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CYCLOADDITION MECHANISM AND THE SOLVENT DEPENDENCE OF RATE

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Abstract - The dependence of cycloaddition rate constants on solvent polarity is a significant mechanistic criterion. Various model reactions are discussed. The slow step of the 2 + 2 cycloaddition of tetracyanoethylene (TCNE) to enol ethers is the formation of a zwitterionic intermediate. The log k_2 values show an unusually high influence of solvent polarity and are linearly related to the empirical solvent parameter E_T. The inclusion of alcohols as solvents calls for the application of the Koppel-Palm four-parameter equation; the non-specific Coulombic term is found to be of greatest importance. The dipole moments of the transition states of zwitterion formation can be evaluated. - The small solvent dependencies of Diels-Alder reactions and 1,3-dipolar cycloadditions signal minute changes of polarity during the activation process. These concerted cycloadditions have early transition states. - The cyclobutanone formation from ketenes and enol ethers proceeds by a concerted $_{\pi}2_a + _{\pi}2_s$ mechanism. The reaction of dimethylketene with N-isobutenyl-pyrrolidine produces a 2 : 1 adduct besides the cyclobutanone as a 1 : 1 adduct. The product ratio depends on the dimethylketene concentration; the quantitative evaluation establishes two competing mechanisms of cyclobutanone formation. Their rates respond differently to the change of solvent polarity; a competition of the concerted with a zwitterionic pathway is highly probable.

INTRODUCTION

Despite many common features, physicists and chemists differ in their way of thinking. The physicist tends to isolate a phenomenon, focusing it and investigating its pure and untainted manifestation. The chemist, however, is accustomed to deal with the complexity of intertwined phenomena. Something as intricate, mingled and knotty as chemical reactivity would drive a physicist to despair. The chemist patiently attempts to disentangle the complexity with the never-ending optimism that the final result will be clear and straight. In particular, it is the chemist's inclination to simplify and to be satisfied with approximations, thus arousing the distrust of his colleague from physics. The way the chemist has tackled with the problem of the solvent dependence of rate may serve as an example par excellence.

The knowledge of the fact that the rate constant is influenced by the nature of the solvent, is no novelty. When running reactions on a preparative or even industrial scale, the optimal choice of the solvent is of prime importance. Not all reactions respond in the same way in their rates to the change of the solvent; the stunning differences pose a fascinating theoretical problem.

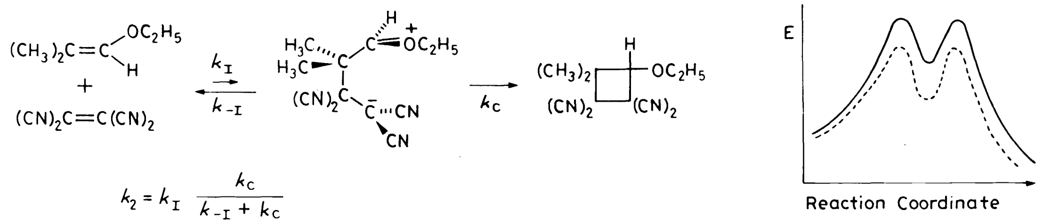
The rate constant is determined by the free energy difference between reactants and transition state.

Changes of solute-solvent interaction during activation will influence the rate constant. Reactions which are accompanied by an increase of charge separation in their activation process are accelerated in solvents of increasing polarity. Charge separation and polarity of the solute find a numerical scale in the dipole moment, although not a fully adequate one; the dipole moment does not reflect the degree of charge dissipation. The term "solvent polarity", however, lacks clarity to such an extent that the above statement is not explanatory, but rather could be used as a definition of solvent polarity.

No physical constant can be procured as a simple measure of solvent polarity. Many phenomena contribute : Coulombic forces, dipole-dipole attraction, dispersion forces, hydrogen-bonding , electrophilic and nucleophilic interaction etc. Organic and inorganic chemists have introduced impirical scales of solvent polarity which are based on rates, equilibria or spectroscopic phenomena. Albeit it was not fully understood what solvent polarity and solvation mean, the solvent dependence of rate has been applied as a mechanistic criterion.

2+2 CYCLOADDITIONS OF TCNE AND ENOL ETHERS

Scheme 1



$$k_2 = k_I \frac{k_c}{k_{-I} + k_c}$$

The cyclobutane formation from tetracyanoethylene (TCNE) and ethyl isobutenyl ether may serve as an example (Scheme 1). Manifold evidence supports a reaction path in which the electron-rich and the electron-deficient ethylene derivative initially combine to form a zwitterion; in a subsequent step, the cyclobutane ring is closed (Ref. 1). Experiments with cis,trans isomeric enol ethers reveal that the zwitterionic intermediate can undergo rotation at the former double bond of the enol ether and that a partial reversal to the reactants takes place (Ref. 2,3). The overall second-order rate constant is a composite of k_I for zwitterion formation and a partition coefficient of the short-lived intermediate; $k_C / (k_{-I} + k_C)$ is the fraction of the zwitterion which goes on to product (Ref. 4).

Table 1. 2+2 Cycloadditions of TCNE and ethyl isobutenyl ether ; rate constants in various solvents

Solvent	E_T kcal mol^{-1}	$10^3 k_2$ at 25°C L mol^{-1} sec^{-1}
Cyclohexane	31.2	0.140
CCl_4	32.5	0.128
Ether	34.6	0.589
Tetrahydrofurane	37.4	5.55
Ethyl Acetate	38.1	14.9
Chloroform	39.1	14.5
Dichloromethane	41.1	59.8
Benzonitrile	42.0	284
Acetone	42.2	120
Acetonitrile	46.0	629

With more than three powers of ten, the model reaction exhibits an unusually high influence of solvent polarity on rate (Table 1, Ref. 3,5). Solvent effects of this magnitude were unknown before in cycloaddition chemistry. The Dimroth-Reichardt parameter E_T is chosen as an empirical measure of solvent polarity (Ref. 6, 7); it constitutes the excitation energy of a dye at the long-wave absorption maximum. A 4,900-fold rate increase in changing the medium from carbon tetrachloride to acetonitrile corresponds to a decrease of the activation free energy by 5.0 kcal mol^{-1}.

In the energy profile of Scheme 1 the solid curve may refer to the nonpolar medium. The broken line for the highly polar solvent illustrates the lower activation barriers. The charge separation reaches a maximum for the fully developed zwitterion which holds its brief siesta in the trough. The distance between the two energy profiles should attain its greatest value here. The material arriving in the dip is quickly partitioned into the competing pathways of dissociation back to the reactants and ring closure to the cyclobutane. Both of these exothermic reactions of the zwitterion have early transition states which are structurally still close to the zwitterion itself. The decreases of charge separation should be moderate and similar when the zwitterion climbs the activation barriers of dissociation and cyclization. The pertinent rate constants, k_{-I} and k_C, occur in a fraction; another reason for expecting the partition coefficient to show a small or zero dependence on solvent polarity.

