

Reviews

Correlation methods for analyzing and predicting reactivities in nucleophilic substitution processes

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Various approaches used for analyzing and predicting reactivity in nucleophilic substitution reactions at saturated carbon atoms were systematized and compared. The similarities between these approaches, their scopes, advantages, and disadvantages were established. The trends and outlooks in the further development of qualitative and quantitative models for describing dependences of the reactivities of substances on the physicochemical properties of substrates and nucleophiles were analyzed.

Key words: theoretical organic chemistry; nucleophilic substitution reactions, reactivity; reaction coordinate diagrams, correlation analysis.

Analyzing and especially predicting the reactivity of organic compounds has attracted interest among chemists for many years. Special attention has been paid to nucleophilic substitution reactions, which have served as a test of the validity of almost every new method for analyzing reactivity. This is explained by the fact that, on the one hand, nucleophilic substitution reactions have been studied in detail and extensive experimental material is available for them, and, on the other hand, it is a field where many problems are still poorly explained even at the qualitative level by the most popular theories. Some researchers believe that quantitative predictions of reactivity are not reliable at the modern level of science.¹⁻³ Nevertheless, several approaches have been developed to date that make it possible to predict rather exactly the rates and directions of nucleophilic substitution reactions for at least a series of structurally similar reagents.

Linear free energy relationships (LFER)

Brønsted and Pedersen⁴ pioneered in finding the quantitative correlation between the reaction rate and the properties of reagents, studying the deprotonation of nitramide by various bases (B). They found that the reaction rate is determined by the basicity of the carboxylate anions used and suggested the following equation:

$$\log k_B = C + \beta \cdot pK_{HB} \quad (1)$$

where k_B is the reaction rate constant, pK_{HB} is the acidity of the conjugated acid, and C and β are constants.

In 1935, Hammett pointed out⁵ the general character of this equation and its applicability to reactions of other types, including nucleophilic substitution reac-

tions (using the reactions of methyl iodide with substituted dimethyl anilines as an example). In fact, in the nucleophilic substitution reaction (Eq. (2)), the nucleophile $:Y^-$ acts as a particle donating an unshared electron pair, *i.e.*, it is a Lewis base.



Therefore, it would be expected that the ability of a compound to give its unshared electron pair to bond formation (which can be measured, for example, using pK_{HY}) would substantially affect the reaction rate. Expression (3) is also widely used at the present time for correlating and analyzing experimental results as well as predicting reaction rates in a series of structurally similar nucleophiles.⁶⁻¹⁰

$$\log k_Y = C_1 + \beta_{nuc} \cdot pK_{HY} \quad (3)$$

The Brønsted equation (1) is used to determine the dependence of the reaction rate on the strengths not only of bases but also of acids involved in a transformation. Similarly, in nucleophilic substitution processes, the ease of the detachment of the leaving group $:X^-$ measured by pK_{HX} should characterize the ability of a substrate to react. The corresponding expression was suggested by Hammett and Pfluger¹¹ for analyzing the reactions of trimethylamine with methyl esters of carboxylic acids (Eq. (4)) and has been widely used^{10,12-15} for revealing the dependence of the rate of the reaction of a nucleophile with several substrates with different leaving groups and for predicting the reaction rates for new leaving groups.

$$\log k = C_2 + \beta_{lg} \cdot pK_{HX} \quad (4)$$

Changes in the structure of the hydrocarbon fragment (R) of a substrate should also affect the strengths of bonds and the reaction rate. Although the classic Brønsted equation does not allow this effect to be expressed quantitatively, it can be done by the particular form suggested by Hammett¹⁶ for the description of the effects of substituents in the aromatic ring on the dissociation constant of benzoic ($\rho = 1$), arylacetic, and other aromatic acids (Eq. (5)).

$$\log(k/k_0) = \rho\sigma \quad (5)$$

In this equation, σ is a constant that shows how a substituent affects the corresponding equilibrium or reaction rate. Rate constants of many reactions, including those of nucleophilic substitution, are well described by Eq. (5). Usually k_0 is accepted as the reaction rate of an aromatic compound not substituted at the ring (for the hydrogen atom $\sigma = 0$).

Since electron-withdrawing substituents increase the dissociation constant of benzoic acid, stabilizing the negative charge on the benzoate ion, they have positive σ values, while $\sigma < 0$ for electron-donating substituents. The coefficient $\rho = 1$ in Eq. (5) shows that in the given

reaction series the substituents exert precisely the same effects on the reaction rate as on the dissociation constant of the corresponding benzoic acid. When $\rho > 1$, the substituent effect remains qualitatively the same, but becomes more pronounced quantitatively. When $\rho < 0$, substituents that facilitate the dissociation of benzoic acids retard the process (and *vice versa*).

Such an opposite effect should appear, for example, in S_N1 reactions of neutral substrates, where the positive charge on the C atom increases. For example, the solvolysis of substituted benzhydryl chlorides in ethanol at 25 °C is described¹⁷ by the Hammett equation with $\rho = -5.09$. Large positive ρ values are observed for reactions whose transition states (TS) have considerable negative charges. For example, in the case of methyl benzoates, the rate of alkaline hydrolysis, which occurs *via* an addition-elimination mechanism, obeys¹⁷ the Hammett equation with $\rho = 2.23$.

In S_N2 reactions, the change in the charge on the aliphatic C atom is usually rather small on going from reagents to TS. Therefore, ρ values are also small and can be positive¹⁸ or negative¹⁹ depending on the reagents and the reaction conditions.

For many S_N1 reactions, a better correlation is observed when the modified constants σ^+ are used. These constants take into account the strong resonance interaction between an atom with an increasing positive charge and a substituent at the aromatic ring. The solvolysis of *para*-substituted cumyl chlorides in 90 % aqueous acetone²⁰ is used as a standard reaction for the estimation of σ^+ ($\rho^+ = 1$). Sometimes the correlation between rates and σ^+ values is also used for S_N2 reactions.^{21,22} Other constants, that allow one to describe the effect of the introduction of a functional group on reaction rates more precisely than σ or σ^+ , have also been suggested. The values of various constants for a wide range of functional groups are presented in several reviews²³⁻²⁶ and monographs.²⁷⁻³¹

The equations presented above are generalized on the basis of the Leffler theory of the transition state.³² Leffler suggested that the most general expression for the description of the dependence of the energy barrier (and hence, the rate of the chemical reaction as well) on the thermodynamic parameters of the process be used (Eq. (6)):

$$\Delta E^\ddagger = \alpha + \beta\Delta E^\circ, \quad (6)$$

where α is the intrinsic activation energy for the processes in the absence of a thermodynamic driving force, and β characterizes the position of the TS on the reaction coordinate. Leffler also clarified the physical meaning of this expression (and its particular cases). For strongly exothermic reactions $\beta \cong 1$, for strongly endothermic reactions $\beta \cong 0$, and $\beta \cong 0.5$ for reactions that occur with a slight change in ΔE° . This dependence of the TS position on the exothermic nature of the process is usually called the Hammond postulate,³³ and is most often formulated at the present time in the following

way: "the transition state becomes more reactant-like in its structure and energy as the exothermicity of the reaction increases".

As follows from the Brønsted—Hammett—Leffler approach, the selectivity of the process is related to the reactivity: when the reactivity of one of the reagents increases, the coefficient β in Eq. (6) (or ρ in the Hammett equation) becomes smaller. As a consequence, the sensitivity to the difference in ΔE^\ddagger (or in σ values) decreases when the second reagent is replaced, and more active compounds are less selective. For example, in the reactions of aniline derivatives with substituted benzyl tosylates, the most reactive nucleophile (*p*-toluidine) is the least selective with respect to a change in substituents in the benzyl group ($\rho = -0.56$ in methanol at 35 °C). The selectivity increases as the activity decreases: $\rho = -1.05$ for *p*-chloroaniline and -1.34 for *p*-nitroaniline.²² By analogy, the coefficient β_{nuc} increases from 0.19 for the most active *p*-methylbenzyl tosylate to 0.45 for the least reactive *p*-nitro derivative.

Linear correlations (3)—(6) and their various analogs are widely used to evaluate the extent of bond breaking and formation in TS and hence, to draw conclusions about the mechanism according to which a reaction occurs. These correlations are possible only in the case when the mechanism remains unchanged on going from one reagent to another in a given reaction series. A change in the reaction mechanism results in a break in the linear dependence of ΔE^\ddagger on ΔE° ($\log k$ on σ or pK). Such a break for the acidic hydrolysis of substituted ethyl benzoates in concentrated sulfuric acid³⁴ is presented in Fig. 1.

Two inflections were found³⁵ in the dependence of the logarithm of the reaction rate of the hydrolysis of substituted cumyl chlorides and cumyl *p*-nitrobenzoates $ZC_6H_4CMe_2X$ on σ^+_{Z} . These inflections are assigned to the transition from ion-pair solvolysis ($\sigma^+_{Z} < -0.08$) to direct solvolysis of the reagents ($-0.08 < \sigma^+_{Z} < 0.12$)

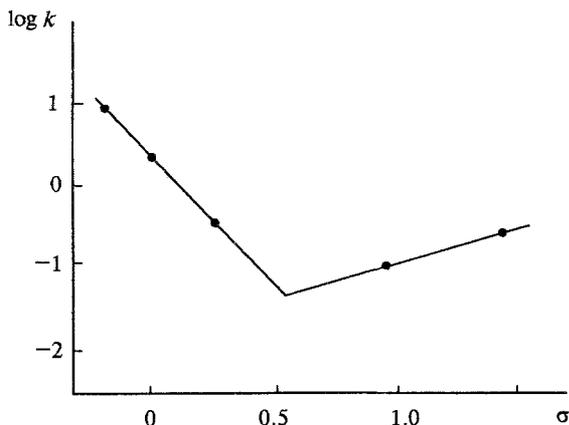


Fig. 1. Dependence of the logarithm of the rate constant of the hydrolysis (k/h^{-1})³⁴ of substituted ethyl benzoates in 99.9 % H_2SO_4 on σ .

and to the concerted pericyclic elimination of HX ($\sigma^+_{Z} > 0.12$) in accord with the reaction products observed.

Changing the substituents can not only sharply change the reaction mechanism but can also shift the position of the TS within the same mechanism. According to the Leffler description, this corresponds to changes in the coefficients ρ (β_{nuc} , β_{lg} , etc.) and hence, distortion of the dependence of ΔE^\ddagger on ΔE° . In order to solve this problem, the following equation was suggested:³⁶

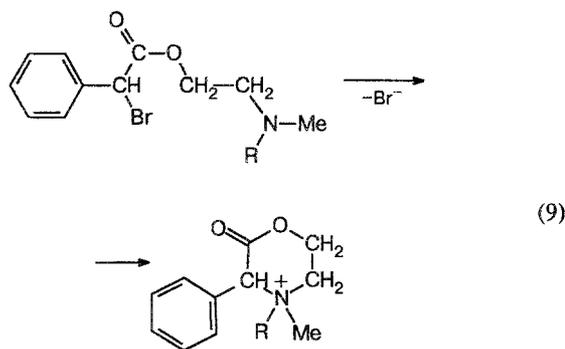
$$\log(k/k_0) = \rho[\sigma_X + r(\sigma^+_{X} - \sigma_X)]. \quad (7)$$

Coefficient r allows one to take into account the change in the contribution of the carbocationic structure to the TS of the reaction as a result of the change in the extent of breaking and/or making of bonds.

Such complicated two- and multi-parametric correlations are also used in some other cases. For example, when a substituent is introduced at a position near the reaction center, steric effects acquire great significance. To take these effects into account, Taft^{37,38} suggested the following equation:

$$\log(k/k_0) = \sigma^*\rho^* + \delta E_S, \quad (8)$$

where σ^* is a measure of the substituent polarity and E_S is a measure of its steric requirements. A good correlation between the reaction rates of intramolecular nucleophilic substitution (Eq. (9)) and the values predicted by the Taft equation (8) was also found.³⁹



Swain and Lupton⁴⁰ suggested the following expression:

$$\log(k/k_0) = fF + rR, \quad (10)$$

where R takes into account the resonance effect of the substituent and F takes into account the corresponding field effect. They found that for the majority of various σ values (σ_{meta} , σ_{para} , σ^+ , σ^- , etc.), there is the interconnection described by Eq. (11).

$$\sigma = fF + r'R \quad (11)$$

This approach removes to a large extent the question of what constants of substituents can be used for the analysis of a particular given reaction. Taft^{24,41} and

Ehrens⁴² also separated the substituent effects into inductive and resonance effects (Eq. (12)).

$$\log(k/k_0) = \sigma_I \rho_I + \sigma_R \rho_R + \sigma_R^+ \rho_R^+ + \sigma_R^- \rho_R^- \quad (12)$$

Equation (13), suggested by Kreevoy and Taft,^{43,44} makes it possible to take into account inductive, steric, resonance, and hyperconjugative effects of substituents simultaneously.

$$\log(k/k_0) = \rho^* \sigma^* + \delta E_S + \partial n \cdot h + \Psi \quad (13)$$

Here h is a constant that characterizes the sensitivity of the process to the hyperconjugative effects of substituents, which are considered proportional to the number of α -C—H bonds ($\partial n = n - 3$). The parameter Ψ is assumed constant for all π -electron systems regardless of their structures. The resonance contributions of substituents without groups with π -electrons are equal to zero.

