

SOLVENT EFFECTS ON CHEMICAL REACTIVITY

Christian Reichardt

Department of Chemistry, Philipps-University,

Hans-Meerwein-Straße, D - 3550 Marburg, Fed. Rep. Germany

Abstract - Typical examples for different types of solvent effects on chemical reactivity are given, e. g. solvent effects on reaction rates, on the position of chemical equilibria, on competitive reaction mechanisms, on dichotomic reaction paths, on chemoselectivity, and on stereoselectivity. According to their solvent sensitivity, most organic reactions can be classified into dipolar transition-state reactions, isopolar transition-state reactions, and free-radical transition-state reactions, typical examples of which are given.

Attempts to describe the solvation capability by virtue of empirical parameters of solvent polarity are mentioned. Particular attention is merited by the $E_T(30)$ -parameter, an empirical parameter derived from a negatively solvatochromic pyridinium-N-phenolate betaine dye as reference compound. Some examples of the application of this $E_T(30)$ -scale to solvent-sensitive chemical reactions are given.

INTRODUCTION

In 1862, Marcelin Berthelot, Professor at the Collège de France in Paris (Fig. 1) and his coworker Léon Péan de Saint-Gilles carried out a remarkable experiment (Ref. 1): They mixed together equivalent amounts of acetic acid and ethanol and measured the rate of esterification by determining at distinct time intervals the amount of the resulting ethyl acetate.

In order to study the influence of temperature on the reaction rate, one part of the reaction mixture was put in the cool cellar, whereas the other part was kept in the warmer laboratory rooms. The influence of the reaction volume (i.e. the concentration of the reaction partners) was examined by diluting the reaction mixture with different inert organic solvents such as diethyl ether and benzene.

It happens that - at constant temperature, time and concentration - the reaction rate was very low in the ethereal solution, only traces of ester could be detected. In benzene solution, however, a substantial amount of ester was formed. In their classical paper "Recherches sur les affinités", published in 1862, Berthelot and St. Gilles stated that "... the esterification is disturbed and decelerated on the addition of neutral solvents not belonging to the reaction" (Ref. 1). That was the first experimental observation showing that solvents may have an influence on chemical reactions.

But these interesting results seem to have been forgotten for many years. It was only in 1887 that Nicolai Menshutkin (Fig. 2), Professor at the University of Sankt Petersburg, again took up these investigations.

After thorough studies on the esterification reaction and on the alkylation of tertiary amines with alkyl halides, he concluded, in 1890, that a reaction cannot be separated from the medium in which it is performed (Ref. 2).



Fig. 1. Marcelin Berthelot
(1827 - 1907)
[GDCh-Bildarchiv,
Frankfurt].

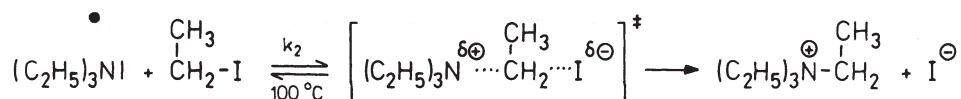


Fig. 2. Nikolai Menshutkin
(1842 - 1907)
[GDCh-Bildarchiv,
Frankfurt].

He found, for example, that a solvent change from *n*-hexane to benzyl alcohol for the reaction between triethylamine and ethyl iodide causes a 742-fold rate increase (Fig. 3).

Solvent Effect on Reaction Rate:

S_N2 Displacement Reaction of Triethylamine with Ethyl Iodide



Solvent	<i>n</i> -Hexane	Benzene	Methanol	Benzyl alcohol
k_2^{rel}	1	36	287	742
solvent polarity				

Fig. 3. Solvent effects on a Menshutkin reaction (Ref. 2).

After strong efforts to find a correlation between this kind of solvent effect and distinct physical or chemical properties of the solvents used, he stated resignedly in 1900 that there is only a very loose connection between the physical properties of organic solvents and their influence on reaction rates. This statement, even now, 120 years after the first discovery of solvent effects on reaction rates, is to some extent still valid.

The influence of solvents on the position of chemical equilibria was discovered for the first time in 1896 by Ludwig Claisen in Aachen (Ref. 3),

Arthur Hantzsch in Würzburg (Ref. 4), Ludwig Knorr in Jena (Ref. 5), and Johannes Wislicenus in Würzburg (Ref. 6), simultaneously with the discovery of keto-enol tautomerism in β -dicarbonyl compounds, an example of which is shown in Fig. 4 (Ref. 7, 8).

Solvent Effect on Chemical Equilibrium :

Keto-Enol Tautomerism of Ethyl Acetoacetate

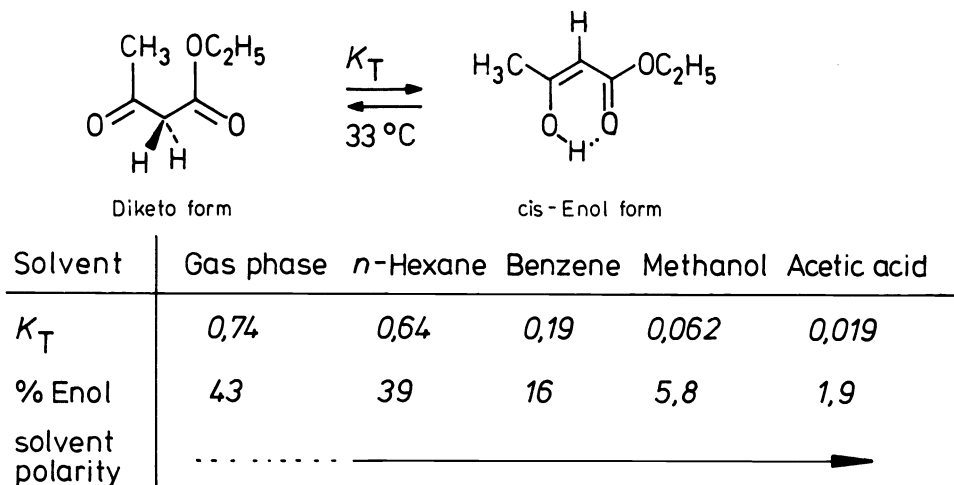


Fig. 4. Solvent effects on a tautomeric equilibrium (Ref. 7, 8).

The tautomeric equilibrium constants of ethyl acetoacetate for this cis-enolizing β -dicarbonyl compound indicate an increasing enol content with decreasing solvent polarity.

TYPES OF SOLVENT EFFECTS ON CHEMICAL REACTIVITY

This short historical introduction has already given two examples of solvent effects on reaction rates and chemical equilibria. Dealing with solvent effects on chemical reactivity includes, however, a greater variety of solvent effects. Four typical examples, taken mainly from recent publications, are shown in Fig. 5 ... 8.

First, a solvent can drastically change the mechanism of a reaction. An example is the thermolysis of arene diazonium salts in solution (Fig. 5),

Solvent Effect on Competitive Reaction Mechanisms :

Dediazoniation of Arenediazonium Salts

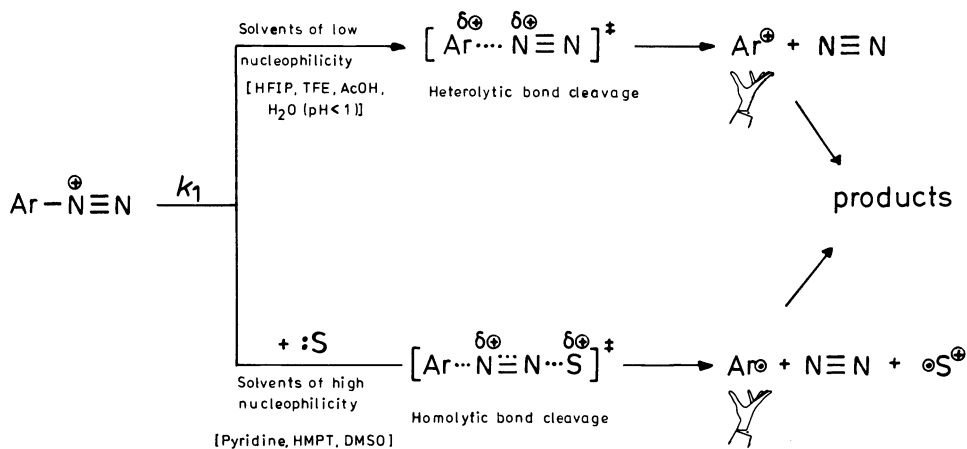


Fig. 5. Solvent effects on competitive reaction mechanisms (Ref. 9).

where two competitive reaction mechanisms have been established. These investigations were mainly carried out by Zollinger and his coworkers (Ref. 9).

