Kinetics and Mechanism of the Formation of Girard T Hydrazones from Naphthaldehydes

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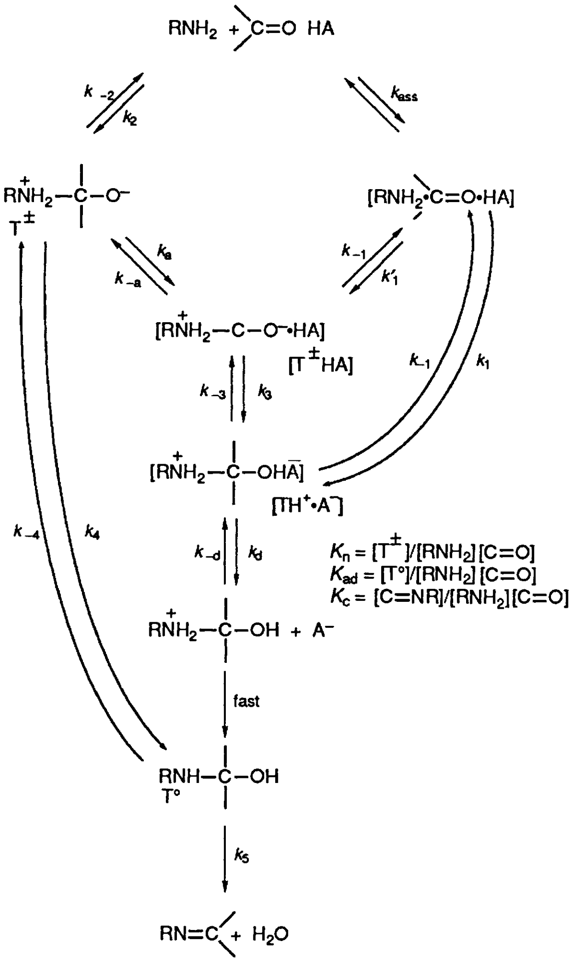
In aqueous solution, Girard T hydrazone formation from naphthaldehydes does not proceed to completion under the conditions used. The corresponding equilibrium constants have been determined and employed to calculate the rate of the reaction at completion. For all the reactions studied, the pH–rate profiles, extrapolated to zero buffer concentration, show one break at pH 4–5, characteristic of a change in the rate-determining step from aminomethanol dehydration to aminomethanol formation on going from pH 7 to pH 1. The formation of the aminomethanol 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 vary from 0.24 to 0.26. We suggest a stepwise preassociation mechanism for the reaction catalysed by carboxylic acids.

The addition of nucleophilic nitrogen reagents to carbonyl compounds occurs in two stages: formation of an aminomethanol intermediate (T°) and subsequent dehydration of the aminomethanol to yield the imine product.[1,2] Detailed studies of the mechanism of the addition of nitrogen nucleophiles to carbonyl compounds[3–7] have demonstrated the generality of the mechanism outlined in Scheme 1. The acid-catalysed formation of the neutral intermediate aminomethanol (T°) can occur by at least three separate mechanisms. (i) A diffusion controlled trapping in which a free zwitterionic intermediate ($T^{\pm}$), formed in the initial attack step, undergoes proton transfer to give the neutral intermediate T° in a subsequent step (or steps) that may or may not be kinetically significant. (ii) A stepwise preassociation mechanism characterized by association of the carbonyl compound, the nucleophile and the catalyst to form an encounter complex that subsequently gives rise to an associated zwitterionic intermediate ($T^{\pm}{\cdot}HA$); subsequent steps then lead to the neutral intermediate. (iii) A synchronous preassociation mechanism in which association of the carbonyl compound, the nucleophile and the catalyst forms an encounter complex which converts to the neutral intermediate T° *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 manifested by breaks in the pH–rate profile, by breaks in structure–reactivity correlations, by non-linear plots of rate constants against catalyst concentration, by variation of the Brønsted α exponent for general acid catalysis, and by changes in isotope effects.[3–7]