Multi-parametric equations can be used only in the case when the postulate of the additivity and independence of interactions of different formal types is fulfilled.²⁸ More detailed discussions about the use of linear correlations for taking into account substituent effects in a nucleophile, leaving group, or hydrocarbon fragment can be found, for example, in the known review (Ref. 26) and in the monographs (Refs. 28, 45–48).

Absolute rate constants of nucleophilic substitution reactions and their correlations with the properties of reagents can change considerably on going from one solvent to another. In general, it is possible to use the order of the relative reactivity as an indicator of the nucleophilicity (nucleofugacity) inherent in one or another particle only in the gaseous phase, because the differences in the specific and non-specific interactions of substances with solvents strongly affect the rates of the corresponding reactions. The effect of solvation on the rate and mechanism of nucleophilic substitution reactions is discussed, in particular, in several monographs.^{49–52}

When the solvent effect on the reaction rate is caused only by changes in the dielectric permeability (ϵ) and/or polarizability of the medium, it can be described^{27,29,49,50} by the linear dependence of $\log k$ on $1/\epsilon$ or by more complicated functions, for example, $(\epsilon - 1)/(2\epsilon + 1)$ or $(\epsilon - 1)/(\epsilon + 2)$. However, such cases are rare for processes involving the participation (formation) of ions. Therefore, some specific constants of solvents are recommended for the estimation of reaction rates.

The Grunwald—Winstein equation is the most often used for this purpose now^{53,54}:

$$\log(k/k_0) = mY, \quad (14)$$

where Y is the ionizing strength of the solvent and m is the sensitivity of the substrate changes in Y . The authors chose the solvolysis of *tert*-butyl chloride as the standard process. However, this scale subsequently came under criticism and modified series of ionizing strengths were

suggested. They are based on the solvolysis of adamantyl derivatives (chloride (Y_{Cl}),⁵⁵ tosylate (Y_{OTs}),⁵⁶ and others). For cationic substrates, the scale is based on the solvolysis of the triethyloxonium ion.⁵⁷ Different scales of ionizing strengths of solvents are compared, for example, in one of Kevill's works.⁵⁸

Adamantyl substrates were chosen because they do not undergo S_N2 reactions and hence, a solvent cannot manifest its nucleophilic properties. However, when the solvent offers nucleophilic assistance to the solvolysis of the substrate, the correlations relative to Y (Y_{Cl} , Y_{OTs}) become insufficient. In this case, the extended^{54,56} Grunwald—Winstein equation is used:

$$\log(k/k_0) = mY + lN, \quad (15)$$

where N characterizes the nucleophilicity of the solvent and the coefficient l is a measure of the nucleophilic assistance and is used as one of the mechanistic criteria to distinguish S_N1 , S_N2 , and ion-pair mechanisms of nucleophilic substitution reactions.^{58–60}

Pal'm wrote²⁸ that "since solvation effects are related to several interactions of independent types, any mono-parametric approach... is not versatile". In this connection, various equations with many parameters have been suggested for the description of the effect of the solvent on rates of nucleophilic substitution reactions. Pal'm used the following expression:

$$\log(k/k_0) = yY + pP + eE + bB. \quad (16)$$

Here the coefficient $Y = (\epsilon - 1)/(\epsilon + 2)$ characterizes the medium polarity and $P = (n^2 - 1)/(n^2 + 2)$ characterizes its polarizability, while E serves as a measure of the solvent acidity and B is the measure of its basicity. The values of these parameters for various solvents are presented in the monograph cited above.²⁸

It was also shown²⁸ that for the S_N2 reaction described by Eq. (17), only one of the four parameters is significant: $\log(k/k_0)$ correlates with E at $e = -0.358$.



In other words, solvents prone to specific electrophilic solvation retard the reaction due to the stabilization of the Cl^- ion in the initial state. On the other hand, in the solvolysis of *tert*-butyl chloride, coefficient e is positive due to the stabilization of the Cl^- anion. In this case, other parameters of the solvent used in expression (16) are also important. Equation (18) is obtained from processing the results, and it turns out that $\log k_0$ nearly coincides with $\log k$ in the gaseous phase.

$$\log k = -19.50 + 5.67Y + 17.27P + 0.379E \quad (18)$$

Another multi-parametric equation is suggested by Taft.⁶¹

$$\log(k/k_0) = a\alpha + b\beta + s\pi^* + d\delta_H^2/100 \quad (19)$$

Here α is the proton-donating capability of the solvent in the formation of hydrogen bonds (compare with E in

Eq. (16)); β is its proton-withdrawing capability (to be an acceptor of hydrogen bonds, analog of B in Eq. (16)); π^* is the index of the dipolarity—polarizability of the solvent; and δ_H^2 is the Hildebrand parameter, which characterizes the ability of the solvent to form cavities for molecules, associates, and TS. This method gives very good results for the description, for example, of effects of solvents on the rates of Menshutkin's reaction (typical S_N2 reaction) and of the solvolysis of *tert*-butyl chloride (typical S_N1 reaction).⁶²

As mentioned above, it has become conventional to judge the reaction mechanism and the properties of the TS by the values and signs of the coefficients in the Grunwald—Winstein, Pal'm, or Taft—Kamlet equations. At the same time, it is repeatedly emphasized^{28,62} that the conclusions based on this reasoning should be considered somewhat skeptically.

All equations discussed above are general and can be used for studying processes of different types. In addition, one- and multi-parametric linear correlations are suggested for analyzing and predicting the rates of nucleophilic substitution reactions. For example, the Swain—Scott expression⁶³ (Eq. (20)) is often used:

$$\log(k/k_0) = sn + s'e, \quad (20)$$

where n is the nucleophilicity of the attacking reagent, e is the electrophilicity of the substrate, and s and s' are the sensitivities of the substrate and nucleophile to changes in nucleophilicity and electrophilicity, respectively. Water was chosen⁶³ as the standard nucleophile ($n = 0$) and methyl bromide was accepted as the standard substrate ($s = 1$; $e = 0$).

In their work, Swain and Scott⁶³ processed reactions of various substrates from ethyl tosylate to benzoyl chloride and benzenesulfonyl chloride by Eq. (20). The validity of Eq. (20) has also been confirmed for many

other cases.^{64–66} Nevertheless, some authors suggest that both the scale of nucleophilicity n and the equation itself should be modified. The work of Pearson,¹ in which the n values are given for many nucleophiles, but methyl iodide is chosen as the standard substrate, should be mentioned. Peterson and co-workers⁶⁷ built a scale of nucleophilicity based on the reaction rates of pentamethylene iodonium salts. The Peterson scale describes reactions in which strong steric effects are manifested better than those based on the reaction rates of methyl derivatives.⁶⁷ The values of various parameters of nucleophilicity of several particles suggested by different authors are presented in Table 1.

As can be seen from the data in Table 1, nucleophilicity correlates poorly with basicity with respect to hydrogen pK_a for a wide variety of attacking atoms and substituents. This fact is all the more important, because for a series of nucleophiles of the same type the basicities with respect to hydrogen and carbon are linearly related.^{68–70} Therefore, Edwards suggested⁷¹ the two-parametric equation:

$$\log(k/k_0) = \alpha E_n + \beta H, \quad (21)$$

where $H = (pK_a + 1.74)$ characterizes the basicity of the nucleophile ($pK_a = -1.74$ for water as the standard nucleophile) and $E_n = (E^\ominus + 2.60)$ is the potential of its oxidation (the electrode potential of reaction (22) is equal to 2.60 V).



Edwards subsequently modified⁷² his equation, presenting it in the form of expression (23), because the value of E_n itself depends on the basicity of the nucleophile (H) and its polarizability (P).

$$\log(k/k_0) = \alpha' P + \beta' H \quad (23)$$

Table 1. Parameters of nucleophilicity for anions and neutral molecules

Nucleophile	n_{MeBr}^{28}	n_{MeI}^1	n_{Pt}^1	$n_{\text{R}_2\text{Br}^+}^{67}$	$N^+_{\text{H}_2\text{O}}^{76}$	pK_a^{28}	$E_{\text{ox}}/\text{V}^{28}$
$\text{S}_2\text{O}_3^{2-}$	6.36	8.95	7.34			1.86	-0.08
SO_3^{2-}	5.10	8.53	5.79		7.90	7.26	-0.03
CN^-	5.10	6.70	7.14		3.67	9.14	0.19
HS^-	5.10	8.00				6.96	0
I^-	5.04	7.42	5.46	5.3		(-10)	-0.54
SCN^-	4.77	6.70	5.75	5.2		-0.74	-0.77
NH_3	4.23	5.50	3.07		3.89	9.48	-0.76
HO^-	4.20			3.6	4.75	15.74	-0.95
$\text{SC}(\text{NH}_2)_2$	4.10	7.27	7.17			-0.96	-0.42
N_3^-	4.00	5.78	3.58		7.60	4.72	-1.02
Br^-	3.89	5.79	4.18	4.1		(-8)	-1.09
NO_2^-		5.35	3.22		3.04	3.35	-0.87
$\text{C}_5\text{H}_5\text{N}$	3.60	5.23	3.19		5.00	5.30	-1.40
Cl^-	3.04	4.37	3.04	3.1		(-5)	-1.36
AcO^-	2.72	4.30	<2.00	2.5	2.95	4.72	-1.65
SO_4^{2-}	2.50	3.50				2.00	-2.01
F^-	2.00	2.70	<2.20	0.8	3.45	3.16	-2.87
H_2O	0			0	0	-1.74	-2.60
MeOH		0	0	0.57	0.5		

When $\alpha = 0$, the Edwards equation is transformed into the classic Brønsted equation (1). In addition, it is mentioned²⁸ that there is a rather good correlation between n and E_n and therefore, the Swain—Scott equation is a particular case of the Edwards equation for $\beta \cong 0$. Thus, the Edwards equation can be considered to some extent as a mathematical expression of the principle of hard and soft acids and bases (HSAB)^{1,2,73,74}: hard bases (high H , low P) react preferably with hard acids (large β' , small α') and soft bases (high P , low H) react with soft acids (large α' , small β').

The Swain—Scott and Edwards equations were suggested for processing the data on the kinetics of the reaction in aqueous solutions. It has been already mentioned above that a solvent exerts a very strong effect on the rates of nucleophilic substitution reactions and can change the relative reactivities of nucleophiles. It has been suggested^{75–78} that the scale of the nucleophilicity of a particular particle in a particular solvent be built. The following equation has been used^{75–78} for the reactions of stabilized carbocations with nucleophiles:

$$\log k_{\text{Nu}}^{\text{S}} = \log k_{\text{H}_2\text{O}}^{\text{H}_2\text{O}} + N^+, \quad (24)$$

where k_{Nu}^{S} is the rate constant for the reaction of a carbocation with a nucleophile Nu in the solvent S, and N^+ is a constant that characterizes this nucleophilic system.

For many substrates studied, the sensitivities toward N^+ are nearly equal. Therefore, the sensitivity constant used in the Swain—Scott, Hammett, Brønsted—Leffler, and other equations does not appear in Eq. (24). However, correlations between the rates of the reactions with nucleophiles and the values of N^+ have been found for other cases, which indicates that the substrates have sensitivities other than those of the standard substrates used.^{79,80} In this case, Eq. (24) takes the form

$$\log(k/k_0) = S^+ N^+. \quad (25)$$

The N^+ values are also presented in Table 1. Some other parameters of the nucleophilicity have also been used,^{81–84} but they have not received wide recognition and hence, are not discussed in this review.

In addition to Eqs. (21)–(25), the quantitative scales of nucleofugacity (L) have been developed for the description of reactivity of compounds in nucleophilic substitution (and elimination) reactions. Thornton⁴⁹ presented the scale of reactivity for substrates MeX in $S_{\text{N}}2$ reactions with the methoxide ion in methanol (methyl bromide was taken as the standard). The rates of many other $S_{\text{N}}1$ and $S_{\text{N}}2$ reactions have been analyzed on the basis of this scale and Eq. (26).

$$\log(k/k_0) = \gamma L \quad (26)$$

As shown,²⁸ the nucleofugacity L is related to the nucleophilicity of the leaving group by Eq. (27), which is similar to expression (21) suggested by Edwards.

$$L = -1.99 - 0.30E_n - 0.33H \quad (27)$$

Table 2. Constants of nucleofugacity for leaving groups²⁸

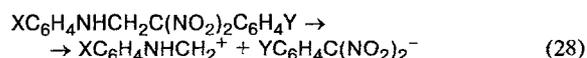
Nucleofug	L	τ	τ_{Ar}
F	-3.60	0	2.890
Cl	-1.61	3.40	0
Br	0	4.79	0.004
I	-0.04	5.35	-0.637
OH_2^+	-0.17		
NMe_3^+	-3.54		
SMe_2^+	-3.01		
OMe	-6.45		-3.120
O_2CMe	-4.68		-1.370
ONO_2	-1.90		
OSO_2Me	-0.25		
OTs	0.63		1.29

The analysis of the contributions of the variables makes it possible to conclude that L depends mainly on H , *i.e.*, on the basicity of the leaving group.

