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Nucleophilic Substitution Reactions. Modern Ideas About the Mechanism and Reactivity

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The mechanism of S_N2 reactions is discussed on the basis of gas-phase experimental data and quantum-chemical calculations: the energy relations, stereochemistry, and the form of the potential energy surface. The results of modern kinetic measurements and calculations are presented. The experimental data for the reactions in solution are discussed at the level of qualitative quantum-chemical concepts. The causes of the strong influence of the solvent on the kinetics of these reactions are analysed and the empirical correlations between the kinetic and thermodynamic characteristics and the link between the correlations and modern theoretical ideas are examined.
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I. INTRODUCTION

During the last fifteen years, the ideas about the mechanism of nucleophilic substitution in aliphatic compounds have changed beyond recognition. Previous concepts have been revised as a result of studies on the kinetics of gas-phase S_N2 reactions with the aid of new mass-spectrometric methods, especially after the experimental results have been confirmed by quantitative quantum-chemical calculations. It was found that the potential energy surface (PES) profile for these reactions is much more complex than had been suggested previously and the mechanisms corresponding to it do not fit within the simplest kinetic schemes which have been generally accepted. The strong influence of the solvent on these reactions has become evident. The mechanism of S_N2 processes in a polar medium is much closer to previous schemes than the mechanism of the gas-phase reactions. Elementary theoretical considerations as regards reactivity which ignore fully or almost fully the influence of the medium have paradoxically proved to be applicable only to reactions in a polar solvent, since only such S_N2 reactions have the usual PES profile.

In the present review an attempt has been made to summarise and treat systematically the advances in recent years. The familiar nucleophilic substitution reactions have become the subject of the latest experimental and theoretical studies. The principles of the corresponding approaches and research methods are examined in the present review in fair detail. Furthermore, the methods used in the kinetic interpretation of mass-spectrometric experiments, the problems of the theory of chemical reactions in polar media, the correlation between kinetic and thermodynamic characteristics in terms of the Marcus equation, and certain other features of modern theoretical chemistry are also discussed.

II. THEORETICAL RESEARCH METHODS

1. Quantum-Chemical Calculations

Exhaustive information about the mechanism of the reaction of a chemical system can be obtained by calculating the PES. Within the framework of the activated complex theory, it is sufficient to find the geometrical configurations of the minimum corresponding to the reactants and the saddle point corresponding to the transition state (TS) of the reaction and then to estimate the height of the potential barrier from the difference between their absolute energies. In the case of a complex mechanism, one has to investigate complex PES with several minima and saddle points, whereupon the TS with the minimum energy usually corresponds to the preferred reaction pathway. More detailed investigations of PES involve the calculation of reaction pathways, i.e. of multidimensional curves in the internal coordinate space in which energy minima are attained in all the sections orthogonal with respect to their direction. Finally, for simple systems calculations of the dynamics of the movement of the representative point in the PES, classical or quantum, are feasible. This level of theoretical analysis is higher than that involving the calculation of the rate constants in terms of the activated complex theory.

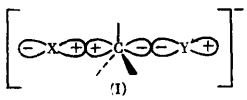
Both semiempirical and non-empirical quantum-chemical methods are used at present for the calculation of the PES. The semiempirical procedures (for example, CNDO/2, MINDO/3, MNDO, etc.) require a moderate expenditure of computer time and are frequently used in studies on complex reactions. Unfortunately they are not immune to uncontrollable errors, which are sometimes serious. In particular the standard semiempirical methods are unsuitable for the calculation of the saddle points of the simplest S_N2 reactions.

The non-empirical self-consistent field methods (for example, STO-3G, 3-21G, 4-31G, 6-311G, etc.) are much more laborious (in the incomplete list of non-empirical methods quoted above, the size of the basis set, the labour involved in the calculation, and the quality of the latter increase in the order in which the methods are listed). It has come to be assumed that calculations by the 3-21G or 4-31G method are sufficient for the determination of the geometry of stationary points. In order to achieve reliable energy estimates, it is necessary to expand the basis set and also to take into account electronic correlation. The latter improvement implies going beyond the framework of the self-consistent field procedure. Among the methods whereby correlations can be taken into account, which have been applied successfully to S_N2 reactions, mention should be made of the CEPA-PNO scheme (the approximation of interacting electron pairs).

2. Qualitative Methods of the Reactivity Theory

The traditional approach, in which the geometrical structures of the transition and initial states are postulated on the basis of intuitive considerations (the validity of the choice of the model can be checked in principle by calculating the PES for the simplest cases), is widely used. For models specified in this way, an elementary quantum-chemical assessment is made of the energy relations, i.e. of the tendency towards a change in the height of the potential barriers in the reaction series.

As an example, we shall consider a model for the TS of an S_N2 reaction at a saturated carbon atom. It has the structure (I):



(I)

where X is the nucleophile and Y the leaving group. It is assumed that the atoms X, C, and Y are located on the same axis, which is at right angles to the plane of the trigonal system of the bonds involving the carbon atom. The main element of the electronic structure of such TS is a delocalised three-centre four-electron system made up of three *p* orbitals, which overlap in phase, as shown in Scheme (I). For this system, it is possible to carry out an elementary calculation by the Hückel method or to apply the perturbation theory to the interaction, assuming that the substrate–nucleophile bond (C.X) is much weaker than the "intramolecular" bond C–Y (which is hardly justified). According to the perturbation theory, only the interactions between the occupied and unoccupied molecular orbitals (MO) of the reactants contribute to the energy. Its simplest version, the method of frontier orbitals (FMO), takes into account the contribution to the interaction energy only from a single pair: the highest occupied orbital of the nucleophile (HOMO)—the lowest unoccupied orbital of the substrate (LUMO). Thus it is sometimes possible to predict or explain the characteristics of the variation of the reactivity in reaction series.

In order to analyse the energy of the interaction in the TS, the latter is sometimes subdivided into a series of contributions (several versions of such subdivision are known): Coulombic (E_{coul}), polarisation (E_{pol}), charge transfer or delocalisation (E_{ct}), exchange repulsion ($E_{ex,rep}$), exchange (E_{exch}), and dispersion (E_{disp}):

$$E = E_{coul} + E_{pol} + E_{ct} + E_{ex,rep} + E_{exch} + E_{disp}. \quad (1)$$

Some of these quantities are combined in a single term. The interaction energy can be calculated by Eqn.(1) using fairly sophisticated quantum-mechanical methods—semiempirical or non-empirical.

3. Correlations

In the present review we shall examine only certain aspects of the application of correlations to nuclephilic substitution reactions, namely those for which it is possible to associate the relations with more fundamental approaches. Equations which are strictly speaking empirical can be often derived from a qualitative quantum-chemical analysis or from general geometrical considerations concerning the structure of multidimensional PES. Such derivations sometimes follow simply from the outward similarity of the equations and expansions of the molecular orbital perturbation theory as in the case of linear correlations of the Hammett type. In other cases the considerations are not so trivial. This applies to the Marcus equation, which is now a subject of a vigorous discussion in connection with exchange reactions to which the S_N2 reactions belong.

III. SUBSTITUTION REACTIONS AT A SATURATED CARBON ATOM

1. Stereochemical Specificity

The stereochemistry of S_N2 reactions has been investigated theoretically already in the course of 50 years at a wide variety of levels: ranging from simple electrostatic

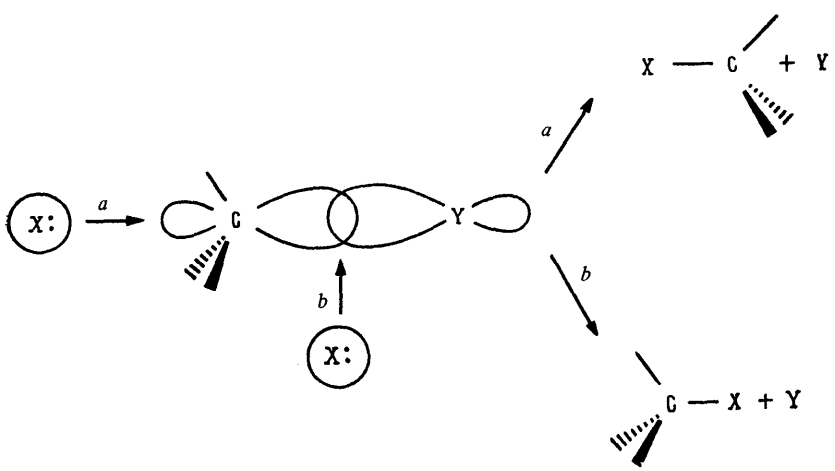


Figure 1. The rear (*a*) and frontal (*b*) attack in reactions of the S_N2 type.

estimates to modern semiempirical[1-7] and non-empirical[8-13] quantum-chemical calculations. Two directions of attack on the saturated substrate by the nucleophile X, differing in the relative disposition of X and of the leaving group Y, are distinguished (Fig.1): the rear direction, where X attacks the substrate from the side opposite to that of Y, and the frontal direction, where X attacks the substrate from the side of Y. Stereochemically different products correspond to these reaction pathways. Attack from the rear leads to the inversion of configuration (Walden inversion), while frontal attack results in the retention of configuration at the central atom of the substrate.

In the case of a saturated carbon atom, it has been established theoretically that the reaction with inversion of configuration is preferred Thus the search for the TS in the $H^- + CH_4$ system by the STO-3G method without symmetry-dependent limitations led to a configuration with D_{3h} symmetry[13] (Fig.2). The analysis of the form of the MO calculated by the CNDO/2 method for the $F^- + CH_3F$, $H^- + CH_4$, and $NH_3 + CH_3F$ reactions[2] also leads to the conclusion that the configuration is inverted. Analysis of the components of the total energy, calculated by a semiempirical method[3,4] for the $Cl^- + CH_3Cl$ system, shows that the Coulombic and exchange contributions of expansion (1) favour inversion and that the Coulombic component predominates over long distances. The delocalisation contribution is relatively small over long distances but becomes significant when the reactants approach one another and attack from the rear is then also favoured.

Experiment confirms that inversion of configuration is always observed in reactions of the S_N2 type at a saturated carbon atom. This fact has been firmly established for reactions both in solution and in the gas phase. In the first gas-phase experiments,[17] it was already shown that the nucleophilic reaction of Cl^- with *cis*- and *trans*-4-bromocyclohexanols takes place with inversion. The stereochemistry of substitution in positively charged intermediates under the influence of water in the gas phase has been investigated by the ion–cyclotron resonance (ICR) method.[18] The substitution takes place via the S_N2 mechanism to the extent of 64–98% (depending on the substrate) with inversion of configuration at the carbon atom.

The simplest three-centre four-electron model can be used to compare the electronic structures of the TS corresponding to the rear and frontal attack. The open-chain TS model for attack from the rear was indicated above in Scheme (I). The cyclic TS illustrated in Fig.3 corresponds to frontal attack. The open-chain and cyclic TS structures differ by too many parameters to enable comparison of their energy relations, even at the qualitative level, to be made. However, for each TS it is possible to analyse the conditions favouring the given stereochemical direction of the reaction. For example, the factors which increase the probability of frontal attack can be discovered by the qualitative analysis of the relative stability of the cyclic TS.[7,10,19] We shall examine these considerations in greater detail as a typical example of a qualitative approach to the MO theory. A similar treatment of the open-chain TS is described below.

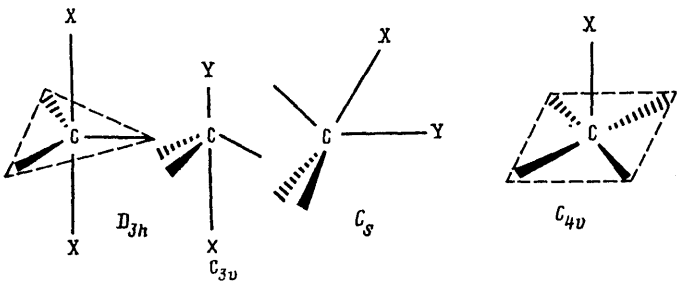


Figure 2. The possible configurations of the TS in S_N2 reactions.

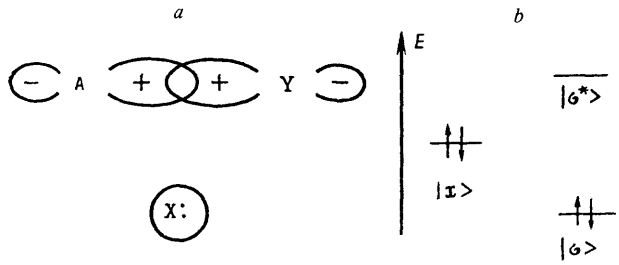


Figure 3. Schematic illustration of the three-centre cyclic TS in reactions of the S_N2 type (*a*) and the disposition of the energy levels (*b*).

