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Activation parameter changes as a mechanistic tool in S_N2 reactions in solution

Vladislav Mikhailovich Vlasov *

Nikolay Nikolaevich Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation

** Corresponding author at: Nikolay Nikolaevich Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation.*
Tel.: +7.383.3308833. Fax: +7.383.3309752. E-mail address: vmvlasov@nioch.nsc.ru (V.M. Vlasov).

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ABSTRACT

Recent applications of activation parameters variation approach to the elucidation of S_N2 reaction mechanisms have led to further clarifications of structures of transition states involved in the concerted reaction pathway. S_N2 reactions in solution are reviewed with special emphasis of activation parameter variation $\Delta X^{\neq}$ ($X = H$, S and G) with substituents in the nucleophile, leaving and nonleaving groups applying linear free energy relationships in order to evaluate the resultant $\delta\Delta X^{\neq}$ reaction constants. The use of internal enthalpy reaction constants $\delta\Delta H^{\neq}_{int}$ as a mechanistic tool is stressed when the structure of transition state in S_N2 reaction is changed. Variations of the activation parameters in S_N2 reactions and their mechanisms were analyzed.

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1. Introduction

A significant part of reactions carried out in organic and bioorganic chemistry involve the bimolecular nucleophilic reactions (BNRs) in solution [1,2]. These reactions play important role in organic synthesis [1,2]. Among them, bimolecular nucleophilic substitution at sp^3 carbon (S_N2) constitutes a fundamental reaction type [1-4]. This reaction proceeds preferentially through backside nucleophile attack of the nucleophile at the carbon atom (S_N2-b) with concerted expulsion of the leaving group and with inversion of configuration at carbon. The latter is in general more efficient because it has a lower reaction barrier than the corresponding front side S_N2-f pathway, which goes with retention of configuration [1-4]. The nature of the reactants or solvents influences both the kinetics and mechanism of S_N2 reactions [5-7]. Various experimental kinetic and theoretical studies have therefore been devoted to obtain a better understanding of the mechanisms of these processes [3-5,8-11]. Among traditional experimental methods, kinetic isotope effects [12-15] and linear free energy relationships (LFER) [16-19] have most frequently been used to study mechanisms of BNRs, in particular the nature of transition states (TSs) [20-22]. Besides, the influence of the variations of substituents in reactants on activation parameters in BNRs including S_N2 reactions was demonstrated [23-27].

The effects of structural changes in the nucleophile, leaving and non-leaving groups on the activation parameters of the S_N2 reactions are quantitatively described using the Hammett or Hammett-like substituent constants [16-19,28-30] for aromatic systems [31-33]. Substituent effects are among the most important concepts of structural effects [31]. A search in the last 5 years using ISI Scifinder returned over 8700 papers containing the term "*substituent effects*" in the title or abstract.

In this review recent advances in the detailed analysis of the relationship between the mechanisms and the activation parameter variations with substituents in the nucleophile, leaving and non-leaving groups for the S_N2 reactions in solution are surveyed.

2. Substituent effects on the activation parameters

Generalized analysis of structural effects on the activation parameters of S_N2 reactions implies separation of substituent effects into enthalpy and entropy contributions to the ρ value in the general Hammett equation (Equation (1)) [34-41]. In Equation (1), the parameter σ is

$$\Delta X^{\neq} = \delta\Delta X^{\neq}\sigma + \Delta X^{\neq}_{o} \ (X = H, S, G) \quad (1)$$

substituent constant, the slope $\delta\Delta X^{\neq}$ determines the selectivity of the substituent effect on the activation parameters $\Delta X^{\neq}$ ($X = H$, S and G), and the free term $\Delta X^{\neq}_{o}$ is the corresponding activation parameter for unsubstituted compound. Therefore, the reaction constant $\delta\Delta X^{\neq}$ may be regarded as an analog of the Hammett ρ value.

In keeping with the Hepler solvation theory [34,35], reaction constant $\delta\Delta X^{\neq}$ is the sum of internal ($\delta\Delta X^{\neq}_{int}$) and external ($\delta\Delta X^{\neq}_{ext}$) constituents related, respectively, to the chemical reaction and solvation processes (Equation (2)) [34-41].

$$\delta\Delta X^{\neq} = \delta\Delta X^{\neq}_{int} + \delta\Delta X^{\neq}_{ext} \ (X = H, S, G) \quad (2)$$

The changes in the $\delta\Delta S^{\neq}$ values caused by the variation of the remote substituent on the aromatic ring result from the changes in solvation of the external constant $\delta\Delta S^{\neq}_{ext}$ (Equation (3)).

$$\delta\Delta S^{\neq} = \delta\Delta S^{\neq}_{int} + \delta\Delta S^{\neq}_{ext} \quad (3)$$

Therefore, it is possible to believe that in the Equation (3) the internal constant $\delta\Delta S^{\neq}_{int}$ is independent of the substituent in the absence of steric effects ($\delta\Delta S^{\neq}_{int} \approx 0$) and $\delta\Delta S^{\neq} \approx \delta\Delta S^{\neq}_{ext}$ [34,35,42,43]. In this case, the magnitudes of $\delta\Delta H^{\neq}_{ext}$ (Equation (4)) and $\delta\Delta S^{\neq}$ can be

$$\delta\Delta H^{\neq} = \delta\Delta H^{\neq}_{int} + \delta\Delta H^{\neq}_{ext} \quad (4)$$

compensated to each other by Equation (5) [34,35,42,43]. As can be seen from the general

$$\delta\Delta H^{\neq}_{ext} = T_{comp}\, \delta\Delta S^{\neq} \quad (5)$$

compensation relationship given by Equation (6), the slope is the compensation temperature T_{comp}

$$\delta\Delta H^{\neq} = \delta\Delta H^{\neq}_{int} + T_{comp}\, \delta\Delta S^{\neq} \quad (6)$$

and the intercept is the internal enthalpy constant $\delta\Delta H^{\neq}_{int}$ for the given reaction series [34-41]. Obviously, if the $\delta\Delta H^{\neq}_{int}$ value is equal to zero, the $\delta\Delta H^{\neq}$ value ($\delta\Delta H^{\neq} = \delta\Delta H^{\neq}_{ext}$) is determined by the solvation influence only. In another case when the compensation temperature is equal to zero, the $\delta\Delta H^{\neq}$ value is governed by the magnitude of the $\delta\Delta H^{\neq}_{int}$ constant.

The equations (Equations (1-6)) describing the influence of the substituents on the changes of the reaction constants $\delta\Delta X^{\neq}$ ($X = H, S, G$) are used for the analysis of S_N2 reactions.

3. Reaction constants $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$

Variations of the activation parameters $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ in the S_N2 reactions with neutral and charged nucleophiles in various solvents in Table 1 reflect the sensitivity of activation parameters to substituent nature in the leaving groups, nucleophiles and nonleaving groups and strongly depend on solvation of reactants and TSs (Scheme 1) [24-27,37-40]. Negative values of $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ indicate enhanced solvation of the corresponding TS-1 upon introduction of electron-withdrawing substituents R (entries 15-17, 25-28, 34-36 in Table 1). At the same time, their positive values suggest stronger solvation of the initial reactants with electron-withdrawing groups R (entries 5, 10, 11, 19-24, 29, 30, 37, 39-42 in Table 1). In some cases, solvation of the initial reactants dominates which may lead to positive values of $\delta\Delta S^{\neq}$ and small negative values of $\delta\Delta H^{\neq}$ (entries 1-4, 6-9, 12, 13 in Table 1).

There are three compensation relationships between $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ for S_N2 reactions at saturated carbon atom including the changes of the substituents R in the leaving group (entries 1-13 in Table 1), nonleaving group (entries 15-29) and nucleophiles (entries 30-42) (Figure 1).

The lines *II* and *III* from Figure 1 combine a relatively fast reactions [50,53-67] and the compensation relationships for these lines are tested at a confidence level of >95% [27,43]. The slopes of the lines *II* and *III* correspond to compensation temperatures T_{comp} equaling 380 and 370 K, respectively. These values are higher than the mean experimental temperature T_{exp} (entries 15-42 in Table 1) and it must be concluded that the compensation relationships are not caused by experimental errors [68]. As for the exact physical-chemical sense of the enthalpy-entropy compensation, this is still a debated question [43,69-71]. Nevertheless, when $T_{comp} > T_{exp}$, it is necessary to accept the existence of a real correlation between the values of $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ [68].

The line *I* from Figure 1 combines a more slower reactions (entries 1-13 in Table 1) in a relatively narrow range of the values of $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$. Therefore, the compensation equation for this line was tested at the >92% confidence level and the slope of the line *I* corresponds to compensation temperature T_{comp} equaling 290 K. This temperature is lower than the middle experimental temperature T_{exp} (entries 1-13 in Table 1). The latter indicates some experimental errors upon the determination of the reaction rate constants leading to the existence of the compensation dependence between the values of $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ [43,68-71].

There is the one deviation from line *I* (Figure 1) depicting the dependence of $\delta\Delta H^{\neq}$ versus $\delta\Delta S^{\neq}$ for the reactions of substituted N-methylpyridinium salts with iodide ion (entry 14 in Table 1). These reactions are characterized by very low rate constants ($k_2 = 1\times10^{-12}$ - 1×10^{-9} dm^3·mol^{-1}·s^{-1}) [50] and by a large negative value of $\delta\Delta H^{\neq}$ [24,27]. An analogous deviation from the dependence of $\delta\Delta H^{\neq}$ versus $\delta\Delta S^{\neq}$ for the line *III* (Figure 1) is connected with a large positive value of $\delta\Delta S^{\neq}$ for the reactions of N-substituted anilines with benzyl bromide in methanol (entry 40 in Table 1). A lower rate constants characterize also these reactions in comparison with the same rate constants for the parent reactions of entry 41 in Table 1. The latter have a large positive value of $\delta\Delta S^{\neq}$. Obviously, the arrangement of lines *I* - *III* and entries 14 and 40 on Figure 1 reflects the reactivity order of S_N2 reactions with decreasing the values of $\delta\Delta H^{\neq}$ [24,27].

