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Nucleophilic Substitution Reactions of trans-4-(Para-substituted phenoxy)-3-buten-2-ones

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Abstract: Reactions of trans-4-(para-substituted phenoxy)-3-buten-2-ones (1–6) with primary amines to give 4-alkylamino-3-buten-2-ones in water are characterized by (1) rates which are first order in amine and 1–6, (2) a Hammett type $\rho^* = 0.11$ for reactions of 1–6 with aminoethanol, (3) $\beta_{nuc} = 0.37$ for reactions of 4-(p-anisoxy)-3-buten-2-one (1) with ethyl glycinate, trifluoroethylamine, 2-ethoxyethylamine, 2-aminoethanol, and n-butylamine, (4) a deuterium solvent kinetic isotope effect $k_2(H_2O)/k_2(D_2O) = 0.98$ for reaction of 1 with 2-aminoethanol, and (5) a Ritchie N^+ coefficient of 1 ± 0.2 for reactions of 1 with imidazole, ethyl glycinate, n-butylamine, and hydroxide ion. Reactions of thiols with the title compounds give 4-alkylthio-3-buten-2-ones at low concentrations of thiol and 4,4-dialkylthiobutan-2-ones at high concentrations of thiols. The former reactions are characterized by (1) rates which are first order in thiolate anion and 1–6 and (2) $\rho^* = 0.14$ for reactions of 1, 4-(p-chlorophenoxy)-3-buten-2-one (4), and 4-(p-nitrophenoxy)-3-buten-2-one (6) with N-acetylcysteine. These data support an addition–elimination reaction with nucleophilic attack rate determining. The kinetics of the reactions of 1 and 4 with morpholine and N-methylaminoethanol appear to provide evidence for the partitioning of the putative 1- and 4-amine addend between 1 and 4 and products.

Introduction

For reactions of trans-3-methoxy-4'-substituted acrylophenones with primary amines in water to give 3-alkylamino-4'-substituted acrylophenones and methanol, an addition–elimination reaction mechanism previously established[1-11] for aromatic and vinylic nucleophilic substitution reactions was postulated and attack of amines at the 3 carbon to give zwitterionic intermediates was indicated by the data to be the rate-determining step in this complex reaction.[12] The present study describes the kinetics results of some reactions of trans-4-(para-substituted phenoxy)-3-buten-2-ones (1–6) with amines and thiols (eq 1, X = CH$_3$O (1), CH$_3$ (2), H (3), Cl (4), CN (5), NO$_2$ (6); Y = NH, S).

$$p\text{-X}\text{—}C_6H_4OCH\text{=}CHCOCH_3 + RYH$$
$$\rightarrow p\text{-X}\text{—}C_6H_4OH + RYCH\text{=}CHCOCH_3 \quad (1)$$
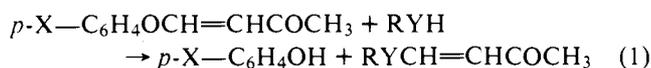
These reactions likely take place via a similar addition–elimination mechanism, and the data suggest that, for reactions of 1–6 with primary amines and with thiols, nucleophilic attack is rate determining. For reactions of 1 and 4 with secondary amines, there is kinetics evidence for the formation of zwitterionic intermediates.

Experimental Section

Apparatus. The apparatus used was previously described.[12]

Reagents and Compounds. 4-(Para-substituted phenoxy)-3-buten-2-ones (1–6) were available from a previous study or were prepared as needed by following the published procedure.[13] 3-Butyn-2-one (Pfaltz and Bauer), phenols, amines, and thiols (Aldrich) were purchased and purified as necessary. Certified ACS grade inorganic salts and organic solvents were purchased from Fisher. Deuterium oxide and DCl were purchased from Diaprep, Inc. Tap distilled water was redistilled through a Corning AGla still.

Kinetics. The reactions of 1–6 with amines and thiols were monitored by recording the increase or decrease in absorbance vs. time at the following wavelengths (nm): 1, 265, 282; 2, 265, 285; 3, 260, 285; 4, 262, 290; 5, 275; 6, 250, 410. Reactions were carried out under pseudo-first-order conditions ([1–6] = 10^{-4} to 10^{-5} M) at 30 °C, and ionic strength was maintained at 0.1 M by using added KCl. The pH of each solution remained constant throughout runs. Reactions were started by adding 1–6 in methanol or dioxane from a calibrated syringe to 3-mL cuvettes filled with appropriate solution which had been brought to reaction temperature. Pseudo-first-order rate constants were obtained by multiplying the slopes of plots of $\log((A_\infty - A_i)/(A_\infty - A_t))$, for absorbance increase, and $\log((A_i - A_\infty)/(A_t - A_\infty))$ for absorbance decrease vs. time by 2.303. pD was calculated by adding 0.4 to pH meter readings.[14]

Products. cis-4-tert-Butylamino-3-buten-2-one. A 1.7-g (10 mmol) quantity of 3 was added to 0.8 g (10 mmol) of tert-butylamine in 50 mL of water. To this mixture was added 2 drops of concentrated HCl and the mixture was stirred at room temperature until aliquots of the reaction mixture showed no further change in absorbance at 285 nm. The mixture was diluted with 50 mL of water and this was extracted with 100 mL of CHCl$_3$. The CHCl$_3$ extract was dried over anhydrous

