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Energetics of bimolecular nucleophilic reactions in solution

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Abstract. Published data on the activation parameters of bimolecular nucleophilic reactions in solution are generalised and described systematically. The factors that influence the relation between the activation parameters in these reactions are discussed. The relationships between the mechanisms of bimolecular nucleophilic substitution and addition reactions and their activation parameters are considered, and the role of the enthalpy – entropy compensation effect is analysed. The bibliography includes 229 references.

I. Introduction

Bimolecular nucleophilic reactions (BNR) provide the basis for the synthesis of various classes of organic compounds. These include S_N2, S_NAr, S_NV and Ad_N reactions, reactions at the carbonyl carbon atom, reactions of carbocations with anions, *etc*.[1] There is a substantial body of data on the kinetics and mechanisms of these reactions (see, for examples, Refs 2 – 6). However, after the publication of the monograph by Leffler and Grunwald,[6] no generalisations of the changes in the enthalpy of activation ($\Delta H^{\neq}$), the entropy of activation ($\Delta S^{\neq}$) and the activation free energy ($\Delta G^{\neq}$) for bimolecular nucleophilic reactions were made although the number of studies on kinetics and mechanisms of these reactions is being increased steadily. It was demonstrated[6] that the enthalpy and entropy of activation depend much more substantially on the reaction mechanism than the activation free energy. Hence, analysis of the main factors responsible for the ratio between the enthalpy and entropy contributions to the energy barrier for the reaction is of great importance. The present review is devoted to systematisation and analysis of the data on the energetics of the main types of bimolecular nucleophilic reactions in solution. Particular attention is given to the relationship between the reaction mechanisms and the activation parameters. In some cases, a comparison with the data for gas-phase reactions is performed. Of special interest are bimolecular nucleophilic reactions, that proceed by similar mechanisms and at nearly the same rates but are substantially different in the activation parameters.

In the present review, the enthalpy – entropy compensation effect, which is widely discussed in the literature, is considered from the viewpoint of factors responsible for changes in the activation parameters of bimolecular nucleophilic reactions in solution. Based on the published data, the difference between the compensation and isokinetic effects or their equality are noted.

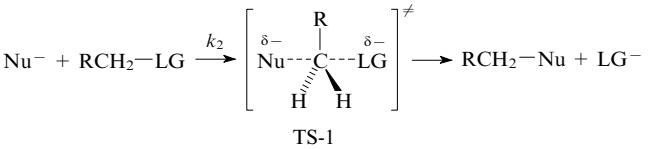
Emphasis is given to typical bimolecular reactions of organic chemistry. For bimolecular reactions of inorganic compounds, only selected data for ligand substitution reactions of complex compounds are considered.

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II. S_N2 reactions

S_N2 reactions in solution are characterised by negative entropies of activation $\Delta S^{\neq}$ because the transition states (TS) are well organised.[7 – 10] The values of $\Delta S^{\neq}$ depend on the nature of the substrate and nucleophile and the reaction conditions.[8 – 12] For example, the entropy of activation of S_N2 reactions at the saturated carbon atom involving anionic nucleophiles in proton-donor and polar aprotic solvents vary in the range from -2.3 to -83.1 J mol^{-1} K^{-1} (Table 1).



TS-1

Nu is a nucleophile and LG is a leaving group.

It should be noted that negative $\Delta S^{\neq}$ for both fast and slow reactions vary in a narrow range (for example, see entries 3, 6, 14, 25, 27 and 33 in Table 1). Apparently, the structural features of TS-1 play the decisive role in the determination of $\Delta S^{\neq}$. An increase in the entropy of activation (smaller negative $\Delta S^{\neq}$) corresponds to the less organised and earlier TS-1 on the S_N2 reaction coordinate characterised by a lower degree of formation

Table 1. Rate constants and activation parameters for S_N2 reactions at the saturated carbon atom of RCH_2LG with anionic nucleophiles.

Substrate RCH_2LG	Entry	Nucleophile	Solvent	Temperature /°C	k_2 /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
MeCl	1	KSCN	MeOH	71.1	2.51×10^{-4}	93.3	44.0	108.8	13
	2	KSCN	DMF	71.1	0.266×10^{-2}	77.8	69.0	102.2	13
MeI	3	KSCN	MeOH	60.1	1.46×10^{-2}	77.1	49.2	92.5	13
	4	PhONa	MeOH	59.2	2.66×10^{-3}	89.9	24.5	98.1	14
	5	4-$NO_2C_6H_4ONMe_4$	MeCN	30	0.854×10^{-2}	61.8	80.8	86.3	15
	6	2,4-$(NO_2)_2C_6H_3ONMe_4$	MeCN	30	3.18×10^{-5}	76.2	79.7	100.3	15
	7	4-$NO_2C_6H_4CO_2NMe_4$	MeCN	30	4.57×10^{-2}	66.6	51.0	82.0	15
	8	3,5-$(NO_2)_2C_6H_3CO_2NMe_4$	MeCN	30	1.25×10^{-2}	63.1	73.5	85.4	15
	9	2-$ClC_6H_4CO_2NMe_4$	MeCN	30	8.08×10^{-2}	68.9	38.7	80.6	15
	10	Me_4NBr	MeCN	30	25.8×10^{-2}	69.1	28.4	77.7	15
	11	tetramethylammonium 1,3-dimethylbarbiturate	MeCN	30	2.98×10^{-2}	60.5	74.7	83.1	15
	12	tetramethylammonium 3,4,5,6-tetrachlorophthalimide [a]	MeCN	30	13.7×10^{-2}	59.1	66.6	79.3	15
EtI	13	4-$NO_2C_6H_4ONMe_4$	MeCN	30	0.279×10^{-2}	68.7	67.3	89.1	15
	14	2,4-$(NO_2)_2C_6H_3ONMe_4$	MeCN	30	1.33×10^{-5}	77.4	83.1	102.6	15
	15	4-$NO_2C_6H_4CO_2NMe_4$	MeCN	30	1.07×10^{-2}	68.0	58.3	85.7	15, 16
	16	3,5-$(NO_2)_2C_6H_3CO_2NMe_4$	MeCN	30	0.29×10^{-2}	68.8	66.7	89.0	15
	17	2-$ClC_6H_4CO_2NMe_4$	MeCN	30	1.51×10^{-2}	70.6	47.0	84.8	15
	18	Me_4NBr	MeCN	30	1.08×10^{-2}	77.4	27.2	85.6	15
	19	tetramethylammonium 1,3-dimethylbarbiturate	MeCN	30	0.18×10^{-2}	68.2	72.5	90.2	15, 17
	20	tetramethylammonium 3,4,5,6-tetrachlorophthalimide [a]	MeCN	30	0.615×10^{-2}	66.8	67.0	87.1	15, 18
	21	tetramethylammonium 3,4,5,6-tetrachlorophthalimide [a]	MeCN–MeOH [b]	30	0.184×10^{-4}	89.5	40.5	101.8	18
	22	tetramethylammonium succinimide [a]	MeCN	30	1.65×10^{-1}	58.4	67.4	78.8	19
	23	tetramethylammonium succinimide [a]	MeCN–MeOH [b]	30	0.474×10^{-4}	92.4	23.0	99.4	19
	24	$Et_2HCCO_2NMe_4$	MeCN	30	3.56×10^{-1}	60.8	53.1	76.9	20
	25	$Et_2HCCO_2NMe_4$	MeCN–MeOH [b]	30	0.28×10^{-5}	100.8	18.8	106.5	20
	26	$Et_2HCCO_2NMe_4$	MeCN–MeOH [c]	30	6.24×10^{-4}	92.2	2.3	92.9	20
Bu^nBr	27	PhSNa	DMF	−21	0.53	49.8	51.0	62.7	21
$PhCH_2Cl$	28	NaN_3	MeOH	75	6.3×10^{-3}	81.5	59.4	102.1	21
	29	MeONa	MeOH	70	3.23×10^{-3}	82.3	47.4	98.6	22
n-$C_6H_{13}OTs$	30	NaN_3	DMSO	30	4.83×10^{-3}	77.8	32.6	87.6	23
	31	KSCN	DMSO	30	0.165×10^{-4}	83.6	51.8	99.3	23
	32	Bu^n_4NCl	DMSO	30	1.67×10^{-3}	84.4	18.4	90.0	23
AlkO–$-SO_2Ar$ [d]	33	n-$C_{16}H_{33}PBu^n_3Cl$	cyclo-C_6H_{12}	30	1.0607	59.8	43.9	73.1	24
	34	n-$C_{16}H_{33}PBu^n_3Br$	cyclo-C_6H_{12}	30	0.6123	63.1	41.0	75.5	24
	35	n-$C_{16}H_{33}PBu^n_3I$	cyclo-C_6H_{12}	30	0.3073	66.9	33.9	77.1	24

Note. Hereinafter, in the tables $\Delta H^{\neq}$ and $\Delta G^{\neq}$ are given in kJ mol^{-1}; $\Delta S^{\neq}$, in J mol^{-1} K^{-1}.
[a] Names are given according to IUPAC nomenclature; [b] 1 M MeOH; [c] 0.1 M MeOH; [d] Alk = n-C_8H_{17}, Ar = 4-$NO_2C_6H_4$.

and longer Nu–C bond (entries 3 and 4, 8 and 9, 16 and 17, 21 and 23, 31 and 32 in Table 1).[3,25]

Gas-phase ion-molecular S_N2 reactions are also characterised by low $\Delta S^{\neq}$ indicative of a high degree of organisation of the transition state.[7,10,26,27] For example, $\Delta S^{\neq}$ for the gas-phase reactions of alkyl bromides with chloride ions at high pressure varies in the range from −83.6 to −100.7 J mol^{-1} K^{-1} (Refs 26 and 27); $\Delta S^{\neq}$ for the reactions of substituted benzyl chlorides with phenolate and benzenethiolate anions, in the range from −160 to −170 J mol^{-1} K^{-1} (calculations by the PM3 method).[7]

The enthalpy of activation for ion-molecular S_N2 reactions varies in a broad range and is generally smaller for faster reactions (for example, entries 1 and 2, 3 and 4, 5 and 6, 13 and 14, 22 and 23, 24 and 25, 27 and 28, 30 and 31 in Table 1). The enthalpies for faster reactions slightly increase only in the case of a sharp increase in the entropy (entries 31 and 32 in Table 1). The rates of all these reactions are controlled by the enthalpy of activation because $\Delta H^{\neq} \gg T\Delta S^{\neq}$ in all cases (see Table 1).[10] This type of reactions is characterised by the isokinetic relationship with the isokinetic temperature β = 6103 K,[10] which is substantially higher than the experimental temperature range. However, the isokinetic relation-

ship with a lower isokinetic temperature (β = 1130 K) is observed for S_N2 reactions at the sp^3-hybridised carbon atom involving the thiosulfate ion in aqueous organic media, which is evidence for another (apparently, catalytic) reaction pathway in these media.[11]

The activation parameters for the reactions of ethyl iodide with anionic nucleophiles substantially depend also on the composition of the solvent (entries 20 and 21, 22 and 23, 24 and 25, 26 in Table 1).[16–20] There is no linear correlation between the parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for the reaction of each nucleophile with EtI in MeCN–MeOH with variation of percentage of MeOH. It should be noted that linear relationships between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were obtained considering the thermodynamic parameters of the passage from one solvent to another as well as the number of alcohol molecules involved in hydrogen bonding with anionic species.[16–20]

The enthalpy of activation for the reactions of MeI is always lower than that for the analogous reaction with EtI due to a decrease in the steric hindrance in the transition state, as exemplified by the reactions of MeI and EtI with structurally different anionic nucleophiles (entries 5–20 in Table 1); the correlations between $\Delta H^{\neq}$(MeI) and $\Delta H^{\neq}$(EtI) for series of related nucleophiles have been revealed.[15] An analogous influence of the structure of the substrate was found for gas-phase S_N2 reactions.[26,27] The corresponding calculations for the gas phase and solutions were carried out.[28]

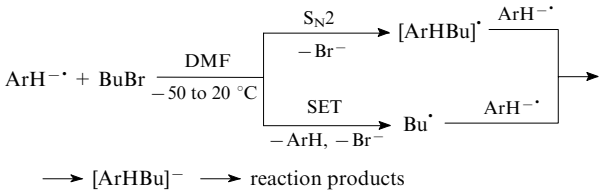
Based on a comparison of the changes in the entropy of activation for the reactions of MeI and EtI with nucleophiles containing one reaction centre (for example, entries 5 and 13, 10 and 18, 12 and 20 in Table 1) in MeCN, it was concluded that partial desolvation of the nucleophilic centre in the formation of the transition state is the major factor responsible for the relative reactivities of alkyl iodides.[15]

The values of $\Delta G^{\neq}$ for the ion-molecular S_N2 reactions are rather high (see Table 1) due primarily to a contribution of the desolvation energies of the nucleophile and TS-1.[3,22,24] Quantum-chemical calculations, which were performed with consideration of the solvent effect on the activation free energies for S_N2 reactions, agree well with experimental values.[28–31] For example, the calculated $\Delta G^{\neq}$ for the reactions of MeCl with Cl^- in DMSO, MeOH and H_2O are 133.7, 145.9 and 147.5 kJ mol^{-1}, respectively.[28] For the reaction of EtCl with CN^- in DMSO, the calculated $\Delta G^{\neq}$ is equal to 100.7 kJ mol^{-1} (Ref. 29), whereas the experimental $\Delta G^{\neq}$ is equal to 94.5 kJ mol^{-1}.[30]

For the reactions of *trans*-γ-derivatives of allyl chlorides YCH=CHCH$_2$Cl with Cl^- and LiCl, the calculated energy barriers correlate with the substituent constants σ_p to give the reaction constants ρ = −8.3 and ρ = +18.8, respectively.[31] An analogous substituent effect in the $\rho\sigma$ correlations is observed for ion and ion-pair reactions in solution as well. It was demonstrated that the ionic structure of the transition state is stabilised by double-bond polarisation rather than by the conjugation effect. At the same time, a substantial charge delocalisation is observed for the ion-pair structure of the transition state.[31]

The calculated activation barriers for the gas-phase S_N2 reactions F^- + MeX (X = F, Cl, CN, OH, SH, NH_2 and PH_2) give the following series of the nucleofugic ability of the substituent X (the activation barriers in kJ mol^{-1} are given in parentheses): Cl (−51.0) > F (−3.3) > SH (11.7) > CN (56.8) > OH (67.3) > PH_2 (82.3) > NH_2 (137.1).[32] It should also be noted that the experimental and calculated rate constants for the gas-phase reaction MeBr + Cl^- agree well with each other in a broad temperature range.[33]

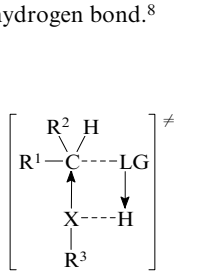
The enthalpy-controlled S_N2 reactions of aromatic radical anions with alkyl bromides in DMF in the temperature range from −50 to 20 °C are characterised by low enthalpies of activation (29.3–34.3 kJ mol^{-1}) and essentially negative entropies of activation (−79.8 to −54.3 J mol^{-1} K^{-1}).[9] Interestingly, the increase in the temperature leads to a switch of the S_N2-reaction mechanism to the single-electron transfer (SET) mechanism, which is accompanied by an increase in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ to 47.6–56.8 kJ mol^{-1} and 20.9 J mol^{-1} K^{-1}, respectively.[9]



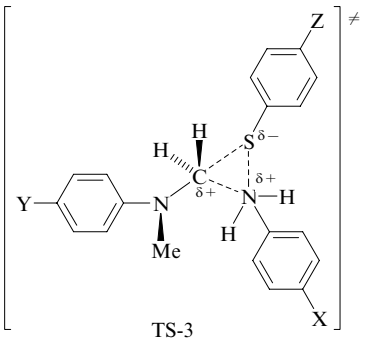
ArH is anthracene, Bu = Bu^n, Bu^s, Bu^t.

The same features were observed for the reactions of alkyl chlorides with NO^-.[34]

Generally, S_N2 reactions at the saturated carbon atom with neutral O-, S- and N-nucleophiles proceed slowly and are characterised by very low $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (Table 2) compared to the parameters for analogous reactions with charged nucleophiles (see Table 1). A noticeable decrease in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ is attributed to the structural features of the transition states. The frontal attack of the nucleophile on the substrate gives rise to the four-membered transition state TS-2 involving a hydrogen bond[35,40–42] or the three-membered transition state TS-3 without the involvement of a hydrogen bond.[8]



TS-2



TS-3

X = O, S, NH;
LG = $OSO_2C_6H_4Z$, Br.

Cyclic TS-2 and TS-3 are late states characterised by a higher degree of the bond formation and cleavage.[8,42]

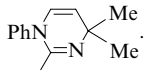
It should be noted that S_N2 reactions at the saturated carbon atom with neutral nucleophiles can be controlled by both the enthalpy and entropy (Table 2). For example, methanolysis of 1-phenylethyl 4-nitro-benzenesulfonate (Table 2, entries 1 and 2) in a mixture of protic and aprotic solvents is controlled by the enthalpy unlike the entropy-controlled reaction in a protic solvent. However, an analogous change in the nature of the solvent in the reactions of ethyl α-bromoacetate with HetSH (Table 2, entries 3 and 4) and aminolysis of allyl bromide (Table 2, entries 7–10) leads to the opposite change in the control. Evidently, higher stabilisation of TS-2 for faster reactions in both protic and aprotic media leads to a decrease in both $\Delta H^{\neq}$ and $\Delta S^{\neq}$, resulting in the entropy control of the reaction (Table 2, entries 1, 4–7 and 9).

In the reactions of ethyl α-bromoacetate with HetSH in various protic and aprotic solvents (Table 2, entries 3 and 4), the enthalpy–entropy compensation effect with the compensation temperature β = 292 K (below the limit of the experimental temperature range) is observed.[36] However, the change in the energetics of the reaction of ethyl α-bromoacetate with thiol in methanol under changes in the nature of the substituent in S-nucleophiles is described by the compensation relation with β = 338 K (above the limit of the experimental temperature range).[36] At the same time, aminolysis of allyl bromide in an aprotic solvent (Table 2, entries 7 and 9) is characterised by the compensation relation with β = 220 K (much lower than the limit of the experimental temperature range), whereas no linear relationship between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ is observed for this reaction in methanol.[37]

Table 2. Rate constants and activation parameters for S_N2 reactions at the saturated carbon atom of R^1R^2CHLG with neutral nucleophiles.

Substrate R^1R^2CHLG			Entry	Nucleophile	Temperature /°C	Solvent	k_2 /litre mol^{-1} s^{-1} (see [a])	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
R^1	R^2	LG									
Ph	Me	4-$NO_2C_6H_4SO_3$	1	MeOH	25	MeOH	2.89×10^{-4}	41.8	216.9	106.5	35
Ph	Me	4-$NO_2C_6H_4SO_3$	2	MeOH	25	MeOH – MeCN (1 : 1)	0.658×10^{-4}	58.1	178.9	111.4	35
CO_2Et	H	Br	3	HetSH [b]	45	MeOH	19.4×10^{-3}	60.1	91.2	88.3	36
CO_2Et	H	Br	4	HetSH [b]	45	Me_2CO	44.3×10^{-3}	31.2	171.4	85.7	36
PhNMe	H	4-$NO_2C_6H_4S$	5	4-$MeOC_6H_4NH_2$	45	MeOH	4.07×10^{-1}	19.2	192.3	80.4	8
PhNMe	H	4-MeC_6H_4S	6	4-$MeOC_6H_4NH_2$	45	MeOH	1.95×10^{-3}	21.7	229.9	94.8	8
$CH_2=CH$	H	Br	7	4-$MeOC_6H_4NH_2$	30	DMF	8.1×10^{-3}	43.1	133.8	83.6	37
$CH_2=CH$	H	Br	8	4-$MeOC_6H_4NH_2$	30	MeOH	1.69×10^{-3}	64.3	87.8	90.9	37
$CH_2=CH$	H	Br	9	$PhNH_2$	30	DMF	3.3×10^{-3}	42.9	152.1	89.0	37
$CH_2=CH$	H	Br	10	$PhNH_2$	30	MeOH	0.91×10^{-3}	62.0	100.3	92.4	37
Me	H	I	11	Et_3N	25	MeOH	4.08×10^{-5}	75.0	97	103.9	38, 39
Me	H	I	12	Et_3N	25	Bu^nOH	1.73×10^{-5}	78.6	92	106.0	38, 39
Me	H	I	13	Et_3P	25	MeOH	14.95×10^{-5}	48.6	155	94.8	39
Me	H	I	14	Et_3P	25	Bu^nOH	6.172×10^{-5}	64.5	110	97.3	39

[a] In entries 1 and 2, the pseudo-first-order rate constant k_1 /s^{-1}; in entries 3 – 10, the rate constant of the formation of the transition state TS-2 or TS-3 as the rate-determining step in the nucleophilic attack of the substrate; in entries 11 – 14, the rate constant of decomposition of ion pairs (see the reaction equation).

[b] Het = .

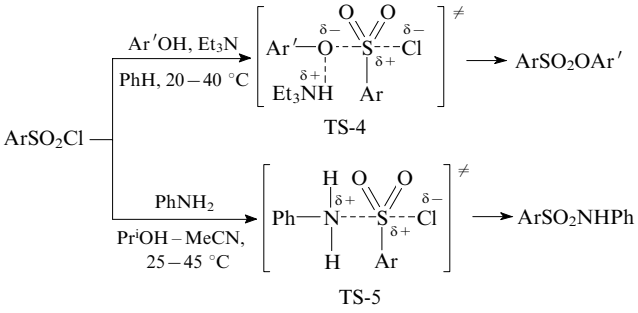
Studies of the quaternisation reactions of aliphatic amines with MeI in an aqueous solution revealed an isokinetic relationship with a negative isokinetic temperature. This fact provides evidence for a stepwise reaction mechanism involving the reversible formation of the ion pair in the first step followed by its dissociation to form free ions.[12]

$$R_3N + MeI \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \{R_3NMe^+I^-\} \xrightarrow{k_2} R_3NMe^+ + I^-$$

The quaternisation reactions $Et_3N + EtI$ in solutions of alcohols (entries 11 and 12 in Table 2) correspond to the isokinetic relationship with the positive isokinetic temperature $\beta = 730$ K (higher than the experimental temperature range).[38,39] The use of Et_3P as a nucleophile in the latter reaction (entries 13 and 14 in Table 2) leads to a decrease in the isokinetic temperature to 347 K. Therefore, a substantially lower degree of desolvation of Et_3P compared to Et_3N is required, and the positive isokinetic temperatures for both reactions in alcoholic solutions confirm the concerted mechanism.[39]

A comparison of the energetics of reactions at the saturated carbon atom with charged and neutral nucleophiles demonstrated that these reactions are characterised by very close activation free energies $\Delta G^{\neq}$ in spite of the difference in the structure of transition states (TS-1 and TS-2 or TS-3). Therefore, these differences are reflected primarily in the changes in the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$.[6]

The substitution reactions at the sulfur atom of the sulfo group with anionic and neutral nucleophiles that proceed by a concerted mechanism *via* the trigonal-bipyramidal transition states TS-4 and TS-5 have very low enthalpies ($\Delta H^{\neq} = 8-40$ kJ mol^{-1}) and entropies of activation ($\Delta S^{\neq}$ from -220 to -277 J mol^{-1} K^{-1}) if the reactivity is entropy-controlled.[43,44]

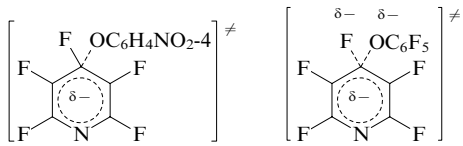


Ar = Ph, 5-$C_{10}H_6SO_2Cl$.