In solvents of low nucleophilicity such as hexafluoroisopropanol (HFIP) or trifluoroethanol (TFE) the first and rate-limiting step is a heterolytic cleavage of the diazonium ion to give an aryl cation and molecular nitrogen, followed by rapid reaction of the cation with any available nucleophile.

In solvents of high nucleophilicity and low redox potential such as pyridine or dimethylsulfoxide (DMSO), however, a homolytic decomposition of the diazonium ion is favoured to give an aryl radical and consequent reaction products.

Thus, depending on the solvent used, a substrate can react by two completely different reaction mechanisms, as shown by this dediazonation reaction.

Different reaction mechanisms and sometimes different reaction products can be obtained from the same reaction partners simply by changing the solvent. A nice example of this is the cycloaddition reaction of an imidazo[2,1-b]thiazole with dimethyl acetylene dicarboxylate (Fig. 6), which has been studied by Abe and coworkers (Ref. 10).

Solvent Effect on Dichotomic Reaction Paths:

Cycloaddition Reaction of Imidazo[2,1-b]thiazole with Dimethyl Acetylenedicarboxylate

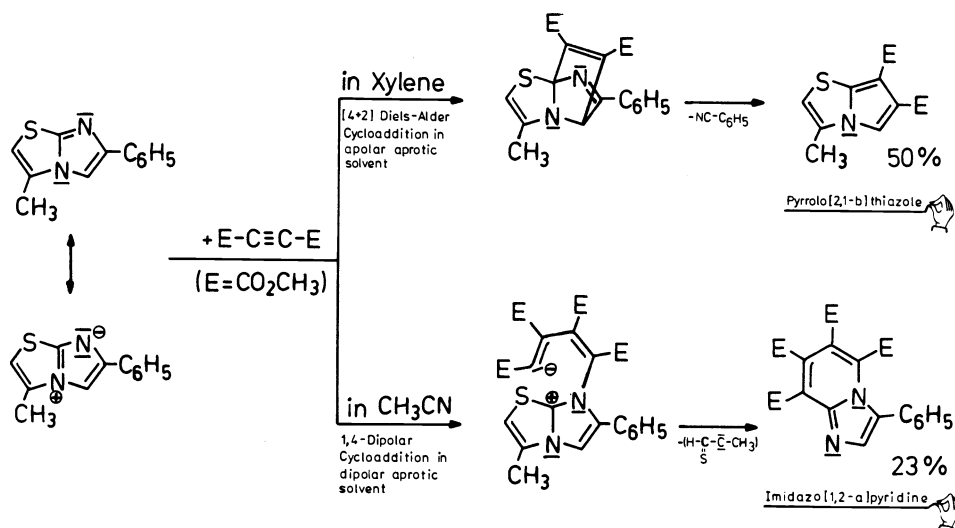


Fig. 6. Solvent effects on dichotomic reaction paths (Ref. 10).

In an apolar aprotic solvent such as xylene, a normal Diels-Alder reaction takes place to give as the final product a pyrrolo[2,1-b]thiazole. However, when the same reaction is carried out in a dipolar aprotic solvent such as acetonitrile, an imidazo[1,2-a]pyridine is obtained as the result of an 1,4-dipolar cycloaddition reaction.

This cycloaddition reaction clearly demonstrates that the choice of solvent can determine the principal product of a reaction.

A further example shows the solvent effect on chemoselectivity, i.e. on functional group differentiation (Fig. 7).

The reduction of the bifunctional compound 11-bromoundecyl tosylate with lithium aluminium hydride in different solvents has been examined by Krishnamurthy (Ref. 11). In diethyl ether, the reaction proceeds with the selective reduction of the tosylate group to give n-undecyl bromide, whereas in diglyme, the bromine substituent is selectively reduced to yield n-undecyl tosylate.

This reaction is an impressive example of how solvents can be used to modify both the chemoselectivity and reactivity of a complex metal hydride. Thus, by a careful choice of solvent, it should be possible, using the same reagent, to selectively react the various functional groups in an organic molecule.

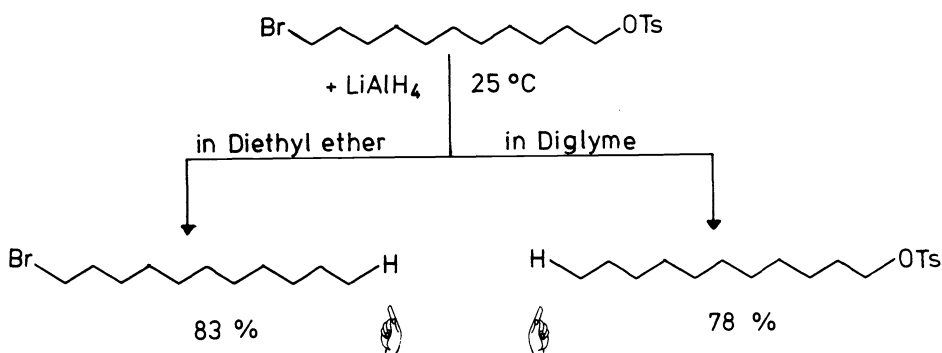
Solvent Effect on Chemoselectivity:Reduction of 11-Bromoundecyl Tosylate with LiAlH_4 

Fig. 7. Solvent effects on chemoselectivity (Ref. 11).

One unusual example of solvent effects on the stereoselectivity of a reaction is the Grignard-reaction between racemic 3-phenylbutanone and phenylmagnesium bromide (Fig. 8). This reaction has been studied in solvents of different polarity by Pérez-Ossorio and coworkers (Ref. 12).

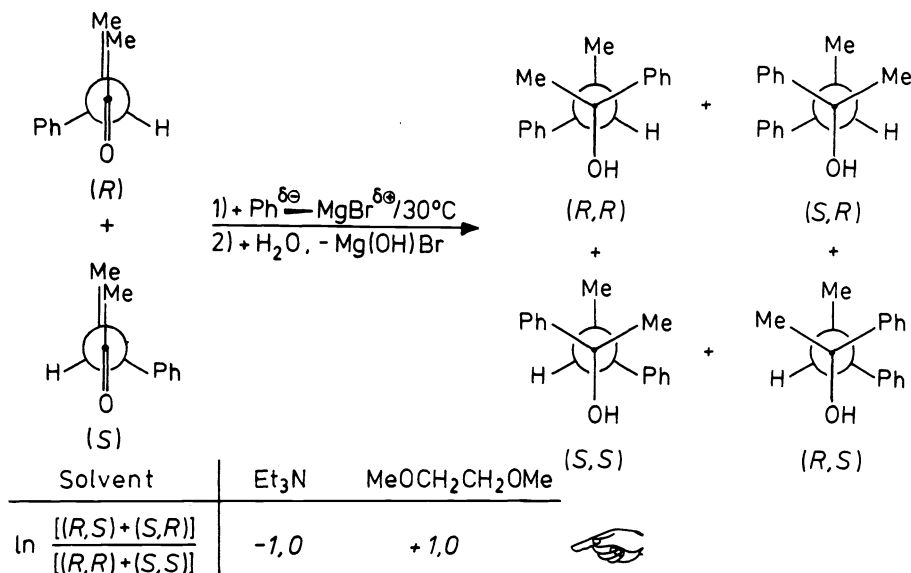
Solvent Effect on Stereoselectivity:Grignard-Reaction between (\pm)-3-Phenylbutanone and $\text{C}_6\text{H}_5\text{MgBr}$ 

Fig. 8. Solvent effects on stereoselectivity (Ref. 12).

The reaction of this ketone with the Grignard reagent should lead to two pairs of enantiomers, the (R,R)- and (S,S)- as well as the (S,R)- and (R,S)-forms. Interestingly enough, the ratio in which these two pairs of enantiomers are formed, is strongly solvent-dependent as shown by the figures in the table (Fig. 8). In going from the apolar triethylamine to the more polar glyme, an increasing amount of the (S,R)- and (R,S)-form is formed (from 26 to 73 %).

Therefore, the activated complex leading to the (S,R)- and (R,S)-product must be more dipolar and hence more strongly solvated in polar solvents.

In conclusion, the extent of asymmetric induction in nucleophilic reactions of chiral carbonyl compounds is not only sterically controlled (cf. Cram's Rule), but may also be influenced to some extent by the solvent.