We studied[8] the kinetics and mechanism of addition of phenylhydrazine, a strongly basic nitrogen nucleophile (pK_a = 4.91 ± 0.02) to benzaldehydes, naphthaldehydes, and formyl-1,6-methano[10]annulenes in 50% aqueous ethanol (v/v) at 25.0 °C and ionic strength 0.50 mol dm^{-3}. It was not possible to study the mechanism of these reactions in water owing to the insolubility of the products in this solvent. The formation of the aminomethanol catalysed by carboxylic acids, proceeds by the stepwise pathway.

Recently[9] we studied the addition of Girard T reagent [$NH_2NHC(O)CH_2\overset{+}{N}(CH_3)_3Cl^-$], a weakly basic nitrogen nucleophile (pK_a = 2.09 ± 0.03) to *p*-substituted benzaldehydes in water, at 25.0 °C and ionic strength 0.50 mol dm^{-3}. 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.[10] Correlation of the catalytic constants of the various carboxylic acids for the formation of the aminomethanol from the benzaldehyde gave a value of α = 0.29. Again, the formation of aminomethanol, catalysed by carboxylic acids, proceeds by the stepwise pathway.



Scheme 1

In this work, we studied the kinetics and mechanism of addition of Girard T reagent to 1- and 2-naphthaldehyde in water, at 25.0 °C and ionic strength 0.50 mol dm^{-3}, in order to compare the behaviour of these aldehydes with that of benzaldehydes.

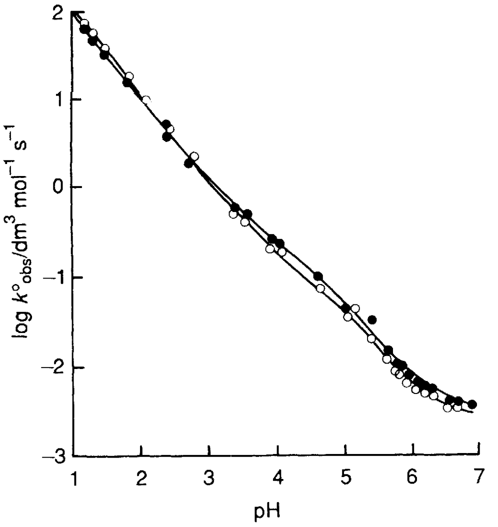


Fig. 1 Dependence of the observed rate constants on pH for the reaction of Girard T reagent free base with 1-naphthaldehyde (open circles) and 2-naphthaldehyde (full circles) extrapolated to zero concentration of general acid catalyst. The solid curves are theoretical profiles for the overall reactions rate, k°_{obs}, at zero buffer concentration, calculated from eqns. (5) and (6) by using the rate constants of Table 1.

Experimental

Materials.—All reagents employed were obtained commercially. With the exception of reagent grade inorganic salts, formic acid, and acetic acid, which were used as received, 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 aldehydes in purified ethanol were prepared and maintained under nitrogen atmosphere in the refrigerator for at most one week.

Equilibrium Constants.—The equilibrium constants for the overall reaction between Girard T reagent and the aldehydes were determined spectrophotometrically, in aqueous solution, ionic strength 0.50 mol dm^{-3}, and pH 2, using a Zeiss PMQ II spectrophotometer thermostatted 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}–5.00×10^{-2} mol dm^{-3}) and a constant concentration of the aldehyde (5.0×10^{-5} mol dm^{-3}). The absorbance of the Girard T hydrazone at infinite time (A_{∞}) was measured and the value of $A_T = A_{\infty} - A_0$ calculated. At high concentration of Girard T reagent, the value 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 constants (K_c) were determined from the slopes of plots of $(A_P - A_T)[RNH_2]$ against A_t, employing eqn. (1).