Evidently, these transition states, which are formally similar to the trigonal-bipyramidal transition state TS-1 in S_N2 reactions, are much more organised. It should also be noted that the reaction of benzenesulfonyl chloride with phenols in the presence of Et_3N is characterised by the compensation relation with $\beta = 171$ K (calculated using the experimental data [43]), which is substantially lower than the limit of the experimental temperature range.[43]

III. S_NAr reactions

The energetics of bimolecular S_NAr reactions depends on the nature of the leaving group and the nucleophile.[45] The reactivity in these processes is generally controlled by the enthalpy.[46–51] Table 3 gives the rate constants for the rate-determining step of the formation of the transition state TS-6 or TS-7 and the activation parameters for S_NAr reactions of various substituted arenes ArLG with charged hard and soft nucleophiles in protic and aprotic solvents. As can be seen from these data, $\Delta S^{\neq}$ varies from -250 to 255 J mol^{-1} K^{-1} and $\Delta H^{\neq}$ varies from 3.8 to 232 kJ mol^{-1}. The very low enthalpies of activation correspond to very low (large negative) entropies of activation (entries 14, 39, 41 and 42 in Table 3). In these cases, the reactivity is entropy-controlled. However, other S_NAr reactions listed in Table 3 are



TS-6 TS-7

entropy-controlled regardless of the electrophilicity of the substrate and the nature of the nucleophile, the leaving group, and the solvent. Ttransition states in the reactions of 2,2′-dinitrodiphenyl ether (entry 14 in Table 3) and halogen-substituted pyridines (entries 39 and 41 in Table 3) with sodium phenolate derivatives are well organised due to desolvation of the nucleophile in the formation of the transition state and weak solvation of the delocalised transition state, for example, of TS-6, approaching the σ complex.[21,49,51,59] By contrast, the entropy control of the reaction of 4-pentafluorophenoxy-2,3,5,6-tetrafluoropyridine with KF (entry 42 in Table 3) is most likely associated with the change from the S_NAr reaction mechanism to the concerted mechanism *via* the transition state TS-7.[58,60,61] The more ordered (compared to TS-6) transition state TS-7 is typical of bimolecular concerted reactions with very low $\Delta S^{\neq}$.[62]

The switch from the entropy control of the reaction to the enthalpy control can be achieved by varying the nucleophile. An increase in the negative charge delocalisation in a nucleophile leads to a decrease in its desolvation energy. Examples are provided by the reactions of 2-chloro-5-nitropyridine with sodium 4-methoxy- and 4-nitrophenolate in methanol (entries 39 and 40 in Table 3). The use of nucleophiles with a more delocalised charge (electron-withdrawing NO_2 group) instead of nucleophiles with a less delocalised charge (electron-donating MeO group) allows one to change the character of control of the reaction.[51]

Analysis of the activation parameters for the S_NAr reactions given in Table 3 revealed a number of compensation relations and isokinetic relationships (Fig. 1).[63–65] Straight line *I* in Fig. 1 relates primarily to fast reactions (entries 10, 12, 27–31 and 33–37 in Table 3) with rate constants $k_2 > 1 \times 10^{-4}$ litre mol^{-1} s^{-1} and only the reaction of 4-nitrobenzonitrile with CsF in DMSO (entry 15 in Table 3) is slow [$k_2(80\ ^\circ C) = 1.58 \times 10^{-7}$ litre mol^{-1} s^{-1}] due to a substantial increase in the entropy contribution as a result of the formation of the late transition state and, consequently, a slight change in the

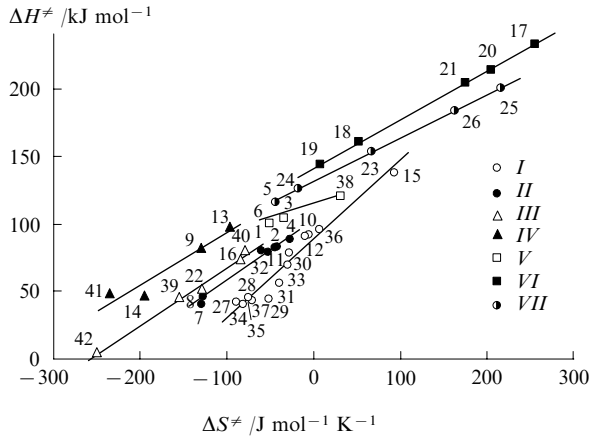


Figure 1. Compensation plots for the S_NAr reactions of substituted arenes ArLG with charged nucleophiles (the numbering of the points corresponds to the entries in Table 3).
(*I*) $r = 0.975$, $n = 13$, $s = 6.9$; (*II*) $r = 0.990$, $n = 7$, $s = 2.89$; (*III*) $r = 0.996$, $n = 5$, $s = 3.16$; (*IV*) $r = 0.959$, $n = 4$, $s = 8.8$; (*V*) $r = 0.999$, $n = 3$, $s = 0.46$; (*VI*) $r = 0.999$, $n = 5$, $s = 0.52$; (*VII*) $r = 0.999$, $n = 4$, $s = 0.88$.

Table 3. Rate constants and activation parameters for S_NAr reactions at the sp^2-hybridised carbon atom in compounds ArLG with charged nucleophiles.

Substrate		Entry	Nucleophile	Temperature /°C	Solvent	k_2 /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
Ar	LG									
4-$NO_2C_6H_4$	I	1	PhSNa	0	MeOH	3.40×10^{-6}	81.1	60.3	99.1	46, 47
	F	2	PhSNa	0	MeOH	7.79×10^{-6}	82.8	43.9	94.9	47
	I	3	MeONa	0	MeOH	2.45×10^{-9}	104.5	34.3	113.7	46, 47
	F	4	MeONa	0	MeOH	6.26×10^{-6}	88.6	27.6	96.1	46, 47
	I	5	NaN_3	0	MeOH	3.67×10^{-12}	116.2	43.9	128.3	46, 47
	F	6	NaN_3	0	MeOH	1.55×10^{-9}	100.7	52.3	115.0	47
	F	7	9-PhFlK [a]	35	DMSO	8.48×10^{-2}	41.8	129.6	81.8	52
	F	8	9-PhFlK [a]	35.5	DMSO	1.55×10^{-2}	46.6	128.3	86.2	52
	Br	9	4-$NO_2C_6H_4ONa$	120	1,3-DMI [b]	1.76×10^{-5}	81.9	129.2	132.7	50
	NO_2	10	MeONa	25	MeOH	1.7×10^{-4}	91.1	10.5	94.2	53
	F	11	RbF	25	DMSO	0.928×10^{-4}	83.6	41.8	97.5	54
	NO_2	12	CsF	80	DMSO	1.0×10^{-4}	92.0	8.4	95.0	55
	2-$NO_2C_6H_4O$	13	4-$NO_2C_6H_4ONa$	120	1,3-DMI [b]	6.22×10^{-6}	97.8	97.4	136.1	50
2-$NO_2C_6H_4$	2-$NO_2C_6H_4O$	14	3-$NO_2C_6H_4ONa$	120	1,3-DMI [b]	2.8×10^{-4}	47.2	194.8	123.7	50
4-NCC_6H_4	NO_2	15	CsF	80	DMSO	1.58×10^{-7}	137.9	−92.0	105.4	55
	NO_2	16	3,4-$Me_2C_6H_3OH\cdot K_2CO_3$	130	DMAA	0.1	73.2	84.7	107.3	56
3-$NO_2C_6H_4$	NO_2	17	3,4-$Me_2C_6H_3OH\cdot K_2CO_3$	150	DMAA	3.16×10^{-3}	232.4	−254.7	124.7	56
	NO_2	18	3-$NO_2C_6H_4OH\cdot K_2CO_3$	125	DMF	4.0×10^{-6}	160.0	−52.0	135.5	57
	F	19	3-$NO_2C_6H_4OH\cdot K_2CO_3$	125	DMF	2.0×10^{-6}	144.0	−7.0	140.7	57
	NO_2	20	$PhOH\cdot K_2CO_3$	125	DMF	2.0×10^{-5}	215.0	−204.0	133.8	57
	F	21	$PhOH\cdot K_2CO_3$	125	DMF	1.0×10^{-5}	205.0	−175.0	135.4	57
3,4-$(NC)_2C_6H_3$	NO_2	22	3,4-$Me_2C_6H_3OH\cdot K_2CO_3$	90	DMF	6.6×10^{-2}	51.2	128.4	95.1	56
3-NO_2-5-$CF_3C_6H_3$	NO_2	23	3-$NO_2C_6H_4OH\cdot K_2CO_3$	70	DMF	7.0×10^{-8}	154.0	−66.0	131.4	57
	F	24	3-$NO_2C_6H_4OH\cdot K_2CO_3$	70	DMF	5.0×10^{-8}	126.0	18.0	132.2	57
	NO_2	25	$PhOH\cdot K_2CO_3$	70	DMF	3.0×10^{-7}	201.0	−215.0	127.3	57
	F	26	$PhOH\cdot K_2CO_3$	70	DMF	3.0×10^{-7}	183.0	−162.0	127.4	57
2,4-$(NO_2)_2C_6H_3$	I	27	PhSNa	0	MeOH	5.17	44.7	74.8	65.2	47
	Cl	28	PhSNa	0	MeOH	3.90	40.8	82.2	63.2	48
	F	29	PhSNa	0	MeOH	1.29×10^{2}	44.7	52.3	58.9	47
	I	30	MeONa	0	MeOH	3.08×10^{-4}	79.2	28.4	86.9	47
	F	31	MeONa	0	MeOH	1.74	56.4	40.1	67.3	47
	I	32	NaN_3	0	MeOH	1.74×10^{-5}	79.2	53.5	93.8	47
	F	33	NaN_3	0	MeOH	2.04×10^{-2}	69.6	30.5	79.2	47
	Cl	34	Et_4NN_3	−20	DMF	0.153	45.6	75.7	64.7	21
	4-$NO_2C_6H_4O$	35	Et_4NN_3	−20	DMF	0.217	42.2	89.1	64.7	21
	I	36	Et_4NCl	60	DMF	1.05×10^{-2}	96.3	−6.1	94.3	21
	NO_2	37	MeONa	25	MeOH	16.3	43.9	72.7	65.6	53
(η^6-C_6H_5)Fe(C_5H_5)$^+$ (see [c])	Cl	38	NaN_3	0	MeOH	1.90×10^{-9}	121.0	−30.8	112.6	48
5-$NO_2C_5H_3N$	2-Cl	39	4-$MeOC_6H_4ONa$	40	MeOH	1.40×10^{-3}	45.1	154.2	93.4	51
	2-Cl	40	4-$NO_2C_6H_4ONa$	40	MeOH	0.24×10^{-4}	79.8	78.6	104.4	51
C_5F_4N	4-F	41	4-$NO_2C_6H_4OK$	30	MeCN	0.72	48.5	235.2	119.8	58
	4-C_6F_5O	42	KF	30	MeCN	5.14	3.8	250.0	79.6	58

[a] 9-Phenylfluorenylpotassium; [b] 1,3-dimethylimidazolidin-2-one; [c] in this case, η^6-coordinated PhCl serves as the substrate.

entropy of solvation. Line *II* in Fig. 1 includes rather slow reactions with $k_2 = 1 \times 10^{-6} - 1 \times 10^{-2}$ litre mol^{-1} s^{-1} (entries 1, 2, 4, 7, 8, 11 and 32 in Table 3) with the most typical activation parameters.[46] Line *III* contains points for both fast (entry 42 in Table 3) and rather slow reactions (entries 16, 22, 39 and 40 in Table 3). The characteristic feature of the latter plot is a very strong decrease in the entropy in entries 22, 39 and 42. This can be attributed to an increase in the desolvation energy of the localised nucleophile (*cf.* entries 39 and 40 in Table 3)[51] or an increase in the desolvation energy of the nucleophile due to the formation of the early transition state with a more electrophilic substrate (*cf.* entries 16 and 22 in Table 3)[53] as well as to a switch from the S_NAr mechanism to the concerted mechanism (entry 42 in Table 3).[58] Line *IV* (Fig. 1) includes data for reactions (entries 9, 13, 14 and 41 in Table 3) with low $\Delta S^{\neq}$. Low $\Delta S^{\neq}$ for reactions 14 and 41 were discussed above. A decrease in $\Delta S^{\neq}$ for slow reactions 9 and 13 can be attributed to the formation of the early transition state.[48, 53] The reactions of halogen-substituted arenes with sodium methoxide and azide are described by straight line *V* (entries 3, 5, 6 and 38 in Table 3). It should be noted that these reactions are very slow and characterised by high $\Delta H^{\neq}$ and $\Delta S^{\neq}$ due apparently to stabilisation of the ground state of the nucleophile and, as a consequence, the formation of the late transition state.[48, 53]

Lines *VI* (entries 17 – 21 in Table 3) and *VII* (entries 23 – 26) in Fig. 1 characterise slow reactions with very high $\Delta H^{\neq}$ and $\Delta S^{\neq}$, both relationships being isokinetic.[57] The activation free energies (120 – 140 kJ mol^{-1}) for all reactions corresponding to lines *VI* and *VII* are close to the range of $\Delta G^{\neq}$ determining the kinetics of S_NAr reactions of weakly activated arenes with O-charged nucleophiles.[46] The enthalpy and entropy of activation for the reactions of *meta*-substituted arenes with complexes of phenols with K_2CO_3 (Scheme 1) vary in unusually broad ranges. High sensitivity of the parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ to the structure of the reagents is due to the possible changes in the geometry of complex **1**.[66, 67] Apparently, it is this property of complex **1** that determines similarity of these reactions to heterogeneous and enzymatic catalysis characterised by unusually broad ranges of $\Delta H^{\neq}$ and $\Delta S^{\neq}$.[68 – 70] Then the transformation of complex **1** can occur either synchronously *via* the transition state TS-8 or stepwise *via* complex **2** and the transition state TS-9. Both pathways afford σ complex **3**. The formation of the latter is the rate-determining step and is characterised by usual activation free energies $\Delta G^{\neq}$.[46]

The chemical nature of the observed compensation relations is confirmed by the fact that the observed compensation temperatures are noticeably different from the experimental temperature

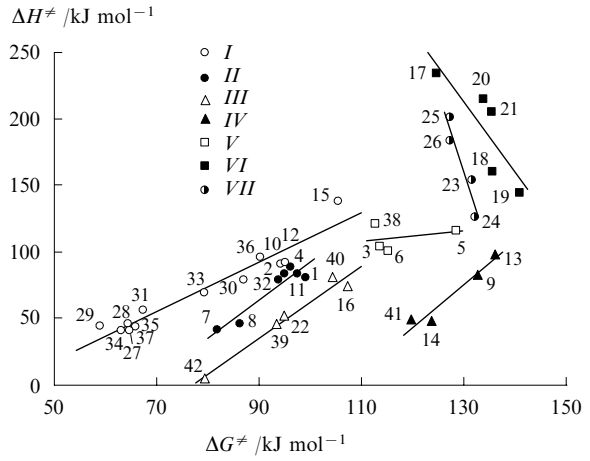
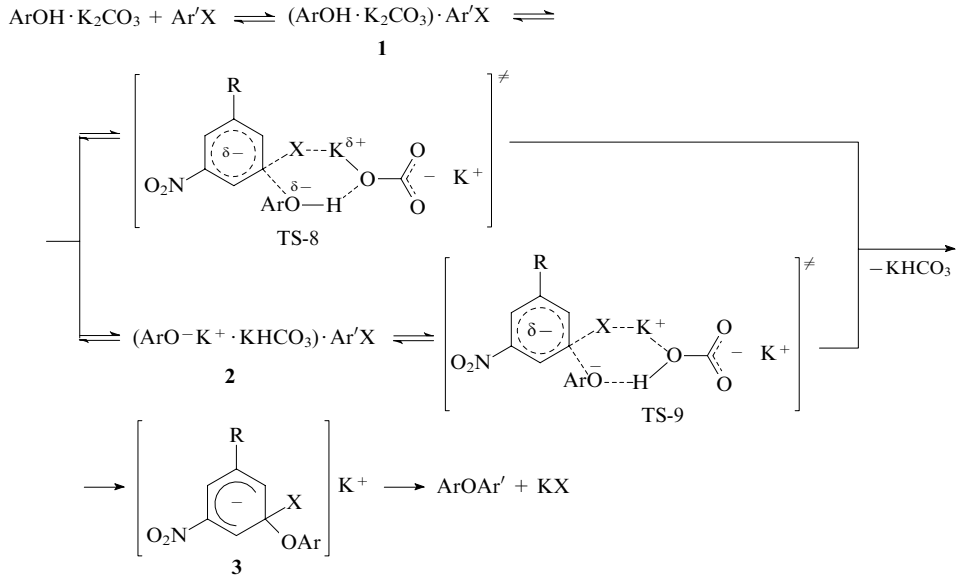


Figure 2. Plots of the enthalpies *vs* the activation free energies for the S_NAr reactions of substituted arenes ArLG with charged nucleophiles (the numbering of the points corresponds to the entries in Table 3). (*I*) $r = 0.966$, $n = 13$, $s = 8.0$; (*II*) $r = 0.949$, $n = 7$, $s = 6.6$; (*III*) $r = 0.983$, $n = 5$, $s = 6.4$; (*IV*) $r = 0.971$, $n = 4$, $s = 7.4$; (*V*) $r = 0.950$, $n = 3$, $s = 3.6$; (*VI*) $r = 0.835$, $n = 5$, $s = 24.0$; (*VII*) $r = 0.951$, $n = 4$, $s = 12.5$.

range. In addition, the relationships between the enthalpies of activation and the activation free energies for these reactions were found (Fig. 2).[71 – 73] The opposite slopes of the lines in Fig. 2 are associated with considerable positive values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for the reactions described by lines *VI* and *VII*. As a result, $\Delta H^{\neq}$ can be larger than $\Delta G^{\neq}$ (entries 17 – 21, 23, 25 and 26 in Table 3).

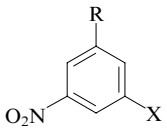
Due to the kinetic enthalpy – entropy compensation effect represented by lines *I*, *II*, *VI* and *VII* in Fig. 1 for different S_NAr reactions, it became possible to compare the substitution effect of the nitro group and the fluorine atom on the energetics of these reactions.[74] For example, a comparison of the activation parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) for the substitution of the nitro group and the fluorine atom in 1,4-dinitro- and 4-fluoronitrobenzene in the reactions with ^{18}F-labelled fluoride ions in DMSO (entries 11 and 12 in Table 3) demonstrated that the selectivity of replacement of these groups (k_{NO_2}/k_F ratio) is controlled by the entropy of activation.[53, 54] Evidently, the replacement of the nitro group (entry 11) is characterised by the earlier transition state on the

Scheme 1



reaction coordinate compared to the replacement of the fluorine atom (entry 12).[74]

Recently, it has been demonstrated [57, 66, 75] that the selectivity of replacement of the nitro group and the fluorine atom in the reactions of *meta*-substituted nitrobenzenes with phenols and arenethiols in the presence of K_2CO_3 in DMF at 40–125 °C is entropy-controlled because in all cases $T\Delta\Delta S^{\neq} > \Delta\Delta H^{\neq}$, where $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{NO_2} - \Delta S^{\neq}_{F}$ and $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{NO_2} - \Delta H^{\neq}_{F}$. Changes in the entropy $\Delta\Delta S^{\neq}$ have positive values (*cf.* entries 18 and 19, 20 and 21, 23 and 24, 25 and 26 in Table 3, lines *VI* and *VII* in Fig. 1), and, consequently, the reactions of fluoroarenes **4** and **5** with the $ArOH \cdot K_2CO_3$ complexes are more organised than analogous reactions of nitroarenes **6** and **7**.



4–7

X = F: R = H (**4**), CF_3 (**5**); X = NO_2: R = H (**6**), CF_3 (**7**).

Hence, the S_NAr substitution of the nitro group in compounds **6** and **7** is characterised by the earlier transition state on the reaction coordinate compared to the substitution of the fluorine atom in compounds **4** and **5**.[57, 66, 75] It should be noted that the replacement of the nucleophile $ArOH \cdot K_2CO_3$ by $2\,ArOH \cdot K_2CO_3$ has no effect on the character of the control of the reactivity of compounds **5** and **7**. In this case, the selectivity of substitution is also entropy-controlled.[76]

It was demonstrated [77, 78] that changes in the nature of the medium can lead to a switch from the entropy control of regioselectivity in S_NAr reactions to the enthalpy control. For example, the *ortho* to *para* isomer ratio in S_NAr reactions resulting in the replacement of halogens in alcohols as the solvents is entropy-controlled.[79, 80] A comparison of the substitution of the fluorine and chlorine atoms in halonitrobenzenes shows that the fluorine atoms in monohalonitrobenzenes are replaced primarily due to smaller steric requirements of the *ortho*-fluorine atom (Table 4). However, the reverse situation is observed for dihalonitrobenzenes because the entropy control of the reactions in MeOH favours the *ortho*-substitution due to steric hindrance for solvation in the transition state (see Table 4).[80] However, the entropy control of the reactions of fluoronitrobenzenes with alkoxides changes to the enthalpy control at low temperature in liquid NH_3, resulting in sharp enhancement of *ortho*-substitution (see Table 4).

Table 4. Rate constant ratios of the replacement of halogens in the *ortho* and *para* positions of halonitrobenzenes with sodium methoxide in methanol (25 °C) or liquid ammonia (−70 °C) and the differences between the activation parameters for these reactions.

Compound	Solvent	k_o/k_p	$\Delta\Delta H^{\neq}$ (see [a])	$\Delta\Delta S^{\neq}$ (see [a])	$\Delta\Delta G^{\neq}$ (see [a])	Ref.
2- and 4-$ClC_6H_4NO_2$	MeOH	0.27 [b]	5.77	13.4	0.91	80
2,4-$Cl_2C_6H_3NO_2$	MeOH	1.98 [b]	–	–	–	80
2- and 4-$FC_6H_4NO_2$	MeOH	0.69	−4.56	−9.6	−1.7	79–81
	NH_3 (liq.)	2.85	−8.38	−24.7	−5.0	77
	NH_3 (liq.)	1.60 [c]				78
2,4-$F_2C_6H_3NO_2$	MeOH	1.22	–	–	–	80
		1.35	–	–	–	81
	NH_3 (liq.)	2.6	−5.23	−9.94	−2.0	78
		(3.3 [d])				78
		1.85 [c]				78

[a] Here and in Table 5, $\Delta\Delta H^{\neq} = \Delta H^{\neq}_o - \Delta H^{\neq}_p$, $\Delta\Delta S^{\neq} = \Delta S^{\neq}_o - \Delta S^{\neq}_p$ and $\Delta\Delta G^{\neq} = \Delta G^{\neq}_o - \Delta G^{\neq}_p$; [b] at 90 °C; [c] at −33 °C; [d] in the reaction with MeOK.

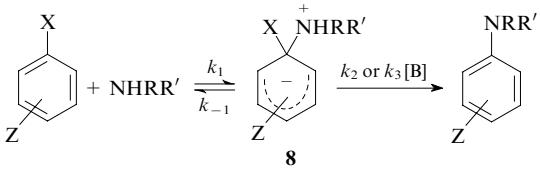
Table 5. Rate constant ratios of the replacement of the fluorine atom in the *ortho* and *para* positions of 2,4-difluoronitrobenzene with lithium phenolates 4-RC_6H_4OLi in liquid NH_3 (−55 °C) and the differences between the activation parameters for these reactions.[82, 83]

R in 4-RC_6H_4OLi	k_o/k_p	$\Delta\Delta H^{\neq}$	$\Delta\Delta S^{\neq}$	$\Delta\Delta G^{\neq}$
Bu^t	0.96	2.7	12.0	0.09
Me	1.30	−1.7	−5.3	−0.54
H	1.45	−0.9	−1.1	−0.66
	(2.36) [a]	(−4.4) [a]	(−11.9) [a]	(−1.81) [a]
F	1.58	−0.9	−0.5	−0.79
MeO	1.20	−2.1	−8.3	−0.29

[a] Data for the reaction with PhONa at −55 °C (see [78]).

The regioselectivity of replacement of the halogen atom can be influenced also by the structure of the nucleophile. Table 5 gives data on the regioselectivity of replacement of the fluorine atom in 2,4-difluoronitrobenzene under the action of lithium phenolates 4-RC_6H_4OLi in liquid ammonia. From these data it follows that the replacement of the *ortho*-fluorine atom is more favourable from the point of view of the enthalpy than the replacement of the *para*-fluorine atom. For the substituents R in nucleophiles, this tendency decreases in the series 4-MeO > 4-Me > H ≈ F. However, the enthalpy favours the replacement of the *para*-fluorine atom in the case of R = Bu^t.[83] This fact is associated with a change in the structure of the transition state. The replacement of the *ortho*-fluorine atom under the action of lithium phenolates containing electron-donating substituents where the higher positive charge is localised on the *ortho*-carbon atom with respect to the nitro group gives the early transition state. A decrease in the nucleophilicity of 4-$Bu^tC_6H_4OLi$ due to the greater polarisability of the Bu^t group shifts the transition state toward the intermediate σ complex, *i.e.*, favours the formation of the late transition state and the replacement of the *para*-fluorine atom.[83]

Of neutral nucleophiles, only amines were studied in detail in aromatic nucleophilic substitution reactions.[45, 74] Unlike the reactions of charged nucleophiles, S_NAr reactions of primary and secondary amines can be catalysed by bases. The second amine molecule can serve as such a base.