A similar example of solvent effects on stereoselectivity has been found recently by Benoiton et al. in the solvent-dependent synthesis of epimeric dipeptides (Ref. 13).

These four examples have already given us a strong impression of the different ways in which solvents can affect chemical reactivity. However, the second part of this review will deal with only one aspect, namely the influence of the solvent on reaction rates together with the various solvent properties responsible for it. Rate constants are fairly sensitive indicators of even small, solvent-induced energy differences: a change of 10 % in the rate at 25 °C corresponds to a change of only 250 Joule/Mol (ca. 60 cal/mol) in the free energy of activation.

CLASSIFICATION OF ORGANIC REACTIONS BY MEANS OF THEIR SOLVENT SENSITIVITY

In the light of the transition-state theory, solvent effects on rate constants depend on the relative stabilization of the reactant molecules and the corresponding activated complex through solvation. An understanding of the factors which control the solvent dependence of reaction rates requires knowledge of both the direction and magnitude of the changes which occur in the educt and transition state solvation.

The early pioneering work of Hughes and Ingold in the 1930's in nucleophilic substitution and elimination reactions is well known (Ref. 14, 15, 16). Using a simple qualitative solvation model which allows only pure electrostatic interaction between ions or dipolar molecules and solvent molecules in both the initial and transition states, they divided all nucleophilic substitution and elimination reactions into different charge types. Based on reasonable assumptions as to the expected extent of solvation in the presence of electric charges, they stated that, a change to a more polar solvent will either increase or decrease the reaction rate, depending on whether the activated complex is more or less dipolar than the initial state. A change in solvent polarity will have a negligible effect on the rates of reactions which involve little or no change in the charge density on going from reactants to the activated complex.

A more general classification of organic reactions with respect to solvent effects, not restricted to substitution and elimination reactions, is shown in Fig. 9 (Ref. 17).

Classification of Organic Reactions

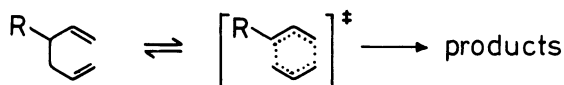
(a) Dipolar Transition State Reactions: Large solvent effects

e.g.



(b) Isopolar Transition State Reactions: Small solvent effects

e.g.



(c) Free-Radical Transition State Reactions: Small solvent effects

e.g.

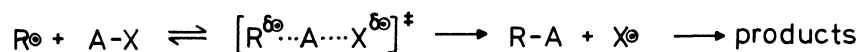
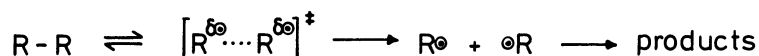


Fig. 9. Classification of organic reactions

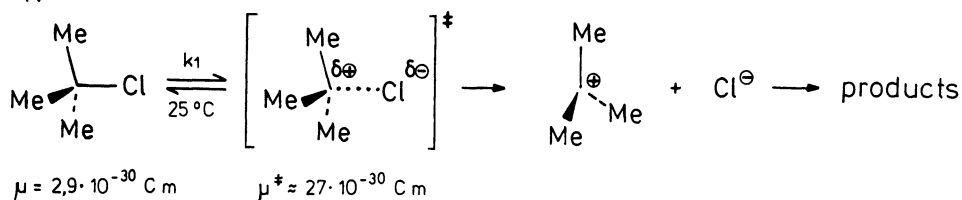
According to this scheme, organic reactions can be roughly divided into three classes depending on the character of the activated complex involved: dipolar, isopolar and free-radical transition state reactions.

Here are now some typical examples, chosen from the recent literature to illustrate the theoretical and practical usefulness of this classification. These examples show for which reactions a solvent change may be useful in obtaining a desired rate acceleration.

Dipolar transition state reactions with large solvent effects can be found amongst ionization, displacement, elimination, and fragmentation reactions. The Figs. 10 and 11 show two examples.

A Dipolar Transition State Reaction: Large solvent effect

S_N1 Solvolysis of *tert*-Butylchloride



Solvent	Benzene	Acetone	DMF	Methanol	Water
k_1^{rel}	1	$1,9 \cdot 10^2$	$4,8 \cdot 10^3$	$1,1 \cdot 10^6$	$4,2 \cdot 10^{10}$
solvent polarity	—————▶				

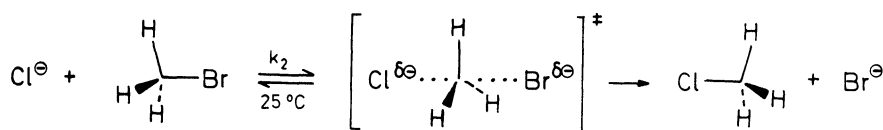
Fig. 10. Solvent effects on the S_N1 solvolysis of *tert*-butylchloride (Ref. 18, 19).

A classical example is the S_N1 solvolysis of *tert*-butylchloride (Fig. 10). The transition state of this ionization reaction involves a partial separation of unlike charges. The increased solvation of the resulting dipolar activated complex relative to the less dipolar starting molecule, leads to a huge rate acceleration with increasing solvent polarity. The rates differ by 10 powers of ten in going from benzene to water (Ref. 18, 19). Protic solvents such as methanol and water play an additional role in this case: they act as an hydrogen-bond donating electrophile by solvating the incipient chloride ion.

In strong contrast to the ion-forming solvolysis of *tert*-butylchloride, the S_N2 displacement reaction between chloride ions and uncharged methylbromide is much slower in water than in dipolar aprotic solvents (Fig. 11).

A Dipolar Transition State Reaction: Large solvent effect

S_N2 Displacement Reaction of Methylbromide with Chloride Ion



Solvent	Protic solvents		Dipolar aprotic solvents		Gas phase
	Water	Methanol	DMF	Acetone	No solvent
k_2^{rel}	1	1,3	$8 \cdot 10^4$	$6 \cdot 10^5$	$2 \cdot 10^{15}$
E_a [kJ/mol]	ca. 1		ca. 10^5		ca. 10^{15}
solvent polarity	←—————▶				

Fig. 11. Solvent effects on a S_N2 displacement reaction (Ref. 20, 21, 22).

This difference can be as large as 5 powers of ten (Ref. 20). Due to the dispersal of negative charge during the activation process, the transition state is less solvated in solvents of increasing polarity. In going from dipolar aprotic to protic solvents, the chloride ion is further stabilised through hydrogen-bonding. The result is that in water the initial reactants are much more stabilised than the large transition state anion, so the free energy of activation is higher in water and the reaction is therefore slower.

This ionic S_N2 reaction is one of the rare examples which have been studied both in solution and in the gas phase (Ref. 21, 22). A new technique, called Pulsed-Ion Cyclotron -Resonance Spectrometry (ICR mass spectrometry), makes it possible to examine reactions of isolated ions and molecules in the absence of any solvation (Ref. 23, 24).

Until recently, mainly solution-phase data have been used in attempts to describe nucleophilicities and leaving-group abilities in terms of the structural and thermodynamic properties of the reactants. Solvent interference, however, makes it difficult to distinguish the intrinsic properties of the reactants from the solvation effects. In the absence of solvent molecules the intrinsic reactivity of the naked reactants can be measured and distinguished from the effects attributable to solvation.

The result in this case is truly remarkable. In the gas phase the reaction of chloride ion with methylbromide is faster by a factor of 15 powers of ten than it is in water. Whereas in solution the activation energy amounts up to 103 kJ/mol, in the gas phase the reaction possesses an intrinsic activation energy of only 11 kJ/mol (Ref. 20, 21). These and other results lead to the conclusion that reaction rates in solution are primarily determined by the amount of energy needed to destroy the solvation shells during the activation process, and only to a minor extent by the intrinsic properties of the reactants. In other words, in solution reactions the solvent is almost solely responsible for the observed rate constants.

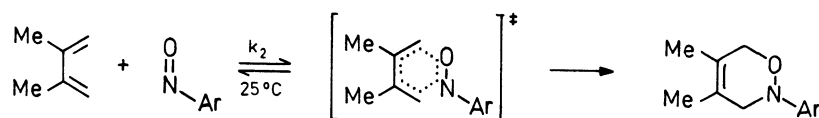
Another class of organic reactions showing only small solvent effects are isopolar transition state reactions. By definition, isopolar activated complexes differ very little in charge distribution from the initial reactants and can be found in pericyclic reactions such as cycloaddition, sigmatropic, electrocyclic, and cheletropic reactions. Two examples shall illustrate the lack of solvent sensitivity of pericyclic reactions (Figs. 12 and 13).