Table I. Second-Order Rate Constants for Reactions of 4-(Para-substituted phenoxy)-3-buten-2-ones (1-6) with Primary Amines in Aqueous Solution[a]

compd	amine[b]	k_2, M^{-1} min^{-1c}	no. of k_{obsd}	pH range	concn range of amine
1 (CH$_3$O)	AE	17.8 ± 1.5	30	8.05-9.31	0.02-0.10
1	AE[d]	18.9 ± 1.2	6	9.07	0.1 -1.0
1	AE[e]	18.2 ± 0.6	20	9.34-9.60	0.02-0.10
2 (CH$_3$)	AE	23.6 ± 1.8	19	8.05-9.02	0.02-0.10
3 (H)	AE	25.4 ± 0.5	20	8.05-9.03	0.02-0.10
4 (Cl)	AE	27.8 ± 0.8	15	8.06-9.03	0.02-0.10
5 (CN)	AE	38.1 ± 3.5	15	8.05-9.02	0.02-0.10
6 (NO$_2$)	AE	47.0 ± 0.6	10	8.01-8.50	0.02-0.10
1	EGN	2.14 ± 1.1	15	7.50-7.85	0.02-0.10
1	EEA	12.2 ± 0.2	15	8.74-9.41	0.02-0.10
1	TBA	0.43 ± 0.03	15	10.39-10.91	0.02-0.10
1	NBA	25.5 ± 0.4	10	9.54-10.51	0.02-0.10
1	TFEA	0.52 ± 0.04	6	6.35	0.05-0.50
6	TFEA	0.57 ± 0.03	9	6.20	0.05-0.50
1	IM	0.32 ± 0.03	27	7.01-8.02	0.02-0.50
6	IM	0.62 ± 0.03	27	7.01-8.02	0.02-0.50

[a] t = 30 °C, μ 0.1. [b] AE (aminoethanol, pK_a = 9.40), EGN (ethyl glycinate, pK_a = 7.59), EEA (ethoxyethylamine, pK_a = 9.34), TBA (*tert*-butylamine, pK_a = 10.57), NBA (*n*-butylamine, pK_a = 10.5), TFEA (trifluoroethylamine, pK_a = 5.75), IM (imidazole, pK_a = 7.0). [c] The reported errors are standard deviations. [d] μ 1.0. [e] The solvent is D$_2$O; pK_a (D$_2$O) = 9.99.
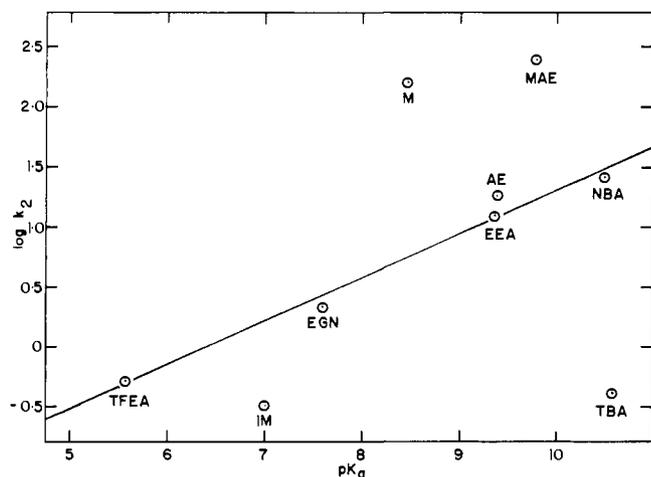
Figure 1. Plot of log k_2 (Table I) vs. pK_a of the conjugate acid of the nucleophile reactant for reactions of **1**. Abbreviations are those defined in Tables I and III. For M and MAE, k_1 values of Table III were used to compute log k_2 for those amines. The least-squares line is drawn for TFEA, EGN, EEA, AE, and NBA data.

Na$_2$SO$_4$ and concentrated in vacuo. Chromatography of the concentrate over neutral alumina using CHCl$_3$ as eluent gave 70% of 4-*tert*-butylamino-3-buten-2-one which was crystallized from hexanes and had: mp 91 °C (dec); NMR (CDCl$_3$) δ 1.2 (s, 9 H, (CH$_3$)$_3$C), 2.0 (s, 3 H, CH$_3$CO), 4.9 (d, J = 7.5 Hz, 1 H, CHCO), 6.5-7 (q, J_{ab} = 7.5 Hz, $J_{ab,ab}$ = 12 Hz, 1 H, NCH), 10-10.5 (s, broad, 1 H, NH). General spectral characteristics of the reactions of **1-6** with amines in water solution. Reactions of **1-6** with solutions of amine buffers such as aminoethanol and trifluoroethylamine are spectrally characterized by a loss of absorbance at ca. 260 nm and a concomitant increase of absorbance at ca. 290 nm with an isosbestic point of ca. 270 nm. The final spectra resemble a mixture of para-substituted phenol and 4-alkylamino-3-buten-2-one. Reaction of aqueous aminoethanol with butynone generates a product, 4-(β-hydroxyethylamino)-3-buten-2-one, with an absorbance maximum at 297 nm. Reaction of **1** with 0.1 M imidazole (pH 7) shows decreased low and high wavelength absorbance and formation of a peak at 271 nm with isosbestic points at 255 and 300 nm. After long times, the 271-nm peak slowly decreases. Butynone reacts with imidazole to give 271-nm absorbing material, which slowly reacts further as shown by slow absorbances loss at long times. General spectral characteristics of the reactions of **1, 4,** and **6** with thiols in water solution. Reactions of **1**,

