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Substituent and Solvent Effects on the Rate of the Reaction of 2-Methyl-4-phenyl-thiazole Ethiodide with Substituted Benzaldehydes

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Condensation of 2-methyl-4-phenyl-thiazole ethiodide (**1**) with aromatic aldehydes in presence of piperidine as base catalyst has been studied kinetically at different temperatures. The rate in presence of low concentration of piperidine ($< 0.5\,M$) is found to be represented by the third order equation $v = k'$ [**1**] [aldehyde] [piperidine]. On the other hand the rate in presence of $\geq 1.013\,M$ piperidine is represented by the second-order equation: $v = k'$ [**1**] [aldehyde]. It is concluded from the kinetic results that the dehydration step of the intermediate aldol compound is the rate determining step of the reaction. The dependence of the mechanism of the reaction and the thermodynamic parameters of activation on the molecular structure of the various aromatic aldehydes used is discussed. In various organic solvents, the rate of the reaction increases as the dielectric constant of the medium is increased. The energy of activation and the thermodynamic parameters of activation were calculated and discussed in terms of solvent properties.

Substituenten- und Lösungsmittel-Effekte auf die Geschwindigkeit der Reaktion zwischen 2-Methyl-4-phenylthiazol-ethiodid und substituierten Benzaldehyden

Die Kinetik dieser Kondensation wurde bei verschiedenen Piperidin-konzentrationen (basischer Katalysator), unter Variation der Temperatur und in Abhängigkeit von der Polarität des Lösungsmittels für verschiedene sub-stituierte Benzaldehyde untersucht. Bei niedriger Piperidinkonzentration ge-horcht die Reaktion einer Gleichung dritter Ordnung: $v = k'$ [Thiazol] [Ald.] [Pip.]; bei großer Konzentration ($\geq 1.013\,M$) gilt eine Gleichung zweiter Ordnung: $v = k'$ [Thizol] [Ald.]. Es wird ein Mechanismus vorgeschlagen, wobei der geschwindigkeitsbestimmende Schritt die Dehydratisierung des inter-mediär gebildeten Aldols ist. Aktivierungsenergien und andere thermo-dynamische Parameter wurden bestimmt und im Hinblick auf die Lösungs-mittelpolarität diskutiert.

Introduction

It has long been recognized that substituents in the 2-position of the thiazole ring were subject to the same types of activation as occurs with similar substituents when located either *ortho* or *para* nitro groups on a benzene ring. Thus 2-methyl thiazole can be condensed with aromatic aldehydes to give stilbene-like products. *Kaufmann* and *Vallete*[1] reported that the methiodide of methylpyridines and quinolines react more readily under milder reaction conditions than the tertiary bases. In the preceding paper we discribed the kinetics of the condensation reaction of 2-picoline ethiodide[2] with some romatic aldehydes in presence of base catalyst. The kinetic results of these investigations were explained by a mechanism in which the rate determining step was considered as the dehydration of the aldol compound.

In continuation of the above studies, we aimed to investigate the kinetics of the condensation reaction of 2-methyl-4-phenyl-thiazole ethiodide (**1**) with some aromatic aldehydes such as: *p*-hydroxy-benzaldehyde, *p*-*N*-dimethylbenzaldehyde, salicylaldehyde, vanilline, benzaldehyde and *p*-nitrobenzaldehyde in presence of piperidine as a base catalyst. Furthermore, the work is extended to include investigation of this reaction in various organic solvents of varying dielectric constants. This was made with the aim to clarify the role of polarity of the solvent on the reaction rate and to collect more informations concerning the reaction mechanism. The thermodynamic functions of the activated complex are also discussed.

Experimental

Materials

1. *2-Methyl-4-phenyl-thiazole ethiodide* (**1**)

2-Methyl-4-phenyl-thiazole was prepared according to[3]. **1** was obtained by mixing 1.0 mol of this base with 1.2 mol of ethyl iodide in a sealed tube at 100 °C for two days. The product was treated with water and benzene. The filtered aqueous solution was boiled with charcoal, filtered and evaporated till near dryness whereby a crystalline colourless product was deposited (m. p. 176 °C). The results of analysis of the solid product is in agreement with the composition of this compound.

