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Kinetics of the reaction of β-alkoxyvinyl methyl ketones with amines

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ABSTRACT: The kinetics of the reaction of β-alkoxyvinyl methyl ketones $R^1O—CR^2=CH—COCX_3$ (**1a–e**) (**a**, $R^1=CH_3$, $R^2=H$, X=H; **b**, $R^1=C_2H_5$, $R^2=H$, X=F; **c**, $R^1=C_2H_5$, $R^2=H$, X=Cl; **d**, $R^1=R^2=CH_3$, X=Cl; **e**, $R^1=R^2=CH_3$, X=F) with aliphatic amines was studied in various solvents. The details of appropriate enaminoketone (**2a–d**) formation are discussed in terms of an addition–elimination reaction. It is shown that the limiting step of the reaction is the decomposition of a zwitterionic intermediate, and that the observed second-order reaction rate constants are a function of the solvent's relative permittivity ε_r. At high amine concentrations in non-polar solvents, the third-order rate coefficient appears in the reaction rate equation as a consequence of a catalyzed route of the intermediate decomposition. The reaction has low $\Delta H^{\neq}$ and high negative $\Delta S^{\neq}$ values owing to the formation of a highly polar zwitterionic intermediate. Its lifetimes are determined mainly by the electron-withdrawing ability of $COCX_3$. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: β-alkoxyvinyl methyl ketones; amines; kinetics

INTRODUCTION

The methyl vinyl carbonyl group is one of the most versatile and useful entities in organic synthesis.[1] Substitution of a methyl group by a trifluoromethyl group changes abruptly the chemical properties of enones.[1,2] We have been concerned for some time both with the synthetic use of trifluoromethyl vinyl ketones[2,3] and with mechanistic aspects[4] involved in the reaction of these compounds with amines. Thus, we have shown that ethoxyvinyl trifluoromethyl ketone is a convenient and comprehensive starting reagent for the synthesis of various fluorine-containing compounds such as heterocycles, enones, enaminones, and chelate complexes. Moreover, it was found that the reaction kinetics of β-alkoxyvinyl alkyl ketones with nucleophiles, containing amino groups, are strongly dependent upon the substituents at the carbonyl C-atom, solvent polarity and the structure of the amino-containing nucleophiles.[4] Proceeding with this work we have become interested in trihalomethyl vinyl ketones and their reaction with nucleophiles. We reasoned that trihalomethyl vinyl ketones, besides being obviously valuable synthetic intermediates[3,5] are also very interesting substances for mechanistic studies. We therefore decided to extend our work to the systems **1a–e** by changing the α- and β-substituents, the nucleophile, and the solvent. The aim of this work was to ascertain the rate-determining step of this multi-step reaction.

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EXPERIMENTAL

Materials. (*E*)-4-Methoxy-3-buten-2-one (**1a**) was purchased from Fluka (λ_{max} = 262 nm in hexane). (*E*)-1,1,1-Trifluoro-4-ethoxy-3-buten-2-one (**1b**) (λ_{max} = 260 nm in hexane) and (*E*)-1,1,1-trichloro-4-ethoxy-3-buten-2-one (**1c**) (λ_{max} = 263 nm in hexane) were synthesized from trichloroacetic and trifluoroacetic anhydride, respectively, and ethyl vinyl ether as described.[6] (*E*)-1,1,1-Trichloro-4-methoxy-3-penten-2-one (**1d**) (λ_{max} = 265 nm in hexane) and (*E*)-1,1,1-trifluoro-4-methoxy-3-penten-2-one (**1e**) (λ_{max} = 263 nm in hexane) were obtained as described.[7]

Uv–visible spectra of the appropriate products of the reaction of **1a–d** with amines have been published.[1,4,5]

The NMR spectra were all in accord with the molecular structures. All β-alkoxyvinyl methyl ketones

Table 1. Kinetic data and activation parameters for the reaction of **1a–c** and **e** with amines at various concentrations of the enones

Enone	Amine	Solvent	T (°C)	Concentration range (M)[a]	k'[b]	k''[c]	k'/k''[d]	$\Delta H^{\neq\prime}$[e]	$\Delta S^{\neq\prime}$[f]	$\Delta H^{\neq\prime\prime}$[e]	$\Delta S^{\neq\prime\prime}$[f]
1a	Et_2NH	n-C_6H_{14}	20	0.05–0.8	2.61×10^{-4}	3.93×10^{-4}	1.51	49.6 ± 1.9	-144 ± 6	20.6 ± 4.0	-239 ± 12
			40	0.1–0.9	1.02×10^{-4}	7.19×10^{-4}	7.05				
		$CHCl_3$	20	0.1–0.9	7.84×10^{-4}	2.05×10^{-4}	2.61	43.9 ± 9.0	-149 ± 13	40.9 ± 3.6	-175 ± 16
			40	0.1–0.9	2.64×10^{-3}	6.40×10^{-4}	2.42				
		CH_3CN	20	0.1–0.8	2.03×10^{-3}	0.00	0.00	39.8 ± 4.2	-167 ± 16	—	—
			40	0.1–0.8	1.37×10^{-2}	0.00	0.00				
	n-$BuNH_2$	CH_3CN	25	0.05–0.5	2.62×10^{-3}	0.00	0.00	34.9 ± 6.9	-173 ± 11	—	—
			40	0.05–0.5	5.39×10^{-3}	1.31×10^{-3}	0.24				
1b	Et_2NH	n-C_6H_{14}	20	$(0.5–3.5) \times 10^{-3}$	4.44	0.00	0.00	18.9 ± 5.5	-167 ± 2	—	—
			40	$(0.5–3.5) \times 10^{-3}$	7.77	0.00	0.00				
	i-Pr_2NH	n-C_6H_{14}	20	0.05–0.5	3.04×10^{-3}	1.55×10^{-3}	0.51	30.8 ± 3.6	-188 ± 16	21.0 ± 3	-227 ± 11
			40	0.05–05	7.27×10^{-3}	2.87×10^{-3}	3.95				
		$CHCl_3$	20	0.01–0.1	4.20×10^{-2}	2.26×10^{-2}	0.54	20.1 ± 7	-202 ± 22	43.5 ± 7	-126 ± 13
			40	0.01–0.1	7.58×10^{-2}	8.44×10^{-2}	1.11				
		CH_3CN	20	0.01–0.5	1.52×10^{-1}	6.14×10^{-1}	4.04	11.2 ± 2	-222 ± 16	67.9 ± 7	-17 ± 13
			40	0.01–0.5	2.17×10^{-1}	3.89	17.9				
1c	Et_2NH	n-C_6H_{14}	20	$(0.5–5) \times 10^{-3}$	7.86×10^{-1}	0.00	0.00	24.3 ± 2	-163 ± 16	—	—
			40	$(0.5–5) \times 10^{-3}$	1.58	0.00	0.00				
		$CHCl_3$	20	$(0.5–5) \times 10^{-3}$	4.79	0.00	0.00	18.4 ± 9	-169 ± 13	—	—
			40	$(0.5–5) \times 10^{-3}$	8.28	0.00	0.00				
1e	Et_2NH	CH_3CN	20	$(0.5–5) \times 10^{-2}$	9.63×10^{-2}	0.00	0.00	26.2 ± 3	-175 ± 14	—	—
			40	$(0.5–5) \times 10^{-2}$	2.04×10^{-1}	0.00	0.00				
	n-$BuNH_2$	n-C_6H_{14}	25	0.05–0.25	6.64×10^{-3}	1.88×10^{-1}	28.3	41.3 ± 4	-145 ± 16	0.6 ± 3.1	-256 ± 10
			40	0.05–0.25	$2.0911e^{-2}$	2.03×10^{-1}	9.7				
		CH_3CN	20	$(0.5–5) \times 10^{-3}$	2.19	0.00	0.00	22.6 ± 3	161 ± 9	—	—
			40	$(0.5–5) \times 10^{-3}$	4.22	0.00	0.00				