The τ and τ_{Ar} scales have also been suggested for the description of the nucleofugacity in reactions of nucleophilic substitution at acyl^{85,86} and aromatic⁸⁷ C atoms, respectively. However, a small number of leaving groups was studied in these works and hence, the significance of these scales is rather limited. The values of L , τ , and τ_{Ar} for several leaving groups are presented in Table 2.

Summarizing the preceding, it can be mentioned that the use of the linear correlations discussed in this Section allows one to explain many results that have been observed in studying the kinetics of nucleophilic substitution reactions and to predict the rates of processes yet unstudied. The method considered is simple, descriptive, and has a clear physical meaning. Therefore, it is often used by organic chemists. At the same time, this approach has several serious disadvantages.

First, the order of reactivity of nucleophiles depends on the leaving group used and the substituents in the substrate.^{1,27,28,34,88} The same can be said about the orders of nucleofugacity of leaving groups and the effect of substituents in the hydrocarbon fragments. Therefore, the use of LFER requires the introduction of the crossing terms. According to Lee,^{89,90} it is precisely these ρ_{XY} type crossing constants that characterize the extent of breaking/formation of bonds in TS. This approach is also supported by other authors.⁹¹ However, formal analysis shows²⁸ that the significance of the crossing constants is not higher than that of ρ_{X} , ρ_{Y} , *etc.* In fact, a study of the $S_{\text{N}}1$ reaction occurring according to Eq. (28) at various temperatures and in various solvents^{92–94} showed a systematic variation of ρ_{XY} up to a change in the sign.



The reaction rates in the general form are described by a polylinear dependence up to terms of the fourth order. However, when this dependence is used, a nega-

tive activation energy is predicted for $X = H$ and $Y = 3,5-(NO_2)_2$, which questions the validity of LFER in principle.

Second, LFER imply^{95,96} the fulfillment of isokinetic dependences ($\log k^{T_1}$ is proportional to $\log k^{T_2}$). Therefore, the rates of all reactions in the series are equal at some temperature called isokinetic (T_{iso}), *i.e.*, β in the Brønsted equation (ρ in the Hammett equation) vanishes, and the sign of β (ρ , m , s , *etc.*) changes to the opposite for the "transition" *via* T_{iso} . Therefore, any conclusions about the reaction mechanism based on signs and values of coefficients β (ρ) must take into account the isokinetic temperature.^{23,28}

Third, there are a lot of facts that allow one to doubt the validity of the physical background of the linear correlations. For example, reaction series have been found for which the β coefficient in the dependence of ΔE^\ddagger on ΔE° is less than zero or higher than unity.^{97,98} In addition, it has been mentioned⁹⁹ that the results of the measurements of the kinetic isotope effect, which characterizes the geometry of TS, are often inconsistent with the conclusions drawn on the basis of the β or ρ values.

Fourth, the linear dependence of ΔE^\ddagger on ΔE° is usually not fulfilled for a sufficiently wide range of changes in ΔE° in the reaction series.⁹⁸

Fifth, the analysis of TS in terms of the Brønsted equation results in the observation of enhanced reactivities of the nucleophiles bearing the atom with an unshared electron pair at the α -position (α -effect).^{100,101} Although various explanations of this effect have been suggested,^{83,101–105} no method has appeared to date, which could predict the α -effect (and its extent if any) in reactions with a particular substrate in a given medium. The nature of the α -effect is discussed hitherto.

Finally, there are many sets of various constants for substituents and parameters of nucleophiles and leaving groups. Therefore, it is often difficult to determine the most suitable set for a particular reaction series. In addition, no justified recommendations concerning the preferableness of any particular linear correlations in one or another particular case have yet been developed.

Nonlinear correlations between the energy barrier and the exothermicity of the reaction

One of the most often used methods for at least partially overcoming the mentioned disadvantages of linear correlations can be reduced to the use of equations that use terms of higher orders with respect to ΔE° . The first such expression was suggested by Marcus¹⁰⁶ for the description of the height of the energy barrier in electron transfer reactions (Eq. (29)).

$$\Delta E^\ddagger = \Delta E_0^\ddagger + \frac{\Delta E^\circ}{2} + \frac{(\Delta E^\circ)^2}{16\Delta E_0^\ddagger} \quad (29)$$

Here ΔE_0^\ddagger is the intrinsic activation energy independent

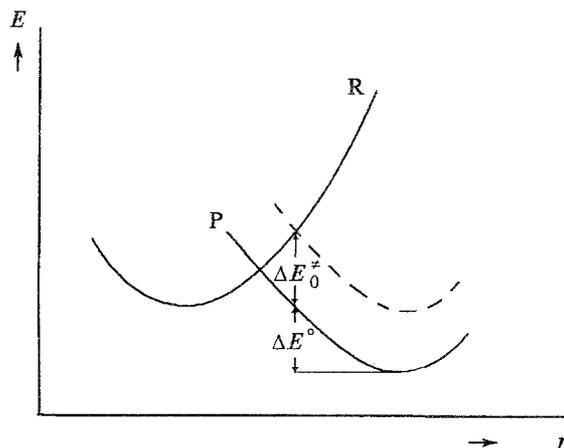
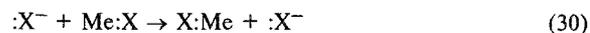


Fig. 2. Determination of the intrinsic reaction barrier according to the Marcus theory. The energy of the TS is lower than that at the point of intersection between the energy curves of the reactants (R) and products (P) by the value of the resonance interaction between their electron states.

of the exothermic effect of the process. The Marcus theory is based on the assumption that the energy is described by a parabolic function (Fig. 2) when the perturbation of the electron density on the reagents is small. The intersection of the two parabolas corresponding to the reactants (R) and the products (P) determines the position and height of the energy barrier.

The Marcus theory assumes that the process is adiabatic, *i.e.*, at the intersection point the probability of the transition of the system from the curve of the potential energy corresponding to the reactants to the curve corresponding to the products is equal to unity. At the same time, the Marcus theory is based on classic, not quantum chemical, treatment of the potential energy surface (PES) of the system. Therefore, it does not take into account¹⁰⁷ the electron interaction between the states in the region of the intersection of the parabolas ("avoided crossing") responsible for the adiabatic process. This approach can be justified only for processes with a high transition probability at very low (≤ 1 kcal mol⁻¹) energy of the interaction of two states. This condition is true for electron transfer reactions, but is violated in the case of transfers of an atom, proton, and various charged and uncharged groups, including those in nucleophilic substitution reactions.

Nevertheless, it has been found that the Marcus equation describes well the kinetics of the transfer of a hydrogen atom,^{108,109} proton,^{109–113} hydride ion,^{114,115} CH₃⁺ cation,^{116–124} *etc.* The intrinsic activation energies (ΔE_0^\ddagger) for identity S_N2 reactions (Eq. (30)) in the gaseous phase and in solution are presented in Table 3.



The analysis of the data presented in Table 3 shows that both in the gaseous phase and in solution, the intrinsic reactivity increases as the X atom reacting in the nucleophile changes its position in the periodic system

Table 3. Intrinsic activation energies ($\Delta E_0^\ddagger/\text{kcal mol}^{-1}$) of S_N2 reactions (see Eq. (30)) in the gaseous phase and in different solvents

X	Gas phase	H ₂ O	MeOH	DMF	MeCN	Sulfolane
CN ⁻	35.0 ⁶⁹	50.9 ¹¹⁷				
HO ⁻	29.0 ¹²⁴	41.8 ¹¹⁷				
F ⁻	26.0 ⁶⁹	31.8 ¹¹⁷				
	19.5 ¹²⁴	30.7 ¹²⁴				
HS ⁻	15.6 ¹¹⁸	23.5 ¹²⁴				
Cl ⁻	10.0 ⁶⁹	26.5 ¹¹⁷	28.2 ¹¹⁶	22.7 ¹¹⁶	19.6 ¹¹⁶	
	11.6 ¹²⁴					
Br ⁻	9.7 ¹²⁴	23.7 ¹¹⁷	22.9 ¹¹⁶	18.4 ¹¹⁶	15.8 ¹¹⁶	
I ⁻		23.2 ¹¹⁷	21.0 ¹¹⁶	16.0 ¹¹⁶		12.8 ¹²³
NO ₃ ⁻		26.5 ¹¹⁷				
CF ₃ SO ₃ ⁻						18.6 ¹¹⁷
MeOSO ₃ ⁻						18.4 ¹²³
PhSO ₃ ⁻		35.6 ¹¹⁷				21.1 ¹²¹
MeSO ₃ ⁻		34.6 ¹¹⁷				
ClO ₄ ⁻		37.0 ¹¹⁷				
Me ₂ O						18.6 ¹¹⁷

from left to right ($\text{OH}^- < \text{F}^-$; $\text{HS}^- < \text{Cl}^-$) and from the top down ($\text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^-$; $\text{HO}^- < \text{HS}^-$). It can be said as a first approximation that the intrinsic energy barrier is directly related to the basicity of the nucleophile.

The correlation between the energy barrier of identity reactions of nucleophilic substitution (see Eq. (30)) in the gaseous phase and the affinity of a nucleophile $:\text{X}^-$ toward the Me^+ cation (*MCA*) has also been observed previously.¹²⁵ A similar correlation between the rate constant of identity reaction (30) in sulfolane and the equilibrium constant of the reaction of MeX with the standard nucleophile has been found.¹²¹ At the same time, the basicity of the nucleophile expressed by its proton affinity (*PA*), the affinity toward the Me^+ cation, or by $\text{p}K_{\text{HX}}$ is not the only factor determining $\Delta E_0^\ddagger(\text{X}, \text{X})$. The correlation mentioned above is valid only for structurally similar nucleophiles.

One of the most important postulates of the Marcus theory is that for non-identity reactions (2) the curvatures of both parabolas are equal and are the average of those of the two identity reactions, as is reflected by Eq. (31).

$$\Delta E_0^\ddagger(\text{Y}, \text{X}) = 0.5[\Delta E_0^\ddagger(\text{Y}, \text{Y}) + \Delta E_0^\ddagger(\text{X}, \text{X})] \quad (31)$$

This assumption makes it possible to estimate the intrinsic activation energies of unstudied reactions and to extend the possibilities of predicting the reactivity using the Marcus theory. Equation (31) is usually fulfilled for nucleophilic substitution reactions,^{99,116–118} but deviations from the principle of the arithmetic mean are also known.^{69,111}

The use of the Marcus equation allows one to explain the curvatures of the Brønsted dependences for a fairly wide variation of ΔE° and to estimate the limits of

the applicability of LFER. Equation (29) can be written as follows:

$$\Delta E^\ddagger = \Delta E_0^\ddagger + \Delta E^\circ \left(\frac{1}{2} + \frac{\Delta E^\circ}{16\Delta E_0^\ddagger} \right), \quad (32)$$

where ΔE_0^\ddagger is the analog of coefficient α in the Brønsted–Leffler equation (6), and the Brønsted coefficient β is determined by correlation (33).

$$\beta = \frac{1}{2} + \frac{\Delta E^\circ}{16\Delta E_0^\ddagger} \quad (33)$$

When the intrinsic activation energies for the reactions of a given series are high, the coefficient β changes only slightly as ΔE° changes. However, when the value of ΔE_0^\ddagger is sufficiently small, even small increases in ΔE° result in an experimentally observed change in β , *i.e.*, in the appearance of curvature in the plot of ΔE^\ddagger vs. ΔE° .

It has been shown for nucleophilic substitution at the methyl group in sulfolane¹²⁶ that the contribution of the last term in the Marcus equation (29) is insignificant. Several simplifications transform the Marcus equation into expression (34), in which the first term characterizes the properties of the methylating agent and the second term characterizes only those of the nucleophile.

$$\log(k/k_0) = M_X + N_Y \quad (34)$$

When M_X values are close for several electrophiles (as, for example, for stabilized di- and triarylmethyl cations), correlation (34) is transformed into Eq. (24). At the same time, the approach suggested¹²⁶ does not allow one to explain the different sensitivities of substrates to the nucleophilicities of attacking particles, which is

reflected, for example, by the Swain—Scott expression (20) or the modified Ritchie equation (25).