Only a very small solvent effect, a factor of two, is found in the Diels-Alder-cycloaddition reaction of 2,3-dimethylbutadiene with 4-chloro-1-nitrobenzene (Fig. 12). This supports the formulated one-step mechanism with synchronous bond formation without any creation, destruction or dispersal of charge during the activation process (Ref. 25, 26).

The [3,3]sigmatropic rearrangement of allyl S-methyl xanthate also exhibits a low sensitivity to solvent polarity (Fig. 13). The reaction in polar glycol is only 21 times faster than it is in apolar n-hexadecane (Ref. 27). This confirms the concerted reaction mechanism which involves very little change in charge separation between the initial and transition states.

An Isopolar Transition State Reaction: Small solvent effect

[4+2] Cycloaddition of 2,3-Dimethylbutadiene with 4-Chloro-1-nitrosobenzene



Ar = -C₆H₄-p-Cl

Solvent	Toluene	Dichloromethane	Ethanol	Nitrobenzene
k_2^{rel}	1,0	1,4	2,0	2,2
ΔG^\ddagger [kJ/mol]	87,0	86,2	85,4	
solvent polarity	—————→			

Fig. 12. Solvent effects on a Diels-Alder cycloaddition reaction (Ref. 25)

An Isopolar Transition State Reaction: Small solvent effect

[3,3] Sigmatropic Rearrangement of Allyl S-Methyl Xanthate

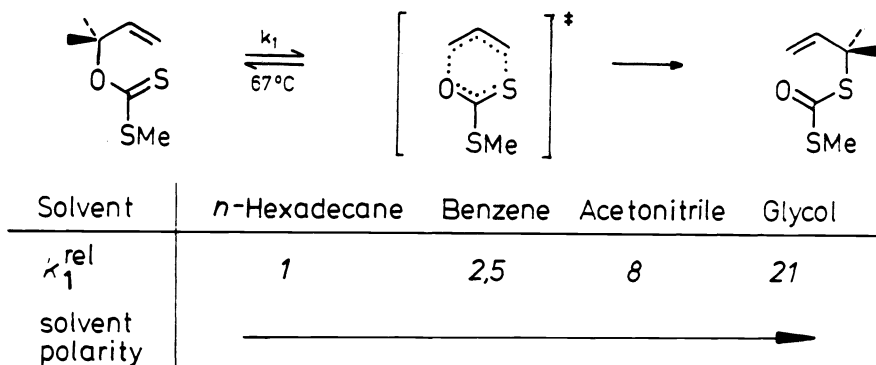
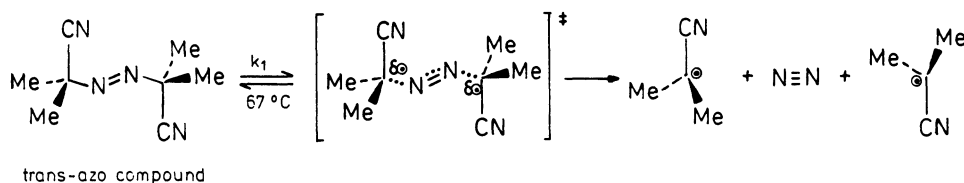


Fig. 13. Solvent effects on the rearrangement of allyl S-methyl xanthate (Ref. 27).

A third category of organic reactions involves free-radical transition states, formed by the creation of unpaired electrons during radical pair formation or atom transfer reactions. In reactions of this type only negligible solvent effects have been normally observed. When the solvent itself, however, participates as a reactant and is incorporated into the products of the reaction, the situation is different. Two typical examples are shown in Figs. 14 and 15.

A Free-Radical Transition State Reaction: Small solvent effect

Thermolysis of Azobisisobutyronitrile



Solvent	Decalin	Chlorobenzene	<i>o</i> -Dichlorobenzene	<i>N,N</i> -Dimethylaniline
k_1^{rel}	1,0	1,4	1,5	1,6
E_a [kJ/mol]	148	133	131	128
solvent polarity	—————→			

Fig. 14. Solvent effects on the thermolysis of azobisisobutyronitrile (Ref. 28).

The thermolysis of azobisisobutyronitrile (Fig. 14), an apolar trans-azo compound, is not at all sensitive to medium effects as shown by the nearly equal relative first-order rate constants measured in different solvents (Ref. 28). This is in agreement with a homolytic, concerted two-bond scission mechanism, producing two neutral radicals as intermediates without any charge separation.

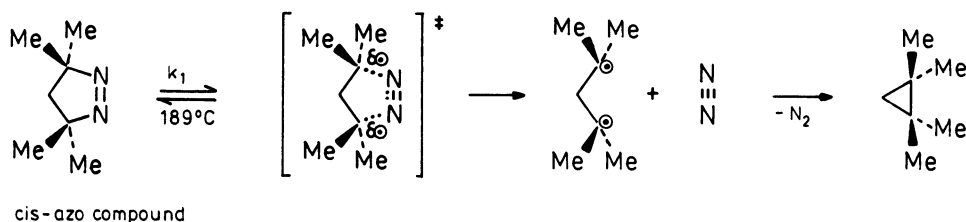
Contrary to the negligible solvent effect obtained in the decomposition of trans-azo alkanes, the thermolysis of cis-azo alkanes such as 3,3,5,5-tetramethyl-1-pyrazoline reveals a small but significant solvent effect (Fig. 15). Again, there is no charge separation during the activation process. But a cis-azo compound exhibits a small permanent dipole moment, which is lost during the reaction. Therefore, with increasing solvent polarity the reaction rate decreases due to the better solvation of the dipolar starting molecule (Ref. 29, 30).

In conclusion, it can be stated that a great variety of organic reactions can be reasonably classified according to their sensitivity to changes in the surrounding medium. Vice versa, the application of the solvent influence

on a reaction as a criterion for the elucidation of its mechanism is also possible. Unfortunately, investigations of solvent effects on rates have often been studied only in a very small number of solvents (sometimes only two). In such cases, no far-reaching conclusions about the interrelation between solvent effect and reaction mechanism can be drawn. As a rule, the reaction under consideration should be investigated in as many solvents of different polarity as possible. It is recommended to use a minimum of at least five solvents of different polarity in order to get a reliable picture of the solvent effect under study.

A Free-Radical Transition State Reaction: Small solvent effect

Thermolysis of 3,3,5,5-Tetramethyl-1-pyrazoline



Solvent	Gas phase	Ethylbenzene	Cyclohexanone	Glycol
k_1^{rel}	11	8	6	1
solvent polarity	----->			

Fig. 15. Solvent effects on the thermolysis of 3,3,5,5-tetramethyl-1-pyrazoline (Ref. 29, 30).

EMPIRICAL PARAMETERS OF SOLVENT POLARITY

Having discussed the solvent susceptibility of reactions, the question remains, which solvent property is responsible for medium effects, and whether it is possible to describe these solvent effects in a more quantitative manner.

Organic chemists usually attempt to understand solvent effects in terms of the polarity of the solvent. It is, however, not easy to define this property, and it is even more difficult to assess it quantitatively.

Seduced by the simplicity of electrostatic solvation models, attempts at expressing solvent polarity quantitatively, usually involve physical solvent properties such as dielectric constant, dipole moment, or refractive index. But this procedure is often inadequate, especially since it does not take account specific solute-solvent interactions like hydrogen-bonding, charge-transfer forces etc..

Hence, from a more practical point of view, it seems reasonable to understand solvent polarity in terms of the overall solvation capability of a solvent, this in turn being determined by the sum of all the molecular properties responsible for the solute-solvent interaction (Ref. 15, 31). It is obvious that solvent polarity thus defined cannot be described quantitatively by a single physical parameter.

In such situations other indices of solvent polarity are sought.

The lack of comprehensive theoretical expressions for calculating solvent effects and the inadequacy of defining solvent polarity in terms of simple physical constants has led to the introduction of pure empirical scales of solvent polarity (Ref. 31, 32, 33).

Based on the assumption, that particular solvent-dependent chemical reactions or spectral absorptions may serve as suitable model processes, reflecting all the possible solute-solvent interactions in the solvation game, several empirical parameters of solvent polarity have been introduced by different authors.