$$(A_P - A_T)[RNH_2] = \frac{1}{K_c}A_T - \frac{A_A}{K_c} \quad (1)$$

Kinetic Measurements.—Rate constants were measured spectrophotometrically at 25.0 °C in aqueous solution and ionic strength 0.50 mol dm^{-3} with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostatted cell holder. The final concentration of ethanol introduced into the reaction mixtures from the naphthaldehyde stock solution 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 naphthaldehydes was 3.3×10^{-5} mol dm^{-3} and, in all cases, a sufficient excess of nucleophile was employed such that pseudo-first-order rate behaviour was observed. First-order rate constants (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 naphthaldehydes does not proceed to completion, since a plot of k *vs.* nucleophile concentration gives a straight line that does not pass through the origin. The k_{obs} value for the reaction going to completion was calculated by eqn. (2), where k_{obs} is the

$$k_{obs} = \frac{k}{[RNH_2] - 1/K_c} \quad (2)$$

pseudo-second-order rate constant, k is the pseudo-first-order rate constant, $[RNH_2]$ is the concentration of the Girard T reagent, as free base, and K_c is the equilibrium constant for the overall reaction.

Constant pH was maintained by using carboxylic acid–carboxylate buffers. At high concentration of the buffers, the dehydration step (which is subject to hydronium ion catalysis, but is not significantly catalysed by the carboxylic acid) becomes partially rate limiting.[3,11] Correction of k_{obs} for the contribution of the dehydration step ($k_{ad}k_5$) employing eqn. (3) gave k_{ad}, the rate constant for the addition step.

$$k_{ad} = k_{obs}/(1 - k_{obs}/k_{ad}k_5a_{H^+}) \quad (3)$$

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^0_{ad}, the rate constant for the addition step catalysed by the hydronium ion plus water. We then calculated the value of $k^{\circ}_{overall}$ at zero buffer concentration, using eqn. (4).

$$k^{\circ}_{overall} = \frac{k^{\circ}_{ad}}{1 + k_{ad}/k_{ad}k_5a_{H^+}} \quad (4)$$

The observed pH–rate profile was fitted using the steady-state rate law[3,4] given by eqns. (5) and (6), where k°_{obs} is

$$k^{\circ}_{obs} = k^{\circ}_{ad}K_{ad}k_5a_{H^+}/(k^{\circ}_{ad} + K_{ad}k_5a_{H^+}) \quad (5)$$

$$k^{\circ}_{ad} = k_1a_{H^+} + K_nk_4 \quad (6)$$

the second-order rate constant for the 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 non-catalysed formation of the aminomethanol.

Results and Discussion

Since the reaction between Girard T reagent and the naphthaldehydes is not complete under the conditions in which it was studied in this work, we determined the corresponding values of the equilibrium constants for the overall reaction (K_c) which are given in Table 1.

Fig. 1 presents the pH–rate profiles for Girard T hydrazone formation from the naphthaldehydes. All the points were corrected for the influence of the equilibrium and of the dehydration on the formation of the aminomethanol and were extrapolated to zero buffer concentration, as described in the experimental section. Note that for both naphthaldehydes the pH–rate profiles for Girard T hydrazone formation show a small break in the pH range 4–5, characteristic of the transition from rate-determining aminomethanol formation at more acidic pH values to aminomethanol dehydration at more basic values.