8

The apparent second-order rate constant k_A at a stationary concentration of σ complex **8** can be calculated from the commonly accepted mechanism of S_NAr reactions with amines:[45, 74]

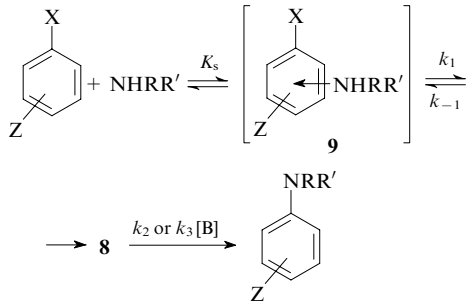
$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]}.$$

Table 6 lists the rate constants (k_A) and the activation parameters for S_NAr reactions of various arenes ArLG with primary and secondary amines in protic, aprotic polar and nonpolar solvents. It should be noted that for most of the reactions listed in Table 6 (entries 1, 2, 4–15 and 18–23), $k_A = k_1$ because $k_2 + k_3[B] \gg k_{-1}$, and the formation of σ complex **8** is the rate-determining step of the reaction. However, the reactions in nonpolar n-hexane (entries 3, 16 and 17, Table 6) are characterised by a more complex dependence of k_A on [B], which includes the equilibrium constant K_s of the formation of n–π-electron-donating complex **9** prior to the formation of σ complex **8**, decomposition of the latter being the rate-determining step.[85]

Table 6. Rate constants and activation parameters for the S_NAr reactions at the sp^2-hybridised carbon atom in compounds ArLG with amines.

Substrate ArLG		Entry	Nucleophile	Temperature /°C	Solvent	k_A /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
Ar	LG									
4-$NO_2C_6H_4$	NO_2	1	piperidine	25	MeCN	2.3×10^{-6}	48.1	192.3	105.4	84
2,4-$(NO_2)_2C_6H_3$	Cl	2	piperidine	0	MeOH	1.95×10^{-3}	46.2	126.2	80.7	48
	Cl	3	Bu^nNH_2	26	n-C_6H_{14}	2.35×10^{-2}	21.0	218.0	86.2	85
	Cl	4	piperidine	40	$MeCO_2Et-CHCl_3$ [a]	0.29×10^{-2}	25.5	174.4	80.1	86
	Cl	5	piperidine	40	PhMe–MeOH [a]	3.45×10^{-2}	47.4	113.3	82.9	87
	Cl	6	piperidine	40	1,1,1-Cl_3CMe–MeOH [a]	3.93×10^{-2}	34.3	175.6	89.3	87
	Cl	7	$PhNH_2$	50	EtOH	2.69×10^{-4}	44.1	177.2	101.3	88
	F	8	$PhNH_2$	50	EtOH	1.68×10^{-2}	24.1	204.0	90.0	88
	NO_2	9	$PhNH_2$	50	EtOH	2.11×10^{-1}	29.9	165.7	83.4	88
	Cl	10	morpholine	0	MeOH	1.7×10^{-3}	48.9	126.2	83.4	48
	Cl	11	$(NH_2)_2C{=}NH$	0	MeOH	3.5×10^{-3}	51.7	108.6	81.3	48
	Cl	12	$(NH_2)_2C{=}S$	0	MeOH	7.1×10^{-8}	76.1	108.6	105.7	48
2,6-$(NO_2)_2C_6H_3$	Cl	13	$PhNH_2$	50	EtOH	1.98×10^{-4}	56.7	140.4	102.0	89
	F	14	$PhNH_2$	50	EtOH	8.77×10^{-3}	36.6	171.0	91.8	89
	NO_2	15	$PhNH_2$	50	EtOH	3.26×10^{-1}	34.5	145.5	81.5	89
3-NO_2-5-$CF_3C_6H_3$	Cl	16	Bu^nNH_2	27	n-C_6H_{14}	9.4×10^{-6}	18.0	267.0	97.8	85
	Cl	17	piperidine	26	n-C_6H_{14}	3.6×10^{-4}	27.0	206.0	88.6	85
2,4,6-$(NO_2)_3C_6H_2$	Cl	18	$PhNH_2$	50	EtOH	3.34	29.9	142.8	76.0	89
	F	19	$PhNH_2$	50	EtOH	334	15.7	148.5	63.7	89
	NO_2	20	$PhNH_2$	50	EtOH	4.21×10^{3}	15.7	127.5	56.9	89
$(\eta^6\text{-}C_6H_5)Fe(C_5H_5)^+$ (see [b])	Cl	21	piperidine	0	MeOH	3.37×10^{-7}	73.5	98.0	100.3	48
	Cl	22	morpholine	0	MeOH	3.08×10^{-9}	82.0	105.0	110.7	48
	Cl	23	$(NH_2)_2C{=}NH$	0	MeOH	1.09×10^{-3}	29.4	193.0	82.1	48

[a] Molar ratio is 1 : 1; [b] in this case, η^6-coordinated PhCl serves as the substrate.



As can be seen from Table 6, $\Delta S^{\neq}$ varies from -265 to -98 J mol^{-1} K^{-1} and $\Delta H^{\neq}$ varies from 15.7 to 82.0 kJ mol^{-1}. It should be noted that low $\Delta H^{\neq}$ correlate with very low $\Delta S^{\neq}$, which corresponds to the entropy control of the reactivity, *i.e.*, $T\Delta S^{\neq} > \Delta H^{\neq}$ (entries 1, 3, 4, 6–9, 14–20 and 23, Table 6). However, in other cases, where both the entropy and enthalpy noticeably increase (entries 2, 5, 10–13, 21 and 22, Table 6), the reactivity is controlled by the enthalpy regardless of the structure of the amine and substrate.

The entropy control can be switched to the enthalpy control by changing the solvent. For example, the reactions in a binary solvent system including MeOH is entropy-controlled if 1,1,1-trichloroethane is used as the second component, whereas these reactions are enthalpy-controlled in the presence of toluene instead of 1,1,1-trichloroethane due to a change in the contribution of the hydrogen bond between piperidine and MeOH (entries 5 and 6, Table 6).[87]

Analysis of the activation parameters for the S_NAr reactions with amines revealed a number of the enthalpy–entropy compensation relations (Fig. 3). Straight line *I* in Fig. 3 includes data for very slow reactions (entries 1, 7, 12, 13 and 22, Table 6) with the rate constants $k_A = 3.08\times10^{-9}$–2×10^{-4} litre mol^{-1} s^{-1} and high $\Delta H^{\neq}$ and $\Delta S^{\neq}$. Line *II* (entries 2, 5, 6, 10, 11 and 14) relates to the data for rather slow S_NAr reactions with amines. Faster reactions are described by line *III* (entries 4, 8, 9, 15, 18 and 23); very fast reactions, by line *IV* (entries 19 and 20). The reactions described by the compensation plots *III* and *IV* are characterised by very low $\Delta H^{\neq}$ and $\Delta S^{\neq}$. Line *V* (entries 3, 16 and 17, Table 6) almost coincides with line *III*, but low $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for these reactions are associated with a change in the mechanism of S_NAr

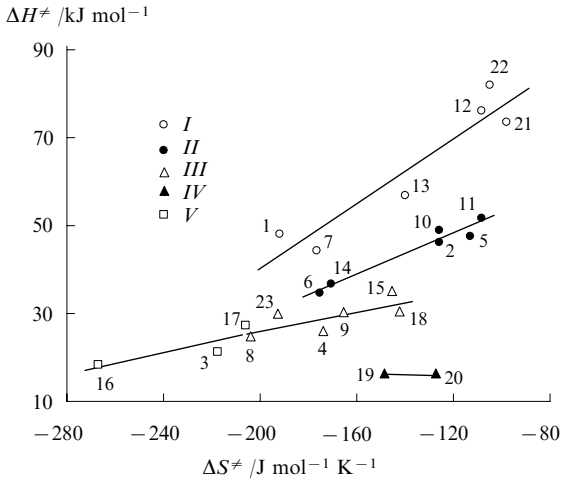


Figure 3. Compensation plots for the S_NAr reactions of substituted arenes ArLG with amines (the numbering of the points corresponds to the entries in Table 6).
(*I*) $r = 0.940$, $n = 6$, $s = 6.0$; (*II*) $r = 0.975$, $n = 6$, $s = 1.74$; (*III*) $r = 0.73$, $n = 6$, $s = 2.8$; (*IV*) and (*V*) $r = 0.864$, $n = 3$, $s = 3.3$.

reactions in nonpolar n-hexane due to formation of complex **9** (see above).[85]

Analysis of the relationships between the enthalpies of activation and the activation free energies for the same S_NAr reactions with amines (Fig. 4) confirms the chemical nature of the observed enthalpy–entropy compensations presented in Fig. 3,[71–73] and reveals the following characteristic feature: slower reactions are described by line *I* with the opposite slope compared to lines *II*–*IV* for faster reactions (see Fig. 4). The latter fact reflects the highest sensitivity of changes in $\Delta H^{\neq}$ depending on $\Delta S^{\neq}$ for the same reactions (line *I* in Fig. 3 has the largest slope).

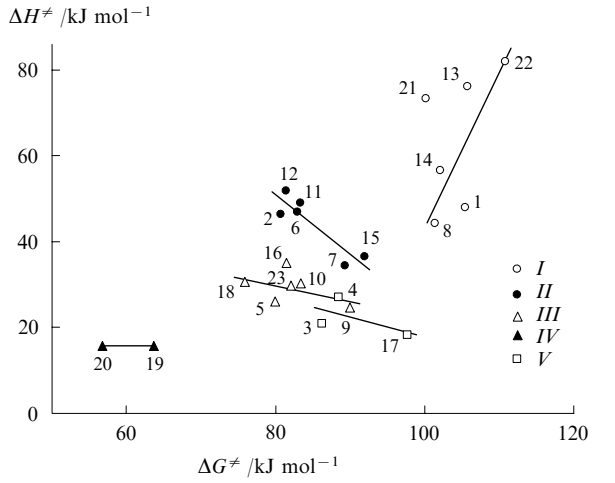


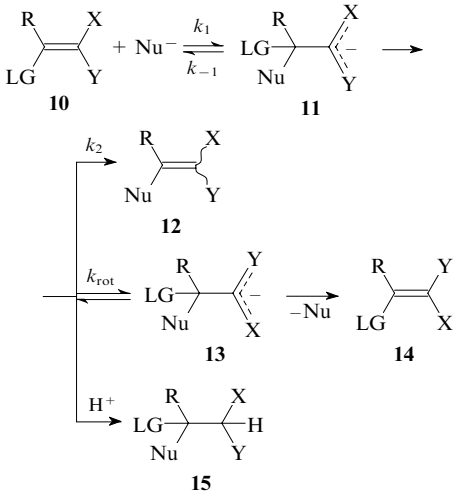
Figure 4. Plots of the enthalpies *vs* the activation free energies for the S_NAr reactions of substituted arenes ArLG with amines (the numbering of the points corresponds to the entries in Table 6).

A comparison of the activation parameters for the substitution of the nitro group and the fluorine atom in a series of nitro- and fluoroarenes under the action of aniline (entries 8 and 9, 14 and 15, 19 and 20, Table 6) shows that the selectivity of replacement of these groups ($k_A^{NO_2}/k_A^F$ ratio) is controlled by the entropy of activation. Evidently, the replacement of the nitro group (entries 9, 15 and 20) is characterised by the earlier transition state on the reaction coordinate compared to the replacement of the fluorine atom (entries 8, 14 and 19).

To summarise the results of consideration of the activation parameters for S_NAr reactions, let us note the following characteristic features: $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$ vary in very broad ranges and there is no common enthalpy–entropy compensations for the reactions with both charged and neutral nucleophiles even in terms of the same reaction mechanism involving the formation of a σ complex as the rate-determining step. It should be emphasised that complexation between the substrate and the nucleophile can contribute significantly to changes in the activation parameters.

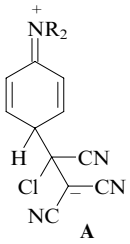
IV. S_NV and Ad_N reactions

Nucleophilic vinylic substitution (S_NV) can proceed by different mechanisms.[90–94] If the S_NV reaction proceeds according to the addition–elimination mechanism, it has much in common with the nucleophilic addition to electron-deficient alkenes **10** (Ad_N reaction) because both S_NV and Ad_N reactions involve the same addition step of the nucleophile to the double bond to form carbanion **11** (products **12** and **15**, respectively). As a rule, the nucleophilic attack is the rate-determining step (rate constant k_1), but this is not necessarily the case.[91,95,96] For example, the apparent second-order rate constant for *E*–*Z* isomerisation of compound **10** under the action of various amines giving rise to product **14** is not the constant k_1 but reflects a more complex process where the internal rotation with the constant k_{rot} giving rise to carbanion **13** can be the rate-determining step. This conclusion is supported by very low values of $\Delta H^{\neq}$ (8.8–18.4 kJ mol^{-1}) and $\Delta S^{\neq}$ (from −242.4 to −179.7 J mol^{-1} K^{-1}) for these reactions.[91]

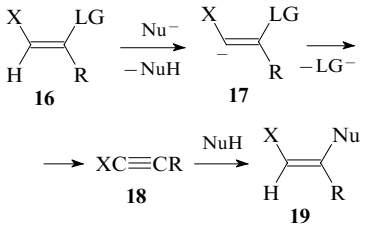


X and Y are electron-withdrawing groups.

Very low values of $\Delta H^{\neq}$ are also typical of S_NV reactions with amines in which the nucleophilic attack with the rate constant k_1 is not the rate-determining step.[90,96] For example, very low $\Delta H^{\neq}$ (3.3–8.4 kJ mol^{-1}) and $\Delta S^{\neq}$ (from −234.1 to −217.4 J mol^{-1} K^{-1}) for the S_NV reactions of tricyanovinyl chloride with *N*,*N*-dialkylanilines in chloroform are indicative of the complex character of the apparent rate constant, which is evidently close to the rate constant for elimination of the chloride ion from intermediate zwitterion **A**.[90,91]



The activation parameters are also useful in proving the elimination–addition (E–Ad_N) mechanism of S_NV reactions.[92] It appeared that positive values of $\Delta S^{\neq}$ provide reliable evidence that S_NV reactions proceed by this mechanism. Under the action of strong bases, a proton can be abstracted from compound **16** to give carbanion **17**, from which the LG group is eliminated to form acetylenic derivative **18**, and the latter is involved in the addition reaction producing alkene **19**.



X is an electron-withdrawing group.

For example, *Z* isomer **16** (the *trans* orientation of the H atom and the leaving group LG) reacts with both hard nucleophiles RO^- and soft nucleophiles RS^- to form acetylenic derivative **18** and substitution product **19**.[92,97] The fact that the reactions of *Z* isomers **16** with alkoxides RO^- proceed according to the E–Ad_N mechanism is evidenced by positive values of $\Delta S^{\neq}$ (entries 4 and 6, Table 7).[97,98]

Table 7. Apparent rate constants and activation parameters for S_NV reactions of a series of substrates with charged nucleophiles.[a]

Substrate	Entry	Nucleophile	Temperature /°C	Solvent	k /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
(*E*)-ClCH=CHC(O)C_6H_4OMe-4 (**20**)	1	PhSNa	−10	MeOH	4.97	9.4	−81.5	30.8	97
	2	MeONa	0	MeOH	1.84×10^{-2}	13.1	−76.9	34.1	97
(*Z*)-ClCH=CHC(O)C_6H_4OMe-4 (**21**)	3	PhSNa	−10	MeOH	0. 304	9.8	−97.8	35.5	97
	4	MeONa	0	MeOH	1.27×10^{-2}	18.5	2.1	17.9	97
(*E*)-ClCH=CHCN (**22**)	5	EtONa	0	EtOH	2.90×10^{-2}	68.5	−31.4	77.1	98
(*Z*)-ClCH=CHCN (**23**)	6	EtONa	0	EtOH	15.5×10^{-2}	101.2	101.2	73.6	98
(*E*)-BrCH=CHCN (**24**)	7	EtONa	0	EtOH	3.25×10^{-2}	74.4	−8.8	76.8	98
Cl_2C=$CHSO_2Ph$ (**25**)	8	4-$MeOC_6H_4SNa$	30	MeOH	1.58	34.9	−127	73.4	99
	9	PhSNa	30	MeOH	0.767	62.4	−41.9	75.1	99
	10	4-$NO_2C_6H_4SNa$	30	MeOH	0.522	73.3	−9.2	76.1	99
	11	MeONa	30	MeOH	0. 655	87.9	40.2	75.7	100
	12	EtONa	20	EtOH	7.5	97.1	102.5	67.1	100

[a] LG = Cl, except for entry 7, where LG = Br.

The S_NV reactions with charged nucleophiles resulting in the replacement of halogen in compounds **20**–**25** proceed at similar rates (see Table 7) and their activation parameters obey the enthalpy–entropy compensations (Fig. 5). Straight line *I* includes the reactions of compounds **20** and **21** with O- and S-anions characterised by very low $\Delta H^{\neq}$, whereas line *II* includes data for the reactions of compounds **22**–**25** with O- and S-anions characterised by high $\Delta H^{\neq}$. It should be noted that changes in $\Delta H^{\neq}$ are little sensitive to changes in $\Delta S^{\neq}$ for the reactions of compounds **20** and **21** (line *I*) due apparently to the entropy control of these reactions. The linear relationship between $\Delta H^{\neq}$ and $\Delta G^{\neq}$ is observed only for these reactions, the sensitivity of $\Delta H^{\neq}$ to changes in $\Delta G^{\neq}$ is also very weak. By contrast, $\Delta G^{\neq}$ for the reactions of compounds **22**–**25** varies in a narrow range (74.4 ± 2.4 kJ mol^{-1}, see Table 7), resulting in the absence of the dependence of $\Delta H^{\neq}$ on $\Delta G^{\neq}$ and the enthalpy control of these reactions.

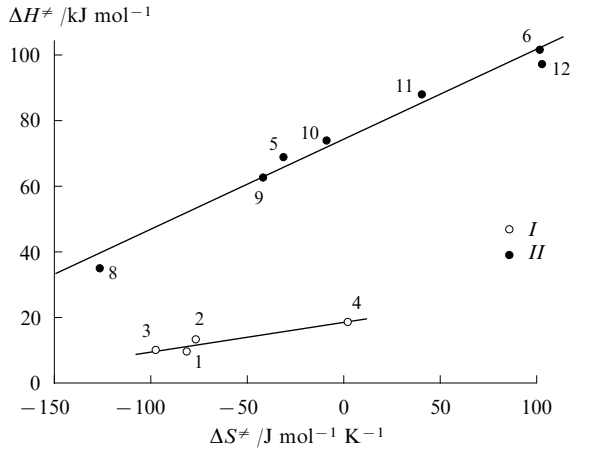
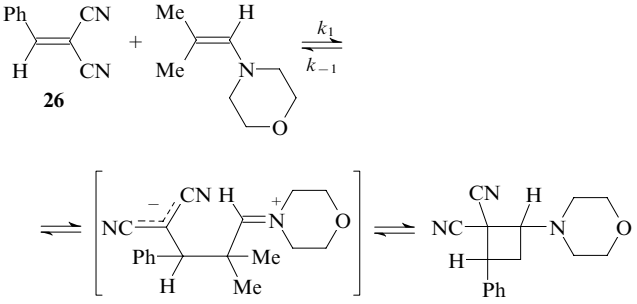


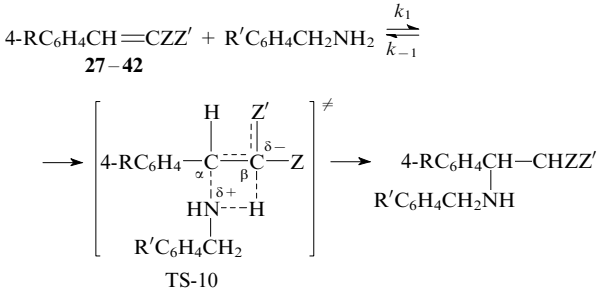
Figure 5. Compensation plots for the S_NV reactions resulting in the replacement of halogen in compounds **20**–**25** with charged nucleophiles (the numbering of the points corresponds to the entries in Table 7). (*I*) $r = 0.947$, $n = 4$, $s = 1.6$; (*II*) $r = 0.988$, $n = 8$, $s = 3.48$.

In the case of charged nucleophiles, the nucleophilic addition to activated alkenes **10** *via* intermediate carbanion **11** giving rise to Ad_N reaction product **15** occurs very rapidly in both water or 50% aqueous DMSO [93] and anhydrous DMSO.[101] The rate constant k_1 (20 °C) varies in the range of 10^4–10^7 litre mol^{-1} s^{-1} depending on the nature of substrate **10** and the nucleophile, but the data on the activation parameters for these reactions are lacking.[93, 101] The Ad_N reactions of activated alkenes with neutral nucleophiles proceed much more slowly.[93, 101] For some of these reactions, the activation parameters were determined.[101–110]

The rate constant k_1 (20 °C) of the reaction of benzylidenemalononitrile (**26**) with morpholinoisobutene as a π-nucleophile in CH_2Cl_2 is 1.24×10^{-2} litre mol^{-1} s^{-1}, and the activation parameters $\Delta H^{\neq} = 19.8$ kJ mol^{-1} and $\Delta S^{\neq} = -214$ kJ mol^{-1} K^{-1}.[101] The [2 + 2]-cycloaddition reactions proceeding (the entropy control) stepwise *via* a zwitterionic intermediate are characterised by very low $\Delta S^{\neq}$ (as in this reaction).[101, 111]



The rate constants and the activation parameters for the Ad_N reactions of activated alkenes with amines in acetonitrile are given in Table 8. Depending on the electrophilicity of alkene and the nucleophilicity of the amine, the rate constants vary by five orders of magnitude, $\Delta H^{\neq}$ varies from 2 to 65 kJ mol^{-1}, and $\Delta S^{\neq}$ varies from −267 to −40 J mol^{-1} K^{-1}. These substantial changes in the activation parameters are associated with the difference in the mechanism of these reactions. It was demonstrated [105–110] that activated alkenes **27**–**42** react with benzylamines in acetonitrile according to the concerted mechanism in one step *via* the cyclic four-membered transition state TS-10.



Hence, these reactions are characterised by low $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and the entropy control of the reactivity (entries 1–8, 11–14,

Table 8. Rate constants and activation parameters for the Ad_N reactions of activated alkenes with amines in MeCN.