Most of the charge separation will take place in the ascending portion of the energy profile which ranges from the reactants to the transition state; this portion is subject to the high influence of solvent polarity. Thus, the lowering of the first high barrier is responsible for the greater cycloaddition rate in the polar solvent.

Why does one assume equal heights for the two barriers which surround the trough of the zwitterion? Experiments with the cis,trans isomeric 1-butenyl ethyl ethers furnish the rate ratio of ~1 for dissociation and cyclization of the zwitterion in acetonitrile (Ref. 2). We will assume that the barrier heights are not much different in the example of ethyl isobutenyl ether, i.e., the partition coefficient would be in the region of 0.5.

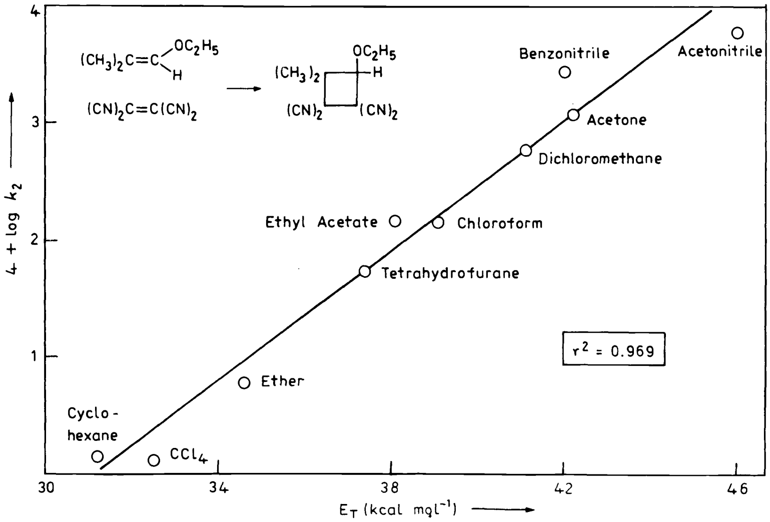


Fig. 1 Cycloaddition of TCNE to ethyl isobutenyl ether at 25°C; influence of solvent polarity on the rate constant

The log k_2 values measured in ten solvents (Ref. 3,8) are plotted in Fig. 1 versus the parameter E_T and define a straight line of fair quality. The correlation coefficient - r^2 is used to make the deviation from 1.0 better visible - amounts to 0.97.

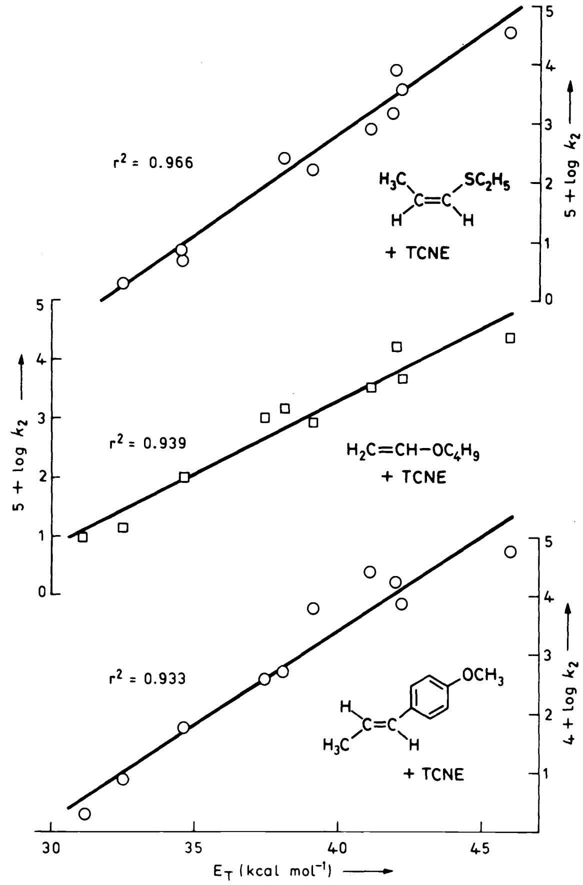
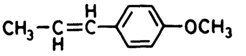
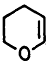
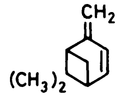


Fig. 2 The rates of further TCNE cycloadditions plotted versus E_T

Rate measurements of TCNE cycloadditions to anethole, vinyl butyl ether and cis-propenyl ethyl sulfide were likewise carried our in ten solvents (Fig. 2, Ref. 5,9). Here too, lo k_2 entertains relations of tolerable

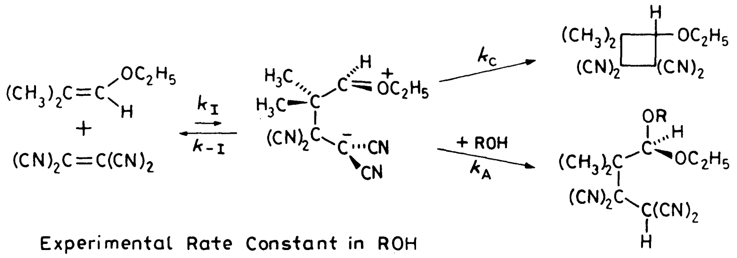
Table 2. Ratios of rate constants for 2 + 2 cycloadditions of TCNE in acetonitrile and carbon tetrachloride at 25°C

		k_{CH_3CN} / k_{CCl_4}
$H_2C{=}CH{-}OC_4H_9$		1 700
$(CH_3)_2C{=}CH{-}OC_2H_5$		4 900
		7 800
 2,3-Dihydropyrane		17 000
$(CH_3)_2C{=}CH{-}SC_2H_5$		2 900
$CH_3{-}CH{=}CH{-}SC_2H_5$	*cis*	17 100
	trans	16 800
 Verbenene		21 000

linearity with the empirical parameter E_T.

In Table 2 rate ratios in acetonitrile and carbon tetrachloride are listed for various 2 + 2 cycloadditions of tetracyanoethylene. The high rate ratios involve diminutions of activation free energies by 4.4 - 5.9 kcal mol^{-1}. Surprisingly, thioenol ethers display solvent influences of the same size as enol ethers do. The trans-fixed diene system of verbenene cannot undergo Diels-Alder addition. Instead, 2 + 2 cycloaddition at the exocyclic double bond occurs; the high solvent influence suggests a zwitterion of the allyl cation type as an intermediate (Ref. 10).

Scheme 2



Experimental Rate Constant in ROH

$$k_2 = k_I \frac{k_C + k_A}{k_{-I} + k_C + k_A}$$

	Acetal	Cyclobutane
Methanol	88 %	12 %
Ethanol	79 %	21 %

For $k_{-I} \sim k_C$ and $k_A \sim 4 k_C$

$k_2 \approx 0.83\ k_I$

	$10^3 k_2$ at 25°C L mol^{-1} sec^{-1}	E_T kcal mol^{-1}
Ethanol	214	51.9
Methanol	331	55.5
Acetonitrile	629	46.0

The zwitterionic intermediate from TCNE and ethyl isobutenyl ether is interceptible by alcohols (Scheme 2); open-chain acetals with the malodinitrile group at the other end are formed (Ref. 11). In the case of cis,trans isomeric enol ethers different alkoxy residues in enol ether and alcohol produce diastereomeric acetals. Their structure elucidation (Ref. 12) demonstrates that the zwitterions are U-shaped and that the alcohol attacks the carboxonium ion from the outside.

