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Review Commentary

Role of nucleophilic solvation and the mechanism of covalent bond heterolysis

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ABSTRACT: Based on data obtained mainly by the verdazyl method, the effects of a solvent on the rates of the heterolyses of 20 substrates (*t*-BuCl, *t*-BuBr, *t*-BuI, 1-AdBr, 1-AdI, 1-AdOTs, 1-AdOPic, 1-chloro-1-methylcyclopentane, 1-bromo-1-methylcyclopentane, 1-chloro-1-methylcyclohexane, 1-bromo-1-methylcyclohexane, 2-bromo-2-methyladamantane, *p*-methoxyneophyl tosylate, 2-chloro-2-phenylpropane, *p*-methoxybenzotrichloride, Ph_2CCl_2, 7α-bromocholesterol benzoate, 1-chloro-1-phenylethane, Ph_2CHBr, 3-bromocyclohexene) were analyzed in a wide set of protic and aprotic solvents. The heterolysis rate of tertiary substrates decreases with increase in solvent nucleophilicity, but for secondary substrates it does not depend on solvent nucleophilicity. The negative effect of nucleopilic solvation is caused by the solvation of a contact ion pair, which appears before the limiting step. The lack of nucleophilic solvent assistance indicates that a solvent-separated ion pair of substrates appears after the limiting step. The limiting step involves the interaction of a contact ion pair with a solvent cavity, resulting in the formation of a cavity-separated ion pair of substrates. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: heterolysis; tertiary substrates; secondary substrates; verdazyl method; solvent effects; nucleophilic solvation; solvent cavity; mechanism

INTRODUCTION

The reactions of unimolecular heterolyses (S_N1, $E1$, $F1$ and solvolysis) have been the subject of constant research for more than 70 years. The limiting step of these reactions occurs through the ionization of the covalent bond with the formation of cationoid intermediates. Ingold offered free carbocation as an intermediate, Hammett considered that the formation of an ion pair had to precede the formation of free carbocation and Winstein gave evidence for the formation of two ion pairs—the contact ion pair (CIP) and the solvent-separated ion pair (SSIP)[1–3] (Scheme 1).

It was supposed that in the limiting reaction step, an SSIP or free carbocation would form, which gave the reaction products. At present this scheme of the mechanism is conventional for unimolecular heterolysis, although the intermediate formation of SSIP is often not taken into account when interpretations of S_N1 and $E1$ reaction mechanisms are discussed. This is caused, above all, by the fact that it is not sufficiently intelligible how the transformation of a CIP into an SSIP and the reverse process (the external return of an ion pair) occur. Many researchers consider that CIP dissociation cannot limit the reaction rate, so far as this process is diffusive.

The inferences of the heterolysis mechanism are based mainly on studies of solvation and salt effects, which were little studied prior to our reports.[4–7] The nature of the solvation of the reaction's transition state (equilibrium or non-equilibrium) was vague, the concepts of the role of nucleophilic solvation remained debatable and the relation between salt effects and the structure of cationoid intermediates is not based firmly enough. The usually studied (earlier and now) solvolysis reactions are not informative enough, because the kinetic relations in these reactions are uncertain, the solvation effects are monotonic and the salt effects appear to be inexpressive. Superposition of the electrostriction effect and the destruction of the solvent structure in a protic solvent hampers the use of activation parameters for mechanistic inferences. The widespread use of mixed solvents introduces an additional vagueness to interpretations of the solvation effects.

Therefore, detailing of the heterolysis mechanism has stagnated at the level of the Winstein scheme, which was proposed 50 years ago.[8] Further development of notions about the reaction mechanism called for new methods of research.

The run of unimolecular heterolyses reactions is usually slow: the half-conversion time for *t*-BuCl in a polar

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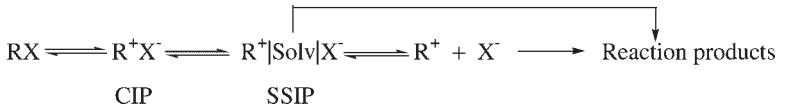


Scheme 1

solvent such as $PhNO_2$ is 160 years. Therefore, the accumulation of available data occurred slowly and with difficulty until 1974, when a verdazyl method of kinetic and mechanism studies was drawn up for the reactions of unimolecular heterolysis.[4,9] It substantially reduced the experimentation time and allowed data inaccessible by other methods to be obtained.

THE VERDAZYL METHOD

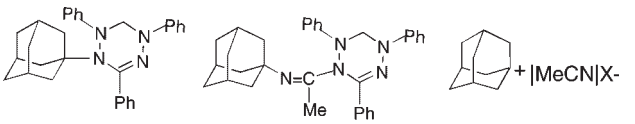
This is an indicator method.[4] Reaction is conducted in the presence of small quantities ($\sim 10^{-4}$ mol l^{-1}) of stable 1,3,5-triphenylverdazyl radical (Vd·), which quickly and quantitatively reacts with the substrate's SSIP. As a result, reaction products are formed: in the S_N1 reaction they are verdazylium salt (Vd^+X^-) and the product of verdazyl alkylation. In the $E1$ reaction the latter product quickly disintegrates to an olefin and leucoverdazyl (VdH). In solvolysis reactions, VdH and a reaction product with the solvent (ROS) are formed. The reaction proceeds according to a stoichiometric equation (Scheme 2).

Regardless of the reaction type (S_N1, $E1$, solvolysis), 1 mol of a substrate reacts with 2 mol of Vd· and forms 1 mol of Vd^+X^-. The reaction rate is followed spectrophotometrically by a decrease in Vd· concentration ($\lambda_{max} \approx 720$ nm) and/or by a increase in Vd^+X^- concentration ($\lambda_{max} \approx 540$ nm). The reaction rate undergoes a first-order kinetic equation:

$$v = -\mathrm{d}[\mathrm{Vd}^{\bullet}]/2\mathrm{d}t = \mathrm{d}[\mathrm{Vd}^+X^-]/\mathrm{d}t = k[\mathrm{RX}]$$

The substrate concentration usually exceeds the Vd· concentration by 5–10^5-fold and the conversion level is low. It can reach 0.0001% and, therefore, in a few hours allows the determination of rates for reactions with a half-time of up to 1000 years.

The idea that Vd· reacts with SSIP but not with CIP is supported by the fact that S_N1 reaction products depend on the solvent nature in aprotic media. Under 1-AdOPic, 1-AdOTs and 1-AdI heterolyses in propylene carbonate and sulfolane, the product of verdazyl alkylation (**a**) is formed, but in MeCN the reaction product (**b**) includes a solvent molecule.[4]



(a) **(b)** **(c)**

Formation of the product (**b**) probably occurs through an interaction between 1-AdX and a solvent molecule placed in the interionic space of SSIP (**c**) and through the following reaction of the latter ion pair (**c**) with a verdazyl molecule.