Substrate	Entry	Nucleophile	Temperature /°C	k /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
4-$MeOC_6H_4CH{=}C(NO_2)Ph$ (**27**)	1	4-$MeOC_6H_4CH_2NH_2$	25	1.90×10^{-2}	15.5	221.5	81.5	106
	2	4-$ClC_6H_4CH_2NH_2$	25	0.89×10^{-2}	20.1	213.2	83.6	106
4-$BrC_6H_4CH{=}C(NO_2)Ph$ (**28**)	3	4-$MeOC_6H_4CH_2NH_2$	25	11.3×10^{-2}	15.9	209.0	78.2	106
	4	4-$ClC_6H_4CH_2NH_2$	25	3.69×10^{-2}	19.2	204.8	80.2	106
4-$MeOC_6H_4CH{=}C(CN)C_6H_4NO_2$-4 (**29**)	5	4-$MeOC_6H_4CH_2NH_2$	30	1.17×10^{-3}	29.3	200.6	89.1	106
	6	4-$ClC_6H_4CH_2NH_2$	30	0.399×10^{-3}	28.8	213.2	92.3	106
4-$BrC_6H_4CH{=}C(CN)C_6H_4NO_2$-4 (**30**)	7	4-$MeOC_6H_4CH_2NH_2$	30	4.74×10^{-3}	28.4	192.3	85.7	106
	8	4-$ClC_6H_4CH_2NH_2$	30	1.07×10^{-3}	31.3	196.5	89.8	106
$PhCH{=}C(CN)C_6H_4NO_2$-4 (**31**)	9	$PhCH_2NH_2$	30	1.26×10^{-3}	–	–	–	106
	10	$PhCH_2NH_2$	30	5.54[a]	33.3	120.3	69.8	102
(*E*)-4-$MeC_6H_4CH{=}CHNO_2$ (**32**)	11	4-$MeOC_6H_4CH_2NH_2$	25	2.55×10^{-2}	2.1	267.5	81.9	105
	12	4-$ClC_6H_4CH_2NH_2$	25	0.649×10^{-2}	2.1	254.9	78.2	105
(*E*)-4-$NO_2C_6H_4CH{=}CHNO_2$ (**33**)	13	4-$MeOC_6H_4CH_2NH_2$	25	1.28	3.8	229.9	72.3	105
	14	4-$ClC_6H_4CH_2NH_2$	25	0.206	4.2	242.4	76.5	105
(*E*)-$PhCH{=}CHNO_2$ (**34**)	15	$PhNH_2$	25	41.1×10^{-5}	48.2	148.0	92.3	103
	16	3-$MeOC_6H_4NH_2$	25	64.6×10^{-5}	43.0	162.0	91.3	103
	17	3-$NO_2C_6H_4NH_2$	25	2.70×10^{-5}	57.0	141.0	99.0	103
	18	4-$MeOC_6H_4NH_2$	25	337.0×10^{-5}	38.8	163.0	87.4	103
	19	4-$NO_2C_6H_4NH_2$	25	3.06×10^{-5}	56.6	142.0	98.9	103
4-$MeC_6H_4CH{=}C(CN)_2$ (**35**)	20	4-$MeOC_6H_4CH_2NH_2$	25	4.44	23.4	133.8	63.3	107
	21	4-$ClC_6H_4CH_2NH_2$	25	0.831	25.5	137.9	66.6	107
4-$NO_2C_6H_4CH{=}C(CN)_2$ (**36**)	22	4-$MeOC_6H_4CH_2NH_2$	25	1.65	24.2	146.3	67.8	107
	23	4-$ClC_6H_4CH_2NH_2$	25	0.204	24.2	158.8	71.5	107
$PhCH{=}C(CN)_2$ (**26**)	24	$PhCH_2NH_2$	25	7.14×10^{-3} (see [b])	36.1	163.0	84.6	104
	25	$PhCH_2NH_2$	25	1.45[c]	47.1	82.0	71.3	104
	26	4-$MeOC_6H_4CH_2NH_2$	20	4.06[c]	41.7	92.0	68.9	104
	27	4-$NO_2C_6H_4CH_2NH_2$	20	0.18[c]	51.0	80.0	74.5	104
	28	3-$NO_2C_6H_4CH_2NH_2$	20	0.14[c]	65.1	40.0	76.8	104
	29	3-$NH_2C_6H_4CH_2NH_2$	20	3.20[c]	40.6	97.0	69.5	104
4-$MeOC_6H_4CH{=}C(CO_2Et)_2$ (**37**)	30	4-$MeOC_6H_4CH_2NH_2$	20	2.08×10^{-2}	25.5	209.0	86.7	108
	31	4-$ClC_6H_4CH_2NH_2$	20	0.559×10^{-2}	27.2	209.0	88.4	108
4-$BrC_6H_4CH{=}C(CO_2Et)_2$ (**38**)	32	4-$MeOC_6H_4CH_2NH_2$	20	9.37×10^{-2}	26.8	192.3	83.1	108
	33	4-$ClC_6H_4CH_2NH_2$	20	1.86×10^{-2}	27.2	200.6	86.0	108
4-$MeOC_6H_4CH{=}$ (**39**)	34	4-$MeOC_6H_4CH_2NH_2$	25	2.08	25.5	154.7	71.6	109
4-$BrC_6H_4CH{=}$ (**40**)	35	4-$MeOC_6H_4CH_2NH_2$	25	3.76	26.3	158.8	73.6	109
4-$MeOC_6H_4CH{=}C(Ac)CO_2Et$ (**41**)	36	4-$MeOC_6H_4CH_2NH_2$	25	0.767×10^{-2}	20.5	217.4	85.3	110
4-$ClC_6H_4CH{=}C(CO_2Et)_2$ (**42**)	37	4-$MeOC_6H_4CH_2NH_2$	25	2.38×10^{-2}	22.2	200.6	82.0	110

[a] The second-order rate constant (k_1) of the addition of benzylamine to substrate **31**.[102] [b] The second-order rate constant (k) of the addition of the nucleophile to substrate **26** according to a non-catalytic mechanism: $k = k_1k_2/k_{-1}$.[104] [c] The second-order rate constant (k_1) of the addition of the nucleophile to substrate **26** to form a zwitter-ionic intermediate.[104]

20–23 and 30–37, Table 8). The formation of the transition state TS-10 occurs due to a lag in the resonance delocalisation of the negative charge of the C_β atom to the activating groups Z and Z′ and a higher degree of N–H bond cleavage, than would be expected in the case of synchronous resonance delocalisation.[105–110] The compensation plots of $\Delta H^{\neq}$ *vs* $\Delta S^{\neq}$ for the Ad_N reactions of alkenes **26**–**42** with amines are shown in Fig. 6. Straight line *I* in this figure represents the reactions of β-nitrostyrenes **32** and **33** with benzylamines. These reactions are characterised by the late transition state TS-10 on the reaction coordinate and the lowest values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$.[105] The reactions of β-nitrostilbenes **27** and **28**, β-cyano-4′-nitrostilbenes **29** and **30**, benzylidenemalonates **37** and **38** and ethyl α-acetyl-β-phenylacrylates **41** and **42** with benzylamines are characterised by enthalpy–entropy compensation plot *II* (see Fig. 6). The transition state TS-10 for these reactions is earlier because the degree of the lag in the resonance delocalisation of the negative charge of the C_β atom to the activating groups Z and Z′ decreases.[106, 108, 110]

It should be noted that the activation parameters for the reactions of benzylideneindane-1,3-diones **39** and **40** and -malononitriles **35** and **36** with benzylamines form straight line *III* (Fig. 6) with the almost constant $\Delta H^{\neq}$ due to the difference in the structure of TS-10. The reactions of compounds **39** and **40** afford the more loose transition state TS-10.[107, 109] For compounds **35** and **36** possessing substantially higher electrophilicity,[112] the C_α reaction centre becomes more positive in TS-10 compared to the starting compounds due to strong polarisation of the $C_\alpha-C_\beta$ bond by two CN groups.[107]

The activation parameters for the reactions of β-nitrostyrene (**34**) with anilines (entries 15–19, Table 8) and the reactions of compound **26** with benzylamines (entries 25–29, Table 8) in MeCN are described by compensation plots *IV* and *V*, respec-

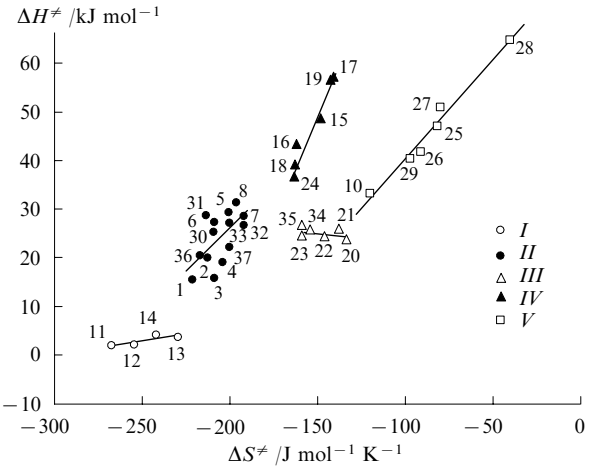


Figure 6. Compensation plots for the Ad_N reactions of activated alkenes **26**–**42** with amines in MeCN (the numbering of the points corresponds to the entries in Table 8).

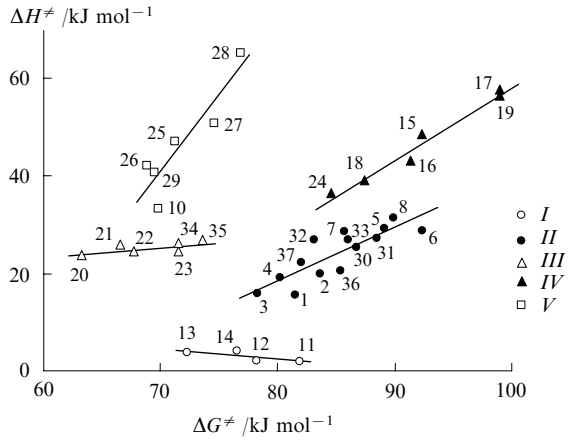
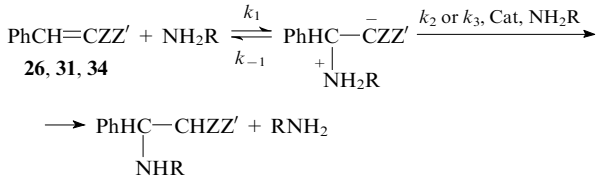


Figure 7. Plots of the enthalpies *vs* the activation free energies for the Ad_N reactions of activated alkenes with amines in MeCN (the numbering of the points corresponds to the entries in Table 8).

tively (see Fig. 6). These reactions are characterised by substantially higher $\Delta H^{\neq}$ and $\Delta S^{\neq}$, and the reactivity is controlled by the enthalpy. The reactions of compound **26** with benzylamines and the reactions of compound **34** with anilines in MeCN were demonstrated to proceed stepwise *via* the intermediate formation of zwitterions,[103, 105] like analogous reactions in aqueous solution.[93] The formation of zwitterions is the rate-determining step of the reactions of compound **34** with anilines,[103] whereas the non-catalytic (k_2) and catalytic (k_3) transformations of zwitterions are the slowest steps in the reactions of compound **26** with benzylamines.



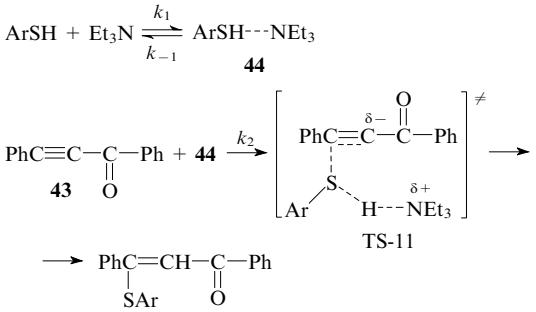
Hence, the calculated non-catalytic rate constant $k = k_1 k_2/k_{-1}$ for the latter reaction (entry 24, Table 8) is small, and the activation parameters for this reaction correspond to compensation plot *IV* (see Fig. 6).

Interestingly, the activation parameters for the reaction of β-cyano-4′-nitrostilbene (**31**) with benzylamine in MeCN (entry 10, Table 8) correspond to the compensation plot *V* (see Fig. 6). The proposed mechanism of this reaction [102] involves very fast nucleophilic addition to substrate **31** to form a zwitterion followed by slow catalytic transformation of the latter into the reaction product. However, a concerted mechanism involving the formation of the transition state TS-10 was proposed for this reaction elsewhere.[106] The rate constants of this reaction k_1 are substantially different (*cf.* entries 9 and 10, Table 8). The kinetic isotope effect for the reaction of compound **31** with $PhCH_2NH_2$ determined in the study [102] ($k_H/k_D = 5.49$) differs from that estimated in the study [106] (2.55–2.66), although both values are indicative of the contribution of the N—H bond to the structure of the transition state.

A comparison of the relationships between the enthalpies of activation and the activation free energies for the Ad_N reactions of activated alkenes with amines (Fig. 7) confirms the chemical nature of the compensation relations presented in Fig. 6.[71–73] It should be noted that faster reactions form lines *I*, *III* and *V* with smaller $\Delta G^{\neq}$.

The Ad_N reactions of activated alkynes with various nucleophiles proceed rather rapidly, and the activation parameters vary in the ranges of $\Delta H^{\neq}$ from 0 to 54.3 kJ mol^{-1} and of $\Delta S^{\neq}$ from -300 to -120 J mol^{-1} K^{-1} (Table 9). Interestingly, there are Ad_N reactions of activated alkynes with nucleophiles for which the enthalpy of activation is equal to zero (entries 1–5 and 10, Table 9).[113, 114, 116]

In the attack of arenethiols ArSH on the triple bond of 1,3-diphenylprop-1-yn-3-one (**43**) in the presence of the non-nucleophilic base Et_3N in toluene, the nucleophile is involved in the reaction as complex **44**.[113]



Hence, the effective rate constant of the process is $k_{eff} = (k_1/k_{-1})k_2$, and the enthalpy of formation of complex **44** is close to the activation energy of the rate-determining step of the reaction with the rate constant k_2 *via* the transition state TS-11. Very low negative values of $\Delta S^{\neq}$ and the isoenthalpy character of the reaction are consistent with the structure of TS-11, in which Et_3N is involved in the S—H bond cleavage (entries 1–4, Table 9).[113] Complex **44** can also be formed in the analogous reaction in a more polar medium (in methanol), but at a low concentration of Et_3N. An increase in the concentration of Et_3N in methanol leads to the formation of the ion pairs $\{ArS^- Et_3HN^+\}$ and a sharp increase in the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for their reactions with compound **43** (entries 5 and 6, Table 9).[114] Consequently, the formation of H-complex **44** before the formation of the transition state TS-11 is responsible for the entropy control of the reaction of compound **43** with arenethiols in the presence of Et_3N.[113, 114]

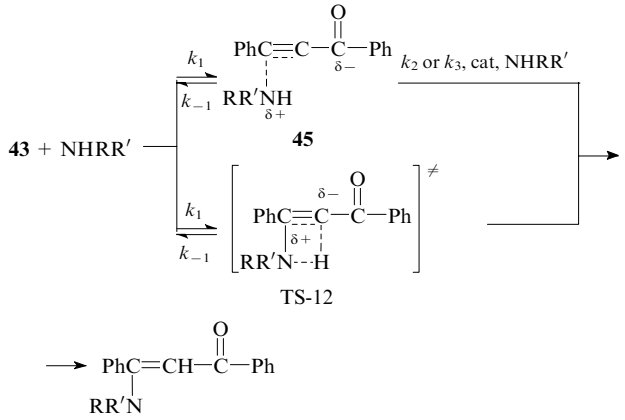
The rates of the Ad_N reactions of alkyne **43** with amines at low concentrations of the latter (0.03–0.2 mol litre^{-1}) are independent of the concentration of amines if the reactions proceed in ethanols or aprotic polar solvents (entries 7–23, Table 9).[115–119] This is possible if $k_2 + k_3[\text{amine}] \gg k_1$. In the latter case, the rate of the overall process is controlled by the rate of the nucleophilic attack of amine (k_1). Based on the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for these reactions, it can be concluded that the reaction mechanism changes from stepwise (*via* zwitterion **45**) to concerted

Table 9. Rate constants and activation parameters for the Ad_N reactions of 1,3-diphenylprop-1-yn-3-one (**43**) with arenethiols in the presence of Et_3N and with amines.

Nucleophile	Entry	Temperature /°C	Solvent	k /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
4-$MeOC_6H_4SH$ – Et_3N	1 [a]	0	PhMe	3.6×10^{-3} (see [b])	0	288.4	78.7	113
PhSH – Et_3N	2 [a]	0	PhMe	4.4×10^{-3} (see [b])	0	280.1	76.4	113
4-$NO_2C_6H_4SH$ – Et_3N	3 [a]	0	PhMe	20.0×10^{-3} (see [b])	0	217.4	59.3	113
4-MeC_6H_4SH – Et_3N	4 [a]	0	PhMe	4.0×10^{-3} (see [b])	0	284.2	77.6	113
	5 [c]	0	MeOH	0.37 (see [b])	0	250.0	68.3	114
	6 [d]	0	MeOH	7.4 (see [b])	39.0	83.0	61.7	114
Piperidine	7	40	95% EtOH	5.1×10^{-2}	44.7	126.6	83.6	115
Morpholine	8	40	95% EtOH	1.5×10^{-2}	39.7	152.6	86.5	115
	9	40	MeCN	3.06×10^{-3}	16.3	241.0	91.7	116
	10	40	DMF	4.2×10^{-3}	–	300.0	93.9	116
Et_2NH	11	40	95% EtOH	1.25×10^{-2}	39.3	154.7	86.9	115
Bu^i_2NH	12	40	95% EtOH	2.76×10^{-3}	30.9	194.8	91.1	115
$PhNH_2$	13	50	EtOH	1.55×10^{-4}	42.2	187.3	102.7	117
	14	50	95% EtOH	1.85×10^{-4}	39.7	193.5	99.5	118
4-$MeOC_6H_4NH_2$	15	50	95% EtOH	1.86×10^{-3}	38.9	175.6	92.0	118
4-$BrC_6H_4NH_2$	16	50	95% EtOH	0.92×10^{-4}	39.3	200.6	101.2	118
4-$ClC_6H_4NH_2$	17	50	95% EtOH	0.94×10^{-4}	39.3	200.6	101.2	118
Bu^nNH_2	18	40	95% EtOH	5.8×10^{-3}	47.6	137.9	90.1	119
	19	40	MeCN	5.27×10^{-3}	42.9	152.0	90.5	116
	20	40	DMF	2.88×10^{-2}	28.9	183.0	86.2	116
Bu^iNH_2	21	40	95% EtOH	3.26×10^{-3}	51.4	127.9	91.4	119
$PhCH_2NH_2$	22	40	95% EtOH	4.18×10^{-3}	48.1	136.7	90.9	119
$HOCH_2CH_2NH_2$	23	40	95% EtOH	2.85×10^{-3}	54.3	120.0	91.8	119

[a] An excess of Et_3N with respect to arenethiol; $[Et_3N] = 0.1$ mol litre^{-1}; [b] the apparent second-order rate constant; [c] at $[Et_3N] = 1.5\times10^{-5}$ mol litre^{-1}; [d] at $[Et_3N] = 1.5\times10^{-2}$ mol litre^{-1}.

(*via* the cyclic transition state TS-12) depending on the nature of amine and the solvent.



Aprotic polar solvents are more favourable for the concerted mechanism due to weak solvation of zwitterion **45**.

Figure 8 presents the enthalpy–entropy compensations for the Ad_N reactions of compound **43** with amines. Plot *I* characterises the reactions of alkyne **43** with secondary aliphatic amines, which have very low $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and are entropy-controlled (entries 7–12 in Table 9). Correspondingly, the transition state TS-12 is late.

The activation parameters for the reactions of compound **43** with anilines are described by straight line *II* with almost constant $\Delta H^{\neq}$ (see Fig. 8). In spite of high $\Delta H^{\neq}$, these reactions are also characterised by low $\Delta S^{\neq}$ and, on the whole, the entropy control (entries 13–17, Table 9). Evidently, these reactions have the earlier transition state TS-12.

The reactions of alkyne **43** with primary aliphatic amines (line *III*, Fig. 8) are characterised by high $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and the enthalpy control (entries 18–23 in Table 9). In this case, the reactions proceed stepwise *via* zwitterion **45**.[116]

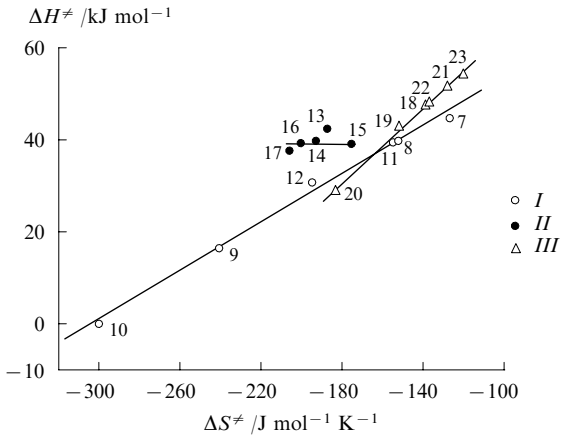


Figure 8. Compensation plots for the Ad_N reactions of activated alkyne **43** with amines in various media (the numbering of the points corresponds to the entries in Table 9).
(*I*) $r = 0.997$, $n = 6$, $s = 1.54$; (*II*) $r = 0.947$, $n = 4$, $s = 2.53$ (point 13 is omitted); (*III*) $r = 0.998$, $n = 6$, $s = 0.62$.

A comparison of the relationships between the enthalpies and the activation free energies for the Ad_N reactions of compound **43** with amines (Fig. 9) shows that lines *I* and *III* have opposite slopes, which confirms the above conclusion about the difference in the character of the control of the reaction depending on the structure of primary or secondary amines. Line *II* in Fig. 9 demonstrates that $\Delta H^{\neq}$ is independent of changes in $\Delta G^{\neq}$ for the reactions of alkyne **43** with anilines (*cf.* line *II* in Fig. 8).

Both the S_NV and Ad_N reactions are characterised by $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$ varying in very broad ranges and the absence of the common enthalpy–entropy compensation effect. It should also be noted that positive $\Delta S^{\neq}$ allow the reliable identification of the

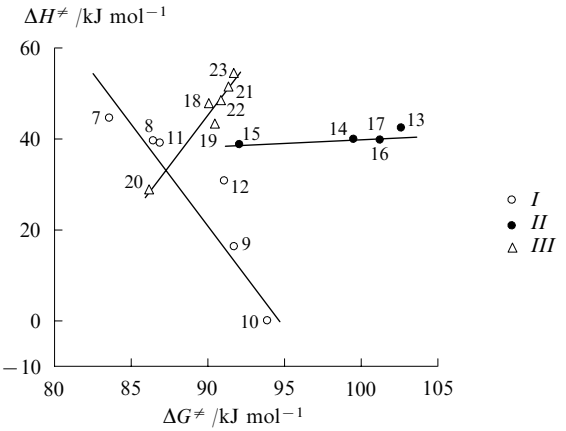


Figure 9. Plots of the enthalpies *vs* the activation free energies for the Ad_N reactions of activated alkyne **43** with amines in various media (the numbering of the points corresponds to the entries in Table 9).
(*I*) $r = 0.975$, $n = 5$, $s = 4.9$; (*II*) $r = 0.697$, $n = 5$, $s = 0.29$; (*III*) $r = 0.967$, $n = 6$, $s = 2.5$.

$E–Ad_N$ mechanism in S_NV reactions and that complexation of a nucleophile with a base and the use of aprotic polar solvents can substantially change the activation parameters for Ad_N reactions.

V. Reactions at the carbonyl carbon

The energetics of bimolecular nucleophilic reactions at the carbonyl carbon atom was extensively analysed.[6, 71, 72, 120, 121] In the last 10–15 years, these reactions were also extensively studied, the main attention being given to elucidation of their detailed mechanism based on both the kinetic data at different temperatures and for different substrates, nucleophiles and solvents and the data on the kinetic isotope exchange.[5, 41, 122–128]

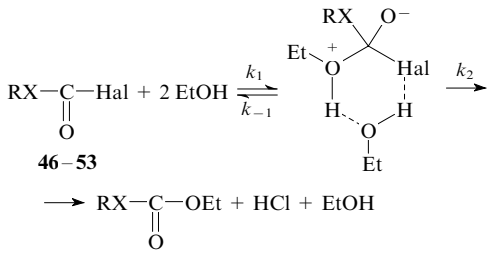
Table 10 gives the rate constants and the activation parameters for bimolecular reactions of carboxylic acid halides with neutral nucleophiles (alcohols and amines) in various media. The rate constants of these reactions vary by 4–5 orders of magnitude; $\Delta H^{\neq}$, from 14.9 to 82.3 kJ mol^{-1}; $\Delta S^{\neq}$, from −238 to −53.8 J mol^{-1} K^{-1}. The fact that the activation parameters vary in broad ranges is attributed to the difference in the mechanisms of these reactions. Ethanolysis of haloformates **46**–**53** was demonstrated [129, 130] to proceed as addition–elimina-

Table 10. Apparent rate constants and activation parameters for bimolecular reactions of carboxylic and thiocarboxylic acid halides with alcohols and amines in various media.

