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Kinetics of reaction of β-alkoxyvinyltrifluoromethyl ketones with nucleophiles containing amino groups

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Abstract

The reaction kinetics of β-alkoxyvinylalkyl ketones with nucleophiles containing amino groups are strongly dependent upon the substituent on the C atom of the carbonyl group, solvent polarity and structure of the amino-containing nucleophiles.

Keywords: Kinetics; β-Alkoxy-vinyl trifluoro-methyl ketone; Amino-containing nucleophiles

Reaction of β-alkoxyvinyltrifluoromethyl ketones with amines give high yields of the corresponding β-aminovinyltrifluoromethyl ketones [1] through a single step reaction. Recently [2] the 4,4,4-trifluoro-3-oxo-1-butenyl group has been proposed as a suitable protecting group for the N–H terminal unit of amino acids in peptide synthesis.

It is known [3] that the interaction of β-alkoxyvinyl ketones with amines occurs via two possible routes (Scheme 1). The common feature of (i) and (ii) is the formation of a polar transition state (TS), stabilization of which plays a key role in this process. Substitution of CH_3 by CF_3 leads to significant electron density redistribution in the β-alkoxyvinyl ketone, NMR ^{13}C data show this clearly [1], in particular the ^{13}C signal of the β-carbon exhibits a downfield shift of 5.9 ppm, indicating a decrease of electron density at the reaction center. It is natural to assume that similar differences in electron density distribution should exist in the transition state, thus causing changes in reactivity of (1).

The aim of this work is the estimation of the influence of the C(2)-substituent and/or solvent polarity on β-alkoxy-

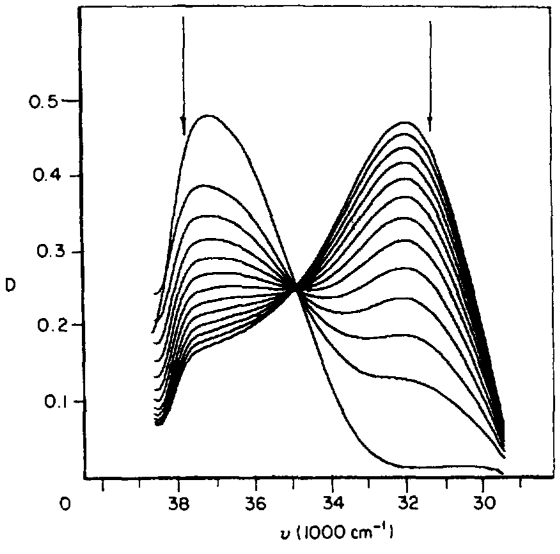

Fig. 1. Absorption spectra of reaction mixture of (1a) with (2d) in DMSO at 293 K (analytical frequencies on which kinetic measurements have been held are marked by arrows; spectra were registered every 10 s).

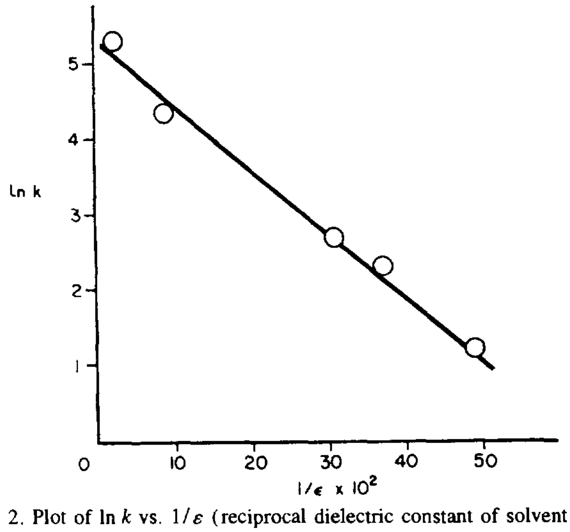

Fig. 2. Plot of ln k vs. $1/\varepsilon$ (reciprocal dielectric constant of solvent): 1, CH_3COH; 2, $C_2H_4Cl_2$; 3, mixture of 35% molar $C_2H_4Cl_2$ and 65% molar c-C_6H_{12} mole part; 4, mixture of 23.2% molar $C_2H_4Cl_2$ and 76.8% molar c-C_6H_{12}; 5, c-C_6H_{12}.

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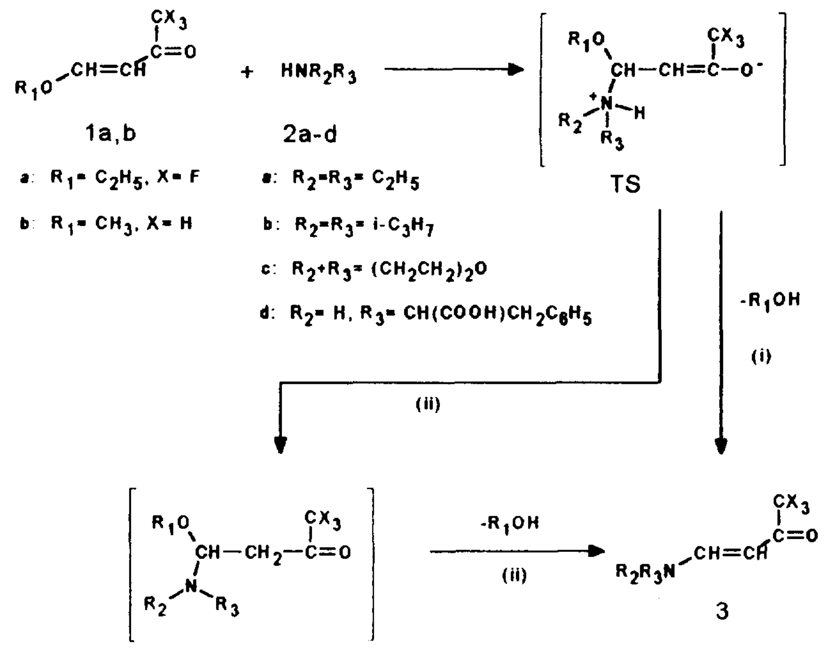