4, and **6** with dilute mercaptoethanol solutions (10^{-3} to 10^{-4} M) are spectrally characterized by a decrease in low wavelength absorbance and a concomitant increase in absorbance at 297 nm with an isosbestic point at 277 nm. The 297-nm band is also formed when butynone reacts with thiol; actually, the absorbance maximum here is 300 nm. Reactions of those substrates with concentrated mercaptoethanol solutions (10^{-1} to 10^{-2} M) are spectrally characterized by an "instantaneous" formation of the 297-nm band, which decreases with time to give the spectrum of the appropriate phenol. The rate constants for loss of 297 nm absorbance are identical for **1, 4,** and **6** and the value of this constant is 337 ± 14 M^{-1} min^{-1}, 0.02-0.08 M mercaptoethanol, pH 7.81. This rate constant is essentially equal (345 ± 15 M^{-1} min^{-1}) to that for loss of 300-nm absorbance for reaction of the butynone-mercaptoethanol adduct, generated in situ from butynone and dilute mercaptoethanol, in 0.02-0.08 M mercaptoethanol solution. The adduct, which is likely 4-(β-hydroxyethylthio)-3-buten-2-one, can be synthesized from equimolar amounts of butynone, mercaptoethanol with a trace of triethylamine in dioxane. The NMR spectrum (CDCl$_3$) of the crude product shows δ 2.2 (s, 3 H, OH, SCH$_2$), 3.87 (t, 2 H, OCH$_2$), 6.3 (d, J = 7.5 Hz, 1 H), and 7.6 (d, J = 7.5 Hz, 1 H, HC=CH). The crude product showed an absorbance maximum at 300 nm in dilute mercaptoethanol solution, and the loss of absorbance at 300 nm in 0.02-0.08 M mercaptoethanol solution takes place with a rate constant of 350 ± 15 M^{-1} min^{-1}.[32]

Results

Reactions of **1-6** in aqueous primary amine buffer solutions to give 4-alkylamino-3-buten-2-ones (eq 1) obey the rate law of eq 2 where f is the fraction of free amine present in the buffer solution.

$$\text{rate}/[\mathbf{1-6}] = k_{obsd} = k_2 f[\text{amine}]_{total} + k_{OH}a_{OH} \quad (2)$$

Plots (not shown) of k_{obsd} vs. the concentration of total amine at constant pH gave as slope $k_2 f$ and intercept $k_{OH}a_{OH}$. The second-order rate constant k_2 (Table I) was obtained by dividing the slope by f ($=K_a/(K_a + a_H)$). The intercept values were those expected based on the known a_{OH} and k_{OH} values.[13] Reactions of **1** and **6** with imidazole buffer solutions also followed the rate law of eq 2. A Hammett-type plot of log k_2, for reactions of **1-6** with aminoethanol, vs. σ^*, a comparative substituent constant calculated from the ionization constants of para-substituted phenols, gave ρ^* = 0.11 ± 0.01. A plot of log k_2 vs. pK_a (Figure 1) for reactions of **1** with trifluoroethylamine, ethyl glycinate, 2-ethoxyethylamine, 2-aminoethanol, and *n*-butylamine gave β_{nuc} = 0.37 ± 0.03 as slope. Log k_2 for reactions of **1** with *tert*-butylamine and imidazole

Table II. Second-Order Rate Constants for Reactions of 4-(Para-substituted phenoxy)-3-buten-2-ones (**1, 4, 6**) with *N*-Acetylcysteine (NAC) and Mercaptoethanol (ME) in Phosphate Buffer[a]

compd	thiol	k_2, M^{-1} min^{-1} [b]	no. of k_{obsd}	pH range	concn range of thiol
1 (CH$_3$O)	NAC	3548 ± 100	12	6.85–7.0	0.00067–0.00603
4 (Cl)	NAC	5803 ± 68	6	6.78	0.00067–0.00603
6 (NO$_2$)	NAC	10175 ± 120	6	6.85–7.0	0.00067–0.00603
1	ME	(1.92 ± 0.09) × 10^4	28	7.34–7.91	0.0002–0.0045
4	ME	(4.27 ± 0.7) × 10^4	12	7.5–7.91	0.0002–0.0045
6	ME	(1.31 ± 0.13) × 10^5	8	7.7–7.91	0.0002–0.0045

[a] t = 30 °C, μ = 0.1, at pH 6.77 reaction of **4** with 2 × 10^{-3} M NAC in 0.01, 0.03, and 0.07 M phosphate buffer gave k_{obsd} (min^{-1}) 0.159, 0.152, 0.152, respectively; pK_a^{SH}(NAC) = 8.62, pK_a(ME) = 9.45. [b] The reported errors are standard deviations.

Table III. Rate Data for Reactions of 4-(Para-substituted phenoxy)-3-buten-2-ones (**1, 4, 6**) with Morpholine (M) and *N*-Methylaminoethanol (MAE) in Aqueous Solution[a]

compd	amine[b]	k_1, M^{-1} min^{-1} [c]	$(k_{-1} + k_4)/$ k_2^A, M × 10^4 [c]	f	no. of k_{obsd}	concn range of amine	r[d]
6 (NO$_2$)	M	142 ± 7		0.21	6	0.02–0.2	0.9952
1 (CH$_3$O)	M	156 ± 2	11.6 ± 0.5	0.21	7	0.01–0.2	0.9948
1	M	171 ± 15	8.3 ± 0.8	0.04	6	0.01–0.1	0.9835
1[e]	M	165 ± 3	5.0 ± 0.6	0.2	6	0.01–0.1	0.9477
1[f]	M	144 ± 1	4.6 ± 0.1	0.08	6	0.01–0.1	0.9991
4 (Cl)	M	171 ± 3	7.3 ± 0.3	0.09	6	0.01–0.1	0.9970
4	M	161 ± 2	8.0 ± 0.5	0.21	7	0.01–0.2	0.9907
4[e]	M	178 ± 3	4.7 ± 0.6	0.2	6	0.01–0.1	0.9530
1	MAE	251 ± 6	16.8 ± 0.2	0.5	9	0.01–0.12	0.9686
4[c]	MAE	217 ± 3	3.0 ± 0.4	0.18	6	0.01–0.1	0.9723
4	MAE	248 ± 7	9.5 ± 1	0.18	6	0.01–0.1	0.9770
4	MAE	266 ± 6	3.6 ± 2	0.48	5	0.01–0.08	0.7567
4	MAE	260 ± 3	3.6 ± 0.4	0.18	6	0.01–0.1	0.9723