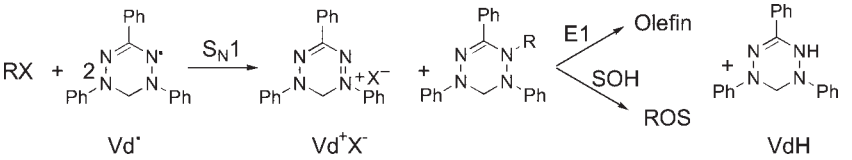
Heterolysis of Ph_2CCl_2 in acetone was studied in the presence of NaI and in the presence of Vd·.[4] In the former case the rate-limiting step involves interaction between NaI and contact ion pair of substrate ($v = k_2$ [Ph_2CCl_2] [NaI]) and in the latter case the rate-limiting step is the reaction of Vd· with the later intermediate ($v = k$ [Ph_2CCl_2]). Therefore, Vd· does not react with the contact ion pair of the substrate.

Usually, a plot of [Vd·] vs time is linear ($v = k_0$, $k = k_0$/[RX]); however, it can sometimes have an S-like curve (Fig. 1). The first segment (inductive period) reflects transmission of the reaction system into a stationary state, when $\mathrm{d}[\mathrm{Int}]/\mathrm{d}t = 0$. The second (linear) segment is used for calculation of the k_0 value. The reduction or acceleration of a reaction rate on the third segment is caused by the salt effect of Vd^+X^-. It must be taken into account that under a low concentration of a verdazyl indicator the reaction rate can be limited by the interaction of Vd· with SSIP, $v = k_2[\mathrm{RX}][\mathrm{Vd}^{\bullet}]$ [S_N2 (C^+) reaction].

If solvolysis reactions run according to an S_N2 or S_N2–ion pair mechanism and, under some circumstances, according to the an S_N1 ($E1$) mechanism, a verdazyl indicator reacts with acid formed under solvolysis:

$$\mathrm{HX} + 2\mathrm{Vd}^{\bullet} \rightarrow \mathrm{Vd}^+X^- + \mathrm{VdH}$$

It is impossible to use the verdazyl method in acidic solvents, as verdazyl reacts quickly with carboxylic acids,



Scheme 2

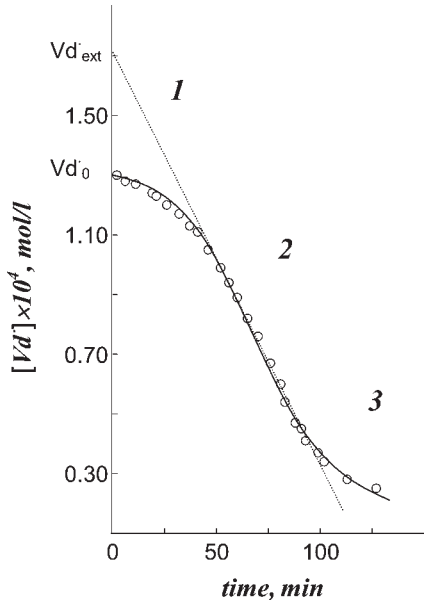


Figure 1. Kinetic curve for $PhCH_2Cl$ solvolysis in the presence of $Vd^{\bullet}$ (EtOH, 25 °C, $[PhCH_2Cl]$ 0.727 mol l^{-1}, $[Vd^{\bullet}]_0$ 1.3×10^{-4} mol l^{-1}, $k = 1.83 \times 10^{-8}$ s^{-1})

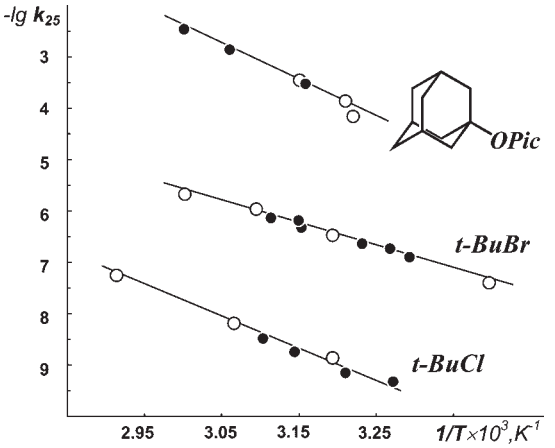


Figure 2. Plot of logarithms of rate constants vs temperature^{-1} for *t*-BuBr heterolysis in acetone,[11,12] for *t*-BuCl heterolysis in $PhNO_2$[13,14] and for 1-AdOPic heterolysis in sulfolane.[15,16] ●, Data obtained by the verdazyl method; ○, data obtained by other methods

and in $MeNO_2$ solution, verdazyls undergo rapid decomposition. *E*1 reactions in DMSO have to be monitored by Vd^+X^- formation, since VdH is quickly oxidized by the solvent and produces $Vd^{\bullet}$. If an *E*1 reaction is carried out in a polar protic solvent (MeOH) for a long period, air oxygen can oxidize VdH to $Vd^{\bullet}$ and thus cause experimental errors. In such a case 1,5-diphenyl-3-(4-nitrophenyl)verdazyl has to be used as an indicator, since the corresponding VdH is sufficiently stable. If alkyl iodides are studied, it is necessary to take into account the equilibrium that takes place in non-polar solvents:[4]

$$2Vd^+I^- \rightleftharpoons 2Vd^{\bullet} + I_2$$

Experimental errors in the reaction rates determined by the verdazyl method usually average 1–3%. In non-polar aprotic solvents the errors can reach 5–7%.

The verdazyl method is simple and convenient in action. It is widely approved and heterolysis kinetics have been studied for more than 30 substrates, usually in 20–40 solvents. When data have been obtained by both the verdazyl and other methods, close data coincidence was shown in more than 30 cases.[4] Such a coincidence is illustrated in Fig. 2 and Table 1. The verdazyl method allows S_N1 reaction rates in aprotic solvents to be followed quickly and reliably. The method appeared to be especially effective for salt effects studies, which allowed the mechanism of the action of neutral salts in heterolyses reactions to be essentially revised.[6,7] Careful studies of solvation effects and salt effects by the verdazyl method clarified considerably the mechanism of covalent bond heterolysis.