Establishing the relationship between the Marcus theory and the linear correlations analyzed above, we should mention that the Edwards correlations (see Eqs. (21) and (23)) cannot be considered as particular cases of the Marcus equations. The Marcus theory does not describe in an explicit form the dependence of the energy barrier on the polarization or oxidation potential of the nucleophile. The only method for the explanation of this dependence based on this theory is the assumption that the polarizability of nucleophiles and the sensitivity of substrates to its changes contribute to the values of the intrinsic activation energies ΔE_0^\ddagger of the corresponding reactions. However, we do not know of any publications with this kind of analysis.

The Marcus theory has been widely used for the past fifteen years to describe the kinetics of S_N2 reactions in the gaseous phase and in solution. This theory reproduces well the results of measurements of the energy barrier for reactions with relatively small changes in ΔE° , and the use of its postulate (see Eq. (31)) makes it possible to predict activation energies of yet unstudied reactions.

At the same time, this approach has been repeatedly criticized for the following reasons. Equation (29) does not reproduce the dependence of ΔE^\ddagger on ΔE° for highly exothermic and highly endothermic reactions. The boundary conditions

$$\Delta E^\ddagger = 0 \quad \text{at} \quad \Delta E^\circ \leq -4\Delta E_0^\ddagger,$$

$$\Delta E^\ddagger = \Delta E^\circ \quad \text{at} \quad \Delta E^\circ \geq 4\Delta E_0^\ddagger$$

narrow the admissible interval of the change in ΔE° and do not allow one to explain values $\beta > 1$ or $\beta < 0$ in the Brønsted equation. The assumption of the additivity of the intrinsic activation energies (see Eq. (31)) sometimes gives a considerable error.^{69,111} Finally, it is doubtful that the postulate about the equal curvatures of the intersecting parabolas for non-identity reactions is valid.

The works of Formosinho have been devoted^{127–129} to the problem of the asymmetry of the intersecting curves. Formosinho modified the Marcus approach, taking into account the difference between the force constants n and m of the R—X and R—Y bonds, respectively. In his model of intersecting states, the position and the height of the energy barrier can be found from the following expressions:

$$E_1 = nx^2, \quad (35)$$

$$E_2 = m(d-x)^2 + \Delta E^\circ, \quad (36)$$

$$E_1 = E_2. \quad (37)$$

Here d is the distance between two minima on the PES and x is the distance travelled by the R fragment moving from the leaving group to the nucleophile. By denoting

the ratio of the two force constants m/n as ε , Eq. (38) can be easily obtained. The Brønsted slope β of the plot of ΔE^\ddagger vs. ΔE° is determined by expression (39) and the curvature of this dependence (c) is determined by correlation (40).

$$\Delta E^\ddagger = \frac{\Delta E_0^\ddagger}{(1-\varepsilon)^2} \left\{ 2\varepsilon + \left[\frac{\Delta E^\circ(1-\varepsilon)}{\Delta E_0^\ddagger} \right]^{1/2} \right\}^2 \quad (38)$$

$$\beta = \frac{\partial \Delta E^\ddagger}{\partial \Delta E^\circ} = \frac{1}{1-\varepsilon} \left\{ 1 - \varepsilon \left[\varepsilon + \frac{\Delta E^\circ(1-\varepsilon)}{4\Delta E_0^\ddagger} \right]^{-1/2} \right\} \quad (39)$$

$$c = \frac{\partial^2 \Delta E^\ddagger}{\partial (\Delta E^\circ)^2} = \frac{\varepsilon}{\Delta E_0^\ddagger} \left[4\varepsilon + \frac{\Delta E^\circ(1-\varepsilon)}{\Delta E_0^\ddagger} \right]^{-1/2} \quad (40)$$

The boundary conditions change slightly in this approach:

$$\Delta E^\ddagger = 0 \quad \text{at} \quad \Delta E^\circ \leq -4\varepsilon\Delta E_0^\ddagger,$$

$$\Delta E^\ddagger = \Delta E^\circ \quad \text{at} \quad \Delta E^\circ \geq 4\Delta E_0^\ddagger.$$

Although Formosinho's approach is somewhat more exact than the Marcus theory, the expressions obtained are noticeably complicated and inconvenient to use. In addition, ΔE_0^\ddagger is not the true intrinsic energy barrier, i.e., when $\Delta E^\circ = 0$ the activation energy is determined by the following expression:

$$\Delta E^\ddagger = \Delta E_0^\ddagger \left(1 - \frac{1}{1 + \sqrt{\varepsilon}} \right)^2. \quad (41)$$

Developing this approach for electron transfer reactions, Cannon showed¹³⁰ that Eq. (38) can be presented as expansion (42)

$$\Delta E^\ddagger = e\Delta E_0^\ddagger + \frac{\Delta E^\circ}{2}\sqrt{e} + \frac{(\Delta E^\circ)^2}{16\Delta E_0^\ddagger\sqrt{e}}, \quad (42)$$

$$\text{where } e = \left(1 - \frac{1}{1 + \sqrt{\varepsilon}} \right)^2.$$

This correlation and the corresponding expressions (43) and (44) for the slope and curvature of the Brønsted dependences are considerably more convenient to use and are transformed into the Marcus equations for identity reactions and other cases when $m/n = \varepsilon = 1$.

$$\beta = \frac{\partial \Delta E^\ddagger}{\partial \Delta E^\circ} = \frac{\sqrt{e}}{2} + \frac{(\Delta E^\circ)^2}{8\Delta E_0^\ddagger\sqrt{e}} \quad (43)$$

$$c = \frac{\partial^2 \Delta E^\ddagger}{\partial (\Delta E^\circ)^2} = \frac{1}{8\Delta E_0^\ddagger\sqrt{e}} \quad (44)$$

Like the Marcus theory, the Formosinho approach can be used only within a certain interval of changes in ΔE° . To solve the problem of highly exothermic (endothermic) reactions, Lewis and More O'Ferrall suggested¹³¹ an equation based not on parabolic, but on hyperbolic functions of intersecting energy curves (Eq. (45)).

$$\Delta E^\ddagger = \frac{\Delta E^\circ}{2} + \left[\left(\frac{\Delta E^\circ}{2} \right)^2 + (\Delta E_0^\ddagger)^2 \right]^{1/2} \quad (45)$$

In this case, when $\Delta E^\circ \rightarrow \infty$, ΔE^\ddagger asymptotically approaches ΔE° , and when $\Delta E^\circ \rightarrow -\infty$, $\Delta E^\ddagger \rightarrow 0$. The intrinsic barrier is similar to that used in the Marcus equation, and the slopes and curvatures of the Brønsted dependences are expressed as follows:

$$\beta = \frac{\partial \Delta E^\ddagger}{\partial \Delta E^\circ} = \frac{1}{2} + \Delta E^\circ \left[(\Delta E^\circ)^2 + 4(\Delta E_0^\ddagger)^2 \right]^{-1/2} \quad (46)$$

$$c = \frac{\partial^2 \Delta E^\ddagger}{\partial (\Delta E^\circ)^2} = \frac{1}{2} \left[(\Delta E^\circ)^2 + 4(\Delta E_0^\ddagger)^2 \right]^{-1/2} - \frac{\Delta E^\circ}{2} \left[(\Delta E^\circ)^2 + 4(\Delta E_0^\ddagger)^2 \right]^{-3/2} \quad (47)$$

One more method for predicting the height of the energy barrier is connected with the BEBO method (bond energy—bond order).¹³² It is based on the assumption that the sum of the orders of breaking and forming bonds is constant in the course of the reaction. In this case, the activation energy is determined by Eq. (48) where V_X and V_Y are the energies of the heterolytic breaking of the R—X and R—Y bonds, respectively, and n^\ddagger is the bond order in the transition state of the reaction.

$$\Delta E^\ddagger = V_Y - V_X \left(1 - n^\ddagger \right)^{p_X} - V_Y \left(n^\ddagger \right)^{p_Y} \quad (48)$$

Using the BEBO method, Levine and Agmon¹³³ derived Eq. (49), which in several cases¹³⁴ better describes the kinetics of S_N2 reactions than the usual Marcus equation.

$$\Delta E^\ddagger = \Delta E_0^\ddagger + \frac{\Delta E^\circ}{2} + \frac{\Delta E_0^\ddagger}{\ln 2} \ln(\cosh \tau) \quad (49)$$

Murdoch has shown¹³⁵ that all these correlations and the expressions of Le Noble,¹³⁶ Kurz,¹³⁷ Zavitsas,^{138,139} Bell,¹⁴⁰ London—Eyring—Polanyi—Sato,¹⁴¹ Scandola—Balzani,¹⁴² Miller,¹⁴³ etc., are particular cases of the general equation

$$\Delta E^\ddagger = \Delta E_0^\ddagger (1 - g_2) + \Delta E^\circ (1 + g_1), \quad (50)$$

where g_1 and g_2 are the odd and even functions of ΔE° , respectively. Depending on the forms of g_1 and g_2 ,

Eq. (50) can be transformed into any of the correlations discussed.

In addition, Eq. (50) demonstrates one evident general feature of all of the approaches mentioned: the energy of the system is divided into two components. One of them increases from zero for reactants to some maximum value and then decreases again to zero for products. This component is described by the term $\Delta E_0^\ddagger (1 - g_2)$. The other component smoothly changes on going from reactants to products and can be expressed by the term $\Delta E^\circ (1 + g_1)$. A more detailed discussion of the applications of Eq. (50) and its physical background can be found in the works of Murdoch.^{144–146}

Summarizing the data presented in this Section, it can be mentioned that nonlinear correlations as a whole better describe the energy profile of the reaction, they allow one to explain the curvature of the dependence of ΔE^\ddagger on ΔE° for a fairly wide range of changes in the exothermicity of the reaction in a given series, and some of these correlations also help to reveal the reasons for anomalous Brønsted coefficients ($\beta < 0$ or $\beta > 1$). At the same time, in the majority of cases, nonlinear correlations give a good approximation of the dependence ΔE^\ddagger on ΔE° only in particular regions (for example, the Marcus equation approximates this dependence near the point $\Delta E^\circ = 0$), which sometimes results in substantial errors in other regions of the dependence. In this connection, it is reasonable to use the most adequate nonlinear correlations in each particular case. The majority of the equations are rather complicated, which also restricts their use. Finally, all of these approaches consider the TS to be a system that partially resembles the reactants and partially resembles the products. This does not allow one to take into account the properties of TS that do not correspond to any of the ends of the reaction coordinate and, hence, does not allow one to reflect adequately various specific effects caused by these properties.

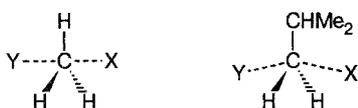
Description of the nucleophilic substitution reaction by the More O'Ferrall diagram

The fact that the structural and electronic parameters of TS of nucleophilic substitution reactions can resemble not only reactants and products, but also other, additional states of the system, has been considered by Ingold.¹⁴⁷ However, the concept of TS properties that are exhibited neither by the reactants nor by the products, had no distinct qualitative or quantitative expression for a long time. The work of Thornton,¹⁴⁸ who suggested a rather simple approach to the analysis of the effect of substituents on the geometry of TS, was the first step in this direction. The main characteristic of this work is that it takes into account the perturbations of the energy function caused by substituents both along the reaction coordinate itself and along the routes perpendicular to the reaction coordinate.

As known, a TS of a system is a saddle point on the PES corresponding to a minimum of the energy of the system along any direction different from the reaction route. The stereoelectronic parameters of other stationary points on the PES affect the position of this minimum. For example, the normal coordinate of TS for S_N2 reactions can be presented as $[Y \rightarrow \leftarrow R X \rightarrow]$. Another type of vibration in TS is also possible: $[\leftarrow Y \leftarrow R X \rightarrow]$. The introduction of substituents into fragments Y, R, or X changes the relative energies of the reactants and products to facilitate or hinder normal vibrations. This is followed by the changes in the position and energy of TS according to the Hammond postulate.

However, varying reaction fragments also affects the perpendicular vibrations, and in several cases this influence turns out to be very significant. The carbanion state $[Y:R:X]^-$, which have the same bond lengths Y—R and R—X as in the reactants and products, and the carbocation structure $[:Y^- + R^+ + :X^-]$, which has infinitely separated reaction fragments, are the reference states in the analysis of perpendicular vibrations. On going from one of these states to the other, the energy of the system passes through a minimum (TS of the reaction). The position of this minimum when one reference state is relatively more stable than the other state shifts toward stable state. The requirement that the position of TS changes in such a way for the stabilization of one of the perpendicular reference states is called the Thornton rule.

In addition to the lengthening/shortening of the bonds, their bending is also significant. For example, an increase in the volumes of the Y, R, and X groups results in a change in the Y—R—X angle to decrease steric hindrances:



Therefore, the complete analysis of the effect of a substituent on the position and energy of the TS of a reaction is possible only when all valence and deformation force constants in the TS of the system are taken into account.

