{N}....C\overset{...}{=}O...H..\overset{\delta+}{O}H_2]$$

1


$$[RH_2\overset{\delta+}{N}....C\overset{...}{=}\overset{\delta-}{O}\cdot H\text{-}\overset{+}{O}H_2]$$

2

Carbinolamine formation between Girard T reagent and para-substituted benzaldehydes is subject to general acid catalysis by carboxylic acids. The Brønsted plots for the general acid catalysis have slopes (α) between 0.19 and 0.37 (Figure 4 and Table IV). Although the values of α are certainly larger than zero, there is only a small extent of proton transfer from the general acid catalyst to the carbonyl oxygen. These α values are consistent with transition state 2 in which the catalyst stabilizes the developing negative charge by hydrogen bonding. The attack by 2-methylthiosemicarbazide,[19] thiosemicarbazide,[12] and acethydrazide[5] exhibit very similar Brønsted plots for the acid-catalyzed reaction, the values of α being 0.2, 0.15, and 0.11, respectively.

In this work, the values of the catalytic constants for the carboxylic acids in the carbinolamine formation were found

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(28) Wolfenden, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 2763–2768.

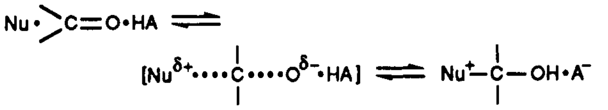
to be sensitive to the presence of substituents on the benzaldehyde, with $\rho^+ = 0.70$ (Figure 3).

The reversible addition of nitrogen nucleophiles to an eletrophilic center such as carbonyl oxygen frequently proceeds with general acid–base catalysis, according to the class of rections[20] involving proton transfer to and from an electrophilic reagent.

The structure–reactivity behavior for this reaction can be described by the reaction coordinate–energy diagram[18,29–31] in Figure 5. The axes of this diagram are defined such that the x axis corresponds to the progress of proton transfer from the acid to the carbonyl group, as measured by the Brønsted coeficient, α, and the y axis to the progress of C–N bond formation, as measured by β_{nuc} (the slope of a plot of log k against pK_{nuc}).

It appears to be well established[3,4] that general acid catalyzed solution reactions of moderately basic nitrogen nucleophiles to reactive carbonyl compounds generally occur by a mechanism that involves formation of a zwitterionic intermediate, $T^{\pm}$ (Figure 5), which is then trapped by a kinetically significant general acid catalyzed proton transfer to the oxygen of $T^{\pm}$. Alternative mechanisms for catalysis should become significant as the stability and lifetime of $T^{\pm}$ are decreased, for example, by decreasing the basicity of the nucleophile[5,6] or the eletrophilic character of the carbonyl compound.[3,25] The addition of a weakly basic nucleophile corresponds to the pathway along the diagonal of the diagram (Figure 5). The intermediate $T^{\pm}$ does not exist or is too unstable to be able to participate in a preassociation mechanism.

The addition of weakly basic nucleophiles to benzaldehydes is assisted by stabilization of the developing charge on the carbonyl oxygen atom by hydrogen bonding to a buffer acid (eq 7).



$$\mathrm{Nu}\cdot{>}\mathrm{C{=}O}\cdot\mathrm{HA} \rightleftharpoons [\mathrm{Nu}^{\delta+}\cdots\overset{|}{\underset{|}{\mathrm{C}}}\cdots\mathrm{O}^{\delta-}\cdot\mathrm{HA}] \rightleftharpoons \mathrm{Nu}^{+}{-}\overset{|}{\underset{|}{\mathrm{C}}}{-}\mathrm{OH}\cdot\mathrm{A}^{-} \quad (7)$$

The general acid catalysis of carbinolamine formation between Girard T reagent and para-substituted benzaldehydes must proceed by a reaction coordinate corresponding to a pathway that is predominantly diagonal.[18,21,32] Increasing the strength of the acid would be expected to shift the transition state to an earlier position along the reaction coordinate, with a corresponding decrease in the extent of C–N bond formation; perpendicular to the reaction coordinate, the effect would be to increase the extent of O–H bond formation (Figure 5). The overall effect, in particular, the decreased extent of C–N bond formation, could account for the smaller value of ρ^+ for the reaction catalyzed by hydronium ion, which is insensitive to the substituent effect.

The carbinolamine formation from Girard T reagent and para-substituted benzaldehydes exhibits an increase in the Brønsted α values (0.19–0.37) for general catalysis as the carbonyl compound becomes less reactive. The overall effect of increasing the reactivity of substituted benzaldehyde would be to decrease the extent of O–H bond formation in the transition state, which could account for the smaller values of α (see Figure 5).

Thus, it is not clear whether the hydronium ion and buffer catalysis occur by a qualitatively different mechanism. Indeed, the different σ^+ values may simply reflect suitable differences in the structure of the transition state and location of the reaction trajectory on the energy diagram.

Acknowledgment. We are indebted to Dr. Frank H. Quina for helpful comments concerning this work.

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Methoxide-Catalyzed Decomposition of Diarylmethyl (Arylsulfonyl)methyl Sulfoxides: A Sulfine-Forming Elimination on the $(\mathrm{E1cB})_{rev}/(\mathrm{E1cB})_{irrev}$ Borderline[1]

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Received July 27, 1990

In 7:3 CH_3OH–DMSO (v/v) in the presence of methoxide ion, diarylmethyl (arylsulfonyl)methyl sulfoxides ($Ar_2CHS(O)CH_2SO_2Ar'$) **4**, undergo elimination remarkably easily to afford the diarylsulfine and the aryl methyl sulfone (eq 4). Comparison of the rate of cleavage of **4** (k_{elim}) and the rate of disappearance of the ^{1}H NMR signal (k_{CHSO}) for the $Ar_2C\mathit{H}S(O)$ proton in CD_3OD–DMSO shows that the mechanism for the elimination is on the $(\mathrm{E1cB})_{rev}/(\mathrm{E1cB})_{irrev}$ borderline, (k_{CHSO}/k_{elim}) ranging from 1.2 to 5.2, depending on the nature of the Ar and Ar′ groups in **4**. Slight changes in structure can shift the mechanism from $(\mathrm{E1cB})_{rev}$ to $(\mathrm{E1cB})_{irrev}$ as a result of their effect on the partitioning of the α-sulfinyl carbanion intermediate ($Ar_2\bar{C}S(O)CH_2SO_2Ar'$) **5**, between cleavage to diarylsulfine plus $ArSO_2CH_2^-$ (step k_{ii}, eq 8) and protonation to regenerate **4** (step k_{-i}). Structural changes that make $Ar'SO_2CH_2$ a better leaving group increase k_{ii}/k_{-i}[MeOD] and shift the mechanism toward $(\mathrm{E1cB})_{irrev}$ as does also an increase in the percentage of DMSO in the solvent. Structural changes in Ar that enhance the stability of **5** decrease k_{ii}/k_{-i}[MeOD] and shift the mechanism toward $(\mathrm{E1cB})_{rev}$. It is also shown that for **4** in general k_{ii} appears larger than would be expected for a leaving group of the basicity of $Ar'SO_2CH_2^-$. Repulsion between the dipoles of the S(O) and SO_2 groups in **5** is thought to be responsible.

Earlier work[2,3] on base-catalyzed, sulfine-forming eliminations of (diarylmethyl)sulfinyl compounds has revealed that while the methoxide-induced elimination of methyl diarylmethanesulfinates **1**, eq 1, takes place by an

0022-3263/91/1956-1424$02.50/0