2. *2-Styryl-4-phenyl-thiazole ethiodides*

2-Styryl-4-phenyl-thiazole thiodide derivatives were prepared in similar manner to the method described by *Phillips*[4]. It is worthy to mention that in most cases a resinous substance was obtained which was triturated several times with ether and light petroleum to give the solid product. The products were crystallized several times from methanol. The results of analysis of the solid products are in agreement with the composition of these compounds.

3. *Aromatic aldehydes* used in this investigation (*p*-hydroxybenzaldehyde, *p*-*N*-dimethylbenzaldehyde, salicyldehyde, vanilline, benzaldehyde and *p*-nitro-

benzaldehyde) and piperidine were all laboratory grade products. The *organic solvents* (methanol, ethanol, isopropanol and isoamylalcohol) were all of spectroscopically pure grade.

Kinetic Procedure

The reaction mixture was first prepared by mixing equal volumes of stock alcoholic solutions $(0.1\,M)$ **1** and aldehyde in 25 ml measuring flasks followed by the addition of the calculated amount of piperidine $(1.01\,M)$, then the whole was completed to the mark with absolute ethanol. The reaction was followed by taking accurately measured volumes of the reaction mixture at different time intervals, then diluting as soon as possible to a definite volume (25 ml) by ethanol. This usually led to a checking the reaction. The visible absorption of this solution was measured at the wavelength corresponding to the maximum absorption of the alcoholic solution of 2-styryl-4-phenyl thiazole ethiodide containing the same amount of piperidine as in the measured reaction medium. It is worthy to mention that the other constituents present in the reaction medium do not absorb in this region.

For investigation of the medium effect the same kinetic procedure is followed except ethanol is replaced by the other organic solvents.

The initial concentrations of **1** and aldehyde which were found to be suitable for following this reaction were usually $1 \times 10^{-2}\,\mathrm{mol\,dm^{-3}}$. Some experiments for the reaction of **1** with p-N-dimethylbenzaldehyde in presence of $1.013\,M$ piperidine were, however, carried out in ethanol at 25 °C with varying initial concentrations of the reactants between 0.1×10^{-2} to $2 \times 10^{-2}\,M$ to establish the optimum initial value.

Table 1. $\lambda_{\max}$ and $\varepsilon_{\max}$ for 2-styryl-4-phenyl-thiazole ethiodide, derivatives

X	$\lambda_{\max}$ nm	$\varepsilon_{\max}$ cm^2 mol^{-1}
p-H	520	3 200
p-NO$_2$	520	2 830
p-OH, m-OCH$_3$	550	12 000
p-OH	550	12 300
o-OH	520	16 400
p-N(CH$_3$)$_2$	490	8 600

The maximum absorption wavelengths at which measurements have been made together with the different molar extinction coefficients of the 2-styryl-4-phenyl-thiazole ethiodides derivatives corresponding to the various aromatic aldehydes used in this investigation are given in Tab. 1. The kinetic measurements with various aromatic aldehydes were carried out in the temperature range 25-45 °C except with salicylaldehyde which was investigated in the range 5-25 °C.

The rate constants of the reactions investigated were calculated from the simple second-order equation and the reaction was followed for not less than 70% completion.

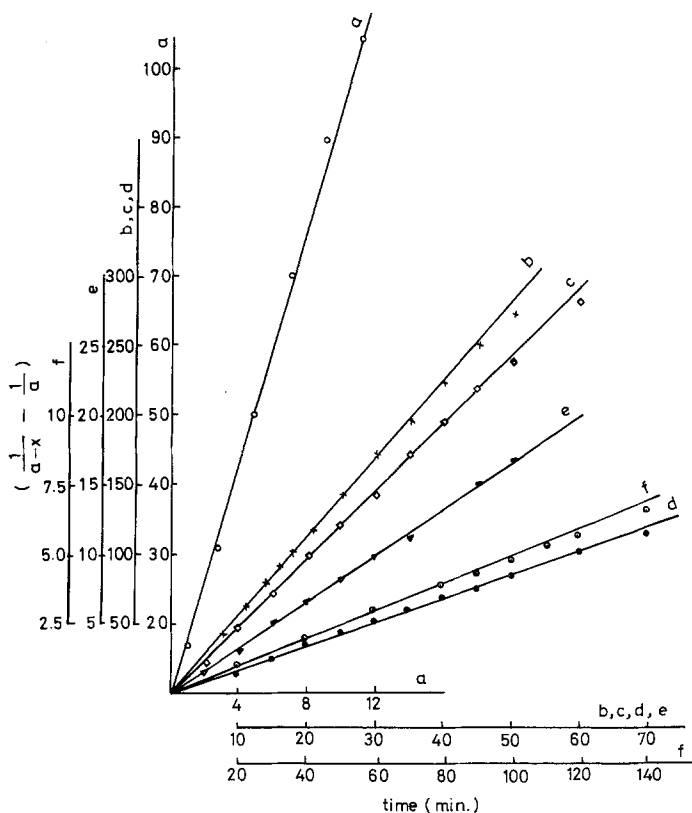The absorbance measurements were carried out on a Carl-Zeiss spectrophotometer model VSU. 2-P.