[a] Concentration range of the amine used for establishing the second-order kinetics.
[b] $dm^3\ mol^{-1}\ s^{-1}$.
[c] $dm^6\ mol^{-2}\ s^{-1}$.
[d] $dm^3\ mol^{-1}$.
[e] $kJ\ mol^{-1}$.
[f] $J\ mol^{-1}\ K^{-1}$.

Table 2. Kinetic and activation parameters of the reaction of enones **1a–d** with diethylamine

Enone	Solvent	k_{obs} (l mol^{-1} s^{-1})[a]	$\Delta G^{\neq}$ (kJ mol^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})
1a	Methanol	$(2.72 \pm 0.06) \times 10^{-2}$	80.5 ± 1.9	30.8 ± 1.7	-170 ± 6
	2-Propanol	$(1.62 \pm 0.02) \times 10^{-2}$	81.8 ± 1.2	31.6 ± 0.8	-173 ± 3
	n-Butanol	$(2.31 \pm 0.02) \times 10^{-2}$	80.9 ± 0.8	29.3 ± 0.5	-176 ± 2
	t-Butanol	$(7.66 \pm 0.06) \times 10^{-3}$	83.6 ± 1.2	42.7 ± 1.0	-140 ± 8
	n-Decanol	$(1.87 \pm 0.12) \times 10^{-3}$	—	—	—
	DMSO[b]	$(1.39 \pm 0.06) \times 10^{-3}$	87.7 ± 0.8	38.7 ± 0.5	-167 ± 2
	Acetonitrile	$(1.99 \pm 0.06) \times 10^{-3}$	86.9 ± 4.1	40.7 ± 3.7	-157 ± 8
	1,2-Dichloroethane	$(1.50 \pm 0.02) \times 10^{-3}$	87.6 ± 2.7	35.6 ± 2.5	-177 ± 8
	Chloroform	$(7.84 \pm 0.04) \times 10^{-4}$	89.2 ± 3.0	40.0 ± 2.7	-168 ± 2
	Dibutyl ether	$(2.42 \pm 0.02) \times 10^{-4}$	89.3 ± 1.3	29.1 ± 1.0	-205 ± 2
	1,4-Dioxane	$(3.76 \pm 0.04) \times 10^{-4}$	91.0 ± 1.7	44.9 ± 1.4	-157 ± 5
	Triethylamine	$(6.19 \pm 0.02) \times 10^{-4}$	89.8 ± 2.3	20.4 ± 2.0	-236 ± 10
	Cyclohexane	$(3.46 \pm 0.04) \times 10^{-4}$	91.2 ± 1.8	37.5 ± 1.5	-183 ± 5
	Hexane	$(2.55 \pm 0.04) \times 10^{-4}$	91.9 ± 2.0	41.7 ± 1.6	-171 ± 3
1b	Methanol	76.82 ± 0.23[c]			
	n-Butanol	93.31 ± 0.28[c]			
	n-Pentanol	93.05 ± 0.27[c]			
	n-Decanol	95.32 ± 0.31[c]			
	1,2-Dichloroethane	67.93 ± 0.21	67.2 ± 2.1	17.7 ± 1.9	-168 ± 6
	Chloroform	30.87 ± 0.18	63.4 ± 1.6	17.5 ± 1.4	-156 ± 5
	1,1,2-Trichloroethene	21.50 ± 0.12	64.3 ± 2.2	14.5 ± 2.1	-170 ± 7
	Tetrachloromonomethane	9.03 ± 0.08	66.4 ± 1.5	17.3 ± 1.3	-167 ± 4
	Cyclohexane	6.46 ± 0.05	67.2 ± 2.1	17.7 ± 1.9	-168 ± 6
	Hexane	4.32 ± 0.02	68.2 ± 1.8	18.4 ± 1.5	-168 ± 4
1b[d]	Acetonitrile	$(9.07 \pm 0.02) \times 10^{-2}$	76.9 ± 1.5	21.9 ± 1.2	-188 ± 4
	1,2-Dichloroethane	$(4.59 \pm 0.02) \times 10^{-2}$	79.4 ± 2.1	28.9 ± 1.9	-172 ± 6
	Chloroform	$(2.12 \pm 0.02) \times 10^{-2}$	81.2 ± 2.6	32.8 ± 1.4	-173 ± 5
	1,1,2-Trichloroethene	$(1.92 \pm 0.02) \times 10^{-2}$	81.5 ± 1.8	23.2 ± 2.1	-199 ± 4
	Tetrachloromonomethane	$(6.38 \pm 0.06) \times 10^{-3}$	84.1 ± 1.5	29.3 ± 1.3	-187 ± 8
	Hexane	$(3.26 \pm 0.03) \times 10^{-3}$	85.7 ± 2.5	28.1 ± 1.5	-197 ± 9
1c	Methanol	6.85 ± 0.01	69.2 ± 2.6	32.2 ± 2.5	-126 ± 8
	n-Pentanol	7.26 ± 0.01	69.2 ± 3.9	29.8 ± 3.8	-135 ± 13
	n-Octanol	6.20 ± 0.01	69.2 ± 2.8	30.2 ± 2.6	-133 ± 9
	Acetonitrile	11.40 ± 0.05	69.3 ± 1.3	12.8 ± 1.2	-175 ± 4
	1,2-Dichloroethane	5.53 ± 0.02	67.6 ± 2.0	11.9 ± 1.7	-189 ± 6
	Chloroform	3.79 ± 0.02	68.5 ± 2.7	25.5 ± 2.5	-177 ± 5
	1,1,2-Trichloroethene	2.40 ± 0.01	69.6 ± 1.3	23.8 ± 1.0	-157 ± 3
	Tetrachloromonomethane	1.28 ± 0.01	71.2 ± 1.0	25.2 ± 0.7	-156 ± 3
	Hexane	0.67 ± 0.005	72.7 ± 1.0	24.3 ± 0.9	-165 ± 7
1d	Methanol	$(8.99 \pm 0.08) \times 10^{-3}$	83.2 ± 0.9	33.3 ± 0.7	-170 ± 3
	1,2-Dichloroethane	$(7.26 \pm 0.07) \times 10^{-3}$	83.8 ± 1.3	31.7 ± 1.2	-178 ± 5
	Chloroform	$(2.62 \pm 0.06) \times 10^{-3}$	82.2 ± 1.4	37.8 ± 1.5	-165 ± 5
	1,1,2-Trichloroethylene	$(1.94 \pm 0.05) \times 10^{-3}$	87.0 ± 1.2	37.3 ± 1.1	-169 ± 1
	Tetrachloromonomethane	$(7.19 \pm 0.09) \times 10^{-4}$	89.4 ± 1.7	42.1 ± 1.6	-162 ± 5
	Hexane	$(3.50 \pm 0.10) \times 10^{-4}$	91.2 ± 1.2	36.6 ± 1.0	-186 ± 4
1e	Acetonitrile	$(9.80 \pm 0.08) \times 10^{-2}$	77.6 ± 0.9	26.5 ± 1.2	-175 ± 7
	Hexane	$(2.18 \pm 0.05) \times 10^{-3}$	81.7 ± 0.9	27.5 ± 1.3	-185 ± 9