Substrate	Entry	Nucleophile	Temperature /°C	Solvent	k /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
MeOC(O)Cl (**46**)	1	EtOH	30.3	EtOH	0.69×10^{-4} (see [a])	58.0	155.0	105.0	129
	2	EtOH	30.0	EtOH	0.38×10^{-5}	59.0	154.0	105.7	130
	3	cyclo-$C_6H_{11}OH$	30.0	cyclo-$C_6H_{11}OH$	0.10×10^{-6}	69.0	134.0	109.6	130
EtOC(O)Cl (**47**)	4	EtOH	30.2	EtOH	0.56×10^{-4} (see [a])	65.0	135.0	105.9	129
	5	$PhNH_2$	25	Dioxane	0.206	20.5	189.0	77.8	131
	6	PhNHMe	25	Dioxane	0.196	24.5	174.0	77.2	131
	7	$PhNHPr^n$	25	Dioxane	0.0379	21.4	201.0	82.3	131
	8	$PhNHPr^i$	25	Dioxane	0.2699×10^{-3}	61.1	108.0	93.8	131
	9	PhNHC$_6$H$_{11}$-cyclo	25	Dioxane	0.2944×10^{-3}	67.9	84.0	93.3	131
$Pr^nOC(O)Cl$ (**48**)	10	EtOH	35.7	EtOH	1.05×10^{-4} (see [a])	54.0	169.0	105.2	129
$Pr^iOC(O)Cl$ (**49**)	11	EtOH	35.3	EtOH	0.26×10^{-4} (see [a])	82.0	87.0	108.4	129
$PhCH_2OC(O)Cl$ (**50**)	12	EtOH	29.6	EtOH	1.2×10^{-4} (see [a])	60.0	143.0	103.3	129
PhOC(O)Cl (**51**)	13	EtOH	30.7	EtOH	44.0×10^{-4} (see [a])	47.0	156.0	94.3	129
	14	4-$ClC_6H_4NH_2$	15	MeCN	1.16	23.8	142.1	66.8	132
	15	3-$ClC_6H_4NH_2$	15	MeCN	0.550	23.8	163.0	73.2	132
	16	3-$NO_2C_6H_4NH_2$	15	MeCN	0.0931	32.6	146.3	76.9	132
	17	$PhNH_2$	15	MeCN	4.25	21.7	154.7	68.6	132
PhOC(O)F (**52**)	18	EtOH	35.0	EtOH	61.0×10^{-4} (see [a])	47.0	157.0	94.6	129
EtSC(O)Cl (**53**)	19	EtOH	39.8	EtOH	0.88×10^{-4} (see [a])	53.0	173.0	105.4	129
4-$MeOC_6H_4OC(O)Cl$ (**54**)	20	4-MeC_5H_4N	25	MeCN	11.5	29.7	125.4	67.7	133
	21	4-NCC_5H_4N	25	MeCN	0.0201	28.0	183.9	83.7	133
	22	C_5H_5N	25	MeCN	5.50	28.8	133.8	69.3	133
4-$NO_2C_6H_4OC(O)Cl$ (**55**)	23	C_5H_5N	25	MeCN	58.9	30.1	108.7	63.0	133
4-$MeOC_6H_4OC(S)Cl$ (**56**)	24	4-$MeOC_6H_4NH_2$	15	MeCN	1.12	16.3	188.1	73.3	134
	25	4-$ClC_6H_4NH_2$	15	MeCN	0.0669	15.9	209.0	79.2	134
4-$ClC_6H_4OC(S)Cl$ (**57**)	26	4-$MeOC_6H_4NH_2$	15	MeCN	8.68	17.1	196.5	76.6	134
	27	4-$ClC_6H_4NH_2$	15	MeCN	0.361	16.7	196.5	76.2	134
$Me_2C{=}CHC(O)Cl$ (**58**)	28	MeOH [b]	30	C_6H_6	29.23×10^{-3}	49.2	111.0	83.2	135
	29	MeOH [b]	30	CCl_4	63.59×10^{-3}	30.8	166.0	81.2	136
	30	MeOH [b]	30	Me_2CO	1.09×10^{-3}	29.8	203.0	91.4	136
	31	EtOH [b]	30	C_6H_6	10.57×10^{-3}	35.7	165.0	85.7	135
	32	Bu^nOH [b]	30	C_6H_6	9.98×10^{-3}	30.1	184.0	85.9	135
	33	$PhCH_2OH$ [b]	30	C_6H_6	6.75×10^{-3}	14.9	238.0	86.9	135
	34	Bu^tOH [b]	30	C_6H_6	1.21×10^{-3}	65.4	85.0	91.2	135
$CH_2{=}C(Me)C(O)Cl$ (**59**)	35	MeOH [b]	30	C_6H_6	0.60×10^{-3}	29.7	208.6	92.9	137
	36	MeOH [c]	30	C_6H_6	1.03×10^{-3}	47.6	143.3	91.0	137
	37	MeOH [d]	30	C_6H_6	4.37×10^{-3}	71.6	53.8	87.9	137

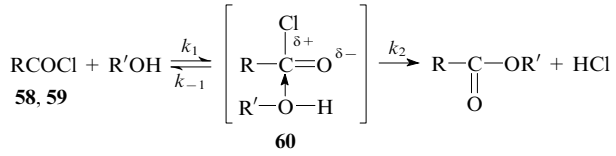
[a] The apparent first-order rate constant /s^{-1}; [b] the molar ratio substrate : nucleophile is 1 : 1; [c] the molar ratio substrate : MeOH is 4 : 1; [d] the molar ratio substrate : MeOH is 7 : 1.

tion *via* a cyclic intermediate due to the involvement of the associated form of ethanol.



R = Alk, Ar; Hal = F, Cl; X = O, S.

Alcoholysis of acid chlorides **58** and **59** proceeds apparently through the initial formation of charge-transfer complex **60**, which is transformed into an activated complex and then into the reaction products.[135–137]



The rate constants of alcoholysis of compounds **58** and **59** depend on the nature of the solvent (entries 28–30 in Table 10),[136] the structure of alcohol (entries 28 and 31–34 in Table 10) [135] and the acid chloride to alcohol ratio (entries 35–37 in Table 10).[137]

Figure 10 shows the compensation plots for alcoholysis of compounds **46**–**53**, **58** and **59**. Line *I* describes ethanolysis reactions characterised by high $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and the enthalpy control in spite of the proposed structure of the cyclic six-membered transition state.[129]

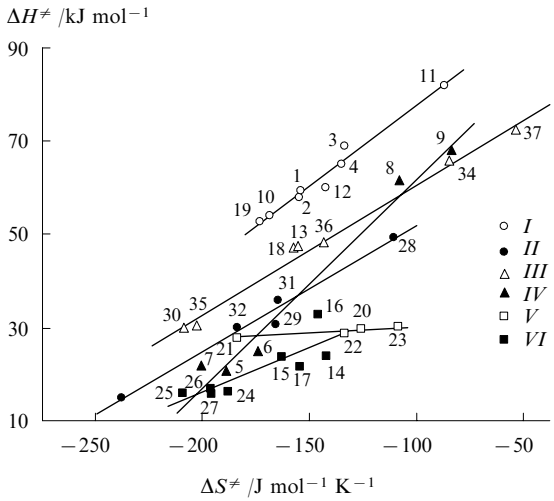
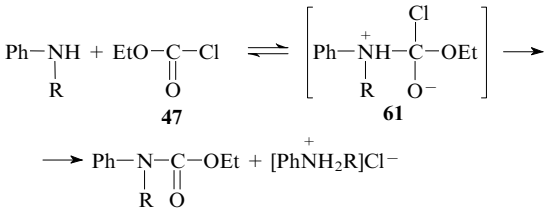


Figure 10. Compensation plots for the reactions of carboxylic and thiocarboxylic acid halides with alcohols and amines (the numbering of the points corresponds to the entries in Table 10).
(*I*) $r = 0.985$, $n = 8$, $s = 1.75$; (*II*) $r = 0.989$, $n = 5$, $s = 2.1$; (*III*) $r = 0.994$, $n = 7$, $s = 1.94$; (*IV*) $r = 0.988$, $n = 5$, $s = 4.1$; (*V*) $r = 0.943$, $n = 4$, $s = 0.4$; (*VI*) $r = 0.844$, $n = 8$.

The alcoholysis reactions of phenyl haloformates **51** and **52** together with the reactions of acid chlorides **58** and **59** form compensation line *III* (see Fig. 10) because of conjugation of the double bond with the C=O group in these compounds. Hence, these reactions proceed *via* complex **60** with both the enthalpy and entropy control.

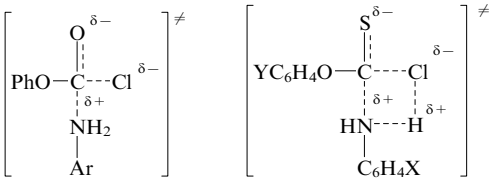
The reactions of acid chloride **58** with primary alcohols in low polar solvents are described by compensation plot *II* (see Fig. 10) with the lowest $\Delta H^{\neq}$ and $\Delta S^{\neq}$, the reactivity being entropy-controlled. Apparently, the formation of complex **60** plays an essential role under these conditions.[135, 137]

A comparison of the activation parameters for the reactions of ethyl (**47**) and aryl chloroformates **51**, **54** and **55** and their sulfur-containing analogues **56** and **57** with pyridines and anilines (see Table 10) shows that changes in the parameters depend on the nature of the nucleophile.[131–134] For example, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are low (entries 5–7, 14–17 and 20–27 in Table 10) and aminolysis reactions of these compounds are entropy-controlled. However, aminolysis of these compounds is characterised by different compensation plots (lines *IV*–*VI* in Fig. 10). For example, line *IV* relates to the activation parameters for the reactions of chloroformate **47** with *N*-alkylanilines (entries 5–9 in Table 10) and is indicative of a high degree of order of the transition state giving rise to intermediate **61** the decomposition of which affords reaction products.[131]



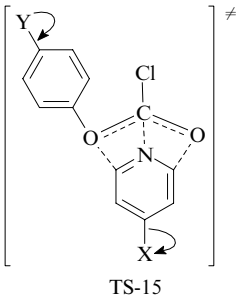
An increase in steric hindrance to the attack on *N*-isopropyl- and *N*-cyclohexylanilines (entries 8 and 9 in Table 10) leads to an increase in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and, consequently, to a looser transition state, the reactions being enthalpy-controlled.[131]

Compensation plot *VI* (see Fig. 10) combines the activation parameters for the reactions of anilines with phenyl chloroformate **51** and its sulfur-containing analogues **56** and **57**. These results do not contradict to the concerted mechanism of these reactions in MeCN *via* the transition state TS-13 for compound **51** [132, 133] and TS-14 for compounds **56** and **57**.[134] However, these reactions in aqueous solution proceed stepwise to form intermediate **61**.[134]



TS-13 TS-14

Aminolysis of aryl chloroformates **54** and **55** with pyridines in MeCN also proceeds stepwise and involves the formation of intermediate **61** as the rate-determining step *via* the transition state TS-15, which is generated as a results of conjugation of the O–C–O fragment in aryl chloroformate with the π system of the pyridine ring.[133]



TS-15

Compensation plot *V* (Fig. 10) is close to the isoenthalpy relation and reflects the interaction between the substituent Y in

the aryl fragment and the pyridine fragment through the π-bond system in TS-15.[133]

A comparison of the relationships between the enthalpies and the activation free energies for the above-described reactions (Fig. 11) confirms the chemical nature of the compensation plots presented in Fig. 10.[71–73] Lines *I*, *IV* and *II*, *III*, *V*, *VI* in Fig. 11 have opposite slopes due to the difference in the character of the control of the reactivity depending on the structure of the nucleophile.

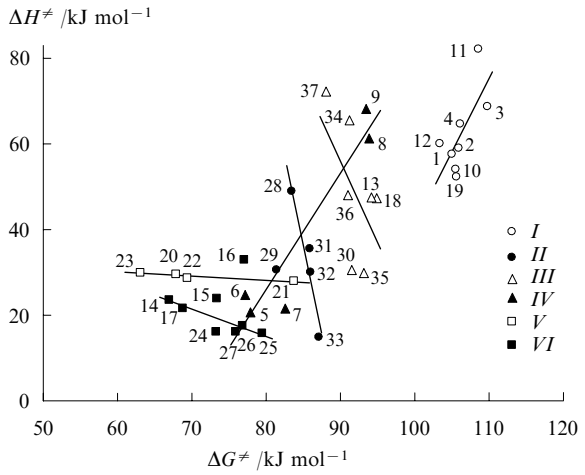
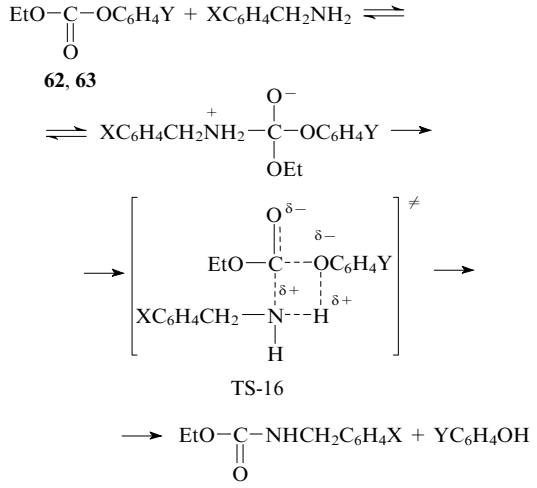


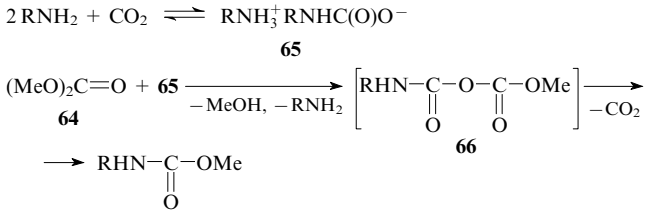
Figure 11. Plots of the enthalpies *vs* the activation free energies for the reactions of compounds **46**–**59** with alcohols and amines (the numbering of the points corresponds to the entries in Table 10).

Aryl chloroformates **51**, **54** and **55** are good models for calculations of the electrophilicity and prediction of the reaction mechanism with neutral and charged nucleophiles.[138] The electrophilicities of alkyl aryl and diaryl carbonates were also calculated.[138] Hence, it is of interest to compare the rate constants and the activation parameters for the reactions of carbonates with nucleophiles and the mechanisms of these reactions. Aminolysis of aryl ethyl carbonates **62** and **63** with benzylamines in MeCN is characterised by high $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (entries 1 and 2 in Table 11) and proceeds stepwise *via* a zwitterionic intermediate, the transformation of which into the reaction products *via* TS-16 is the rate-determining step of the reaction.[139] Low rate constants of the reactions of carbonates **62** and **63** characterise their moderate electrophilicities.[138]



Y = 3-NO_2 (**62**), 4-CN (**63**); X = 4-MeO, 3-Cl.

Aminolysis of dimethyl carbonate **64** in the presence of CO_2 involves two steps; it is a slower reaction and is characterised by the activation parameters varying in a very broad range depending on the structure of alkylamine (entries 3–7 in Table 11).[140] The nucleophilic attack of the ion pair of carbamate anion **65** on the carbonyl carbon atom in compound **64** giving intermediate **66** is the rate-determining step.



A steric interaction between the substituents R in ion pair **65** and the methyl groups in compound **64** results in changes in $\Delta H^{\neq}$ and $\Delta S^{\neq}$,[140] which are described by the compensation relation (line *I*, Fig. 12)

$$\Delta H^{\neq} = 118.1 + 0.34\,\Delta S^{\neq} \quad (r = 0.996,\ s = 3.28,\ n = 5).$$

However, the same reactions on the $\Delta H^{\neq} - \Delta G^{\neq}$ coordinates form two lines with opposite slopes, which reflects the enthalpy (entries 3, 6 and 7 in Table 11) and entropy (entries 4 and 5 in Table 11) control of the reactivity.

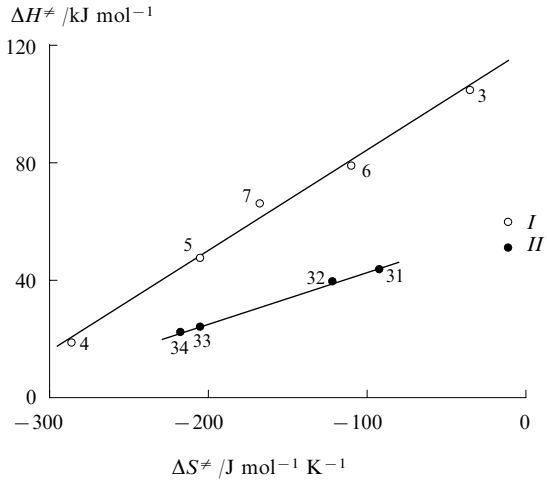


Figure 12. Compensation plots for the reactions of carbonyl compounds **64** and **81**, **82** with amines (the numbering of the points corresponds to the entries in Table 11).

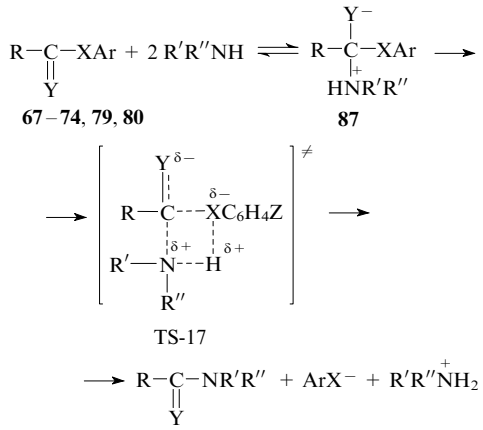
Aminolysis reactions of esters **67**–**74** and thioesters **75**–**79** with benzylamines (entries 8–21, 24 and 25 in Table 11), piperidine, piperazine (entries 28–30 in Table 11) and anilines (entries 22, 23, 26 and 27 in Table 11) involve two steps, where elimination of the leaving group from tetrahedral intermediate **87** is the rate-determining step.[141–147] The only exception is the reaction of thioester **80** with piperidine in water (entry 30 in Table 11) where the formation of an intermediate is the rate-determining step.[147] Decomposition of zwitterionic intermediate **87** occurs *via* the cyclic transition state TS-17.[141–147]

The reactions of compounds **67**–**70** with benzylamines (entries 8–15 in Table 11) and the reactions of compounds **77** and **78** with benzylamines and anilines (entries 24–27 in Table 11) are characterised by high activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ due to which these reactions are enthalpy-controlled. On the contrary, the reactions of compounds **71**–**76** with benzylamines and

Table 11. Apparent rate constants and activation parameters for bimolecular reactions of carbonyl compounds with various nucleophiles.

Substrate	Entry	Nucleophile	Temperature /°C	Solvent	k /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
$EtOCO_2C_6H_4NO_2$-3 (**62**)	1	4-$MeOC_6H_4CH_2NH_2$	25	MeCN	1.10×10^{-3}	62.7	71.1	83.8	139
$EtOCO_2C_6H_4CN$-4 (**63**)	2	3-$ClC_6H_4CH_2NH_2$	25	MeCN	0.477×10^{-3}	60.2	87.8	86.4	139
$(MeO)_2C{=}O$ (**64**) [a]	3	Pr^nNH_2	71.2	–	11.19×10^{-6}	104.9	35.6	109.1	140
	4	$PhCH_2NH_2$	72.2	–	11.28×10^{-6}	18.8	285.8	117.2	140
	5	$CH_2{=}CHCH_2NH_2$	72.2	–	7.64×10^{-6}	47.6	205.6	118.6	140
	6	Bu^nNH_2	71.2	–	13.05×10^{-6}	79.0	109.7	116.7	140
	7	Bu^sNH_2	70.2	–	1.086×10^{-6}	66.0	167.4	123.5	140
$MeCO_2C_6H_4Cl$-4 (**67**)	8	4-$MeC_6H_4CH_2NH_2$	25	DMSO	0.102	52.7	87.8	78.9	141
	9	4-$ClC_6H_4CH_2NH_2$	25	DMSO	0.039	52.3	96.1	80.9	141
$MeCO_2C_6H_4CN$-4 (**68**)	10	4-$MeC_6H_4CH_2NH_2$	25	DMSO	1.65	45.6	96.1	74.3	141
	11	4-$ClC_6H_4CH_2NH_2$	25	DMSO	1.03	43.5	100.3	73.4	141
$Bu^tCO_2C_6H_4Cl$-4 (**69**)	12	4-$MeC_6H_4CH_2NH_2$	35	DMSO	0.068×10^{-3}	56.4	121.2	92.5	141
	13	4-$ClC_6H_4CH_2NH_2$	35	DMSO	0.0266×10^{-3}	61.0	133.8	100.9	141
$Bu^tCO_2C_6H_4CN$-4 (**70**)	14	4-$MeC_6H_4CH_2NH_2$	35	DMSO	25.3×10^{-3}	46.8	125.4	84.2	141
	15	4-$ClC_6H_4CH_2NH_2$	35	DMSO	17.3×10^{-3}	48.9	129.6	87.5	141
cyclo-$C_3H_5CO_2C_6H_4CN$-3 (**71**)	16	4-$MeC_6H_4CH_2NH_2$	35	MeCN	0.675×10^{-3}	22.5	234.1	94.6	142
cyclo-$C_3H_5CO_2C_6H_4NO_2$-4 (**72**)	17	4-$MeC_6H_4CH_2NH_2$	35	MeCN	39.4×10^{-3}	27.2	183.9	83.8	142
cyclo-$C_4H_7CO_2C_6H_4CN$-3 (**73**)	18	4-$MeC_6H_4CH_2NH_2$	35	MeCN	1.49×10^{-3}	22.6	225.7	92.1	143
cyclo-$C_4H_7CO_2C_6H_4NO_2$-4 (**74**)	19	4-$MeC_6H_4CH_2NH_2$	35	MeCN	86.6×10^{-3}	22.2	192.3	81.4	143
$PhCH_2C(S)SC_6H_4Br$-4 (**75**)	20	4-$MeOC_6H_4CH_2NH_2$	−25	MeCN	241.0	10.9	154.7	50.8	144
$PhCH_2C(S)SC_6H_4Me$-4 (**76**)	21	4-$CF_3C_6H_4CH_2NH_2$	−25	MeCN	0.083	10.9	221.5	68.1	144
	22	4-$MeOC_6H_4NH_2$	35	MeCN	5.34×10^{-4}	18.4	246.6	94.4	145
	23	3-$ClC_6H_4NH_2$	35	MeCN	0.061×10^{-4}	19.6	280.1	105.9	145
$EtC(S)SC_6H_4Br$-4 (**77**)	24	$PhCH_2NH_2$	−25	MeCN	98.2	37.2	96.1	62.0	146
$EtC(S)SC_6H_4Me$-4 (**78**)	25	$PhCH_2NH_2$	−25	MeCN	7.25	35.5	83.6	57.1	146
	26	4-$MeOC_6H_4NH_2$	35	MeCN	5.05×10^{-3}	53.1	117.0	89.1	145
	27	3-$ClC_6H_4NH_2$	35	MeCN	0.0242×10^{-3}	66.9	117.0	102.9	145
MeC(O)SPh (**79**)	28	piperidine	45	H_2O	56.9	31.8	111.6	67.3	147
	29	piperazine	45	H_2O	9.2	36.4	112.9	72.3	147
$MeC(O)SC_6H_4NO_2$-4 (**80**)	30	piperidine	45	H_2O	589.0	41.0	63.5	61.2	147
$PhNHC(O)SC_6H_4Me$-4 (**81**)	31	4-$MeOC_6H_4CH_2NH_2$	30	MeCN	2.18	43.9	92.0	71.5	148
	32	4-$ClC_6H_4CH_2NH_2$	30	MeCN	0.451	39.3	121.2	76.0	148
$EtNHC(O)SC_6H_4Me$-4 (**82**)	33	4-$MeOC_6H_4CH_2NH_2$	30	MeCN	6.96×10^{-3}	24.2	204.8	86.3	149
	34	4-$ClC_6H_4CH_2NH_2$	30	MeCN	3.06×10^{-3}	22.6	217.4	88.5	149
4-$NO_2C_6H_4C(O)SC_6H_4Me$-4 (**83**)	35	4-$MeOC_5H_4N$	35	MeCN	4.49×10^{-3}	31.4	188.1	91.2	150
	36	4-NCC_5H_4N	35	MeCN	0.0337×10^{-3}	31.4	229.9	104.5	150
$MeC(S)SC_6H_4Me$-4 (**84**)	37	4-MeC_5H_4N	40	MeCN	15.3×10^{-4}	34.7	188.1	93.6	151
	38	3-ClC_5H_4N	40	MeCN	0.0394×10^{-4}	35.5	234.1	108.8	151
4-$MeOC_6H_4C(O)CH_2Br$ (**85**)	39	3-MeC_5H_4N	35	MeCN	6.21×10^{-3}	6.7	71.1	29.3	152
	40	3-NCC_5H_4N	35	MeCN	0.0355×10^{-3}	36.4	213.2	104.2	152
$PhCO_2C_6H_3(NO_2)_2$-2,4 (**86**)	41	4-$Me_2NC_5H_4N$	45.2	44% EtOH	41.2	9.6	184.8	68.3	153
	42	3-MeC_5H_4N	45.2	44% EtOH	41.2×10^{-3}	54.3	101.6	86.6	153

[a] Aminolysis of this substrate (entries 3 – 7) was performed in the presence of CO_2.