Direct calculations have shown that the difference between the TS energies for the rear and frontal attack is sufficiently large to assume that the inversion of configuration at the saturated carbon atom is preferred (Table 1 and Fig.2). A high symmetry of the TS corresponding to inversion obtains only if the nucleophile and the leaving group are monatomic anions. For polyatomic nucleophiles and leaving groups and also for asymmetrically substituted substrates, the conclusion that the configuration is inverted remains but the symmetry of the TS is distorted to a greater or lesser extent.[14-16] According to a non-empirical calculation,[14] the angle α(C–X–Y) for X, Y = HO, HOO, NH_2, CN, SH, OCH_3, or OC_2H_3 deviates from 180° by an amount up to 4°. For example, in the $[FCH_3OF]^-$ system the angle α(F–C–O) = 176°, while in the $[HOOCH_3OOH]^-$ system we have α(O–C–O) = 182.4°. In the presence of a methyl substituent at the carbon atom of the substrate, α(X–C–Y) = 150°.[16]

We introduce the following notation: $|x\rangle$ is the HOMO (or AO) of the nucleophile X and $|a\rangle$ and $|y\rangle$ are the AO of the central atom A of the substrate and of the leaving group Y (Fig.3) contributing most to the LUMO $|\sigma^*\rangle$ of the substrate:

$$|\sigma^*\rangle = (|a\rangle - \lambda|y\rangle)(1+\lambda^2)^{-1/2} \cong |a\rangle - \lambda|y\rangle . \quad (2)$$

Within the framework of perturbation theory, the stabilisation of the TS is determined by the interaction of the HOMO $|x\rangle$ of the nucleophile and the LUMO $|\sigma^*\rangle$ of the substrate. The matrix elements of the Hamiltonian *h* will be designated as follows:

$$\langle a|h|a\rangle = \alpha_a; \quad \langle x|h|x\rangle = \alpha_x; \quad \langle y|h|y\rangle = \alpha_y;$$
$$\langle a|h|y\rangle = \beta_{ay}; \quad \langle a|h|x\rangle = \beta_{ax}; \quad \langle x|h|y\rangle = \beta_{xy} .$$

It is assumed that they satisfy the relations

$$\alpha_x, \alpha_y \ll \alpha_a < 0; \quad 0 < \lambda \cong \beta_{ay}/(\alpha_y - \alpha_a) \ll 1; \quad 0 < \lambda' \cong \beta_{ay}/(\alpha_x - \alpha_a) \ll 1. \quad (3)$$

This means that the electronegativity of the central atom A is much smaller than the electronegativity of the nucleophile X and of the leaving group Y and that on the energy scale the differences between the electronegativities are large compared with the strength of the corresponding bond.

The energy of interaction of the orbitals $|x\rangle$ and $|\sigma^*\rangle$ is

$$\Delta E = 2\langle x|h|\sigma^*\rangle/(\langle x|h|x\rangle - \langle\sigma^*|h|\sigma^*\rangle) < 0 \ .$$

When the higher powers of the small quantities λ and λ' are neglected, the above expression reduces to

$$\Delta E \simeq -2(\beta_{ax}^2 - 2\lambda\beta_{ax}\beta_{xy})/(\alpha_a - \alpha_x) \ . \qquad (4)$$

It follows from Eqn.(4) that the decrease of the quantity λ stabilises the TS. According to Eqn.(3), λ (the contribution of the AO $|y\rangle$ to the LUMO $|\sigma^*\rangle$ of the substrate) diminishes with increase of α_a and with decrease of α_y. Consequently decrease of the electronegativity of the central atom and increase of that of the leaving group promote frontal attack. This is confirmed by direct calculations and by experiments on nucleophilic substitution at a silicon atom, which is less electronegative than a carbon atom. Calculations of the TS energies for different configurations have shown that, although frontal attack on the silicon atom is energetically less favourable than attack from the rear, it is so to a lesser extent than for a carbon substrate (Table 1). Whereas reactions of the S_N2 type at a saturated carbon atom always proceed with inversion, in substitution at a silicon atom configuration is retained[21-24] (in this case frontal attack is preferable to attack from the rear, although the mechanism in the given instance differs from S_N2).

Table 1. The relative TS energies with inversion (D_{3h}, C_{3v}) and retention (C_s, C_{4v}) of configuration.

System	E, kcal mol^{-1}				Method (basis set)	Refs.
	C_{3v}	D_{3h}	C_s	C_{4v}		
CH_5^-	—	0	56.8	54.3	(7.3/3) → [4.2/2]	[8]
CH_5^-	—	0	54.5	54.5	two-exponential function, minimal Slater basis set	[9]
CH_5^-	—	0	15	—	PNDO	[1]
$CH_3F_2^-$	—	0	56.4	—	4-31G	[12]
$CH_3(CN)_2^-$	—	0	15	—	MNDO	[6]
SiH_4F^-	0	—	9	—	STO-3G	[19]
SiH_4Cl^-	0	—	33.6	—	STO-3G	[19]
SiH_5^-	—	0	—	2.9	(12.9/5) → [6.4/2]	[20]

The increase of the electronegativity of Y within the limits of a single Group of the Periodic System (on replacement of Cl by F or of SR by OR) also favours retention of configuration.[19,24] Furthermore, analysis of the denominator in Eqn.(4) makes it possible to understand the effect of electronegativity of the nucleophile. The conclusion that an increase of α_x facilitates frontal attack is apparently indirectly confirmed by the dependence of the stereochemical specificity of certain S_N2 reactions in aprotic solvents on the hardness of the nucleophile.[24] Finally, the inclusion of the central atom of the substrate in the strained cyclopropane ring favours retention of configuration. This result, obtained by calculation using the extended Hückel method (EHM),[7,10] can be explained qualitatively by the fact that the corresponding change in the degree of hybridisation diminishes λ by diminishing the absolute value of β_{ay}. We may note that, even for the reaction with cyclobutane, a similar EHM calculation[5,10] predicts inversion in agreement with a non-empirical calculation[11] and experiment.[25]

The elementary considerations presented above are not faultless even within the framework of the simplest model employed. It is sufficient to point out that a change in the nature of A, X, and Y should influence not only the corresponding quantity α but also β in Eqn.(3) or (4) (for example, via a change in the A–X and A–Y bond lengths). In discussing the role of the electronegativity of the atom A, no account was taken of the effect of α_a in the denominator of Eqn.(4), the result of which is the opposite of that of the effect of λ. Steric effects can be excluded in by no means all the examples examined. Finally, one should consider simultaneously how the above factors influence the stability of the alternative open-chain TS.

2. The Mechanism of the Gas-Phase Reactions

Fig.4 illustrates the complex PES profile along the reaction coordinate of the reaction

$$X^- + CH_3Y \rightarrow XCH_3 + Y^- \ . \qquad (5)$$

It is now generally accepted that the mechanism of the simplest gas-phase reactions (5) is described by a two-well potential curve. The minima correspond to the prereaction complex $[X^-.CH_3Y]$ and the postreaction complex $[XCH_3.Y^-]$ with highly asymmetric structures and localised charges. The bonds represented by dots are mainly electrostatic in nature: the corresponding internuclear distance is still too large for the formation of strong covalent bonds. The bonds in the CH_3Y and XCH_3 molecules which enter into the composition of the corresponding complexes are almost undistorted and are largely covalent. The conversion of the first complex into the second proceeds via the saddle point on the PES, to which corresponds the TS $[XCH_3Y]^-$ with a more or less symmetrical structure and a delocalised charge.

The order of magnitude of the stability of the electrostatic complexes can be estimated for the energy of the ion–dipole interaction over the distance corresponding to the sum of the van der Waals radii of the corresponding atoms. Estimates in the range $U \cong 10$–20 kcal mol^{-1} are thus obtained. The formation of ion–molecule complexes has been established in a number of gas-phase experiments.[26-31] Their measured formation energies agree with the above estimate. Thus the bond energy of the complex $Cl^-.CH_3CN$ is 16 kcal mol^{-1},[27] while those of the complexes $Hal^-.CH_3Hal$ range from 8.6 to 14.4 kcal mol^{-1}.[28-30] The non-equivalence of the X and Y atoms in symmetrical systems (X = Y = Cl) has been demonstrated by isotopic analysis of the reaction products:

$$[^{35}Cl \cdot CH_3^{37}Cl]^- + CH_3CF_3 \rightarrow [^{35}Cl \cdot CH_3CF_3] + CH_3^{37}Cl \ ,$$

where one of the reactants was the complex of the $^{35}Cl^-$ anion with the $CH_3^{37}Cl$ molecule prepared beforehand.[31]

The complexes are apparently not formed in polar solvents. At any rate, liquid-phase experiments provide no evidence for their formation. Up to the beginning of the 1970's, kinetic studies of reactions of type (5) were performed exclusively in the liquid phase and no considerations indicating the possibility of complex mechanisms were put forward. The first convincing piece of evidence was obtained in the theoretical calculation by Dedieu and

Veillard.[32] The main result of this study was the prediction of a two-well PES profile for reaction (5) with X, Y = H, F.

Kinetic studies of gas-phase reactions (5) using the mass-spectrometric technique involving afterglow in a stream,[33–36] the ICR method,[17,37–41] and the pulsating electron beam method[42] yielded final evidence in support of the view that they have a complex mechanism. Approximately 100 kinetic constants have now been measured for such reactions. Table 2 lists the rate constants k for the $X^- + CH_3Y$ reactions; the data for reactions with substituted substrates $CR^1R^2R^3$ are not included. The constants k measured by the afterflow in a stream method are systematically higher than those obtained by the ICR method. The determination of the parameters of a two-well PES from the results of a kinetic experiment presents serious difficulties. Two different procedures for the estimation of the activation barrier ΔE (Fig. 4), based on different hypotheses concerning the reaction mechanism, were used in Table 2. The Arrhenius equation, in which the pre-exponential factor represents the collision frequency, was employed in the first of these.[36] The large number of ΔE values close to zero, supporting a complex PES profile, is striking: the reactions for which $\Delta E < 0$ also fell within the group. The second estimate[39–41] is based on the Kassel–Marcus theory (RRKM); for this model, $\Delta E < 0$.

Table 2. The experimental rate constants k (cm^3 molecule^{-1} s^{-1}), the efficiencies f, and the enthalpies Q_{XY} (kcal mol^{-1}) of the gas-phase reactions $X^- + CH_3Y \rightarrow XCH_3 + Y^-$ as well as estimates of ΔE and E_{XY} (kcal mol^{-1}) (Fig. 4).

X	$k\cdot10^9$	f	$-Q_{XY}$	ΔE	E_{XY}	Refs.
			Y=F			
O	1.1	0.48	27	—	—	[36]
CHF	0.41	0.23	—	—	—	[36]
CH_3NH	0.05	0.03	43	2.1	—	[36]
OH	0.025	0.011	18	2.7	—	[36]
NH_2	0.0176	0.0076	32	2.9	—	[36]
H	0.015	0.0020	56	3.7	—	[36]
CH_3O	0.014	0.0074	23	2.9	—	[36]
CN	⩽0.003	⩽0.002	4	⩾3.8	—	[36]
C	⩽0.002	⩽0.0008	25	⩾4.2	—	[36]
C_2	⩽0.002	⩽0.001	5	⩾4.1	—	[36]
CH_3S	⩽0.001	⩽0.0006	4	⩾4.3	—	[36]
CCH	⩽0.0003	⩽0.0002	34	⩾4.5	—	[36]
			Y=Cl			
H	3.0	0.35	88	0.62	—	[36]
OH	1.6	0.68	48	—	—	[39]
OH	1.5	0.62	50	0.28	—	[36]
F	0.80	0.35	29	—	—	[39]
F	0.58	0.25	28	—(0.9—3.2)	8.1—5.8	[41]
F	1.9	0.83	32	0.1	—	[36]
O	1.7	0.71	59	—	—	[36]
CH_3NH	1.7	0.85	75	0.1	—	[36]
NH_2	1.5	0.63	64	0.3	—	[36]
CH_3O	0.49	0.25	39	—	—	[39]
CH_3O	0.60	0.30	42	—(3.1—7.2)	5.9—1.8	[41]
CH_3O	1.3	0.68	55	0.23	—	[36]
C_2H_5O	1.3	0.29	—	—	—	[33]
$(CH_3)_3CHO$	1.1	0.26	—	—	—	[33]
C_6H_5	0.87	0.22	—	—	—	[33]
t-C_4H_9-C_6H_4	0.80	0.22	—	—	—	[33]
CH_2Cl	0.51	0.30	—	—	—	[36]
C	0.30	0.11	57	1.3	—	[36]
t-C_4H_9	0.16	0.10	35	—(2.4—4.7)	6.6—4.3	[41]
t-C_4H_9	0.80	0.20	—	—	—	[33]
CH_3S	0.078	0.045	31	—	—	[39]
CH_3S	0.11	0.065	36	1.6	—	[36]
CD_3S	0.052	0.03	29	—(1.3—4.0)	7.7—5.0	[41]
HCC	0.052	0.024	51	—(0.8—4.2)	8.2—4.8	[41]
HCC	0.13	0.062	66	1.6	—	[36]
S	0.030	0.016	24	2.4	—	[36]
$C_6H_5C(CH_3)_2$	0.026	0.007	—	—	—	[33]
$C_6H_5CHCH_3$	0.024	0.006	—	—	—	[33]
SH	0.017	0.0089	22	2.8	—	[36]
$C_6H_5CH_2$	0.015	0.004	51	—	—	[33]

Table 2 (cont'd.).

