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Solvent influence on reaction mechanism of the nucleophilic substitution of β-substituted alkoxyvinyl trifluoromethyl ketones with piperidine

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Multiple linear regressions of solvent effects on reactivity of β-substituted β-alkoxyvinyl trifluoromethyl ketones $R^1O—CR^2=CH—COCF_3$ (1a, b) [(1a), $R^1=R^2=CH_3$; (1b), $R^1=C_2H_5$, $R^2=C(CH_3)_3$] with piperidine (2) [$(CH_2)_5NH$] in nine aprotic and six protic solvents were obtained. Values of ln *k* in dimethyl sulfoxide are out of the regression in view of electrophilic solvent catalysis. For 1a (*E-s-Z-o-Z*) and 1b (*Z-s-Z-o-Z*), single regressions were obtained for all studied solvents, whereas for 1b (*E-s-Z-o-Z*) and 1b (*E-s-Z-o-E*) protic and aprotic solvents form separate correlations. In the first two cases, the rate retardation due to nucleophile protonation by alcohols is compensated by the rate acceleration via electrophilic solvent assistance whereas in the second two cases the rate retardation predominates and protic solvents form separate correlations with Reichardt's solvent parameter E_T^N. Hence, in those cases the reaction rate depends mostly on the solvent's hydrogen-bond donor (HBD) acidity (α). The poor proton-donating ability of enones 1a, b accounts for the negligible effect of solvent's basicity (β) on the reaction rate. For systems for which a single regression is observed, the main influence on the reaction rates comes from the solvent's dipolarity/polarizability (π*).

Keywords: multiple linear regression; nucleophilic substitution; β-substituted alkoxyvinyl trifluoromethyl ketones

INTRODUCTION

It has been long recognized[1] that solvents often affect chemical reactivity, this involving, for example, shifts of the position of chemical equilibria (thermodynamic aspect) as well as significant changes in reaction rate constants (kinetic aspect).

For many years, most studies of solvent effect on reaction rates were limited to simple correlations of rate constants (as log *k*) with some particular solvent parameters, such as dielectric constants (ε_r), dipole moments (μ), viscosities (η), solubility parameters (δ), and spectroscopically determined parameters such as *Z* and E_T (empirical parameters considered to reflect solvent polarity, acidity, basicity, etc.). Several reviews on this subject have been published.[1–4]

In general, solvent properties can be divided into acidity, basicity, and polarity; of these, solvent polarity has attracted the most attention and is the most difficult to deal with.[5] According to Reichardt's determination of solvent polarity, it is determined by the solvent's solvation capability (or solvation power) for reactants and activated complexes as well as for molecules in their ground and excited states. This in turn depends on the action of all possible, specific, and nonspecific, intermolecular forces between solvent and solute molecules. Only those interactions leading to definite chemical alterations of the solute molecules through protonation, oxidation, reduction, complex formation, or other chemical processes are excluded.[1]

It is obvious that there is no single solvent parameter that will satisfactorily correlate log *k* values for a variety of different reactions.[6] Therefore, multiple linear regression is a versatile procedure, especially for interpreting solvent effects.[1,7,8] Kamlet, Abboud, and Taft (KAT) developed a new generalized relationship for studying linear free-energy relationships (LFER) of solute/solvent interactions.[9] Termed the linear solvation energy relationship (LSER), it has the form:

$$\begin{aligned}\text{Solute property} = {} & \text{solvent dipolarity/polarizability} \\ & + \text{solvent hydrogen} - \text{bond acidity} \\ & + \text{solvent hydrogen} - \text{bond basicity} \\ & + \text{solvent bulk/cavity formation} \end{aligned} \quad (1)$$

When the KAT Eqn (1) is applied to a given reaction in a number of solvents, Eqn (1) takes form (2):

$$\ln k = \ln k_0 + s\pi^* + a\alpha + b\beta + h\delta_H^2 \quad (2)$$

in which logarithms of rate constants (*k*) are related to the following solvent properties: solvent's dipolarity/polarizability (π^*), hydrogen-bond donor (HBD) acidity or electrophilicity (α), H-bond acceptor basicity or nucleophilicity (β), and the Hildebrand solubility parameter (δ_H^2). Multiple linear regression gives optimized values of the coefficients *s*, *a*, *b*, and *h*, as well as

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for the intercept ln k_0 term, which refers to the reaction in cyclohexane ($\pi^* = \alpha = \beta = 0.00$), if δ_H^2 is excluded.

Earlier[10] we investigated the solvent influence on reaction of β-ethoxyvinyl α-trifluoromethyl ketones with diethylamine in six aprotic and four protic solvents and revealed that ln k gives good correlations with $1/\varepsilon_r$ (ε_r = relative permittivity of a solvent). This fact enabled us to conclude that this reaction occurs through the formation of a highly dipolar activated complex, which is stabilized by polar solvents. Continuing the study of solvent influence on the reaction mechanism of nucleophilic substitutions of β-substituted alkoxyvinyl trifluoromethyl ketones with secondary amines, we chose two β-substituted trifluoromethyl ketones, namely (3*E*)-1,1,1-trifluoro-4-methoxy-pent-3-en-2-one (**1a**) and (3*E*,*Z*)-1,1,1-trifluoro-4-ethoxy-5,5-dimethylhex-3-en-2-one (**1b**) as model substrates of the reaction with the secondary amine piperidine, having a high pK_a (11.1) and a relatively small bulkiness.[11]

EXPERIMENTAL

Materials

(3*E*)-1,1,1-Trifluoro-4-methoxy-pent-3-en-2-one (**1a**) and (3*E*,*Z*)-1,1,1-trifluoro-4-ethoxy-5,5-dimethylhex-3-en-2-one (**1b**) were synthesized as described earlier[11] and stored under dry N_2. Compound **1a** exists presumably as (*E*)-isomer [91–92% of the (*E-s-Z-o-Z*) form and 8–9% of the (*E-s-Z-o-E*) form],[12] whereas compound **1b** consists of the (*E*)-isomer [26–46% of the (*E-s-Z-o*-Z) conformer] and the (*Z*)-isomer [54–74% of the (*Z-s-Z-o-Z*) conformer, depending on the solvent used],[12] as in Fig. 1.