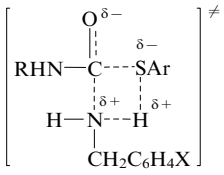
Y = X = O; Y = O, X = S; Y = X = S.

anilines (entries 16 – 23 in Table 11) and of compound **79** with piperidine (entry 28 in Table 11) are characterised by lower activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and the entropy control. The activation parameters for aminolysis of compounds **67** – **79** fall within two ranges (with low and high $\Delta H^{\neq}$ and $\Delta S^{\neq}$), however no enthalpy – entropy compensation effect is observed. The more organised transition states of the TS-17 type for aminolysis of compounds **71** – **76** are attributed to hydrogen bonding with the $ZC_6H_4X^-$ leaving group.[142, 143]

A decrease in the contribution of the latter to the structure of TS-17 due to an increase in the steric effect of the substituent R in the substrate (for example, R = Et) [145] or the solvent effect [141, 147] results in a looser structure of the transition state TS-17 and an increase in the activation parameters.

A much stronger donor effect of the PhNH and EtNH groups in thiocarbamates **81** and **82** leads to a switch from the stepwise mechanism to the concerted mechanism in the reactions of these compounds with benzylamines (entries 31 – 34 in Table 11).[148, 149] The transition state TS-18 for these reactions involves a four-

membered ring, which is more rigid in the presence of a strong electron-donating substituent (R = Et).[149]



TS-18

The activation parameters for these aminolysis reactions are characterised by the compensation relations between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (line *II* in Fig. 12) and between $\Delta H^{\neq}$ and $\Delta G^{\neq}$:

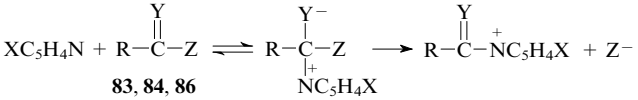
$$\Delta H^{\neq} = 60.0 + 0.17\,\Delta S^{\neq} \ (r = 0.999,\ s = 0.38,\ n = 4),$$

$$\Delta H^{\neq} = 138.1 - 1.31\,\Delta G^{\neq} \ (r = 0.997,\ s = 0.94,\ n = 4),$$

which confirms the chemical nature of the compensation effect.[71–73]

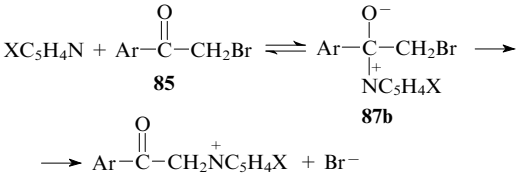
It should be noted that the activation parameters for aminolysis of thiocarbamates **81** and **82** proceeding by the concerted mechanism and aminolysis of esters and thioesters proceeding by the stepwise mechanism vary in the same range. Recently, it has been demonstrated that the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for the aminolysis of carbonates **62** and **63**[139] are rather close to those of related thiocarbonates[138] although the reactions of carbonates proceed by the stepwise mechanism, whereas the reactions of thiocarbonates occur by the concerted mechanism.[139, 148, 154] Evidently, to estimate unambiguously the reaction mechanism, it is necessary to use the activation parameters along with the correlation analysis and data on the kinetic isotope effect.[5, 41, 122–128]

The reactions of ester **86** and thioesters **83** and **84** with pyridines proceed stepwise *via* tetrahedral intermediate **87a**.[150, 151, 153]



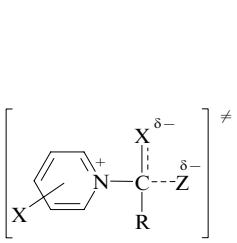
83, **84**, **86** **87a**

The reaction of phenacyl bromide **85** also proceed *via* an analogous intermediate.[152]

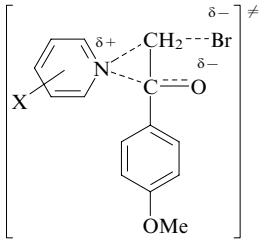


85 **87b**

The formation of intermediates **87a**,**b** was demonstrated to be the rate-determining step of the reactions with more basic pyridines, whereas decomposition of these intermediates is the rate-determining step of the reactions with weakly basic pyridines in low polar MeCN (entries 35–40 in Table 11).[150–152] However, the influence of the basicity of pyridines on the reaction mechanism in aqueous-alcoholic media is less significant due to an increase in the contribution of solvation of the transition state TS-19. As a result, decomposition of the corresponding intermediate was the rate-determining step for all the pyridines examined.[153] Aminolysis reactions with pyridine, in which decomposition of intermediates is the rate-determining step, are characterised by much lower entropies of activation (entries 36, 38, 40 and 41 in Table 11). The latter fact is associated with the more organised and more solvated transition states TS-19 and TS-20 for the transformations of intermediates **87a** and **87b**, respectively.[150–152]

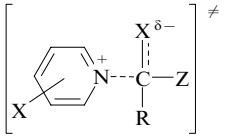


TS-19

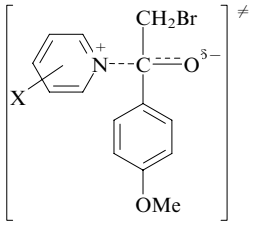


TS-20

The less organised and less solvated transition states TS-21 and TS-22 are typical of the reactions of pyridine with compounds **83**–**86** involving the formation of the corresponding intermediates as the rate-determining step.



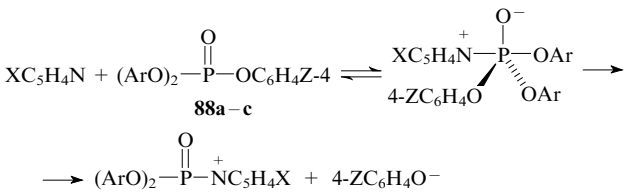
TS-21



TS-22

An increase in $\Delta S^{\neq}$ is either not accompanied by changes in $\Delta H^{\neq}$ (entries 35–38 in Table 11) or is accompanied by a decrease (entries 39 and 40 in Table 11) or even an increase in these parameters (entries 41 and 42 in Table 11). Therefore, no compensation effects were observed for the reactions of compounds **83**–**86** with pyridine, although almost all reactions are entropy-controlled (entries 35–41 in Table 11). The reaction of ester **86** with weakly basic pyridine in aqueous EtOH, which is enthalpy-controlled is the exception (entry 42 in Table 11).[153]

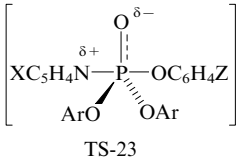
Aminolysis of carbonyl compounds with pyridine is similar in the energetics and the reaction mechanism to analogous reactions of triaryl phosphates. For example, study of the kinetics of the reactions of aryl bis(4-methoxyphenyl) phosphates **88a**–**c** with pyridines in MeCN showed that the activation parameters vary in broad ranges depending on the basicity of pyridine and the nature of the substituent Z in the leaving group ($\Delta H^{\neq}$ from 5.4 to 39.3 kJ mol^{-1} and $\Delta S^{\neq}$ from -259.2 to -137.9 J mol^{-1} K^{-1}). The use of less basic pyridine (X = 3-Cl) and a better nucleofuge containing an electron-withdrawing substituent Z (Z = CN or NO_2) leads to a sharp decrease in the activation parameters.[155]



88a–**c**

Ar = 4-MeOC$_6$H$_4$; Z = Cl (**a**), CN (**b**), NO_2 (**c**).

This is associated with the fact that the reaction proceeds by the concerted mechanism *via* the transition state TS-23 with the apical arrangement of the nucleophile and the leaving group.



TS-23

The more basic pyridine (X = 4-Me) and the poorer leaving group in the substrate (Z = Cl) lead to an increase in $\Delta H^{\neq}$ and $\Delta S^{\neq}$,

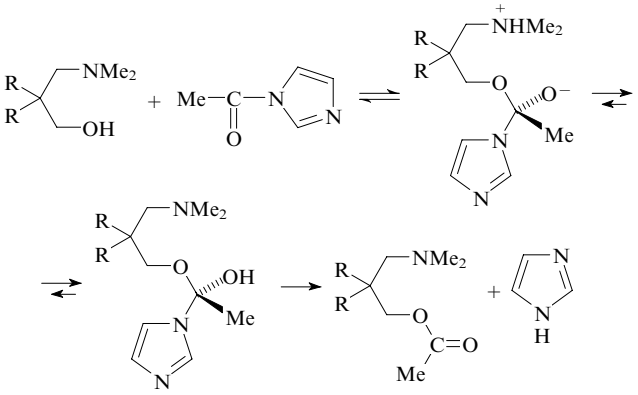
which is associated with the fact that this reaction proceeds by the stepwise mechanism involving the formation of an intermediate as the rate-determining step.[155] The activation parameters are described by the common compensation relations

$$\Delta H^{\neq} = 77.83 + 0.279\,\Delta S^{\neq}\ (r = 1.0,\ s = 0.014,\ n = 3),$$

$$\Delta H^{\neq} = 524.11 - 5.74\,\Delta G^{\neq}\ (r = 0.999,\ s = 0.167,\ n = 3)$$

for the reactions proceeding by different mechanisms.[155]

Alcoholysis of *N*-acetylimidazole with 2,2-dialkyl-3-(*N*,*N*-dimethylamino)propan-1-ols in MeCN at 25–65 °C occurs stepwise and involves, as the rate-determining step, the formation of a tetrahedral intermediate, which is then transformed into the reaction products.[62]

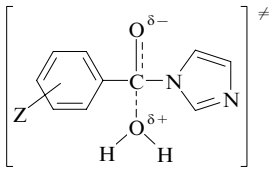


These reactions are characterised by very low entropies of activation ($\Delta S^{\neq}$ from -210 to -171 J mol^{-1} K^{-1}), moderate enthalpies of activation ($\Delta H^{\neq} = 27.4$–40.9 kJ mol^{-1}) and the entropy control.[62] There is the enthalpy–entropy compensation

$$\Delta H^{\neq} = 91.2 + 0.30\,\Delta S^{\neq}\ (r = 0.935,\ s = 1.43,\ n = 8).$$

However, the isokinetic relationships between the activation parameters depend on the structures of the substituents R in the starting amino alcohol.[62]

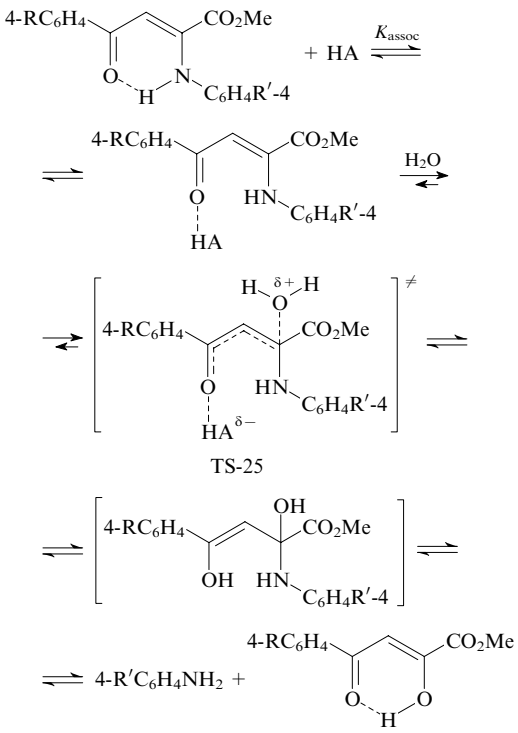
Non-catalysed hydrolysis of substituted *N*-benzoylimidazoles in 10% aqueous MeCN proceeds *via* the transition state TS-24 with pronounced charge separation. The substituent Z has a considerable effect on solvation and $\Delta S^{\neq}$.



TS-24

For example, $\Delta S^{\neq}$ varies from -186.4 J mol^{-1} K^{-1} for Z = 4-Me to -136.7 J mol^{-1} K^{-1} for Z = 4-NO$_2$; $\Delta H^{\neq}$, from 43.5 to 50.6 kJ mol^{-1} for Z = Me and NO$_2$, respectively. The entropy control of the reaction changes to the enthalpy control with increasing electron-withdrawing properties of the substituent Z.[156] Evidently, the energy parameters for alcoholysis of acylimidazoles are very close to those for hydrolysis of these compounds.

Hydrolysis of enamines in 50% aqueous dioxane in the presence of an acetate buffer occurs stepwise and involves the addition *via* the transition state TS-25 as the rate-determining step to form an intermediate and then the reaction products.[157]



TS-25

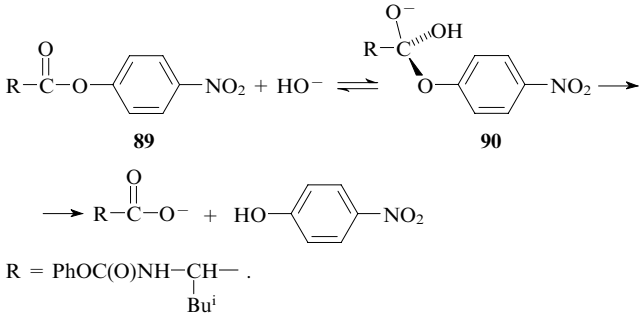
R = H: R′ = H, Br, NO$_2$; R = Me, R′ = H;
R = MeO, R′ = H; R = NO$_2$, R′ = H.

The activation parameters are close to those for hydrolysis of *N*-benzoylimidazoles in the case of the entropy control of the reaction.[157] The hydrolysis reactions of the above-mentioned enamines are characterised by the following relation

$$\Delta H^{\neq} = 107.4 + 0.31\,\Delta S^{\neq}\ (r = 0.990,\ s = 1.5,\ n = 8),$$

which indicates that the equilibrium constant of association of the substrate with the buffer component HA makes a contribution to the apparent rate constant.[157]

Alkaline hydrolysis of esters occurs stepwise and involves the formation of a tetrahedral intermediate as the rate-determining step.[125] For example, hydrolysis of ester **89** in 10% aqueous MeCN proceeds *via* intermediate **90** and is characterised by very low activation parameters: $\Delta H^{\neq} = 13.5$ kJ mol^{-1} and $\Delta S^{\neq} = -277.1$ J mol^{-1} K^{-1}.

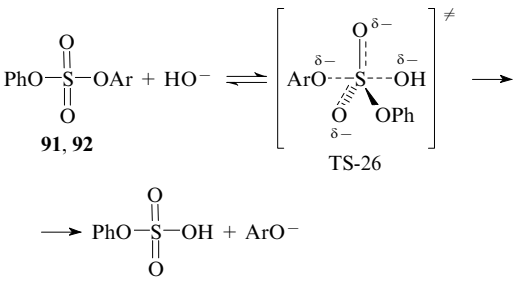


89 **90**

R = PhOC(O)NH–CH(Bu^i)–.

Hydrolysis is sharply accelerated in the presence of polymeric bases as catalysts. In this case, the activation parameters are substantially higher: $\Delta H^{\neq} = 55.6$–65.6 kJ mol^{-1}, $\Delta S^{\neq}$ from -62.7 to -12.6 J mol^{-1} K^{-1}. The reaction is controlled by the enthalpy.[158] The isokinetic relationship with $\beta = 313$ K found for the catalytic process is due to the contribution of the equilibrium constant between substrate **89** and the catalyst to the apparent rate constant.[158]

In 10% aqueous dioxane, alkaline hydrolysis of diaryl sulfates **91** and **92**, *viz*., sulfur-containing analogues of diaryl carbonates, proceeds apparently by the concerted mechanism *via* the transition state TS-26 and is characterised by high activation parameters ($\Delta H^{\neq}$ = 88.0 and 84.8 kJ mol^{-1} and $\Delta S^{\neq}$ = −37.0 and −50.2 J mol^{-1} K^{-1} for compounds **91** and **92**, respectively) and the enthalpy control of the reactivity.[159]

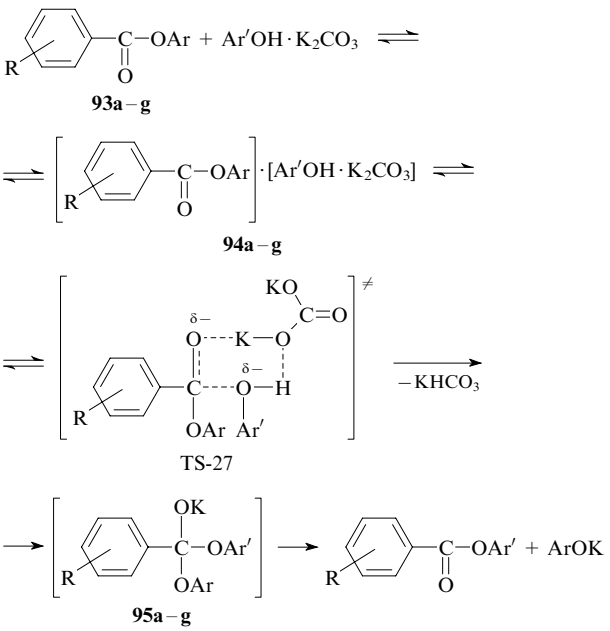


Ar = 4-Cl-3-$NO_2C_6H_3$ (**91**), 4-$NO_2C_6H_4$ (**92**).

It should be noted that the reactions of diaryl carbonates with phenolate anions in aqueous solution also proceed by the concerted mechanism.[160]

Transesterification can occur by different mechanisms.[125] For example, the reaction of 4-nitrophenyl acetate with 4-chlorophenolate in aqueous media proceeds throught the one-step concerted mechanism[123] with the activation parameters $\Delta H^{\neq}$ = 51.4 kJ mol^{-1}, $\Delta S^{\neq}$ = −75.7 J mol^{-1} K^{-1} and $\Delta G^{\neq}$ = 74.0 kJ mol^{-1}. These parameters are only slightly smaller for the reaction in 90% aqueous DMSO or for the reaction with butane-2,3-dione monooximate as the nucleophile, the enthalpy control being retained.[161]

The activation parameters for transesterification of 4-nitrophenyl benzoates **93a**–**g** with the nucleophile 4-$ClC_6H_4O^-K^+$ differ substantially from those for the reaction with the 4-$ClC_6H_4OH \cdot K_2CO_3$ complex.[67, 162]



R = 4-MeO (**a**), 4-Me (**b**), H (**c**), 4-Br (**d**), 4-CF_3 (**e**), 3-NO_2 (**f**), 4-NO_2 (**g**); Ar = 4-$NO_2C_6H_4$, Ar′ = 4-ClC_6H_4.

An increase in the electron-withdrawing properties of the substituent R in benzoates **93a**–**g** leads to a substantial decrease in the relative values of the parameters $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ for transesterification reactions due apparently to the characteristic features of complexes **94a**–**g**. The transformation of the latter through the cyclic transition state TS-27 into intermediates **95a**–**g** is the rate-determining step of the process.[162] The reactions of benzoates **93a**–**g** are characterised by the compensation relations

$$\Delta\Delta H^{\neq} = 2.23 + 0.39\,\Delta\Delta S^{\neq} \quad (r = 0.999,\ s = 1.67,\ n = 7),$$

$$\Delta\Delta H^{\neq} = -9.49 + 4.64\,\Delta\Delta G^{\neq} \quad (r = 0.984,\ s = 6.35,\ n = 7)$$

the reactivity being enthalpy-controlled.[162] It should be noted that the isokinetic relationship for transesterification reactions is observed only for benzoates **93c**–**g** (see Ref. 162) due to destabilisation of the ground state of these compounds.[125, 163–165]

Bimolecular nucleophilic reactions at the carbonyl carbon atom, like the reactions considered in the previous sections, are characterised by very broad ranges of the activation parameters within one class of substrates. It should be noted that complexation between carbonyl compounds and nucleophiles plays a considerable role in the changes in the activation parameters.

VI. Reactions of carbocations with nucleophiles

The energetics of the reactions of stable carbocations with nucleophiles is of particular interest because, first, the formation of the bond between these species is the rate-determining step and, second, most of these reactions are described by either Ritchie's equation[166, 167]

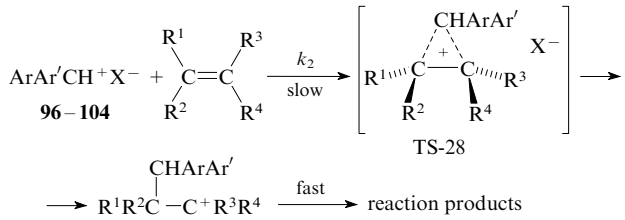
$$\log\frac{k}{k_0} = N_+,$$

where k and k_0 are the rate constants of the reaction of the substrate with this nucleophile and water, respectively, and N_+ is the nucleophilicity, or by the equation proposed by Mayr and coworkers,[167–169]

$$\log k(20\ ^\circ\mathrm{C}) = s(N + E),$$

where s is the specific parameter of the nucleophile (s = 1 for 2-methylpent-1-ene), N is the nucleophilicity for the nucleophile and E is the electrophilicity for the electrophile.

The rate constants and the activation parameters for the reactions of benzhydryl and benzopyrylium cations with neutral π-nucleophiles (alkenes and dienes) vary within broad ranges. The rate constants vary by 7–8 orders of magnitude; $\Delta H^{\neq}$, from 0 to 53 kJ mol^{-1}; $\Delta S^{\neq}$, from −180 to −80 J mol^{-1} K^{-1}.[168–175] These broad ranges are attributed to the fact that the structure of the transition state TS-28 and its position on the reaction coordinate substantially depend on the nature of the reagents.[170, 171, 175]



Hence, there is no common enthalpy–entropy compensations for the above-mentioned reactions of cations with π-nucleophiles. However, the compensation relations are observed for the reactions of benzhydryl cations with the same nucleophile, for example, for the reactions of cations **96**–**100** with alkene $Pr^nMeC{=}CH_2$ (entries 1, 4, 6, 8 and 10, Table 12) or $Me_2C{=}CHMe$ (entries 2, 5, 7, 9 and 11 in Table 12), the reactions of cations **101**–**104** with alkene $CH_2{=}C(OPh)OSiMe_3$ (entries 12, 15, 18 and 20 in Table 12) or with 1-(trimethylsilyloxy)cyclopentene (entries 14, 17 and 19 in Table 12) and the reactions of cations **96**, **101** and **102** with alkenes $Me_2C{=}CMe_2$ and $Me_2C{=}C(OMe)OSiMe_3$ (entries 3, 13 and 16 in Table 12).

In the reactions of the cations with π-nucleophiles characterised by the activation parameters $\Delta H^{\neq}$ < 30 kJ mol^{-1} and $\Delta S^{\neq}$ < −100 J mol^{-1} K^{-1}, the reactivity is entropy-controlled. If these parameters are larger than the above-mentioned values,

Table 12. Rate constants and activation parameters for bimolecular reactions of benzhydryl carbocations with alkenes in CH_2Cl_2.[a]

Substrate	Entry	Nucleophile	k_2 /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
4-MeOC$_6$H$_4$(Ph)CH$^+$ (**96**)	1	Pr^{n}MeC=CH$_2$	2.58×10^1	19.5	119.0	43.7	168
	2	Me$_2$C=CHMe	2.47×10^2	7.5	159.0	39.8	168
	3	Me$_2$C=CMe$_2$	5.62	8.0	188.0	46.2	168
(4-MeOC$_6$H$_4$)$_2$CH$^+$ (**97**)	4	Pr^{n}MeC=CH$_2$	2.92×10^{-2}	29.7	125.0	55.1	170
	5	Me$_2$C=CHMe	8.38×10^{-2}	21.9	155.0	53.4	170
4-MeOC$_6$H$_4$(4-MeC$_6$H$_4$)CH$^+$ (**98**)	6	Pr^{n}MeC=CH$_2$	3.38	22.7	120.0	47.1	170
	7	Me$_2$C=CHMe	1.83×10^1	13.6	151.0	44.3	170
4-PhOC$_6$H$_4$(Ph)CH$^+$ (**99**)	8	Pr^{n}MeC=CH$_2$	2.86×10^2	15.3	119.0	39.4	170
	9	Me$_2$C=CHMe	3.92×10^3	5.3	147.0	35.1	170
(4-MeC$_6$H$_4$)$_2$CH$^+$ (**100**)	10	Pr^{n}MeC=CH$_2$	3.40×10^3	11.6	117.0	35.4	170
	11	Me$_2$C=CHMe	6.79×10^4	−1.4	117.0	156.0	170
(4-pyr-C$_6$H$_4$)$_2$CH$^+$ (**101**)[b]	12	CH$_2$=C(OPh)OSiMe$_3$	2.35	44.9	85.0	69.8	171
	13	Me$_2$C=C(OMe)OSiMe$_3$	2.32×10^1	31.1	112.0	63.9	171
(4-Me$_2$NC$_6$H$_4$)$_2$CH$^+$ (**102**)	14	1-Me$_3$SiO-C$_5$H$_7$-cyclo	3.61×10^{-1}	40.8	114.0	74.2	171
	15	CH$_2$=C(OPh)OSiMe$_3$	9.45	37.9	97.0	66.3	171
	16	Me$_2$C=C(OMe)OSiMe$_3$	7.96×10^1	25.7	121.0	61.1	171
(4-mor-C$_6$H$_4$)$_2$CH$^+$ (**103**)[c]	17	1-Me$_3$SiO-C$_5$H$_7$-cyclo	1.05×10^1	33.6	111.0	66.1	171
	18	CH$_2$=C(OPh)OSiMe$_3$	1.38×10^2	32.3	94.0	59.8	171
(4-Ph$_2$NC$_6$H$_4$)$_2$CH$^+$ (**104**)	19	1-Me$_3$SiO-C$_5$H$_7$-cyclo	5.80×10^1	24.3	128.0	61.8	171
	20	CH$_2$=C(Ph)OSiMe$_3$	5.41×10^2	22.5	116.0	56.5	171

[a] Reactions were carried out at −70 °C (entries 1–11) and 20 °C (entries 12–20); [b] pyr is pyrrolidino; [c] mor is morpholino.

the enthalpy makes a larger contribution to the activation free energy of these reactions.