[a] t = 30 °C, μ 0.1. [b] M (morpholine), MAE (*N*-methylaminoethanol), pK_a = 8.5 (M), pK_a = 9.8 (MAE). [c] The reported errors are standard deviations. [d] Correlation coefficient for the double-reciprocal plot of eq 4. [e] The substrate was added in methanol (vs. dioxane). [f] D$_2$O was the solvent; pK_a(D$_2$O) = 8.96 (M).

showed negative deviations of 1.8 and 0.7 log units, respectively: those for morpholine and *N*-methylaminoethanol showed positive deviations of 1.5 and 1.2 log units, respectively.[31] A plot of log k_2 vs. N$^+$ [15] for reactions of **1** with imidazole, ethyl glycinate, *n*-butylamine, and hydroxide ion gave slope 1.02 ± 0.23 (r = 0.953); log k_2 for reaction of **1** with morpholine showed a +0.9 log unit deviation.[31] For reactions of **1** with aminoethanol, k_2(H$_2$O)/k_2(D$_2$O) = 0.98.

Reactions of **1, 4,** and **6** with *N*-acetylcysteine and mercaptoethanol in aqueous solution followed the rate law of eq 3

$$\text{rate}/[\textbf{1,4,6}] = k_{obsd} = k_2 f[\text{RSH}]_{total} + k_{OH}a_{OH} \quad (3)$$

and at constant pH plots of k_{obsd} vs. [RSH]$_{total}$ gave slope $k_2 f$, from which k_2 (Table II) could be evaluated, and intercept $k_{OH}a_{OH}$.[13] Secondary plots of slopes vs. f gave no intercept, showing that thiolate is the reactive thiol species and that the neutral thiol is either unreactive or very weakly so. A Hammett-type plot of log k_2 vs. σ^* for reactions of **1, 4,** and **6** with *N*-acetylcysteine gave ρ^* = 0.14 ± 0.03; similarly, for reactions of **1, 4,** and **6** with mercaptoethanol, ρ^* = 0.26 ± 0.04.

Reactions of **6** with morpholine followed the rate law of eq 2. However, reactions of **1** and **4** with morpholine and *N*-methylaminoethanol appear not to follow that rate law: plots of k_{obsd} vs. the concentration of total amine exhibit very slight upward curvature under our reaction conditions: the high reactivity of this system and the inconstancy of pH over large concentration ranges, especially at low f, made impractical collection of rate data at high and low amine concentrations. Assumption of linearity of the plots for reactions of **1** and **4** with these secondary amines resulted in negative intercepts in all cases. Plots of k_{obsd}/[amine]$_{total}$ vs. [amine]$_{total}$ gave rectangular hyperbolas (Figure 2).[4] Plots of (k_{obsd}/[amine]$_{total}$)$^{-1}$
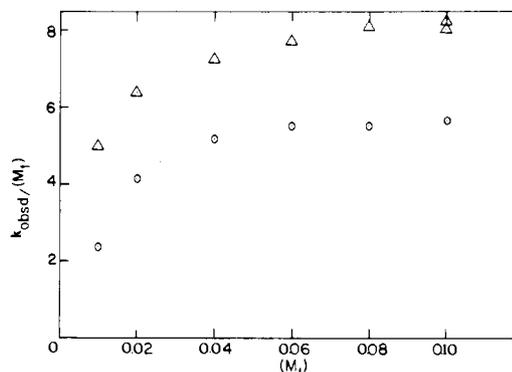
Figure 2. Plot of the apparent second-order rate constant, k_{obsd}/[M$_t$], vs. the molar concentration of total morpholine species, [M$_t$], for reactions of **1** with morpholine, f = 0.04 (circles), and with morpholine in D$_2$O, f = 0.08 (triangles).

vs. [amine]$_{total}^{-1}$ were generally linear and appeared to follow eq 4.

$$(k_{obsd}/[\text{amine}]_{total})^{-1} = a/(f^2[\text{amine}]_{total}) + b/f \quad (4)$$

From the slopes and intercepts, the constants of Table III were obtained. In Table III, k_1 and $(k_{-1} + k_4)/k_2^A$ are constants of Scheme I described in the Discussion section and k_1 corresponds to $1/b$, while $(k_{-1} + k_4)/k_1 k_2^A$ corresponds to a of eq 4. For reactions of **1** with morpholine, k_1(H$_2$O)/k_1(D$_2$O) = 1.1 and $(k_{-1} + k_4)/k_2^A$(H$_2$O)/$(k_{-1} + k_4)/k_2^A$(D$_2$O) = 1.8.

Discussion

Reactions of **1–6** with primary amines to give 4-alkylam-

Scheme I

$$\text{ROCH}=\text{CHCOR}_1 + \text{R}_2\text{NH}_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{\overset{+}{\text{R}_2\text{NH}_2}}{\underset{|}{\text{ROCH}}}-\overset{\overset{\text{O}^-}{|}}{\text{CH}}=\text{CR}_1$$
$$(\text{Z}^{\pm})$$

$$\xrightarrow[{k_{-2}\text{A R}_2\text{NH}_3^+, \, k_{-3}\text{OH}}]{k_2\text{A R}_2\text{NH}_2, \, k_3\text{OH OH}^-} \overset{\overset{\text{R}_2\overset{..}{\text{N}}\text{H}}{|}}{\underset{|}{\text{ROCH}}}-\overset{\overset{\text{O}^-}{|}}{\text{CH}}=\text{CR}_1$$
$$(\text{Z}^-)$$