Fig. 1. Second order plots of $1/a-x-1/a$ against time for the reaction of **1** with different aromatic aldehydes: a Salicylaldehyde (20 °C); b p-Dimethylamino-benzaldehyde (35 °C); c p-Hydroxybenzaldehyde (35 °C); d Vanilline (35 °C); e Benzaldehyde (35 °C); f p-Nitrobenzaldehyde (35 °C)

Results and Discussion

Reaction Mechanism

Several measurements in ethanol at 25 °C has been carried out with varying initial concentrations of **1** and p-dimethylaminobenzaldehyde $(0.1-2 \times 10^{-2} M)$ and piperidine $(0.2-1.5 M)$. It was shown that the reaction is first order in each of **1** and aldehyde. On the other hand the order with respect to piperidine was found to be unity in presence of low concentrations of the catalyst $(< 0.5 M)$. Thus the rate in presence of low concentration of piperidine can be represented by the third order equation $v = k'$ [**1**] [aldehyde] [piperidine]. However, as the con-

centration of piperidine in the reaction medium is increased, the order
with respect to piperidine decreases and reaches zero in presence of
$\geq 1.01\,M$, where the reaction rate becomes independent of piperidine
concentration. Thus in presence of $\geq 1.01\,M$ piperidine the rate of the
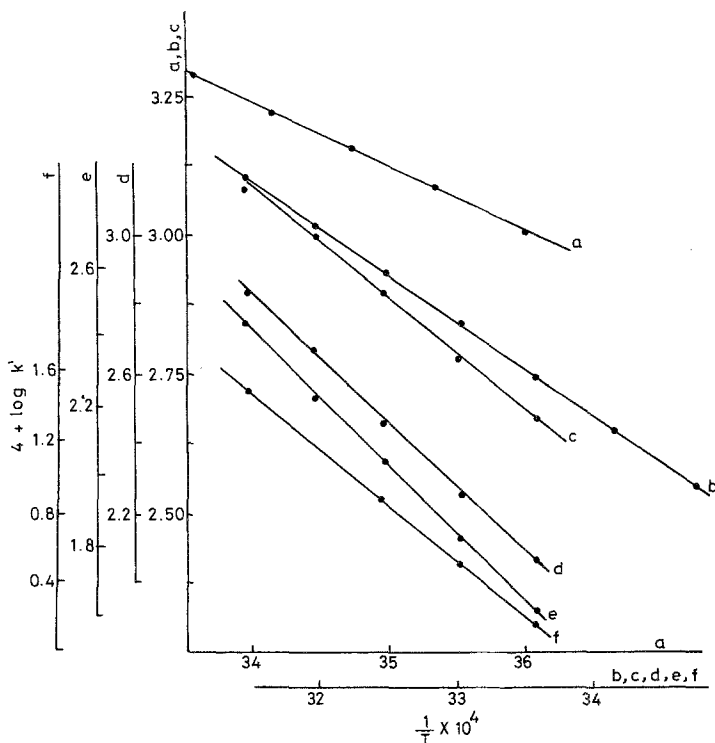reaction under investigation can be represented by the second order

Fig. 2. *Arrhenius* plots for the second order reaction of **1** with aldehydes *a-f*
(see Fig. 1)

equation $v = k'$ **[1]** [aldeyde]. This behaviour strongly substantiates
the catalytic role of piperidine on such type of reactions where its
important role is mainly restricted to the formation of the carbanion **2**
[step (1)] and piperidine is generated again in step (3) as shown below.