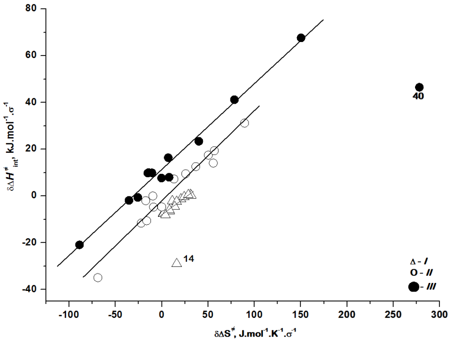


Figure 1. The plots of $\delta\Delta H^{\neq}$ *versus* $\delta\Delta S^{\neq}$ for S_N2 reactions with the substituents R in the leaving group $YCH_2ZC_6H_4R$ (*I*), nonleaving group $RC_6H_4ZCH_2X$ (*II*) and nucleophile $RC_6H_4Z^-$ (RC_6H_4ZH) (*III*); values of $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ are taken from Table 1; line *I*, $\delta\Delta H^{\neq} = (-8.0 \pm 0.3) + (0.29 \pm 0.03)\, \delta\Delta S^{\neq}$, $r = 0.950$, $s = 1.1$, $n = 13$; line *II*, $\delta\Delta H^{\neq} = (-1.5 \pm 1.2) + (0.38 \pm 0.03)\, \delta\Delta S^{\neq}$, $r = 0.973$, $s = 4.1$, $n = 11$; line *III*, $\delta\Delta H^{\neq} = (11.4 \pm 0.9) + (0.37 \pm 0.02)\, \delta\Delta S^{\neq}$, $r = 0.990$, $s = 3.32$, $n = 12$; the compensation equations for lines *I* – *III* are tested at the 92%, 95.7% and 97.6% confidence level, respectively [43]; the identity of the numbers is the entry number in Table 1.

4. S_N2 Reactions with neutral nucleophiles

The changes in the free energy of activation reaction constant, $\delta\Delta G^{\neq}$, in the S_N2 reactions reflect the influence of the

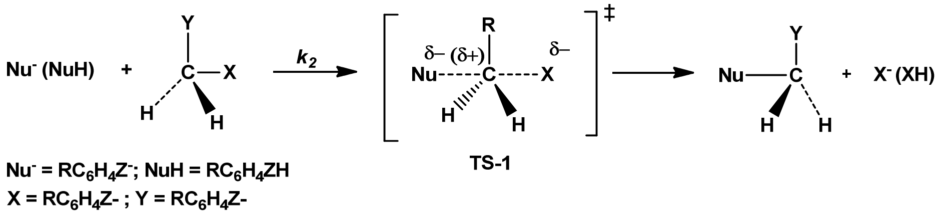
Table 1. Effects of the substituents R in the leaving groups $YCH_2ZC_6H_4R$, nonleaving groups $RC_6H_4ZCH_2X$ and nucleophiles $RC_6H_4Z^-$ (RC_6H_4ZH) on the reaction constants $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ in S_N2 reactions at saturated carbon atom YCH_2-X with neutral NuH (RC_6H_4ZH) and charged nucleophiles Nu^- ($RC_6H_4Z^-$) in various solvents [24,27,44-67].

Entry	Reactants	Solvent	$N(m)$ [a]	T_{exp}/ [b] K	$\delta\Delta H^{\neq}$/ [c] $kJ.mol^{-1}.\sigma^{-1}$	$\delta\Delta S^{\neq}$/ [c] $J.mol^{-1}.K^{-1}.\sigma^{-1}$	Reference
Substituents R are varied on leaving groups $YCH_2ZC_6H_4R$							
1	$Me-OSO_2C_6H_4R + H_2O$	H_2O	6(3)	323	-2.1	11.3	24,27,44
2	$Me-OSO_2C_6H_4R + EtOH$	EtOH	5(3)	343	-1.4	20.6	24,27,45,46
3	n-Pr-$OSO_2C_6H_4R$ + MeOH	MeOH	6(3)	323	-2.4	16.0	24,27,47
4	n-Pr-$OSO_2C_6H_4R$ + EtOH	EtOH	6(3)	323	-0.4	24.1	24,27,47
5	n-Pr-$OSO_2C_6H_4R$ + i-PrOH	i-PrOH	6(3)	323	0.6	30.8	24,27,47
6	$CH_2=CH-CH_2-SO_2C_6H_4R + H_2O$	H_2O	4(3)	313	-7.5	1.3	24,27,48
7	$CH_2=CH-CH_2-SO_2C_6H_4R + H_2O$	90% Di-oxane +10% H_2O	4(3)	313	-6.4	8.6	24,27,48
8	$CH_2=CH-CH_2-SO_2C_6H_4R$ + MeOH	MeOH	8(3)	313	-7.5	1.9	24,27,47
9	$CH_2=CH-CH_2-SO_2C_6H_4R$ + EtOH	EtOH	8(3)	313	-4.6	14.0	24,27,47
10	$CH_2=CH-CH_2-SO_2C_6H_4R$ + i-PrOH	i-PrOH	8(3)	313	0.2	31.8	24,27,47
11	$CH\equiv C-CH_2-OSO_2C_6H_4R$ + MeOH	MeOH	8(3)	323	0.5	28.6	24,27,49
12	$CH\equiv C-CH_2-SO_2C_6H_4R$ + EtOH	EtOH	8(3)	323	-6.0	8.3	24,27,49
13	$CH\equiv C-CH_2-OSO_2C_6H_4R$ + i-PrOH	i-PrOH	8(3)	323	-8.2	4.0	24,27,49
14	$RC_5H_4N^+-Me + I^-$	MeCN	5(4)	298	-29.0	16.1	24,27,50
Substituents R are varied on nonleaving group $RC_6H_4ZCH_2X$							
15	$RC_6H_4CH_2Cl + NH_3$	Liquid NH_3	5(4)	298	-2.22	-9.06	51,52
16	$RC_6H_4NHC(O)-CH_2Cl + PhNMe_2$	n-Octanol	9(3)	440	-34.9	-69.0	24,27,53
17	$RC_6H_4CH_2Br$ + PhNH2	MeCN	5(3)	308	-2.0	-17.3	24,27,54
18	$RC_6H_4CH_2Cl + PhNH_2$	MeCN	5(3)	318	0.0	-9.6	24,27,54
19	$RC_6H_4CH_2Br + C_5H_5N$	MeOH	3(3)	298	17.5	50.2	24,27,55
20	$RC_6H_4CH_2Br + C_5H_5N$	DMF	3(3)	298	9.5	25.8	24,27,55
21	$RC_6H_4CH_2Cl + C_5H_5N$	MeOH	3(3)	298	31.2	89.3	24,27,55
22	$RC_6H_4CH_2Cl + C_5H_5N$	DMf	3(3)	298	19.4	56.8	24,27,55
23	$RC_6H_4CH_2Br + C_5H_5N$	MeCN	7(3)	290	12.6	36.8	24,27,56
24	$RC_6H_4CH_2Br + C_5H_5N$	Ionic liquid	7(3)	290	7.3	13.1	24,27,56
25	$3-NO_2-4-C_6H_3C(O)CH_2Br + HSCH_2COOH$	MeOH	5(4)	303	-4.75	-8.93	57
26	$3-NO_2-4-C_6H_3C(O)CH_2Br$ + PhSH	MeOH	5(4)	303	-4.66	-0.03	57
27	$4-C_6H_4C(O)CH_2Br$ + PhSH	MeOH	5(4)	303	-10.59	-16.24	57
28	$RC_6H_4CH_2Cl$ + PhSLi	MeOH	5(3)	293	-11.6	-22.2	24,27,58
29	$RC_6H_4CH(Me)Br$ + LiBr	Acetone	5(3)	303	14.1	55.6	24,27,59
Substituents R are varied on nucleophiles $RC_6H_4Z^-$ (RC_6H_4ZH)							
30	$RC_6H_4NMe_2$ + MeI	MeOH	8(4)	328	16.4	7.0	24,27,39,60
31	$RC_6H_4NMe_2$ + MeI	MeCN	5(4)	313	10.0	-14.2	24,27,39,61
32	$RC_6H_4NMe_2$ + MeI	Acetone	5(4)	313	9.8	-15.1	24,27,39,61
33	RC_5H_4N + MeI	MeCN	5(4)	298	9.9	-10.7	24,27,39,50
34	$RC_6H_4NH_2 + CH_2=CH-CH_2Br$	DMF	5(3)	303	-20.9	-88.8	24,27,62
35	$RC_6H_4NH_2 + PhCH_2Br$	MeCN	4(3)	308	-1.9	-35.4	24,27,54
36	$RC_6H_4NH_2 + PhCH_2Cl$	MeCN	5(3)	318	-0.6	-25.8	24,27,54
37	$RC_6H_4NH_2 + PhCH_2Br$	EtOH	7(3)	303	8.0	7.9	24,27,63
38	$RC_6H_4NH_2 + PhCH_2Br$	$PhNO_2$	5(3)	303	7.7	-0.3	24,27,63
39	$RC_6H_4NH_2 + PhC(O)CH_2Br$	EtOH	5(3)	308	23.4	40.0	64,65
40	$RC_6H_4NHR + PhCH_2Br$	MeOH	5(4)	303	46.5	278.0	66
41	$RC_6H_4SO_2Na + BrCH_2CH=CHCN$	50 vol% EtOH-H_2O	3(5)	318	41.2	78.4	27,67
42	$RC_6H_4SO_2Na + BrCH_2CH=CHBr$	50 vol% EtOH-H_2O	3(5)	318	67.6	150.3	27,67

[a] N is the number of reactions, and m is the number of rate constants at different temperatures.