$$\begin{matrix} \text{Z}^{\pm} \xrightarrow{k_4} \\ \text{Z}^- \xrightarrow{k_b} \end{matrix} \Bigg\} \quad \overset{\overset{\text{R}_2\overset{..}{\text{N}}\text{H}}{|}}{\underset{|}{\text{CH}}}=\overset{\overset{\text{O}}{\parallel}}{\text{CH}\overset{|}{\text{C}}}\text{R}_1 + \text{ArOH}$$
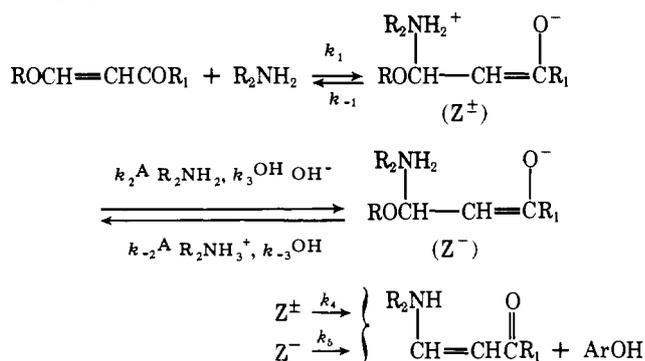
ino-3-buten-2-ones are characterized by (1) rates which are first order in **1–6** and amine, (2) $\rho^* = 0.11$ for reactions of **1–6** with 2-aminoethanol, (3) $\beta_{nuc} = 0.37$ for reactions of **1** with trifluoroethylamine, ethyl glycinate, 2-ethoxyethylamine, 2-aminoethanol, and *n*-butylamine, (4) a deuterium solvent kinetic isotope effect of 1 for reaction of **1** with 2-aminoethanol, and (5) an N^+ coefficient of ca. 1 for reactions of **1** with imidazole, ethyl glycinate, butylamine, and hydroxide ion. We suggest that these data support an addition–elimination mechanism such as the one established for aromatic nucleophilic substitution reactions of dinitroaryl ethers with amines,[3,4,6] and reactions of electrophilic olefins with amines[16] and suggested for reactions of 3-methoxy-4'-substituted acrylophenones with amines[12] (Scheme I). For the extensively studied diaryl ethers, the rate-determining step depends on the nature of the leaving group: generally k_1 is rate determining for reactants with good leaving groups.[4] However, in some cases involving phenolic leaving groups deprotonation of $Z^\pm$ by amine is rate determining, while departure of the leaving group from Z^- can be rate determining when the leaving group is poor (methoxy).[6] In the latter case, in aprotic solvents, general acid catalysis may be a feature of the product-forming step. For reactions of *trans*-3-methoxy-4-substituted acrylophenones with primary amines,[12] we suggested that the mechanism of Scheme I applies with k_1 rate determining on the basis of $\rho = 1$, β-methyl substitution decreases reactivity 90-fold, and a deuterium solvent kinetic isotope effect of 1.

Reactions of **1–6** with primary amines under our reaction conditions are first order in amine and $\rho^* = 0.1$ for reactions of **1–6** with aminoethanol and with hydroxide ion.[13] Our failure to detect higher order amine terms coupled with the small ρ^* values suggests that the addition–elimination mechanism of Scheme I, with k_1 rate determining, is a better candidate mechanism than is an SN_2 mechanism. In a previous study, we addressed the question of whether **1–6** react with amines via an E1cB mechanism with α-proton transfer rate determining to give butynone and para-substituted phenols. Here the final aminolysis product could result from rapid reaction of butynone with amines. For **1–6**, we reject that mechanism on the basis that **6**-1,3,4-d_5 reacts about three times more rapidly with *N*,*N*-dimethylaminoethanol than does **6**.[13]

The sensitivity of **1** to the basicity of the amine nucleophile in aminolysis reactions is virtually identical with that of 3-methoxy-4'-dimethylaminoacrylophenone as measured by $\beta_{nuc} = 0.37$.[12] This result suggests similar transition states for reactions of these compounds with amines. For both compounds, *tert*-butylamine is less reactive than predicted from the LFER and the pK_a: reasonably this amine in its reactions with these compounds imposes unfavorable steric constraints on the transition state for formation of $Z^\pm$ (Scheme I). Rather poor N^+ correlations were obtained for reactions of these compounds with nucleophiles which include hydroxide ion, but the slopes of the LFER's are the same (1 ± 0.2). This result and the fact that the N^+ parameter was devised for reactions of

nucleophiles with electrophiles support the hypothesis that attack of **1–6** by primary amines is rate determining. However, log k_2 for reaction of **1** with morpholine showed a positive deviation for the correlation, suggesting that factors other than solvation play a role in this reaction.

There is no solvent isotope effect for reactions of **1** and 3-methoxy-4'-methoxyacrylophenone[12] with aminoethanol and for reaction of **6** with *N*,*N*-dimethylaminoethanol.[13] These results are in accord with rate-limiting reaction of primary amines at C-4 of **1–6** (Scheme I). The result that a tertiary amine reacts with **6** shows that proton transfer is not a requirement for reaction, which can occur by the k_1 and k_4 pathways of Scheme I.