X	$k\cdot10^9$	f	$-Q_{XY}$	ΔE	E_{XY}	Refs.
Cl	~0.006	~0.003	0	—	—	[39]
C_3	⩽0.005	⩽0.002	37	⩾3.8	—	[36]
S_2	⩽0.001	⩽0.0006	1	⩾4.4	—	[36]
CN	⩽0.001	⩽0.0005	27	—	—	[39]
CN	⩽0.0004	⩽0.0002	36	⩾5.0	—	[36]
NO_2	⩽0.001	⩽0.00059	7	⩾4.4	—	[36]
			Y=Br			
H	3.7	0.43	95	0.50	—	[36]
OH	1.9	0.84	56	—	—	[39]
OH	0.99	0.43	57	0.50	—	[36]
C	1.3	0.48	64	0.43	—	[36]
CH_3NH	1.3	0.72	82	0.19	—	[36]
O	1.1	0.48	66	—	—	[36]
NH_2	1.1	0.48	71	0.43	—	[36]
CH_3O	0.72	0.40	48	—	—	[39]
CH_3O	0.73	0.40	49	—(3.9—8.6)	6.1—1.4	[41]
CH_3O	1.1	0.61	62	0.29	—	[36]
			Y=Br			
F	0.60	0.28	37	—	—	[39]
F	1.2	0.59	39	0.31	—	[36]
S	0.46	0.26	31	0.80	—	[36]
CH_2Br	0.42	0.32	—	—	—	[36]
t-C_4H_9	0.41	0.30	43	—(4.0—6.8)	6.0—3.2	[41]
HCC	0.31	0.16	59	—(2.2—7.0)	7.8—3.0	[41]
HCC	0.52	0.26	73	0.80	—	[36]
SH	0.30	0.18	29	1.0	—	[36]
CH_2CN	0.29	0.18	55	—	—	[41]
$CH_2C(O)CH_3$	0.18	0.12	25	—	—	[41]
CH_3S	0.14	0.091	39	—	—	[39]
CH_3S	0.52	0.35	43	0.62	—	[36]
S_2	0.033	0.024	8	2.2	—	[36]
C_2	0.032	0.016	44	2.5	—	[36]
CN	0.02	0.01	35	—	—	[39]
CN	0.03	0.016	43	2.4	—	[36]
CH_3COO	0.020	0.014	17	—(2.6—6.1)	7.4—3.9	[41]
PhN	0.019	0.015	48	—	—	[41]
Cl	0.012	0.0070	8	—	—	[39]
Cl	0.021	0.012	7	2.6	—	[36]
Br	<0.01	<0.008	0	—	—	[39]
NO_2	⩽0.001	⩽0.0006	14	⩾4.4	—	[36]
			Y=CF_3COO			
OH	1.4	0.47	68	—	—	[39]
F	1.1	0.39	49	—	—	[39]
CH_3O	1.0	0.43	60	—	—	[39]
CH_3S	0.50	0.25	52	—	—	[39]
Cl	0.045	0.021	21	—	—	[39]
CN	0.03	0.01	48	—	—	[39]
Br	~0.005	~0.003	13	—	—	[39]
			Y=C_6H_5O			
OH	0.08	0.03	38	—	—	[39]
F	0.08	0.03	19	—	—	[39]
CH_3O	0.024	0.012	30	—	—	[39]
CN	~0.007	~0.003	18	—	—	[39]
CH_3S	<0.005	<0.003	22	—	—	[39]
			Y=CH_3O			
CD_3O	<0.001	<0.0005	0	—	—	[39]
			Y=SH			
CH_3S	0.8	0.5	12	—	—	[39]

Remarks. The measurements of Bohme and Young[33] and Tanaka et al.[36] were made by the method of afterglow in a stream and the ΔE were estimated from the Arrhenius equation with the pre-exponential factor equal to the collision frequency; Pellerite and co-workers[39,41] carried out their measurements by the ICR method, ΔE was estimated by the RRKM method, and E_{XY} was calculated on the assumption that the formation energy of the complex is −9 kcal mol^{-1}.

The efficiency $f = k/k_C$ is defined as the ratio of the observed rate constant k to the gas-phase kinetic rate of collision k_C. The range of the gas-phase ion–molecule reaction rates is usually small. For example, the proton transfer reactions in systems with a localised charge are rapid and $f \cong 1$ for such processes. The low efficiency and the long range of its variation indicate an unusual character of the reactions quoted in Table 2.

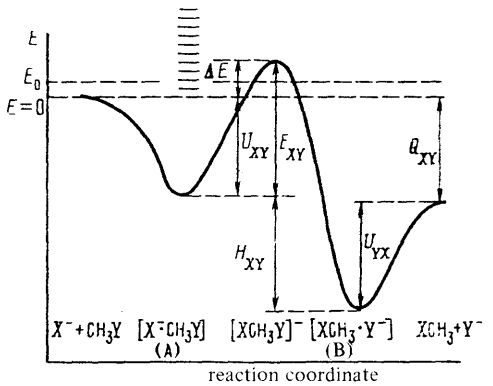


Figure 4. The PES profile for a gas-phase reaction of the S_N2 type; E_0 is the kinetic energy of the reactants and the short horizontal lines represent schematically the energy levels of the "hot" prereaction complex located above the intrinsic energy of the reactants ($E = 0$).

A model kinetic description of a multistage exothermic process with a two-well potential profile has been proposed by Brauman and co-workers[39–41] and is based on the scheme

$$X^- + CH_3Y \underset{k_1}{\overset{k_0}{\rightleftarrows}} [X^- \cdot CH_3Y] \qquad (6)$$

$$[X^- \cdot CH_3Y] \xrightarrow{k_2} \text{products} \qquad (7)$$

to which correspond simple expressions for the observed rate constant and efficiency:

$$k = k_0 k_2/(k_1 + k_2) \ , \qquad f = (1 + k_1/k_2)^{-1} \ . \qquad (8)$$

The relation $k_1/k_2 \gg 1$ corresponds to the data in Table 2. This inequality may be ensured even for negative ΔE with a not unduly large absolute value (the barrier for the process with k_2 is lower than the barrier for the process with k_1), because the large distance between the reactants in the TS of the reverse reaction (6) increases the freedom of their relative movement.

The simplest estimate of the k_1/k_2 ratio within the framework of the activated complex theory is

$$k_1/k_2 = (A_1/A_2)\exp(\Delta E/RT) \ . \qquad (9)$$

The pre-exponential factors A_1 and A_2 are calculated by standard methods. Eqn.(9) is valid if the distribution function for the complexes $[X^-.CH_3Y]$ corresponds to equilibrium, i.e. if the rate of deactivation (as a result of collisions) of the "hot" complexes formed via reaction (6) is much higher than the rate of their decomposition defined by the constants $k_1 + k_2$. Experiments[39–41] carried out at a low pressure (10^{-5}–10^{-6} mmHg) do not satisfy this relation. The statistical unimolecular decomposition theory (RRKM) was used to estimate k_1/k_2 under such conditions. It was assumed that the "hot" complex formed decomposes via one of the possible pathways, without undergoing even a single collision, and that its energy $E = E_0 + U_{XY} = E_0 + E_{XY} - \Delta E$ (Fig.4) is distributed statistically among the internal degrees of freedom. The following approximate expression is valid within the framework of this model:[39]

$$\frac{k_1}{k_2} \cong \frac{\int_{U_{XY}}^{\infty} G_1(E - U_{XY}) \exp(-E/kT)\, dE}{\int_{U_{XY}}^{\infty} G_2(E - E_{XY} - \Delta E_{rot}) \exp(-E/kT)\, dE} \ , \qquad (10)$$

where $G_1(E)$ and $G_2(E)$, i.e. the numbers of the vibrational-rotational states in a microcanonical ensemble with the energy E for the corresponding activated complexes, were calculated by the RRKM method (the energy arguments are indicated in brackets; ΔE_{rot} is the adiabatic change in the rotational energy in the TS). The independent experimental estimate $U = -9$ kcal mol^{-1} was adopted for the energy of formation of the complexes U_{XY}, after which only one unknown parameter remains in Eqn.(10)—the height of the internal barrier E_{XY}; this quantity was chosen in such a way that the experimental efficiencies were consistent with Eqn.(8).

Unfortunately the results obtained are not unambiguous because of the arbitrary choice of the activated complex models in the calculation of G_1 and G_2 (see the scatter of the estimates of ΔE and E_{XY} in Table 2). In order to refine the model, more detailed experimental information is essential.

A temperature variation of the rate constant k has been investigated[42] in the range 25–390 °C for the reactions

$$Cl^- + RBr \rightarrow ClR + Br^-$$
$$R = CH_3,\ C_2H_5,\ \text{iso-}C_3H_7,\ n\text{-}C_4H_9,\ \text{iso-}C_4H_9.$$

The ratio k_1/k_2 was estimated using the activated complex theory [Eqn.(9)] on the grounds that the experiment was performed at a fairly high pressure (~4 mmHg). The estimates of their height proved to be much less ambiguous:

R	CH_3	C_2H_5	n-C_4H_9	iso-C_3H_7	iso-C_4H_9
E_a, kcal mol^{-1}	−2.5	0.8	−0.5	5.1	5.7

According to Eqn.(9), negative values of ΔE should lead to a negative observed activation energy E_a, which in a rough estimate agrees with ΔE as regards absolute magnitude (in an exact calculation account is taken of the temperature variation of the pre-exponential factors). The negative value $E_a \cong -2$ kcal mol^{-1} has indeed been observed in the reaction with the CH_3Br substrate.

The validity of such treatment of kinetic experiments is far from evident. In a non-equilibrium situation the very kinetic scheme defined by Eqns.(6) and (7), which ignores the direct mechanism involving the collision of the species, unassociated with the formation of the pre-reaction complex, is doubtful. If an appreciable fraction of the reaction product is formed via the direct mechanism, Eqn.(8) has no significance. Quantum-dynamic calculations have shown[43,44] that the contribution of the direct process to the formation of products is different in different systems. For thermally neutral and endothermic reactions ($Q_{XY} \geq 0$), it is appreciable. On the other hand, for exothermic reactions ($Q_{XY} < 0$), the direct mechanism leads to almost complete reflection (the probability of reflection in the direct process, amounting to 0.998 for $\Delta E = -1.9$ kcal mol^{-1}, has been found for $H^- + CH_3F$) and its contribution to the reaction may be neglected. In this case the reaction does indeed proceed

via the formation of the complex $[X^-.CH_3Y]$ and it would be incorrect to calculate the efficiency f by Eqns.(8) and (10). The low efficiency is associated with the low probability of the formation of the complex. It can be calculated from the formula:[45]

$$f = (h/kT)\sum_{\lambda} P_{0\lambda}k_{2\lambda}\exp(-E_\lambda/kT),$$

where h is the Planck constant, $P_{0\lambda}$ the probability of the formation of the "hot" complex in the vibrational state λ with the energy E_λ (reckoned from the energy of the reactants $E = 0$—see Fig.4), and $k_{2\lambda}$ the rate constant for the decomposition of this state to the products. The quantities $P_{0\lambda}$ and $k_{2\lambda}$ are found in the dynamic calculation.

Table 3. Results of the calculations of the parameters of the complexes or TS of the type $[XCH_3Y]^-$ by various methods.

Bond lengths, Å		ΔE, kcal mol^{-1}	Method (basis set)	Refs.
X—C	C—Y			
		$[HCH_3H]^-$		
1.225	1.225	—13.3[a]	MINDO/3	[70]
1.189	1.189	—26.1[a]	CNDO/BW	[72]
1.250	1.250	—2.4[a]	MNDO	*b*
1.481	1.481	46.0	STO-3G	[14]
1.702	1.702		3-21G	[14]
1.730	1.730	48.8	4-31G	[14]
1.715	1.715		6-311G*	[14]
1.736	1.736	51.7	(10 6/5) → [5 4/3]	[52]
—	—	46.2	*c*	[52]
—	—	51.2	*d*	[52]
—	—	47.2	*e*	[52]
1.736	1.736	63.6	(8.4/4) → [4 2/2]	[53]
		56.4	*f*	[53]
2.00	2.00	48.0	semiemp.	[72]
		$[HCH_2F]^-$		
—	—	—57.3[a]	MINDO/3	[70]
2.41	1.88	16.7	semiemp.	[72]
1.924	1.726	—12.4	4-31G	[14]
1.937	1.958	12	(8.4/4) → [4.2/2]	[53]
—	—	10	*f*	[53]
1.937	1.958	3.8	(11.7/6 → [5.3/3])	[32]
		$[FCH_2F]^-$		
1.45	1.45	—88.3[a]	CNDO/2	[74, 69]
—	—	—33.4[a]	STO-3G	[12]
1.643	1.643	40	MNDO	*b*
1.828	1.828	—14.6	4-31G	[12]
1.878	1.878	—8.8	(9.5/4) → [5.3/3]	[46]
—	—	—3.3	(9,5/4) → [5,3/3] + diffuse AO	[49]
1.94	1.94	5.2	semiemp.	[72]
—	—	—2.2	6-311G*	[14]
1.878	1.878	7.9	(11.7/6 → [5.3/3]	[32]
1.823	1.823	0.2	(10 6/5) → [5.4/3]	[52]
—	—	2.1	*c*	[52]
1.805	1.805	4.2	(8.4/4) → [4.2/2]	[53]
—	—	8.9	*f*	[53]
		$[ClCH_2Cl]^-$		
2.150	2.150	4.4	MNDO	[73]
—	—	—10	3-21G	[62]
2.382	2.382	—10.9	4-31G	[14]
—	—	3.6	6-311G*	[75]
2.391	2.391	2.2	(8.4/4) → [4.2/2]	[53]
—	—	9.7	*f*	[53]

[a]Complex, there is no saddle point on the PES; all the remaining configurations correspond to saddle points on the PES.