[b] The middle temperature of experiments; temperature range in which the reaction rate constants were determined is twenty.

[c] The reaction constants $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ are estimated by Equation 1 using σ constants [28].



Scheme 1

substituent R in the leaving group (entries 1-24 in Table 2), non-leaving group (entries 25-50) and nucleophile (entries 51-79). The values of $\delta\Delta G^{\neq}$ are negative for the reaction series in which the substituent R is varied in the leaving group and, particularly, in the nonleaving group and nucleophile (entries 27, 28, 46-50, 76, 78 in Table 2). On the other hand, reaction series in which change is only made to substituent R in the nucleophile (entries 51-75, 77, 79) and in the nonleaving group (entries 25, 26, 29-45) are characterized by positive values of $\delta\Delta G^{\neq}$. Such variations in the signs of the $\delta\Delta G^{\neq}$ values are common according to the Hammett-like equation $\delta\Delta G^{\neq} = -2.303RT_{exp}\rho$ [16,38]. However, the dependence $\delta\Delta G^{\neq}$ *versus* ρ does not speak about peculiarities of the mechanisms of the S_N2 reactions because the Hammett ρ values may depend on the contributions of the TS structure in the concerted mechanism or the formation of the complexes before forming the trigonal-bipyramidal TS-1 [24,27,40,41].

A lot of examples of the reaction constants $\delta\Delta G^{\neq}$ and $\delta\Delta H^{\neq}_{int}$ are presented in Table 2, where is clearly noted that these constants are approximately equal; therefore, linear dependence between $\delta\Delta H^{\neq}_{int}$ and $\delta\Delta G^{\neq}$ has been developed for entries 1-13, 24, 29, 30, 36, 47-49, 51-54 and 57-59 in Table 2 (Figure 2) [24]. Free term in this equation corresponds to the $\delta\Delta G^{\neq}_{ext}$ value and close to zero ($\delta\Delta G^{\neq}_{ext} = \delta\Delta H^{\neq}_{ext} - T_{exp}\,\delta\Delta S^{\neq}_{ext} \approx 0$ [24,27,36-42]).

Table 2. Values of the reaction constants $\delta\Delta G^{\neq}$ and $\delta\Delta H^{\neq}_{int}$, the Brønsted slopes β_R, the Hammett reaction constants ρ_R, cross-interaction constants ρ_{RR} in S_N2 reactions at saturated carbon atom YCH_2-X with neutral nucleophiles in various solvents.

Entry	Reactants	Solvent	$\delta\Delta G^{\neq}$/ [a] $kj.mol^{-1}\ \sigma^{-1}$	$\delta\Delta H^{\neq}_{int}$/ [b] $kJ.mol^{-1}.\sigma^{-1}$	β_R [c]	ρ_R [d]	ρ_{RR} [e]	Reference
Substituents R are varied on leaving groups $YCH_2ZC_6H_4R$								
1	$Me-OSO_2C_6H_4R + H_2O$	H_2O	-5.7	-5.7	-	0.93	-	24,27,44
2	$Me-OSO_2C_6H_4R$ + EtOH	EtOH	-8.4	-7.9	-0.45	1.41	-	24,27,45,46
3	*n*-Pr-$OSO_2C_6H_4R$ + MeOH	MeOH	-7.6	-7.5	-	1.28	-	24,27,47
4	*n*-Pr-$OSO_2C_6H_4R$ + EtOH	EtOH	-8.2	-8.1	-	1.34	-	24,27,47
5	*n*-Pr-$OSO_2C_6H_4R$ + *i*-PrOH	*i*-PrOH	-9.3	-9.3	-	1.52	-	24,27,47
6	$CH_2=CH-CH_2-OSO_2C_6H_4R + H_2O$	H_2O	-7.9	-7.9	-	1.31	-	24,27,48
7	$CH_2=CH-CH_2-OSO_2C_6H_4R + H_2O$	90% dioxane + 10% H_2O	-9.1	-9.1	-	1.52	-	24,27,48
8	$CH_2=CH-CH_2-OSO_2C_6H_4R$ + MeOH	MeOH	-8.1	-8.1	-	1.40	-	24,27,47
9	$CH_2=CH-CH_2-OSO_2C_6H_4R$ + EtOH	EtOH	-9.0	-9.1	-0.51	1.51	-	24,27,47
10	$CH_2=CH-CH_2-OSO_2C_6H_4R$ + *i*-PrOH	*i*-PrOH	-9.7	-10.0	-	1.61	-	24,27,47
11	$CH\equiv C-CH_2-OSO_2C_6H_4R$ + MeOH	MeOH	-8.7	-8.6	-	1.25	-	24,27,49
12	$CH\equiv C-CH_2-OSO_2C_6H_4R$ + EtOH	EtOH	-8.7	-8.7	-	1.41	-	24,27,49
13	$CH\equiv C-CH_2-OSO_2C_6H_4R$ + i-PrOH	i-PrOH	-9.5	-9.5	-	1.54	-	24,27,49
14	$Me-OSO_2C_6H_4R + PhNH_2$	MeOH	-7.55 (-7.9)	- (-7.33)	-0.39	1.16	0.30	72
15	$Me-OSO_2C_6H_4R + PhNH_2$	MeCN	-8.66 (-8.13)	- (-8.46)	-0.45	1.33	0.32	72
16	$Me-OSO_2C_6H_4R + PhNMe_2$	MeOH	-7.07 (-6.67)	- (-6.85)	-0.36	1.09	0.24	73
17	$Me-OSO_2C_6H_4R + PhNMe_2$	MeCN	-8.91 (-8.43)	- (-8.71)	-0.46	1.38	0.25	73
18	$CH_2=CH-CH_2-OSO_2C_6H_4R + PhNH_2$	MeCN	-7.55 (-7.58)	- (-7.33)	-0.34	1.24	0.37	74
19	$CH_2=CH-CH_2-OSO_2C_6H_4R + PhNMe_2$	MeCN	-7.87 (-7.94)	- (-7.95)	-0.35	1.30	0.30	74
20	$CH\equiv C-CH_2-OSO_2C_6H_4R + PhNH_2$	MeCN	-7.23 (-7.27)	- (-7.01)	-0.32	1.19	0.29	75
21	$CH\equiv C-CH_2-OSO_2C_6H_4R + PhNMe_2$	MeCN	-8.77 (-8.79)	- (-8.57)	-0.39	1.44	0.25	75
22	$PhCH_2$- $OSO_2C_6H_4R$ + 4-$MeC_6H_4NMe_2$	Acetone	-12.27 (-12.67)	- (-12.10)	-0.71	2.08	<0	76
23	$PhCH_2$- $OSO_2C_6H_4R + PhNH_2$	MeOH	-10.34 (-8.13)	- (-10.15)	-0.45	1.33	-0.10	8,77
24	$PhCH_2$- $OSO_2C_6H_4R + C_5H_5N$	Acetone	-10.78 (-11.64)	-9.54 (-11.64)	-0.65	1.92	-	78
Substituents R are varied on nonleaving group $RC_6H_4ZCH_2X$								
25	$RC_6H_4CH_2Cl$ + liquid NH_3	Liquid NH_3	0.48 (-0.04)	- (0.77)	-	0	-	51
26	$RC_6H_4CH_2Cl + C_5H_{11}N$ (R = 4-Me, H, 4-Cl, 4-COOMe)	Liquid NH_3	1.52 (1.60)	- (1.82)	-	-0.27	-	52
27	$RC_6H_4CH_2Cl + C_5H_{11}N$ (R = 4-COOMe, 4-CN, 4-NO_2)	Liquid NH_3	-3.83 (-4.11)	- (-3.58)	-	0.67	-	52
28	$RC_6H_4NHC(O)-CH_2Cl + PhNMe_2$	n-Octanol	-4.5	-8.0	-	0.49	-	24,27,53
29	$RC_6H_4CH_2Br + PhNH_2$	MeCN	3.3	4.7	-	-0.55	-	24,27,54
30	$RC_6H_4CH_2Cl + PhNH_2$	MeCN	3.1	3.7	-	-0.51	-	24,27,54
31	$RC_6H_4CH_2Br + C_5H_5N$	MeOH	2.5	-2.1	-	-0.66	-	24,27,55
32	$RC_6H_4CH_2Br + C_5H_5N$	DMF	1.8	-0.6	-	-0.31	-	24,27,55
33	$RC_6H_4CH_2Cl + C_5H_5N$	MeOH	4.6	-3.6	-	-0.78	-	24,27,55
34	$RC_6H_4CH_2Cl + C_5H_5N$	DMF	2.5	-2.7	-	-0.49	-	24,27,55
35	$RC_6H_4CH_2Br + C_5H_5N$	MeCN	1.9	-1.4	-	-0.32	-	24,27,56
36	$RC_6H_4CH_2Br + C_5H_5N$	Ionic liquid	3.5	2.3	-	-0.56	-	24,27,56
37	$RC_6H_4CH_2Cl + PhNH_2$	MeOH	3.99 (3.91)	- (4.32)	-	-0.65	-0.75	79
38	$RC_6H_4CH_2Cl + PhNH_2$ (R = 4-MeO, 4-Me, H)	EtOH	27.6 (27.1)	- (28.2)	-	-4.46	-0.93	80
39	$RC_6H_4CH_2Cl + PhNH_2$ (R = H, 4-Cl, 4-NO_2)	EtOH	2.40 (2.39)	- (2.71)	-	-0.40	-0.93	80
40	$RC_6H_4CH_2Br + PhNH_2$ (R = 4-Me, H, 4-Cl, 4-NO_2)	MeOH	4.36 (4.46)	- (4.69)	-	-0.74	-0.78	81
41	$RC_6H_4CH_2Br + PhNH_2$ (R = H, 4-Cl, 4-NO_2)	MeOH	3.45 (3.49)	- (3.77)	-	-0.58	-0.78	81
42	$RC_6H_4CH_2Br + PhNMe_2$	Acetone	6.71 (6.28)	- (7.07)	-	-1.04	-1.14	82
43	$PhCH_2-OTs + PhNMe_2$	MeCN	11.67 (11.94)	- (12.08)	-	-1.97	-	83
44	$RC_6H_4CH(Me)Br + C_5H_5N$ (R = 4-MeO, 4-MeS, 4-PhO, 4-MeO-3-Cl)	MeCN	30.1 (29.9)	- (30.7)	-	-4.92	-	84
45	$RC_6H_4CH(Me)Br + C_5H_5N$	MeCN	8.0 (8.2)	- (8.4)	-	-1.36	-	84
46	4-$RC_6H_4C(O)CH_2Br + HSCH_2COOH$	MeOH	-7.20 (-7.45)	- (-6.98)	-	1.22	-	57
47	3-NO_2- 4-$RC_6H_3C(O)CH_2Br$ + $HSCH_2COOH$	MeOH	-2.33 (-2.41)	-1.36 (-2.06)	-	0.39	-	57
48	4-$RC_6H_4C(O)CH_2Br$ + PhSH	MeOH	-5.67 (-5.94)	-4.42 (-5.44)	-	0.97	-	57
49	3-NO_2- 4-$RC_6H_3C(O)CH_2Br$ + PhSH	MeOH	-4.65 (-4.84)	-4.65 (-4.41)	-	0.79	-	57
50	4-$RC_6H_4C(O)CH_2Br + PhNH_2$	MeOH	-6.28 (-6.30)	- (-6.05)	-	1.03	0.11	85
Substituents R are varied on nucleophiles RC_6H_4ZH								
51	$RC_6H_4NMe_2$ + MeI	MeOH	14.1	13.8	0.45	-2.10	-	24,27,39,60
52	$RC_6H_4NMe_2$ + MeI	MeCN	14.4	15.3	-	-2.43	-	24,27,39,61
53	$RC_6H_4NMe_2$ + MeI	Acetone	14.6	15.4	-	-2.40	-	24,27,39,61
54	RC_5H_4N + MeI	MeCN	13.1	13.9	0.38	-2.27	-	24,27,39,50
55	$RC_6H_4NH_2 + CH_2=CH-CH_2Br$	DMF	6.0	12.0	0.43	-1.17	-	24,27,62
56	$RC_6H_4NH_2 + PhCH_2Br$	MeCN	9.0	11.2	0.31	-1.47	-	24,27,54
57	$RC_6H_4NH_2 + PhCH_2Cl$	MeCN	7.9	8.9	0.26	-1.23	-	24,27,54
58	$RC_6H_4NH_2 + PhCH_2Br$	EtOH	5.6	5.1	-	-0.89	-	24,27,63
59	$RC_6H_4NH_2 + PhCH_2Br$	$PhNO_2$	7.8	7.8	-	-1.63	-	24,27,63
60	$RC_6H_4NH_2 + PhC(O)CH_2Br$	EtOH	11.1	8.6	-	-1.86	-	64,65
61	$RC_6H_4NH_2 + PhC(O)CH_2Br$	MeOH	11.1 (11.0)	- (11.5)	0.66	-1.81	0.11	85
62	$RC_6H_4NH_2 + PhCH_2Br$	EtOH	8.61 (8.47)	- (9.0)	0.49	-1.40	<0	80
63	$RC_6H_4NH_2 + PhCH_2Cl$	EtOH	5.36 (5.25)	- (5.70)	0.31	-0.87	-0.93	80
64	$RC_6H_4NH_2 + Me-OSO_2Ph$	MeOH	10.61 (9.63)	- (11.0)	0.60	-1.59	0.30	72
65	$RC_6H_4NH_2 + Me-OSO_2Ph$	MeCN	11.65 (10.90)	- (12.05)	0.65	-1.80	0.32	72
66	$RC_6H_4NMe_2 + Me-OSO_2Ph$	MeOH	15.05 (14.0)	- (15.5)	0.66	-2.31	0.24	73
67	$RC_6H_4NMe_2 + Me-OSO_2Ph$	MeCN	14.66 (13.45)	- (15.10)	0.62	-2.22	0.25	73
68	$RC_6H_4NH_2 + CH_2=CH-CH_2-OSO_2Ph$	MeCN	11.15 (10.61)	- (11.55)	0.66	-1.75	0.37	74
69	$RC_6H_4NMe_2 + CH_2=CH-CH_2-OSO_2Ph$	MeCN	12.67 (12.30)	- (13.09)	0.57	-2.03	0.30	74