The solvents used were analytically pure (Aldrich) and were further purified by published methods,[13] stored under N_2, and distilled prior to use. Piperidine was purified by standard method and stored under N_2 in darkness.

Kinetic measurements

Kinetic measurements were carried out under pseudo-first-order conditions by adding 10 μl of a 10^{-2} M (if not stated otherwise, refer footnote for Table 1) solution of the substrate (**1a,b**) to 2 ml of the piperidine solution in thermostated 1.0 cm quartz cells (Hellma) at a temperature of 25°C (with accuracy ±0.2°C). The kinetic measurements were followed by UV–Vis spectrophotometry at fixed wavelengths (λ = 303–332 nm, depending on the product absorption). The product accumulation kinetics was recorded by registration of the optical density changes at the analytical wavelength. All kinetic runs were followed at least for three to four half-lives. The reaction rate constants were calculated by the Guggenheim method using

$$\ln(D_{t+\Delta t} - D_t) = -kt + \ln(D_\infty - D_0)(1 - e^{-k\Delta t}) \quad (3)$$

where D_0 is the initial optical density of the substrate, D_t and $D_{t+\Delta t}$ are the optical densities of the product at time t and $(t + \Delta t)$, respectively (Δt being a constant time increment), D_∞ is the final optical density of product, and k is the rate constant. Equation (2) describes a straight line whose slope yields the rate constant k. Guggenheim's method was selected as more reliable[11] in comparison with the traditional 'infinity' method. The observed second-order coefficients (k_{obsd}) were obtained by dividing the pseudo-first-order coefficients by the amine concentration.

The investigated systems possess some peculiarities. Firstly, in many cases (as in Table 1) the observed second-order constant k_{obsd} increases linearly with the increase in amine concentration according to

$$k_{obsd} = k' + k''[\text{Piperidine}] \quad (4)$$

In systems where k_{obsd} is independent of the amine concentration, the second-order rate constants were determined as the average of at least 10 experiments. Secondly, β-substituted alkoxyvinyl trifluoromethyl ketones form various stereoisomeric forms due to the hindered rotation around the C=C double bond, C_{sp^2}—C_{sp^3} single bond, and the C_{sp^2}—O single bond.[11,12] To elucidate the labeling of the existing stereoisomers of the enones studied (Fig. 1), we denote the C=C double bond configuration of **1a,b** with the first capital letter (*E*) or (*Z*). The conformational possibilities of **1a,b** are given by the hindered rotation of the trifluoroacetyl group around the C_{sp^2}—C_{sp^3} single bond with the carbonyl group oriented away or toward the double C=C bond. This orientation is denoted by the second capital letter (-*s-E*) or (-*s-Z*), respectively. In a similar manner, we denote the conformers due to rotation of the alkoxy group. Thus, the third capital letter (-*o-E*) or (-*o-Z*) stands for the *cis*- or *trans*-orientation of that group relative to the C=C double bond.

It is known[12] that enone **1a** in aprotic solvents exists presumably as the (*E-s-Z-o-Z*) stereoisomer (Fig. 1) with a percentage of 91% (in *n*-hexane) and 92% (in acetonitrile),

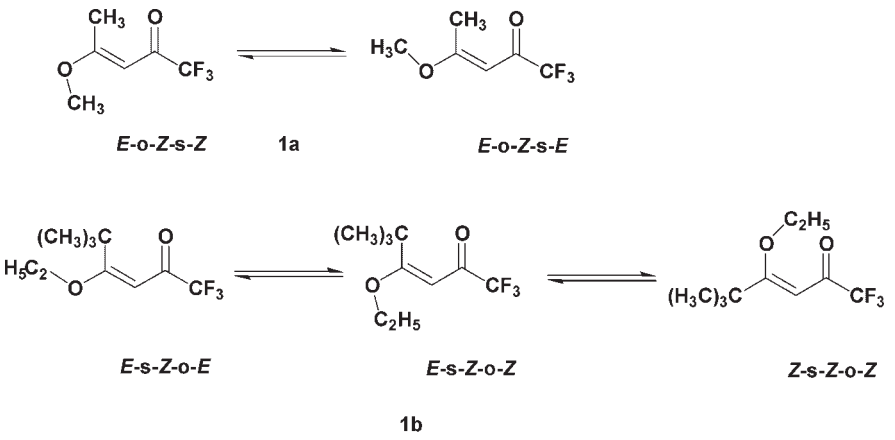

Figure 1. Existing conformations of the enones **1a,b** in solvents of different polarity (according to Reference [12])

Table 1. Kinetic data for the reaction of the enones (**1a,b**) with piperidine (**2**) at 25°C