This approach is very characteristic of the experimental chemist, but it is regarded with mistrust by theoretical chemists. However, organic chemistry has always made use of the qualitative, empirical rule that similar compounds react in similar ways, and that similar changes in the structure or in the reaction medium produce similar changes in the chemical reactivity.

One of the first verifications of this rule was the introduction of the so-called Hammett equation for the calculation of substituent effects on chemical reactivity, using the ionization of substituted benzoic acids in water at 25 °C as a reference process (Ref. 34, 35).

The model processes used to establish such empirical scales of solvent polarity have been reviewed (Ref. 31, 32, 33). Only one of these parameters, introduced some years ago as the so-called E_T (30)-scale (Ref. 36), shall be mentioned and its application for the description and prediction of solvent effects on reaction rates will be shortly demonstrated.

Fig. 16

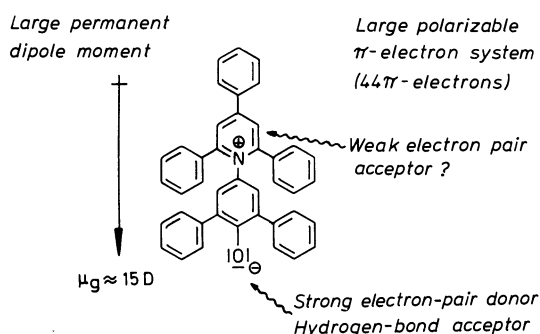
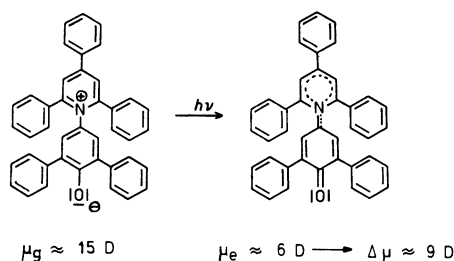


Fig. 16. Ground state properties of the standard 2,4,6-triphenyl-N-(2,6-diphenyl-4-phenoxide)-pyridinium betaine (no. 30 in Ref. 36).

Fig. 17



Solvent	C ₆ H ₅ OCH ₃	CH ₃ COCH ₃	i-C ₅ H ₁₁ OH	C ₂ H ₅ OH	CH ₃ OH
λ [nm]	769	677	608	550	515
E _T [kcal/mol]	37.2	42.2	47.0	51.9	55.5
Solution colour	yellow	green	blue	violet	red

$$E_T [\text{kcal/mol}] \cong h \cdot c \cdot \tilde{\nu} \cdot N = 2,859 \cdot 10^{-3} \cdot \tilde{\nu} [\text{cm}^{-1}]$$

Fig. 17. Solvent-dependent intramolecular charge-transfer absorption of the 2,4,6-triphenyl-N-(2,6-diphenyl-4-phenoxide)-pyridinium betaine, proposed as solvent polarity indicator (Ref. 37). μ_g and μ_e are the permanent dipole moments in the electronic ground and excited state of a betaine dye with two tert-butyl groups instead of the two 2,6-diphenyl groups next to the oxygen atom.

By virtue of its exceptionally large negative solvatochromism, the pyridinium-N-phenoxide betaine dye shown in Fig. 16 is particularly suitable as a standard dye for the determination of an empirical solvent parameter (Ref. 37). This betaine dye exhibits (i) a large permanent dipole moment of about 15 Debye, suitable for the registration of dipole-dipole and dipole-induced dipole interactions between solute and solvent, (ii) a large polarizable π -electron system, consisting of 44 π -electrons, suitable for the registration of dispersion interactions, and (iii) the phenolic oxygen atom represents a highly basic electron-pair donor centre, suitable for specific hydrogen-bond interactions with protic solvents.

With increasing solvent polarity, the long-wavelength absorption band of this betaine dye is shifted hypsochromically due to the increasing stabilization of the dipolar ground-state relative to the less dipolar first excited state (Fig. 17).

The long-wavelength solvatochromic absorption band is situated at 810 nm in diphenyl ether and at 453 nm in water as solvents. With the corresponding solvent-induced hypsochromic shift of 357 nm ($\cong \Delta E_T = 28 \text{ kcal/mol} = 117 \text{ kJ/mol}$), this betaine dye still holds the world record in solvatochromism.

The molar transition energies, E_T , of this betaine dye measured in kcal/mol, have been proposed as empirical parameters of solvent polarity (Ref. 36). A high E_T -value corresponds to high solvent polarity, i.e. the solvent has a high solvating ability.

Since the greater part of the solvatochromic range lies within the visible region, it is even possible to make a visual estimate of the solvent polarity. The solution color of this betaine dye is red in methanol, violet in ethanol, green in acetone, blue in isoamyl alcohol, and greenish-yellow in anisole. With suitable binary solvent mixtures, almost every colour of the visible spectrum can be obtained.

The limitations of the E_T -scale are: (i) no E_T -values can be obtained for acidic solvents since protonation of the phenolic oxygen atom of the betaine dye leads to disappearance of the solvatochromic absorption band; (ii) due to the low volatility of the betaine dye, no gas-phase E_T -values can be determined; and (iii) E_T -values for nonpolar solvents such as hydrocarbons cannot be directly measured due to the low solubility of the standard betaine dye in those solvents.

The last problem can be overcome by the use of alkyl-substituted betaine dyes (Ref. 36, 38). One recent example is shown in Fig. 18 (Ref. 38).

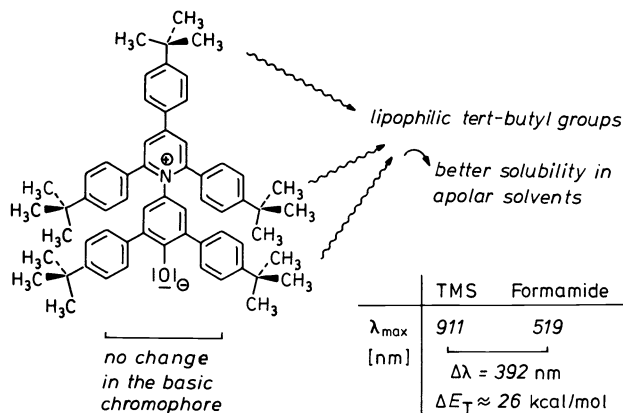


Fig. 18. A new secondary penta-tert-butyl-substituted betaine dye for the determination of $E_T(30)$ -values for non-polar solvents (Ref. 38).

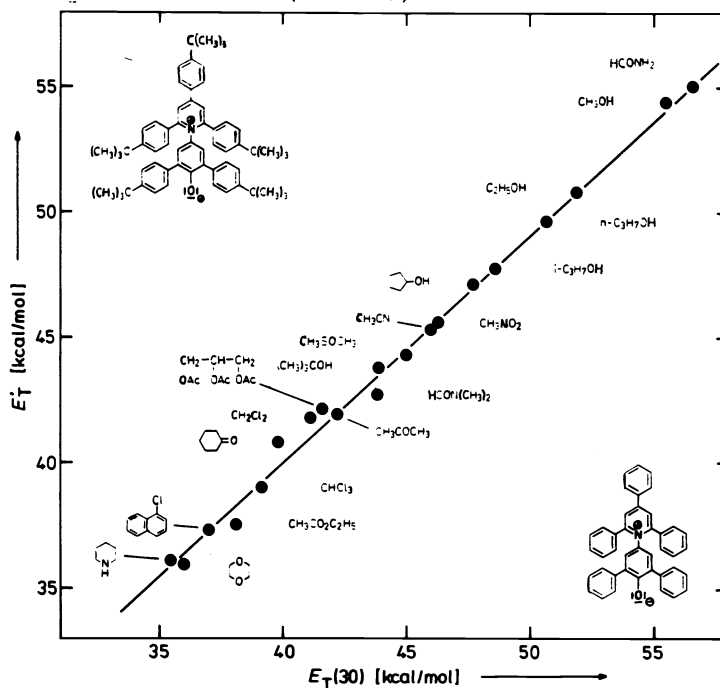


Fig. 19. Correlation between the E_T -values of 2,4,6-triphenyl-N-(2,6-diphenyl-4-phenoxide)-pyridinium betaine [$E_T(30)$ -values] and its penta-tert-butyl-substituted derivative (E_T' -values) for twenty solvents (Ref. 38).
 $E_T' = 0.914 \cdot E_T(30) + 3.43$ ($n = 20$; $r = 0.997$).