Table 2. (Continued).

Entry	Reactants	Solvent	$\delta\Delta G^{\neq}$/ [a] kj.mol^{-1} σ^{-1}	$\delta\Delta H^{\neq}_{int}$/ [b] kJ.mol^{-1}.$\sigma^{-1}$	β_R [c]	ρ_R [d]	ρ_{RR} [e]	Reference
70	$RC_6H_4NH_2 + CH\equiv C\text{-}CH_2\text{-}OSO_2Ph$	MeCN	10.55 (10.05)	- (10.95)	0.63	-1.66	0.29	75
71	$RC_6H_4NMe_2 + CH\equiv C\text{-}CH_2\text{-}OSO_2Ph$	MeCN	12.53 (12.18)	- (12.94)	0.57	-2.01	0.25	75
72	$RC_6H_4NMe_2 + PhCH_2\text{-} OSO_2C_6H_4Cl\text{-}4$	Acetone	13.73 (14.13)	- (14.16)	0.49	-2.33	<0	76
73	$RC_6H_4NH_2 + PhCH_2\text{-} OSO_2Ph$	MeOH	4.97 (5.07)	- (5.31)	0.29	-0.84	-0.10	8,77
74	$RC_6H_4NH_2 + PhCH_2Cl$	MeOH	9.08 (9.32)	- (9.46)	0.55	-1.54	-0.75	79
75	$RC_6H_4NH_2 + PhCH_2Br$	MeOH	8.31 (8.53)	- (8.68)	0.46	-1.41	-0.78	81
76	$PhCH_2NHR + PhCH_2Br$ (*tert*-Bu, *i*-Pr, *n*-Bu, Et, Me)	MeOH	-37.77 (-39.50)	- (-37.86)	-10.2	6.49	-	66
77	$PhCH_2NHR + PhCH_2Br$ (Me, H, Ph)	MeOH	10.11 (10.42)	- (10.50)	3.38	-1.72	-	66
78	$4\text{-}RC_6H_4SH + 3\text{-}NO_2C_6H_4C(O)CH_2Br$	MeOH	-5.77 (-6.06)	- (-5.54)	0.41	0.99	0	57
79	$RC_6H_4NMe_2 + PhCH_2Br$	Acetone	5.49 (5.43)	- (5.83)	-	-0.90	-1.14	82

[a] Calculated by Eyring equation; values in parentheses are calculated by the Hammett-like equation $\delta\Delta G^{\neq} = -2.303RT_{exp}\rho$ [16,38].

[b] Calculated by Equation 6; values in parentheses are calculated by Equation: $\delta\Delta H^{\neq}_{int} = (0.29 \pm 0.12) + (1.01 \pm 0.01)\ \delta\Delta G^{\neq}$ (Figure 2).

[c] Calculated by Brønsted equation; the calculations use the values of pK for methyl transfer [46] in entries 2, 9, 14 – 24, substituted N,N-dimethyl anilines in 50% water EtOH [86] in entries 51, 66, 67, 69, 71, 72, substituted pyridines in MeCN [87] in entry 54, substituted anilines in H_2O in entries 76 and 77 [66] and 55, 61-64, 73-75 [88], in MeCN in entries 56, 57, 65 and substituted benzenethiols in entry 78 [57].

[d] Calculated by Hammett equation; σ constants are taken from [28]; σ* constants are used in entries 76 and 77 and taken from [28].

[e] Calculated by Equation $\log (k_{RR'}/k_{HH}) = \rho_R\sigma_R + \rho_{R'}\sigma_{R'} + \rho_{RR'}\sigma_R\sigma_{R'}$ in entries 14-23, 37-42, 49, 50, 61-75, 78, 79.

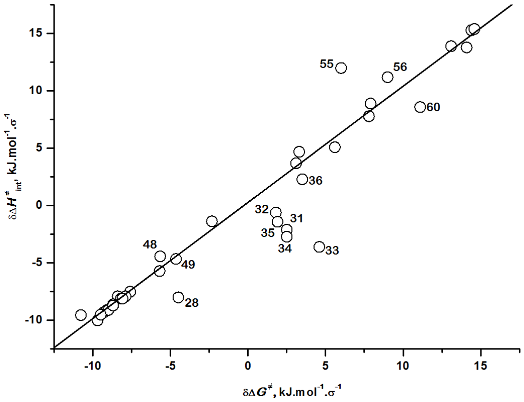


Figure 2. The plots of $\delta\Delta H^{\neq}_{int}$ *versus* $\delta\Delta G^{\neq}$ for S_N2 reactions of entries 1-13, 24, 29, 30, 36, 47-49, 51-54 and 57-59 in Table 2: $\delta\Delta H^{\neq}_{int} = (0.29 \pm 0.12) + (1.01 \pm 0.01)\ \delta\Delta G^{\neq}$, $r = 0.998$, $s = 0.61$, $n = 27$; the identity of the numbers is the entry number in Table 2.