Enone	Solvent	Concentration of amine (M)[a]	Stereoisomeric form	'Uncatalyzed' process[b] (k')	'Catalyzed' process[cd] (k'')
1a[e]	*n*-Hexane	$(1–8) \times 10^{-3}$	*E-s-Z-o-Z*	1.04×10^{-1}	0.00
	c-Hexane	$(1–8) \times 10^{-3}$	*E-s-Z-o-Z*	1.31×10^{-1}	0.00
	Di-*n*-butyl ether	$(1–8) \times 10^{-3}$	*E-s-Z-o-Z*	2.75×10^{-1}	0.00
	1,4-Dioxane	$(1–8) \times 10^{-3}$	*E-s-Z-o-Z*	7.15×10^{-1}	31.16
	Tetrahydrofuran	$(1–8) \times 10^{-3}$	*E-s-Z-o-Z*	9.51×10^{-1}	0.00
	Ethyl acetate	$(0.5–4.5) \times 10^{-3}$	*E-s-Z-o-Z*	8.41×10^{-1}	33.59
	Acetonitrile	$(0.5–1.15) \times 10^{-3}$	*E-s-Z-o-Z*	3.79	783.50
	N,N-Dimethyl acetamide	$(0.5–1.0) \times 10^{-3}$	*E-s-Z-o-Z*	3.99	852.63
	Dimethyl sulfoxide	$(0.5–1.0) \times 10^{-3}$	*E-s-Z-o-Z*	21.59	0.00
	Acetonitrile + dimethyl sulfoxide	$(0–1) \times 10^{-2}$[f]	*E-s-Z-o-Z*	3.71	15.70
	t-Butanol	$(1–4.5) \times 10^{-3}$	*E-s-Z-o-Z*	1.51	0.00
	n-Butanol	$(0.5–4) \times 10^{-3}$	*E-s-Z-o-Z*	1.56	0.00
	i-Propanol	$(0.5–4) \times 10^{-3}$	*E-s-Z-o-Z*	1.75	0.00
	n-Propanol	$(0.5–3) \times 10^{-3}$	*E-s-Z-o-Z*	2.04	0.00
	Ethanol	$(0.8–1.5) \times 10^{-3}$	*E-s-Z-o-Z*	1.54	0.00
	Methanol	$(0.8–1.5) \times 10^{-3}$	*E-s-Z-o-Z*	1.19	0.00
			E-s-Z-o-E	0.02	449.64
1b	*n*-Hexane	0.5–1.0	*Z-s-Z-o-Z*	1.93×10^{-3}	7.58×10^{-4}
		0.5–1.0	*E-s-Z-o-Z*	3.08×10^{-4}	1.40×10^{-4}
	c-Hexane	0.2–0.8	*Z-s-Z-o-Z*	2.33×10^{-3}	8.80×10^{-4}
		0.2–0.8	*E-s-Z-o-Z*	2.77×10^{-4}	0.00
	Di-*n*-butyl ether	0.1–0.8	*Z-s-Z-o-Z*	6.08×10^{-3}	0.00
		0.1–0.8	*E-s-Z-o-Z*	4.09×10^{-4}	0.00
	1,4-Dioxane	0.1–0.8	*Z-s-Z-o-Z*	1.33×10^{-2}	1.72×10^{-4}
		0.1–0.8	*E-s-Z-o-Z*	1.01×10^{-3}	0.00
	Ethyl acetate	0.05–0.3	*Z-s-Z-o-Z*	1.55×10^{-2}	7.02×10^{-3}
		0.05–0.3	*E-s-Z-o-Z*	9.59×10^{-4}	0.00
	Methanol	0.05–0.4	*Z-s-Z-o-Z*	6.69×10^{-3}	-6.15×10^{-3}
		0.05–0.4	*E-s-Z-o-E*	0.00	4.58×10^{-3}
		0.05–0.4	*E-s-Z-o-Z*	6.77×10^{-4}	7.96×10^{-3}
	Ethanol	0.10–0.45	*Z-s-Z-o-Z*	3.64×10^{-3}	-2.33×10^{-3}
		0.10–0.45	*E-s-Z-o-E*	0.00	5.20×10^{-3}
		0.10–0.45	*E-s-Z-o-Z*	9.13×10^{-4}	-9.06×10^{-4}
	i-Propanol	0.15–0.50	*Z-s-Z-o-Z*	3.66×10^{-3}	-4.70×10^{-3}
		0.15–0.50	*E-s-Z-o-E*	3.20×10^{-4}	5.574×10^{-3}
		0.15–0.50	*E-s-Z-o-Z*	1.29×10^{-3}	-1.29×10^{-4}
	n-Butanol	0.20–0.50	*Z-s-Z-o-Z*	4.09×10^{-3}	-5.62×10^{-3}
		0.20–0.50	*E-s-Z-o-E*	5.53×10^{-6}	5.16×10^{-3}
		0.20–0.50	*E-s-Z-o-Z*	1.06×10^{-3}	2.40×10^{-3}
	t-Butanol	0.20–0.50	*Z-s-Z-o-Z*	2.09×10^{-3}	-1.87×10^{-3}
		0.20–0.50	*E-s-Z-o-E*	7.94×10^{-4}	6.16×10^{-3}
		0.20–0.50	*E-s-Z-o-Z*	1.92×10^{-3}	-5.89×10^{-4}
	n-Propanol	0.20–0.45	*Z-s-Z-o-Z*	4.40×10^{-3}	-4.86×10^{-3}
		0.20–0.45	*E-s-Z-o-E*	1.08×10^{-4}	5.25×10^{-3}
		0.15–0.45	*E-s-Z-o-Z*	1.04×10^{-3}	2.46×10^{-3}
	Acetonitrile	0.05–0.12	*Z-s-Z-o-Z*	3.51×10^{-2}	9.92×10^{-2}
		0.05–0.12	*E-s-Z-o-Z*	7.23×10^{-3}	-7.33×10^{-3}
	N,N-Dimethyl acetamide	0.04–0.10	*Z-s-Z-o-Z*	7.39×10^{-2}	7.22×10^{-2}
		0.04–0.10	*E-s-Z-o-Z*	7.25×10^{-3}	0.00
	Dimethyl sulfoxide	0.01–0.07	*Z-s-Z-o-Z*	6.57×10^{-2}	0.371
		0.01–0.07	*E-s-Z-o-Z*	5.76×10^{-2}	−0.620

[a] Concentration range of the amine used for establishing the second-order kinetics.
[b] $L\,mol^{-1}\,s^{-1}$.
[c] $L^2\,mol^{-2}\,s^{-1}$.
[d] Negative values are due to adding of the less polar **2** to more polar solvents.[11]
[e] Enone concentration is 1×10^{-4} M.
[f] Concentration of dimethyl sulfoxide in acetonitrile; piperidine concentration is fixed, 5.5×10^{-4} M.