ROLE OF NUCLEOPHILIC SOLVATION

The reaction rate of unimolecular heterolysis depends strongly on the nature of the solvent. A change of reaction medium from hexane to water increases the rate of *t*-BuCl heterolysis by 14 orders of magnitude.[34] This is caused by intensive solvation of the transition state. The rates of unimolecular heterolysis reactions depend mainly on the solvent's polarity and electrophilicity or on its ionizing power. The polarizability, nucleophilicity and cohesion of a solvent are of less importance.[5] An increase in the reaction rate as the solvent polarity and electrophilicity increase is clearly understood—the increase in polarity raises the stability of a cationoid intermediate, and electrophilic solvation of a nucleofuge is a driving force of heterolysis. The nucleophilic effect of a solvent is under constant debate. Some papers insist that solvent nucleophilicity does not affect the reaction rate,[1,35–37] others maintain the availability of solvent nucleophilic assistance,[38–41] and still others report that a rise in solvent nucleophilicity decreases the reaction rate.[4,5,42–44]

Ingold and Winstein did not discuss the significance of nucleophilic solvation in heterolytic reactions. However, they thought that the return reactions from free carbocation or SSIP affect the reaction rate, and these processes must depend on nucleophilic solvation. The rate depression in the presence of a salt with a common ion (salt effect of mass action law) and the sharp rate rise in the presence of perchlorates, which was based on the idea of the suppression of an ion pair's external return step (special salt effect), were considered as proof for the essential influence of external return reactions on the rates of heterolyses reactions.[1,45]

The studies of salt effects by the verdazyl method showed that the nature of these effects differed from that postulated, an external return from carbocation or SSIP not being essential.[6,7] If only external return were to

Table 1. Comparison of heterolyses rate constants obtained by the verdazyl method and by other methods

Substrate	Solvent	Temperature (°C)	$-\log k$ Verdazyl method	Other methods
t-BuCl	MeCN	45.0	7.56[a 9]	7.59[17]
	2-PrOH	25.0	7.79[18]	7.82[19]
	t-BuOH	25.0	8.39[18]	8.30[19]
	$PhNO_2$	25.0	9.86[a 13]	9.74[a 14]
t-BuBr	MeCN	25.0	5.90[9]	5.92[20]
	MeCOMe	25.0	7.87[11]	7.93[12]
	2-PrOH	25.0	5.92[18]	5.96[21]
PhCHClMe	EtOH	25.0	6.68[22]	6.66[23]
Ph_2CCl_2	EtOH	25.0	3.03[24]	3.06[25]
p-$MeOC_6H_4CHCl_2$	85% aq. dioxane	25.0	3.94[24]	4.05[26]
1-AdOPic	MeOH	25.0	4.68[27]	4.68[a 16]
	EtOH	25.0	4.76[27]	4.76[16]
	Sulfolane	45.5	3.49[15]	3.44[16]
$PhCMe_2Cl$	MeCN	25.0	5.28[28]	5.28[29]
	EtOH	25.0	3.42[28]	3.45[29]
	1,2-Dichloroethane	25.0	6.33[28]	6.40[29]
	AcOEt	25.0	7.66[28]	7.84[29]
$PhCH_2Cl$	MeOH	25.0	7.23[10]	7.21[30]
	EtOH	25.0	7.74[10]	7.77[31]
1-Chloro-1-methylcyclopentane	EtOH	25.0	5.34[32]	5.25[33]

[a] Calculated from temperature dependence of k values.

be affected by solvent nucleophilicity, the reaction rate had to depend on the concentration and nature of the added nucleophile and, consequently, on an analytical method of reaction mixture because of competition between the reaction of the intermediate with the nucleophile and the reaction of external return. For example, NaOH addition should raise the reaction rate, but infact it does not affect the rate or even slows it.[46–48]

We have studied the heterolysis kinetics of about 30 substrates by the verdazyl method and there was no case when the step of external return affected the rate of the heterolysis reactions studied.[4–7,42]

The nucleophilic effect of a solvent under S_N1 and $E1$ reactions and solvolyses have been intensively studied in recent decades.[5,36,37,43,49–51] The elucidation of the nature of this phenomenon remains an important problem in physical organic chemistry.

The analysis of solvation effects in solvolysis reactions is usually carried out with the help of one- and two-parameter Grunwald–Winstein equations:[38–41]

$$\log(k/k_0) = mY \quad (1)$$

$$\log(k/k_0) = mY + lN \quad (2)$$

here k_0 and k are solvolysis rate constants in 80% aqueous EtOH and the explored solvent, respectively, m is the reaction's sensitivity to ionizing solvent power Y ($m = 1$ for 1-AdCl) and l is the reaction's sensitivity to solvent nucleophilicity N ($l = 1$ for MeOTs).

Equation (1) is applied for comparison of solvent effects on the rates of the solvolyses of diverse substrates. Existing deviations in a less nucleophilic medium (fluorinated alcohols) are used to come to a conclusion about the nucleophilic effect of a solvent.[38–41] However, so far as the less employed nucleophilic solvents are strong electrophiles, so such an approach makes it difficult to separate a nucleophilic from an electrophilic effect.[5,42] For example, comparison of the solvolysis rates of *tert*-butyl with adamantyl substrates in less nucleophilic solvents shows a deviation of log $k_{t\text{-BuX}}$ values in the direction of rate lowering, which one can interpret as a deviation of log k_{AdX} values in the direction of a rate rise. If nucleophilic solvent assistance for adamantyl substrates is impossible for steric reasons, it is easy come to a conclusion about nucleophilic solvent assistance in the solvolyses of *tert*-butyl substrates.[38–41,49,52] These deviations can be explained with the same success as the stronger sensitivity of adamantyl substrates to the electrophilic effect of a solvent.[40,42,43,50,53] Uncertainty of inferences follows from a comparison of relative rates. Based on such facts, it is impossible to draw a conclusion about how nucleophilicity affects the reaction rate–increasing or decreasing it. Three centuries ago, phlogiston theory was grounded on the basis of a similar approach.

Equation (2) is of little use for the estimation of the nucleophilic solvent effect, because the parameters Y and N do not reflect any single property of a solvent.[54] Gajewski showed that N depends on the polarity, electrophilicity and nucleophilicity of a solvent.[43] In some cases, Eqn (2) gives absurd results when $l > 1$,[55] in other cases when $l < 0$ the results are realized as artefacts,[39,51,56] and when $l = 0.1$–0.3 a conclusion is drawn about nucleophilic solvent assistance to heterolysis.[38–41,56]

Although Eqns (1) and (2) were of little use for studies of the nucleophilic solvent effect, they have been widely

used, especially in recent times. Presumably, the simplicity of the experiment's interpretation turned out to be too attractive. The poor efficacy of these equations led to the creation of the scales of ionizing solvent power for each nucleofuge (Y_X) and for different alkyl groups (Y_R).[38–40,51] The number of these scales is continually growing.