The trapping of the zwitterion in alcohols as solvents is not complete. In the example given, methanol traps 88 % and ethanol 79 % of the zwitterion; 12 and 21 % of the cyclobutane derivative is still formed. The interception by alcohol with the pseudo first-order constant k_A constitutes a third reaction of the zwitterion. The experimental second-order rate constant now contains a partition coefficient which is made up from the rate constants of three competing reactions. Under the assumptions stated in Scheme 2, one expects a partition coefficient of roughly 0.8, not a dramatic change compared with 0.5 in acetonitrile.

Thus, the log k_2 values in alcohols should still fulfil the linear relation with the empirical parameter E_T. The small table in Scheme 2 reveals an irritating discrepancy. Although the E_T values of ethanol and methanol are substantially higher than that of acetonitrile, the second-order overall rate constants are smaller.

The inclusion of the alcohol values in the linear regression spoils the plot; the correlation coefficient drops to 0.73 (Fig. 3). At such occasions chemists will remember how complex a function solvation is. A

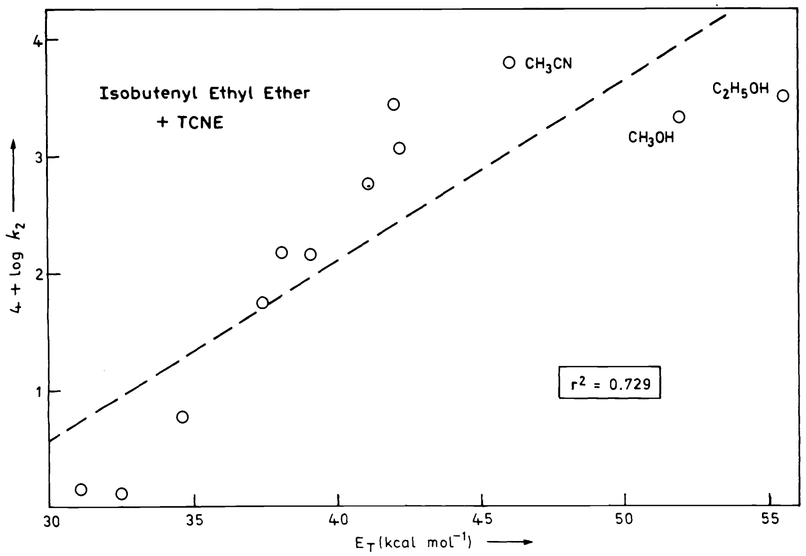
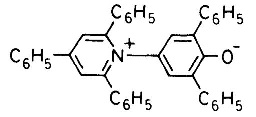


Fig. 3 Rate constants including alcohols plotted versus E_T

slightly immoral recipe is to limit the relation to a certain group of solvents, for instance non-hydroxylic ones in the given example. The game reminds of "corriger la fortune" and its wide usage is no consolation. Is chemistry too difficult for chemists ?

On should not fall a victim to the simplistic approach of expressing the intricate network of physical phenomena by a single solvent parameter. Any empirical measure of solvent polarity is based on a model system. Linear correlations can only be expected as long as the solvent influence on the studied system closely conforms with that of the model.



Pyridinium phenoxide dye of Dimroth and Reichardt

The E_T parameter is based on the solvatochromism of a pyridinium phenoxide. It is easily measurable and values for more than 150 solvents were tabulated by Reichardt (Ref. 6). The positive charge of the dye is highly screened. Solvation of the anionic part is more important and, therefore, E_T values mainly reflect the electrophilicity and the hydrogen-bond donor activity of the solvent (Ref. 13).

Multi-parameter correlations have been proposed which separate various phenomena of solute-solvent interaction and offer a more general solution (Ref. 13). Without weighing the merits and failures of various proposals, it may be stated that Hermann Graf in the author's laboratory found the approach of Koppel and Palm (Ref. 14) useful. It is a four-parameter equation, and one should be aware of the danger of involving too many parameters. The late Gustav Tammann, professor of physical chemistry at Göttingen, once criticized a seminar talk by pointing out that seven parameters are sufficient for describing an elephant.

In the Koppel-Palm equation (Scheme 3) k_o ist the rate constant in the gas phase and capital Y, P, E and B constitute independent parameters which contribute additively to log k. The small letters y, p, e and b characterize the corresponding regression coefficients in the least-square fit. Y and P are non-specific sol-

Scheme 3. Four-parameter equation of Koppel and Palm

$$\log k = \log k_0 + yY + pP + eE + bB$$

Polarization Y

$(\varepsilon - 1)/(\varepsilon + 2)$

$(\varepsilon - 1)/(2\varepsilon + 1)$

Polarizability P

$(n^2 - 1)/(n^2 + 2)$ or $(n^2 - 1)/(2n^2 + 1)$

Electrophilic Solvating Power E

$$E = E_T - 25.57 - 14.39\,Y - 9.08\,P$$

Nucleophilic Solvating Power B

$$B = \tilde{\nu}^{o}_{CH_3OD} - \tilde{\nu}_{CH_3OD\cdots B}$$

vent-solute interactions and stand for polarization and polarizability. The polarization parameter Y is a function of the dielectric constant ε and represents the Coulombic term. The polarizability P is based on the refractive index of the solvent. Y and P can be expressed by several related functions of ε and n^2 according to different theoretical approaches.

The specific solvent-solute parameters E and B stand for the electrophilic and nucleophilic solvating power. E, the measure of the Lewis acidity of the solvent, is obtained from the Dimroth-Reichardt parameter E_T by subtraction of the portions coming from polarization and polarizability. The pyridinium phenoxide loses much of its ground state dipole moment on electronic excitation which involves intramolecular charge transfer. Finally, the wave numbers of the IR stretching frequency of deuteriomethanol serve as a measure of the Lewis basicity of the solvent. The gas phase frequency $\tilde{\nu}^{o}$ is reduced by hydrogen bonding to acceptor solvents; the shift is defined as B.