Reactions of **1, 4,** and **6** with *N*-acetylcysteine dianion and with mercaptoethanol anion most likely take place by an addition–elimination mechanism with the addition step rate limiting (Scheme I). This conclusion is supported by the product analysis study described in the Experimental Section and by the insensitivity of these reactions to electronic effects in the leaving group. As predicted by the mechanism of Scheme I, proton transfer is not a requirement for reactions of **1–6** with anionic nucleophiles. The typically greater reactivity of thiolate ions vs. amines of comparable pK_a toward sp^2 carbon is seen in this study:[17-20] mercaptoethanol anion is ca. 10^3 more reactive than aminoethanol toward **1–6**. The reactivity difference has been attributed to the high carbon basicity of sulfur.[26] In speculation, sulfhydryl-containing biomolecules should be most sensitive to modification by **1–6** which could be cytotoxic reagents.[22,23]

Reactions of **1** and **4** with morpholine and *N*-methylaminoethanol provide kinetics evidence for formation of an intermediate such as $Z^\pm$ (Scheme I) on the reaction path. This evidence initially took the form of very slight upward curvature of the plots of k_{obsd} vs. concentration of secondary amine and ultimately of a fit of the data to eq 4.[24] The mechanism of Scheme I, established for aromatic nucleophilic substitution reactions, gives rise to eq 5 if $Z^\pm$ and Z^- are at low steady-state concentrations.

$$k_{obsd}/[\text{R}_1\text{R}_2\text{NH}]_{total}$$
$$= \frac{(k_1k_4f/k_2^A) + k_1f^2[\text{R}_1\text{R}_2\text{NH}]_{total} + k_3^{OH}[\text{OH}^-]/k_2^A}{(k_{-1}+k_4)/k_2^A + f[\text{R}_1\text{R}_2\text{NH}]_{total} + k_3^{OH}[\text{OH}^-]/k_2^A}$$
$$(5)$$

In order to reduce eq 5 to the double-reciprocal form of eq 4, we assumed that $k_3^{OH}[\text{OH}^-]/k_2^A$ and k_1k_2f/k_2^A were negligible in this study. We accepted these assumptions for the following reasons. (1) The data fit eq 4 reasonably well (Table III). (2) The ratio k_4/k_2^A for morpholinolysis of 2,4-dinitrophenyl phenyl ether[6] and for hydrazinolysis of *p*-chlorophenyl acetate[25] was estimated to be ca. 10^{-2}. Based on that value the crude estimates of the values of k_1k_4f/k_2^A for **1–6** are small (ca. 10^{-1} or less). (3) For morpholinolysis of 2,4-dinitrophenyl phenyl ether,[6] k_3^{OH}/k_2^A is ca. 10^2, and for **1–6** the product of that ratio and the concentration of hydroxide ion is quite small under the conditions of the study. (4) A plot of $k_{obsd}/[\text{R}_1\text{R}_2\text{NH}]_{total}$ vs. $[\text{R}_1\text{R}_2\text{NH}]_{total}$ at constant pH, following eq 5, would give a rectangular hyperbola with a nonzero intercept. As far as we can tell, the intercepts are zero or very close to zero which supports the assumption that the k_1k_4f/k_2^A and $k_3^{OH}[\text{OH}^-]/k_2^A$ terms are small.

A much simpler, if less complete, mechanism that satisfies the experimental results (eq 4) and requires no assumption of limits in the rate law is that of Scheme II.[26] This mechanism requires a proton transfer from $Z^\pm$ to give products, and Scheme II leads to the steady state-derived rate law of eq 6 which in double-reciprocal form has the form of eq 4. The k_1 values of Table III are the same for Scheme II as for Scheme I, but the $(k_{-1}+k_4)/k_2^A$ values of Table III that were derived for Scheme I become k_{-1}/k_2^A values of Scheme II. If for

Scheme II

$$1\text{-}6 + R_1R_2NH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Z^{\pm} \xrightarrow{k_2{}^A\ R_1R_2NH} \text{products}$$
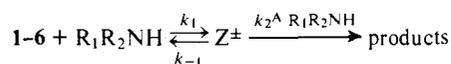
$$k_{\text{obsd}}/[R_1R_2NH]_{\text{total}} = k_1 f^2 [R_1R_2NH]_{\text{total}}/((k_{-1}/k_2{}^A) + f[R_1R_2NH]_{\text{total}} \quad (6)$$

Scheme I $k_{-1} > k_4$, as was estimated to be the case for morpholinolysis of 2,4-dinitrophenyl phenyl ether,[4] then the data of Table III refer to the partitioning of $Z^{\pm}$ between **1–6** and Z^- (Scheme I) or **1–6** and products (Scheme II).

Some points can be gleaned from the data of Table III and deserve comment. One is that secondary amines are more reactive than are primary amines (Table I) of comparable basicity or of comparable nucleophilicity as shown by their positive deviations from a log k vs. N^+ plot. Coupled with this exhalted reactivity is a decreased sensitivity of the reactions of morpholine and *N*-methylaminoethanol with **1** and **4**: β_{nuc} for these reactions is ca. 0.15 (two points) vs. $\beta_{\text{nuc}} = 0.37$ for primary amines, and it could be concluded that the transition state to $Z^{\pm}$ is reached earlier in the reactions of **1–6** with secondary amines than with primary amines. The generally poor N^+ correlation obtained for reactions of primary amines and hydroxide ion with **1** and the failure of that correlation to accommodate log k for morpholine suggests that factors other than desolvation are involved in the aminolysis of **1–6** or else the N^+ treatment is simply invalid for this system.[27] Another point is that the partitioning ratios are ca. 10^{-3} and they are not particularly sensitive to either the amine ($\Delta pK_a = 1$) or the substrate. Bernasconi et al.[6] have estimated for morpholinolysis of 2,4-dinitrophenyl phenyl ether that $k_{-1}/k_2{}^A$ is ca. 10^{-3} when acetone is solvent and ca. 10^{-1} when 10% dioxane in water is solvent. Based on these results the ratio for **1–6** is low but not unreasonably so and may simply be viewed as a property of this system. The result that partitioning of $Z^{\pm}$ is detectable in reactions of **1** and **4** with secondary amines but not with primary amines has been addressed by Bernasconi[3] and by Hirst et al.[7] in aromatic nucleophilic substitution reactions of 2,4-dinitrophenyl ethers. The explanation is that $Z^{\pm}$ is stabilized by internal hydrogen bonding between the ammonium group and the *o*-acinitronate anion, or the enolate anion in the case of **1–6**, that reduces k_{-1} regardless of whether primary or secondary amines are reactants. For $Z^{\pm}$ formed from secondary amines, however, $k_2{}^A$ is reduced below its value for $Z^{\pm}$ formed from primary amines since a noninternally hydrogen bonded proton can be removed more easily by another amine molecule or water than can the internally hydrogen bonded proton. A 10^3 difference between $k_2{}^A$ values could be expected[28] and partitioning of $Z^{\pm}$ becomes kinetically detectable. Support for the existence of intramolecular hydrogen bonding in $Z^{\pm}$ is provided by the result that primary amines react with 3-methoxy-4'-substituted acrylophenones[12] and with **3** to give cis aminolysis products, while secondary amines react to give trans products. This result could be rationalized on the basis that the geometry of the hydrogen-bonded $Z^{\pm}$ formed from primary amines is preserved in the product, while a nonintramolecularly hydrogen-bonded proton is lost in a product-forming step.