The research that has been carried out in recent decades showed that more reliable data concerning the nature of solvation effects could be obtained with application of linear free energy relationship multiparameter equations for correlation analysis using independent parameters that reflected individual solvent properties: polarity (function of the dielectric constant of a solvent, ε), polarizability (function of refraction index, n), dipolarity π^* (polarity + polarizability), electrophilicity (AN, E, α), nucleophilicity (DN, B, β) and cohesion δ^2 (parameter of solvent self-association).[5,35,36,57,58]

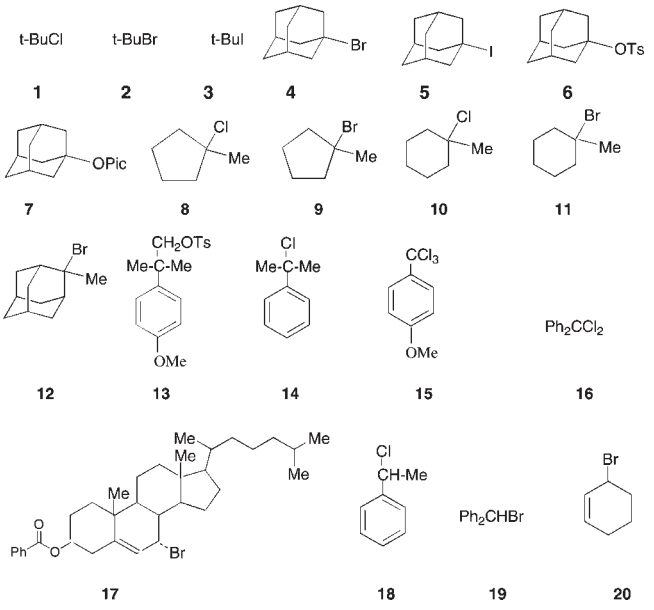
For correlation analysis of solvation effects we used the Koppel-Palm equation [Eqn (3)],[35] the Kamlet–Taft equation [Eqn(4)][36] and Eqn (5):

$$\log k = a_0 + a_1\frac{\varepsilon - 1}{\varepsilon + 1} + a_2\frac{n^2 - 1}{n^2 + 1} + a_3E + a_4B + a_5\delta^2 \quad (3)$$

$$\log k = a_0 + a_1\pi^* + a_2\alpha + a_3\beta + a_4\delta^2 \quad (4)$$

$$\log k = a_0 + a_1E_T(Z) + a_2f(n) + a_3B + a_4\delta^2 \quad (5)$$

Correlation analysis was carried out for the substrates **1**–**20** in 20–40 solvents.[4,5,13,15,27,28,32,34,42,59–70] More than 80% of the rate constants were obtained by the verdazyl method.



In no case did we monitor a rise of the reaction rate with increase in solvent nucleophilicity. The reaction rate does not depend on solvent nucleophilicity for the heterolyses of secondary substrates **17**–**20**, where a nucleophilic attack from the rear is possible. For heterolyses of the rest of the substrates, where nucleophilic attack from the rear is strongly hindered or impossible, the rates of heterolyses decrease with increase in solvent nucleophilicity.

When the reaction rate does not depend on solvent nucleophilicity, it correlates well with solvatochromic parameters of solvent ionizing power (E_T, Z) or with solvent polarity and electrophilicity parameters. For example, for Ph_2CHBr (**19**) heterolysis in a set of eight protic (1–8 here and further solvent numbering follows Fig. 3) and 19 aprotic (11–20, 22, 23, 26–28, 30, 31, 34, 37) solvents the following obtained:[62]

$$\log k_{19} = -10.2 + 2.88f(\varepsilon) + 0.0978E; \quad R = 0.979, N = 27$$

$$\log k_{19} = -21.9 + 0.0868E_T; \quad R = 0.978, N = 27$$

The following correlations were obtained for bromide **20** heterolysis in nine protic (1, 2, 4–10) and 23 aprotic solvents (11–23, 26–30, 32, DMSO, AcOEt, $CHCl_3$, dioxane):[70]

$$\log k_{20} = -9.64 + 2.72f(\varepsilon) + 0.0700E; \quad R = 0.972, N = 32$$

$$\log k_{20} = -19.5 + 0.0476Z; \quad R = 0.984, N = 32$$

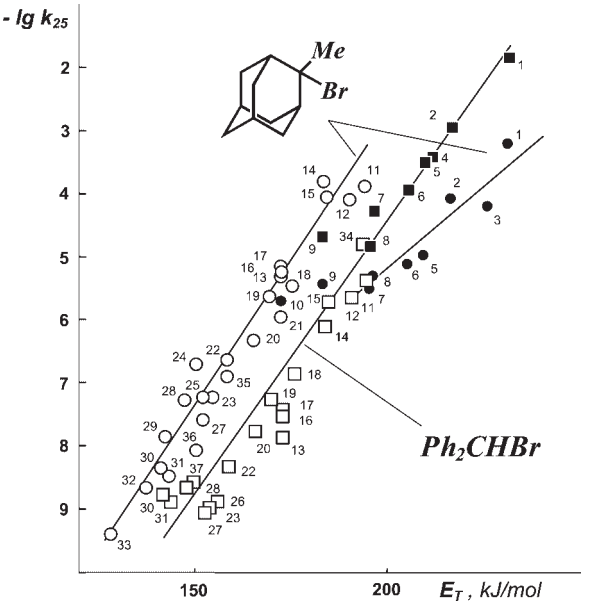


Figure 3. Effect of the ionizing power of a solvent, E_T, on the heterolyses rates of 2-bromo-2-methyladamantane and Ph_2CHBr. ●, ■, Protic solvents; ○, □, aprotic solvents. Solvents: 1, MeOH; 2, EtOH; 3, AcOH; 4, PrOH; 5, BuOH; 6, 2-PrOH; 7, 2-BuOH; 8, cyclohexanol; 9, *t*-BuOH; 10, *t*-AmOH; 11, propylene carbonate; 12, MeCN; 13, 1,2-dichloroethane; 14, sulfolane; 15, γ-butyrolactone; 16, PhCN; 17, $PhNO_2$; 18, acetone; 19, PhCOMe; 20, cyclohexanone; 21, EtCOMe; 22, 1,2-dichlorobenzene; 23, PhCl; 24, PhI; 25, PhBr; 26, THF; 27, PhOEt; 28, Ph_2O; 29, benzene; 30, toluene; 31, *o*-xylene; 32, *p*-xylene; 33, cyclohexane; 34, $MeNO_2$; 35, $PhCO_2Et$; 36, $MeCCl_3$; 37, dioxane; 38, DMSO