[b]Our results.

[c,d,e]The calculation was performed with addition of polarisation and diffuse functions to the (10,6/5) → [5,4/3] minimal basis set, namely: [c]d(C) and p(H); [d]d(C); [e]p(H).

[f]The configuration interaction was taken into account by the CEPA-PNO method in terms of the minimal basis set (8,4/4) → [4,2/2].

Thus the low efficiency of the non-activated ($\Delta E < 0$) reactions under non-equilibrium conditions (low pressure) can be accounted for solely within the framework of a dynamic calculation. It is caused by the marked energy exchange between the reaction coordinate and the transverse vibrational degrees of freedom in the region of the free reaction complex.

3. Calculations of the Potential Energy Surfaces

Reactions (5) of the S_N2 type at a saturated carbon atom have been investigated vigorously by quantum-chemical methods—mainly non-empirical methods[11-14,32,46-66] and more rarely by semiempirical methods.[1,7,10,15,16,67-73] The complex two-well profile of the potential curves is reproduced satisfactorily only in calculations at a sufficiently high level. Practice has demonstrated that semiempirical methods are as a rule unsuitable for the calculation of the PES for such reactions; this is illustrated in Table 3. Their application has therefore been restricted to the study of qualitative relations (the study of stereochemistry or of the effect of substituents). Methods using the approximation involving the neglect of differential overlap (NDO) yield a qualitatively incorrect potential surface for reaction (5), predicting the formation of a stable pentacoordinate complex (the presence of a minimum on the PES), for example CH_5^- or $CH_3F_2^-$, instead of the saddle point.[67,70] The geometry of these complexes differs considerably from the geometry of the TS calculated by non-empirical methods: the axial bonds in the complex are shorter by ~0.5 Å than in the TS.

The stability of the structures $[XCH_3Y]^-$ is found to be too high in calculations by semiempirical methods for two reasons. Firstly, the form of the valence atomic orbitals of X and Y changes appreciably and their atomic charges are altered in the course of the reaction, which is characteristic of anionic reactions where X and Y are isolated atoms, particularly when X = Y = H. If X and Y are molecular residues, then the errors diminish because of the delocalisation of the excess electron densities.

Secondly, the NDO approximation introduces a significant error. The empirical inclusion of non-orthogonality effects in the parameters of the semiempirical methods is intended for neutral molecules and cations (included in the calibration set in the optimisation of the parameters of the MINDO and MNDO methods). As a result, one of the components of the total energy, namely the contribution of the exchange repulsion, is underestimated if the excess electron populations on the atoms of the reaction centre are large. In calculations for cationic systems, the latter defect is removed. This is confirmed by the result, likely to be correct, obtained in calculations for cationic reactions by the MINDO/3 [71] and MNDO [16] methods. The potential curves for S_N2 reactions with neutral nucleophiles, $\ddot{X} + RN_2^+ \rightarrow XR^+ + N_2$ (R = CH_3 or C_2H_5), calculated by the MNDO method, have a characteristic two-well profile with minima 3–10 kcal mol^{-1} deep and separated by a barrier. However, the parametrisation of the MNDO method successfully models the exchange repulsion also in certain anionic systems. For example, two-well potential curves have been obtained for the following anionic S_N2 reactions: $CN^- + CH_3CN$,[6] $Cl^- + RCl$ (R = alkyl or $R'C_6H_4CH_2$), and $X^- + CH_3Cl$ (X = Cl, HO, HS, CH_3O, CH_3S, H_2N, CN, NC, or HCC).[73] The best result was obtained for X = Cl (Table 3). This is because the calibration of the parameters of the Cl atom in the MNDO method reproduces its electron affinity, i.e. is in fact designed for the description of the Cl^- anion. For the majority of other anions with the charge localised on one

atom, the errors in the heats of formation are now as much as 20–30 kcal mol^{-1} and this affects the calculated energy parameters of the reactions.[73] Calculations with the aid of MNDO, as well as other NDO methods, for the $H^- + CH_4$ reaction yield a false minimum for the symmetrical configuration and the barrier of the $F^- + CH_3F$ reaction is unacceptably high (Table 3).

The semiempirical method based on the explicit allowance for the AO non-orthogonality effects[76,77] has been used successfully in the calculations on the kinetics of a series of S_N2 reactions. In this method the integrals are parametrised in terms of an atomic basis set and are then converted to an orthogonal basis set. This procedure eliminates the disadvantages of the NDO approximation and the method yields characteristic two-well curves for reactions (5) with X, Y = H, F, Cl, or OH.[72]

The effect involving a change in the form of the AO following a change in the atomic charges, indicated above, cannot be taken into account in non-empirical methods employing a minimal basis set either. It can be estimated by comparing the results of calculations in terms of the STO-3G basis set and in terms of an extended basis set (Table 3). The axial bonds in a TS of the type of CH_5^- found in terms of the limited STO-3G basis set are too short. A more significant feature is that the forms of the potential curve for the $F^- + CH_3F$ reaction correspond to the formation of a stable complex instead of the TS, as in semiempirical methods.

The electronic correlation contribution in calculations on reactions (5) is weak (Table 3) and, according to the available calculations,[53,66] does not introduce significant changes into the barrier on the PES.

A series of studies[14,32,53,58,59,72] have been devoted to systematic calculations of the PES for reactions (5), including the TS and complexes. The results of the best calculations are presented in Table 4. The majority of the PES have been calculated in terms of the moderate 4-31G basis set with two exponential functions with respect to the valence shell. Table 3 illustrates the effect of the basis set. A reliable geometry of the stationary points is usually obtained at the level of the 4-31G basis set. However, in order to obtain reliable energy parameters, a wider basis set is required. Thus the energies of the TS in the $F^- + CH_3F$, $Cl^- + CH_3Cl$, and $H^- + CH_3F$ systems, calculated in terms of the 4-31G basis set[12,14] and by the CEPA-PNO method {balanced basis set (8,4/4) contracted to [4,2/2] taking into account electron correlation}[53] differ by 20 to 25 kcal mol^{-1} and have opposite signs relative to the energies of the reactants. A saddle point is not obtained in the PES for the $H^- + CH_3Cl$ [56] and $F^- + CH_3Cl$ [14] reactions in the 4-31G method, which conflicts with the calculations in terms of a wider basis set.

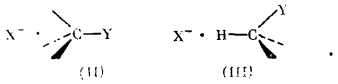
Two minima on the potential energy profile correspond to electrostatic ion–molecule complexes. The calculated characteristics of the complexes agree with the experimental data. Their calculated energy of formation is in most cases between −10 and −20 kcal mol^{-1}. The complexes are highly asymmetric. When X = Y, the length of one bond (X.C) is more than 2.5 Å, while that of the other (C–X) is close to the equilibrium value in the substrate. The calculated length of the X.C bond sometimes depends significantly on the basis set of the computational method. In [H^-.CH_3F] the length of the H.C bond, calculated in terms of the 4-31G basis set, is 2.64 Å, whilst that calculated in terms of 6.311G*

Table 4. The geometrical and energy characteristics of the PES for the reactions $X^- + CH_3Y \rightarrow XCH_3 + Y^-$ (bond length, Å; energy, kcal mol^{-1}).

No.	X	Y	Complex (A)			Transition state				Complex (B)			Q_{XY}	Method (basis set)	Refs.
			X·C	C–Y	U_{XY}	X–C	C–Y	E_{XY}	ΔE	X–C	C·Y	U_{YX}			
1	H	H	—	—	—	1.736	1.736	—	56.4	—	—	—	0	(8.4/4)→[4.2/2] + Cl	[53]
2	F	F	—	—	—	1.805	1.805	—	8.9	—	—	—	0	ditto	[53]
3	HCC	CCH	3.253	1.465	−8.8	2.124	2.124	50.4	41.6	—	—	—	0	4-31 G	[14]
4	NC	CN	3.086	1.459	−14.9	2.112	2.112	43.8	28.9	—	—	—	0	ditto	[14]
5	$N\overline{H}_2$	$\overline{N}H_2$	—	—	−10.0	2.002	2.002	37.7	27.7	—	—	—	0	»	[14]
6	$C\overline{N}$	$\overline{N}C$	2.902	1.441	−14.6	2.013	2.013	28.5	13.9	—	—	—	0	»	[14]
7	$C\overline{H}_3O$	$\overline{O}CH_3$	2.876	1.450	−11.5	1.898	1.898	23.5	12.0	—	—	—	0	»	[14]
8	HS	$\overline{S}H$	3.442	1.914	−9.9	2.450	2.450	15.5	5.6	—	—	—	0	»	[14]
9	HO	$\overline{O}H$	2.807	1.463	−15.7	1.908	1.908	21.2	5.5	—	—	—	0	»	[14]
10	HOO	$\overline{O}OH$	—	—	−13.2	1.920	1.920	18.7	5.3	—	—	—	0	»	[14]
11	FO	$\overline{O}F$	2.962	1.468	−22.0	1.932	1.932	18.8	−3.2	—	—	—	0	»	[14]
12	Cl	Cl	—	—	—	2.391	2.391	—	9.7	—	—	—		(8.4/4)→[4.2/2] + Cl	[53]
13	H	OH	2.875	1.461	−13.0	1.838	1.844	18.5	5.5	—	—	−60.6[a]	−47.4	4-31 G	[14]
14	H	CCH	2.966	1.468	−11.7	1.886	1.991	34.9	23.2	—	—	−54.1[a]	−48.2	4-31 G	[14]
15	H	F	—	—	—	1.937	1.958	—	10	—	—	—	−53.8	(8.4/4)→[4.2/2] + Cl	[53]
16	H	Cl	—	—	—	2.117	2.122	—	−6.8	—	—	—	−86.7	ditto	[53]
17	H	CN	2.829	1.463	−20.4	1.964	1.923	23.6	3.2	—	—	−83.8[a]	−78.2	4-31 G	[14]
18	H	$\overline{N}H_2$	—	—	—	1.764	1.981	—	27.4	—	—	−34.0[a]	−23.5	ditto	[14]
19	H	$\overline{N}C$	2.752	1.453	−20.6	2.075	1.773	9.7	−10.9	—	—	−103.7[a]	−99.6	»	[14]
20	H_2N	$\overline{F}$	—	—	—	1.728	2.138	—	−13.4	—	—	—	−43.3	»	[14]
21	H_2N	CN	—	—	—	2.169	1.933	—	3.1	—	—	—	−94.7	»	[14]
22	HO	$\overline{C}CH$	—	—	—	1.960	2.054	—	23.4	—	—	—	−0.7	»	[14]
23	HO	Cl	2.28	1.86	−29.0	2.03	2.06	2.3	−26.7	1.45	3.29	−5.7	−46.9	semiemp.	[72]
24	HO	F	2.573	1.461	−22.8	1.775	1.973	9.1	−13.7	1.466	2.579	−38.3	−19.4	4-31 G	[14]
25	HO	CN	2.742	1.456	−24.5	2.018	1.966	27.0	2.5	1.451	3.158	−39.6	−30.8	ditto	[14]
26	F	$\overline{C}N$	2.552	1.459	−27.9	1.902	2.008	29.3	1.4	1.440	2.976	−25.2	−11.4	»	[14]
27	F	$\overline{O}OH$	2.727	1.450	−25.2	1.907	1.832	14.1	−11.1	1.451	2.713	−31.8	−13.8	»	[14]
28	F	NC	—	—	—	1.973	1.899	—	−15.2	—	—	—	−32.7	»	[14]
29	F	$\overline{O}F$	—	—	—	1.986	1.765	—	−26.0	—	—	—	−38.0	4-31 G	[14]
30	F	Cl	—	—	—	2.178	2.072	—	−15.7	—	—	—	−45.0	(8.4/4)→]4 2/2] + Cl	[53]

[a]Complex of type (III).

basis set is 3.06 Å.[14] The bond in the complex can be formed in two ways, to which correspond two local minima on the PES:[12,14]



(II) (III)

For X = Y = F, the energy of complex (II) is lower by only 0.1 kcal mol^{-1} than that of complex (III) and the barrier to the transformation (II) → (III) is 0.8 kcal mol^{-1}.[12] On the other hand, if the substrate is CH_4, then the complex of type (III) is more stable.

The configuration of the TS of reactions (5) corresponds to the apex of the internal barrier. The energy of the TS can be not only higher ($\Delta E > 0$) but also lower ($\Delta E < 0$) than those of reactants (Table 4 and Fig. 4). This has apparently been confirmed by experiment.[36,41,42]

The geometry and the changes in the X–C and C–Y distances in the TS compared with equilibrium X–C and C–Y bond lengths are listed in Table 5 for some reactions. The X–C and C–Y bonds in the TS are longer than the equilibrium bonds by 0.3–0.8 Å and differ greatly for a series of reactions based both on the nucleophile and on the leaving group.

Table 5. The geometry of the TS and the energy characteristics of reactions of type (5); the changes in the length of the axial bonds relative to the equilibrium values in the substrates XCH_3 and CH_3Y (the bond lengths are in Å, the angles in degrees, and the energy in kcal mol^{-1}) (the calculation was performed in terms of the 4-31G basis set using Mitchell's data[14]).