Table 3. Koppel-Palm parameters of solvents

	Y	P	E	B
Cyclohexane	0.254	0.256	(0)	25
CCl_4	0.292	0.273	(0)	31
Diethyl Ether	0.527	0.217	(0)	129
Tetrahydrofurane	0.687	0.246	(0)	145
Ethyl Acetate	0.626	0.227	1.53	89
Chloroform	0.559	0.265	3.16	39
Dichloromethane	0.726	0.255	2.78	43
Benzonitrile	0.890	0.308	0.74	97
Acetone	0.868	0.220	2.11	123
Acetonitrile	0.924	0.212	5.16	103
Ethanol	0.887	0.221	11.52	123
Methanol	0.914	0.203	14.89	123

In Table 3 the Koppel-Palm parameters are given for the twelve solvents in which the rate constants for the TCNE reaction with ethyl isobutenyl ether have been measured. The computerized least-square treatment furnishes an excellent fit (Ref. 8) :

$$\log k_2 = -(4.92 \pm 0.64) + (6.50 \pm 0.37)\,Y - (1.46 \pm 2.41)\,P + (0.0054 \pm 0.016)\,E - (0.0102 \pm 0.0019)\,B$$

Multiple Correlation Coefficient $R^2 = 0.990$

Normalization of Parameter Influence

Y 75 %, P 2.2 %, E 1.3 %, B 21.5 %

The ± values indicate the standard deviations. For P and E the standard deviation is larger than the regression coefficient; this means that these parameters do not contribute noticeably to the quality of the fit. The four parameters have different scales and dimensions. Normalization supplies the influence of the solvent parameters percentage-wise. Indeed, the polarizability parameter P and the electrophilic solvating power E can be neglected. The remaining two solvent parameters are the polarization effect Y and - to a lesser degree - the nucleophilic solvating power B. On bringing the term B with a positive sign to the left side of the equation, one can check the result graphically.

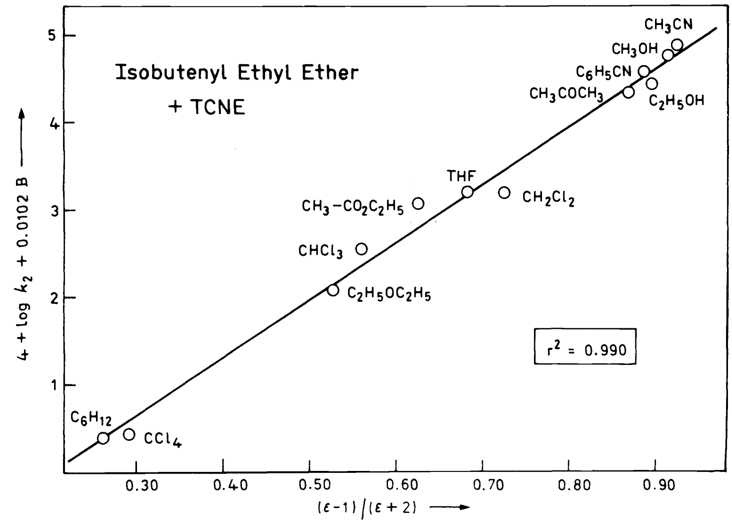


Fig. 4 Plot of log k_2 in a two-parameter equation (polarization effect Y and nucleophilic solvating power B)

The log k_2 values + 0.01 B are plotted in Fig. 4 versus the function of the dielectric constant, $(\varepsilon - 1)/(\varepsilon + 2)$, for the twelve solvents. The rate constants in alcohols fit the straight line and no longer give reason for complaint.

What do the data reveal about the rate process, i.e., the zwitterion formation from the reactants (Scheme 1)? Electrophilic solvation does not show up in the result, because the interaction with the enol ether, the starting material, appears to match that with the well dispersed negative charge of the malodinitrile anion in the incipient zwitterion. The nucleophilic power of the solvent contributes with 22 % and shows a negative sign. Thus, nucleophilic solvation of the highly electrophilic TCNE in the ground state must exceed that of the incipient carboxonium function in the transition state. The influence of the polarization term Y totals 75 % and indicates the change of Coulombic energy in creating the zwitterion in a medium of high dielectric constant. The result accords well with the assumption that the solvent-sensitive step is the formation of a zwitterion from reactants of low polarity.

In their review article of 1972 Koppel and Palm evaluated 70 series of solvent dependencies in terms of the four-parameter equation (Ref. 14). Only very few rate series with such a preponderance of the non-specific polarization term Y were listed.

How will the correlation change upon omitting the 22 % contribution by the solvent nucleophilicity B ? One finds the one-parameter correlation of log k_2 with the function of the dielectric constant, $(\varepsilon - 1)/(\varepsilon + 2)$, less satisfactory than the two-parameter relation of Fig. 4. The values of diethyl ether and tetrahydrofurane as the most nucleophilic solvents are located notably below the line; the ethers bind TCNE and slow down the rate. Still a linear relation holds with $r^2 = 0.935$.

$$\ln k = \ln k_0 - \frac{1}{k_B T}\left(\frac{\varepsilon - 1}{2\varepsilon + 1}\right)\left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_\ddagger^2}{r_\ddagger^3}\right) + \frac{\Phi_A + \Phi_B - \Phi_\ddagger}{k_B T} \qquad (1)$$

$$\Delta G = \frac{\mu^2}{r^3}\left(\frac{\varepsilon - 1}{2\varepsilon + 1}\right) + \Phi \qquad (2)$$

In 1934 Kirkwood devised a simple electrostatic model for the free energy change on bringing a spherical dipolar molecule from a vacuum into a continuum with the dielectric constant ε (Ref. 15). According to Eq. (1) the free energy change is proportional to the square of the dipole moment μ and to the function $(\varepsilon - 1)/(2\varepsilon + 1)$; r is the radius of the sphere. The non-electrostatic interaction Φ can be neglected under certain conditions.

In 1940 Laidler and Eyring derived Eq. (2) which describes the rate constant of the reaction A + B → C as a function of solvent polarity (Ref. 16). In addition to the dipole moments of the reactants A and B, the dipole moment of the transition state, μ, appears in the equation. It should be possible to calculate the dipole moment of the transition state from the slope of the straight line.

The reason why this equation hardly ever has been applied for that purpose appears evident. The expression deals with the purely electrostatic interaction, and the specific solvent-solute interplay is neglected; as a rule, the relation is bound to fail. However, the 2 + 2 cycloaddition of TCNE to enol ethers reveals a strong predominance of the non-specific polarization effect Y in its solvent dependence of the rate constant.

An approximate linearity exists between the Clausius-Mosotti function $(\varepsilon - 1)/(\varepsilon + 2)$ and Kirkwood's expression $(\varepsilon - 1)/(2\varepsilon + 1)$. Plots of log k_2 for the 2 + 2 cycloadditions of TCNE to isobutenyl ethyl ether, 2,3-dihydro-4H-pyrane and vinyl butyl ether versus Kirkwood's ε-function show linear regressions of medium quality (Fig. 5). Rate constants in alcohols are included. Thus, the conditions are fulfilled for evaluating the dipole moments of the transition state from the slopes of the straight lines in Fig. 5 by applying Eq. (2).