The introduction of five tert-butyl groups into the peripheric phenyl groups does not change the basic chromophore, but does yield a more lipophilic betaine dye. Although not more soluble in water it is now soluble in hydrocarbons such as n-hexane and even in tetramethylsilane (TMS).

The excellent linear correlation between the E_T -values of these two betaine dyes in twenty solvents allows the calculation of $E_T(30)$ -values for solvents in which the standard betaine dye is not soluble.

At present, $E_T(30)$ -values for more than 200 organic solvents and for many binary solvent mixtures are available (Ref. 31, 33).

Definition of E_T -Values and Normalized E_T^N -Values

$$E_T [\text{kcal/mol}] \equiv h \cdot c \cdot \tilde{\nu} \cdot N = 2,859 \cdot 10^{-3} \cdot \tilde{\nu} [\text{cm}^{-1}] \quad (1)$$

$$E_T^N \equiv \frac{E_T(\text{Solvent}) - E_T(\text{TMS})}{E_T(\text{Water}) - E_T(\text{TMS})} = \frac{E_T(\text{Solvent}) - 30,7}{32,4} \quad (2)$$

Correlation between the two scales:

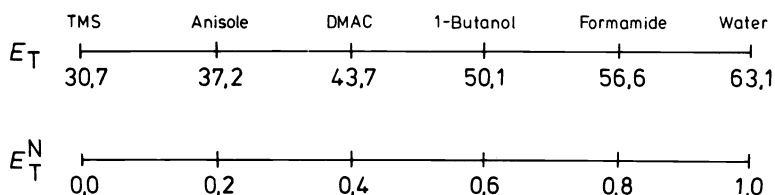


Fig. 20. Definition and correlation of E_T -values and normalized E_T^N -values.

Unfortunately, E_T -values have by definition the dimension of kcal/mol, a unit which should be abandoned in the framework of SI-units.

Therefore, the use of the so-called normalized E_T^N -values has been recently recommended (Ref. 38, 39). E_T^N -Values are defined according to equation (2) in Fig. 20 as the quotient of two differences: the difference between the E_T -values of the solvent under consideration and of tetramethylsilane, and the difference between the E_T -values of water and of tetramethylsilane. Hence, the corresponding E_T^N -scale ranges from 0.0 for tetramethylsilane, the least polar solvent, to 1.0 for water, the most polar solvent. These E_T^N -values are thus dimensionless numbers such as Hammett's σ substituent constants (Ref. 34, 35).

APPLICATIONS OF SOLVENT POLARITY PARAMETERS TO CHEMICAL REACTIVITY

Since solvent polarity parameters such as the E_T -scale are established in an empirical way, their usefulness has to be tested in the same manner. Therefore, some applications of the E_T -parameter to chemical reactivity shall be given, using some of the solvent-dependent reactions as examples which have been mentioned in the first part of this review (Figs. 21 ... 24).

The S_N1 solvolysis of tert-butylchloride has been already mentioned as an example of solvent effects on chemical reactivity (Ref. 18, 19). Fig. 21 shows the correlation between the E_T -values and the ionization rate of tert-butylchloride. The linear correlation between the solvent polarity parameter and the rate of this typical dipolar-transition-state reaction is so good that rate constants for further solvents can easily be calculated.

This astonishingly good correlation between the spectroscopically determined solvent polarity parameter and the kinetically determined rate constants, shows that the light absorption of the solvatochromic betaine dye is in fact a good model for the estimation of solute-solvent interactions in dipolar-transition state reactions.

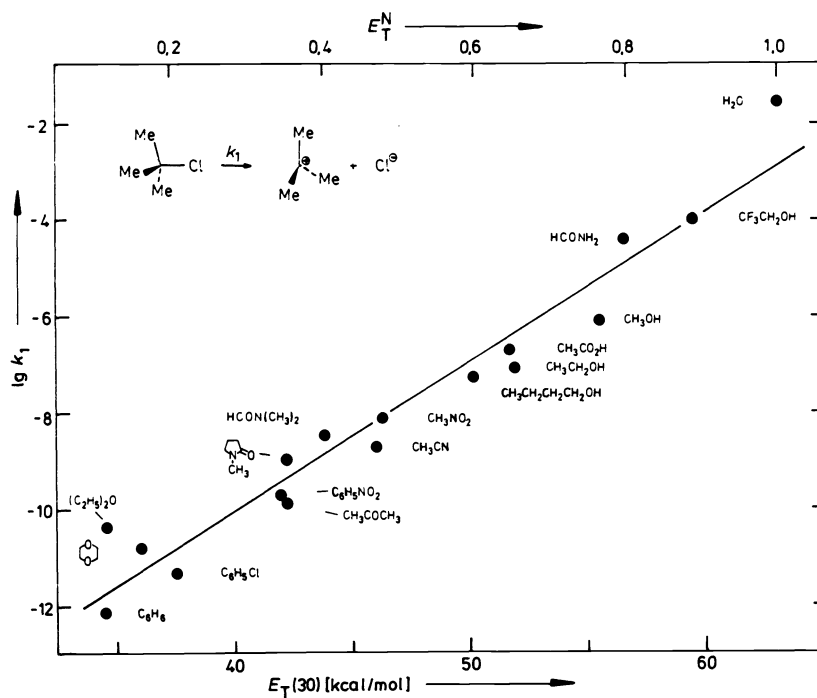


Fig. 21. Linear correlation between $E_T(30)$ -values and $\lg k_1$ of the S_N1 solvolysis of tert-butylchloride at 25°C:
 $\lg k_1 = 0.312 \cdot E_T(30) - 22.55$ ($n = 17$; $r = 0.972$).

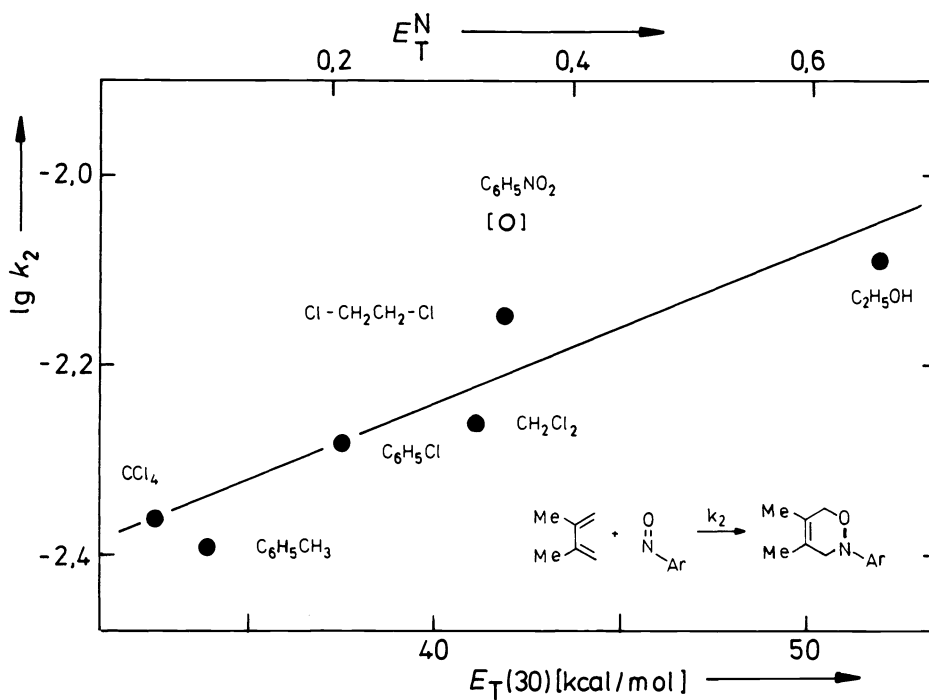


Fig. 22. Linear correlation between $E_T(30)$ -values and $\lg k_2$ of the [4+2] cycloaddition reaction of 2,3-dimethylbutadiene with 4-chloro-1-nitrosobenzene at 25°C:
 $\lg k_2 = 0.016 \cdot E_T(30) - 2.88$ ($n = 6$; $r = 0.936$).

In spite of only small solvent effects, even isodipolar-transition-state reactions such as the Diels-Alder cycloaddition of 2,3-dimethylbutadiene with 4-chloro-1-nitrosobenzene (Ref. 25) exhibit a satisfactory linear correlation with the solvent polarity parameter E_T (Fig. 22). The gentle slope of the correlation line is typical for concerted cycloaddition reactions with a one-step mechanism involving little or no dipolarity change during the activation process. Similar gentle slopes have been observed for other pericyclic reactions such as the 1,3-dipolar cycloaddition reactions studied by Huisgen and coworkers (Ref. 40).