X	Y	R(X–C)	Δ(X–C)	R(C–Y)	Δ(C–Y)	α(H–C–Y)	ΔE	H_{XY}	Q_{XY}
H	F	1.92	0.82	1.73	0.29	96.3	−12.4	−62.5	−66.8
H_2N	F	2.14	—	1.73	0.29	94.1	−13.4	—	−63.3
HO	F	1.97	0.42	1.78	0.34	93.2	−13.7	−15.5	−49.4
HCC	F	2.11	0.64	1.84	0.40	90.3	−5.0	−21.3	−48.7
CH_3O	F	1.94	0.46	1.82	0.38	90–91.5	−4.2	—	−5.7
H	CN	1.96	0.86	1.92	0.48	97.5	3.2	−63.4	−78.2
H_2N	CN	2.17	—	1.94	0.49	95–96.2	2.1	—	−54.7
HO	CN	2.02	0.57	1.97	0.53	95–95.8	2.5	−15.1	−30.8
F	CN	1.96	0.46	2.01	0.57	92.8	1.4	2.7	−11.4
H	NC	2.08	0.98	1.77	0.33	99.6	−10.8	−83.1	−99.6
H	CN	1.96	0.86	1.92	0.48	97.5	3.2	−63.4	−78.2
H	F	1.92	0.82	1.73	0.29	95.3	−12.4	−62.5	−66.8
H	CCH	1.89	0.79	2.00	0.54	95.1	23.2	−42.4	−48.2
H	OH	1.84	0.74	1.84	0.39	91.7	5.5	−47.0	−47.0
H	NH_2	1.76	0.66	1.98	—	94.6	27.4	—	−23.5
H	H	1.74	0.64	1.74	0.64	90	48.8	0	0
F	OF	1.99	0.55	1.77	0.33	93.3	−26.0	—	−38.0
F	NC	1.97	0.53	1.85	0.41	95.2	−15.2	—	−32.7
F	OC_2H_3	1.94	0.50	1.82	—	91–97	−12.0	—	−22.9
F	OOH	1.91	0.47	1.83	0.38	90.2	−11.4	−6.6	−13.8
F	NC	1.90	0.46	2.01	0.56	92.8	1.4	2.7	−11.4

It was noted earlier[14,32,72] that Hammond's postulate holds in the X_i + CH_3Y reactions, which is illustrated in Table 5. This is a familiar, consistent relation between the structure of the TS and the heat of reaction, according to which the position of the TS shifts less along the reaction coordinate the higher the heat change Q. The change in the valence angle Δ(H–C–Y) or the increase in the bond length Δ(C–Y) in TS of the type $[XCH_3Y]^-$ compared with the equilibrium values in the substrate CH_3Y can be adopted as measures of the above shift. Table 5 shows that both quantities are correlated with Q. This apparently exhausts the simple regularities in gas-phase reactions. The correlation usually postulated between the height of the activation barrier of the reaction ΔE and the heat of reaction Q is not observed, in agreement with gas-phase experiments, if it is assumed that the measured reaction rate constant characterises the height of the barrier ΔE (Table 2).

The lack of simple correlations for gas-phase reactions of the S_N2 type can be accounted for by two causes. Firstly, for a complex two-well profile of the potential curve, the conditions essential for the derivation of the Bell–Evans–Polanyi principle or Hammond's postulate do not hold (they are considered in Appendix 2). From this standpoint, one is more justified in expecting a correlation between the geometry of the TS and the heat of the "complex → complex" stage, which is equal to H.

The estimation of reactivity-nucleophilicity, the mobility of the leaving group (nucleofugacity), etc. from calculated data is also difficult owing to the complex form of the PES. An uncertainty arises because it is not known which of the calculated quantities, ΔE or E, should be used as the measure of the reactivity. Furthermore, as stated in Section III.2, the kinetic models for the description of multistage S_N2 processes are not unambiguous and it is not clear whether the characteristics of the potential curve are susceptible to a simple kinetic interpretation.

Secondly the lack of simple relations is associated with the fact that the replacement of X or Y in the reaction centre XCY alters the structure of the TS too drastically. For example, this is manifested in the length of the axial bonds. Table 5 shows that the quantities Δ(C–Y) differ in the range 0.1–0.3 Å even in narrow series. Different TS actually correspond to series in which the nucleophile X or the leaving group Y are altered. This explains why the experimental nucleophilicity series (variation of X) depend on the leaving group Y and the nucleofugacity series (variation of Y) depend on the nucleophile X.[37,72]

4. Attempts at a Theoretical Study of Reactions in Solution. Problems Involving Allowance for the Medium

The gas-phase experiments and quantum-chemical calculations examined above refer to reactions of isolated chemical systems. However, S_N2 reactions in solution are of direct practical interest. They require special consideration, as can be seen from the following facts:

(1) The rates of typical S_N2 reactions decrease by 10–20 orders of magnitude on passing from the gas phase to a polar solvent[36,39,78] [the logarithm of the rate constant for the F^- + CH_3Cl reaction at 25 °C is 11.7 (litre mol^{-1} s^{-1}) in the gas phase and −7.8 (litre mol^{-1} s^{-1}) in water].

(2) The activity series of nucleophiles can be different in the gas phase and in solution and also vary as a function of the solvent (the gas-phase activity series $F^- > Cl^- > Br^- > I^-$ is inverted on passing to proton-donating media[79]).

(3) The solvent can alter the mechanism of an S_N2 reaction: in solution the latter can proceed via a preliminary stage involving the formation of ion pairs up to the change of the mechanism to the S_N1 type.

Such a marked influence of the solvent on the chemical process is specific to reactions with participation ions. Strong electrostatic (ion–dipole) interactions arise in these systems. They in fact determine the characteristic features of reactions in polar media. The intensity of the ion–dipole interactions is comparable to that of interactions responsible for the chemical reaction proper in an isolated system. Any theory, quantitative or qualitative, claiming to explain the kinetics of S_N2 reactions in solution cannot ignore the presence of the medium.

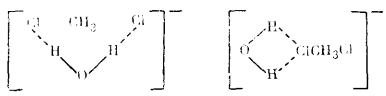
Attempts at experimental[33,80–83] and theoretical[62] study of the influence of the solvent have been undertaken in relation to S_N2 reactions with participation of a small number of solvating molecules. In gas-phase experiments with hydrated nucleophilic species,[80,81] i.e.

$$HO^- \cdot n H_2O + CH_3Br \begin{cases} \longrightarrow HOCH_3 + Br^- \cdot n H_2O \ , & (11) \\ \longrightarrow HOCH_3 + Br^- + n H_2O \ . & (12) \end{cases}$$

measurements were made of the rate constants (in cm^3 molecule^{-1} s^{-1}) and the following values were obtained at 300 K: 10^{-9} ($n = 0$); $(6 \pm 2) \times 10^{-10}$ ($n = 1$); $(2 \pm 1) \times 10^{-12}$ ($n = 2$); 2×10^{-13} ($n = 3$); in aqueous solution: $k = 2.3 \times 10^{-25}$ cm^3 molecule^{-1} s^{-1}.[78] The processes follow pathway (12), which is preferred for thermodynamic reasons: when $n \geq 3$, reaction (11) becomes endothermic. Indeed, it has been found[81] that the ionic ratio in the reaction product $Br^-.H_2O/(Br^- + Br^-.H_2O) = 0.04–0.07$.

Mechanism (12) has also been confirmed by systematic study of the reaction $X^-.nS + CH_3Y \rightarrow XCH_3 + (n - m)Y^- + mS$ (Y = Cl or Br; X = OD, CH_3O, C_2H_5O, CH_3COCH_2, HCOO, or CH_3COO).[82] It is of interest to compare with these data the quantum-chemical calculation of the PES for the reaction $Cl^-.nH_2O + CH_3Cl \rightarrow ClCH_3 + Cl^-.nH_2O$ ($n = 0, 1, 2$) by a non-empirical method (3-21G basis set) with complete optimisation of the geometry.[62]

According to the calculation, the prereaction electrostatic complexes are formed also in the case of the solvated nucleophile. Solvation increases their energy and the height of the internal barrier E (Fig.4). The relief of the PES with one and especially two water molecules becomes very much more complex: intermediate structures, corresponding to different mechanisms of the transfer of H_2O molecules from the nucleophile to the leaving group, appear. Two TS with similar energies have been found for $n = 1$:



The first corresponds to the simultaneous occurrence of the chemical and solvation rearrangements, while in the second the solvation rearrangement follows the chemical rearrangement. For $n = 2$, the following consecutive mechanism is energetically preferable: transfer of H_2O—chemical rearrangement—transfer of H_2O:

$$(H_2O)_2 \cdot Cl^- + CH_3Cl \rightarrow H_2O \cdots Cl^- \cdot CH_3Cl \cdots H_2O \rightarrow$$
$$\rightarrow H_2O \cdots ClCH_3 \cdot Cl^- \cdots H_2O \rightarrow ClCH_3 + Cl^- \cdot (H_2O)_2 \ .$$

Several alternative reaction pathways have been observed together with that indicated above. The simultaneous occurrence of the H_2O transfer and of the chemical rearrangement is the least favourable pathway.

Both experiment and calculation demonstrate the importance of solvation effects. On the other hand, it is evident that systems with a small number of solvent molecules are not successful models of reactions in solution. Indeed, although the measured constants did decrease, they remained within the range of "gas-phase" values. The formation of a desolvated anion in the reaction products is a specifically gas-phase mechanism, which does not occur in solution. The complex mechanisms of the transfer of water molecules noted in the calculation also have hardly any bearing on the real mechanisms in solution, where a collective rearrangement of the solvation shell, involving simultaneously many solvent molecules, is most probable.

The necessity to take into account explicitly a large number of solvent molecules is the main problem of the modern theory of chemical reactions in polar media. Two methods for its solution are being developed.[84,85] The so-called supermolecular approach considers the chemical system and the molecules of the medium on an equal basis in a single quantum-chemical calculation of the PES. An example is provided by the calculation described above.[62] It is clear from its consideration that the "supermolecules" for which the calculation is made must be fairly large. An analogous calculation of the solvation energies of ions with model potentials (which is technically incomparably simpler than the calculation of the PES) requires an explicit consideration of at least three coordination spheres, i.e. several hundred solvent molecules. In order to obtain concordant quantitative results, it is essential to optimise their positions and orientations, which are self-consistently determined by the electric field of the entire assembly of species forming the supermolecule and not only by the field of the "parent" ion. If account is taken of the multiplicity of the energy minima and the corresponding multiplicity of the reaction mechanisms, which is inevitable in such an investigation (an indication of this can be seen even in the simplest example discussed), then one can imagine how great are the technical difficulties in the solution of the problem.

Recent calculations for the $Cl^- + CH_3Cl$ reaction in water[75,86] and in dimethylformamide (DMF) [87] have demonstrated the present possibilities of this branch of research. The potential gas-phase reaction profile was calculated by a non-empirical method in terms of the 6-31G basis set. The interaction of the chemical subsystem with solvent molecules was taken into account with the aid of empirical atom–atom potentials calibrated against preliminary non-empirical calculations for simple model systems. This made is possible to take into account 250 water molecules and 180 DMF molecules surrounding the chemical subsystem. The configuration of the solvation shell was optimised by the Monte Carlo method. As a result of the calculation, the minima on the PES, to which correspond the electrostatic complexes found, as usual, for the gas phase, disappeared for the reactions in solution. The observed heights of the potential barriers proved to be 26.3 kcal mol^{-1} for the reaction in water and 19.3 kcal mol^{-1} for the reaction in DMF. The corresponding experimental activation energies are 26.6 and 22.7 kcal mol^{-1}.

In the second approach, the medium is regarded as a dielectric continuum in which the chemical system is immersed. For elementary situations, the solvation energy U can be determined from simple formulae. For example, for a spherical ion with a radius r in a medium having a dielectric constant ε, it can be calculated from the Born formula

$$U = e^2(1 - 1/\varepsilon)/2r \ .$$

In order to describe the chemical reaction in the continuous model, it is necessary to calculate the energy of the electrostatic interaction of the chemical system (with a complex distribution of electric charges) with the dielectric medium. The calculation is based on the same principles which lead to the Born formula, but in this case a cumbersome computer computation is required.[88] Ideally the calculation should be self-consistent, i.e. it should take into account the converse effect of the potential of the medium on the structure of the chemical system and the distribution of the electric charge in the latter.[89,90] There exist serious difficulties both in the selection of the dielectric constant (it does not agree with the usual macroscopic value) and in the selection of the size of the cavity in which the reacting system is placed. The

existing methods for the estimation of the size of the cavity, for example from the polarisability,[91] are not unambiguous.

All the foregoing considerations are based on the assumption that the solvation effects can be described within the framework of the activated complex theory. Only in this case is it sufficient to consider the stationary configurations of the initial and transition states of the reacting species + medium system. This is by no means evident. The orientational movements of solvent molecules which optimise the energy may not keep up with the movement of the reacting molecule; non-equilibrium reaction conditions then obtain.[92,93] In the continuous model the effective dielectric constant of the non-equilibrium medium diminishes.