Fig. 1 illustrates the second-order rate plots for the condensation
reaction of **1** with the various aromatic aldehydes used in this
investigation in presence of $1.01\,M$ piperidine, at $35\,°C$ except with
salicylaldehyde at $20\,°C$. The second-order rate constants at different

Table 2. *Specific rate constant (k') values at different temperatures, activation 35 °C for the reaction of* **1** *with different aromatic aldehydes*

Aldehyde	10^2 k'/s^{-1} mol^{-1} l					
	5 °C	10 °C	15 °C	20 °C	25 °C	30 °C
Salicylaldehyde	10.70	12.20	14.30	16.70	19.40	
p-dimethylaminobenz-aldehyde					5.55	6.87
p-hydroxybenzaldehyde					4.70	5.90
Vanilline					1.15	1.74
Benzaldehyde					0.42	0.66
p-Nitrobenzaldehyde					0.014	0.032

temperatures obtained on carrying the reaction with the aromatic aldehydes are compiled in Tab. 2 together with the corresponding activation energies. The latter were determined graphically by application of the *Arrhenius* equation which was followed precisely within the temperature range used (cf. Fig. 2).
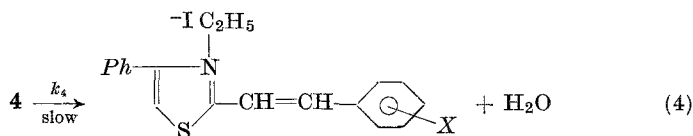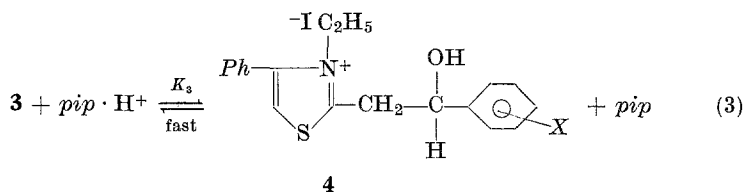
The mechanism of reaction of aromatic aldehydes with **1** in presence of high concentration of piperidine ($\geq 1.01\,M$) is like the one of 2-picoline[2] where the rate determining step is the dehydration of the aldol intermediate. This was assumed although the other steps have some influence on the overall rate. This is shown by the alteration of the rate on the use of different aldehydes or on carrying the reaction in different solvents as is shown below.

The mechanism of this reaction can be represented as follows (*pip* = piperidine):

$$(1)$$

1   **2**

$$(2)$$

3
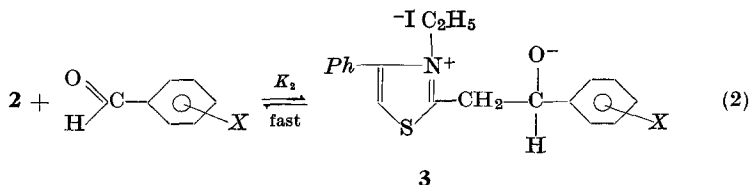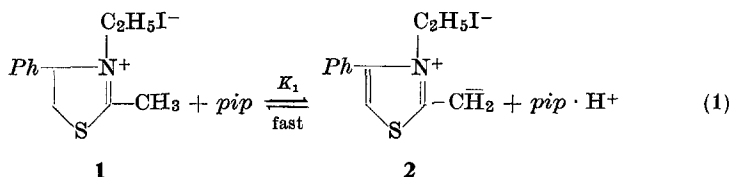
energies (E_a), *frequency factors* (A) *and thermodynamic parameters of activation at in ethanol medium in presence of 1.01 M piperidine*