[a] At 293 K.
[b] Dimethyl sulfoxide.
[c] At higher temperatures the reaction is too fast to be followed.
[d] Reaction with *i*-Pr_2NH.

were stored under N_2 at 4 °C and were purified by distillation before use.

Solvents. All solvents were analytically pure (Aldrich, Fluka) and were further purified by published methods.[8] Acetonitrile was purified by a four-step method,[9] stored under N_2 and distilled prior to use. Diethylamine and *n*-butylamine were purified by standard methods.

Kinetic experiments. Kinetic measurements were carried out under pseudo-first-order conditions by adding 10 µl of a 10^{-2} M solution of the substrate (**1a–d**) to 2 ml of the amine solution (5×10^{-2} M for **1a** and **b**, 5×10^{-4} M for **1c** and **d** and 5×10^{-3} M for **1e** unless stated otherwise) in thermostated (with accuracy ±0.2 °C) quartz 10 mm cells (Hellma) at various temperatures (20 –50 °C in 5 °C steps). The kinetic runs were followed by UV–visible spectrophotometry utilizing a Carl Zeiss Jena M40

Table 3. ^{13}C NMR chemical shifts (δ) for enones **1a–d** measured in various solvents (all values in ppm relative to acetonitrile at 25 °C)

$$R^1O\text{—}\overset{4}{C}R^2\text{=}\overset{3}{C}H\text{—}\overset{2}{C}O\overset{1}{C}X_3$$

Enone	Solvent	C(2)	$C_\alpha(3)$	$C_\beta(4)$
1a	Methanol-d_1	200.18	107.23	165.92
	Pentanol	198.36	106.93	164.85
	DMSO-d_6	197.48	108.28	165.14
	Acetonitrile-d_3	197.78	107.70	164.55
	Chloroform-d	197.77	107.04	163.86
	Tetrachloromethane	194.75	106.97	162.80
1b	DMSO-d_6	180.12	98.63	169.78
	Acetonitrile-d_3	180.59	98.57	169.94
	Chloroform-d	180.29	98.24	168.35
	Tetrachloromethane	179.50	98.30	167.73
	Cyclohexane-d_{12}	179.46	98.16	167.62
1c	DMSO-d_6	181.74	96.74	170.40
	Acetonitrile-d_3	182.08	96.72	169.94
	Chloroform-d	181.29	96.42	167.85
	Tetrachloromethane	180.27	96.52	167.50
	Cyclohexane-d_{12}	179.05	96.29	165.86

spectrophotometer. The reactant consumption and product accumulation kinetics were recorded virtually simultaneously by real changes in the optical densities of two bands (where it was possible owing to solvent transmission). In cases of an $E \rightleftharpoons Z$ isomerization of the reaction product the kinetics were registered by reactant consumption only. The kinetic measurements were carried out at suitable analytical wavelengths on the slopes of the appropriate spectral bands in the region 256–263 nm (for reactants) and 303–328 nm (for products). Control experiments showed virtual irreversibility of the reaction under the conditions used.