If heterolyses of tertiary substrates are studied, where a nucleophilic attack from the rear is impossible or strongly hindered, it is necessary also to take into account nucleophilicity, polarizability, and cohesion parameters, or some of them, to obtain a close correlation ($R \geq 0.95$).[5] For example, correlation analysis of the data for bromide **12** heterolysis in 10 protic (1–3, 5–10, $PhCH_2OH$) and 24 aprotic (11–25, 27–33, 35, 36) solvents gave.[63]

$$\log k_{12} = -5.75 + 1.94f(\varepsilon) + 1.01E - 0.427B + 0.00807\delta^2; \quad R = 0.951, N = 34$$

If Eqn (4) is applied to 1-AdI heterolysis in 12 protic [1–3, 6, 8, 10, H_2O, $(CF_3)_2CHOH$, CF_3CH_2OH, HCO_2H, HexOH, $PhCH_2OH$] and seven aprotic solvents (11, 12, 15–18, 20), the plot follows a three-parameter equation:[61]

$$\log k_5 = -9.49 + 2.62\alpha - 3.05\beta + 0.0241\delta^2; \quad R = 0.955, N = 19.$$

The display of the negative effect of nucleophilic solvation depends strongly on the reaction conditions: solvent set, structure of the substrate and nature of the nucleofuge, and also on the equation applied for correlation analysis. This effect is best identified in protic solvents, but is much more difficult to identified in aprotic solvents. The most reliable data are obtained when equal numbers of protic and dipolar aprotic solvents are used for the regression. The negative effect of nucleophilic solvation is clearly displayed in the heterolysis of adamantyl substrates, where rearside nucleophilic solvation is impossible, but more weakly for substrates, where such solvation is only hindered. The significance of the negative effect of nucleophilic solvation increases with the diminution of the electronegativity of the atom bearing a negative charge ($O < Cl < Br < I$), i.e. with the lowering of electrophilic solvent assistance which masks this effect. A negative effect of nucleophilic solvation is displayed best with the use of Eqn (5) and worst with the use of Eqn (4). This is caused by the complexity of the parameter π^*, which reflects both the polarity and polarizability of a solvent, as solvent polarizability is able to either increase or decrease the reaction rate.

The heterolysis rates of tertiary substrates in protic solvents decrease, except in a few cases, with the increase in solvent nucleophilicity. For example, for tosylate **13**, solvolysis in seven solvents [1–4, H_2O, $(CF_3)_2CHOH$, CF_3CH_2OH] we obtained

$$\log k_{13} = -2.87 - 15.4f(n) - 0.728B + 0.000699\delta^2; \quad R = 0.998, N = 7$$

On omitting B, $R = 0.891$, and on omitting $f(n)$, $R = 0.64$.

t-BuCl solvolysis data in 19 solvents [1–10, H_2O, $(CF_3)_2CHOH$, CF_3CH_2OH, HCO_2H, HexOH, OctOH, $HCONH_2$, PhOH, *i*-BuOH] result in

$$\log k_1 = -12.6 + 0.0364E_T - 1.14B + 0.0175\delta^2; \quad R = 0.972, N = 19$$

On omitting B, $R = 0.936$.

For chloride **8**, solvolysis in 12 solvents (1–6, 8–10, CF_3CH_2OH, HexOH, *i*-BuOH) gave

$$\log k_8 = -4.20 + 13.9f(\varepsilon) - 12.4f(n) - 1.78B; \quad R = 0.978, N = 12$$

On omitting B, $R = 0.810$, and on omitting $f(n)$, $R = 0.960$.

For bromide **9**, solvolysis in 10 solvents (1, 2, 4–6, 8–10, *i*-BuOH, HexOH) gave

$$\log k_9 = -2.33 + 1.20\alpha - 3.82\beta; \quad R = 0.953, N = 10$$

On omitting β, $R = 0.788$.

The negative effect of nucleophilic solvation can always be identified if kinetic data in an approximately equal number of protic and aprotic solvents are considered. For example, for chloride **15** heterolysis in eight protic (5–10, *i*-BuOH, HexOH) and eight aprotic (11, 12, 14–17, 21, 1,1,2,2-tetrachloroethane) solvents gave

$$\log k_{15} = -4.53 + 1.93E - 7.99f(n) - 0.0340B + 0.00187\delta^2; \quad R = 0.963, N = 16$$

On omitting B, $R = 0.936$, and on omitting $f(n)$, $R = 0.902$.

In some cases, a negative effect of nucleophilic solvation on the heterolyses of substrates, where rearside nucleophilic solvation is impossible, is displayed even when a wide set of aprotic solvents is chosen for correlation analysis. For example, for bromide **12** heterolysis in 26 solvents (11–25, 27–33, 35–37, CH_2Cl_2) the plot obtained was

$$\log k_{12} = -2.30 + 0.107E_T - 4.51B; \; R = 0.950, N = 26$$

On omitting B, $R = 0.920$.

In a wide set of aprotic solvents (20–30), heterolyses rates for tertiary substrates usually depend on polarity, electrophilicity and cohesion, and the nucleophilic effect is not displayed. When only dipolar aprotic solvents are used, a negative effect of nucleophilic solvation can be identified in some cases. For example, for heterolyses of chlorides **14** and **16** in eight solvents (11–13, 15, 18, 19, $MeNO_2$, DMFA for **14** and 11–14, 16–18, 20 for **16**) the following were obtained:

$$\log k_{14} = -15.8 + 0.0476E_T - 0.186B + 0.00282\delta^2; \quad R = 0.969, N = 8$$

On omitting B, $R = 0.940$.

$$\log k_{16} = -6.86 + 0.00394\delta^2 - 4.26f(n);$$
$$R = 0.977,\ N = 8$$

On omitting $f(n)$, $R = 0.914$.

Heterolysis rates of secondary substrates do not depend on solvent nucleophilicity in either aprotic or protic solvents. One can explain the independence of the reaction rate of solvent nucleophilicity when we assume that the initial state (covalent substrate) undergoes nucleophilic solvation and that this solvation does not change when a transition state is formed. An additional nucleophilic solvation of the arising carbocation occurs after a limiting step during SSIP formation. Equilibrium solvation of the transition state occurs[71] when the transition state is reached by one of the solvates of the initial state. During this period ($\sim 10^{-13}$ s),[72] a solvent does not have enough time to respond to the occurring changes, because the time of translational–rotatory relaxation for a solvent molecule is 10^{-10}–10^{-11} s.[73]

The negative effect of nucleophilic solvation can be explained by the additional nucleophilic solvation of CIP, which appears before the limiting step of the reaction.[5,42] This stabilizes the intermediate and hampers the formation of the transition state. An especially strong effect is observed in protic solvents, which is apparently caused by the formation of hydrogen bonds between the solvent molecules which perform the nucleophilic solvation of the carbocation and electrophilic solvation of a nucleofuge. Owing to such a solvation, a sharp decline of the plot of log$k$ vs Z (E_T) is observed on transition from aprotic to protic solvents. That is why the reaction rate constants in protic solvents are a few powers of ten lower than one could expect from the linear plot in aprotic solvents.