As a consequence of all these problems, the published calculations of the PES for ion–molecule reactions in a polar solvent are usually far from perfect. The frankly empirical approaches employed have been discussed, for example, in the review of Abronin et al.[84] For nucleophilic substitution reactions, the continuous model has been used in calculations for the $X^- + CH_3F$ reactions, where X = OH or CN.[91]

The most elementary approach links the solvation effect to the shift of the energies of the frontier MO. For S_N2 reactions, calculations by the STO-3G method showed[94] that the formation of clusters of nucleophilic anions with several water molecules reduces the energies of the HOMO of the nucleophile, the effect increasing in the sequence $I^- < Br^- < Cl^-$. According to perturbation theory, the decrease of the HOMO level of the nucleophile, which increases the difference between this energy and the energy of the LUMO of the substrate, reduces the reactivity of the Cl^- ion to a greater extent than that of Br^- ion and the latter to a greater extent than the reactivity of I^-. Hence it follows that the nucleophilicity series $Cl^- > Br^- > I^-$, characteristic of aprotic solvents and the gas phase, can be inverted in a protic solvent.

We shall now consider the main causes of the changes which the PES for gas-phase S_N2 reactions undergo in solution. One of them is well known and consists in the fact that the electric charge in the TS is delocalised and the corresponding solvation energy is much smaller than the solvation energy of the nucleophilic ion with a localised charge. The loss of solvation energy has been estimated in several semiempirical calculations for the $F^- + CH_3F$ reaction.[74,95,96] According to the calculation by the MINDO/3 method, it amounts to 31 kcal mol^{-1}.[96] Calculation by the CNDO/2 method leads to clearly high values, which vary in the range 62–100 kcal mol^{-1} as a function of the number of water molecules incorporated in the solvation shell.[74] A similar value (105 kcal mol^{-1}) has been obtained in the solvation model on the basis of the CNDO/2 method.[95] In the continuous model, the solvation energy differences calculated by the CNDO/2 method for the $X^- + CH_3F$ reaction[91] are 43 (X = OH) and 12.7 kcal mol^{-1} (X = CN).

Although the semiempirical methods used are unsuitable for calculations on gas-phase reactions, the estimated solvation effect, which amounts to several tens of kcal mol^{-1}, is likely to be correct in terms of order of magnitude.

The second cause of the change in the form of the potential curve on passing from the gas phase to the solution becomes evident when the energies of the successive desolvation of ions are examined in relation to $F^-.nH_2O$: $\Delta H_{n,\,n-1}$ = −13.2 (n = 5), −13.5 (n = 4), −13.7 (n = 3), −16.6 (n = 2), and −23.3 kcal mol^{-1} (n = 1).[97] The reaction with the substrate is preceded by the formation of a contact ion–molecule pair with partial desolvation of the ion and the substrate in accordance with the idealised scheme

$$X^-\cdot nS + CH_3Y\cdot mS \rightleftarrows [X^-\cdot CH_3Y][(n+m-2)S] + 2S, \qquad (13)$$

where S is a solvent molecule. At this stage the amount of energy expended is approximately equal to the energy of the removal of one H_2O molecule from the complete hydration shell of the nucleophilic ion. Together with the remaining solvation effects, it amounts to ~20 kcal mol^{-1} for F^-. This is sufficient to understand why the formation of the electrostatic complexes is not observed in a polar solvent: the energy of their formation in the gas phase is as a rule less than the positive heat of reaction (13). The potential curves for the next, chemical stage proper, i.e.

$$[X^-\cdot CH_3Y][(n+m-2)S] \rightarrow \text{products}, \qquad (14)$$

are smoothed out acquiring the usual profile illustrated in Fig. 5. The barriers indicated by dashed lines correspond to the preliminary reaction (13) in which the solvation shells of the reactant are rearranged. In stage (14) the solvent exerts its influence in the usual way—via the shifts of the energies of the initial and transition states.

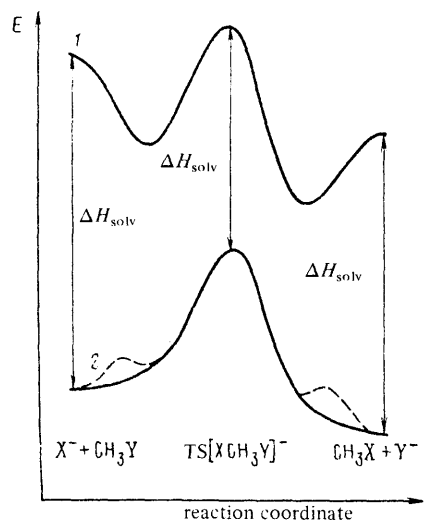


Figure 5. The change in the PES profile for an S_N2 reaction on passing from the gas phase (curve *1*) to a polar solvent (curve *2*). The dashed lines are explained in the text.

These considerations apply in the model calculation for reaction (14) with X, Y = F, Cl, or H.[98] The water molecules were replaced by point charges, forming dipoles. Their disposition and magnitudes were chosen so as to reduce the observed total solvation energies of the anions and the energies of their partial desolvation. In the calculation for reaction (14), one dipole each was removed from the solvation shell of the nucleophile and the substrate. In each external electric field specified in this way, the PES was calculated by a semiempirical method specially devised for calculations for the corresponding gas-phase reactions.[76,77]

The calculation reproduced the smooth potential profile for the reaction, because postulates designed to achieve this result were incorporated in the basis of the model of solvation shells adopted. The potential barrier found reflects the experimentally observed trends. It is of interest to compare the geometries of the TS found in solution and in

the gas phase for the F^- + CH_3Cl reaction, where these changes are most pronounced: $R(C-F)$ = 2.06 Å in solution and 2.14 Å in the gas phase and $R(C-Cl)$ = 2.35 Å and 2.24 Å in solution and in the gas phase respectively.

Thus, even if we confine ourselves to the description of the reactions in solution with the aid of the activated complex theory and the non-equilibrium character of the solvation effect is neglected, their standard treatment requires a significant revision. The calculation of the energy changes employing the "gas-phase" configurations of the reactants and of the activated complex is inadequate. It is necessary to take into account the distortion of the configuration of the PES in the region of the corresponding points under the influence of the medium. In the example considered, it has the character of a moderate correction in the case of the TS. However, in the region of the initial state the deformation of the PES is so great that one is justified in speaking of a change in the reaction mechanism.

5. The Effect of Substituents

The effect of substituents R both in the nucleophile $X(R^1)$ and in the substrate $C(R^2)-Y$ or $C-Y(R^3)$ on the reactivity can be naturally accounted for within the framework of a three-centre four-electron model of the open-chain TS:

$$\underset{\alpha_x}{[X(R^1)} \xrightarrow{\beta_{cx}} \underset{\alpha_c}{C(R^2)} \xrightarrow{\beta_{cy}} \underset{\alpha_y}{Y(R^3)}]^- \quad ;$$

(IV) (TS)

$$\underset{\alpha_x}{X^-(R^1)} + \underset{\alpha_c}{C(R^2)} \xrightarrow{\beta_0} \underset{\alpha_y}{Y(R^3)} \quad \text{(initial state).}$$

(V)

The corresponding Coulombic (α) and resonance (β) integrals are indicated in Schemes (IV) and (V) (the Hückel method).

It was noted above that the variation of the atoms X and Y alters the structure of the reaction centre so much that simple correlations are lacking in the corresponding reaction series. The introduction of substituents R for fixed X and Y makes it possible to construct narrow reaction series in which systematic changes in reactivity are observed.

The corresponding kinetic measurements have been as a rule made in polar aprotic solvents, which makes it possible to to adopt the usual smooth PES profile for the reactions considered. Other aspects of the effect of the solvent are usually ignored in a qualitative treatment.

According to perturbation theory for the interaction ($\beta_{cx}/\beta_0 \ll 1$, although this condition is by no means evident), the interaction of the highest occupied AO (MO) of the nucleophile $|x\rangle$ having the energy α_x with the LUMO of the substrate $|\sigma^*\rangle$ having the energy ε_σ makes the main contribution to the change in the height of the potential barrier. Attempts have sometimes been made to explain the influence of the substituent by its effect on the energies of the corresponding frontier MO (i.e. on α_x or ε_σ). According to the Hückel MO theory, the interaction should alter α_x (for the substituent R^1 in the nucleophile) or ε_σ (for substituents in the substrate) to a greater or lesser extent depending on the nature of the substituent. The interaction with electron-donating substituents (heteroatom with an electron pair) in the α-position induces the greatest effect. It is to be expected that the introduction of such substituents into the nucleophile should increase the relative reactivity (the α-effect), while their introduction into the substrate should diminish it. This model presupposes a purely resonance interaction of the substituent with the reaction centre.

The above treatment presupposes, in particular, that the levels of the substituent MO always lie below the level of the nucleophile HOMO. This is not always so and cases are known where direct calculation does not confirm the increase of the HOMO energy level predicted by the Hückel MO theory.[99] The effect is extremely sensitive to the spatial orientation of the substituent or more precisely of its unshared electron pair. This has been demonstrated by a non-empirical calculation of potential barriers for the $H^- + CH_3R \rightarrow CH_3R + H^-$ reactions, where R = OH, NH_2, or BH_2.[100]

We shall consider a reaction series with variation of a nucleophile of the type $X(R^1)$. In schemes (IV) and (V) it is characterised by the two variable parameters α_x and β_{cx}. For the standard system with $X(R^1_0)$, we shall designate them by α^0_x and β^0_{cx}. The energy of system (IV) relative to the standard system is then given by the following expression according to the perturbation theory:

$$\Delta E = E - E_0 = q^0_x(\alpha_x - \alpha^0_x) + 2P^0_{cx}(\beta_{cx} - \beta^0_{cx}) \ , \qquad (15)$$

where q^0_x is the electronic charge on X and P^0_{cx} is the order of the C–X bond in the TS of the standard system. If account is taken of the fact that α is a measure of the effective electronegativity of the atom X and β is a measure of the effective capacity for the formation of a bond, then Eqn.(15) can be regarded as an analogue of the two-parameter empirical Edwards or Todesco–Bartoli equation[101,102] [in order to complete the derivation, it is necessary to formulate the analogous equation for the initial state (V) and subtract it from Eqn.(15)].

Suppose that only the substituents R^1 at X are varied. One can then fix $\beta_{cx} = \beta^0_{cx}$, which yields a one-parameter equation of the Hammett type. As will be shown below, it is then not essential to apply perturbation theory and α_x can be varied within wide limits.

The variation of the substituents R^2 at C or R^3 at Y can be treated in the same way by varying the corresponding Coulombic parameters α_c or α_y. This corresponds to the induction model of the effect of substituents on reactivity which is an alternative to the resonance model mentioned above.

We shall designate the electronic energies of systems (IV) and (V) by $E(\alpha_i)$ and $E^0(\alpha_i)$ respectively ($i = x, c, y$). Suppose that q_i and q^0_i are the corresponding electronic charges in systems (IV) and (V). Since $q_i = \partial E/\partial\alpha_i$,[103] we have

$$E(\alpha_i + \Delta\alpha) = E(\alpha_i) + \int_{\alpha_i}^{\alpha_i+\Delta\alpha} q_i \, d\alpha \ ;$$

$$E^0(\alpha_i + \Delta\alpha) = E^0(\alpha_i) + \int_{\alpha_i}^{\alpha_i+\Delta\alpha} q^0_i \, d\alpha \ .$$

The reactivity is determined by the quantity

$$\Delta_i = \Delta(\alpha_i + \Delta\alpha) - \Delta(\alpha_i) = [E(\alpha_i + \Delta\alpha) - E^0(\alpha_i + \Delta\alpha)] - [E(\alpha_i) - E^0(\alpha_i)] .$$

We thus obtain the expression

$$\Delta_i = \int_{\alpha_i}^{\alpha_i+\Delta\alpha} (q_i - q^0_i) \, d\alpha \ . \qquad (16)$$

If q_i and q^0_i change only slightly, the result obtained agrees with the conclusion reached from perturbation theory:

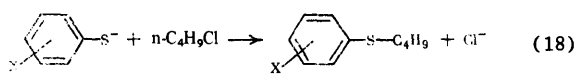
$$\Delta_i \cong (q_i - q^0_i)\Delta\alpha \ . \qquad (17)$$

When α_i changes by $\Delta\alpha$, the system becomes more or less reactive depending on whether the relative stabilisation energy Δ_i is positive or negative. Consequently analysis of

reactivity for a specified $\Delta\alpha$ reduces to the study of the sign of the difference $q_i - q_i^0$ in Eqn.(16) or (17). In the former case $q_i - q_i^0$ is assumed to be a variable-sign quantity.

The sign of $q_i - q_i^0$ for $\alpha_c \gg \alpha_x, \alpha_y$ is examined in Appendix 1. The results of the analysis are used below.