All kinetic runs were followed for at least 3–4 half-lives. The accuracy of rate constant determination was 1–3%. Half-logarithmic anamorphoses of kinetic curves (1) and (2) were straight lines ($r \geq 0.999$) providing pseudo-first-order rate constants (k_{p-f}) with an accuracy $\geq \pm 0.5\%$.

$$\ln([D]_0/[D]_\tau) = f(\tau) \quad \text{(reactant)} \tag{1}$$

$$\ln\{[D]_\infty/([D]_\infty - [D]_\tau)\} = f(\tau) \quad \text{(product)} \tag{2}$$

where $[D]_0$ is the initial optical density of the substrate, $[D]_\infty$ is the final optical density of product and $[D]_\tau$ is the optical density at time τ.

Second- and third-order rate constants. Second-order coefficients (k_{obs}) were obtained by dividing the pseudo-first-order coefficients by the amine concentration (Tables 1 and 2). In some systems the observed second-order rate constant k_{obs} increased with increase in the amine concentration. This rate increase was linear according to the equation

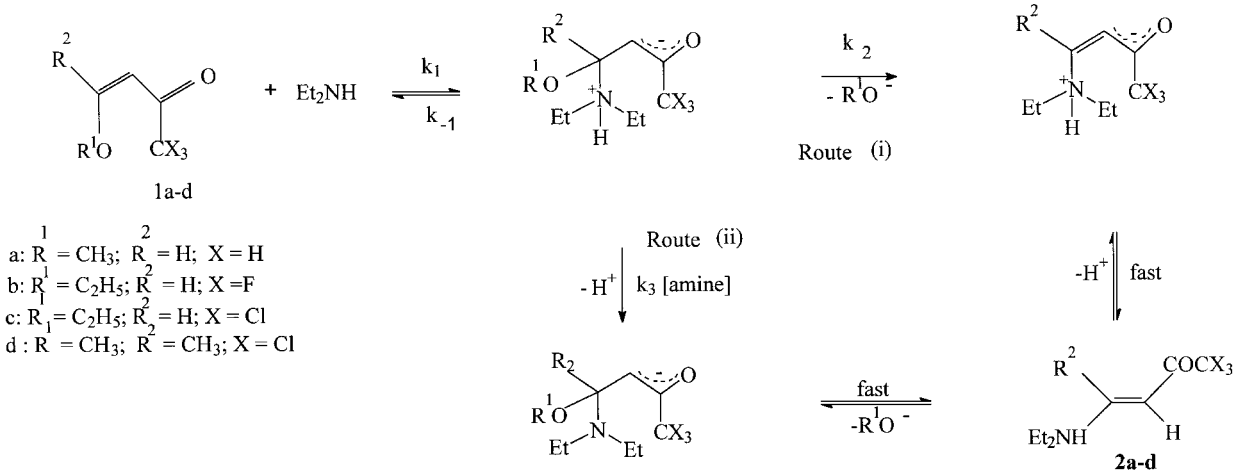
$$k_{obs} = k' + k''[\text{amine}] \tag{3}$$

In the systems where k_{obs} was independent of the amine concentration, the second-order rate constants were determined as the average of at least 10 experiments. The least-squares intercepts, which are the uncatalyzed second-order rate coefficients k', and the slopes, which give the amine-catalyzed third-order rate coefficients k'', and their ratios, k''/k', are given in Table 1. The observed second-order rate constants k_{obs}, obtained at a fixed concentration of diethylamine (see above), and thermodynamic parameters for the reaction of **1a** with diethylamine, evaluated at 20 °C, are listed in Table 2.

^{13}C NMR spectra. The ^{13}C and ^1H NMR spectra were recorded on Bruker UNITY plus 500 MHz and WP-200 spectrometers at 25 °C using standard conditions. The concentrations of the samples varied from 0.2 to 0.5 M; ^{13}C chemical shifts were measured against external CH_3CN and ^{13}C spectra were recorded in proton-decoupled modes; data are given in Table 3.

RESULTS AND DISCUSSION

The reaction under investigation is a specific case of a nucleophilic vinylic substitution via addition–elimination[5] (Adn-E). The Adn-E route is a multi-step reaction.[10]



Scheme 1

Usually the initial nucleophilic attack is rate determining,[10b] but in the presence of the electron-withdrawing group ($COCX_3$) and with a slow leaving group (OAlk) subsequent steps also may appear in the rate equation. Earlier,[4] from the dependence of the pseudo-first-order coefficient on the nucleophile concentration, the reaction of **1a** and **b** with amines was determined to be first order for both enone and amine. At higher amine concentrations (10^2–10^3-fold excess), the second-order rate constant depends on the amine concentration in certain systems (see Table 1).

The details of the reaction of enones **1a–d** with aliphatic amines are given in Scheme 1. The linear dependence of k_{obs} on amine concentration implies the presence of other rate constants in the rate equation. As has been shown by Rappoport and co-workers,[10,11] a steady-state treatment of Scheme 1 gives Eqn. (4) for the observed second-order rate constant:

$$k_{obs} = \frac{k_1 k_2 + k_3[A]}{k_{-1} + k_2 + k_3[A]} \tag{4}$$

according to which

$$k_{obs} = k_1 \tag{5}$$

when $(k_2 + k_3[A]) \gg k_{-1}$, and the reaction is overall second order ([A] = amine concentration). When the uncatalyzed reaction [route (i), Scheme 1] is faster than the catalyzed reaction but slower than the reverse reaction, i.e. $k_{-1} \gg k_2 \gg k_3[A]$, k_{obs} is composite but it is again a second-order constant:

$$k_{obs} = k_1 k_2 / k_{-1} \tag{6}$$

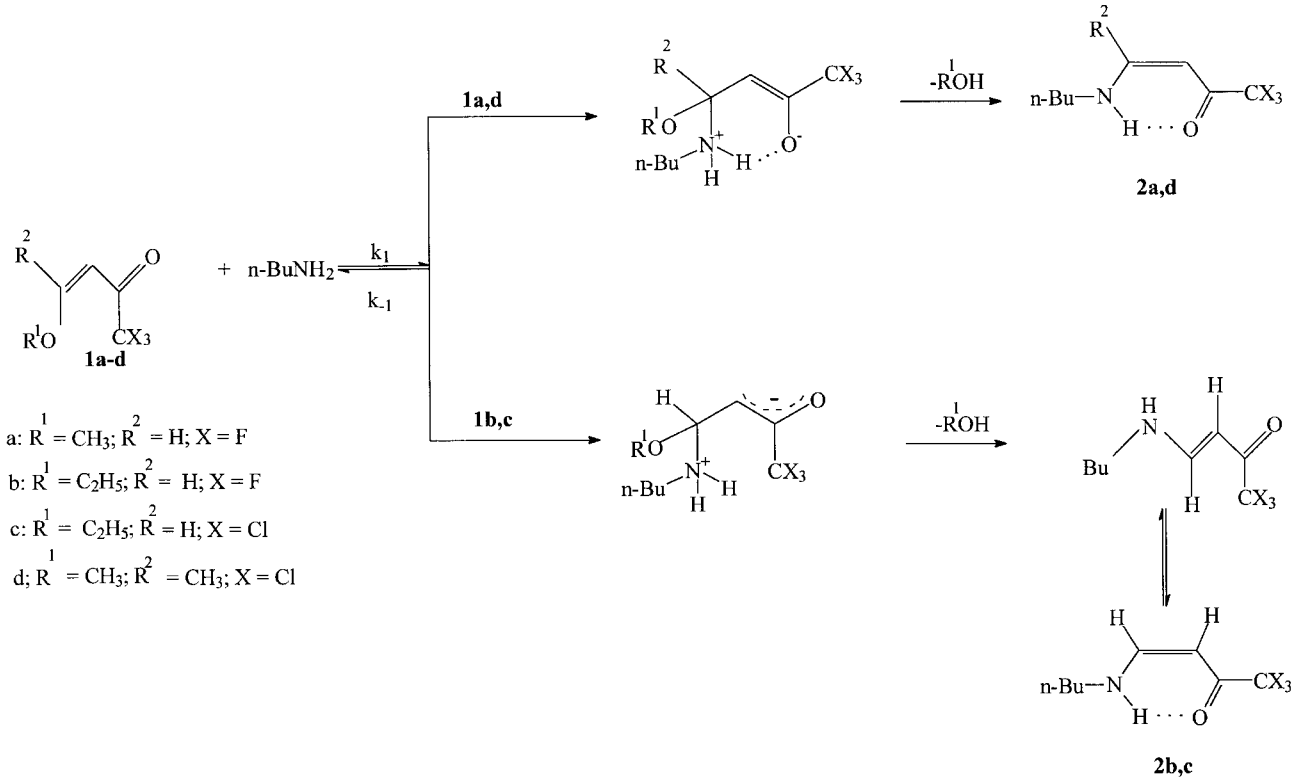
For the catalyzed reaction [route (ii), Scheme 1] when the counter-reaction of zwitterion formation is faster than its decomposition, i.e. $k_{-1} \gg (k_2 + k_3[A])$, k_{obs} is given by the sum of the second- and third-order terms [Eqn. (7)], and it will increase linearly with increase in the amine concentration:[11]

$$k_{obs} = (k_1 k_2 / k_{-1}) + (k_1 k_3 / k_{-1})[A] \tag{7}$$

In certain cases (see Table 1) a linear k_{obs} vs [amine] relationship is observed. Consequently, the reaction follows two competing routes: an uncatalyzed route whose rate constant k' is given by $k_1 k_2 / k_{-1}$, and a catalyzed route whose rate constant k'' is given by $k_1 k_3 / k_{-1}$. Hence the k''/k' values of Table 1 are identical with the k_3/k_2 ratios in Scheme 1 and a measure of the relative importence of the two routes starting from a common intermediate. The ratios observed for the systems **1a–e** are moderate but high enough, being in the region assigned by Rappoport and Topol[11b] in nucleophilic vinylic substitutions as the region of genuine base catalysis. Nevertheles, the values of the k_3/k_2 ratios are in the ranges 1.51–7.05 for diethylamine, 0.51–17.9 for diisopropylamine and 0.24–28.3 for *n*-butylamine, indicating the predominance of the uncatalyzed route (when catalyzed route predominates, the k_3/k_2 ratios are in the range 1000–∞[10,11]), and therefore the k' values in Table 1 are very close to k_{obs} in Table 2.

Reaction of 1a–d with primary amine

The reaction of enones **1a–d** with *n*-butylamine possesses particular features (see Scheme 2). All enones interact as *E*-isomers (Ref. 12 for **2a**; unpublished results for **2b–d**), but the spacial structure of obtaining enaminoketones **2a–d** differs depending on the structure of the intermediate. For **1a** and **1d** the lifetime of the intermediate (IM) is short enough to accomplish 60° counterclockwise



Scheme 2

internal rotation only (route A, Scheme 3) and form an intramolecular H-bond in the zwitterion before expulsion of the leaving group.[10] As a result, a single geometrically pure *Z,Z*-product is obtained (with $\lambda_{max} = 303$ nm for **2a** and 325 nm for **2d**). It is worth mentioning that at least for product **2a** the $E \rightarrow Z$ transition is relatively slow process[13] and even traces of the *E*-isomer can be observed in the course of the reaction (first of all, no isosbestic point was observed in the UV spectra for the systems **1b** and **c** during the kinetic measurements).

A comparison of systems **1c** and **1d** shows that CH_3 as the β-substituent reduces the reaction rate k_{obs} (Table 2) and the lifetime of the intermediate. On the other hand, the intermediate lifetime of **1b** and **c** is prolonged (relative to **1a**) owing to the higher charge dispersal of $COCHal_3$; as a result, predominant 120° clockwise rotation (route B, Scheme 3)[14] occurs, giving the structure where intramolecular H-bonding is impossible. Expulsion of R^1OH gives retained *E*-products **2b** and **c** (with $\lambda_{max} = 307$ and 317 nm, respectively), which isomerizes relatively fast into the *Z,Z* form (with $\lambda_{max} = 315$ and 329 nm, respectively).