More O'Ferrall suggested¹⁴⁹ a visual graphic representation of this approach. The More O'Ferrall diagram for nucleophilic substitution reactions is presented in Fig. 3. The extent of the formation of a new substrate—nucleophile bond (R—Y) is plotted on the horizontal axis, and the extent of the cleavage of bonds with the leaving groups (R—X) is plotted on the vertical axis. The diagram demonstrates that different mechanisms of nucleophilic substitution are possible. The S_N1 reaction (the R—Y bond is formed only after the complete heterolytic cleavage of the R—X bond) can be presented as the reaction route $1 \rightarrow 2 \rightarrow 3$. The reac-

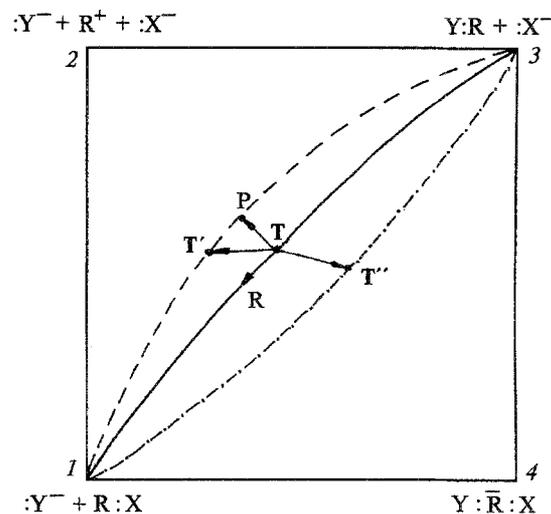


Fig. 3. More O'Ferrall diagram for nucleophilic substitution reactions.

tion route $1 \rightarrow 4 \rightarrow 3$ corresponds to the addition—elimination mechanism, Ad—E, in which the complete formation of a new bond occurs first and only then is the leaving group eliminated. Finally, when the breakage and formation of the R—X and R—Y bonds are simultaneous (S_N2 reaction), the system is characterized by movement from angle 1 to angle 3 along some curve inside the diagram.

Since the extent of concertedness between the weakening and strengthening of these bonds can be different, the whole space of the More O'Ferrall diagram except the two edges corresponds to S_N2 reactions. At the same time, only the movement along the $1 \rightarrow 3$ diagonal corresponds to the "pure" S_N2 reaction for which the extent of breakage of an old bond at each point of the reaction route is equal to the extent of the formation of a new bond. Since only this diagonal is mutually related to the reaction coordinate of the "pure" S_N2 mechanism, it follows from the diagram that the probability of its realization is extremely low. The TS usually has some carbocationic (T, T') or carbanionic (T'') character depending on the reactants and the medium in which the reaction occurs.

Modification of the reaction fragments Y, R, or X (for example, by the introduction of various substituents) should affect the exothermicity of the reaction ΔE^\ddagger and the relative (compared to the reactants) energies of the charged resonance structures corresponding to the perpendicular coordinate of the More O'Ferrall diagram. This should result in changes in the position and energy of the TS of the reaction.

For example, in the case of solvolysis of benzyl derivatives, according to Eq. (51), where Y = ROH, the introduction of electron-donating substituents Z into the aromatic ring of the benzyl compound stabilizes a positively charged product and only slightly affects the energy of a neutral substrate.



As a consequence, according to the Hammond postulate, the TS of the reaction shifts toward the reactants ($T \rightarrow R$). In the case of a donor substituent Z , the carbocationic vertex 2 in the More O'Ferrall diagram ($:Y + ZC_6H_4CH_2^+ + :X^-$) is strongly stabilized, while the carbanionic vertex 4, on the contrary, is destabilized. According to the Thornton rule, the TS shifts toward the stabilized vertex 2 ($T \rightarrow P$), *i.e.*, its character becomes more carbocationic. The total change in the position of the TS is determined by the rule of the sum of the vectors and is shown in Fig. 3 as moving $T \rightarrow T'$.

On the other hand, electron-withdrawing substituents Z (see Eq. (51)) will destabilize products relative to the reactants and decrease the energy of carbanionic vertex 4 compared to that of carbocationic vertex 2. The total change in the position of the TS of the reaction is reflected in this case by the transition $T \rightarrow T''$.

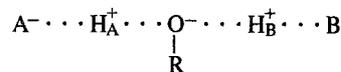
By analogy, the effect of a substituent on the position of the TS and, hence, on such experimentally measured values as the selectivity of the reaction, its sensitivity to the medium, the kinetic isotope effect, *etc.* have been qualitatively analyzed in many works,^{13,18,19,150–161} devoted to nucleophilic substitution reactions. Albery^{99,116,117} and Jencks^{150–154} made a major contribution to the development of this approach. The diagram presented in Fig. 3 has often been called the More O'Ferrall–Jencks diagram. It should be emphasized that the More O'Ferrall diagram is used not only to analyze how substituents change the position of TS. Based on the available experimental data, it also allows one to establish the position of the TS and its properties as well as to estimate difficultly measured values.

For example, the position of the TS along the horizontal coordinate is determined on the basis of the measured values of β_{nuc} or ρ (ρ/ρ_{eq}) in the case of aromatic nucleophiles.^{19,90,116,150,153} To find the position of the TS on the vertical coordinate, β_{lg} (or the corresponding ρ values) are used.^{13,89,116,117,152} The position of the TS along the perpendicular coordinate is established on the basis of data on the kinetic isotope effect^{8,13,155,156} or the sensitivity of the reaction rate to the introduction of substituents into the hydrocarbon fragment.^{151,158,161} When the nucleophile and the leaving group have opposite charges, the position of the TS on the reaction coordinate is also found by coefficient m from Grunwald–Winstein equations (14) and (15), which characterize the sensitivity of the reaction to the change in the ionizing strength of a solvent.^{99,116,151,155}

It has been mentioned above that one should be careful in the use of β , ρ , or m values as indicators of the extent of bond breakage/formation in TS, because it often leads to invalid conclusions. This is also confirmed by several applications of the More O'Ferrall diagram in which the area of the TS is situated in different regions depending on the experimental parameters used.^{99,116} Nevertheless, the More O'Ferrall diagram is an efficient

method for the qualitative analysis of the effects of substituent in reaction fragments on the positions, stereoelectronic properties, and energies of TS, which is confirmed by its wide application.

The quantitative analysis of TS based on More O'Ferrall diagrams has not yet been developed sufficiently and raises many questions. The first attempt at such an analysis was made by Critchlow¹⁶² for proton transfer reactions involving solvent molecules:



It is assumed that the change in the energy of the system along both the reaction and perpendicular coordinates is linear (Eq. (52), analog of the Brønsted equation).

$$G(x,y) = \alpha(G_3 - G_1) + \beta(G_2 - G_4) \quad (52)$$

Gajevski^{163,164} used two mathematically different expressions for the analysis of [3,3]-sigmatropic rearrangements: the linear energy dependence along both coordinates of the More O'Ferrall diagram in the form of Eq. (53) and the corresponding square function (Eq. (54)).

$$G = ax + by + cxy + d \quad (53)$$

$$G = ax^2 + by^2 + cxy + dx + ey + f \quad (54)$$

Expression (54) has previously been used by Jencks¹⁶⁵ to describe reactions of nucleophiles with carbonyl compounds.

Agmon^{166,167} has developed several mathematical models for the analysis of cycloaddition reactions and sigmatropic shifts using the More O'Ferrall diagram. He assumed that the energy profiles along the reaction coordinate and the perpendicular coordinate are described by the same function $G(x,\Delta,\Gamma)$, where x is the independent coordinate, Δ is the difference in the energies of the initial and final states when moving along this coordinate, and Γ is a parameter. In addition, it was assumed that the intrinsic barrier $\Delta G_{r,0}^\ddagger$ along the reaction coordinate is proportional to the intrinsic potential well $\Delta G_{p,0}^\ddagger$ along the perpendicular coordinate. The expression for $G(x,\Delta,\Gamma)$ is written as Eq. (55), and two functions are used as $M(x)$: $4x(1-x)$ and $-[x \ln x + (1-x) \ln(1-x)]/\ln 2$.

$$G(x,\Delta,\Gamma) = x\Delta + \Gamma M(x) \quad (55)$$

The first case corresponds to the Marcus equation extended to both (reaction and perpendicular) coordinates of the More O'Ferrall diagram.

Murdoch analyzed¹⁴⁴ the relation of the More O'Ferrall diagram to the Marcus theory when equations similar to Eq. (54) were used. He also described the necessary assumptions and validity boundaries of the combined approach. The analytic solution of Eq. (54) results in expression (56)

$$\Delta E^* = \Delta E_{00}^* + \frac{1}{2}(\Delta E_{11} + \Delta E_{00}) + \frac{\Delta E^\circ}{2} + \frac{(\Delta E^\circ)^2}{16[\Delta E_{00}^* + 0.5(\Delta E_{11} + \Delta E_{00})]} - \frac{(\Delta E_{11} - \Delta E_{00})^2}{16[0.5(\Delta E_{11}^\circ - \Delta E_{00}^\circ) - \Delta E_{00}^* - 0.5\Delta E^\circ]}, \quad (56)$$

where E_{11}° and E_{00}° are the energies of the vertex structures 2 and 4 of the More O'Ferrall diagram (relative to reactants) for the reaction chosen as the standard and ΔE_{11} and ΔE_{00} are the changes in these energies when substituents are introduced into the reaction fragments.

Nucleophilic substitution at the carbonyl carbon atom^{168,169} and the S_N1 solvolysis of alkyl bromides¹⁶⁰ were analyzed using expression (54) and a more complicated expression (57).

$$G = a_1x^2 + a_2y^2 + a_3x^3 + a_4y^3 + a_5x^4 + a_6y^4 + a_7x^2y^3 + a_8x^3y^2 + a_9x^3y^3 + a_{10}x^2y^2. \quad (57)$$

Good results are obtained in both of the cases, but the latter function gives better results. At the same time, the use of Eq. (57) is associated with a number of inconveniences, because it can be solved only numerically by the iteration procedure. On the other hand, analytic solutions to Eq. (54) can be found, which makes it possible to assign a specific physical meaning to the formal analysis of the stereoelectronic properties of TS.

The approximations of quadratic changes in the energy along the reaction coordinate and linear changes along the perpendicular coordinate have been used too.^{114,170,171,172} It has been assumed that the energies of "loose" vertex structures 2 and "tight" structure 4 correlate with the energy of the heterolytic cleavage of the R—X bond. This approach leads to the modified Marcus equation:

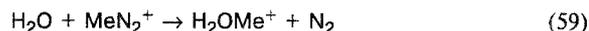
$$\Delta E^* = \Delta E_0^* + \frac{\Delta E^\circ}{2} + \frac{(\Delta E^\circ)^2}{16\Delta E_0^*} + \frac{\tau - 1}{2}\Delta E^\circ, \quad (58)$$

where τ indicates the position of the TS along the perpendicular coordinate ($\tau = 0$ for vertex 2 and $\tau = 2$ for vertex 4).

Thus, the More O'Ferrall diagram is an efficient instrument of the qualitative analysis of the effects of substituents in reaction fragments on the positions and energy of TS. The application of several mathematical models (see Eqs. (52)—(58)) allows one to describe quantitatively TS in reactions of different types. Especially good results can be achieved for the analysis of cycloaddition, sigmatropic rearrangements, and other pericyclic reactions. At the same time, the analysis of the processes of nucleophilic substitution at the aliphatic C atom is associated with several problems.

For nucleophilic substitution reactions, the More O'Ferrall—Jencks diagram reflects only heterolytic S_N2 , S_N1 , and Ad—E mechanisms. However, it is well known^{34,80,88} that nucleophilic substitution can also occur *via* the formation of radical intermediates (SET, $S_{RN}1$, etc.). The More O'Ferrall—Jencks diagram does not allow one to take into account these routes of nucleophilic substitution.

Moreover, for reaction (2) in the gaseous phase in the case of an anionic nucleophile and a neutral substrate, the "loose" form (vertex 2 of the diagram) is more reasonably presented not by the triple-ion structure $[:Y^- + R^+ + :X^-]$, but by an ion and a pair of radicals ($[:Y^- + R^\cdot + X^\cdot]$ or $[Y^\cdot + R^\cdot + :X^-]$), because the energies of such biradical structures are usually lower than the energy of the triple-ion form $[:Y^- + R^+ + :X^-]$. At the same time, the carbocationic state $[H_2O + Me^+ + :N_2]$ is more stable for reaction (59) than the isoelectron system $[H_2O^{\cdot+} + Me^\cdot + :N_2]$ or $[H_2O + Me^\cdot + N_2^{\cdot+}]$. This problem of choosing the "loose" resonance structure corresponding to vertex 2 of the diagram is especially emphasized by Shaik.¹⁷³



The More O'Ferrall diagram also does not allow one to explain some experimental facts repeatedly mentioned in the literature:^{2,28,71,78} the dependence of the reactivity of nucleophiles on their ionization potentials, the change in the order of reactivity of nucleophiles when a substrate is replaced,^{34,104} the super-weak nucleophilicities of perchlorate and sulfonate ions compared to those of common nucleophiles of the same basicities, the α -effect,^{100–105} and a number of other specific features inherent in nucleophilic substitution reactions.