(1) Substituent in the nucleophile: $q_x - q_x^0 < 0$. The reactivity of the nucleophile (the nucleophilicity) increases if the introduction of the substituent diminishes the electronegativity of the nucleophile: $\Delta_x < 0$ if $\Delta\alpha > 0$. This conclusion is consistent with experiment (and the conclusion reached from the resonance model). An increase in basicity (occurring simultaneously with the decrease of electronegativity) is known to increase the reactivity of the nucleophile as a rule. An analogous conclusion has been reached[104] from thermochemical measurements, with the aid of which it was estimated whether the TS is close to either the reactants or products along the reaction coordinate: the TS moves towards the reactants with increase of the basicity of the nucleophile. The rate constants for the $RO^- + CH_3Cl$ gas-phase reactions with R = alkyl (Table 2) and for heteroatomic substituents are correlated with Taft σ^* constants (in this case one should recall that gas-phase two-well potential curves introduce an additional uncertainty into the analysis). The most convincing confirmation of the conclusion concerning the character of the influence of the substituent in the nucleophile is provided by the correlation between the rate constants for the reaction

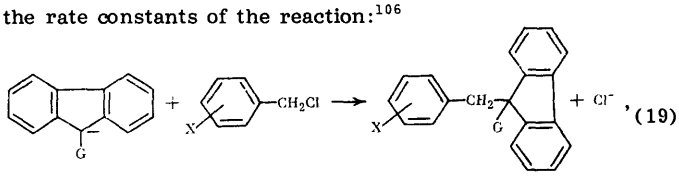


(18)

and the Hammett σ constants for the substituents X [105] (X = NH_2, CH_3O, CH_3, Br, Cl, CF_3, OH, or NO_2). In this series the reaction rate varies by four orders of magnitude.[105]

(2) Substituent in the leaving group: $q_y - q_y^0 > 0$. In this case $\Delta y > 0$ for $\Delta\alpha > 0$. The reactivity diminishes if the substituent reduces the electronegativity of the leaving group (or increases its basicity), which agrees with the claim[104] that an increase in the basicity of the leaving group shifts the TS towards the products and also with the experimental observation that the nucleofugacity diminishes with increase of the basicity of the leaving group.

(3) Substituent at the central atom of the substrate: $q_c - q_c^0 > 0$ if $\beta_{cy}/\beta_0 > \varepsilon$ and $q_c - q_c^0 < 0$ if $\beta_{cy}/\beta_0 < \varepsilon$. In this case the reactivity series depends on the extent to which the C–Y bond in the TS is loosened compared with that in the initial state. The critical ratio of the resonance parameters is always less than unity. For the symmetrical case (X = Y), $\varepsilon = 2^{-\frac{1}{2}}$ (see Appendix 1). This estimate probably changes little when X ≠ Y if the main condition $\alpha_c \gg \alpha_x, \alpha_y$ remains in force. At any rate it is to be expected that the quantity $q_c - q_c^0$ is small in absolute magnitude, i.e. the effect of substituents must be appreciably weaker than in the first two cases. A linear correlation with the σ constants of the substituents X is indeed observed for the rate constants of the reaction:[106]



(19)

where G = phenyl, 2-benzenesulphonyl, CN, or CH_3. The rate constants for different X differ within the limits of 1–2 orders of magnitude. It then follows from the slope of the straight line that $q_c - q_c^0 > 0$. According to calculations by the MNDO method, $q_c - q_c^0 \approx 0.3$ e.s.u. for the $Cl^- + RCl$ systems.[73] The deviation of individual points from the correlation can probably be accounted for both by steric effects and by the inversion of the relation $\beta_{cy}/\beta_c \gtrless \varepsilon$: the lengths of the axial bonds vary within fairly wide limits as a function of the substituent—for example from 1.592 Å for R = F to 1.736 Å for R = OH in the TS $[HCH_2RH]^-$.[14] The reactivities estimated by calculation fit the Hammett correlation. This has been demonstrated in the case of the $Cl^- + XC_6H_4CH_2Cl$ reactions for which calculations were made by the CNDO/2 (X = NH_2, CH_3, F, CF_3, or NO_2) [107] and MNDO (X = F, OH, OCH_3, NH_2 or NO_2) [73] methods.

6. The Application of Correlation Equations

The relative reactivities of a series of nucleophiles (nucleophilicity) can be more or less satisfactorily described by a four-parameter equation of the Edwards type:[101,102]

$$\lg(k_x/k_{x_0}) = A(P_x - P_{x_0}) + B(H_x - H_{x_0}) , \qquad (20)$$

where P_x is a measure of the polarisability of the nucleophile, H_x a measure of its basicity, linked directly to its proton affinity, and X_0 the standard nucleophile. More precisely the symbols X and X_0 correspond to the "nucleophile + solvent" pair, because the nucleophilicity depends on the solvent. Thus Eqn.(20) is suitable for the correlation of nucleophilicities in different solvents. The parameters *A* and *B* characterise the substrate and can be used in principle to correlate data for the relative mobilities of the leaving group Y (nucleofugacities).[102] Nevertheless, X and Y are involved in Eqn.(20) asymmetrically, i.e. the significance of the parameters *P* and *H* in relation to X is different from the significance of *A* and *B* in relation to Y.

For a complex anionic nucleophile R^1X^- differing in the substituents in R^-, a relation of the Brønsted type holds satisfactorily:

$$\lg(k_x/k_{x_0}) = B[pK_a(X) - pK_a(X_0)] , \qquad (21)$$

where pK_a are the basicities of the corresponding nucleophiles. Linear correlations of type (21) have been found, for example, for the reactions of substituted fluorenyl and thiophenoxide anions with benzyl and butyl chlorides in DMSO [105,106] [systems (18) and (19)]. Eqn.(21) reduces to Eqn.(20) if the factors associated with the polarisability are constant in the reaction series. Other correlations (the Swain–Scott, Ritchie, etc. correlations) reduce similarly to Eqn.(20) when the reaction series are narrow.[102]

The reactivity in exchange reactions, including those of the S_N2 type, has been discussed in recent years on the basis of the Marcus equation:

$$U_{XY}^{\neq} = \lambda_{XY} - Q_{XY}/2 + Q_{XY}^2/16\lambda_{XY}$$
$$\lambda_{XY} = (\lambda_{XX} + \lambda_{YY})/2 \qquad (22)$$

where $U_{XY}^{\neq}$ is the height of the potential barrier, identified with the observed activation energy, Q_{XY} the heat of reaction ($Q_{XY} < 0$), and $\lambda_{XX} = U_{XX}^{\neq}$ and $\lambda_{YY} = U_{YY}^{\neq}$ are the barriers for thermally neutral symmetrical reactions. An analogous relation can be formulated also for the free energies $\Delta G_{XY}^{\neq}$, $\Delta G_{XX}^{\neq}$, and $\Delta G_{XY}^{\neq}$. Eqn.(22) was first used to describe the rearrangement of the solvation shells of transition metal ions in electron transfer reactions.[108,109] It was then applied to proton transfer reactions[110,111] and also to the transfer of the methyl group in the gas phase[40,41,112] and in solution.[113–115] Since the heat of reaction can be resolved into increments corresponding to X and Y, i.e. $Q_{XY} = Q_X + Q_Y$ (with an accuracy to within a constant independent of X and Y), it follows that Eqn.(22), like

Eqn.(20), is a four-parameter correlation. The Marcus equation is symmetrical relative to X and Y and, in contrast to Eqn.(20), embraces very wide series, including the variation of both the nucleophile and the leaving group. Its non-linearity makes it possible to explain the deviations from the linear Brønsted relations, which are sometimes observed.

The Marcus parameters differ fundamentally from the parameters of the usual correlations. The latter are normally associated with the electronic structures of the reactants in the spirit of the concept of the influence of the structures of the reactants on the reactivity. The parameters in Eqn.(22) are characteristics of the reactivity (or the PES) and not of the electronic structures of the reactants. From the standpoint of the concept indicated, they themselves require explanation. Nevertheless, they have a clear physical significance and in principle can be determined experimentally. The derivation of the Marcus equation from the overall PES for the exchange reactions is examined in Appendix 2.

For gas-phase S_N2 reactions, the Marcus equation has been used in the treatment of kinetic data obtained by the ICR method[40,41,112] and for the systematic treatment of several tens of liquid-phase reactions.[113-115] Its use is restricted by the insufficiency of experimental information about the heats Q (especially in solution) and about the internal barriers λ. In the studies mentioned above, the quantities λ_{XX} and λ_{YY} were assumed to be adjustable parameters and were selected empirically (ΔG_{XX} in Table 6). If X and Y vary in the same series made up of n members, then it is necessary to know n values of the internal barrier λ for the description of $n(n-1)/2$ asymmetric reactions. Since kinetic measurements have usually been made for by no means all asymmetric processes, the number of reference points exceeds only slightly the number of parameters. In this case the empirical adjustment of the latter is unreliable and ambiguous.

Table 6. The free energies of activation ΔG_{XX} in water[103] and the internal barriers E_{XX} (calculation in terms of the 4-31G basis set[14]) for the symmetrical $X^- + CH_3X$ reactions.

X	ΔG_{XX}, kcal mol^{-1}	E_{XX}, kcal mol^{-1}
H	—	57.3
I	23	—
Br	24	—
Cl	27	5.5
F	32	11.7
NO_2	27	—
TosO	35	—
CH_3SO_3	35	—
$C_6H_5SO_3$	36	—
ClO_4	37	—
OH	42	21.2
CN	51	28.5
HS	—	15.5
HOO	—	18 7
FO	—	18 8
CH_3O	—	23.5
H_2N	—	38
NC	—	43 8
HCC	—	50.4

The contribution of solvation to the activation barrier has been estimated from the Marcus equation in terms of the continuous polar medium model.[116-118] It was postulated that the reaction system moves along the chemical ("gas-phase") reaction coordinate s up to a certain intermediate (not corresponding to a saddle point) value s_0. With s_0 fixed, the system is then moved along the coordinates of the medium, i.e. the solvent undergoes a rearrangement. The rearrangement is characterised by the reorganisation energy E_R calculated from the electrostatic formula[93,108,109]

$$E_R = (\varkappa/2) \int \mathrm{d}V\,[D_1(s_0) - D_2(s_0)]^2 ,$$

where $\varkappa$ is the effective dielectric constant and D_1 and D_2 are the vectors of the electrical induction, generated by the charge distribution in the $X^- + CR_3Y$ chemical subsystem, which correspond to the initial and final states of the solvent for the fixed s_0. The integration is carried out over the entire space around the cavity occupied by the chemical subsystem. The estimates made for the simplest forms of the cavity[117,118] have shown that, in water with X = I and Y = F, Cl, or Br, the quantity E_R varies from 60 to 80 kcal mol^{-1}. In this model the activation energy is

$$U^{\neq} = U(s_0) + [E_R/4 + Q(s_0)/2 + Q(s_0)^2/4E_R] .$$

The expression in square brackets describes the rearrangement of the solvent according to Eqn.(22); here the role of λ_{XY} is assumed by the quantity $E_R/4$ and the modified heat $Q(s_0)$ characterises the rearrangement for a fixed s_0. Calculations by this formula have been compared with experiment for many S_N2 reactions in water and acetone[117,118] and the quantities $U(s_0)$ and $Q(s_0)$ were estimated from thermochemical and spectroscopic data.

Thus the contribution of the solvent to λ_{XY} in Eqn.(22) can be expressed in terms of the reorganisation energy E_R. The contribution of the chemical rearrangement proper should be added to it, having calculated such contribution in terms of the internal barriers λ_{XX} and λ_{YY} in Eqn.(22).

Quantum-chemical calculations of the internal barriers are of undoubted interest in this connection (Table 6). Systematic quantum-chemical study of the PES for simple S_N2 reactions[14,59] made it possible to check how well the Marcus equation holds by comparing directly its predictions with the calculated potential barriers. For the description of reactions between electrostatic complexes, $[X^-.CH_3Y] \rightarrow [XCH_3.Y^-]$, the agreement proved to be very satisfactory in the case of 11 X,Y reaction pairs: H, NC; H, CN; H, F; H, CCH; H, OH; F, SH; HO, CN; HO, F; HCC, F; F, OOH; CN^-, F. The height of the barriers was varied within the limits of 50 kcal mol^{-1}. In order to describe the entire two-well potential curve, Eqn.(22) was modified.[14]

It is noteworthy that both the calibration of the Marcus equation and its comparison with the exact calculation have been carried out on the basis of energetically unreliable calculations in terms of the 4-31G basis set. Nevertheless, the fact that this equation describes satisfactorily model quantum-chemical PES over a very wide energy range indicates the possibility of applying it to real S_N2 reactions. This is apparently the only way of treating systematically wide reaction series with different X and Y within the framework of a simple correlation scheme.

As already mentioned (Section III), simpler schemes, such as the Bell–Evans–Polanyi equation (linear dependence of the activation energy on the heat of reaction) and the Brønsted equation (the analogous relation for free energies) are applicable to a reaction series with variable X or Y. Satisfactory Brønsted relations can be observed only by varying the substituent with a constant reaction centre. Linear relations (21) reduce to Brønsted relations if it is assumed that the heats of reaction Q are linearly related to the basicities of the nucleophiles. Comparison of the calculated affinities of nucleophiles for the proton and the methyl cation[14] demonstrated the likelihood of this hypothesis. Thus one may conclude that Brønsted correlations exist for systems (18) and (19) in DMSO with the reaction rate

constants varying in the range of 4–5 orders of magnitude[105,106] (~10 kcal mol^{-1} on the energy scale). A similar conclusion was reached in the study of other systems.[119,120] The absence of a visible curvature in the Brønsted plots within the framework of the Marcus equation shows that the role of the quadratic term in Eqn.(22) is small, i.e. that the ratio Q_{XY}/λ_{XY} is small. It is of interest that this holds against the background of fairly large systematic changes in the structure of the TS (Table 5). In other words, the derivation of linear relations from equations of type (20), always based on the implicit assumption that the reaction centre is constant, is not convincing.