Primary butylamine was found to be more reactive than secondary diethylamine in the systems **1a** and **1e** (in acetonitrile the relative k' ratios are 3:1 and 23:1, respectively). A similar observation of amine reactivity in nucleophilic vinylic substitution was explained by the formation and cleavage of the intramolecular hydrogen bond in the intermediate.[11a]

Reaction of enones 1a–d with secondary amines

The k' coefficients in Table 1 are very close to or coincide with k_{obs} in Table 2 for the reaction of **1a–d** with

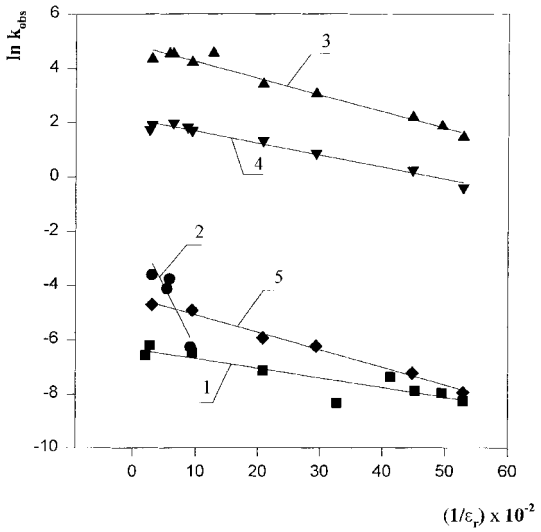
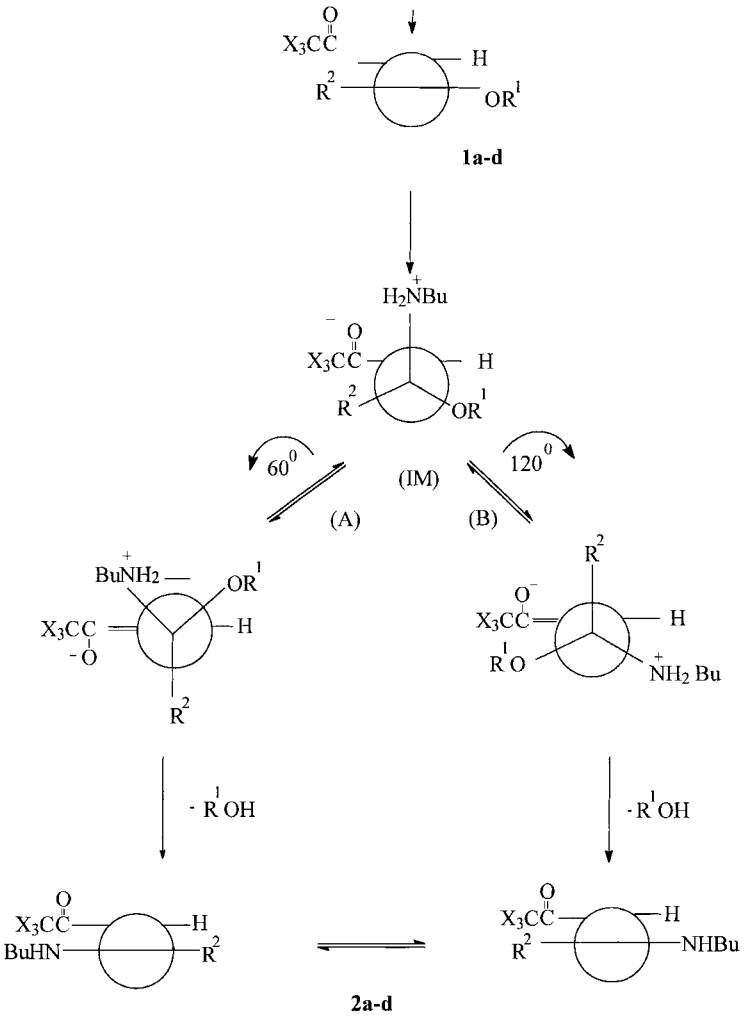


Figure 1. Plots of the logarithm of the observed second-order rate constants (ln k_{obs}) vs resiprocal solvent permittivity ($1/\varepsilon_r$) for the reaction of enones with diethylamine: 1, **1a** in aprotic solvents, $s = -3.40$; 2, **1a** in alcohols, $s = -28.4$; 3, **1b** in aprotic solvents and alcohols, $s = -5.98$; 4, **1c** in aprotic solvents and alcohols, $s = -4.75$; 5, **1d** in aprotic solvents and methanol, $s = -6.62$



Scheme 3

diethylamine because the uncatalyzed route is predominant in the decomposition of the intermediate. As can be seen from Fig. 1, the solvent effects in the reaction of enones **1a–d** are moderate in aprotic solvents: the slope s of the plot of $\ln k_{obs}$ vs $1/\varepsilon_r$ (ε_r = relative permittivity) is in the range from −3.40 (**1a**) to −6.62 (**1d**). The changes in k_{obs} occur in the expected direction: the Kirkwood equation predicts[15] that if a reaction between neutral, dipolar molecules occurs with the formation of an activated complex (AC) with a dipole moment μ_{AC} greater than either μ_{enone} or μ_{amine}, there will be an increase in the rate constant with increasing ε_r. Moreover, the slope s increases in absolute value with the rise of the electron-withdrawing ability of the $COCX_3$ groups (Fig. 1): $s(COCF_3) > s(COCCl_3) > s(COCH_3)$, being a sign of, at least, an increase in the difference $\mu_{enone} - \mu_{AC}$. The CH_3 group as β-substituent evokes a threefold decrease in k_{obs} owing to the lowering of the partial positive charge on the C_β atom due to inductive effect and hence diminishing the enone electrophilicity. ^{13}C chemical shifts have been shown to