This has, in fact, been done by Gerd Steiner in the authors laboratory in the early seventies and the successful application was published in 1973 (Ref. 5), although the final justification came from the recent Koppel-Palm treatment of the rate data by Hermann Graf (Ref. 8). Without giving details, the results of

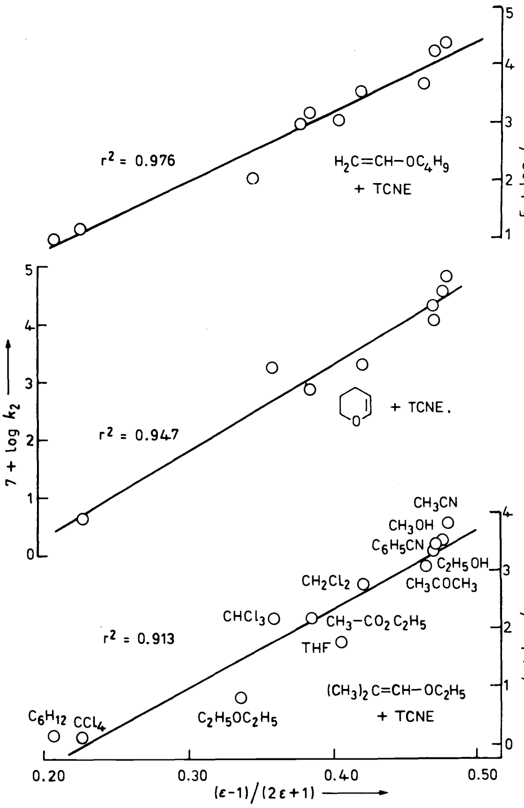
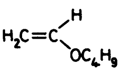
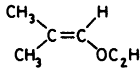
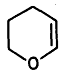
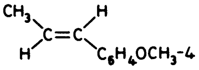


Fig. 5 Relations of log k_2 for three cycloadditions of TCNE to enol ethers with Kirkwood's function of the dielectric constant

Table 4 may be discussed. The calculated dipole moments of the transition states amount to 10.3, 11.0, 10.7 and 14.0 Debye for the four model systems.

The comparison with estimated dipole moments of the zwitterions is based on their gauche structure. The oxonium oxygen was taken as the positive center of the dipole, whereas the negative one is projected into

Table 4. Calculated dipole moments of transition states and zwitterionic intermediates in the cycloadditions of TCNE to enol ethers

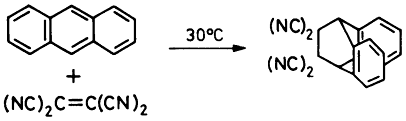
	 $H_2C{=}C(H)OC_4H_9$	 $(CH_3)_2C{=}C(H)OC_2H_5$		 $CH_3(H)C{=}C(H)C_6H_4OCH_3\text{-}4$
$R_\varepsilon = \Delta \log k / \Delta \frac{\varepsilon-1}{2\varepsilon+1}$	11.8	13.2	14.8	19.6
μ Enol Ether	1.25 D	1.28 D	1.33 D	1.76 D
Mol. vol. Enol Ether (ccm)	129	129	91.4	150
Mol. vol. Transition State	236	236	198	257
r Enol Ether	3.7	3.7	3.3	3.9
r Transition State	4.5	4.5	4.3	4.7
$\mu^{\ddagger}$ Transition State	10.3 D	11.0 D	10.7 D	14.0 D
Charge Distance 1,4-Dipole	3.0 Å	3.0 Å	3.5 Å	4.0 Å
„Charge Moment"	14 D	14 D	16 D	19 D
μ estimated for Zwitterion	17 D	17 D	18 D	21 D

the middle of the line which connects the two nitrogen atoms of the malodinitrile anion group. Including the partial moments of the nitrile functions at the tetrahedral carbon, the vector addition results in estimates of 17 - 21 D for the zwitterion.

The calculated dipole moments of the transition states correspond to roughly two thirds of the μ estimates for the fully developed zwitterions. On considering that the charge separation is not yet complete in the transition state, one finds the figures satisfactory. On the other hand, their significance should not be overestimated. The Kirkwood model comprises many simplifications.

SOLVENT DEPENDENCE OF CONCERTED CYCLOADDITIONS

Table 5. Solvent dependence of the rate constant for the Diels-Alder reaction of anthracene and tetracyanoethylene

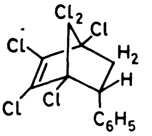


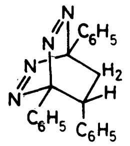
Solvent	E_T kcal mol^{-1}	k_2 L mol^{-1} sec^{-1}
o-Xylene	34·3	0·090
Benzene	34·5	0·48
o-Dichlorobenzene	38·1	4·65
Ethyl Acetate	38·1	0·310
Chloroform	39·1	6·28
Methyl Acetate	40·0	0·457
Cyclohexanone	40·8	0·260
1,2-Dichloroethane	41·9	4·69
Propionitrile	43·7	0·109
Sulfolane	44·0	2·74
Acetonitrile	46·0	2·71
Propylene Carbonate	46·6	1.94

The rate constants of Diels-Alder reactions are notoriously little affected by solvent polarity. The example which exhibits a rather large influence is the 4 + 2 cycloaddition of anthracene and tetracyanoethylene studied by Brown and Cookson (Table 5, Ref. 17). The total spread amounts to a factor of 70; the highest rate constant was measured in chloroform and the lowest in o-xylene. There is no correlation either with the empirical parameter E_T or with a function of the dielectric constant. The reaction in question is HOMO (diene) - LUMO(dienophile) controlled (Ref. 18). How slight is the solvent influence compared with that of 2 + 2 cycloadditions of TCNE !

In Diels-Alder reactions "with inverse electron demand" we face a preponderance of the LUMO(diene) - HOMO(dienophile) interaction. Styrene additions to hexachlorocyclopentadiene and diphenyl-1,2,4,5-tetrazine were measured in five solvents by Sauer (Table 6, Ref. 19). There appears to be a slight increase of the rate constants by a factor of 2 when one enhances the solvent polarity substantially by going from toluene to N,N-dimethylformamide.

Table 6. Diels-Alder reactions of inverse electron demand; solvent dependence of rate constant

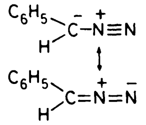


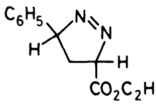


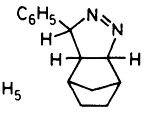
Styrene +		Hexachloro-cyclopentadiene	3,6-Diphenyl-1,2,4,5-tetrazine
Solvent	E_T	$10^5 k_2$, 85°C	$10^4 k_2$, 90°C
Toluene	33.9	6.6	4.4
Dioxane	36.0	6.8	4.9
Ethyl Benzoate		9.5	7.8
Nitrobenzene	42.0	10.2	10.6
Dimethylformamide	43.8	11.1	10.6

1,3-Dipolar cycloaddition is closely related to the Diels-Alder reaction, as the common π-electronic description (${}_{\pi}4_s + {}_{\pi}2_s$) for these concerted reactions underlines (Ref. 20). 1,3-Dipoles are zwitterionic species which possess the 4π-electron system of the allyl anion (Ref. 21). In the physical sense they are quadrupoles, i.e., the negative charge is distributed on either side of the onium center. Thus, their polarity need not necessarily be high. The dipole moment of diazomethane amounts to 1.45 D and that of diphenyldiazomethane to 1.42 D. Diazoalkanes belong to the 1,3-dipoles of the propargyl-allenyl type, as the two resonance structures reveal.