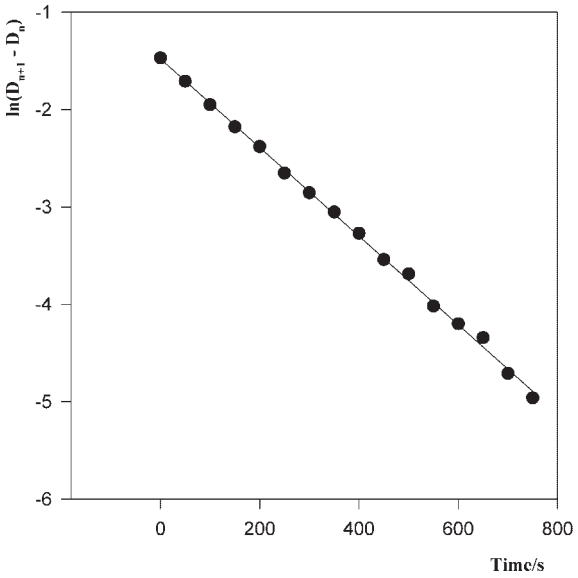

Figure 2. Kinetics of the reaction of **1a** with piperidine **2** ($c = 1.01 \times 10^{-3}$ M) in acetonitrile at 25°C

whereas the (*E-s-Z-o-E*) form has only 9 and 8%, respectively. According to Eqn (4), the kinetic curve is a straight line the slope of which gives k_{obsd}(*E-s-Z-o-Z*) (as in Fig. 2). In alcohols, the percentage of the (*E-s-Z-o-E*) form of **1a** increases slightly (10–12%), but in methanol the percentage of the (*E-s-Z-o-E*) conformer increases significantly (up to 40%, evaluated from the intensities of the $\tilde{\nu}$ (C═O) band in the IR spectra of **1a** in methanol). Correspondingly, the kinetic curve of the reaction of **1a** with **2** in methanol consists of two straight-line sections: the slope of line I (Fig. 3) is the sum of the rate coefficients of the (*E-s-Z-o-Z*) and the (*E-s-Z-o-E*) form. The difficulty is to determine to which conformer, (*E-s-Z-o-Z*) or (*E-s-Z-o-E*), belongs the slope of line II. As it follows from our previous investigations,[11]

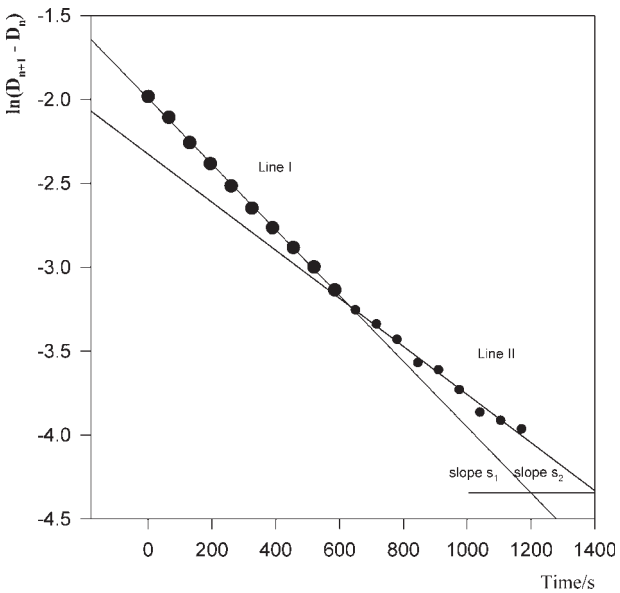

Figure 3. Kinetics of the reaction of **1a** with piperidine ($c = 1.27 \times 10^{-3}$ M) in methanol at 25°C: slope $s_1 = k_{obsd}$ (*E-s-Z-o-Z*) + k_{obsd}(*E-s-Z-o-E*); slope $s_2 = k_{obsd}$(*E-s-Z-o-Z*)

the intermediate **3a** (Scheme 1) of the (*E-s-Z-o-Z*) form decomposes presumably via an 'uncatalized' route, whereas for the (*E-s-Z-o-E*) conformer the 'catalyzed' route predominates. The rate constant k_{obsd} obtained from the slope of line II does not depend on the piperidine concentration ($k' = 1.19$, $k'' = 0.00$; Table 1). Hence, that slope we attribute to the rate coefficient of the (*E-s-Z-o-Z*) form. The rate coefficient of the (*E-s-Z-o-E*) conformer is the difference between the slopes of lines I and II and depends strongly on the piperidine concentration ($k' = 0.02$, $k'' = 450$). Hence, in this case the 'catalyzed' route dominates. The ratio k_{obsd}(*E-s-Z-o-Z*)/k_{obsd}(*E-s-Z-o-E*) is 2.53 (in methanol at [**2**] $= 1 \times 10^{-3}$ M), thus indicating that the (*E-s-Z-o-Z*) conformer is more reactive than the (*E-s-Z-o-E*) form.