The latter means that the dependence of the changes of the free energy of activation is governed mainly by the changes in the internal enthalpy of activation in the S_N2 reactions: $\delta\Delta G^{\neq} \approx \delta\Delta H^{\neq}_{int}$ [24,27,36-42].

The dependence $\delta\Delta H^{\neq}_{int}$ *versus* $\delta\Delta G^{\neq}$ (Figure 2) is used to calculate the reaction constant $\delta\Delta H^{\neq}_{int}$ on the basis of the values of $\delta\Delta G^{\neq}$. The latter may be obtained by the Eyring equation [6] using the reaction rate constants at single temperature for entries 14-23, 25-27, 37-46, 50, 61-79 in Table 2. It was shown that the values of $\delta\Delta G^{\neq}$ calculated by the Eyring equation and the Hammett-like equation between the $\delta\Delta G^{\neq}$ and ρ_R values coincide practically for these entries. It is obvious that the majority of the S_N2 reactions follow through TS-1 according to the dependence $\delta\Delta H^{\neq}_{int}$ *versus* $\delta\Delta G^{\neq}$ (Figure 2).

However, there are the deviations from the dependence depicted in Figure 2 for the S_N2 reactions of entries 28, 31-35, 55, 56 and 60 in Table 2. The deviations of entries 28 and 60 can be explained by the formation of the complexes **1** and **2** before forming the distorted trigonal-bipyramidal TS-2 or TS-3, respectively (Scheme 2) [24,41].

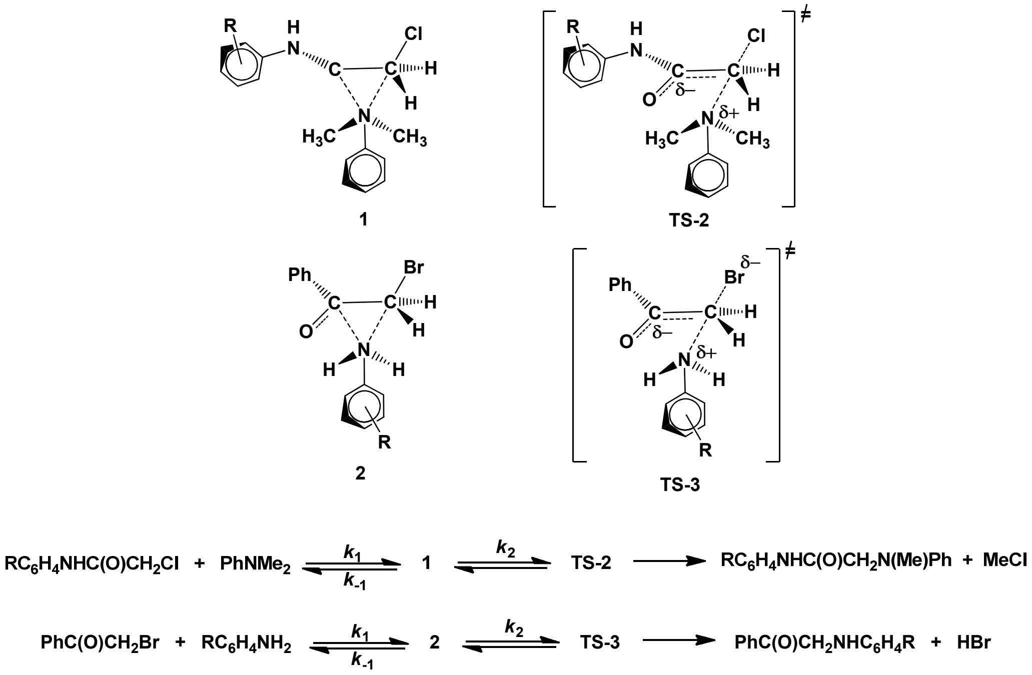
The latter leads to an increase in the magnitudes of $\delta\Delta G^{\neq}$ and a decrease of the $\delta\Delta H^{\neq}_{int}$ values for these reactions. The assumption of the formation of the complexes **1** and **2** is supported by recent DFT computations of phenacyl bromides with pyridines [41]. It is necessary to emphasize that the S_N2 reactions of phenacyl derivatives with benzenethiol (entries 48 and 49 in Table 2) do not lead to the deviations from the dependence between $\delta\Delta H^{\neq}_{int}$ and $\delta\Delta G^{\neq}$ (Figure 2). It is obvious that these reactions follow through TS-1 according to the low positive values of ρ constants [57].

The increase in the magnitudes of $\delta\Delta G^{\neq}$ takes place also for the Menschutkin reactions of benzyl halides with pyridine (entries 31-35 in Table 2) (Figure 2), possibly, due to a change of TS-1 to the distorted trigonal-bipyramidal TS-4 by the influence of the substituents R and solvation [40]. The latter has been confirmed by DFT computations of TS-4 in the reactions of benzyl bromides with pyridine in solutions showing a significant change of their geometry in comparison with a standard structure TS-1 (Scheme 3) [40].

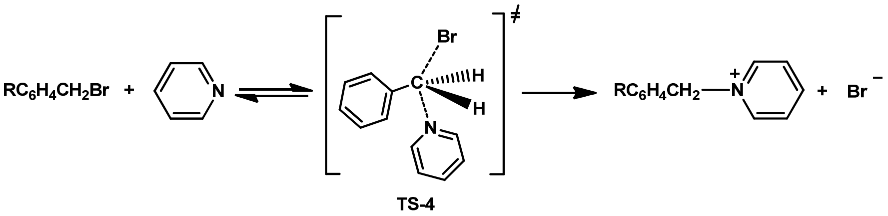
At the same time the variation of the solvent in the Menschutkin reaction of benzyl bromide with pyridine from acetonitrile to ionic liquid (entries 35 and 36 in Table 2) does not give the deviation from the dependence $\delta\Delta H^{\neq}_{int}$ *versus* $\delta\Delta G^{\neq}$ (Figure 2). The origin of that is a lower interaction of ionic liquid with the incipient charges in TS-1 leading to the change in the entropy of the system (entries 23 and 24 in Table 1) [56]. The variation of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ in this Menschutkin reaction depends also on the structure of the ionic liquid cation. The importance of accessibility of the charge centre on the cation and the ability for generalized electrostatic interactions between the nucleophile and the cation of the ionic liquid are responsible for any change in rate constants [89].

The deviations from the dependence $\delta\Delta H^{\neq}_{int}$ *versus* $\delta\Delta G^{\neq}$ for entries 55 and 56 (Figure 2) are connected with the decrease in the magnitudes of $\delta\Delta G^{\neq}$ (Table 2) due to a change in the reaction mechanisms. It was shown that the reactions of allyl and benzyl bromides with anilines involve, possibly, the formation of the four-membered cyclic TS-5 or TS-6, respectively, with frontside attack by nucleophiles (Scheme 4) [8,12,90,91]. Usually the formation of the cyclic TSs with frontside attack by nucleophiles is accompanied by the lower values of activation entropy [90,92].

Taking into account the Hammett-like equation $\delta\Delta G^{\neq} = -2.303RT_{exp}\rho$ [16,38] and considering the relationship between $\delta\Delta H^{\neq}_{int}$ and $\delta\Delta G^{\neq}$ (Figure 2), a correlation between $\delta\Delta H^{\neq}_{int}$ and ρ for S_N2 reactions carrying out through TS-1 also takes place (entries 1-13, 24, 29, 30, 36, 47-49, 51-54, 57-59 in Table 2) (Figure 3) [24]. The intercept in this equation is close to zero and the slope reflects a sensitivity of $\delta\Delta H^{\neq}_{int}$ to a change of ρ equaling $2.303RT_{exp}$. Realization of this dependence becomes possible, as magnitudes of ρ for these S_N2 reactions characterize charge development in TS-1 [16-19, 93-96]. It is obvious that the $\delta\Delta H^{\neq}_{int}$ reaction constants characterize also the degree of developing negative charge in TS-1. The large positive and negative values of $\delta\Delta H^{\neq}_{int}$ indicate essential charge development in TS-1 for the reactions of entries 10, 24, 59 and 60 in Table 2.



Scheme 2



Scheme 3

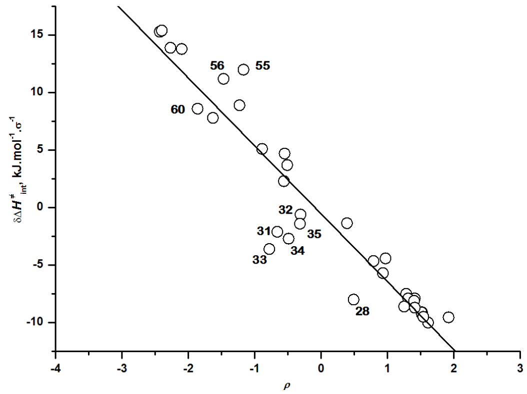


Figure 3. The plots of $\delta\Delta H^{\neq}_{\mathrm{int}}$ *versus* ρ for S_N2 reactions of entries 1-13, 24, 29, 30, 36, 47-49, 51-54 and 57-59 in Table 2: $\delta\Delta H^{\neq}_{\mathrm{int}}$ = (0.27 ± 0.17) - (6.08 ± 0.01) ρ, r = 0.995, s = 0.89, n = 27; the identity of the numbers is the entry number in Table 2.