According to an alternative view,[105] over such a wide range of variation of the reactivity, the Marcus curvature should have been manifested and the linearity of the observed correlations is therefore a special effect whose nature is still obscure and at any rate cannot be accounted for within the framework of the Marcus equation.

It may be that there are systematic deviations from Brønsted correlations. An anomalous increase of reactivity has been observed for a heteroatomic substituent with an unshared electron pair in the nucleophile. The corresponding positive deviations from the Brønsted relation have been called the α-effect.[121–123] In solution the α-effect for S_N2 reactions is weak.[123] Measurements in the gas phase for the X^- + CH_3F reactions (X = OH or OOH) led to the conclusion that this effect is absent.[124] Calculation of the heights of the barriers and heats of the X^- + CH_3F reactions (X = HO, CH_3O, HOO, FO, or HCOO) in terms of the 4-31G basis set[14,19] yielded ambiguous results: a satisfactory linear relation can be drawn through these five points. The calculation also failed to reveal anomalies in the geometrical structure of the TS for reactions with α-substituted nucleophiles (Tables 4 and 5) and also in the energy relations for symmetrical reactions (Tables 4 and 6). The authors[14,99] are therefore inclined to assume that in the gas phase the α-effect is absent for S_N2 reactions and its existence in solution is due to differences between the solvation energies of the normal and α-substituted nucleophiles. Reliable data are apparently still insufficient at the present time for the final solution of this problem.

Attempts to improve the Marcus equation for S_N2 reactions have been published.[125,126] The shifts of the TS in the reaction series not only along the reaction coordinate but also at right angles to it have been considered in these models. In other words, a change in the reaction pathway curve for the reaction series is permitted. Additional empirical parameters appear in the corresponding correlation equations which makes the practical application of such equations relatively ineffective.

IV. APPENDICES

Appendix 1

Analysis of the sign of the quantity $\Delta q_i = q_i - q_i^0$ subject to the condition $\alpha_c \gg \alpha_x, \alpha_y$.

(1) Substitution at the nucleophile.

Here $q_x^0 = 2$ and $1 < q_x < 2$ [127] as a consequence of the partial delocalisation of the unshared electron pair. Thus, $\Delta q_x > 0$.

(2) Substitution at a carbon atom.

In this case $0 < q_c^0 < 1$ and $0 < q_c < 1$, so that the analysis is more complex. We shall carry it out for the symmetrical X–C–X system assuming that the results do not change greatly for X ≠ Y, provided that $\alpha_c \gg \alpha_x, \alpha_y$.

It is possible to introduce the group orbitals $|x_+\rangle = (|x_1\rangle \pm |x_2\rangle)/2^{1/2}$, where $|x_1\rangle$ and $|x_2\rangle$ are the atomic orbitals of different atoms X. The corresponding matrix elements are equal (for the significance of the notation, see Section III):

$$\langle x_+|h|x_+\rangle = \langle x_-|h|x_-\rangle = \alpha_x \ ;$$
$$\langle x_+|h|c\rangle = 2^{1/2}\langle x|h|c\rangle = 2^{1/2}\beta_{cx} \ ;$$
$$\langle x_-|h|c\rangle = 0 \ .$$

As a consequence of symmetry, only one lowest MO of the X–C–X system is bonding; the MO which follows it is non-bonding and does not contribute to q_c. The lowest MO can be formulated thus:

$$\psi_1 = c_{11}|c\rangle + c_{12}|x_+\rangle$$

and the MO which follows it can be written as follows:

$$\psi_2 = c_{21}|c\rangle + c_{22}|x_-\rangle \ .$$

The coefficients of ψ_1 are found from the secular equation for a quasi-two-centre "bond":

$$\underset{\alpha_c}{C}\ \overset{2^{1/2}\beta_{cx}}{\text{———}}\ \underset{\alpha_x}{X_+} \ .$$

In the initial state a two-centre bond is considered (see Section III):

$$\underset{\alpha_c}{C}\ \overset{\beta_0}{\text{———}}\ \underset{\alpha_x}{X} \ .$$

These bonds differ formally only by the value of the resonance integral. We thus obtain

$$\Delta q_c > 0, \quad \text{if} \quad \beta_{cx}/\beta_0 > 1/2^{1/2} \ ;$$
$$\Delta q_c < 0, \quad \text{if} \quad \beta_{cx}/\beta_0 < 1/2^{1/2} \ .$$

(3) Substitution at the leaving group.

An unambiguous conclusion can be reached most simply for the symmetrical situation X = Y examined above. It is sufficient to use the symmetry condition $q_x = q_y$ and the normalisation condition $q_x + q_c + q_y = 4$. Then $q_y = 2 - q_c/2$. In the initial state $q_y^0 = 2 - q_c^0$ according to the normalisation condition. Hence $\Delta q_y = q_c^0 - q_c/2$. This quantity is known to be positive when $\Delta q_c < 0$ (i.e. $\beta_{cx}/\beta_0 < 2^{-1/2}$). In the general case the difference between q_c and q_c^0 is small ($q_c/q_c^0 \cong 1$), so that the relation $\Delta q_y > 0$ always holds.

Appendix 2. The Marcus Equation

The canonical Marcus formula for the height of the chemical reaction barrier has the form of Eqn.(22), where Q_{XY} is the heat of reaction and λ_{XY} the so-called "internal barrier". It was obtained for electron transfer reactions,[108,109] whose PES were modelled by two intersecting paraboloids. The derivation of Eqn.(22) has been revised[110] in relation to the usual reactions with rearrangement of chemical bonds, for which the parabolic approximation of the PES is far from realistic. Subsequently it was modified by various investigators.[128–133]

Eqn.(22), which establishes a non-linear relation between the height of the potential barrier and the heat of reaction, can be obtained as a consequence of simple geometrical properties of PES of a specific type. In the derivation given below, this factor is specially emphasised.

Fig.6a illustrates schematically the two-dimensional c curve—the coordinate of a typical exchange reaction. The points s_1 and s_2, corresponding to the reactants and products, are selected on it (these can be electrostatic or

van der Waals minima; in principle, it is sufficient to choose any points in the asymptotic regions of the reactants or products, where the reaction coordinate becomes a straight line). Suppose that σ is the length of the arc ss_1 linked to the current coordinate s on the c curve and σ_0 is the length of the arc s_2s_1. The variable $\alpha = \sigma/\sigma_0$ is a natural characteristic of the movement of the system from the reactants to the products on the PES.

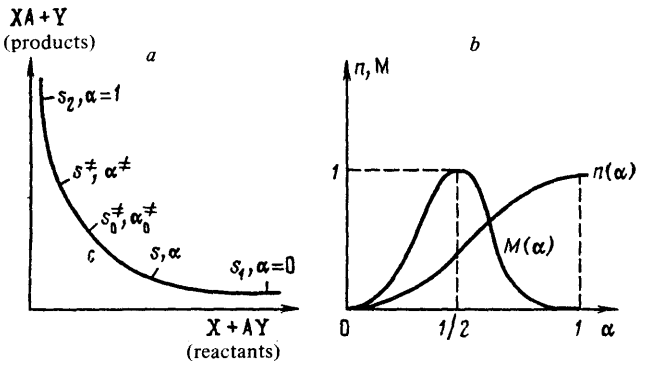


Figure 6. Illustration of the derivation of the Marcus equation: *a*) the S_N2 reaction coordinate; *b*) kinetic [$M(\alpha)$] and thermodynamic [$n(\alpha)$] interpolation functions; $\alpha = (s - s_1)/(s_2 - s_1)$.

The PES profile $U(\alpha)$ is represented by the relation

$$U(\alpha) = n(\alpha)U(1) + \lambda M(\alpha);\ U(1) = Q \qquad (23)$$

The interpolation functions $n(\alpha)$ and $M(\alpha)$ are specified in the following form (see Fig. 6*b*):

$$\begin{aligned} &0 \leqslant n(\alpha) \leqslant 1;\ n(0) = 0;\ n(1) = 1;\ n(1/2) = 1/2;\ dn/d\alpha > 0 \\ &0 \leqslant M(\alpha) \leqslant 1;\ M(0) = M(1) = 0;\ M(1/2) = 1;\ \frac{dM}{d\alpha}(1/2) = 0; \end{aligned} \qquad (24)$$

$$\frac{d^2M}{d\alpha^2}(1/2) = -k < 0 \qquad (25)$$

According to these definitions, both functions are normalised to unity, $n(\alpha)$ increases monotonically and $M(\alpha)$ has a single maximum at $\alpha = 1/2$. The $U(\alpha)$ potential curve is divided into two components: one component (the "thermodynamic contribution") describes the monotonic evolution of heat and the other (the "kinetic contribution") is responsible for the barrier. The main hypothesis is that $n(\alpha)$ and $M(\alpha)$ are the same in the reaction series, i.e. are the same for all X and Y. Eqns. (24) and (25) do not impose serious limitations on the choice of these functions (with the exception of the symmetrical choice of the value of *n* at the point $\alpha = 1/2$—a condition which is discussed below). The methods of their detailed specification discussed in the literature[129,130,132] are always arbitrary and are unsuitable for further treatment.

The quantity $U(1)$ is the heat change and λ is determined from Eqn. (23) for symmetrical reactions [X = Y: $U_{XX}(1) = 0$]:

$$U_{XX}(1/2) = U^{\neq}_{XX} = \lambda_{XX}\ . \qquad (26)$$

The following approximation has been adopted for asymmetric reactions:[110]

$$\lambda_{XY} = (U^{\neq}_{XX} + U^{\neq}_{YY})/2\ . \qquad (27)$$

Subsequently the function (23) is expanded in Taylor's series in the vicinity of the point $\alpha = 1/2$ and the position of the maximum $\alpha^{\neq}$ is found taking into account the quadratic terms of the expansion on the basis of the condition

$$\left.\frac{dU}{d\alpha}\right|_{\alpha^{\neq}} = 0\ . \qquad (28)$$

Elementary calculations using Eqns. (23)–(25) yield

$$U^{\neq} = U(\alpha^{\neq}) = \lambda + U(1)/2 + (n')^2[U(1)]^2/2k\lambda\ , \qquad (29)$$

where

$$n' = \frac{dn}{d\alpha}(1/2)\ .$$

This is the generalised Marcus formula. The canonical formula (22) is obtained from the latter by putting $(n')^2/k = 1/8$. This result is obtained if the PES profile has the form of two intersecting parabolas.[108] According to the above derivation, the quantity $(n')^2/k$ is a characteristic of the interpolation functions $n(\alpha)$ and $M(\alpha)$, which should be selected in such a way that the PES profile is reproduced most effectively for the given reaction series. In an empirical treatment, $(n')/k$ should be regarded as an adjustable parameter. The special selection of Eqn. (22) usually made has persisted partly because of inertia but mainly because it proved to be fairly apt by chance. The coefficient 1/2 of the linear term in Eqn. (29) is obtained on the assumption that $n(1/2) = 1/2$, which is also non-obligatory. It arose as a consequence of the selection of the symmetrical reaction (X = Y) as the standard around which the expansion in Taylor's series is carried out. If reaction series with highly asymmetric TS are studied, it is more convenient to assume that the quantity $n(1/2)$ is yet another adjustable parameter and to calibrate it against data for any reaction chosen as the standard (the choice $\alpha = 1/2$ is permissible for any standard reaction, which need not necessarily be symmetrical). Such treatment of various series of reactions involving the radical abstraction of hydrogen yielded $n(1/2) = 0.54$–0.7.[131]

The non-linearity of Eqn. (29) appeared as a consequence of the variation of the positions of the TS on the reaction coordinate in conformity with the condition for a stationary state [Eqn. (28)]. In linear correlations of the Hammett type, the constancy of the structure of the TS throughout the reaction series is always implied. The same hypothesis is implicit in various approximate quantum-chemical treatments. The fact that the structure of the TS is not postulated but is calculated by a physically well-founded procedure is the fundamental feature distinguishing the Marcus equation among other theories of reactivity.

The shift of the TS along the reaction coordinate is described by the expression

$$\alpha^{\neq} - 1/2 = n'U(1)/k\lambda\ . \qquad (30)$$

For each specific reaction, it is controlled by the ratio of the heat of reaction and the energy of the internal barrier. The shift is appreciable in reaction series with a small force constant *k*—a situation which is characteristic of exchange reactions in which the TS is symmetrical or almost symmetrical and the reaction coordinate is an antisymmetric mode. The application of the Marcus equation to such reactions (these include also the S_N2 reactions) is most fruitful. On the other hand, in reactions involving addition to a multiple bond, where the reaction coordinate virtually coincides with the contraction along the newly formed bond, the force constant is large and the shift defined by Eqn. (30) is negligible.[134] In this case Eqn. (29) becomes linear with an unjustifiably rigidly fixed value of 1/2 for the Brønsted coefficient.

According to this derivation, the shifts defined by Eqn.(30) should not be very large. This is why the use of a symmetrical standard reaction [$n(1/2) = 1/2$] for the description of highly asymmetric TS yields unsatisfactory results.

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