Earlier,[12] we showed that in aprotic solvents there exist two stereoisomeric forms of the enone **1b**, namely the (*Z-s-Z-o-Z*) and the (*E-s-Z-o-Z*) conformers. The corresponding kinetic curve consists of two straight-line sections from which we can evaluate the individual rate constants for each isomer. In previous work,[12] we concluded that in systems with multiple stereoisomeric forms the rate coefficient of each configuration (k_i) can be evaluated from

$$k_i = \sum_{1}^{i} k - \sum_{1}^{i-1} k \qquad (5)$$

In alcohols, additional $\tilde{\nu}$ (C═O) and $\tilde{\nu}$ (C═C) bands appear in the region of double bond vibrations in the IR spectra of **1b**. On the basis of the $\Delta\tilde{\nu}$ criteria[12] [$\Delta\tilde{\nu} = \tilde{\nu}$(C═O) − $\tilde{\nu}$(C═C)], we attribute these bands to the (*E-s-Z-o-E*) conformer. Accordingly, a third straight-line section appears on the kinetic curve (not shown). Using Eqn (5), we estimated all three rate constants k_{obsd} and attributed them to separate stereoisomeric forms in the following way. First, it is known[11] that the (*Z*)-isomers are more reactive in comparison to the (*E*)-isomers. Therefore, we attributed the largest k_{obsd} to the (*Z-s-Z-o-Z*) form. Here again we had to decide to which conformer belongs each residuary rate constant. We ascribe the rate constant which is independent of the piperidine concentration to the (*E-s-Z-o-Z*) conformer. The rate constant k_{obsd}, strongly dependent on the piperidine concentration, is attributed to the (*E-s-Z-o-E*) conformer. The ratio k_{obsd}(*E-s-Z-o-Z*)/k_{obsd}(*E-s-Z-o-E*) is 3.20 (in methanol at [**2**] = 0.1 M) close to that obtained for the respective conformers of the enone **1a** (*vide supra*). It should be emphasized that the enones **1a, b** do not react with alcohols at all or react only very slowly (e.g., the reaction of **1a** with methanol endured several days at ambient temperature).

Since the reaction rates of the enones **1a, b** depend strongly on the medium polarity (*vide infra*), addition of less polar piperidine to highly polar solvents such as alcohols, acetonitrile, etc., decreases the relative permittivity of the solution, thus reducing k_{obsd}. At high amine concentrations, the apparent k'' values can be even negative provided the true value is close to zero.[11] Negative k'' values were observed earlier[11] for the reaction of various β-substituted alkoxyvinyl trifluoromethyl ketones with secondary amines at high concentrations. The same trend is found for the reaction of 1,1,2-tricyano-2-(4-dimethylaminophenyl)ethene with piperidine.[18] In Table 1, all these apparent k'' values are enclosed in brackets. It should be noted that at the piperidine concentrations lower than that in Table 1 the reaction of the enone **1b** with **2** is too slow to be followed. Therefore, we were not able to investigate the reactions at lower amine concentrations.

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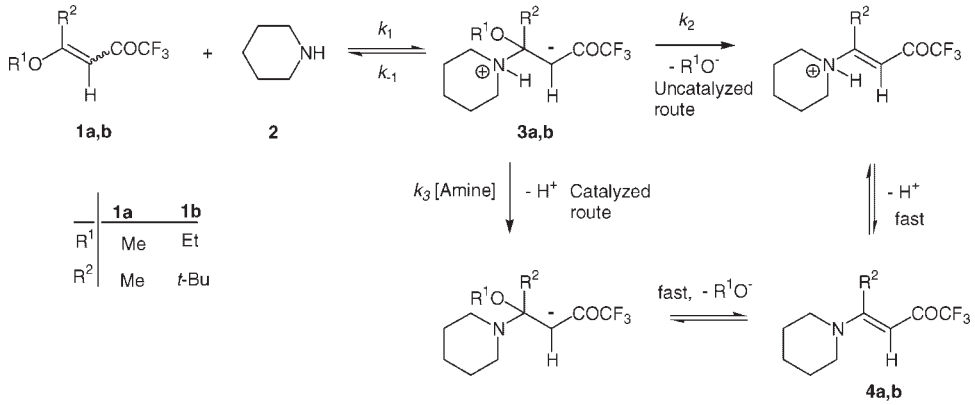
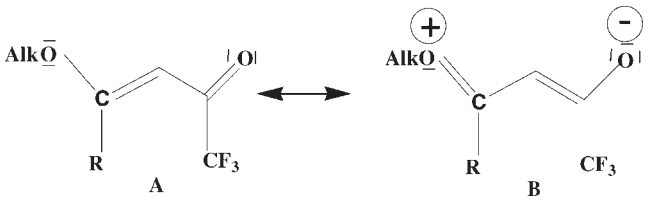


Scheme 1. Mechanism of the reaction of the alkoxyvinyl trifluoromethyl ketones **1a,b** with piperidine **2**

Recently,[11] we have shown that during all kinetic measurements we did not observe any changes in the band shape of products (**4**) in their UV-spectra which contained only one isobestic point. Bluntly speaking, no (*E*) ⇌ (*Z*) isomerization of enaminones **4** was observed during the reaction. In other words, the (*E*)/(*Z*) ratio is established at the moment of product formation.[11] In β-ethoxy vinyl ketone, the barrier of hindered rotation around the C_{sp^2}—O bond, which has significant partial double bond character due to the conjugation between the π electrons of the alternating double bonds and the lone pairs of the oxygen atom, was estimated[16] as large as to 8.2 kcal/mol. In the fluorinated enones **1a, b**, this barrier should be even higher due to the increased contribution of resonance structure **B**. Therefore, at ambient temperature the equilibrium *E-s-Z-o-Z* ⇌ *E-s-Z-o-E* establishes only very slowly.