Figure 3 shows the plots of log$k$ vs Z for 2-bromo-2-methyladamantane and Ph_2CHBr.[5] For an adamantyl substrate, the rate of heterolysis decreases as the solvent nucleophilicity increases, and the plot of log$k$ vs Z is composed of two linear segments. In protic solvents the reaction rates are two to three powers of 10 less than could be calculated from the linear plot of log$k$ vs Z in aprotic solvents. This rate reduction is the price paid for nucleophilic solvation. The log$k$ value for *t*-BuOH and *t*-PentOH ($N = 9$ and 10) remains on the plot approximately half way along between the data for protic and aprotic solvents. This can be explained by steric hindrances appearing with the nucleophilic solvation of the arising carbocation by tertiary alcohol.

For Ph_2CHBr, the rate of heterolysis does not depend on solvent nucleophilicity and forms a linear plot of log$k$ vs Z for both groups of protic and aprotic solvents.

It was shown[74] that 2-adamantyl-2-*tert*-butyl *p*-nitrobenzoate solvolysis in AcOH at 25 °C runs 2.3×10^5 times faster than 2-adamantyl-2-methyl *p*-nitrobenzoate solvolysis under the same conditions. This phenomenon is called the steric acceleration of solvolysis. It can be explained by the lack of a negative effect of nucleophilic solvation in a sterically hindered *tert*-butyl derivative.

The decrease in the reaction rate simultaneously with an increase in solvent nucleophilicity indicates non-equilibrium nucleophilic solvation of the transition state.[75] An additional nucleophilic solvation of CIP results in a different structure of the solvation shells for initial and transition states, which conflicts with the conventional theory of a transition state.[71,76] Application of this theory requires one to consider CIP as the initial state. Then the negative effect of nucleophilic solvation has a simple explanation—as a result of the initial state's stabilization. Additional nucleophilic solvation impedes ion separation and thus raises the activation barrier of the reaction.

The subjection of the reaction rate to the parameter of solvent cohesion energy density is usually explained by the formation of cavities in a solution, which are required for the arrangement of reagent molecules, or by the necessity to enlarge the cavities to displace a transition state more bulky than the initial one.[36,77] If such an effect took place, then the reaction rate would decrease with increase in the parameter δ^2, as was observed for the dissolution of a gas in a liquid,[78] but in all cases the reaction rate increased.[5] A cohesion effect can be explained thus: the greater the solvent self-association energy, the more difficult it is to pull out a solvent molecule for the nucleophilic solvation of CIP.[5,42] The energy of such a solvation has to increase with increase in solvent polarizability, therefore a polarizability parameter often appears in a correlation equation having a negative sign. However, the greater the polarizability and solvent cohesion, the more intense is the transition state solvation, especially in aprotic solvents.

The decrease of the reaction rate when solvent polarizability increases is reliable evidence of the negative effect of nucleophilic solvation, whereas interpretation of the positive effect of solvent cohesion is not always explicit.

A specific feature of adamantyl substrates due to the lack of rearside nucleophilic solvation of the covalent substrate is that the negative effect of nucleophilic solvation in the heterolysis of these compounds is displayed more intensely than in the heterolysis of *tert*-alkyl compounds, where this solvation is only hindered. Abboud and coworkers showed[41,79] that the relative solvolysis rates of bridgehead derivatives in 80% aqueous ethanol correlated well with the relative stabilities of corresponding carbocations in the gas phase, whereas solvolysis rates of *tert*-alkyl derivatives deviated from this plot. They explained such deviations by nucleophilic solvent assistance in the solvolysis of *tert*-alkyl substrates, referring to the fact that the less is the steric hindrance for a rearside nucleophilic attack, the greater are the deviations from a 'bridgehead plot'. These plots indicate differences between the solvation effects of bridgehead and *tert*-alkyl substrates, but tell nothing about the nature of this phenomenon.

To explain these differences somehow, the myth about nucleophilic solvent assistance is used. In fact, the difference is caused by a significantly greater distinction in the nucleophilic solvation of covalent substrates and CIP for the heterolyses of adamantyl substrates than for the heterolyses of *tert*-alkyl substrates. Therefore, the prepotent negative effect of nucleophilic solvation has a place in the heterolysis of adamantyl substrates.

One can find other data in the literature that show that nucleophilic solvation can decrease the rates of S_N1 and $E1$ reactions. The use of the two-parameter Grunwald–Winstein equation for the analysis of solvolytic reactions of tertiary substrates has not once led to the identification of a negative effect of nucleophilic solvation.[39,51,56] The necessary inferences, however, were not made.

Anteunis and Peeters[80] studied in detail the dehydrobromination kinetics of 2-bromo-2-methylpentane in DMFA ($E1$ reaction) by diverse methods and concluded that nucleophilic solvation of CIP led to impasse equilibrium, that essentially brought down the reaction rate.

Graphical analysis of the plot of log$k$ values of *p*-methoxyneophyl tosylate (**13**) solvolysis vs values of donor and acceptor numbers of solvents and comparison of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values in different solvents led Ulrich[44] to the conclusion that the nucleophilic solvation of a substrate's ion pair hindered elimination of a nucleofuge by the S_N1 mechanism. It has already been shown that the negative effect of nucleophilic solvation in the solvolysis of this substrate has been identified with the help of the Grunwald–Winstein equation[56] and also with the help of the Kamlet–Taft equation[64] and Eqn (5). Hence this effect has been shown for one substrate by three different methods.

Recently, Gajewski[43] carried out correlation analysis of solvation effects for *t*-BuCl and 1-AdCl solvolyses in seven solvents [1–3, H_2O, $(CF_3)_2CHOH$, CF_3CH_2OH, HCO_2H] and showed that solvent nucleophilicity decreased the reaction rates. He explained this effect by the stabilization of the initial state of the substrates, especially in water. However, we find a negative effect of nucleophilic solvation in anhydrous media and even in aprotic solvents.

Hence solvent nucleophilicity does not affect the rate of unimolecular heterolysis or decreases it. A lack of nucleophilic solvent assistance in unimolecular heterolyses reactions shows that SSIP forms after the limiting step of the reaction and numerous examples of the negative effect of nucleophilic solvation indicate that CIP forms before the limiting step of the reaction. This has to be reflected in the reaction mechanism.