The fast reactions of highly electrophilic benzhydryl cations **96**, **99** and **100** with alkenes Me$_2$C=CHMe and Me$_2$C=CMe$_2$ are characterised by very low $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (entries 2, 3, 9, 11 in Table 12).[168, 170, 175] Changes in the electrophilicity of the benzhydryl cations were demonstrated [175] to have a stronger effect on $\Delta H^{\neq}$ than on $\Delta S^{\neq}$ (Figures 13 and 14). Hence, negative $\Delta H^{\neq}$ for the reactions of highly electrophilic carbocations can be attributed to the shift of the transition state TS-28 to the earlier position on the reaction coordinate, which is accompanied by an increase in the entropy of activation (entries 3 and 11 in Figures 13 and 14).[175]

The reactivity of carbocations of the triarylmethane series **105**–**119** in the reactions with cyanide ions in aqueous media described by Ritchie's equation is substantially lower than that of the benzhydryl cations, and $\Delta H^{\neq}$ and $\Delta S^{\neq}$ vary in the ranges from 31 to 52 kJ mol^{-1} and from −187 to −40 J mol^{-1} K^{-1}, respectively (Table 13).[176] There is no common compensation relations

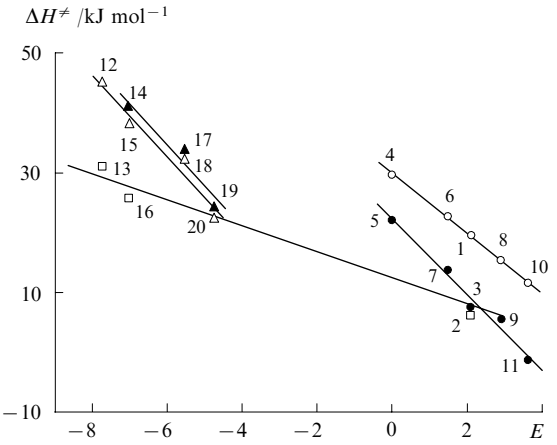


Figure 13. Plots of the enthalpy of activation *vs* the electrophilicity for the reactions of benzhydryl cations with neutral π-nucleophiles (the numbering of the points corresponds to the entries in Table 12).

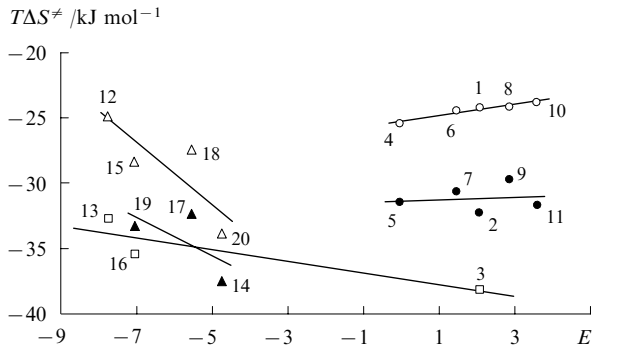


Figure 14. Plots of the entropy ($T\Delta S^{\neq}$) *vs* the electrophilicity for the reactions of benzhydryl cations with neutral π-nucleophiles (the numbering of the points corresponds to the entries in Table 12).

for the latter reactions (as in the case of the reactions of benzhydryl cations). Only certain series of these cations are characterised by the compensation (isokinetic) relations between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (Fig. 15).[176]

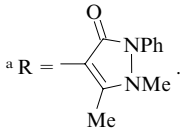
$$\underset{\textbf{105–119}}{Ar^1Ar^2Ar^3C^+} + CN^- \xrightarrow[H_2O]{k_1} \underset{\text{TS-29}}{\left[Ar^1Ar^2Ar^3C^+ \cdots CN^-\right]^{\neq}} \longrightarrow Ar^1Ar^2Ar^3C{-}CN$$

The structure of the transition state TS-29 for the reactions of cations **105**–**116** controlled by the enthalpy of activation is described by a solvent-separated ion pair, whereas the structure of TS-29 for the reactions of cations **117**–**119** controlled by the entropy of activation can be represented as a contact ion pair.[176]

The reaction of the most reactive cation **106** with the CN$^-$ ions is characterised by the highest value of $\Delta S^{\neq}$, whereas the analogous reaction of the least reactive cation **117** is characterised by very low $\Delta S^{\neq}$ (see Table 13). The earlier and less-organised transition state TS-29 and the later and well-organised transition state TS-29 for the reactions of cations **106** and **117**, respectively,

Table 13. Rate constants and activation parameters for bimolecular reactions of cations of the triarylmethane series with the CN^- anion in water at 30 °C.[176]

Cation	Entry	k_1 /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$
(4-MeC_6H_4)R_2C^+ (**105**) [a]	1	28.5	35.5	100.0	65.8
(3-$NO_2C_6H_4$)R_2C^+ (**106**) [a]	2	180	48.9	40.0	61.0
PhR_2C^+ (**107**) [a]	3	42.9	38.7	86.0	64.8
Ph(4-$Me_2NC_6H_4$)(4-MeC_6H_4)C^+ (**108**)	4	11.5	46.1	72.0	67.9
Ph(4-$Me_2NC_6H_4$)(3-$NO_2C_6H_4$)C^+ (**109**)	5	16.5	41.6	84.0	67.1
Ph_2(4-$Me_2NC_6H_4$)C^+ (**110**) [b]	6	12.7	49.0	62.0	67.8
(4-$MeOC_6H_4$)(4-$Me_2NC_6H_4$)(4-MeC_6H_4)C^+ (**111**)	7	7.00	51.9	57.0	69.2
(4-$MeOC_6H_4$)(4-$Me_2NC_6H_4$)(3-$NO_2C_6H_4$)C^+ (**112**)	8	26.5	45.6	72.0	67.4
(4-$MeOC_6H_4$)(4-$Me_2NC_6H_4$)(Ph)C^+ (**113**)	9	9.25	46.0	74.0	68.4
(4-$Me_2NC_6H_4$)$_2$(4-MeC_6H_4)C^+ (**114**)	10	0.743	52.3	75.0	75.0
(4-$Me_2NC_6H_4$)$_2$(3-$NO_2C_6H_4$)C^+ (**115**)	11	1.45	40.1	110.0	73.4
(4-$Me_2NC_6H_4$)$_2$PhC^+ (**116**)	12	0.836	40.4	83.0	74.5
(4-O$^-$-3-$MeOC_6H_3$)$_2$(4-MeC_6H_4)C^+ (**117**)	13	4.73×10^{-3}	30.9	187.0	87.6
(4-O$^-$-3-$MeOC_6H_3$)$_2$(3-$NO_2C_6H_4$)C^+ (**118**)	14	9.48×10^{-3}	41.6	146.0	85.8
(4-O$^-$-3-$MeOC_6H_3$)$_2$PhC^+ (**119**)	15	7.94×10^{-3}	31.7	184.0	87.4

[a] R = 

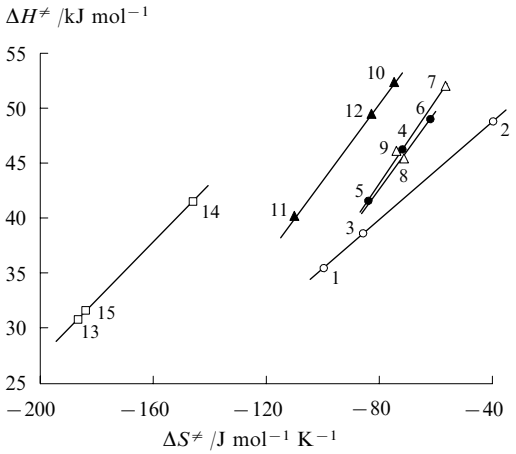
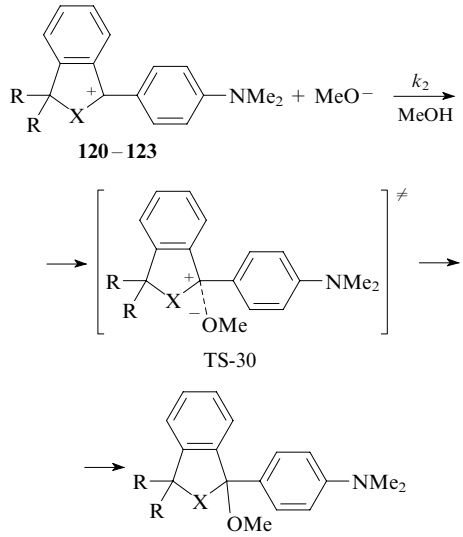


Figure 15. Compensation plots for the reactions of cations **105**–**119** with the cyanide ion (the numbering of the points corresponds to the entries in Table 13).

are not contradictory to the reaction mechanisms through solvent-separated and contact ion pairs.

Heterocarbocations **120**–**123** are very reactive in the reactions with the MeO^- anion in MeOH. Both series of the cations (with X = O and X = S) are characterised by isokinetic relationships and the enthalpy control of the reaction.[177] An increase in the charge on the carbocationic centre leads not only to an increase in the rate constant but also to a decrease in the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$, which is more pronounced in the case of less stabilised oxygen-containing cations **120** and **121**.[177] Presumably, the transition state TS-30 as the solvent-separated ion pair (as in the reactions of cations **105**–**116** with the CN^- anion) provides the best explanation for the character of changes in the activation parameters for the above-mentioned reactions.



Compound	R	X	k_2(25 °C) /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$
120	Me	O	8.71×10^4	30	49
121	3-BrC_6H_4	O	26.3×10^4	19	76
122	Me	S	0.107×10^4	46	32
123	Ph	S	0.16×10^4	42	40

Therefore, the reactions of cationic substrates with neutral and charged nucleophiles are characterised by broad ranges of the rate constants and the activation parameters. Depending on the electrophilicity of the cation and the nature of the nucleophile, the reactions proceed by different mechanisms, which is reflected in the relationship between the activation parameters.

Table 14. Inversion temperatures and differences between the activation parameters for bimolecular addition reactions of Bu^{n}Li and EtMgBr with (2*S*)-lactaldehyde derivatives.

Substrate	Nucleophile	Solvent	T_{inv} /°C	$T > T_{inv}$		$T < T_{inv}$		Ref.
				$\Delta\Delta H_1^{\neq}$ (see [a])	$\Delta\Delta S_1^{\neq}$ (see [a])	$\Delta\Delta H_2^{\neq}$ (see [a])	$\Delta\Delta S_2^{\neq}$ (see [a])	
126	Bu^{n}Li	THF	−26.8	−0.42	−6.65	18.0	68.5	179
	Bu^{n}Li	n-hexane	7.9	−2.42	−18.0	−9.2	−43.5	179
127	EtMgBr	THF	13.9	−5.85	−10.45	−0.25	9.2	183
	EtMgBr	Et_2O	−18.1	−0.42	1.67	−4.85	15.5	183
	EtMgBr	PhOMe	−14.1	3.76	10.45	−2.51	−13.0	183

[a] $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{anti} - \Delta H^{\neq}_{syn}$, $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{anti} - \Delta S^{\neq}_{syn}$.

VII. Miscellaneous reactions

This section deals with the energetics of bimolecular nucleophilic reactions and their stereoselectivities, touches on certain aspects of micellar catalysis and considers the reactions of halide anions with aryl radicals and the reactions of organometallic compounds with neutral and charged nucleophiles.

For kinetically controlled reactions giving rise to two stereoisomers, the selectivity *S* is expressed by the equation

$$S = \frac{k}{k'},$$

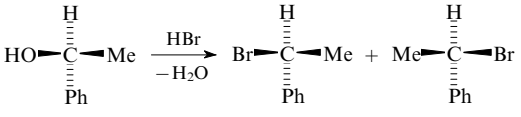
where k and k' are the overall reaction rate constants for the formation of two stereoisomers.[178] The linear dependence of the stereoselectivity on the reverse temperature is described by the modified Eyring equation:[178]

$$\ln\frac{k}{k'} = -\frac{\Delta\Delta H^{\neq}}{RT} + \frac{\Delta\Delta S^{\neq}}{R}.$$

Therefore, the stereoselectivity is expressed in terms of the differences between the enthalpies ($\Delta\Delta H^{\neq}$) and entropies ($\Delta\Delta S^{\neq}$) of activation for two reaction pathways.[178, 179] The entropy and enthalpy can play opposite roles in the formation of a particular stereoisomer, resulting in the selectivity inversion with changes in the reaction temperature and the appearance of the inversion temperature T_{inv} and two systems of the activation parameters: $\Delta\Delta H_2^{\neq}$ and $\Delta\Delta S_2^{\neq}$ at $T < T_{inv}$ and $\Delta\Delta H_1^{\neq}$ and $\Delta\Delta S_1^{\neq}$ at $T > T_{inv}$. In other words, T_{inv} is the temperature at which the domination of the enthalpy or entropy changes (the transition point in an Eyring plot).[162, 163] The isoinversion temperature T_i,† at which the maximum stereoselectivity is expected, is also an important characteristics of the stereochemical results of the reaction. For example, the asymmetric synthesis of esters by the addition of achiral alcohols to non-symmetric disubstituted ketenes catalysed by chiral tertiary amines is characterised by $T_i = 210$ K, whereas for the non-catalysed addition of racemic secondary alcohols to non-symmetrically disubstituted ketenes, $T_i = 259$ K (Ref. 178).

The result of the asymmetric synthesis of amides by the addition of chiral primary amines to non-symmetric disubstituted ketenes also substantially depends on the temperature.[178]

The nucleophilic substitution in secondary alcohol **124** with gaseous HBr affords enantiomers of (*S*)- and (*R*)-(1-bromoethyl)-benzene (**125**) with the ratio depending on the temperature ($T_{inv} = 248$ K).

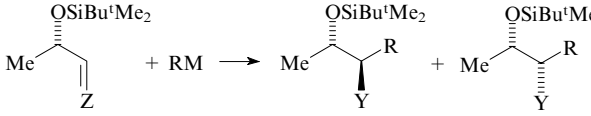


124 (*S*)-(−)-**125** (*R*)-(+)-**125**

† $T_i = \partial(\delta\Delta\Delta H^{\neq})/\partial(\delta\Delta\Delta S^{\neq})$, where $\delta\Delta\Delta H^{\neq} = \Delta\Delta H_2^{\neq} - \Delta\Delta H_1^{\neq}$, $\delta\Delta\Delta S^{\neq} = \Delta\Delta S_2^{\neq} - \Delta\Delta S_1^{\neq}$.

At $T > T_{inv}$, the activation parameters $\Delta\Delta H_1^{\neq}$ and $\Delta\Delta S_1^{\neq}$ are low (−38 kJ mol^{-1} and −161.4 J mol^{-1} K^{-1}, respectively) and the reaction affords predominantly enantiomer (*R*)-**125** with inversion of the initial configuration (S_N2 mechanism). However, at $T < T_{inv}$, $\Delta\Delta H_2^{\neq}$ and $\Delta\Delta S_2^{\neq}$ are high (11.1 kJ mol^{-1} and −36.6 J mol^{-1} K^{-1}, respectively), resulting in the formation of an intermediate adduct of alcohol with HBr, and the reaction proceeds by the S_Ni mechanism to give predominantly enantiomer (*S*)-**125** in which the initial configuration is retained.[178]

The stereoselectivity of the reaction is controlled not only by the temperature but also by the nature of the solvent. The latter is well exemplified by the reactions of carbonyl compounds and their derivatives with various nucleophiles in various media.[179–183] For example, the diastereoselectivity (the ratio of *anti* to *syn* isomers **128** and **129**) of the reactions of (2*S*)-lactaldehyde derivatives **126** and **127** with Bu^{n}Li and EtMgBr in various ethers and n-hexane was found to depend strongly on solvation of the starting substrate[179, 183] and, to a lesser degree, on the nature of the nucleophile.[180]



126, **127** *anti*-**128**, **129** *syn*-**128**, **129**

Z = NSiMe$_3$ (**126**), O (**127**); RM = Bu^{n}Li (for **126**), EtMgBr (for **127**); Y = NH$_2$, R = Bu^n (**128**); Y = OH, R = Et (**129**).

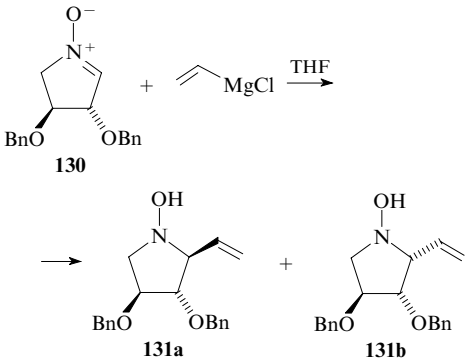
Table 14 gives the inversion temperatures and the differences between the activation parameters for two straight regions in the Eyring plot at $T > T_{inv}$ and $T < T_{inv}$. As can be seen from Table 14, T_{inv} strongly depends on the nature of the solvent and, therefore, this is the temperature at which one solvation cluster is transformed into another cluster, resulting in changes in the difference between the activation parameters and the ratio of *anti* to *syn* diastereomers **128** and **129**.[183]

Negative values of $\Delta\Delta H^{\neq}$ signify that $\Delta H^{\neq}_{syn} > \Delta H^{\neq}_{anti}$, *i.e.*, the enthalpy of activation corresponds to the predominant formation of the *anti* isomer. Positive values of $\Delta\Delta H^{\neq}$ are favourable for the predominant formation of the *syn* isomer.

Since the addition reactions are accompanied by a decrease in the entropy, the transition state leading to the *anti* isomer is more ordered at negative $\Delta\Delta S^{\neq}$ than TS through which the *syn* isomer is formed, and the entropy is favourable for the formation of the *syn* isomer. Positive values $\Delta\Delta S^{\neq}$ are favourable for the formation of the *anti* isomer. The diastereoselectivity, particularly, for the reactions with low $\Delta\Delta H_1^{\neq}$ or $\Delta\Delta H_2^{\neq}$, is entropy-controlled.[183]

The diastereoselectivity of the reaction of chiral nitrone **130** with vinylmagnesium chloride in THF is also entropy-controlled. The ratio of diastereomers **131a** : **131b** = 93 : 7 was demonstrated[184] to remain unchanged in the temperature range from 20 to −80 °C and the diastereoselectivity is entropy-controlled ($\Delta\Delta H^{\neq} = 0$ kJ mol^{-1}, $\Delta\Delta S^{\neq} = 21.7$ J mol^{-1} K^{-1}), which is

indicative of the absence of steric interactions between the substituents in compound **130** and the Grignard reagent.



130 → **131a** + **131b**

However, acceleration of the reaction in the presence of Et_2AlCl as the catalyst leads to the following two regions in the Eyring plot: in the range from 40 to 0 °C, the entropy control of the reactivity and the above-mentioned ratio of diastereomers are retained, whereas the stereoselectivity is almost completely lost in the range from 0 to −94 °C (**131a** : **131b** = 55 : 45 at −94 °C). In the latter case, substantial changes in the parameters $\Delta\Delta H_1^{\neq}$ and $\Delta\Delta S_1^{\neq}$ are observed, which apparently reflects changes in the reaction mechanism at low temperature with the result that the stereoselectivity of the process changes.[184]

The most pronounced changes in stereoselectivity due to changes in the activation parameters for different reaction pathways are the most pronounced in biochemical processes.[185–187] The enantioselectivity E' was found [185] to be changed depending on the temperature in hydrolysis of enantiomeric derivatives of α-amino acids catalysed by the enzyme α-chymotrypsin. For example, E' for the hydrolysis reactions of L- (**132a**) and D-tyrosine methyl esters (**132b**), as well as of *N*-Boc-L- (**132c**) and *N*-Boc-D-tyrosines (**132d**), which is determined by the equation

$$E' = \ln\frac{k_L}{k_D},$$

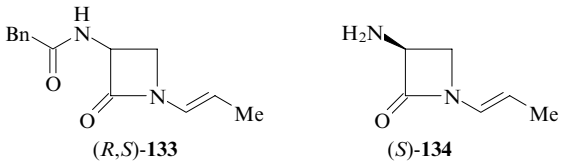
where k_L and k_D are the apparent second-order reaction rate constants for the L- and D-enantiomers, respectively, can be expressed in terms of the differences between the activation parameters $\Delta\Delta H$ and $\Delta\Delta S$ with the use of the modified Eyring equation.

Compound	$\Delta\Delta H$ /kJ mol^{-1}	$\Delta\Delta S$ /J mol^{-1} K^{-1}	T_{inv} /°C
132a,**b**	−22	−31	436
132c,**d**	25	174	−129

Here, $\Delta\Delta H = \Delta\Delta H^{\neq} - \Delta\Delta H_b$ and $\Delta\Delta S = \Delta\Delta S^{\neq} - \Delta\Delta S_b$, and the subscript b indicates binding in a substrate–enzyme–nucleophile complex.

From the Eyring plot it follows that $\Delta\Delta H$ is dominant at $T < T_{inv}$ and the stereochemical purity of the hydrolysis product (α-amino acid) decreases with increasing temperature, whereas $\Delta\Delta S$ prevails at $T > T_{inv}$ and the stereochemical purity increases with increasing temperature.[185]

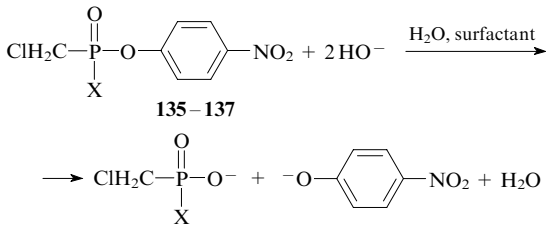
The kinetic resolution of racemic β-lactam **133** by enzymatic hydrolysis in aqueous acetone in the presence of penicillin G acylase leads to an enantiomeric excess of the (*S*) isomer of compound **134** and the non-consumed (*R*) isomer of **133**, the maximum enantioselectivity $E' = 130$ being achieved at 328 K, which is higher than $T_{inv} = 301$ K. This reaction also exemplifies the fact that the formation of clusters of the substrate and the solvent influences both the relative contributions of the activation parameters and the enantioselectivity.[186]



(*R*,*S*)-**133** (*S*)-**134**

The enantioselectivity of enzyme-catalysed transesterification of vinyl acetate with a pair of *R*- and *S*-enantiomeric secondary alcohols in Pr^i_2O in the presence of subtilysine was estimated.[187] The enantioselectivity $E' = \ln(k_R/k_S)$ was demonstrated to decrease with increasing temperature. In this case, the enthalpy–entropy compensation effect and the enthalpy control of the reactivity are observed.[187]

The catalytic effect of supramolecular systems in nucleophilic substitution reactions, in particular, the influence of solubilisation of reagents in micelles of surfactants, was studied.[188, 189] Such nucleophilic reactions as S_N2,[190] S_NAr [191] and alkaline hydrolysis of phosphonates,[192] proceed more rapidly in micellar solution compared to the same reactions in the absence of surfactants. A comparison of the activation parameters for alkaline hydrolysis of esters **135** and **136** shows that these parameters for the reactions in a micellar pseudophase are lower than those in the absence of surfactants (Table 15).