In view of the fact that the investigated reaction proceeds through decomposition of the highly dipolar zwitterionic intermediate **3** (Scheme 1), which occurs presumably via an 'uncatalyzed' route[10] (i.e., $k' \gg k''$[piperidine]), we used the intercepts k' for the multiple regression (Eqn (1)). Exceptions are the system (**1a** + **2**) in methanol and (**1b** + **2**) in studied alcohols, where the decomposition of **3** through the 'catalyzed' route dominates. For this reason, we used in these cases ln k'' in the KAT correlations. The solvatochromic parameters and the Hildebrand solubility parameters δ_H used for multiple linear regressions were taken from reviews.[14,15]

RESULTS AND DISCUSSION

As it was mentioned before that in some cases k_{obsd} depends on the piperidine concentration, pointing out a complex dependence of k_{obsd} on the rate constants of elementary reaction steps.[17] Steady-state treatment of Scheme 1 gave Eqn (6) for the observed second-order rate constant ([A] – amine concentration)[16] according to which $k_{obsd} = k_1$ when $k_{-1} < (k_2 + k_3[A])$, and the reaction is overall second order. When the 'uncatalyzed' reaction is faster than the 'catalyzed' reaction but slower than the reverse reaction, that is,

$$k_{obsd} = \frac{k_1(k_2 + k_3[A])}{k_{-1} + k_2 + k_3[A]} \quad (6)$$

$k_{-1} \gg k_2 \gg k_3[A]$, k_{obsd} is a composite but is still a second-order constant:

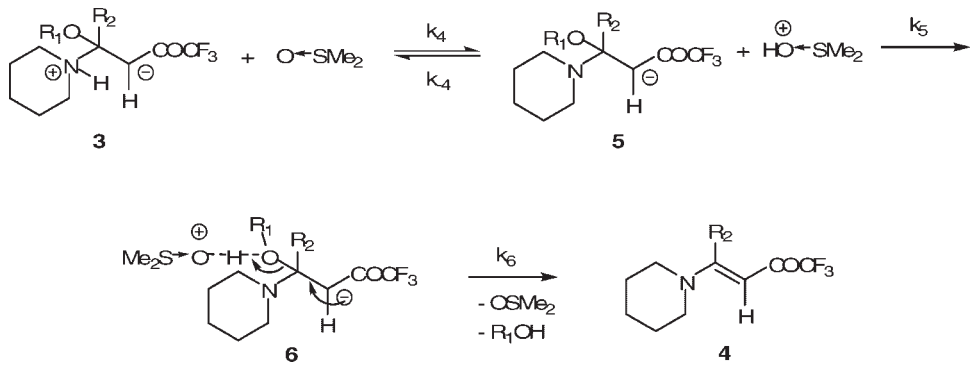
$$k_{obsd} = k_1 k_2 / k_{-1} \quad (7)$$

For the 'catalyzed' reaction, when $k_{-1} \gg (k_2 + k_3[A])$, k_{obsd} is given by the sum of the second- and third-order terms and it increases linearly with the increase of the amine concentration:

$$k_{obsd} = (k_1 k_2 / k_{-1}) + (k_1 k_3 / k_{-1})[A] \quad (8)$$

In this case, the reaction follows two competing routs: an 'uncatalyzed' route whose rate constant k' is given by k_1k_2/k_{-1}, and a 'catalyzed' route whose constant k'' is given by k_1k_3/k_{-1}. Hence, the k''/k' values are identical with the k_3/k_2 ratios and this ratio is a measure of the relative importance of the two routes starting from a common intermediate (Scheme 1). In previous work,[10,11] we showed that the last is the case for alkoxyvinyl trifluoromethyl ketones in reaction with secondary amines. As it follows from Table 1 for the system (**1a** + **2**) in apolar solvents, k'' is near zero (and ratio $k''/k' = 0$), whereas in polar solvents k'' increases and the ratio k''/k' becomes significant (e.g., $k''/k' = 214$ in *N,N*-dimethylacetamide). For comparison, the ratio k''/k' for the reaction of 1,1-dicyano-2-(4-dimethylaminophenyl)-2-trifluoroethoxyethene with the piperidine equals to 514 (in acetonitrile at 30°C).[17]

Nevertheless, in highly polar dimethyl sulfoxide as solvent the rate constant of the 'catalyzed' process, k'', is unexpectedly equal to zero, thus indicating the absence of a 'catalyzed' route for the decomposition of the intermediate **3**. Since there are no signs of a reaction of enones **1a, b** with dimethyl sulfoxide, we assumed that the DMSO molecule participates in the reaction as catalyst (as in Scheme 1). In additional experiments, we revealed a concentration dependence of the rate constant k_{obsd} on the DMSO concentration in acetonitrile (at fixed concentrations of the enone **1a** and piperidine **2**, refer footnote of Table 1). Thus, we obtained a dependence of $k_{obsd} = 3.71 + 15.70 \times$ [DMSO] for which $k''/k' = 4.23$, indicating the presence of DMSO catalysis. The concentration of dimethyl sulfoxide in this system is too small to raise the overall polarity.[11] Hence, in this system a molecule of DMSO participates in the reaction withdrawing a proton from the ammonium moiety and transferring it to the alkoxy group. In other words, in this mixed solvent (acetonitrile + DMSO) an electrophilic catalysis via a specific base-general acid catalysis



Scheme 2. Mechanism of the electrophilic catalysis of the reaction of **1a,b** with **2** by dipolar dimethyl sulfoxide

(Scheme 2, transition state **6**) occurs and $k_{obsd} = k_1k_2/k_{-1} + k_1k_4k_5[DMSO]/k_{-1}k_{-4}$, whereas in pure dimethyl sulfoxide the catalyzed process becomes so fast that $k_{-1} < (k_2 + k_4k_5[DMSO])$ and the reaction becomes of an overall second order, and $k_{obsd} = k_1$.