			E kcal mol^{-1}	$\log A$	ΔF^* kcal mol^{-1}	ΔH^* kcal mol^{-1}	$-\Delta S^*$ cal deg^{-1} mol^{-1}
35 °C	40 °C	45 °C					
			5.49	3.32	18.18	4.91	45.30
8.50	10.40	12.90	8.12	4.69	19.57	7.51	39.18
7.90	9.80	11.80	8.89	5.20	19.61	8.28	36.79
2.90	4.70	6.78	15.52	9.47	20.23	14.91	17.26
1.11	1.66	2.78	19.83	12.11	20.80	19.22	5.14
0.078	0.152	0.310	26.92	15.99	22.42	26.31	−12.61

$$3 + pip \cdot H^+ \underset{\text{fast}}{\overset{K_3}{\rightleftharpoons}} \quad \mathbf{4} \quad + pip \qquad (3)$$

$$4 \xrightarrow[\text{slow}]{k_4} \qquad + H_2O \qquad (4)$$

According to this scheme, the overal rate equation will be

$$\frac{d[4]}{dt} = k'_{obs.}[1] \text{ [aldehyde]}.$$

The observed rate constant is therefore product of the three equilibrium constants of the first three steps (K_1, K_2 and K_3) and the rate constant k_4 of the fourth step.

Addition of water to the ethanolic reaction mixture of 1 with p-N-dimethylbenzaldehyde results in a marked inhibition of the rate (cf. Tab. 3). This indicates that the rate determining step of this reaction will be probably the dehydration step.

Effect of Substituents

The results shown in Tab. 2 indicate that both the rate of this reaction and the activation energy are largely dependent on the molecular structure of the aldehyde used. It is evident that the rate of

Table 3. *Specific rate constant values (k') for the reaction of $1 \times 10^{-2} M$ of both **1** and p-N-dimethyl-benzaldehyde in ethanol—water mixtures at 35 °C in presence of 1.01 M piperidine*

Water % (by volume)	$10^2 k'$ $s^{-1} mol^{-1} l$
0	8.50
5	1.88
10	0.95
15	0.65
20	0.36
25	0.17

the reaction increases as the electron donating character of the substituent (X) increases. This increase can be given by the following sequence:

$$p\text{-}NO_2 < p\text{-}H < p\text{-}OH, m\text{-}OCH_3 < p\text{-}OH < p\text{-}N(CH_3)_2 < o\text{-}OH$$
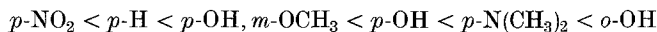
where the activation energy decreases in the same direction. Increase in the electron donating character of the substituent (X) increases the polarity of the aldehyde carbonyl group, which inturn causes a shift in equilibrium of step (2) to the forward direction. This causes an increase in the value of K_2 and reflects itself in a net increase in the reaction rate constant. The slowness of the reaction with p-nitrobenzaldehyde can be attributed to the increase of the bond order of the carbonyl group under the effect of the electron withdrawing character of the nitro group. This results in a low value of K_2 which inturn leads to a decrease in the rate of the reaction.

On the other hand, the extraordinary high rate observed in the reaction with salicylaldehyde is mainly due to the presence of intramolecular hydrogen bond together with the high inductive effect of the OH group in the *ortho* position. This leads to higher polarization of the carbonyl group and hence increase the value of K_2.

The values of the *Arrhenius* frequency factor corresponding to the reaction with each aldehyde are calculated and given in Tab. 2. The rate constants were expressed as:

$k' = 3.23\ _e\text{-}5490/RT$ for salicylaldehyde;
$k' = 4.69\ _e\text{-}8120/RT$ for dimethylaminobenzaldehyde;
$k' = 5.20\ _e\text{-}8890/RT$ for p-hydroxybenzaldehyde;
$k' = 9.47\ _e\text{-}15520/RT$ for vanilline;
$k' = 12.11\ _e\text{-}19830/RT$ for benzaldehyde and
$k' = 15.99\ _e\text{-}26920/RT$ $l\,mol^{-1}\,s^{-1}$ for p-nitrobenzaldehyde.

It is worthy to mention that the condensation of aldehydes with **1** occurs faster than with 2-picoline ethiodide[2]. This is due to the activated methyl group in **1** between the two heteroatoms[5] leading to rapid formation of the carbanion **2**.