MECHANISM OF COVALENT BOND HETEROLYSIS

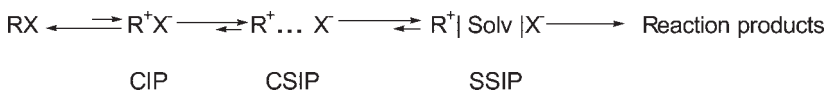
The study of the nature of solvation effects[5] and salt effects[6,7] in unimolecular heterolysis reactions by the verdazyl method led to the conclusion that the conversion of CIP to SSIP must occur in a two-step process: first ions in CIP separate, then a solvent molecule enters into the interionic space.[60,81] A solvent appears to be a discrete medium and ions of CIP have to separate up to the moment when interionic space will be large enough for placing a solvent molecule.[82] *t*-BuCl hydrolysis was modeled by the Monte Carlo method. It was shown[83] that the nucleophilic attack on CIP started only when the ions separated to a distance of $\sim$5 Å.

A cavity structure of a liquid[76,84] helps to display this process more distinctly. The volume of an organic solvent in the liquid phase is $\sim$10% larger than in the solid phase. Such a difference in volume is caused by the cavities which arise in a liquid as a result of density fluctuations (the distance between molecules in liquid and solid phases is equal). The diffusion process in a liquid can occur only with the participation of a cavity. Therefore, the process of ion separation in CIP has to be considered as an interaction between this intermediate and a cavity. Such consideration led to speculation about the formation of another ion pair under heterolysis: a spatially separated or cavity-separated ion pair (CSIP).[4,5,81] Guttman and Resch consider[85] that with consideration of chemical processes it is necessary to take into account not only the interactions of cavities with reagents, but also interactions of cavities with each other.

The lack of an effect of nucleophilic solvent assistance in reactions of unimolecular heterolysis and the presence of the negative effect of nucleophilic solvation conform with the intermediate formation of CSIP in the progress of the conversion of CIP to SSIP and show that CSIP formation must be the rate-limiting step of the unimolecular heterolysis process.

The concept of CSIP formation agrees well with results of quantum chemical analysis of ion separation in a liquid. Two independent groups[86,87] drew the conclusion that there had to be an intermediate between CIP and SSIP on a reaction coordinate, which was called 'a contact ion pair, which begins to split'.

Studies of the effects of ammonium salts and salts of alkali metals on the heterolysis rates of different substrates in aprotic solvents by the verdazyl method have shown that interpretation of the observed salt effects must take into account the intermediate formation of three ion pairs: CIP, CSIP and SSIP.[6,7] The linear increase in the reaction rate with increase in salt concentration is caused by the salt action on a covalent substrate (normal salt effect), whereas if salt interacts with CIP, reaction at first accelerates abruptly, but then this acceleration slows and stops, when $dk/d[salt] = 0$ (special salt effect). If a salt's species react with SSIP or with CSIP, the reaction rate abruptly diminishes, then the rate of diminution slows down reaches $dk/d[salt] = 0$ (negative special salt effect). If a salt affects SSIP then the reaction rate depends on the Vd concentration, but if a salt reacts with CSIP such a dependence is absent. In the case when an anion is the



Scheme 3

salt's acting species, the object of such an action is postulated by the HSAB principle. The softest base ClO_4^- interacts with a covalent substrate, the anion Br^- interacts with CIP and Cl^- interacts with CSIP or SSIP.[6,88,89]

The lifespan of CSIP is close, apparently, to the translational–rotatory relaxation period of a dipole in a liquid phase (10^{-10}–10^{-11} s).[73] This time is sufficient for CSIP to exist as an intermediate species.

Hence the reaction of unimolecular heterolysis runs through the consecutive formation of three ion pairs: CIP, CSIP and SSIP (Scheme 3).

Free carbocation does not form, except in a few cases.[47] The common ion salt effect, subjected to the mass action law, with the help of which free carbocation is usually identified as an intermediate spieces,[1] is caused by salt action on SSIP, not on carbenium ion.[7]

In the first step of heterolysis, CIP is formed in an equilibrium process and the equilibrium is strongly shifted to a covalent substrate.[3,90] In the second, rate-limiting, step, CIP interacts with a solvent cavity. CSIP is formed and quickly converts into SSIP. The latter ion pair forms, also quickly, the reaction products. The second reaction step is, apparently, also the equilibrium step; however, the equilibrium is substantially shifted towards CSIP, and therefore the step of the external return of an ion pair is negligible.

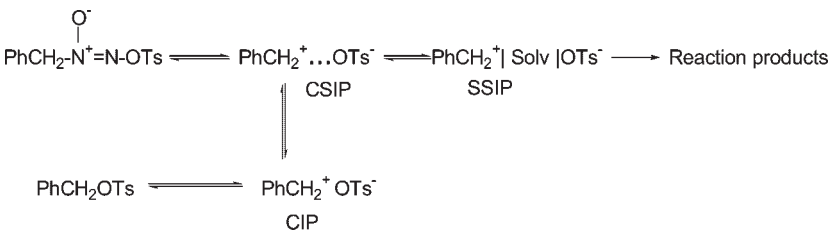
The rate of CIP to CSIP conversion is, apparently, close to the diffusion rate ($\sim 5 \times 10^9$ M^{-1} s^{-1}).[91] Data concerning the dynamics of ion pair conversions were studied by the method of picosecond UV spectroscopy. These data agree with the latter assumption and show that this process can limit the rate of heterolysis.[92,93] One of the causes is a low CIP concentration. It was shown for Ph_2CHBr heterolysis in MeCN[94] that even when the CIP dissociation rate constant exceeds the rate of its formation by nine powers of 10, the rate of the former step can still limit the total reaction rate.