The observed rate constants of the overall reaction (**1a** + **2**) in protic polar solvents (alcohols) is presented exclusively by the reaction rate of an 'uncatalyzed' process [for the (*E-s-Z-o-Z*) conformer], Eqn (7). In protic solvents, it should be taken into consideration an interaction of the solvent molecules not only with piperidine but with the enone too. The H-bonds between the alcohol molecules and piperidine apparently reduce k_1 (due to reduction of the piperidine nucleophilicity) more than they affect k_{-1} and k_2 in $k_{obsd} = k_1k_2/k_{-1}$. On the other hand, H-bonds between solvent and enone (electrophilic solvent assistance) lead to the expulsion of the nucleofuge (via structure **7**, Fig. 4) thus increasing k_2. The overall result depends on the concurrent effects of these two processes. In *t*-butanol, *n*-butanol, *i*-propanol, and *n*-propanol these effects mutually compensate one another, whereas in methanol and ethanol the reduction of the piperidine nucleophilicity prevails over the effect of electrophilic solvent assistance (*vide infra*). Moreover, as stated before the percentage of the (*E-s-Z-o-E*) conformer increases significantly in methanol, enabling us to estimate rate constants of the 'uncatalized' and 'catalyzed' processes for this conformer. It can be easily seen from Table 1 that $k'' \gg k'$ (ratio $k''/k' = 2.25 \times 10^4$), indicating that the reaction occurs almost completely through the 'catalyzed' route.

For the (*E-s-Z-o-Z*) conformer of **1a**, we find a good correlation of ln k' with the solvatochromic parameters of KAT (excepting dimethyl sulfoxide, ethanol, and methanol):

$$\ln k' = (-2.56 \pm 0.30) + (3.57 \pm 0.40)\pi^* + (0.97 \pm 0.29)\alpha - (0.32 \pm 0.35)\beta + (0.73 \pm 0.42)\delta_H^2$$
$$R = 0.992,\ SE = 0.194,\ F(4,7) = 102.88 \quad (9)$$

The largest contribution to this regression makes π^*, and this conclusion is in agreement with results obtained earlier.[10] The sensitivity of **1a**, (*E-s-Z-o-Z*) to α is positive and moderately high, whereas the coefficient *b* for β is negative and close to zero (with regard to standard error of estimation 0.35). In dimethyl sulfoxide, the experimental value of a rate constant of an 'uncatalyzed' process ($k' = 21.59$) is much higher than the value calculated with Eqn (9) (*viz.* 6.17), so the excessive k' value is the consequence of the rate acceleration via an electrophilic catalysis (*vide supra*). On the other hand, k' obtained for ethanol and methanol are also out of the correlation, but these k' values are smaller than the ones calculated with Eqn (9) (*cf.* 1.54 and 3.19 in ethanol; 1.19 and 6.11 in methanol, respectively). The evident rate retardation with decreasing alcohol pK_a we explained by the sharp decrease of k_1 with slight k_2 increase in Eqn (7). Therefore, the overall k_{obsd} lowers abruptly in ethanol and methanol as compared with other alcohols. Moreover, in the highly 'acidic' trifluoroethanol the enones **1a, b** do not react with the amine **2** at all.

The influence of H-bonding between the piperidine and the alcohols is more pronounced in the system (**1b** + **2**), where protic solvents give separate correlations for the conformers (*E-s-Z-o-Z*) and (*E-s-Z-o-E*). The E_T^N scale for alcoholic solvents measures primarily their HBD acidity,[5,19] therefore we correlated ln k' with Reichardt's solvatochromic parameter[1] E_T^N. From Fig. 5 and Eqn (10), it follows that

$$\ln k' = -2.82\,E_T^N - 5.14 \qquad R^2 = 0.997 \quad (10)$$

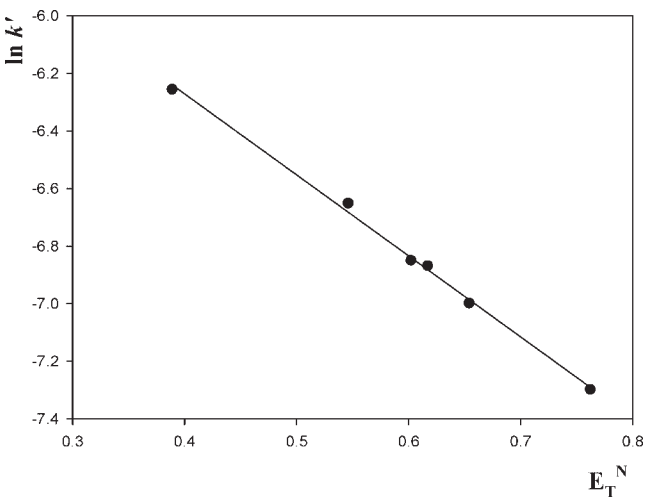


Figure 5. Plot of ln k' *versus* $E_T^N(30)$ for the (*E-s-Z-o-Z*) conformer of enone **1b**.

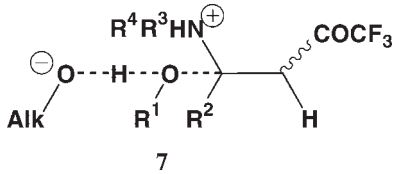


Figure 4. Molecular structure of the intermediate **7**

The slope of the correlation is negative, thus revealing the dominating role of the nucleophilicity decrease in the process due to the formation of H-bonds between **2** and the alcohols. In other words, here again the increase in k_2 does not compensate the k_1 retardation.