In regard to the possibility that protons are transferred in a kinetically detectable way, as predicted by the experimental results which gave rise to eq 4 and by the mechanisms of Schemes I and II, we looked for a deuterium solvent kinetic isotope effect. We recognize that the $(k_{-1} + k_4)/k_2{}^A$ values of Table III show considerable scatter and for reactions of **1** with morpholine the standard deviation is 40% of the mean value so that no rigorous conclusion can be drawn from such an experiment. However, based on the mean values of k_1 and $(k_{-1} + k_4)/k_2{}^A \simeq k_{-1}/k_2{}^A$ of Table III and a single D_2O experiment (Table III), values of 1.1 and 1.8, respectively, were

obtained. The isotope effect on k_1 is small and may reasonably be taken to be 1 based on the uncertainties involved. No isotope effect would be predicted for the mechanisms of Schemes I and II for the k_1 step and this was found to be the case for reactions of **1** with aminoethanol. If the isotope effect on $k_{-1}/k_2{}^A$ is to be believed, then it can be recognized that the k_{-1} step is likely a composite[28,29] of an equilibrium dissociation of hydrogen-bonded $Z^{\pm}$ to a non-hydrogen-bonded $+Z^-$ and a reaction of the latter to give reactants:

$$Z^{\pm} \underset{}{\overset{K}{\rightleftharpoons}} +Z^- \xrightarrow{k} \text{reactants}$$
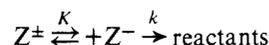
For $K = +Z^-/Z^{\pm}$, $k_{-1} = kK$. No isotope effect is expected for k. $K(H_2O)/K(D_2O)$ should be greater than 1, either for breaking an ion reinforced hydrogen bond or transferring the enol proton to the amine group.[30] The isotope effect on K would have to be 2.7 in order to give an isotope effect of 1.5 on $k_2{}^A$ and the experimental value 1.8: $(k_{-1}/k_2{}^A)^H/(k_{-1}/k_2{}^A)^D = (kK/k_2{}^A)^H/(kK/k_2{}^A)^D = (2.7)(1/1.5) = 1.8$. The foregoing serves to show that the experimental isotope effect is plausible and consistent with the mechanisms of Schemes I and II.

In conclusion, an addition–elimination mechanism (Scheme I), previously proposed for aromatic nucleophilic substitution reactions and vinylic nucleophilic substitution reactions, is adequate at the present time to explain the results of this study. Rate-limiting attack of primary amines, thiolate ions, and hydroxide ions on β-oxy-α,β-unsaturated ketones seems general for these reactions and reactivity is little affected by leaving group tendencies, evidence for the stepwise nature of these reactions. Further there is kinetics evidence for existence of an intermediate ($Z^{\pm}$) on the path to products, although the partitioning of that intermediate is so favorable in the direction of products as to be easily missed experimentally.

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(24) Dr. C. D. Ritchie called to our attention his results (unpublished) that 3-methoxy-4'-substituted acrylophenones react with morpholine to give kinetics in accord with eq 4 (personal communication). We reexamined data reported[12] for reactions of 3-methoxy-4'-dimethylaminoacrylophenone with morpholine and found that such may indeed be the case, although our data do not fit eq 4 well. The following data are provided for anyone interested ([morpholine]$_{\text{Total}}$, k_{obsd}/[morpholine]$_{\text{Total}}$ (M^{-1} min^{-1})): pH 7.85 (μ 0.1), 0.01, 3.4; 0.02, 3.4; 0.02, 3.55; 0.03, 3.0; 0.04, 3.45; 0.04, 3.6; 0.05, 3.52; 0.06, 3.7; 0.08, 3.8; 0.1, 3.87. pH 8.29 (μ 0.1), 0.02, 8.1; 0.04, 8.28; 0.06, 7.15; 0.08, 8.4; 0.1, 8.8. pH 8.27 (μ 1.0), 0.1, 6.86; 0.2, 6.9; 0.2, 6.55; 0.4, 7.09; 0.6, 7.47; 0.8, 7.58; 1.0, 7.47.
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(31) The k_1 values of Table III for reactions of secondary amines with 1, 4, and 6 and the k_2 values of Table I for reactions of primary amines with 1–6 are assumed to be associated with the same nucleophilic attack step (k_1) of Scheme I or II.
(32) We believe that this loss of absorbance at 300 nm in more concentrated (0.02–0.08 M) mercaptoethanol solution is due to Michael reaction of RSH with $RSCH=CHCOCH_3$ to give $(RS)_2CHCH_2COCH_3$.