Scheme 1.

vinyl ketone reactivity based on reaction kinetics of (1) with amino-containing nucleophiles (2) (see Scheme 1). In all cases the reaction was carried out under pseudo-first order conditions [10-fold excess of (2)]. From the dependence of the pseudo-first order constant k on the nucleophile concentration the reaction has been determined to be of first order both for vinyl ketone and nucleophile. Real second order reaction constants calculated from pseudo-first order k are presented in Table 1. The reactant consumption and product accumulation kinetics were recorded virtually simultaneously by real time changes in the optical density of two UV bands. Preliminary experiments showed that (1a,b) do not interact with the solvents chosen, with exception of (1a) which reacted slowly with methanol ($k = 5.1 \times 10^{-6}$ l mol^{-1} s^{-1}). Reaction of (1) with (2) occurs smoothly in almost quantitative yield (more then 99%) giving the isosbestic point in appropriate spectra (see Fig. 1).

Substitution of CH_3 by CF_3 in (1) increases k by up to four orders of magnitude (in CH_3OH, Table 1). From a linear plot of ln k versus $1/\varepsilon$ (reciprocal dielectric constant of solvent) for (1a) (slope equals −8.45, Fig. 2) it follows that the mechanism of reaction does not change with solvent. For (1b) this dependence is more sophisticated depending on the solvent proton-donating ability: the slope for aprotic solvents equals −2.76, whereas that for alcohols is much greater at −27.94 [4]. The Kirkwood equation predicts that if reaction between neutral molecules is accompanied by generation of a polar intermediate (TS) an increase of k should be expected when solvent polarity rises [5]. According to kinetic data obtained for aprotic solvents, the polarity of the transition state increases when CH_3 is substituted by CF_3, owing to electron density redistribution along the system of conjugated bonds. Activation parameters listed in Table 1 demonstrate significant dependence on the C(2) substituent. Change from

Table 1
Kinetic and activation parameters [a] of reaction of β-alkoxylvinyl ketones (1) with nucleophiles (2)

Solvent	Reagents		k^{b} /l mol^{-1} s^{-1}	$\Delta G^{\ddagger}$ /kJ mol^{-1}	$\Delta H^{\ddagger}$ /kJ mol^{-1}	$\Delta S^{\ddagger}$ /J K^{-1} mol^{-1}
	(1)	(2)				
c-C_6H_{12}	a	a	6.46 ± 0.05	67.2 ± 2.1	17.7 ± 1.9	-168 ± 6
c-C_6H_{12}	b	a	$(3.46 \pm 0.05) \times 10^{-4}$	91.2 ± 1.9	37.5 ± 1.5	-183 ± 5
$C_2Cl_2H_4$	a	a	157.1 ± 0.7	59.4 ± 3.3	13.7 ± 0.3	-156 ± 1
$C_2Cl_2H_4$	b	a	$(1.50 \pm 0.02) \times 10^{-3}$	87.6 ± 1.7	35.6 ± 2.5	-177 ± 8
CH_3OH	a	a	$(4.86 \pm 0.16) \times 10^{2}$	–	–	–
CH_3OH	b	a	$(2.72 \pm 0.06) \times 10^{-2}$	80.5 ± 1.9	30.8 ± 1.7	-170 ± 6
c-C_6H_{12}	a	b	$(3.08 \pm 0.06) \times 10^{-2}$	98.8 ± 2.3	27.3 ± 1.2	-243 ± 7
c-C_6H_{12}	a	c	8.23 ± 0.06	66.6 ± 2.0	7.4 ± 1.9	-202 ± 6
DMSO	a	d	4.02 ± 0.41	86.9 ± 3.0	23.2 ± 2.8	-217 ± 10

[a] Temperature range 293–343 K.
[b] At 293 K.

(1a) to (1b) lowers the absolute values of the thermodynamic parameters in absolute values. The spatial and electronic structure of nucleophile (2) also plays an important role: steric hindrance enhancement [cf. (2a) and (2b)] raises $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in absolute value whereas the decrease of negative charge on nitrogen in (2c) compared with that in (2a) (pK 11.09 and 8.33, respectively [6]) lowers $\Delta H^{\ddagger}$ significantly and increases $\Delta S^{\ddagger}$. In the case of phenylalanine (2d) both factors are present, thus decreasing k abruptly [cf. 4.02 $\mathrm{l\ mol^{-1}\ s^{-1}}$ for (2a) and 188 $\mathrm{l\ mol^{-1}\ s^{-1}}$[1] for (2d) in DMSO]. In conclusion, it should be emphasized that substitution of CH_3 by a CF_3 group in β-alkoxyvinylmethyl ketone increases the rate constant by 4–5 orders in the reaction with nucleophiles (here with diethylamine). Kinetic and thermodynamic data obtained show significant differences of electron distribution in transition intermediates of compounds (1a) and (1b) with nucleophiles.

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[1] Calculated from the Kirkwood equation [5].