Not only dipolar and isopolar transition-state reactions but free-radical transition-state reactions with small solvent sensitivity can also be correlated with the solvent polarity parameter E_T as shown in Figs. 23 and 24.

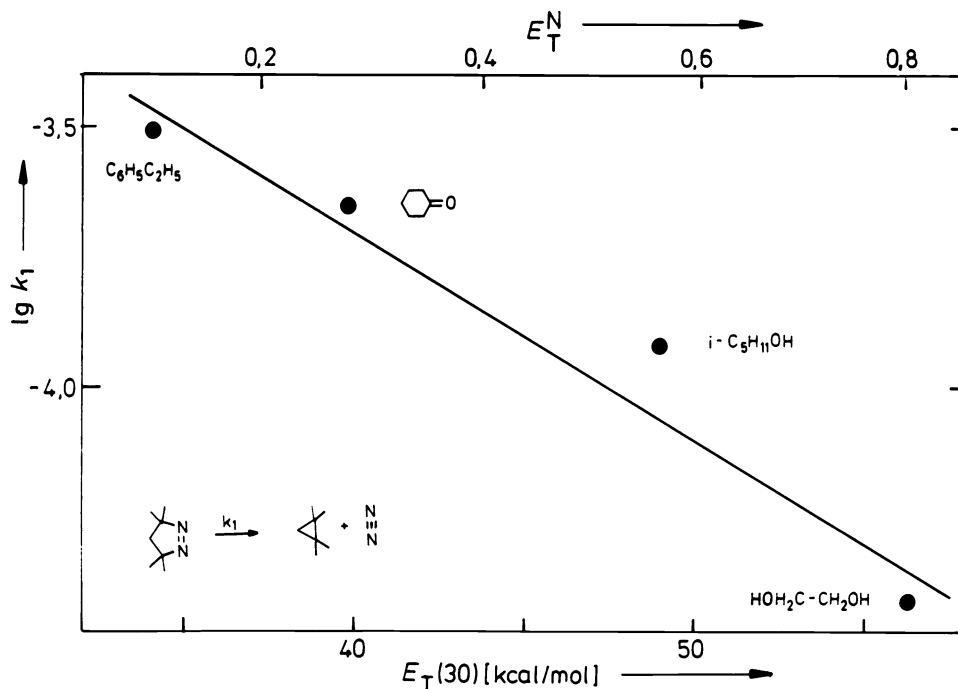


Fig. 23. Linear correlation between $E_T(30)$ -values and $\lg k_1$ of the thermolysis of 3,3,5,5-tetramethyl-1-pyrazoline at 189 °C:

$$\lg k_1 = -0.040 \cdot E_T(30) - 2.10 \quad (n = 4; r = -0.975).$$

The rate of the aforementioned thermolysis of 3,3,5,5-tetramethyl-1-pyrazoline (Ref. 29, 30) correlates well with the E_T -parameter (Fig. 23). The observed rate decrease with increasing solvent polarity is best explained by assuming a decrease in the dipole moment of the dipolar cis-azo compound during activation. Increased solvation of the dipolar reactant molecule relative to the apolar activated complex is compatible with the small solvent effect observed.

The aforementioned Grignard reaction between racemic 3-phenylbutanone and phenylmagnesium bromide is a striking example of solvent influence on stereoselectivity (Ref. 12). As shown in Fig. 24, a surprisingly good linear relationship between the E_T -parameter and the diastereomeric product ratio is found in a large selection of solvents of varying polarity. The fact that the observed stereoselectivity may be additionally influenced by solvent polarity in a predictable manner is of invaluable importance in other asymmetric syntheses.

Four examples of the many E_T -correlations described in the literature (Ref. 31, 33, 41) demonstrate that empirical parameters of solvent polarity are useful tools for predicting chemical reactivity in a semiquantitative manner in different solvents.

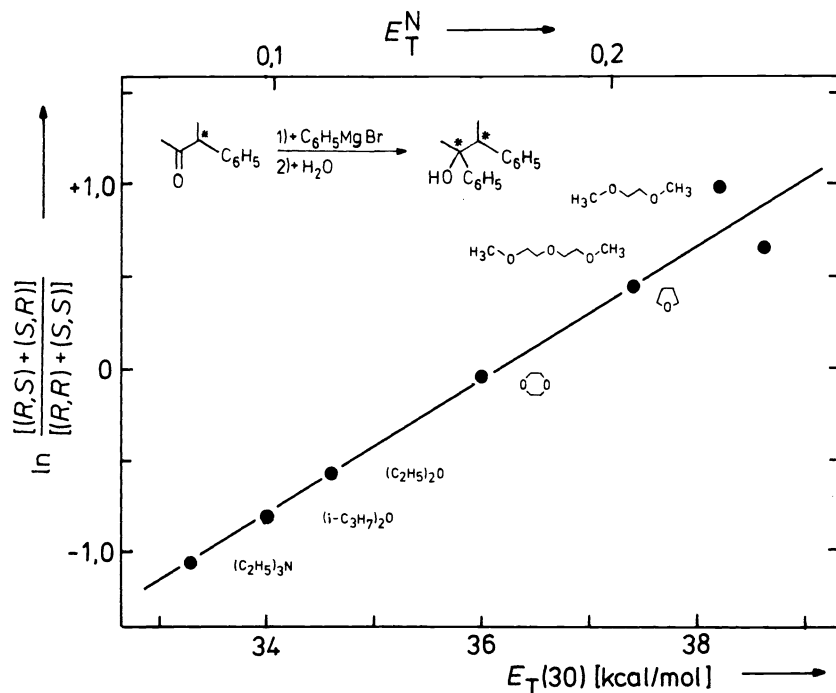


Fig. 24. Linear correlation between $E_T(30)$ -values and the stereoselectivity observed in the Grignard reaction of (\pm)-3-phenylbutanone with phenylmagnesium bromide at 30 °C:

$$\ln[(R,S)+(S,R)]/[(R,R)+(S,S)] = 0.365 \cdot E_T(30) - 13.2$$

($n = 7$; $r = 0.984$).

For an estimate of solvent effects on chemical reactions, empirical parameters of solvent polarity are as useful as the empirically derived Hammett constants used in the prediction of substituent effects in chemical reactions. Both approaches are verifications of the principle of "Linear Free-Energy Relationships" (Ref. 31, 42, 43).

One important reservation should be made. Solvent effects are basically more complicated and more specific than substituent effects. The application of solvent polarity parameters is based on the assumption that, the nature of the solute-solvent interactions in the reference process used to establish a solvent scale is similar to those influencing the reaction under study. This is obviously true only for closely related solvent-sensitive reactions. Therefore, the use of solvent parameters to predict solvent effects should be limited to largely analogous processes.

A large variety of empirical parameters of solvent polarity are presently at the chemist's disposal. This topic has been recently reviewed (Ref. 31, 32, 33). Therefore, it should not be too difficult to find a suitable solvent parameter for a particular reaction under study.

Despite considerable progress in calculating solvent effects on a purely theoretical basis, actually the use of carefully selected empirical solvent polarity parameters is still the most practical and successful method for reliable solvent effect predictions.

During the last ten years there have been various attempts at considering two or more specific solute-solvent interactions simultaneously using multiparameter equations instead of single-parameter correlations (Ref. 15). Different empirical parameters for solvent polarizability, dipolarity, electrophilicity, and nucleophilicity have been separately determined and combined in multiparametric equations. The most ambitious recent approach is that of Taft and coworkers (Ref. 44).

The use of multiparametric equations instead of single-parameter equations has in many cases produced a dramatic improvement in the correlations between solvent-dependent reactions and inherent solvent properties. However, a final solution to the problem of separating solvent polarity into the various solute-solvent components is not yet in sight.

A more detailed explanation of multiparametric equations can be found in Ref. 15, 33 and 44.

FINAL REMARKS

120 years after the discovery by Berthelot and St. Gilles of the solvent influence on chemical reactivity the problem of how to understand and describe solvent influence on chemical reactivity in a more quantitative manner is far from being finally solved.

Most organic reactions can be classified into dipolar, isopolar, and free-radical-transition-state reactions according to their solvent sensitivity. On this basis, the extent and direction of solvent influence on reaction rates can be used as a valuable criterion in the elucidation of reaction mechanisms. Thereby, extreme rather than intermediate solvent effects on chemical reactivity are more conclusive.