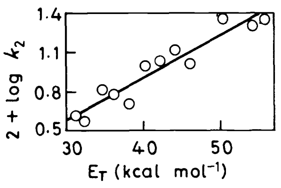
Table 7. 1,3-Dipolar cycloadditions of phenyldiazomethane to acrylic ester and norbornene in various solvents at 25°C







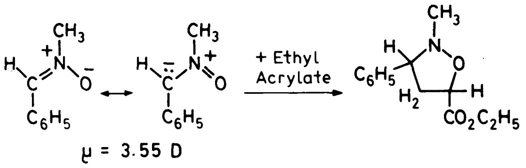
Solvent	E_T (kcal mol^{-1})	Acrylic Ester	Norbornene
		$10^5 k_2$ (L mol^{-1} sec^{-1})	
Cyclohexene	31.2	4 140	9.52
Carbon Tetrachloride	32.5	3 800	7.11
Benzene	34.5	6 420	8.33
Dioxane	36.0	6 120	7.83
Ethyl Acetate	38.1	5 000	6.47
Pyridine	40.2	9 910	8.34
Benzonitrile	42.0	10 900	10.1
Dimethylformamide	43.8	13 100	8.94
Acetonitrile	46.0	10 000	8.38
Butanol	50.2	23 200	10.7
N-Methylformamide	54.1	20 500	11.8
Methanol	55.5	22 100	9.33



The cycloadditions of phenyldiazomethane to acrylic ester and to norbornene were measured over the full range of solvent polarity (Table 7, Ref. 22). The rate constants of ethyl acrylate rise over the small range of 5.8 on going from CCl_4 to methanol; they signify a minute increase of polarity during the activation process. Usually, one cannot expect linear correlations with such a small spread of rate constants, but the relation with E_T is still a straight line, as the diagram reveals.

The rate constants of norbornene are by three powers of ten smaller and vary by the trifling factor of 1.8; their solvent dependence is just scatter. Thus, no polarity change of the substrate during the activation process can be recognized. This behavior harmonizes with the concertedness of these cycloadditions and contradicts the formation of a zwitterionic intermediate in the rate-determining step.

Table 8. Influence of solvent polarity on the cycloaddition rate of N-methyl-C-phenylnitrone and ethyl acrylate at 85°C



Solvent	E_T kcal mol^{-1}	$10^4 k_2$ L mol^{-1} sec^{-1}
Toluene	33.9	4.8
Benzene	34.5	4.2
Dioxane	36.0	2.8
Ethyl Acetate	38.1	2.6
Pyridine	40.2	2.2
Acetone	42.2	1.9
Dimethylformamide	43.8	1.7
Dimethyl Sulfoxide	45.0	1.8
Acetonitrile	46.0	1.6
Nitromethane	46.3	1.7
Ethanol	51.9	0.86
Methoxyethanol	52.3	1.1

N-Methyl-C-phenylnitrone is a 1,3-dipole of the allyl type. The azomethine oxide structure contributes more to the ground state than the carbanionic formula. Nitrones possess higher dipole moments than diazoalkanes, 3.55 D in the example of Table 8. The second order rate constants decrease by the meager factor of 5.6 on changing from the least polar toluene to the highly polar ethanol (Ref. 23).

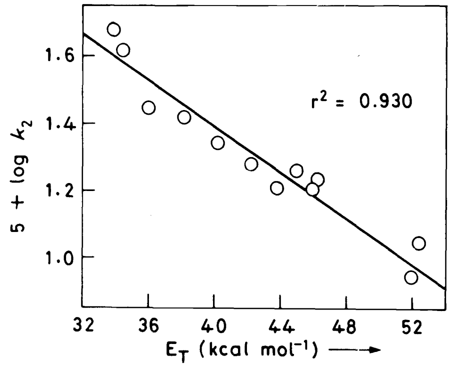
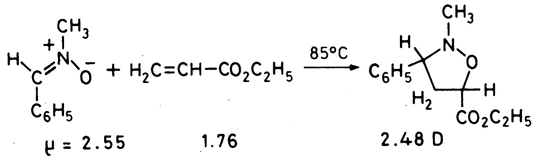


Fig. 6 N-Methyl-C-phenylnitrone and ethyl acrylate; plot of log k_2 versus polarity parameter E_T

In this case, too, the log k_2 values obey a linear relationship with E_T, now with a negative sign of the slope. This signals a tiny decrease of reactant polarity in the activation process. How can one interpret this on the basis of the measured dipole moments of reactants and product ?

Scheme 4



Dipole Moment of Transition State for Zero Change of Polarity.

$$\left(\frac{\mu^2}{r^3}\right)_{1,3\text{-Dipole}} + \left(\frac{\mu^2}{r^3}\right)_{\text{Dipolarophile}} = \left(\frac{\mu^2}{r^3}\right)^{\ddagger}$$

Here $\mu^{\ddagger} = 5.4$ D

Two reactants with dipole moments form one adduct molecule. One may resort to the Kirkwood-Laidler-Eyring equation (Ref. 16) and define in Scheme 4 the dipole moment of the transition state for a zero change of polarity. The sum of the square of the dipole moments of the reactants divided by the cube of the radius of the imaginary spherical molecules should be identical with the corresponding quantity for the supermolecule in the transition state. One uses molecular weights for r^3 and calculates for the example discussed μ = 5.4 D. If two reactants with the dipole moments given here combined to a transition state with 5.4 D, then one should find no influence of solvent polarity on the rate.

The dipole moment of the isoxazolidine derivative, however, amounts to 2.48 D. When concertedness denotes a continuous conversion from reactants to products, then a transition state of lower polarity than 5.4 D is to be expected, and a loss of solvation energy during activation should be the consequence.

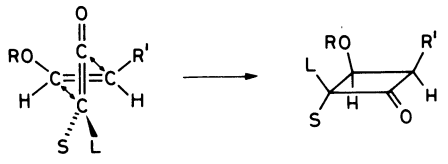
Why is the rate decrease so very small ? The formation of the two new σ-bonds is concerted, but not synchronous. The term "synchronous" characterizes the special case in which the new σ-bonds are equally developed percentage-wise in the transition state. Two musical instruments may play in concert, but with different volumes of sound. Analogously, two new σ-bonds can be created in concert, but to a dissimilar extent in the transition state. Unequal bond formation goes along with partial charges which may somewhat increase the dipole moment of the transition state.

An additional reason for the scanty influence of solvent polarity on the rate of concerted cycloadditions lies in their early transition state. A wealth of evidence points to the reactant-like structure of the transition state (Ref. 21,24). If bond-making has not progressed very far, the polarity change during the activation process must be small, too. Thus, the minor solvent influences on Diels-Alder and 1,3-dipolar cycloadditions are as valuable a diagnostic tool as the large effects observed for zwitterion formation in 2 + 2 cycloadditions.