Table 1 Kinetic constants[a] for the reaction of Girard T reagent with benzaldehyde and the naphthaldehydes, at 25.0 °C and ionic strength 0.50 mol dm^{-3}

Aldehyde	$K_c/10^4$ mol dm^{-3}	k_1/ dm^6 mol^{-2} s^{-1}	K_nk_4/ dm^3 mol^{-1} s^{-1}	$K_{ad}k_5$/ dm^6 mol^{-2} s^{-1}
Benzaldehyde[b]	1.00	7.0×10^2	0.50	4.5×10^3
1-Naphthaldehyde	0.93	1.3×10^3	0.70	4.0×10^3
2-Naphthaldehyde	1.52	1.1×10^3	1.10	5.2×10^3

[a] K_c = equilibrium constant for the overall reaction; K_n = equilibrium constant for formation of zwitterionic intermediate; K_{ad} = equilibrium constant for the formation of neutral aminomethanol intermediate. k_1 = rate constants for aminomethanol formation catalysed by the hydronium ion; K_nk_4 = rate constant of the uncatalysed aminomethanol formation; $K_{ad}k_5$ = rate constant for aminomethanol dehydration catalysed by the hydronium ion. [b] Ref. 9.

Table 2 Catalytic constants for several acids for the formation of the aminomethanol from Girard T reagent and the naphthaldehydes in water, at 25.0 °C and ionic strength 0.50 mol dm^{-3}

Catalyst	pK_a'	pH	k_{AH}/dm^6 mol^{-2} s^{-1}	
			1-Naphthaldehyde	2-Naphthaldehyde
H_3O^+	−1.74	1–2.5	1300	1100
$CNCH_2CO_2H$	2.29	2.37	99	96
$ClCH_2CO_2H$	2.72	2.33	86	85
$ClCH_2CO_2H$	2.72	2.72	76	71
$ClCH_2CO_2H$	2.72	3.35	86	71
HCO_2H	3.59	3.35	27	31
$CH_2BrCH_2CO_2H$	3.83	3.89	29	29
CH_3CO_2H	4.60	4.0	17	17

The values of k_1, K_nk_4 and $K_{ad}k_5$, defined in Scheme 1, for the reaction of Girard T reagent with the naphthaldehydes are presented in Table 1.

The solid curves are the calculated pH–rate profiles based on the rate laws given in eqns. (5) and (6), together with the rate constants collected in Table 1. The fit of the theoretical curves to the experimental points is quite good in both cases.

In the region where the formation of the intermediate T° is rate-determining, the reaction of Girard T reagent with the naphthaldehydes is subject to general acid catalysis by the buffers employed to maintain constant pH. Measurements 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. Thus, slopes of plots of second-order rate constants against the concentration of the acid component of the buffer yield straight lines with equal slopes, regardless of the buffer composition. The catalytic rate constants, determined as described in the experimental section, are collected in Table 2. Brønsted plots for general acid catalysis of aminomethanol formation with 1-naphthaldehyde yield $\alpha = 0.24$ and with 2-naphthaldehyde, $\alpha = 0.26$. The value of α for the reaction of Girard T reagent with benzaldehyde is 0.29.

It has been proposed that the formation of the aminomethanol from the reaction of Girard T reagent with *p*-substituted benzaldehydes proceeds by a stepwise preassociation pathway.[9] Given the similarity between the pH–rate profiles, and the values of the rate constants, and of α between the reactions of Girard T reagent with *p*-substituted benzaldehydes and naphthaldehydes, it is reasonable to propose that the reaction with the naphthaldehydes also proceeds by the stepwise preassociation pathway.

Formation of the aminomethanol in the reaction of phenylhydrazine with *p*-substituted benzaldehydes and the naphthaldehydes proceeds by the concerted pathway.[8] In these reactions the value of α for the formation of the phenylhydrazone from benzaldehyde is 0.26, while that for the two naphthaldehydes is 0.62.

An appreciable variation in the values of α, between different substrates is to be expected for formation of the aminomethanol by the concerted pathway (phenylhydrazine and aldehydes), since the catalyst transfers a proton to the oxygen atom of the carbonyl group of the substrate.

The insensitivity of the values of α to the nature of the substrate, is consistent with formation of the aminomethanol by the stepwise preassociation pathway (Girard T reagent and benzaldehydes[9]), since the catalyst transfers a proton to the negative oxygen atom of the intermediate ($T^{\pm}\cdot AH$).

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