The use of empirical parameters of solvent polarity is still the simplest and most practical method of predicting solvent effects in a more quantitative way. Various empirical solvent scales are now available for this procedure. Multiparameter equations have led to further improvements.

As the selection of suitable reference processes for the determination of empirical parameters of solvent polarity leaves room for subjective decisions, the well-known remark that organic chemistry is not a science but an art (Ref. 35) seems to be not wholly unfounded.

Acknowledgement - I thank Dr. Edeline Wentrup-Byrne, Marburg, for improvements of the English manuscript. The author's own papers cited in this review were sponsored by the Fonds der Chemischen Industrie, Frankfurt (Main), for which the author would like to express his gratitude.

REFERENCES

1. M. Berthelot and L. Péan de Saint-Gilles, Ann. Chim. et Phys., 3. Sér., 65, 385 - 422 (1862); 66, 5 - 110 (1862); 68, 225 - 359 (1863); translated into German and edited by M. and A. Ladenburg in: Ostwald's Klassiker der exakten Naturwissenschaften, Nr. 173, Engelmann, Leipzig 1910.
2. N. Menshutkin, Z. Phys. Chem. 1, 611 - 630 (1887); 5, 589 - 600 (1890); 6, 41 - 57 (1890); 34, 157 - 167 (1900).
3. L. Claisen, Liebigs Ann. Chem. 291, 25 - 111 (1896).
4. A. Hantzsch and O.W. Schultze, Ber. Dtsch. Chem. Ges. 29, 2251 - 2267 (1896).
5. L. Knorr, Liebigs Ann. Chem. 293, 70 - 120 (1896).
6. W. Wislicenus, Liebigs Ann. Chem. 291, 147 - 216 (1896).
7. K.H. Meyer, Liebigs Ann. Chem. 380, 212 - 242 (1911); Ber. Dtsch. Chem. Ges. 47, 826 - 832 (1914).
8. M.T. Rogers and J.L. Burdett, J. Am. Chem. Soc. 86, 2105 - 2109 (1964); Canad. J. Chem. 43, 1516 - 1526 (1965).
9. I. Szele and H. Zollinger, Helv. Chim. Acta 61, 1721 - 1729 (1978); H. Zollinger, Angew. Chem. 90, 151 - 160 (1978); Angew. Chem., Int. Ed. Engl. 17, 141 (1978).
10. N. Abe, T. Nishiwaki, and N. Komoto, Chem. Lett. (Tokyo) 223 - 224 (1980).
11. S. Krishnamurthy, J. Org. Chem. 45, 2550 - 2551 (1980).
12. R. Pérez-Ossorio, A. Pérez-Rubalcaba, and M.L. Quiroga, Tetrahedron Lett. 21, 1565 - 1566 (1980); O. Arjona, R. Pérez-Ossorio, A. Pérez-Rubalcaba, and M.L. Quiroga, J. Chem. Soc., Perkin Trans. II 597 - 603 (1981).
13. N.L. Benoiton, K. Kuroda, and F.M.F. Chen, Tetrahedron Lett. 22, 3361 - 3364 (1981).
14. C.K. Ingold, Structure and Mechanism in Organic Chemistry, 2nd edition, Cornell University Press, Ithaca, London (1969).
15. C. Reichardt, Solvent Effects in Organic Chemistry, Verlag Chemie, Weinheim, New York (1979).
16. C. Reichardt, Chemie in unserer Zeit 15, 139 - 148 (1981).
17. E.M. Kosower, An Introduction to Physical Organic Chemistry, Wiley, New York (1968).
18. S. Winstein and A.H. Fainberg, J. Am. Chem. Soc. 78, 2770 - 2777 (1956); 79, 5937 - 5950 (1957).

19. M.H. Abraham, J. Chem. Soc., Perkin Trans. II, 1343 - 1357 (1972).
20. R. Alexander, E.C.F. Ko, A.J. Parker, and T.J. Broxton, J. Am. Chem. Soc. **90**, 5049 - 5069 (1968); A.J. Parker, Chem. Rev. **69**, 1 - 32 (1969).
21. D.K. Bohme, G.I. Mackay, and J.D. Payzant, J. Am. Chem. Soc. **96**, 4027 - 4028 (1974); K. Tanaka, G.I. Mackay, J.D. Payzant, and D.K. Bohme, Canad. J. Chem. **54**, 1643 - 1659 (1976).
22. J.I. Brauman, W.N. Olmstead, and C.A. Lieder, J. Am. Chem. Soc. **96**, 4030 - 4031 (1974); W.N. Olmstead and J.I. Brauman, J. Am. Chem. Soc. **99**, 4219 - 4228 (1977).
23. J.H. Bowie, Acc. Chem. Res. **13**, 76 - 82 (1980).
24. R.T. McIver, Scientific American **243**, No. 5, 148 - 157 (1980); Spektrum der Wissenschaft **27** (1981).
25. G. Swieton and H. Kelm, J. Chem. Soc., Perkin Trans II 519 - 524 (1979).
26. J. Sauer and R. Sustman, Angew Chem. **92**, 773 - 801 (1980); Angew Chem., Int. Ed. Engl. **19**, 779 (1980).
27. K. Harano and T. Taguchi, Chem. Pharm. Bull. (Tokyo) **23**, 467 - 472 (1975); T. Kawata, K. Harano, and T. Taguchi, Yakugaku Zasshi **95**, 1141 - 1151 (1975); Chem. Abstr. **84**, 16570 f (1976)
28. M.G. Kulkarni, R.A. Mashelkar, and L.K. Doraiswamy, Chem. Engn. Sci. **35**, 823-830 (1980).
29. R.J. Crawford and A. Mishra, J. Am. Chem. Soc. **88**, 3963 - 3969 (1966).
30. W. Duisman and C. Ruchardt, Chem. Ber. **111**, 596 - 605 (1978).
31. C. Reichardt, Angew. Chem. **91**, 119 - 131 (1979); Angew. Chem., Int. Ed. Engl. **18**, 98 - 110 (1979).
32. C. Reichardt, Solvent Scales and Chemical Reactivity, in A.D. Buckingham, E. Lippert, and S. Bratos (eds.), Organic Liquids. Structure, Dynamics, and Chemical Properties, Wiley, Chichester, New York, p. 269 - 291 (1978).
33. C. Reichardt, Empirical Parameters of Solvent Polarity and Chemical Reactivity, in H. Ratajczak and W.J. Orville-Thomas (eds.), Molecular Interactions, Wiley, Chichester, New York, Vol. 3, p. 241 - 282 (1982); in press.
34. L.P. Hammett, J. Am. Chem. Soc. **59**, 96 - 103 (1937).
35. L.P. Hammett, Physical Organic Chemistry, McGraw-Hill, New York (1970); Physikalische Organische Chemie, Verlag Chemie, Weinheim, p. 346 ff. (1973).
36. K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, Liebigs Ann. Chem. **661**, 1 - 37 (1963); K. Dimroth and C. Reichardt, ibid. **727**, 93 - 105 (1969); C. Reichardt, ibid. **752**, 64 - 67 (1971).
37. C. Reichardt, E. Harbusch, and R. Müller, Pyridinium-N phenoxide Betaine Dyes as Solvent Polarity Indicators. Some New Findings, in I. Bertini, L. Lunazzi, and A. Dei (eds.), Advances in Solution Chemistry, Plenum Press, New York, London, p. 275 - 293 (1981).
38. C. Reichardt and E. Harbusch-Görnert, unpublished results.
39. T. M. Krygowski, J.P. Radomski, A. Rzeszowiak, P.K. Wrona, and C. Reichardt, Tetrahedron **37**, 119 - 125 (1981).
40. R. Huisgen, Pure Appl. Chem. **52**, 2283 - 2302 (1980).
41. C. Reichardt and K. Dimroth, Fortschr. Chem. Forsch. **11**, 1 - 73 (1968).
42. N.B. Chapman and J. Shorter (eds.), Advances in Linear Free-Energy Relationships, Plenum Press, London (1972); N.B. Chapman and J. Shorter (eds.), Correlation Analysis in Chemistry. Recent Advances, Plenum Press, London (1978).
43. M. Sjöström and S. Wold, Acta Chem. Scand. B **35**, 537 - 554 (1981).
44. J.L.M. Abboud, M.J. Kamlet, and R.W. Taft, Progr. Phys. Org. Chem. **13**, 485 - 630 (1981).