The linearity between the magnitudes of $\delta\Delta H^{\neq}_{\mathrm{int}}$ and ρ over a wide range of their values (Figure 3) furthermore supports the assumption that there is no change in the mechanism of the S_N2 reactions carried out through TS-1 with the variation of the substituents R in the leaving and nonleaving groups and neutral nucleophile. Therefore, the deviations from the correlation $\delta\Delta H^{\neq}_{\mathrm{int}}$ *versus* ρ give a possibility of offering alternative ways for such S_N2 reactions. For instance, some dissociative ($\rho < 0$) and associative S_N2 reactions ($\rho > 0$) in which the substituent R is varied in the nonleaving group (entries 28, 31-35 in Table 2) and nucleophiles (entries 55, 56 and 60 in Table 2) [8,12,97] deviate from the linear dependence $\delta\Delta H^{\neq}_{\mathrm{int}}$ *versus* ρ (Figure 3). Though this dependence describes normal S_N2 reactions in solution proceeding through TS-1, the deviations of entries 28 and 60 (Table 2) from it are connected with the formation of the complexes **1** and **2**, TS-2 and TS-3 on the reaction coordinate, respectively (Scheme 2) [24,41]. Therefore, the magnitudes of ρ is equal to $\rho = \rho_{\mathrm{eq}}\ (k_1/k_{-1}) + \rho_{\mathrm{nuc}}(k_2)$. The magnitudes of ρ_{nuc} are calculated by equation $\delta\Delta H^{\neq}_{\mathrm{int}}$ *versus* ρ (Figure 3) using the $\delta\Delta H^{\neq}_{\mathrm{int}}$ values (entries 28 and 60 in Table 2), respectively [24].

The deviations of entries 55 and 56 in Table 2 from the dependence $\delta\Delta H^{\neq}_{\mathrm{int}}$ *versus* ρ (Figure 3) are connected with the formation of TS-5 and TS-6, respectively, due to front side attack by nucleophiles (Scheme 4). The large charge development in these transition states leads to the small negative values of ρ [8,12,54]. On the other hand, the deviations of entries 31 – 35 in Table 2 (Figure 3) with a distortion of TS-1 to TS-4 give the increase of the negative values of ρ indicating the less charge development in TS-4 [40].

Table 3. Values of the reaction constants $\delta\Delta G^{\neq}$ and $\delta\Delta H^{\neq}_{int}$, the Brønsted slopes β_R, the Hammett reaction constants ρ_R, cross-interaction constants ρ_{RR} in S_N2 reactions at saturated carbon atom YCH_2-X with charged nucleophiles in various solvents.

Entry	Reactants	Solvent	$\delta\Delta G^{\neq}$ [a] kJ.mol^{-1}.σ^{-1}	$\delta\Delta H^{\neq}_{int}$ [b] kj.mol^{-1}.σ^{-1}	β_R [c]	ρ_R [d]	ρ_{RR} [e]	Reference
Substituents R are varied on leaving groups $YCH_2ZC_6H_4R$								
1	$RC_5H_4N^+$-Me + I^-	MeCN	-33.8	-33.9	-0.95	5.95	-	24,27,50
Substituents R are varied on nonleaving group $RC_6H_4ZCH_2X$								
2	$RC_6H_4CH_2Cl$ + PhSLi	MeOH	-5.1	-3.0	-	0.58	-0.62	24,27,58
3	$RC_6H_4CH_2Cl$ + PhONa	Liquid NH_3	-6.31 (-5.69)	- (-7.79)	-	1.11	0	52
4	$RC_6H_4CH(Me)Br$ + LiBr	Acetone	-2.7	-7.0	-	1.13	-	24,27,59
5	$CH_2=CH-CH_2-OSO_2C_6H_4R$ + sodium 1,2,4-triazolate	Liquid NH_3	-5.11 (-4.41)	- (-7.44)	-	0.89	-	52
Substituents R are varied on nucleophiles $RC_6H_4Z^-$								
6	$BrCH_2CH = CHCN + RC_6H_4SO_2Na$	50 vol% EtOH-H_2O	16.7	12.2	-	- 2.62	-	27,67
7	$BrCH_2CH = CHBr + RC_6H_4SO_2Na$	50 vol% EtOH-H_2O	19.5	12.0	-	- 3.25	-	24,67
8	$PhCH_2Cl + RC_6H_4SLi$	MeOH	2.80 (4.23)	- (0.86)	0.28	-0.58	-0.62	8,58,99
9	$PhCH_2Cl + RC_6H_4ONa$	Liquid NH_3	10.22 (11.08)	- (5.895)	0.42	-1.79	0	52

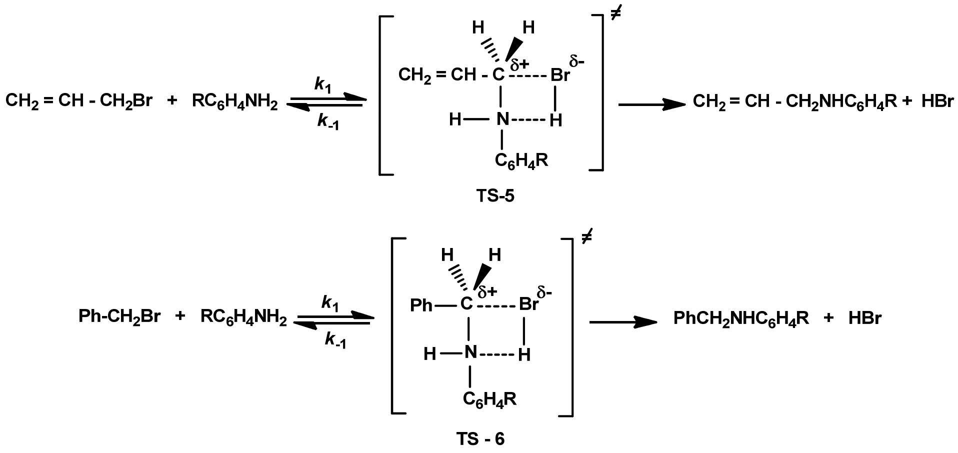
[a] Calculated by Eyring equation; values in parentheses are calculated by the Hammett-like equation $\delta\Delta G^{\neq} = -2.303RT_{exp}\rho$ [16,38].

[b] Calculated by Equation 6; values in parentheses are calculated by Equation 7.

[c] Calculated by Brønsted equation; the calculations use the values of pK for substituted pyridines in MeCN [87] in entry 1, substituted benzenethiols in MeOH [57] in entry 8 and substituted phenols in liquid NH_3 in entry 9 [52].

[d] Calculated by Hammett equation; σ constants are taken from [28]; σ* constants are used in entries 76 and 77 and taken from [28].

[e] Calculated by Equation 9: $\log(k_{RR'}/k_{HH}) = \rho_R\sigma_R + \rho_{R'}\sigma_{R'} + \rho_{RR'}\sigma_R\sigma_{R'}$ in entries 2, 3, 8, 9.



Scheme 4

It is obvious that the deviations from the dependence between $\delta\Delta H^{\neq}_{int}$ and $\delta\Delta G^{\neq}$ or $\delta\Delta H^{\neq}_{int}$ and ρ can be interpreted in terms of a change of transition state structures.

5. S_N2 Reactions with charged nucleophiles

The changes of the reaction constants $\delta\Delta G^{\neq}$, $\delta\Delta H^{\neq}_{int}$ and ρ of the S_N2 reactions with charged nucleophiles are presented in Table 3. The linear dependences $\delta\Delta H^{\neq}_{int}$ *versus* $\delta\Delta G^{\neq}$ and $\delta\Delta H^{\neq}_{int}$ versus ρ have been developed for entries 1, 2, 4, 6, 7 in Table 3 (Equations 7 and 8). The degrease of the slopes in these equations in comparison with that of the analogous equations for the reactions with neutral nucleophiles (Figures 2 and 3) follows from the difference in the values of $\delta\Delta G^{\neq}$ and $\delta\Delta H^{\neq}_{int}$ for entries 2, 4, 6, 7 in Table 3.

$$\delta\Delta H^{\neq}_{int} = (-3.0 \pm 1.4) + (0.87 \pm 0.07\ \delta\Delta G^{\neq}$$
$$r = 0.990,\ s = 3.1,\ n = 5 \qquad (7)$$

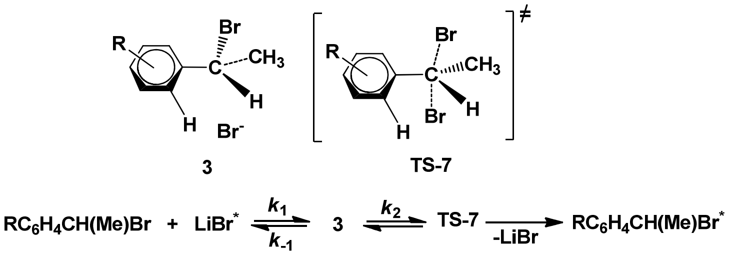
$$\delta\Delta H^{\neq}_{int} = (-2.11 \pm 0.97) - (5.12 \pm 0.29)\rho$$
$$r = 0.995,\ s = 2.17,\ n = 5 \qquad (8)$$

The origin of the differences between $\delta\Delta G^{\neq}$ and $\delta\Delta H^{\neq}_{int}$ for the reactions of entry 4 in Table 3 is, possibly, the formation of the complex **3** before forming the distorted trigonal-bipyramidal TS-7 ((Scheme 5) [24,27]. The latter leads to an increase of the $\delta\Delta G^{\neq}$ value. The assumption is supported by DFT computations of complexes of 1-aryl-1-bromoethanes with bromide ion [40].