The thermodynamic parameters ΔF^*, ΔH^* and ΔS^* for the reaction with the various aromatic aldehydes used are calculated and the results are collected in Tab. 2. However, the observed rate constant is a product of the three equilibrium constants K_1, K_2 and K_3 and the rate constant k_4, likewise the values of ΔF^*, ΔH^* and ΔS^* obtained are the sums of the values of ΔF, ΔH and ΔS for the three equilibria and the ΔF_4^*, ΔH_4^* and ΔS_4^* for step four. It is evident that ΔS^* depends on the type of substituent (X). The higher $-\Delta S^*$ values in case of $X = p\text{-N(CH}_3)_2$ relative to the other substituents indicates a higher solvation of the intermediate compounds **2** and **3** as well as the transition state by the solvent molecules. The extraordinary $-\Delta S^*$ value obtained in case of $X = o\text{-OH}$ can be due to the presence of the OH group in *ortho* position imposing rather severe restrictions on the transition state:
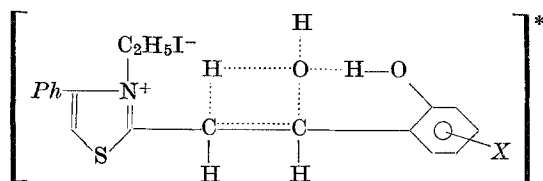
The plot of ΔH^* versus ΔS^* (at 35 °C) gives rise to a straight line as shown in Fig. 3. This indicates that there is no change in the mechanism for such a related series of compounds[6].

Effect of Dielectric Constant

In order to clarify the role of the dielectric constant on the rate of the reaction and to get some informations concerning the reaction mechanism as well as the nature of the transition state, the reaction of **1** with *p*-dimethylaminobenzaldehyde has been investigated in various organic solvents of varying dielectric constant from 14 to 32 (methanol, ethanol, isopropanol and isoamylalcohol). It was found that the reaction follows second-order kinetics in the temperature range investigated and the *Arrhenius* equation is strictly obeyed (Fig. 4). The second-order rate constant at four different temperatures together with
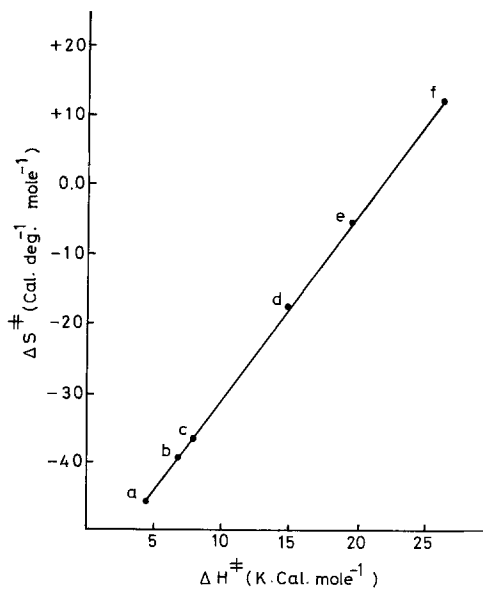
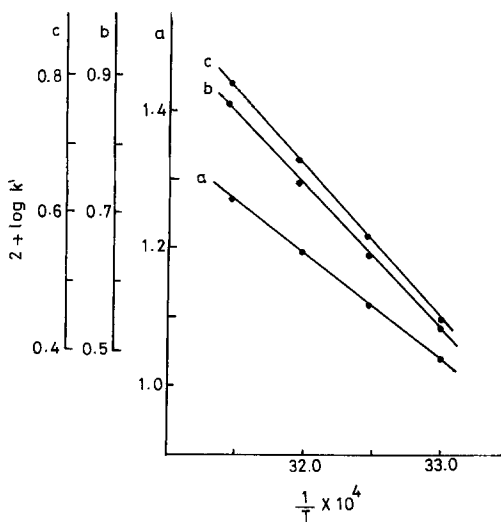Fig. 3. Linear variation of ΔH^* with ΔS^* at 35 °C for aldehydes a–f (see Fig. 1)

Fig. 4. *Arrhenius* plots for the second order reaction of **1** with p-dimethyl-aminobenzaldehyde in various organic solvents: a Methanol; b Isopropanol; c Isoamylalcohol

Table 4. Rate constants, activation energies E and thermodynamic parameters of activation for the reaction of 1×10^{-2} M of both **1** and p-dimethylaminobenzaldehyde in various organic solvents in presence of 1.01 M piperidine