If the rate of heterolysis reaction depends on the interaction between CIP and a solvent cavity, it must also depend on the probability of cavity formation in a solution and, therefore, on solvent cohesion. One would suppose that a decrease in a solvent's cohesion energy would accelerate the reaction. However, the solvents' cohesion decreases in parallel with the diminution of solvent polarity. Furthermore, the lower the cohesion, the greater is the negative effect of nucleophilic solvation. This impedes interpretation of the cohesion effect on the reaction rate. However, one can follow how processes of destruction and consolidation of a solvent structure, which are closely associated with the process of cavity formation, affect the reaction rates. It is known[95] that ultrasound destroys a solvent structure. This results in acceleration of *t*-BuCl hydrolysis.[96] Small additions of non-polar aprotic solvents affect the hydrolysis rate likewise.[97] On the other hand, when a liquid's structure is reinforced, the probability of cavity formation diminishes and the rate of heterolysis decreases. For instance, the rate of $PhCH_2Cl$ hydrolysis has a minimal value under 4 °C[98] that corresponds to the maximum of the water density. The rate of *t*-BuCl solvolysis also has a minimum value in a binary solvent, $(CF_3)_2CHOH$–H_2O. This minimum corresponds to the most well-ordered solvent structure of hexafluoro-2-propanol dihydrate.[99]

The concept of the intermediate formation of CSIP in heterolysis reactions explains the *F*1 reaction mechanism for both neutral and charged nucleofuges.[100] When the solvolysis kinetics were studied for benzylazoxy tosylate (*F*1 reaction) and benzyl tosylate (S_N1 reaction), it was shown that a common intermediate existed for these substrates,[101] but the structure of this intermediate remained incomprehensible. CSIP can be such an intermediate, then it converts into SSIP and CIP (Scheme 4).

Hence the interpretation of the mechanisms of unimolecular heterolysis reactions requires the intermediate formation of CSIP to be taken into account.

Analysis of the data concerning the heterolyses of two tertiary alicyclic compounds can illustrate the effectiveness of a new mechanistic scheme for heterolysis. Figure 4 and Table 2 show the effect of the ionizing power of an aprotic solvent on the heterolyses rates of chloride **10** and bromide **11**.[102] In polar solvents the heterolysis rate for bromide is two powers of 10 greater than for chloride. The reason is that the ionizing solvent



Scheme 4

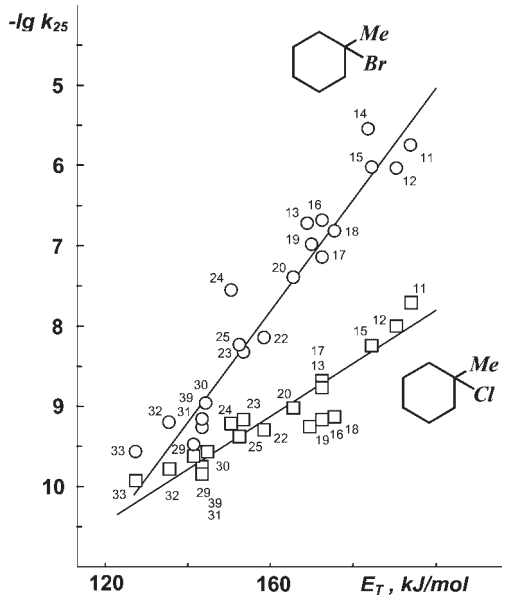


Figure 4. Effect of the ionizing power of a solvent, E_T, on the heterolyses rates of 1-bromo-1-methylcyclohexane and 1-chloro-1-methylcyclohexane. Numbering of solvents as in caption to Fig. 3; 39, Et_2O

power affects bromide about twice as strongly as chloride. This is caused by a greater susceptibility of the easily polarizing C—Br bond to dipolar solvation. If the ionizing power of a solvent decreases, the ratio of heterolysis rates for bromide **11** and chloride **10** decreases. In cyclohexane they differ only slightly.[103]

Table 2. Effect of an aprotic solvent on the heterolyses rates of 1-chloro-1-methylcyclohexane (**10**) and 1-bromo-1-methylcyclohexane (**11**) at 25 °C

		−Log$k$ (k in s^{-1})	
No.	Solvent	**10**	**11**
11	Propylene carbonate	7.69	5.72
12	Acetonitrile	7.98	6.01
13	1,2-Dichloroethane	8.74	6.65
14	Sulfolane	7.61	5.35
15	γ-Butyrolactone	8.22	6.00
16	Benzonitrile	9.14	6.66
17	Nitrobenzene	8.60	7.12
18	Acetone	9.11	6.79
19	PhCOMe	9.23	6.96
20	Cyclohexanone	9.00	7.37
22	*o*-Dichlorobenzene	9.27	8.12
23	Chlorobenzene	9.14	8.30
24	Iodobenzene	9.19	7.53
25	Bromobenzene	9.35	8.21
29	Benzene	9.58	8.94
30	Toluene	9.60	9.45
31	*o*-Xylene	9.82	9.13
32	*p*-Xylene	9.72	9.17
33	Cyclohexane	9.88	9.56
39	Diethyl ether	9.73	9.24

Application of Eqn (3) shows that the heterolysis rate of bromide **11** is affected by solvent polarity 3.9 times more and by electrophilicity 1.6 times more than the rate for chloride **10**:

$$\log k_{10} = -11.0 + 2.07f(\varepsilon) + 0.0345E + 0.00210\delta^2;$$
$$R = 0.954,\ N = 20$$

$$\log k_{11} = -12.1 + 8.08f(\varepsilon) + 0.0541E + 0.00215\delta^2;$$
$$R = 0.964,\ N = 20$$

The difference between the effects of solvent polarity and electrophilicity on the heterolyses rates of **10** and **11** can explain why the rates ratio decreases so sharply in the solvents considered. A comparison of activation parameters ($\Delta H^{\ddagger}_{\mathbf{10}} = 157\ \mathrm{kJ\,mol^{-1}}$, $\Delta S^{\ddagger}_{\mathbf{10}} = 92\ \mathrm{J\,mol^{-1}K^{-1}}$; $\Delta H^{\ddagger}_{\mathbf{11}} = 103\ \mathrm{kJ\,mol^{-1}}$, $\Delta S^{\ddagger}_{\mathbf{11}} = -81\ \mathrm{J\,mol^{-1}K^{-1}}$) evinces a mechanistic cause of the close activity of these compounds in cyclohexane. In bromide heterolysis a solvation of the transition state takes place, $\Delta S^{\ddagger} < 0$, in contrast to the desolvation process in chloride heterolysis, when $\Delta S^{\ddagger} > 0$.

The formation of a transition state occurs when CIP interacts with a solvent cavity. The probability of CSIP formation depends on the lifespan of CIP and on its solvate size. As bromide is easily solvated by aprotic solvents, the reaction in this case passed through an additional solvation of CIP and an increase in its lifespan. Chloride is weakly solvated by aprotic solvents and in this case the reaction passed through a desolvation of CIP and a diminution of its solvate size. An increase in temperature promotes desolvation and hampers solvation; as a result, at 50 °C chloride is about two times more active than bromide, whereas at 25 °C bromide is about two times more active than chloride.

Hence the concept that the heterolysis rate is limited by CIP interaction with a solvent cavity allows one to rationalize the nucleophilic solvent effect and to promote further elaboration of the Ingold–Winstein mechanism.

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