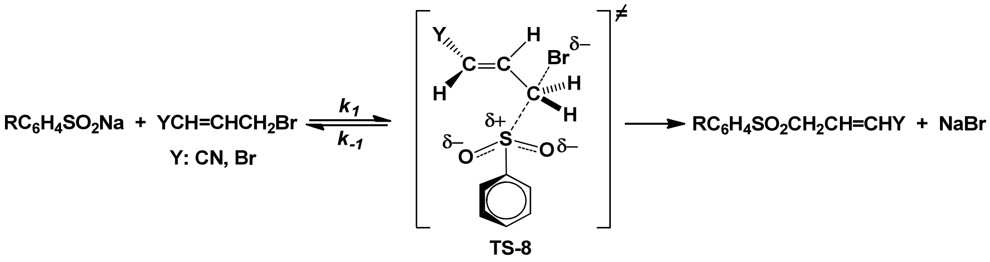
The large magnitudes of $\delta\Delta G^{\neq}$ in comparison with the $\delta\Delta H^{\neq}_{int}$ values for the reactions of entries 6 and 7 in Table 3 can be explained by the formation of the distorted trigonal-bipyramidal TS-8 [27]. The Br-C-S angle deviates from 180 degrees and the longer C – S bond leads to an increase of the $\delta\Delta S^{\neq}$ values (entries 41 and 42 in Table 1) on passing to the electron-withdrawing substituent R in nucleophile (Scheme 6) [67].

It is worth noting that the differences in the magnitudes of the reaction constants $\delta\Delta G^{\neq}$ and $\delta\Delta H^{\neq}_{int}$ for S_N2 reactions with the charged nucleophiles in entries 4, 6 and 7 in Table 3 give a possibility to elucidate some peculiarities of the changes of the transition state structure.

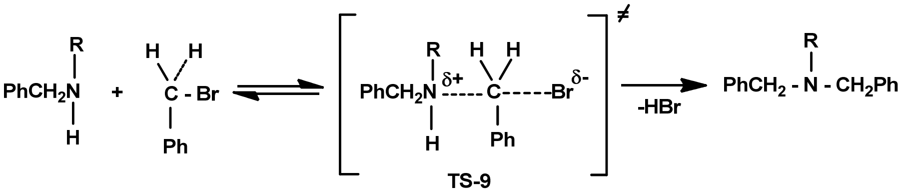
It is very interesting that the S_N2 reaction of charged nucleophile with an ionic electrophile in the medium of the ionic liquid shows a linear dependence of the reaction rate constant upon nucleophile concentration. Such dependence is absent for this reaction proceeding in the molecular solvents. The linear kinetic behavior seen in the ionic liquid solutions clearly indicates that the reactions are not progressing via ion pairs, but via free solvated ions which are considerably less reactive than the ion pairs forming in the molecular solvents. Thus the ionic liquids are extremely dissociating solvents [98].



Scheme 5



Scheme 6



Scheme 7

6. Mechanistic criteria for S_N2 reactions on the basis of the Brønsted and Hammett equations

The concept of the linear free energy relationship developed on the basis of the kinetic researches in the frameworks of the Brønsted and Hammett equations is used most frequently to study the substituent effects into the product relation and the reaction rate for the reaction mechanism [16-19]. Therefore, the analysis of the kinetic data is important to elucidate a properties of the transition state for the S_N2 reactions with the rate-determining step k_c [8,10,73,75,91,92,97,99].

The magnitudes of the Brønsted slopes β_R for the reactions with neutral and charged nucleophiles when the substituents R are varied in benzene derivatives of the leaving group and nucleophile are equal to -0.95÷-0.32 and 0.28÷0.66, respectively (entries 2, 9, 14-24, 51, 54-57, 61-78 in Table 2; entries 1, 8, 9 in Table 3). These values reflect the S_N2 reactions with the mechanism proceeding via TS-1 [8,10,73,75,92,99]. However, there are the reaction series in which the substituent R in the nucleophile is varied in α-position to the reaction center (entries 76 and 77 in Table 2). In these cases, the values of the Brønsted slope β_R are changed from -10.2 up to 3.38 for electron-donating and electron-withdrawing substituents R, respectively [66]. It is obvious that a curved Brønsted plot for these reactions can arise from the variable TS-9 (Scheme 7) [20].

At the same time, the sign and magnitude of the Hammett-like cross-interaction constants $\rho_{RR'}$ where R and R$'$ are the substituents in the leaving and nonleaving groups and nucleophile, respectively, provide mechanistic criteria for the S_N2 reactions [10,73,75,91,92,97,100].

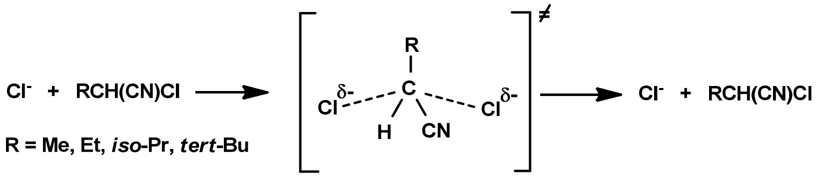
$$\log (k_{RR'}/k_{HH}) = \rho_R\sigma_R + \rho_{R'}\sigma_{R'} + \rho_{RR'}\sigma_R\sigma_{R'} \qquad (9)$$

The magnitude $\rho_{RR'}$ is positive for more active nucleophile and nucleofuge at the variation of the substituent in nucleophile and leaving group. The latter leads to the early TS-1 on the reaction coordinate with a low degree of the formation and breakdown of the bond (entries 14-21, 61-71 in Table 2). On the contrary, the more late TS-1 is formed at negative values of $\rho_{RR'}$ (entries 22, 23, 62, 63, 72-75, 79 in Table 2) [8,12,91]. Therewith, the larger negative values of $\rho_{RR'}$ indicate the formation of TS-5 or TS-6 as a result of the frontside nucleophile-substrate interaction [8,12,90-92]. Further, the magnitude of $\rho_{RR'}$ is negative and almost constant ($\rho_{RR'}$ = -0.70 ± 0.08) upon change of the substituent in nucleophile and nonleaving group. The latter characterizes close degree of the bond formation in TS-1 (entries 37-42, 63, 74, 75, 79 in Table 2; entries 2, 8, 9 in Table 3) [8].

So, the analysis of the cross-interaction constants $\rho_{RR'}$ gave an opportunity to determine the properties of the transition state for the S_N2 reactions in solution including both the backside and frontside attacks by the nucleophile onto the reaction centre.

7. Relationship between the mechanism of S_N2 reactions and the changes of the activation parameters

The activation parameters $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$ are widely used for characterizing the structures of transition states in solution S_N2 reactions [6,16,52,58,92,100]. It was found that the solvolysis of benzyl- and benzhydryl halides follows the S_N2 and S_N1 mechanisms, respectively, as S_N2 reactions show more negative values of $\Delta S^{\neq}$ [101,102].



TS-10

Scheme 8

It was also shown that the interaction of 4,4’-dichlorobenzhydryl bromide with morpholine in DMSO leads to the alkylation product through the S_N2 and S_N1 mechanisms with the ratio of 70, respectively, at more negative value of $\Delta S^{\neq}$ for the S_N2 pathway through TS-1 with backside attack by the nucleophile onto the substrate [103].

The less values of $\Delta G^{\neq}$ and ρ_R are characteristic of the S_N2 reactions than the S_N1 one’s (entry 43 in Table 2) due to the charge decrease in the transition state [83]. Usually, the S_N2 reactions are characterized by the magnitudes of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ equaling 8.0 ÷ 100.8 kJ.mol^{-1} and -2.3 ÷ -277 J.mol^{-1}.K^{-1}, respectively [23,104]. These limit magnitudes for the activation parameters can be used to determine the properties of the transition state structure for the S_N2 reactions. For instance, the low values of $\Delta H^{\neq}$ and the larger negative values of $\Delta S^{\neq}$ characterize the S_N2 reactions with the frontside attack by nucleophile at the α-carbon of the substrate with the formation of the cyclic transition states TS-5 or TS-6 [90,92].

Considering the values of $\Delta G^{\neq}$ and ρ_R, it is seen that the S_N2 reactions with neutral nucleophiles are characterized by the less values of these magnitudes than the analogous reactions with charged nucleophiles (entries 25-27 in Table 2; entries 3, 5 in Table 3). The comparison confirms that there is the small charge onto the α-carbon atom in the TS-1 for the S_N2 reactions with neutral nucleophiles. At the same time, the large sensitivity to a change of substituents in the aromatic ring for these reactions with charged nucleophiles affords to increase a negative charge in the TS-1 [52].

When electron-donating and electron-withdrawing substituents are introduced to the same central carbon at the reaction centre of Menschutkin-type S_N2 reaction, the $\pi - \pi^*$, $\sigma - \pi^*$ and $\pi - \sigma^*$ interactions among these substituents in the transition state cooperatively accelerate this reaction by stabilizing its transition state [105]. However, when electron-donating and electron-withdrawing substituents are varied in α-position to the reaction centre of neutral nucleophile (entries 76, 77 in Table 2), there is a curved Brønsted plot for the S_N2 reactions (Scheme 7) [66] due to the variable TS-9 [20].