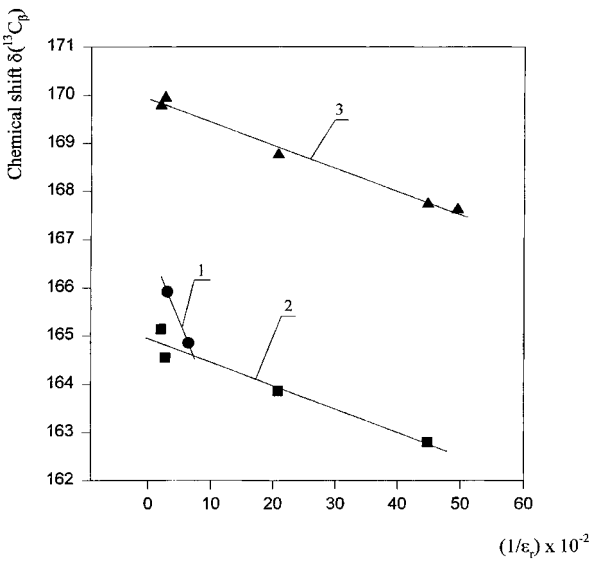


Figure 2. Plots of ^{13}C chemical shifts of the β-carbon atom vs reciprocal solvent permittivity ($1/\varepsilon_r$): 1, **1a** in alcohols; 2, **1a** in aprotic solvents; 3, **1c** in aprotic solvents

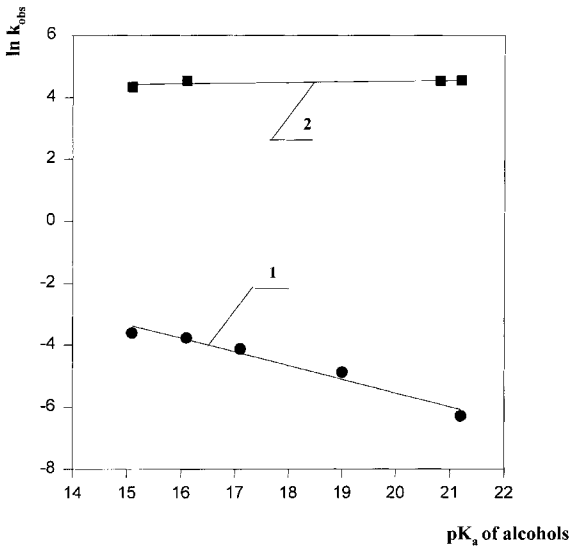


Figure 3. Plots of the logarithm of the observed second-order rate constants (ln k_{obs}) vs pK_a of alcohols:[17] 1, **1a**; 2, **1b**

be dependent on the electron density at carbon atoms of the system[16]

$$R^1O\overset{\beta}{-}C=\overset{\alpha}{C}-C=O$$

From comparison of plots of ln k_{obs} vs $1/\varepsilon_r$ and $\delta^{13}C_\beta$ vs $1/\varepsilon_r$ (cf. Figs 1 and 2), one can conclude that the reaction rate is determined mainly by the charge on C_β of the enone, which strongly depends on its solvation effects by the medium.

The slope *s* for the reaction of **1b** with diethylamine practically coincides with *s* for for the reaction of **1b** with diisopropylamine ($s = -5.98$ and -6.19, respectively), hence the slope *s* is determined presumably by substrate (enone) solvation.

The slope *s* for **1a** in protic solvents (alcohols) is much higher in absolute value than in aprotic solvents (-28.1 and -3.40, respectively, see Fig. 1, plots 1 and 2), whereas for **1b** and **c** the distinction in *s* in alcohols and in aprotic solvents is almost absent (Fig. 1, plots 3 and 4). Indeed, in protic solvents one would expect additional solvent effects due to H-bond formation between solvent and solute.[15] Electron density displacement in hydrogen-bonded **1a** increases the partial positive charge on C_β, thus raising the electrophilicity of enone **1a**. On the other hand, inductive electron-withdrawal of $CHal_3$ decreases significantly the hydrogen-bond basicity of the carbonyl group (cf. pK_{HB} of acetone, 1,1,1-trichloropropan-2-one and 1,1,1-trifluoropropan-2-one: 1.18, 0.00 and -0.06, respectively[17]), and therefore solvent effects for **1b–d** in alcohols are very similar to those in aprotic solvents. From the Brønsted relationship (Fig. 3) it is obvious that the general acid-catalyzed process takes place in system **1a** in alcohols, whereas in system **1b** this effect is not observed.

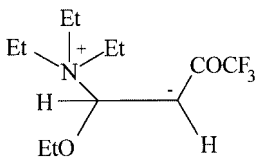
Table 4. Activation parameters of the reaction of enones **1a–d** with *n*-butylamine in hexane at 20 °C

Enone	$\Delta G^{\neq}$ (kJ mol^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})
1a	98.9 ± 2.0	16.8 ± 1.5	-280 ± 12
1b	70.1 ± 1.0	6.2 ± 0.8	-218 ± 3
1c	75.1 ± 1.1	14.8 ± 1.0	-206 ± 8
1d	85.4 ± 1.0	25.9 ± 1.0	-203 ± 2

The k'' constant of the catalyzed route in system **1a** with diethylamine decreases with increasing solvent polarity, whereas in system **1b** with diisopropylamine an increase in k'' with increasing solvent polarity is observed (Table 1). This behavior of k'' in aprotic solvents suggests that in the case of system **1a** the decomposition of the zwitterion intermediate occurs via a less polar transition state in comparison with **1b**.

Reaction of enones 1a and 1b with tertiary amine

Enone **1a** does not react with triethylamine, thus permitting one to estimate the catalyzing influence of tertiary amines on the reaction of **1a** with diethylamine. There was no increase in k_{obs} for the reaction of **1a** with diethylamine in the presence of high concentrations of triethylamine. As can be seen from Table 2 and Fig. 1, the increase in k_{obs} in triethylamine (in comparison with hexane) occurs as a consequence of the rising of relative permittivity of the solvent. On the other hand, the absence of a rate increase by *N*-methylpiperidine for the reaction of 1,1-dicyano-2-(4-dimethylaminophenyl)-2-ethoxy-ethylene with morpholine was interpreted in terms of a specific base–general acid catalysis.[11] In contrast to **1a**, enone **1b** reacts easily with triethylamine ($k_{obs} = 3.70 \times 10^{-2}$ l mol^{-1} s^{-1}) giving the appropriate enamino-ketone **2b**. The reaction mechanism involves the formation of the zwitterion[11]



with subsequent de-ethylation.[7c] This assumption is strongly supported by the fact that trimethylamine does not react with **1b** even at high concentration (0.17 M in hexane), probably owing to the absence of a leaving β-H-atom in the alkyl groups of trimethylamine. Moreover, no rate acceleration of the reaction of **1b** with diethylamine is observed in the presence of triethylamine. The lack of rate acceleration of **1a** and **1b** in the presence of bases

(tertiary amines) does not mean the absence of a catalytic route at all, and can be interpreted as evidence for the predominance of an uncatalyzed route.