Acid- and Base-Catalyzed Dehydration of Prostaglandin E₂ to Prostaglandin A₂ and General-Base-Catalyzed Isomerization of Prostaglandin A₂ to Prostaglandin B₂

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Abstract: Dehydration of prostaglandin E₂ (PGE₂) to prostaglandin A₂ (PGA₂) in aqueous solution is catalyzed by hydrogen ion (k^d_H), hydroxide ion (k^d_{OH}), and quinuclidine (k^d_A). The values of k^d_H and k^d_{OH} are very similar to those for various known enolization reactions and $k^d_H(H_2O)/k^d_H(D_2O) = 0.6$, results that support a mechanism involving rate-determining enolization of PGE₂ during dehydration. Isomerization of PGA₂ to prostaglandin B₂ (PGB₂) is general base catalyzed by tertiary amines with $k^i_A(H_2O)/k^i_A(D_2O) = 1.1$. The rate constants k^i_A and k^i_{OH} for loss of PGA₂ are equal to those for formation of PGB₂ and it is suggested that C-12 proton abstraction is rate determining in the reaction sequence PGA₂ → PGC₂ → PGB₂.

The clinical usefulness of prostaglandin E₂ (PGE₂) in
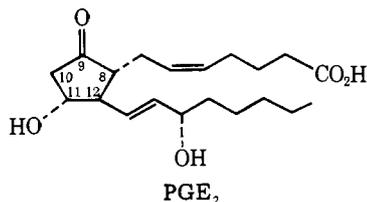
PGE₂

human reproduction[1-5] coupled with its chemical instability in aqueous solution[6-13] has prompted a research activity directed toward preparation of PGE₂ prodrugs and pharmaceutical formulations[14-17] that retain biological activity and possess greater stability. The chemical instability of E and A series prostaglandins was shown[6-13] to involve dehydration of the 9,11-ketol to PGAs in acidic and alkaline solution (eq 1), isomerization of PGAs to PGCs in alkaline solution (eq 1), isomerization of PGCs to PGBs in alkaline solution (eq 1),
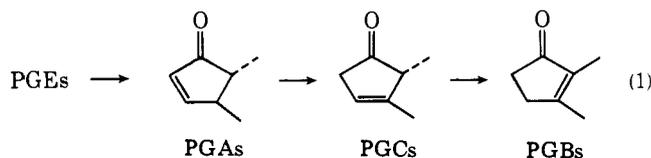
epimerization of PGE₁ to 8-iso-PGE₁ in ethanolic potassium acetate, epimerization of prostaglandins to 15-epiprostaglandins in dilute acid, and allylic rearrangement of 15-epi-PGA₂ to the 13-hydroxy diastereomers of PGA₂. Biochemical transformations of prostaglandins catalyzed by enzymes include dehydration of PGE₂ to PGA₂,[18-20] isomerization of PGAs to PGCs,[21-23] isomerization of PGCs to PGBs,[20] reduction of the 9-keto group to the carbinol,[24,25] oxidation of the C-15 carbinol to the ketone,[26,27] and reduction of the Δ¹³ double bond.[28,29] Little is known of the chemistry of the dehydratase and isomerase enzymes except that they are inhibited by sulfhydryl reagents and they likely do not require cofactors.[18-21,23]

This study was undertaken to probe the nature of the acid-base-catalyzed dehydration-isomerization sequence PGE₂ → PGA₂ → PGC₂ → PGB₂ depicted in eq 1 with a view to contributing to a better understanding of the mechanisms of these transformations. Owing to the variety of prostaglandin chemistry that takes place simultaneously in aqueous solution at any pH, the rate constants reported in this kinetics study do not strictly represent the chemistry of eq 1: 8- and 15-epi-PGE₂ and PGA₂ should be formed during dehydration. However, these epimers are expected to have similar reactivities to PGE₂ and PGA₂ with respect to ring dehydration-isomerization and we suggest that our conclusions of mechanism are little affected by these extraneous events.

Experimental Section

Apparatus. Gilford Model 2400, Beckman Model DBG, and Cary Model 118 spectrophotometers were used. Temperature was maintained with a Tamson T9 circulating water bath connected to thermospacers in the Gilford spectrophotometer. pH measurements were made with a Radiometer PHM 26 meter with GK2321B or GK2321C electrodes.

Reagents. PGE₂ was a gift from Upjohn Co. All reagents were Fisher certified ACS grade except quinuclidine, quinuclidinol (Aldrich), triethylamine (Eastman), D₂O, DCl (99.9% D) (Stohler Isotope Chemicals), K₂HPO₄, and K₃PO₄ (Sigma). Line distilled water was redistilled through a Corning AGla still before use.

Kinetics. All solutions had a calculated ionic strength of 0.5 M (KCl) unless otherwise stated. The temperature of reactions was 30 ± 0.1 °C. The pHs of reactant solutions were measured and found to be constant (±0.04 pH) for all serial dilutions except HCl/KCl and KOH/KCl. Reactions were run under pseudo-first-order conditions and were initiated by addition of PGE₂ in absolute ethanol to aqueous solutions of reactants. The concentration of ethanol was ca. 1% and that of PGE₂ ca. 10^{-4}–10^{-5} M in the 3-mL cuvettes. pK_a values were determined by the method of fractional neutralization. pD was determined from the pH meter reading by adding 0.4 to it.[30] Hydroxide ion activity was determined from K_w/a_H where $pK_w = 13.83$ at 30 °C[31] and deuterioxide ion activity was determined from K_D/a_D where $pK_D = 14.65$ at 30 °C.[32]

Reaction of PGE₂ with hydroxide solution is characterized by an initial increase in optical density (OD) followed by a slower decrease at 224 nm. This decrease is accompanied by an increase in OD at 280