Method of correlation state diagrams

The dependence of the energy barrier of a reaction on the ionization potential of nucleophiles and the electron affinity of substrates is reflected well by the method of correlation state diagrams developed by Shaik and Pross.^{173–178} According to this method, reactants are considered from the formal viewpoint of valence bond theory to have two electrons at the nucleophile Y and one electron at each R fragment and X leaving group: $:Y^- + R^\cdot \cdot X$ (state I). A more complete and exact analysis also takes into account two high-energy states, $:Y^- + R^+ :X^-$ (II) and $:Y^- + :R^- X^+$ (III), and presents the reactants as a hybrid of these three resonance structures. Form I makes the main contribution to the electron configuration of the reactants. The products are described similarly; however, in this case, the resonance structure $Y^\cdot \cdot R + :X^-$ (IV) is considered predominant. In this approach, nucleophilic substitution is considered to be the transformation of the initial state I to the final state IV, *i.e.*, the movement of one

electron from Y to X, which occurs simultaneously with the processes of bond breakage and formation, differing from the usual reactions of single-electron transfer (SET).

When the movement of an electron from Y to X is not accompanied by any changes in the spatial arrangements of the reaction fragments, system I is found in the excited state I^* with the "frozen" geometry of the reagents. In this case, this movement can be considered as a vertical electron transfer, which transforms the reactants to the excited state I^* . To a first approximation, the electron configuration of I^* (one electron per Y, one electron per R, and two electrons per X) coincides with the electron configuration of IV. As a consequence, the geometric relaxation, which takes place at the next stage, transforms the vertically excited states of the reactants to the ground states of the products ($I^* \rightarrow IV$) even at "frozen" electron configurations (without redistribution of electrons between reaction fragments Y, R, and X). This is shown in Fig. 4. The transformation of the products to reactants can occur similarly ($IV \rightarrow IV^* \rightarrow I$).

In terms of this approach, for an easy transformation of reactants to products (for "rolling down", see Fig. 4), the system must first overcome the energy gap (G_R):

$$G_R = IP_{:Y} - EA_{RX}, \quad (60)$$

where IP is vertical ionization potential of the nucleophile and EA is vertical electron affinity of the substrate. By analogy, the transformation of the products to reactants is connected with overcoming the energy gap G_P .

The transition of the system from the state with two electrons at Y, one electron at R, and one electron at X to the state with one electron at Y, one electron at R, and two electrons at X can be achieved not only through vertical electron transfer $I \rightarrow I^*$, but also through the transformation of I to IV^* via breakage of the R—X bond and formation of the R—Y bond at the "frozen" electron configuration followed by the electron relaxation of IV^* to IV at the "frozen" geometry of the products.

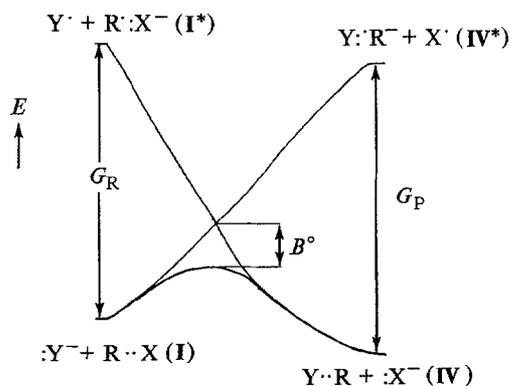


Fig. 4. Shaik—Pröss correlation state diagram for nucleophilic substitution reactions.

The third route is concerted one. It is the route *via* which the S_N2 reaction occurs. Although the system does not transform from state I to state I^* , the energy needed for the $I \rightarrow I^*$ transition is one of the most important factors determining the height of the energy barrier. If vertical electron transfer from Y to RX is endothermic and the geometry relaxation is exothermic, the concerted process is approximately thermally neutral.

The R—X bond lengthens and the distance between R and Y decreases causing an increase in the energy of the state with two electrons at Y, one electron at R, and one electron at X (see Fig. 4, curve $I \rightarrow IV^*$) and a decrease in the energy of the state with one electron at Y, one electron at R, and two electrons at X (see Fig. 4, curve $I^* \rightarrow IV$). As a consequence, these states become more equal structurally and energetically, and the resonance interaction between them continuously increases and reaches a maximum in the region of TS where their energies are equal. The contributions of these resonance structures to the wave function of the system are commensurable, and the process becomes adiabatic (according to Marcus) due to their sufficiently strong resonance, *i.e.*, the transition from one energy curve to another is possible with a probability close to unity, which corresponds to a change in the electron configuration. The energy of the TS turns out to be lower than the energy of the intersection point of the two curves by the value of the resonance interaction between the two states (B°) in the area of TS (see Fig. 4). The quantum chemical description of this behavior of the system is determined by the principle of the non-intersection of the curves corresponding to the thermal and photochemical transformations of the reagents to products (avoided crossing). The resonance interaction of the two geometrically relaxing forms weakens rapidly as one moves away from the TS area to the products, and the weighted factor of the configuration with two electrons at X increases almost to 1, while that of the configuration with two electrons at Y decreases to 0.

Thus, the activation barrier to nucleophilic substitution process (see Fig. 4) is considered to be the energy needed to change in the geometry of the systems such that the transformation of the electron configuration of the reactants to the configuration inherent in the products (subtracting the energy of the resonance interaction B° in the TS) becomes possible. The height of the barrier is determined by Eq. (61)

$$\Delta E^\ddagger = fG_R - B^\circ, \quad (61)$$

where coefficient f shows how many times it differs from the energy gap G_R .

The values f and B° are considered constant for a given reaction series (for example, when one substrate reacts with several nucleophiles). Therefore, the height of the activation barrier and the reaction rate are determined only by the energy gap G_R , *i.e.*, by the vertical

ionization potential of the nucleophile and the vertical electron affinity of the substrate. The ionization potential of the nucleophile is the determining factor when the substrate is fixed and the other parameters are sufficiently equal. In other words, the relation described by the Edwards equation⁷¹ (21) is easily explained from the analysis of correlation state diagrams for S_N2 reactions.

This approach (see Fig. 4) assumes that the radical anion form $RX^{\cdot-}$ appears after the vertical transfer of an electron from the nucleophile $:Y^-$ to the substrate $R:X$. However, it is more correct to consider this form not as a state with two electrons at X and one electron at R, but as the resonance hybrid of two structures: $R^{\cdot}:X^-$ and $:R^-X$. If the second structure (taking into account Y^{\cdot} , this is the state $Y^{\cdot} + :R^-X$ (V)) possesses higher energy than the first structure, the resonance form V can be neglected, and the description presented above seems adequate. If the difference in the energies of these two structures is rather small and form V contributes substantially to the vertically excited state of the reactants, a modification of this diagram method is needed (similar considerations also concern the vertically excited state of the products).

An indirect solution of this problem^{179–181} suggested by the authors of the model consists of varying the curvatures of the energy curves of the products and reactants (Fig. 5). If the electron density distribution in the radical anion of the substrate ($RX^{\cdot-}$) is close to that inherent in state IV (*i.e.*, to the distribution in the products), the relaxation of the geometry occurs readily on going from the reactants to the products (see Fig. 5, curve 1). If the contribution of the resonance structure $:R^-X$ is large, the relaxation of the geometry leading to the products is difficult due to the inevitable electron rearrangement (curve 2). In other words, in this case, the preliminary formation of the "pure" electron configuration $RX^{\cdot-}$ due to the exclusion of the stabilizing resonance form $:R^-X$ involves an additional expenditure of energy, resulting in an increase in the activation barrier (energy of the TS). The extent of its increase is determined by the relative electronegativities (χ) of the reaction fragments Y, R, and X.

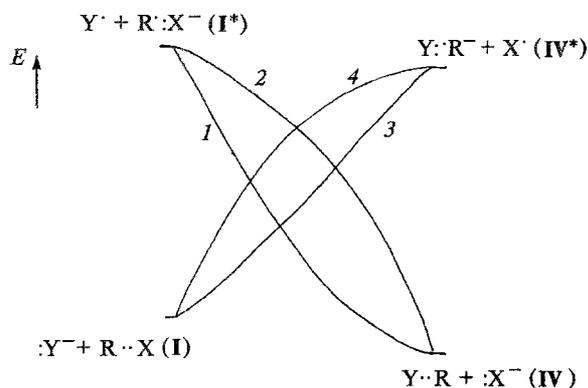


Fig. 5. Dependence of the height of the energy barrier on the curvature factor.

Shaik has shown¹⁸¹ that for identity reactions involving the transfer of the Me^+ cation (see Eq. (30)), coefficient f in Eq. (61) is proportional to the contribution (W_R) of the electron configuration $:R^-X$ to the wave function of the radical anion of the substrate. This allows one to use the value W_R instead of f when compare the energy barriers in identity processes with different nucleophiles X. For non-identity reactions, the curvatures of the energy functions of the two ground states and, hence, coefficient f as well, depend on ΔE^0 , the ratio of the values of G_R and G_P , the degree of localization of the unpaired electrons in $RX^{\cdot-}$, $RY^{\cdot-}$, X^{\cdot} , and Y^{\cdot} , and other parameters of the reactants.¹⁷³

In one of his recent works,¹⁷⁷ Shaik suggested the following equation:

$$\Delta E^\ddagger = \frac{(f_R + f_P)(G_P + \Delta E^0)}{G_R + G_P} G_R - B^0 \quad (62)$$

However, the quantitative verification of Eq. (62) was not performed. The dependences of f on various properties of reactants were also discussed by Shaik and Pross,^{178–180,182} but the character of the conclusions was qualitative rather than quantitative.

Another parameter of Eq. (61), the quantum chemical resonance energy B^0 , is estimated^{124,178,183} for the majority of S_N2 reactions as 15 ± 2 kcal mol⁻¹. Considering TS of S_N2 processes as linear three-centered four-electron systems, TS can be compared with their stable organic analogs: allyl and enolate anions. In the majority of cases, the resonance energies of these anions are¹⁸⁴ 14 to 18 kcal mol⁻¹, which, according to the opinion of the authors of the model, is additional confirmation of its efficiency.¹⁷⁸

The factors affecting the resonance energy B^0 have been analyzed in several works of Shaik.^{178,185–188} It is found, for example, that B^0 depends on the position of the TS both on the reaction coordinate and on the perpendicular (tightness of TS) coordinate,¹⁸⁷ the difference in the energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals in the TS,¹⁸⁸ the distortion of the linearity in the arrangement of the groups X, Y, and R in the TS of S_N2 reactions, the degree of the ionic character of the TS, and a number of other factors.

The Shaik–Pross method does not consider directly the dependence of the energy barrier on the thermodynamic parameters of the process: Eqs. (60) and (61) do not contain ΔE^0 explicitly. To take this dependence into account, it is usually assumed that for non-identity reactions coefficient f decreases as the exothermic character of the process increases. Equation (62) reflects an attempt to demonstrate this dependence, but as mentioned above, the prediction of reactivity on the basis of this equation has not been confirmed by reliable experimental or quantum chemical data on activation energies of S_N2 reactions

The method of correlation state diagrams also takes into account the contributions of additional electron

configurations to the TS, which are not necessary for the adequate description of the reactants and products, but are necessary to describe the TS. Figure 6 presents the correlation state diagram for S_N2 reactions, which shows that an important role is played by resonance structure II ($:Y^- + R^+X^-$), which has fairly high energy in the initial and final regions of the reaction route, and, hence, does not contribute substantially to the wave functions of the reactants and products. However, in the area of the TS, the energy of this structure is comparable to those inherent in ground states I and IV. This causes an increase in the resonance energy B° and a decrease in the energy barrier (see Fig. 6, a).

When the energy of the "carbocationic" configuration II is rather low, the corresponding intermediate can appear in the route along the reaction coordinate (see Fig. 6, b). The inclusion of resonance structure V often turns out to be of the same importance. Some specific effects observed in nucleophilic substitution reactions, for example, the existence of reaction series with Brønsted coefficients $\beta > 1$ and $\beta < 0$, have been explained Shaik and Pross^{173,176,177} by taking the significance of these electron configurations additionally into account.