As it was mentioned in the Experimental part that in all protic solvents the (*E-s-Z-o-E*) conformer of **1b** appears in a quantity which is sufficient for a k_{obsd} estimation. It is worth to note that the decomposition of intermediate **3** occurs presumably via a 'catalyzed' process: k''/k' changes from 10 for *t*-butanol to $+\infty$ for methanol and ethanol. According to data of Rappoport (as in References [17,18] and references therein) for reactions of various substituted ethenes with amines a genuine base catalysis is present when $k''/k' \geq 5$. Similarly to k' of **1b** (*E-s-Z-o-Z*), the rate constant k'' of **1b** (*E-s-Z-o-E*) decreases with the increase of solvent HBD acidity, therefore we correlated ln k'' with E_T^N, according to

$$\ln k'' = -0.77\, E_T^N(30) - 4.78 \qquad R^2 = 0.963 \tag{11}$$

It is clear from this correlation the slope of which is negative that there is a partial compensation between k_1, k_{-1}, and k_3; the increase in solvent acidity stimulates the k_1 retardation in greater extent than the acceleration of k_3 and k_{-1}.

For the (*E-s-Z-o-Z*) form of **1b**, the multiple regression according to Eqn (12) is insignificant, as standard errors of the regression coefficients are too high, making it difficult to interpret this correlation.

$$\ln k' = (-7.61 \pm 21.63) + (6.18 \pm 114.80)\pi^* + (1.34 \pm 6.03)\alpha - (8.44 \pm 10.06)\beta - (2.06 \pm 2.21)\delta_H^2 \quad R = 0.960,\ \mathrm{SE} = 0.22,\ F(4,1) = 2.90 \tag{12}$$

Therefore, we excluded dimethyl sulfoxide (in view of the electrophilic catalysis as it was stated before) and acetonitrile (possessing $\alpha > 0$) from the consideration and obtained then a good multiple regression, according to

$$\log k' = (-5.58 \pm 1.23) + (4.23 \pm 1.13)\pi^* + (1.91 \pm 1.12)\beta - (4.07 \pm 1.89)\delta_H^2 \qquad R = 0.987,\ \mathrm{SE} = 0.30,\ F(3,2) = 30.17 \tag{13}$$

It is evident that π^* exerts the largest influence on reaction rate k'. The coefficient *b* is slightly positive, but taking into account the standard error it is clear that its influence on k' is minimal.

A multiple linear regression for the (*E*)-isomer of **1b** [*viz.* the (*Z-s-Z-o-Z*) conformer] joins together the data for protic and aprotic solvents, according to

$$\ln k' = (-6.16 \pm 0.22) + (3.67 \pm 0.47)\pi^* - (1.40 \pm 0.34)\alpha - (0.34 \pm 0.39)\beta - (0.19 \pm 0.30)\delta_H^2 \qquad R = 0.992,\ \mathrm{SE} = 0.20,\ F(4,8) = 113.48 \tag{14}$$

A repulsion between the OEt and carbonyl C═O group in the (*Z-s-Z-o-Z*) conformer of **1b** promotes the expulsion of the nucleofuge, [11] thus increasing noticeably k_2 which compensates the decrease in k_1. As a consequence, the influence of α on rate constant is relatively small. At the same time, the sensitivity of ln k' to solvent electrophilicity (β) is negligible and both protic and aprotic solvents give a single regression, in which the largest contribution makes π^*. A comparison of Eqns (9) and (14) demonstrates that in both cases, **1a** (*E-s-Z-o-Z*) and **1b** (*Z-s-Z-o-Z*), the maximal influence on the reaction rate has π^*. The coefficients *a* of the α are almost equal, but opposite in sign: in Eqn (9) *a* is positive (+0.97) whereas in Eqn (14) this coefficient is negative (−1.40). We suppose that this is the consequence of a difference in steric factors in these conformers. The (*E-s-Z-o-Z*) stereoisomeric form is more preferable as compared with the (*Z-s-Z-o-Z*) form for H-bond formation between the enone and protic solvent: H-bonding increases the partial positive charge on C_β, which raises the electrophilicity of the enone[10] and, hence, increases k_1. The negligible effect of the solvent's basicity on the reaction rate in all cases (Eqns (9), (13), and (14)) is evidence of the small proton-donating ability (presumably C_α—H) of the enones **1a, b**.

In conclusion, we can state that the largest solvent influence on the rate constant has π^* whereas β has only a negligible effect. In highly polar solvents like dimethyl sulfoxide, electrophilic catalysis via specific base-general acid catalysis accelerates the reaction additionally, changing the reaction mechanism. An overall influence of the acidity of protic solvents on the reaction rate depends on the interactions with both the substrate (enone) and the amine. H-bonding of protic solvents with amine reduces its nucleophilicity, thus lowering the rate of the preequilibrium attack k_1, whereas H-bonding with the carbonyl group and alkoxy group (via intermediate **7**) increases k_1 and k_2 (with the aid of electrophilic solvent assistance). For **1a** (*E-s-Z-o-Z*) and **1b** (*Z-s-Z-o-Z*), these effects compensate one another, while for **1b** (*E-s-Z-o-Z*) and the **1b** (*E-s-Z-o-E*) the influence of the amine nucleophilicity reduction predominates, and the reaction rate depends mostly on the α of protic solvents. The poor proton-donating ability of the enones **1a, b** accounts for the negligible influence of β on the reaction rate.

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