DICHOTOMY OF PATHWAYS IN KETENE CYCLOADDITIONS

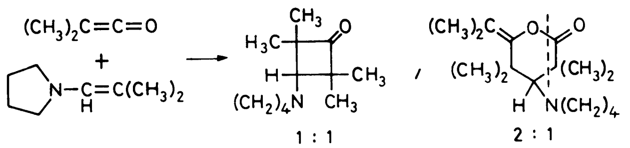
Ketenes undergo 2 + 2 cycloaddition reactions with electron-rich olefins. The additions to cis,trans isomeric enol ethers are stereospecific (Ref. 25). They show unique features in the steric course and in their structure-rate relationship (Ref. 26,27) which cannot be discussed here. The dependence of the rate on solvent polarity is of medium size (Ref. 26). The concerted pathway $({}_{\pi}2_a + {}_{\pi}2_s)$ proposed by the late R.B. Woodward offers the best description (Scheme 5, Ref. 20). A secondary orbital interaction between the electrophilic carbonyl orbital and those of the nucleophilic vinyl ether generates partial charges in the transition state.

Scheme 5



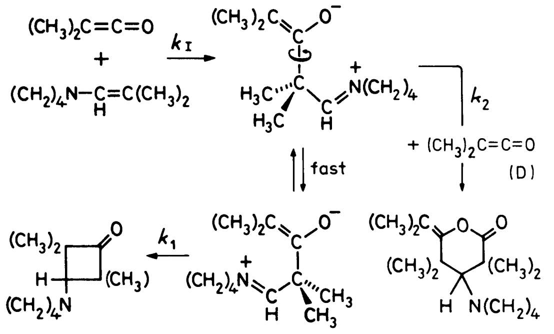
Hasek and Martin (Ref. 28) observed that dimethylketene and N-isobutenyl-dialkylamines give rise to 2 : 1 adducts besides the customary 1 : 1 adducts of the cyclobutanone type. The 2 : 1 adducts turned ou to be δ-methylene-δ-valerolactone derivatives (Ref. 29). It was noticed in our laboratory that the ratio of

Scheme 6



2 : 1 adduct to 1 : 1 adduct rises with increasing concentration of dimethylketene (Ref. 30). The cyclobutanone is not converted to the 2 : 1 adduct with additional dimethylketene. How is the 2 : 1 adduct formed ?

Scheme 7

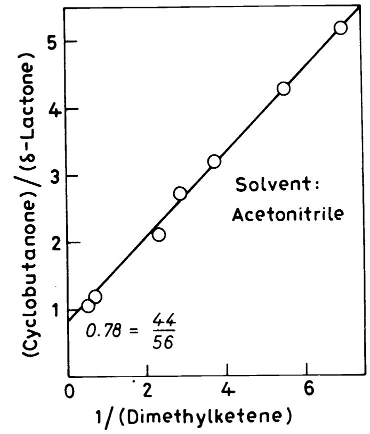


A zwitterionic intermediate is conjectured and illustrated in Scheme 7 by two rotamers in a mobile equilibrium. The iminium-enolate zwitterion produced from the reactants by the rate-determining step k_I should be a high-energy intermediate which quickly enters into competing reactions via its rotameric forms. The cyclization with k_1 is of first order, whereas the addition to another molecule of dimethylketene takes place with the second-order constant k_2. This trapping reaction constitutes a 1,4-dipolar cycloaddition and has many analogies (Ref. 31).

The reaction proceeds quantitatively and the mixture of cyclobutanone and δ-lactone can be analyzed by NMR. In several experiments, carried out by Peter Otto (Ref. 32), the enamine was reacted with 6 - 7 equivalents of dimethylketene, whereby the concentration of the reactants was varied by dilution with the solvent acetonitrile. If the kinetic system is correct, the ratios of cyclobutanone and δ-lactone should define a straight line through the origin when plotted versus the reciprocal dimethylketene concentration D.

Seven experiments were run in acetonitrile as solvent. The ratios of four-membered to six-membered ring products indeed determine a linear function of the inverse dimethylketene concentration (Fig. 7). Thus, the competition of unimolecular ring closure and bimolecular adduct formation is a reality. That the straight

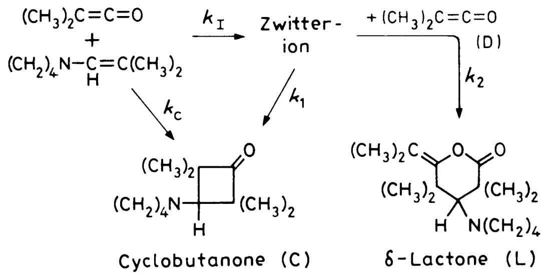
Fig. 7 Dimethylketene and N-isobutenylpyrrolidine in acetonitrile at 20°C; dependence of product ratio on dimethylketene concentration



line does not go through the origin, however, is a flaw of grave consequence. With 1/D = 0 one reaches the fictitious infinite concentration of dimethylketene; here, the zwitterionic species should be completely trapped to give the δ-lactone. The linear function shows an intercept on the ordinate of 0.78; 0.78 is 44/56. There is only one reasonable explanation: 44 % of the cyclobutanone must be generated by a second pathway in which the material does not become exposed to the competition with bimolecular δ-lactone formation.

That two reactants - in our example dimethylketene and N-isobutenylpyrrolidine - furnish one and the same product by two different pathways is not a unique phenomenon in organic chemistry. What is the second reaction ? Probably the scheme has to be supplemented by an additional step, namely the direct formation of the cyclobutanone from ketene and enamine by the concerted ($_{\pi}2_{a}$ + $_{\pi}2_{s}$) route. This pathway is delineated in Scheme 5 for ketene plus enol ether.

Scheme 8



Steady State Treatment

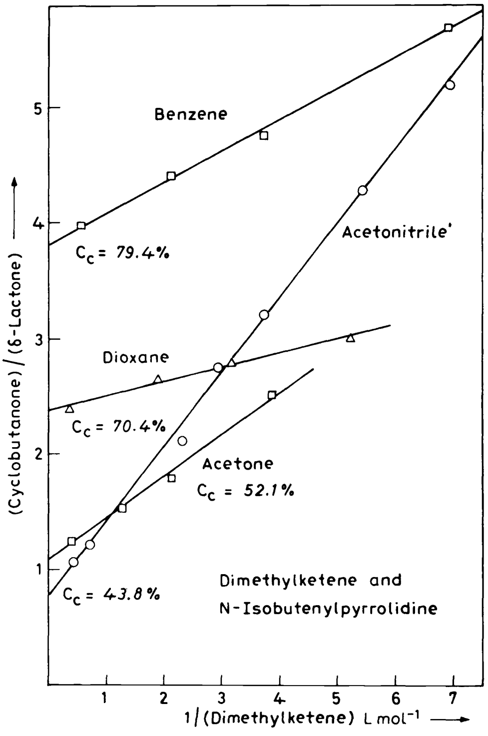
$$\frac{dC}{dL} = \frac{\left(k_C + \dfrac{k_I k_1}{k_1 + k_2 D}\right)}{\dfrac{k_I k_2 D}{k_1 + k_2 D}} = \frac{k_C k_1 + k_C k_2 D + k_I k_1}{k_I k_2 D}$$

$$\frac{C}{L} = \frac{k_C}{k_I} + \frac{k_1}{k_2}\left(1 + \frac{k_C}{k_I}\right)\frac{1}{D}$$