135–**137**

X = EtO (**135**), n-$C_6H_{13}O$ (**136**), $ClCH_2$ (**137**).

In a more concentrated micellar solution, the loss of entropy is apparently associated with a decrease in the degree of mixing and mobility of the reagents.[193] The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are described by the compensation relation

$$\Delta H^{\neq} = 64.61 + 0.242\,\Delta S^{\neq} \quad (r = 0.995,\ s = 0.84,\ n = 4)$$

Table 15. Rate constants of the formation of the transition state as the rate-determining step and activation parameters for hydrolysis of phosphonates **135** and **136** and solvolysis of ester **137** in ethylene glycol in the absence and presence of surfactants at 25 °C.

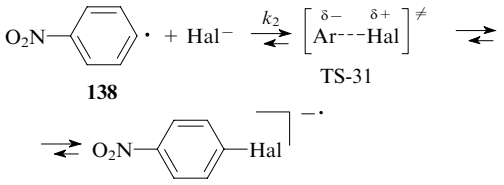
Substrate	Solvent	Surfactant	k_2 /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$	Ref.
135	H_2O	DDPB [a]	4.0	39.3	100.6	69.3	193
	H_2O	–	4.0	46.2	78.6	69.6	193
136	H_2O	DDPB [a]	0.90	30.0	144.4	73.0	193
	H_2O	–	3.0	40.8	98.9	70.2	193
137	$HOCH_2CH_2OH$	SDDS [b]	0.23×10^{-3} (see [c])	95.8	20.1	102.3	194
	$HOCH_2CH_2OH$	–	0.17×10^{-3} (see [c])	76.8	66.6	98.3	194

[a] DDPB is dodecylpyridinium bromide; [b] SDDS is sodium dodecylsulfate; [c] at 50 °C.

for the reactions of ester **135** with the enthalpy control of the reactivity and the reactions of ester **136** with the entropy control. In the latter case, it is the entropy term that is responsible for a decrease in the reactivity in a micellar pseudophase.[193]

However, solvolysis of ester **137** in ethylene glycol in the presence of surfactants is characterised by higher activation parameters compared to those for the reaction in the absence of surfactants, the reactivity being enthalpy-controlled in both reactions (see Table 15). Apparently, an increase in the entropy term for the reaction in the presence of surfactants is attributed to an increase in the contribution of the S_N1 mechanism compared to the S_N2 mechanism, and the reaction rate increases.[194]

The energetics of very fast bimolecular reactions of halide anions with 4-nitrophenyl radical (**138**) in DMF is of interest because such reactions are the key step in processes proceeding by the $S_{RN}1$ mechanism.[195]



138 TS-31

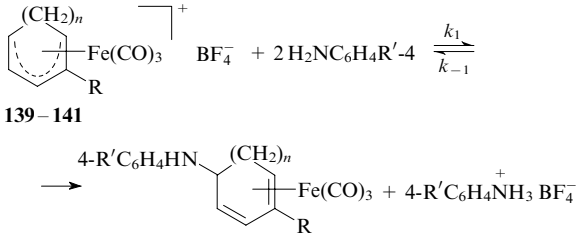
A substantial increase in $\Delta S^{\neq}$ for Br^- and Cl^- compared to that for I^- is apparently due to desolvation of these ions on going from the initial state to the transition state TS-31, and the reactivity is controlled by the enthalpy of activation (Table 16).[195] These reactions are characterised by the compensation relation

$$\Delta H^{\neq} = -25.8 + 1.8\,\Delta G^{\neq} \ (r = 0.954,\ s = 4.8,\ n = 3).$$

Table 16. Rate constants and activation parameters for the reactions of radical **138** with halide anions in DMF.[195]

Hal^-	k_2(295 K) /litre mol^{-1} s^{-1}	$\Delta H^{\neq}$	$-\Delta S^{\neq}$	$\Delta G^{\neq}$
I^-	2.0×10^9	7.6	39.3	19.3
Br^-	1.3×10^8	25.1	2.5	25.8
Cl^-	1.4×10^7	28.9	7.9	31.2

The kinetics of the addition of various nucleophiles to coordinated π-hydrocarbons to form new organometallic derivatives of 1,3-dienes was studied in detail, and the energy parameters for these processes were estimated.[168–171, 196, 197] These reactions are characterised by low activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$.[196, 197] For example, the dissociative addition reactions of anilines to complexes **139**–**141** have high negative $\Delta S^{\neq}$



139–**141**

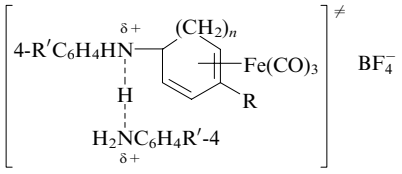
$n = 1$: R = H (**139**), 2-MeO (**140**); $n = 2$, R = H (**141**); R′ = H, Cl.

Table 17. Rate constants and activation parameters for the addition reactions of anilines to complexes **139**–**141** in MeCN at 20 °C.[196]

Substrate	Entry	Nucleophile	k_1 /litre mol^{-1} s^{-1} (see [a])	$\Delta H_a^{\neq}$	$-\Delta S_a^{\neq}$
139	1	$PhNH_2$	2560 [b]	6.2	150
	2	4-$ClC_6H_4NH_2$	993 [c]	23.7	103
140	3	$PhNH_2$	641	17.1	132
	4	4-$ClC_6H_4NH_2$	158 [c]	39.0	64
141	5	$PhNH_2$	397	30.1	92
	6	4-$ClC_6H_4NH_2$	122	28.7	106

[a] Calculated from the equation $k_{obs} = k_1[\text{amine}] + k_{-1}$; [b] at 15.1 °C; [c] at 10.4 °C.

due to formation of the highly organised transition state TS-32 on the coordinate of these reactions (Table 17).[196]



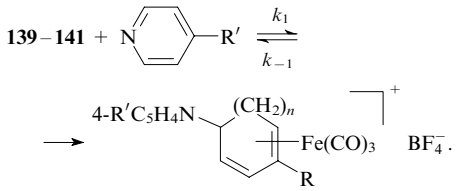
TS-32

In the absence of steric hindrance in a nucleophile, the following compensation relation is observed:

$$\Delta H_a^{\neq} = 62.2 + 0.350\,\Delta S_a^{\neq} \ (r = 0.980,\ s = 2.40,\ n = 6)$$

the association process being controlled by either enthalpy (entries 4 and 5 in Table 17) or entropy (entries 1–3, 6 in Table 17).[196]

The addition of pyridine derivatives to the coordinated dienyl ligand in complexes **139**–**141** occurs according to the equation



The rate constants k_1 and the activation parameters for the process strongly depend on the basicity of pyridine and steric hindrance in the substrate in the formation of the transition state (Table 18).[197] The reaction with more basic pyridine leads to localisation of an early transition state in which the associative bond formation plays an important role. This is confirmed by negative activation volumes $\Delta V_1^{\neq}$, the reactivity being entropy-controlled (entries 2 and 5–8 in Table 18). The late transition state for slow reactions with $\Delta V_1^{\neq}$ equal to zero is characteristic of weakly basic pyridines and substrate **141** with the enthalpy control of the reactivity (entries 1, 6 and 7 in Table 18).[197] The most basic 4-ethylpyridine always leads to negative $\Delta V_1^{\neq}$; the least basic 4-cyanopyridine, to the zero value. Since 4-formylpyridine is intermediate in basicity between the above-mentioned pyridines, the nature of the substrate plays an important role. For the fast reactions (entries 2 and 4), $\Delta V_1^{\neq}$ are negative; for the slow reaction (entry 7), the activation volume is equal to zero.

Very broad ranges of the activation parameters are observed for decarboxylation of the cobalt(III) carbonate complexes *cis*-

Table 18. Rate constants and activation parameters for the addition reactions of pyridines to complexes **139**–**141** in MeCN at 25 °C.[197]

Substrate	Entry	Nucleophile	k_1 /litre mol^{-1} s^{-1} (see[a])	$\Delta H_1^{\neq}$	$\Delta S_1^{\neq}$	$\Delta V_1^{\neq}$ /cm^3 mol^{-1}
139	1	4-NCC_5H_4N	1.2×10^3	42	46	0
	2	4-$CHOC_5H_4N$	1.8×10^3	25	100	−2.9
	3	4-EtC_5H_4N	1.9×10^4	16.9	106	(see [b])
140	4	4-$CHOC_5H_4N$	4.4×10^2	21	123	−9.8
	5	4-EtC_5H_4N	3.1×10^3	15.5	126	−7.8
141	6	4-NCC_5H_4N	30	38	89	0
	7	4-$CHOC_5H_4N$	80	30	107	0
	8	4-EtC_5H_4N	8.4×10^2	26	102	−6.4

[a] Calculated from the equation $k_{obs} = k_1$[pyridine] + k_{-1}; [b] cannot be determined due to a high reaction rate.

$[CoL(CO_3)]^+$ (**142a**–**f**) with water, which occurs according to the scheme

$$cis\text{-}[CoL(CO_3)]^+ + H_2O \xrightarrow[\text{slow}]{k_0} \underset{\mathbf{142a-f}}{} \longrightarrow cis\text{-}[CoL(OH)(HCO_3)]^+ \xrightarrow[-CO_2]{\text{fast}} cis\text{-}[CoL(OH)_2]^{2+}$$

L = $(NH_3)_4$ (**a**), $(en)_2$ (**b**), $(py)_4$ (**c**), *cis*-$(en)_2(H_2O)_2$ (**d**), *trans*-5,12-dimethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene (**e**), 1,4,8,12-tetraazacyclopentadecane (**f**).

Depending on the structure of the ligand L, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ can be either low or very high (Table 19). The first step involving the carbonate ring opening is rate-determining, which is apparently responsible for high positive $\Delta S^{\neq}$ for the reactions of substrates **142c**,**d**,**f**. The reactivity of all complexes **142a**–**f** is enthalpy-controlled. The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are described by the compensation relation [198]

$$\Delta H^{\neq} = 96.6 + 0.28\,\Delta S^{\neq} \ (r = 0.985,\ s = 9.2,\ n = 6).$$

Table 19. Rate constants and activation parameters for decarboxylation of Co(III) carbonate complexes with water at 25 °C.[198]

Substrate	$10^4 k_0$ /s^{-1} (see [a])	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$\Delta G^{\neq}$
142a	1.3	50	−155	96.2
142b	1.2	75	−63	93.7
142c	1.3×10^{-2}	139	109	106.5
142d	710	169	300	79.6
142e	0.75	115	65	95.6
142f	1.2	162	211	99.1

[a] Pseudo-first-order reaction.

The reactivity of guanosine (Guo) in the substitution reaction of the platinum(II) complex *cis*-$[(NH_3)_2Pt(Guo)_2]Cl_2$ with the cyanide ion in water is also enthalpy-controlled.[199] This reaction is rather slow ($k_2 = 2.5 \times 10^{-4}$ litre mol^{-1} s^{-1} at 30 °C) and has high enthalpy of activation ($\Delta H^{\neq} = 76.2$ kJ mol^{-1}) and moderate negative entropy of activation ($\Delta S^{\neq} = -75.2$ J mol^{-1} K^{-1}), which is attributed to the associative mechanism.[199]

$$cis\text{-}[(NH_3)_2Pt(Guo)_2]^{2+} + CN^- \xrightarrow{k_2} cis\text{-}[(NH_3)_2Pt(Guo)(CN)]^+ + Guo$$

Analogous activation parameters are also typical of other substitution reactions of platinum(II) complexes.[199]

Associative substitution reactions of the ruthenium carbonyl clusters $Ru_5C(CO)_{14}L$ (**143a**,**b**) involving phosphorus-containing n-nucleophiles L′ are either enthalpy- or entropy-controlled depending on the structures of the substrate and the nucleophile (Table 20).[200]

$$\underset{\mathbf{143a,b}}{Ru_5C(CO)_{14}L} + L' \xrightarrow[\text{n-}C_7H_{16}]{k_2} Ru_5C(CO)_{13}LL' + CO$$

L = $P(OPh)_3$ (**a**), P(cyclo-$C_6H_{11})_3$ (**b**).

Unexpectedly, faster reactions of compound **143a** with certain P-nucleophiles have positive entropies of activation (entries 1–3 in Table 20). The latter fact can be attributed to weaker binding of the reagents in the transition state accompanied by cleavage of the cluster.[200] Nevertheless, the activation parameters for the reactions of cluster **143a** with P-nucleophiles (entries 1–7 in Table 20) are described by the compensation relation

$$\Delta H^{\neq} = 70.06 + 0.254\,\Delta S^{\neq} \ (r = 0.996,\ s = 2.41,\ n = 7).$$

The reactions of cluster **143b** containing the bulky ligand L with P-nucleophiles are characterised by very low $\Delta S^{\neq}$, resulting in the compensation straight line with a smaller slope

$$\Delta H^{\neq} = 70.43 + 0.186\,\Delta S^{\neq} \ (r = 0.995,\ s = 1.13,\ n = 3),$$

which apparently indicates that the entropy makes a larger contribution to the reactivity of cluster **143b** than to that of cluster **143a**.[200]

Evidently, the kinetics of nucleophilic substitution reactions in complex compounds has a number of specific features. This problem was discussed in the corresponding sections of the reviews.[201–206]

Table 20. Rate constants and activation parameters for the substitution reactions of clusters **143a**,**b** involving phosphorus-containing nucleophiles in n-heptane at 25 °C.[200]

Substrate	Entry	Nucleophile L′	k_2 (see [a])	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$\Delta G^{\neq}$
143a	1	$P(OCH_2)_3CEt$	3.942	80.9	38.4	69.5
	2	$P(OMe)_3$	11.22	81.5	48.9	66.9
	3	$P(OEt)_3$	4.262	74.6	17.5	69.4
	4	$PPh(OMe)_2$	1.838	54.1	−58.7	71.6
	5	$P(OPh)_3$	0.1739	50.1	−91.0	77.2
	6	PPh_2OEt	1.127	30.1	−142.7	72.6
	7	PPh_3	0.0428	17.8	−211.5	80.8
143b	8	$P(OPh)_3$	0.956 [b]	32.9	−199.5	92.4
	9	$PPhMe_2$	20.40	48.7	−113.4	82.5
	10	PPh_2Me	2.797	44.4	−144.5	87.5

[a] In litre mol^{-1} s^{-1}; [b] at 45 °C.

VIII. The role of the enthalpy – entropy compensation effect

The role of the enthalpy – entropy compensation effect and the isokinetic relationship in the elucidation of reaction mechanisms and estimation of their thermodynamic parameters based on correlation series has been extensively discussed in the literature.[6, 63 – 65, 68 – 73, 207 – 214] It should be emphasised that for the true (not erroneous) compensation effect to be manifested, the series of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ must cover ranges substantially larger than the experimental errors.[71, 213] Undoubtedly, the compensation effect for reactions in the condensed phase has a cooperative character and correlates with the motion of the reagent and solvent molecules during an elementary event.[65, 68, 70, 208 – 210, 213, 214] Based on the data surveyed in the present review, conclusions about the role of the compensation effect in bimolecular nucleophilic reactions can be drawn.

For example, the compensation temperature for the S_NAr reactions of substituted arenes with amines was demonstrated to be substantially higher for slow reactions (see Fig. 3). An analogous effect is observed in the reactions of EtI with Et_3N and Et_3P (see Table 2)[39] and the reactions of clusters **143a**,**b** with P-nucleophiles (Table 20).[200] Evidently, an increase in the compensation temperature for related reactions may be indicative of a decrease in the reaction rate.

For bimolecular nucleophilic reactions at the carbonyl carbon atom,[62, 157, 162] with carbocations [168, 170, 171, 176, 177] and with organometallic complexes,[198, 200] the compensation effects are observed with changes in the nature of the substituent in the substrate [157, 162, 168, 170, 171, 176, 177, 198] or the nucleophile,[62, 200] the reaction mechanism remaining unchanged. The slopes of the compensation plots of $\Delta H^{\neq}$ *vs* $\Delta S^{\neq}$ vary in rather broad ranges (from 200 to 700 K).

The reliable determination of the isokinetic relationship for a reaction series suggests a unified mechanism of the processes.[6, 63 – 65, 69] However, the compensation relations can include the activation parameters for related BNR proceeding by different mechanisms. For example, the compensation relations for the S_NV reactions resulting in the replacement of chlorine in compounds **20** – **25** include the activation parameters for reactions proceeding as both addition – elimination and elimination – addition (see Fig. 5).[97 – 100] The compensation relations for the reactions of triaryl phosphates **88a** – **c** with pyridines also include the activation parameters that characterise different substitution mechanisms (stepwise and concerted).[155] The compensation relations for the Ad_N reactions of alkyne **43** with amines include the activation parameters corresponding to the reactions proceeding by the same mechanism (see Fig. 8).[115, 116] The compensation relations for alcoholysis of compounds **51**, **52**, **58** and **59**[129, 135 – 137] and aminolysis of compounds **47**, **51** and **54** – **57** (see Fig. 10)[131 – 134] also characterise the same mechanism.

The compensation plots of $\Delta H^{\neq}$ *vs* $\Delta G^{\neq}$ for the Ad_N reactions of alkyne **43** with amines have opposite slopes depending on the structure of the nucleophile. A positive slope is indicative of the enthalpy control of the reaction, whereas a negative slope confirms the entropy control (see Fig. 9).[115, 116, 119] Analogous compensation plots of $\Delta H^{\neq}$ *vs* $\Delta G^{\neq}$ are observed for the reactions of carbonyl compounds **46** – **59** with alcohols and amines (see Fig. 11)[129 – 137] and of dimethyl carbonate **64** with alkylamines.[140]

However, this is not true for the S_NAr reactions (see Figs 3 and 4) because the compensation relations include the activation parameters with a higher contribution of either the enthalpy or entropy term.[46 – 48, 52 – 58, 84 – 89] The inclusion of substantially different $\Delta H^{\neq}$ and $\Delta S^{\neq}$ in the same compensation relation is also observed for hydrolysis of esters **135** and **136**,[193] the addition of anilines to carbocationic complexes **139** – **141**[196] and substitution reactions of clusters **143a**,**b** with P-nucleophiles.[200]

It should be noted that no compensation effects are observed for certain BNR. For example, the absence of compensation relations for aminolysis of carbonyl compounds **67** – **79** (see Table 11),[141 – 147] the reactions of carbonyl compounds **83** – **86** with pyridine (see Table 11)[150 – 153] and the reactions of carbocations **96** – **104** with neutral π-nucleophiles is apparently associated with the difference in the structure of transition states for each type of reactions.

IX. Relationship between the mechanisms of bimolecular nucleophilic reactions and activation parameters

For bimolecular reactions, $\Delta S^{\neq}$ varies from -41 to -210 J mol^{-1} K^{-1}, and $\Delta S^{\neq}$ for reactions with moderate-density transition states vary in narrower ranges, from -125 to -167 J mol^{-1} K^{-1}.[211] The latter values are similar to the range of $\Delta S^{\neq}$ from -62 to -125 J mol^{-1} K^{-1} for BNR. This criterion is not rigorous because not all factors that influence $\Delta S^{\neq}$ (for example, changes in solvation of the transition states compared to the initial state) were taken into account.[215]

Table 21 gives the limiting values of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for all types of reactions, which were discussed in Sections II – VII of the present review. As can be seen from this table, $\Delta H^{\neq}$ varies from 0 to 232 kJ mol^{-1}; $\Delta S^{\neq}$, from $+300$ to -300 J mol^{-1} K^{-1}. These limiting values of $\Delta S^{\neq}$ noticeably extend the range of this parameter compared to that published earlier.[215] Although $\Delta S^{\neq}$ are calculated by extrapolation to an uncertain temperature,[216] a comparison of the numerical values of $\Delta S^{\neq}$ for various bimolecular reactions may be useful for elucidation of their mechanisms.[217]

Table 21. Limiting activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for various BNR.

Reaction type	Type of nucleophile	$\Delta H^{\neq}$		$-\Delta S^{\neq}$	
		min	max	min	max
S_N2	charged	8.0	100.8	2.3	277
	neutral	19.2	78.6	87.8	220
S_NAr	charged	3.8	232	−255	250
	neutral	15.7	82.0	98.0	265
S_NV	charged	9.4	101	−102	127
	neutral	3.3	18.4	179	242
Ad_N	charged	0	39.0	83.0	288
	neutral	2.0	65.0	40.0	300
Reactions at carbonyl C	charged	13.5	88.0	12.6	277
	neutral	6.7	105	35.6	285
Reactions of carbocations	charged	19.0	52.0	32.0	187
	neutral	0	53.0	46.0	180
Substitution in metal complexes	neutral	17.8	169	−300	211

Of special interest are the limiting values of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for BNR (see Table 21). For example, very low $\Delta H^{\neq}$ (0 – 8 kJ mol^{-1}) are typical of certain S_N2, S_NAr and Ad_N reactions proceeding by the concerted mechanism.[10, 58, 105] The structural features of the transition state can also lead to low $\Delta H^{\neq}$ in S_NV reactions,[90, 91] Ad_N reactions [113, 114, 116] and the reactions of carbonyl compounds and carbocations with neutral nucleophiles.[152, 175] Evidently, low values of $\Delta H^{\neq}$ in these reactions are compensated by very low $\Delta S^{\neq}$.

It is worthy of note that certain S_NAr and S_NV reactions with charged nucleophiles [56, 57, 92, 97, 98, 100] and the reactions of organometallic compounds with neutral nucleophiles [198, 200] are characterised by positive $\Delta S^{\neq}$, which is rather unusual for BNR.[156] The positive values of $\Delta S^{\neq}$ can be attributed to either the influence of the intermediate complex of a substrate with a nucleophile that is formed in S_NAr reactions [57] or the intermediate formation of an acetylene derivative in S_NV reactions [92, 97, 98] or, alternatively, to

the structural features of substrates resulting in an increase in the entropy for the transition state.[198, 200] Positive $\Delta S^{\neq}$ were also observed for catalysed hydrolysis of substituted *N*-benzoylimidazoles in 10% aqueous MeCN due to desolvation of the hydroxide ion.[156]

In some cases, the activation parameters appeared to be useful for elucidation of the reaction mechanisms. For example, positive $\Delta S^{\neq}$ for S_NV reactions confirm the $E-Ad_N$ mechanism.[92, 97, 98, 100] In two-step substitution reactions of carbonyl compounds, the values of $\Delta S^{\neq}$ allow one to identify the rate-determining step.[150–152] An increase in the activation parameters for the reactions of triaryl phosphates with pyridines made it possible to identify the two-step and concerted mechanisms.[155] An increase in these parameters for the reactions of triarylmethyl cations with cyanide ion allowed the researchers to refine the details of the ion-pair mechanism.[176] The activation parameters play an important role in the analysis of the stereochemical result of the reaction.[178–187] It should also be noted that an increase in $\Delta S^{\neq}$ in solvolysis of phosphonate **137** is associated with the change in the reaction mechanism from S_N2 to S_N1.[194] There are also examples of related BNR, which proceed by different mechanisms but are characterised by similar activation parameters.[139, 148, 154] In these cases, it is necessary to use other methods for elucidation of the reaction mechanism.[41, 122–128, 217, 218]

Solvation can have a noticeable effect on $\Delta S^{\neq}$. The latter fact is particularly pronounced for solvation of transition states with a large charge development, resulting in a decrease in $\Delta S^{\neq}$ (Ref. 156) upon solvation of the starting substrate, and influences the diastereoselectivity of the reaction due to a strong change in entropy.[179, 183] Desolvation of a charged nucleophile before the formation of the transition state can lead to both a sharp increase in $\Delta S^{\neq}$ (Refs 156 and 195) and a decrease in this parameter [51, 53] depending on the reaction type.

The formation of an intermediate complex between a neutral nucleophile and a base [113, 114, 120] or between a substrate and a nucleophile [57, 66, 67, 121, 135–137, 162] has a substantial effect on the activation parameters and the reaction mechanism. Hence, the problem of the effect of complexation between the reagents on the energetics and mechanisms of BNR has attracted considerable interest.[219–229]

* * *

In conclusion, there is nowadays a large body of data on the energetics of bimolecular nucleophilic reactions in solution. In the present review, an attempt was made to generalise the results of investigations in this field. The necessity of systematisation is dictated by a rapid increase in the number of studies aimed at refining the theoretical views of the energetics of nucleophilic reactions in organic chemistry and biochemistry.

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