Solvent	D	$k' 10^2$				E	ΔF^*	ΔH^*	$-\Delta S^*$
		s^{-1} mol^{-1}				kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	cal deg^{-1} mol^{-1}
	35°C	30°C	35°C	40°C	45°C		35°C	35°C	35°C
Methanol	31.72	11.11	13.16	15.63	18.52	6.78	19.29	6.17	42.61
Ethanol	23.64	6.87	8.50	10.40	12.90	8.12	20.19	7.51	39.18
Isopropanol	17.81	3.44	4.44	5.55	7.22	9.23	19.96	8.62	36.81
Isoamylalcohol	14.31	2.83	3.72	4.76	6.15	9.98	20.15	9.37	35.01

the activation energies corresponding to the reaction in the various organic solvents are collected in Tab. 4. Examination of the data shows that the rate constant decreases with decrease in dielectric constant on passing from methanol to isoamylalcohol. The inhibition in the rate is
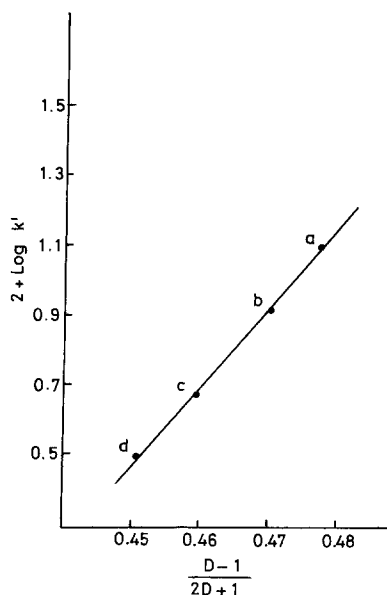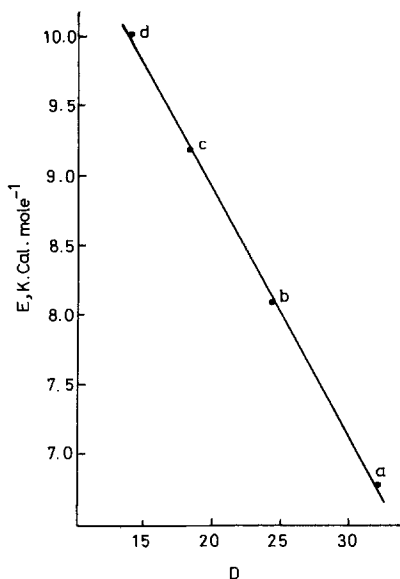

Fig. 5

Fig. 6

Fig. 5. Linear variation of log k' vs $\dfrac{D-1}{2D+1}$ for the reaction with p-dimethylaminobenzaldehyde in different organic solvents: a Methanol; b Ethanol; c Isopropanol; d Isoamylalcohol

Fig. 6. Linear variation of "E" and D for the reaction with p-dimethyl-aminobenzaldehyde in different organic solvents: a–d (see Fig. 5)

almost regular as illustrated by Fig. 5. In this Fig. log k' is plotted as a function of $\dfrac{D-1}{2D+1}$ (on the basis of a plot according to *Kirkwood*'s dipole-dipole interaction theory[7,8]). The reaction in methanol has an activation energy 3.20 kcal mol^{-1} lower than that in isoamylalcohol. Between these two extremes the activation energy increases almost regularly with the decrease of dielectric constant of the alcohol used.

Such relationship is illustrated diagrammatically in Fig. 6, where a straight line is obtained on plotting "E" vs. "D".

The increase in rate of reaction on passing from isoamylalcohol to methanol can be explained on the principles that increase in dielectric constants as well as the solvating power of the medium in this direction[9] will stabilise the carbanion **2**, effectively depressing its recombination rate with a proton. This leads to higher K_1 values which consequently increases the rate of the reaction and hence lowers the activation energy.

The thermodynamic parameters of activation for different organic solvents were calculated and are recorded in Tab. 4. It is evident that the free energy of activation ΔF^* changes slightly with the nature of the solvent. This may indicate that the reaction mechanism is the same in all the solvents studied, where the constancy of ΔF^* is essentially due to the linear compensation between ΔH^* and $-T \Delta S^*$.

Furthermore, it is evident that the entropy of activation passes to higher negative values as the dielectric constant of the medium is increased. This can be ascribed to the high solvation of carbanion **1**, aldol anion **2**, aldol **3** and the transition state by the solvent molecules on changing the reaction medium from isoamylalcohol to methanol.

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