Intercept k_C/k_I

The rate constant k_C in Scheme 8 refers to the one-step cycloaddition whereas the two-step reaction proceeds via the zwitterion by k_I and k_1. Thus, one faces a double branching of the reaction paths, first at the reactant level (k_C and k_I) and afterwards at the zwitterion as a high-energy intermediate (k_1 and k_2D). The concentrations of cyclobutanone and δ-lactone may be denoted by C and L. The steady-state treatment (Scheme 8) provides again a linear dependence of C/L, the ratio of cyclobutanone and δ-lactone, on 1/D, the reciprocal dimethylketene concentration. The intercept of the straight line is k_C / k_I, i.e., the ratio of the rate constants of the concerted cycloaddition and the zwitterion formation. The ratio k_1 / k_2 of the two reactions competing for the zwitterion shows up in the slope combined with k_C / k_I.

Fig. 8 Dependence of product ratio on dimethylketene concentration in various solvents



Linear functions of product ratios versus 1/D are combined in Fig. 8 for four solvents. Further data for cyclohexane, chloroform and chlorobenzene are omitted for the sake of clarity. The intercepts provide via k_C / k_I the percentage contributions of the concerted mechanism which rise with decreasing solvent polarity. In the same sequence the part of the supposed zwitterion mechanism diminishes. The crossing of the straight lines reveals that the slopes which contain k_1 / k_2 do not vary systematically with k_C / k_I, the intercepts.

Kinetic results never prove a conjectured mechanism, but establish compatibility at best. Enamine and dimethylketene enter into parallel reactions with the ratio k_C / k_I as disclosed by the intercept. One branch is connected with a second set of parallel reactions, which produce cyclobutanone and δ-lactone, respecti-

Table 9. Dimethylketene and N-isobutenylpyrrolidine; rate constants of one-step and two-step processes at 25°C

Solvent	% Concerted (k_C)	% Zwitterion via k_I	k_1/k_2 (mol L^{-1})	k_2 overall	k_C	k_I
				10^4 (L mol^{-1} sec^{-1})		
Cyclohexane	~92	~8	0.15	1.35	1.24	0.11
Benzene	79.4	20.6	0.055	11.3	9.0	2.3
Dioxane	70.4	29.6	0.037	17.0	12.0	5.0
Chlorobenzene	~73	~27	~ 0.11	23.1	16.9	6.2
Chloroform	63.4	36.6	0.60	36.5	23.1	13.4
Acetone	52.1	47.9	0.17	71.8	37.4	34.4
Dimethylformamide	–	–	–	97.9	–	–
Acetonitrile	43.8	56.2	0.36	105.9	46.4	59.5

vely. However, any statement about the mechanistic nature of the pathways will be discredited as science fiction by the puritan in kinetics. Here the influence of solvent polarity proves helpful (Ref. 32).

The first and second figure columns of Table 9 indicate that with increasing solvent polarity the percentage of the one-step mechanism decreases in favor of the two-step mechanism which rises from 8 % in cyclohexane to 56 % in acetonitrile. Thus, the two-step mechanism via k_I involves a higher charge separation than the branch with k_C.

$$\text{Overall Rate:} \quad -\frac{dD}{dt} = k_C ED + k_I ED \left(1 + \frac{k_2 D}{k_1 + k_2 D}\right) \tag{3}$$

$$\text{For } k_1 \gg k_2 D: \quad -\frac{dD}{dt} = \left(k_C + k_I\right) ED = k_{2\,\text{overall}}\, ED \tag{4}$$

Photometric measurement of dimethylketene consumption furnished the overall rate constants for the interaction with N-isobutenylpyrrolidine in various solvents (Table 9). The rate equation (3) displays a complex dependence on D, the dimethylketene concentration; E denotes the concentration of enamine. Due to a low initial concentration of dimethylketene in the rate measurements, k_1 becomes larger than k_2D and eq. (3) simplifies to the second order eq. (4) with good approximation. The overall k_2 values are now divided into the partial rate constants k_C and k_I according to their percentage contributions. Obviously, k_I increases much faster than k_C with rising solvent polarity (Table 9).

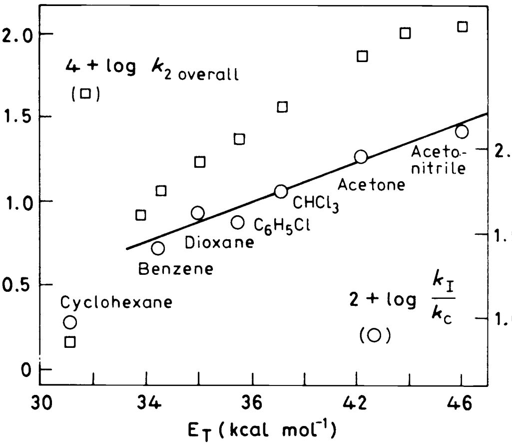


Fig. 9 Dimethylketene and N-isobutenylpyrrolidine; dependence of overall rate constant and of ratio k_I / k_C on solvent polarity

The squares in the diagram of Fig. 9 are the logarithms of the overall rate constants k_2. They increase continuously with the E_T values, but not in a linear mode. The circles are the logarithmic rate ratios k_I/k_C, i.e., zwitterion formation and concerted pathway; their increase with E_T is linear - except for the cyclohexane value - and indicates that k_I is more sensitive to solvent polarity than k_C.

The rate constant k_C is in acetonitrile 37 times larger than in cyclohexene. That suits the concerted mechanism ($_{\pi}2_a + {_{\pi}2_s}$) with its partial charges in the transition state. The 540-fold acceleration of k_I signals a greater charge separation during the activation process, well in accordance with the assumed zwitterion formation (Table 10).

Table 10. Ratios of rate constants in acetonitrile and in cyclohexane

	$k_{\text{Acetonitrile}}/k_{\text{Cyclohexane}}$
Overall Rate k_2	78
Concerted Pathway k_c	37
Zwitterion Formation k_I	540

EPILOGUE

The application of the solvent influence on the reaction rate as a mechanistic criterion requires care and critical attitude. One-step processes pose much less of a problem than complex reactions, to which two of the three model reactions discussed above belong. A reasonable idea about the energy profile is indispensible for the treatment of complex reactions. In consecutive reactions, the relative height of the activation barriers of the first and second step has to be considered, because solvent influences may compensate.

Of course, large and small effects of solvent polarity on rate are more conclusive than values of the middle range. In the elucidation of reaction mechanisms, the solvent dependence should always be used in conjunction with other diagnostic tools.

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