The analysis of the influence of structural changes on the barriers of S_N2 reactions of alkyl halides with cyanide ion in acetonitrile revealed quantitatively the contribution of different substituents to the $\Delta G^{\neq}$ value [106]. For instance, α- and β- methylation of the substrate increases the $\Delta G^{\neq}$ by 8 and 4 kJ.mol^{-1}, respectively. Benzyl and carbonyl substituents decrease significantly the reaction barriers of S_N2 reactions (up to 20-28 kJ.mol^{-1}) [106]. It is noting that the same influence of the substituent variation in α- and β-positions in alkyl halides on the energetic barrier of S_N2 reactions revealed in the gas phase [106,107]. Therewith, in according with Galabov’s work [108], substrate-nucleophile electrostatic interactions in the S_N2 transition state rather than π-conjugation lower net activation barriers and enhance reaction rates unaltered by solvation effects. The energetic barriers and the transition state structure of the gas phase S_N2 reactions of *para*-substituted phenoxides with halomethanes are thermodynamically controlled. Furthermore, the energetics barriers display good linear correlations with the substituent constants σ in the nucleophile [100,109].

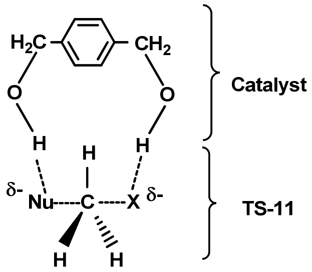
The increase of the chlorine atoms by substitution of hydrogen atoms in methyl chloride leads to the lowest free energy activation barrier for the reaction with OH$^-$ in aqueous solution due to both the solvation effects and the solvent-induced polarization effect [110]. The solvent effect on the activation free energy of the Finkelstein reaction between methyl iodide and Cl$^-$ ions depends linearly on the reaction free energy [111]. It was found that the effects of the microsolvation of water in the $I^- + CH_3I \rightarrow ICH_3 + I^-$ S_N2 reaction can effectively inhibit this reaction increasing the barrier height [112]. The intramolecular hydrogen bonding in alkoxide anions acting as a good model system for studying of intramolecular mictosolvation on nucleophilicity increases the intrinsic barrier height of S_N2 reactions of alkoxides with methyl chloride by ~ 12.5 kJ.mol^{-1} [113].

It was shown that the structure of the TS-1 in the S_N2 reaction between *n*-butyl chloride and thiophenoxide ion is slightly changed in both methanol and DMSO when the reacting nucleophile is the solvent-separated ion-pair and the free ion, respectively. However, the reaction rate in MeOH is significantly lower than in DMSO in the presence of sodium nitrate due to the solvation leading to the tighter transition state [114].

The effect of the substituents γ for the reactions of *trans-γ*-substituted allyl chlorides $\gamma CH{=}CHCH_2Cl$ with Cl$^-$ and LiCl has been studied. It was shown that the computed reaction barriers give reasonable correlations with the Hammett σ_p constants leading to ρ = -8.3 and +18.8, respectively. It is obvious that ionic and ion pair reactions give ρ values of opposite signs [115]. The Hammett correlations for the reactions of benzylic chlorides with ethoxide ion and sodium ethoxide ion pairs give also the ρ values of 2.2 and -0.6 with opposite signs, respectively [116]. Note that an ionic structure of the transition state is stabilized by electrostatic polarization of the double bond than π-conjugation [108]. At the same time, the significant charge delocalization takes place for the ion pair structure of the transition state. In general, ion pair reactions are less favorable than the corresponding ionic reactions [115].

The steric effect in S_N2 reactions of alkyl chloronitriles with chloride ion was quantitatively estimated (Scheme 8). The magnitude of the steric effect, however, is not significantly different in the gas phase and in solution [117]. Moreover, the solvation energy of the S_N2 transition state TS-10 does not depend on the size of the substituent R. The weak size dependence results from the compensation between a direct shielding effect of the substituent and an indirect ionic solvation effect, which arises from the geometric perturbations introduced by the substitution [117].

The influence of microsolvation on the $Cl^- + RCl$ S_N2 reaction, with R being methyl, ethyl, *i*-propyl, and *tert*-butyl, has been investigated in the presence of 0-4 water molecules, and 0-2 molecules of methanol, acetonitrile, acetone, dimethyl ether and propane by the calculations, using B3LYP/6-31 + G* level with the polarizable continuum model (PCM) [118,119].



Scheme 9

The calculated barrier heights increase with the number of solvent molecules and the size of the R substituent. Microsolvation causes only small changes in the TS geometries for the methyl, ethyl, and *i*-propyl substituents, whereas the *tert*-butyl TS becomes significantly looser [118]. Microsolvation decreases the steric effect of the substituent R depending on the dielectric constant of the solvent. The decrease in steric effect of the substituent is due to an increased solvation of the TS mediated by the electron donating effect of the methyl groups at the central carbon. The latter leads to an increased interaction with the solvent [118,119].

It should be noted that the variation of the activation parameters for S_N2 reactions depend on the reacting species and solvents [120-126]. For instance, the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for the reaction of sodium 4-nitrophenoxide and iodomethane in acetone-water mixtures at 25-35 °C form the compensation dependence reflecting electrostatic and specific interactions between a nucleophile and a solvent mixture [120]. However, a Menschutkin reaction between 2-amino-1-methylbenzimidazole and iodomethane in acetonitrile at 20-50 °C leads to non-Arrhenius behavior of the kinetic data steming from the conjunction of a nucleophile with a dipolar aprotic solvent that is protophobic [121].

Recently, a new concept based on selective solvation of the TS-11 by double hydrogen bonding in the reaction of the cyanide ion with ethyl chloride in carbon tetrachloride solution in the presence of 1,4-benzenedimethanol (BDM) was proposed (Scheme 9) [122,123]. The high stability of the BDM-cyanide complex induces a substantial rate acceleration effect leading to lower activation barrier [122,123].

The S_N2 reactions using alkali metal salts MX ($M^+ = Cs^+, K^+$; $X = F^-, Br^-, I^-, CN^-$) as nucleophile agents and $C_3H_7OSO_2CH_3$ as a substrate in the presence of *n*-oligoethylene glycols demonstrate a new concept for elucidating the promoting effects: the nucleophiles react as ion pairs, whose metal cation is coordinated by the oxygen atoms in oligoethylene glycols acting as Lewis base to reduce the unfavorable electrostatic effects of M^+ on X^-. The calculated S_N2 barriers of various nucleophiles ($F^- > CN^- > Br^- > I^-$) were in agreement with experimental observations [125, 126]. The effect of counterion on the reactivity of ion pairs along the backside and frontside reactions $Nu^- + CH_3X \rightarrow CH_3Nu + X^-$ (X = F, Cl, Br; $Nu^- = X^-, Li^+X^-, Na^+X^-, K^+X^-$) in solvent media shows that the calculated energy barriers increase with decreasing the size of counterion [124].

The analysis of the potential energy surfaces of various model S_N2 reactions of $Cl^- + CR_3Cl$ and $Cl^- + SiR_3Cl$ (R = H, Me, Et, OMe) shows that the central S_N2 @C barrier is retained by the interplay of steric and electronic effects between nucleophile and substrate. However, the central S_N2 @Si barrier disappears because there is less steric congestion. Such a comparison of the mechanisms of the S_N2 @C and S_N2 @Si reactions gives the possibility to elucidate the steric nature of the S_N2 barrier [127].

The comparison of the potential energy surfaces of the backside as well as frontside S_N2 reactions of $X^- + CH_3Y$ with X, Y = F, Cl, Br, and I, using DFT at ZORA-OLYP/TZ2P provides that backside S_N2-b barriers increase along the nucleophiles $F^- > Cl^- > Br^- > I^-$ and decrease along the substrates $CH_3F > CH_3Cl > CH_3Br > CH_3I$. Frontside S_N2-f barriers show the same trends but are in all cases much higher (~ 42 ÷ 250 kJ.mol^{-1}) because of more steric repulsion between the nucleophile and leaving group [128,129]. Therewith, the frontside substitution becomes gradually more competitive when the substitution in the substrate becomes bigger and the leaving group / nucleophile become better [9]. However, the solvation of the S_N2 reaction in water of $Cl^- + CH_3Cl$ leads into unimodal reaction profile via one single barrier TS-1 to the product [130]. The significant increase of the energetic barrier by over 63-71 kJ mol^{-1} for the S_N2 reactions of $CN^- + CH_3I$ and $CN^- + C_2H_5I$ occurs in protic and aprotic solvents in comparison with the gas phase. The magnitudes of the electrostatic attraction between the partial negative charges on the nucleophiles in the transition state and the partial positive charge on the α carbon are much larger in the gas phase than in solvent where solvation will reduce these interactions between ions in the transition state [131].

8. Conclusions

The parameters from the linear free energy relationships providing mechanistic criteria for the S_N2 reactions in solution allow one to determine the peculiarities in the mechanism of these reactions.

Compensation relationships between the changes of the activation parameters $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ give a possibility to estimate the changes of the internal enthalpy $\delta\Delta H^{\neq}_{\mathrm{int}}$. These reaction constants give rise to two linear dependences with the values of the reaction constants $\delta\Delta G^{\neq}$ or the Hammett values ρ for S_N2 reactions in solution with neutral and charged nucleophiles. Furthermore, the different deviations from these dependences indicate the alternative TS structures in comparison with the standard structure of TS-1 on the ground of their activation parameter variations.

Computations with the PCM method give a possibility to evaluate the influence of solvation as microsolvation onto the activation parameters in the S_N2 reactions in solution. Moreover, microsolvation can offer greater insight into the role of the hydrogen bonding, conjugation and steric hindrance in these reactions.

The analysis presented opens a perspective to evaluate the effects of substituents in the nucleophile, leaving and nonleaving groups on a wide variety of the reactivity for the S_N2 reactions in solution, thus being of help for practical organic chemists in designing reaction schemes.

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