Activation parameters

Activation parameters of the reaction of **1a–d** with diethylamine and *n*-butylamine are given in Tables 1, and 4. The low values of the activation enthalpies in several nucleophilic vinylic substitutions by amines were used as support for a rate constant according to the uncatalyzed route.[18] $\Delta H^{\neq}$ Activation enthalpies for the reaction of **1a–d** with diethylamine are low and decrease with $COCX_3$ electron-withdrawal enhancement. The low $\Delta H^{\neq}$ values are expected for the combination of reactive nucleophiles and enones, and the highly negative $\Delta S^{\neq}$ values are due to the formation of a dipolar activated complex from neutral precursors.[18]

The $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values can be analyzed as sums of the appropriate enthalpy and enthropy terms for the individual steps of Scheme 1:[11]

$$\Delta H^{\neq'}(\text{uncatalyzed process}) = \Delta H^0 + \Delta H^{\neq}{}_2$$

$$\Delta S^{\neq'}(\text{uncatalyzed process}) = \Delta S^0 + \Delta S^{\neq}{}_2$$

$$\Delta H^{\neq''}(\text{catalyzed process}) = \Delta H^0 + \Delta H^{\neq}{}_3$$

$$\Delta S^{\neq''}(\text{catalyzed process}) = \Delta S^0 + \Delta S^{\neq}{}_3$$

For the reaction of **1a** with diethylamine the higher $\Delta H^{\neq}$ for the uncatalyzed reaction means that $\Delta H^{\neq}{}_2 \gg \Delta H^{\neq}{}_3$. The $\Delta H^{\neq''} - \Delta H^{\neq'} = \Delta H^{\neq}{}_3 - \Delta H^{\neq}{}_2$ values are negative or close to zero (-29 kJ mol^{-1} in hexane and -3 kJ mol^{-1} in chloroform). At the same time, $\Delta S^{\neq}{}_3 - \Delta S^{\neq}{}_2$ are negative (-95 J mol^{-1} K^{-1} in hexane and -26 J mol^{-1} K^{-1} in chloroform). Consequently, in this case the catalysis is due to a favorable enthropy of activation.[11] On the other hand, for the reaction of **1b** with diisopropylamine the trend is reversed: $\Delta H^{\neq}$ is higher for the catalyzed process and $\Delta H^{\neq}{}_3 \gg \Delta H^{\neq}{}_2$ in polar solvents. The $\Delta H^{\neq''} - \Delta H^{\neq'}$ values are positive (-9.8 kJ mol^{-1} in hexane, 23.4 kJ mol^{-1} in chloroform and 56.7 kJ mol^{-1} in acetonitrile), whereas the $\Delta S^{\neq}{}_3 - \Delta S^{\neq}{}_2$ values are positive or close to zero (-39 J mol^{-1} K^{-1} in hexane, 76 J mol^{-1} K^{-1} in chloroform and 205 J mol^{-1} K^{-1} in acetonitrile). Hence in this system the catalysis is due to a favorable entropy of activation, at least in polar solvents.

The $\Delta H^{\neq'}$ and $\Delta S^{\neq'}$ values of the reaction of **1a–d** with diethylamine (Table 1) are very close to or coincide with the observed $\Delta H_{obs}{}^{\neq}$ and $\Delta S_{obs}{}^{\neq}$ values listed in Table 2. This is due to the uncatalyzed route (i) prevailing over base-catalysed route (ii) (Scheme **1**). Activation enthalpies for the reaction of **1a–d** with diethylamine (Table 1) are low and decrease with $COCX_3$ electron-withdrawal enhancement. Low $\Delta H^{\neq}$ values are expected for the combination of reactive nucleophiles and enones, and the highly negative $\Delta S^{\neq}$ values are due to the formation of a dipolar activated complex from neutral precursors.

The passage from hexane to DMSO (the reaction of **1a** with diethylamine) causes a fivefold rate acceleration with a respective decrease in $\Delta G^{\neq}$ by 4.2 kJ mol^{-1}. A similar trend is observed for other enones in aprotic solvents. In alcohols, the Gibbs activation energy of **1a** decreases by 4.1 –7.2 kJ mol^{-1} (compared with $\Delta G^{\neq}$ in DMSO, see Table 2), whereas for the systems **1b** and **1d** no changes in $\Delta G^{\neq}$ are observed. These discrepancies are conditioned by the differences of hydrogen-bond basicities of enones **1a** and **1b–d** (see above).

Although some trends of $-\Delta S^{\neq}$ changes are observed, the differences are too small to serve as a useful mechanistic indicator. Passage from diethylamine to butylamine evokes an almost twofold decrease in $\Delta H^{\neq}$ with a simultaneous increase in $-\Delta S^{\neq}$ (cf. Tables 2 and 4), hence the intermediate formed with primary amines is more polar compared with secondary amines.

In conclusion, the decomposition of the zwitterion intermediate is the limiting step for the reaction of enones **1a–d** with amines, this decomposition occurring presumably via an uncatalyzed route. The logarithm of the second-order rate constant changes linearly with the reciprocal permittivity of solvents. The acceleration of the reaction in alcohols depends on enone H-bond basicity: in halogenated analogs with reduced ability to form hydrogen bonds this additional effect is almost absent. The reaction under investigation has low $\Delta H^{\neq}$ and high negative $\Delta S^{\neq}$ values as a consequence of the formation of a highly polar zwitterion as the intermediate, the lifetime of which is determined mainly by the electron-withdrawing ability of the $COCX_3$ moiety.

Acknowledgements

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