Thus, the Shaik—Pross diagram allows one to interpret the appearance and relative height of the activation barrier at the qualitative level rather simply and efficiently. This diagram is used for analyzing the reactivities of organic compounds in reactions of nucleophilic substitution at aliphatic,^{173–183,188–191} carbonyl,^{192,193} and vinyl¹⁹⁴ carbon atoms, in radical processes,^{187,195} proton transfer reactions,^{177,196,197} and the reactions of nucleophiles with cations¹⁹⁸ and radical cations,^{177,199–201} etc.

At the same time, this diagram method has several disadvantages. The values of f and B° can considerably differ within a reaction series even for the same substrate.^{181,193} It should be pointed out again that there are no methods for the quantitative prediction of f and B° . Moreover, the *ab initio* calculations²⁰² of the potential energy surfaces for four model S_N2 reactions in extended basis sets, taking into account the electron correlation, showed a strong dependence of the parameter B° on the structures of the reactants, and predicted negative (!) values of fG_R for two model identity processes. The latter result cannot be explained in principle in terms of the Shaik—Pross model.

In addition, Eqs. (60) and (61) neglect the dependence of the height of the activation barrier on ΔE° and other parameters of the reactants except the ionization potential of the nucleophile and the electron affinity of the substrate. As a result, the quantitative analysis of TS by these equations has not yet exceeded the level of such correlations as the Brønsted or Edwards equations.

There is also the problem of the determination of the reaction coordinate. When the latter is considered as the direction of the geometric changes, the degree of mixing and the mutual transformation of the two electron states (*i.e.*, in the opinion of the authors of this model, this

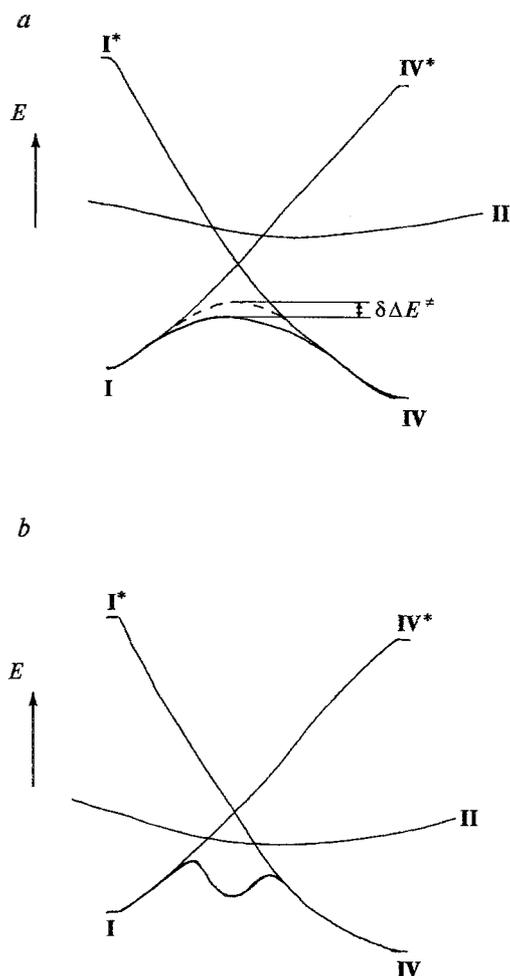


Fig. 6. Decrease in the energy of the TS due to the stabilizing contribution from the additional resonance form II (a) and the appearance of the energy minimum on the route along the reaction coordinate for the rather large stabilizing contribution from the resonance form II (b).

parameter is the essence of the process) can be reflected only indirectly. When the degree of the transformation of one electron configuration to another is accepted as the reaction coordinate, the reaction coordinate is the same for at least two basically different processes: S_N2 and SET.

This coincidence of the reaction coordinates provokes objections. In addition, geometric changes of at least two types corresponding to the breakage and formation of chemical bonds occur in S_N2 reactions. The diagrams described (see Figs. 4–6) cannot show how these two processes are balanced.

In addition, the Shaik—Pross model postulates that the charges on the nucleophile and the leaving group in the TS of all S_N2 reactions are equal, regardless of the reaction exothermicity.¹⁸⁹ However, the results of non-empirical calculations performed at a sufficiently high level^{203–207} are inconsistent with this conclusion. Finally, this model does not explicitly take into account

the possibility of the formation of ion—molecule complexes in S_N2 processes that occur in the gas phase or in aprotic solvents, and, therefore, it is unsuitable for the interpretation of the corresponding experimental material. The disadvantages of the model are caused by the fact that the Shaik—Pross method of correlation diagrams is a simplified variant of the resonance theory, so most of the attention is concentrated only on particular aspects of the mechanism of nucleophilic substitution reaction and several other aspects, which are far from being secondary factors, are ignored.

Cubic reaction diagram for nucleophilic substitution processes

The recently suggested²⁰⁸ cubic reaction diagram (CRD), which allows the simultaneous theoretical analysis of geometric and electronic factors, can unite the advantages of the preceding correlation methods and stimulate the development of this scientific approach. Since there are three aspects primarily related to the nucleophilic substitution process (the breaking of the carbon—leaving group bond (C—X), the formation of the carbon—nucleophile bond (C—Y), and redistribution of the electron density between the reaction fragments), an adequate description of the process requires the use of at least three coordinates corresponding to three different subprocesses. The corresponding CRD is presented in Fig. 7.

In this diagram, the coordinates of the points along the u and v axes are the extents of the cleavage of the old R—X bond and the formation of the new R—Y bond, respectively. Two limiting cases are possible: movement of the reaction system along the **ABC** route (heterolytic cleavage of the R—X bond followed by the

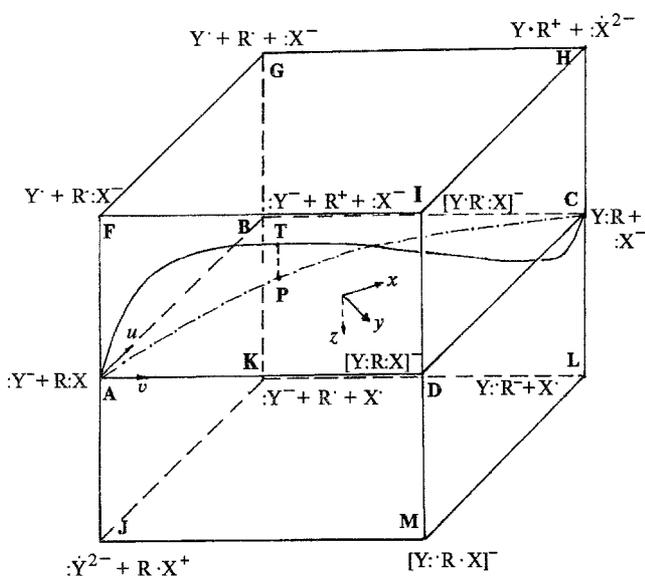


Fig. 7. Cubic reaction diagram for nucleophilic substitution processes.

formation of the R—Y bond), which is typical of the S_N1 mechanism (or $D_N + A_N$, according to the new IUPAC nomenclature^{209,210}) and movement along the **ADC** route (cleavage of the bond with the leaving group only after the complete formation of the R—Y bond) corresponding to the addition—elimination mechanism **Ad—E** ($A_N + D_N$). The latter is usually realized in the processes of nucleophilic substitution at the carbonyl (phosphoryl, sulfonyl) group or at the Si atom.

Many reaction routes with the simultaneous formation and breakage of the R—Y and R—X bonds are covered by the remaining space of the CRD and are related to S_N2 processes. Depending on the degree of synchronization of the breakage and formation of these bonds, TS of S_N2 reactions can have some carbocationic or carbanionic character. The More O'Ferrall—Jencks diagram presents a similar description, because it coincides with the central plane of the CRD and is in fact this particular case.

The basic innovation of the CRD is the third coordinate along which the extent of the redistribution of electrons between reaction fragments is plotted at specified bond lengths of R—X and R—Y. In the general case, this extent differs for different R, X, and Y, which makes the third coordinate necessary. The complete transfer of an electron from one reaction fragment to another is assumed in the limiting case. The introduction of this coordinate reflects the acceptance that it is necessary to modify the More O'Ferrall type diagrams, taking into account the Shaik—Pross approach and emphasizing the significance of the effect of the shift of one electron on the kinetics even of the concerted reaction.

The CRD includes all known mechanisms of nucleophilic substitution processes. The methods for the description of S_N1 , S_N2 , and **Ad—E** mechanisms have been considered above. In addition, one should take into account the single-electron transfer (SET) from a nucleophile to a substrate to form the state $[Y + R : X]^-$ (F), which contains the radical anion form of the substrate. When this electron transfer is accompanied by the cleavage of the R—X bond, the system is presented as $[Y + R + X^-]$ (G). The subsequent reaction between Y^\cdot and R^\cdot results in the products of nucleophilic substitution (**AFGC** or **AGC** is the overall reaction route). One more reaction route, **AKLC**, presents the mechanism of the non-chain $S_{RN}1$ reaction, when first the R—X bond is homolytically split, then the radical anion $R^\cdot : Y^-$ is formed, and is subsequently transformed into the R—Y product.

It is evident that this "movement" through the vertices of the correlation diagram is in general a convenient method for classifying chemical reactions with different alternating elementary steps. It should be mentioned in this context that the consideration of nucleophilic substitution only as a superposition of S_N1 and addition—elimination processes in the More O'Ferrall diagram is limited. The more general cubic correlation diagram reflects both the two-electron processes and

one-electron processes that are not taken into account in the More O'Ferrall diagram. In addition to the already known mechanisms, the CRD also includes non-realized routes of nucleophilic substitution, for example, the reaction route **AJC**. At the beginning of this route, an electron is transferred from a weak electrophile with an increased electron-donating capability to a nucleophilic electron acceptor. Both the nucleophile and the electrophile are activated in this process, which facilitates their reaction to the reaction products of nucleophilic substitution.

The route of the hypothetical S_N2 reaction is shown in Fig. 7 by the solid curve and its projection on the central plane of the cubic diagram is shown by the dotted curve. The position of the TS is denoted by the point **T**, and the point **P** shows its projection on the central plane of the CRD. In terms of this model, the position of the TS along the reaction coordinate and both perpendicular coordinates is determined by the Hammond postulate and the Thornton rule, respectively.

Depending on X and Y, the TS can be located over or under the central plane of the CRD. For example, according to the Hammond postulate, the TS for exothermic reaction (63) should be "early". A large negative charge at the F atom and an almost unchanged charge at the leaving Cl atom correspond to this case.



The nonempirical calculations²⁰⁶ of this reaction by the MP2/6-31++G** method confirm this conclusion showing that the C—F bond will be longer in the TS of this reaction than in the TS of the similar identity reaction (2.013 and 1.836 Å, respectively) and that the C—Cl bond will be shorter than in the TS of the reaction of methyl chloride with Cl^- (2.142 and 2.316 Å, respectively). However, the reactants and products make approximately equal contributions to the wave function of the TS, despite the "early" character of the TS, which is caused by the deviation of the TS from the central plane of the CRD.

In terms of this model, the energy of the TS (and hence, the reaction rate) is determined by the degree of resonance mixing of the nodal structures of the CRD. An increase in the relative stability of one of the forms not only affects the position of the TS along the reaction coordinate and both perpendicular coordinates, but also decreases its energy. The equal stabilization of the two resonance structures at the opposite vertices of the reaction cube exerts no effect on the location of the TS, but decreases its energy. In other words, the value of ΔE^\ddagger depends on the relative stabilities of the structural forms at the nodal points of the CRD. The energies of these forms can be easily determined by several experimentally measured (or easily calculated) properties of the reactants (see Fig. 7).

Equation (64) was derived²¹¹ assuming that the energy of the system varies as the square of the position along each of the coordinates in the CRD.

$$\Delta E^\ddagger = \lambda + \frac{\Delta E^\circ}{2} + \alpha \Delta E^{\circ 2} + \frac{(\Delta E^\circ)^2}{16(\lambda + \alpha \Delta E^{\circ 2})} - \frac{(\Delta E^{\circ 2})^2}{8[HBDE_{RX} + HBDE_{RY} - 2\lambda + (1 - 2\alpha)\Delta E^{\circ 2}]} - \frac{(\chi_{RX} - \chi_{RY} + \chi_{:X} - \chi_{:Y})^2}{8(\eta_{RX} + \eta_{RY} + \eta_{:X} + \eta_{:Y})} \quad (64)$$

Here $HBDE_{RX}$ and $HBDE_{RY}$ are the energies of the heterolytic cleavage of the R—X and R—Y bonds, respectively; $\Delta E^{\circ 2}$ is the energy difference between states **B** and **D** (see Fig. 7); χ is the electronegativity of the particle according to Mulliken; η is its absolute hardness; and λ is the intrinsic activation energy determined by expression (65).

$$\lambda = \alpha(HBDE_{RX} + HBDE_{RY}) + \beta(\eta_{RX} + \eta_{RY} + \eta_{:X} + \eta_{:Y}) \quad (65)$$

Even a brief analysis of Eq. (64) shows that it contains the Marcus equation as a particular case, and the Marcus intrinsic activation energy is a function of both the relative and absolute values of the energy of the heterolysis of the R—X and R—Y bonds, the hardnesses of the reactants and products, and their electro-negativities.

Thus, the three-dimensional reaction diagram suggested (see Fig. 7) in combination with the quadratic dependence (see Eq. (64)) generalizes the approaches considered above and advances a united theoretical model. It was shown²¹² that this model makes it possible to predict rather reliably the height of the energy barrier both in identity and non-identity gas-phase reactions of nucleophilic substitution at the Me^+ cation. According to Eqs. (64) and (65), in the identity reactions of the transfer of Me^+ the height of the energy barrier (in $kcal\ mol^{-1}$) is determined by the methyl cation affinity of the nucleophile, the Mulliken electronegativities of the particles, and their absolute hardnesses (Eq. (66)).

$$\Delta E^\ddagger = 0.416MCA_X + 0.083(\eta_{RX} + \eta_X) - 1.703 \frac{(\chi_{R:X} - \chi_{:Y^-})^2}{4(\eta_{R:X} - \eta_{:Y^-})} - 54.5 \quad (66)$$

The use of Eqs. (64)–(66) makes it possible to predict the height of the energy barrier in non-identity nucleophilic substitution reactions with an accuracy of $\pm 2\ kcal\ mol^{-1}$ (Fig. 8).

In addition, the authors of the model have demonstrated²¹³ that this approach also provides a unified basis

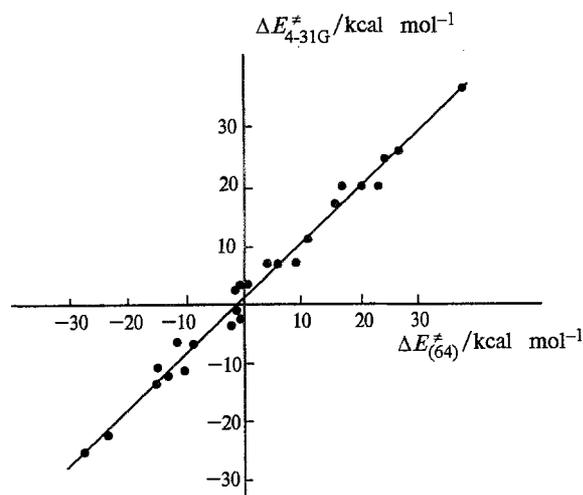


Fig. 8. Correlation between the activation energies of S_N2 reactions calculated by Eqs. (64)–(66) and those obtained from nonempirical calculations in the 4-31G basis¹³⁴ ($\Delta E_{(64)}^{\ddagger}$ and $\Delta E_{(4-31G)}^{\ddagger}$, respectively).

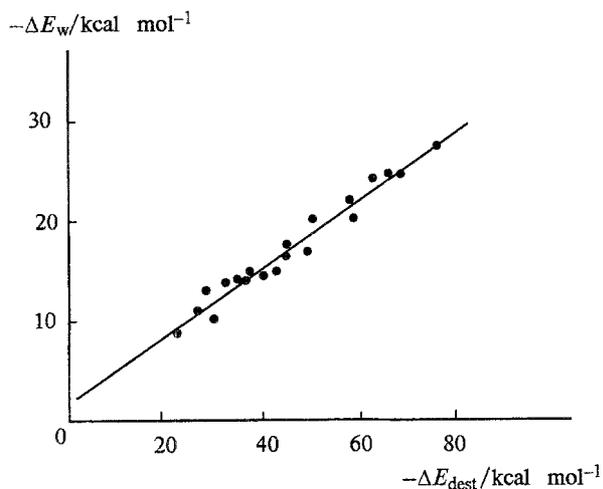


Fig. 9. Dependence of the strengths of the ion–molecule complexes formed in S_N2 reactions in the gas phase on the electron destabilization energy of the reactants, $\Delta E_{dest} = (\chi_{RX} - \chi_Y)^2/[4(\eta_{RX} + \eta_Y)]$.

for the estimation of energies of both TS and the minima formed in nucleophilic substitution reactions occurring in the gas phase or in an aprotic solvent (Fig. 9). This quantitative estimation is impossible for the approaches discussed in the previous Sections.

Like the other approaches discussed above, the CRD has disadvantages, which, nevertheless, are directly related to its advantages. In fact, simplicity and visuality, which are the most attractive features of LFER, are also inherent in CRD, but they limit the ability of CRD to give more complete and exact descriptions of the reaction kinetics for any considerable variation in the structures of the reactants. The reliable qualitative and quantitative analysis of any process of nucleophilic substitution

involves the use of nonempirical quantum chemical methods of a fairly high level (especially in combination with the Monte-Carlo or molecular dynamics methods). However, these calculation procedures are rather expensive, cumbersome, and complicated, and their results are not visual. The More O'Ferrall diagram and various nonlinear correlations are directed to a more accurate description of the TS than that by LFER, while the Shaik–Pross approach, on the other hand, tends to make the quantum chemical analysis more visual, although this decreases its accuracy, precision, and reliability.

Taking this into account, it seems that CRD approach the optimum (at least from the viewpoint of organic chemists) ratio of simplicity and clearness, on the one hand, to accuracy and precision, on the other hand. Various multi-dimensional reaction diagrams²¹⁴ are more general. In these diagrams, each coordinate corresponds to one isolated subprocess of the reaction studied, which is also allowed in the corresponding quantum chemical methods. In this case, visuality is provided by the representation of different two- and three-dimensional projections of the multi-dimensional reaction diagram. This approach to the problem is especially efficient for complex reactions in which the breakage and/or formations of more than two bonds occur. At the same time, it can be successfully used for the analysis of relatively simple processes, including nucleophilic substitution processes.

Studies of the effect of the medium on the mechanism and kinetic parameters of nucleophilic substitution reactions have received much attention recently.²¹⁵ In terms of CRD, the solvent effect can be described by changing the energies of all of the states at the nodal points of the CRD. Correspondingly, the positions and energies of TS change, for example, according to the same quadratic approximation. This approach allows one to explain why the energy profiles of typical S_N2 reactions in the gas phase and in the majority of aprotic media have two wells, while they are unimodal character for alcoholic and aqueous solutions.^{215–218}

In fact, the value of ΔE_{dest} for a solvent is determined not by the ionization potential and electron affinity of the reactants, but by the corresponding redox potentials, whose absolute values are considerably lower. Moreover, using a polar solvent to increase the stabilization of the resonance state corresponding to the nodal point **J** vs. **F** (see Fig. 7), results in a sharp decrease in ΔE_{dest} , and the differences in the stabilizations of the reactants (**A**) and their excited forms (**F**, **J**) by hydrogen bonds enhance this effect in proton-donating media.

The routes of identity S_N2 reactions and the structures of their TS change slightly when the solvent is varied.^{219,220} Some increase in the carbocationic character of the TS is observed²²¹ on going from the gas phase to more polar media. However, the changes can be very substantial for non-identity processes, especially if the nucleophile is neutral and the leaving group is

negative (or conversely). Considerable modifications of the reaction route and the structure of the TS are found, for example, in the theoretical study of Menshutkin reactions.^{217,222–224} As mentioned above, all this can be rather reliably reflected in terms of a slightly improved CRD.

The effect of the solvent on the chemical reaction rate is not restricted by the factors presented above. Experimental studies of TS of compounds in solutions and theoretical analyses of S_N2 processes by the methods of molecular dynamics and reaction trajectories testify that the non-equilibrium character of the solvation of a system (including that of TS) in the course of a reaction should exert a strong effect on the rate of nucleophilic substitution. The deviations of Brønsted coefficients from the expected values that are observed in several cases, are explained^{225,226} by the principle of non-perfect synchronization of the reaction: when the stabilization of the products or destabilization of the reactants by resonance effects, solvent, *etc.* occurs more slowly than the other parts of the reaction (for example, bond cleavage or formation), the reaction rate constant is lower than that predicted by the simplified correlations obtained in the absence of these effects (and *vice versa*). The solvent effect is often manifested as a noticeable retardation of the chemical reaction due to a lag in the rearrangement of the solvate shell around the reaction system.

Several theoretical works, in which both a qualitative physical interpretation of the phenomenon and its quantitative explanation using S_N2 ^{227–230} and S_N1 processes^{231–233} as examples are presented, have appeared recently. To make the obtained results visual, the authors of these works used an analog of the More O'Ferrall diagram, *i.e.*, a two-dimensional diagram (Fig. 10), where the degree of conversion of the dissolved reaction system is plotted along the vertical axis and the generalized coordinate of the solvent (the extent of the change in the solvate shell around the reacting system in the course of the reaction) is plotted on the horizontal axis. The changes in the dissolved reacting system and the solvate shell can be synchronous (curve 1), can first be only the arrangement of the solvent that initiates the chemical process itself, (curve 2), or they can reflect some degree of lag in the transformations of the solvation shell against the background of the chemical transformation itself (curve 3).

Since in terms of CRD the S_N2 reaction is already divided into three model stages: (1) breakage of the R—X bond, (2) formation of the R—Y bond, and (3) electron relaxation, a fourth coordinate is needed in order to take into account the probable non-equilibrium solvation. It is difficult to present visually the corresponding four-dimensional space, but its different two- and three-dimensional projections can be used. It is likely that two three-dimensional projections can provide a rather complete and efficient description: the CRD (see Fig. 7) and the three-dimensional diagram

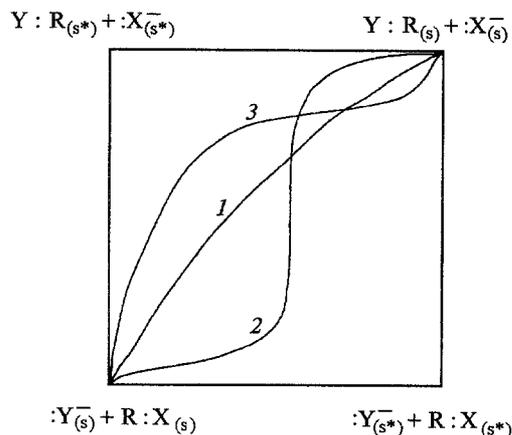


Fig. 10. Analog of the More O'Ferrall diagram for the description of the influence of dynamic solvent effects. The index (s) corresponds to the equilibrium solvation and the index (s^*) corresponds to the non-equilibrium solvation of dissolved particles.

supplemented CRD (Fig. 11), where the extent of the shift of an electron from Y to X is plotted on axis r , the extent of the breakage of the R—X bond and the formation of the R—Y bond (some functional dependence is assumed between these values) is plotted on axis t , and the generalized coordinate of the solvent is plotted on axis s . This diagram is likely to combine the Shaik—Pross method of correlation diagrams and the visual presentation of dynamic solvent effects due to the introduction of the generalized coordinate.

Thus, nucleophilic substitution reactions in solution have been analyzed by stages and the results obtained have been integrated to establish the common features in the projections of the complete multi-dimensional

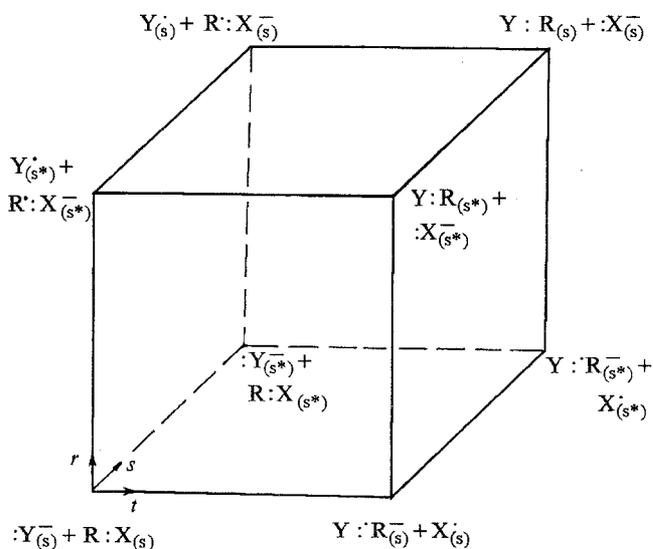


Fig. 11. Three-dimensional projection of the multi-dimensional diagram of a nucleophilic substitution reaction in solution.

reaction diagram (MDRD). Of course, the MDRD approach may provoke objections from some "orthodox" practical chemists, who often prefer less accurate but simpler models, and "uncompromising" theoreticians, who accept only rigorously justified calculation schemes. At the same time, any theoretical apparatus has advantages and disadvantages, and therefore the choice of one or another method is in fact predetermined by the character of the problems to be solved and the estimation of the method's suitability for particular researchers. Therefore, theoretical developments of new methods for the analysis and prediction of the reactivities of organic substances will be still actual in the future.

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