

Substituent Effects on the Activation Parameter Changes for the Aminolysis in the Bimolecular Nucleophilic Reactions in Solution

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Abstract: Variation of the activation parameters for the aminolysis in the S_N2 , acyl-transfer, S_NAr and Ad_N reactions offers an additive mechanistic tool for the studies of these reactions in solution. This approach uses the substituent effects on the benzene and pyridine rings to the variation of the activation parameters, ΔX^\ddagger ($X = H, S, G$), in the above reactions in the frameworks of the Hammett – like equations in order to evaluate the resultant $\delta\Delta X^\ddagger$ reaction constants. The single linear dependences of the internal enthalpy constants $\delta\Delta H^\ddagger_{int}$ on the $\delta\Delta G^\ddagger$ and the Hammett ρ constants show that the substituent effects in the leaving and nonleaving groups and nucleophiles on the mechanistic features in aminolysis of bimolecular nucleophilic reactions are governed by the magnitude of $\delta\Delta H^\ddagger_{int}$ when one of the steps of the process is the single rate-determining step.

Keywords: Aminolysis in solution, nucleophilic reactions, activation parameters, reaction mechanism.

INTRODUCTION

A significant part of reactions carried out by the pharmaceutical and agrochemical industries involve aminolysis in the bimolecular nucleophilic reactions (BNRs) in solution [1,2]. The aminolysis with amines and pyridines in the BNRs plays also an important role for both organic chemistry [3,4] and biochemistry [5]. These include S_N2 , acyl-transfer, S_NAr and Ad_N reactions, etc [3-6]. The nature of the reactants or solvents influences both the kinetics and mechanisms of these reactions [7,8]. Various experimental kinetic and theoretical studies have therefore been devoted to obtain a better understanding of the mechanisms of the aminolysis in the nucleophilic reactions of the substitution and addition [5-19]. Among traditional experimental methods, kinetic isotope effects [8,20-22] and linear free energy relationships [23-26] have most frequently been used to study mechanisms of BNRs, in particular the nature of transition states (TSs) [27-29].

The activation parameters are widely used for characterizing the TS structures for BNRs [8,23-27,30]. Some generalizations of the changes in the enthalpy of activation (ΔH^\ddagger), the entropy of activation (ΔS^\ddagger), and the activation free energy (ΔG^\ddagger) for these reactions were made [23,30]. The influence of the variations of substituents in substrates and amines on activation parameters in S_N2 , acyl-transfer, S_NAr and Ad_N reactions was demonstrated [30-36]. The effects of substituents on the aromatic ring were used in order to

evaluate the contribution of changes of the activation parameters in these reactions in the frameworks of the Hammett – like equation (1) [37,38].

$$\Delta X^\ddagger = \delta\Delta X^\ddagger \sigma + \Delta X^\ddagger_o \quad (X = H, S, G) \quad (1)$$

In this equation, σ is the Hammett constant of the substituent, the slope ($\delta\Delta X^\ddagger$) is the selectivity of its influence on the activation parameters ΔX^\ddagger ($X = H, S, G$), and the term ΔX^\ddagger_o is the activation parameters for the unsubstituted compound. Therefore, the reaction constant $\delta\Delta X^\ddagger$ is analogous to the Hammett one ρ .

Recent analysis of the reaction constants, $\delta\Delta X^\ddagger$ ($X = H, S, G$), has revealed a number of $\delta\Delta H^\ddagger$ versus $\delta\Delta S^\ddagger$ compensation equations for typical BNRs for which a substituent is varied on the leaving and nonleaving groups, as well as on the charged and neutral nucleophiles [31]. In addition, the variations of the reaction constants $\delta\Delta X^\ddagger$ [eqn (1)] were discussed in the context of estimating the changes in the internal and external reaction constants, $\delta\Delta X^\ddagger_{int}$ and $\delta\Delta H^\ddagger_{ext}$, respectively [eqn (2)] [31].

$$\delta\Delta X^\ddagger = \delta\Delta X^\ddagger_{int} + \delta\Delta X^\ddagger_{ext} \quad (2)$$

In keeping with the Hepler solvation theory [37,38], in this equation the reaction constants $\delta\Delta X^\ddagger$ are divided into internal ($\delta\Delta X^\ddagger_{int}$) and external ($\delta\Delta X^\ddagger_{ext}$) terms, which refer to the chemical reaction and the solvation process, respectively [31-36]. It was found that a single Hammett-like linear dependences between $\delta\Delta H^\ddagger_{int}$ versus $\delta\Delta G^\ddagger$ and $\delta\Delta H^\ddagger_{int}$ versus ρ for the BNRs have been developed for which the k_c or k_1 steps were rate-determining [eqn (3) and (4)] (Scheme 1) [31].

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$$\delta\Delta H_{\text{int}}^{\ddagger} = (-0.21 \pm 0.15) + (1.00 \pm 0.01) \delta\Delta G^{\ddagger} \quad (3)$$

$$r = 0.996, s = 1.29, n = 82$$

$$\delta\Delta H_{\text{int}}^{\ddagger} = (-0.3 \pm 0.2) - (6.0 \pm 0.1) \rho \quad (4)$$

$$r = 0.994, s = 1.7, n = 82$$

This scheme shows the main mechanisms of the aminolysis in the $S_{\text{N}}2$ [6-8], acyl-transfer [5], $S_{\text{N}}\text{Ar}$ [14-16] and Ad_{N} reactions [19] proceeding both by concerted and stepwise pathways. It should be noted that the mechanism of aminolysis with neutral amines in $S_{\text{N}}2$ [31,33-35,39], and Ad_{N} reactions [40-43] is concerted proceeding through a single TS with the k_{c} step as the rate-determining one (Scheme 1). At the same time the aminolysis in the acyl-transfer and $S_{\text{N}}\text{Ar}$ reactions proceed by a different mechanisms. The aminolysis with neutral amines in the acyl-transfer reactions can follow both a concerted [44,45] and a stepwise mechanism [31,32,46-53], for which the nucleophilic attack with the k_{c} and k_1 (or k_2) steps are to be rate-determining, respectively. The nucleophilic substitution mechanism $S_{\text{N}}\text{Ar}$ (addition – elimination) in arenes with neutral amines depends on the reaction medium and substrate structure [14-17]. Normally, general base catalysis occurs in nonpolar aprotic solvents [54,55]. However, in dipolar aprotic solvents the general base catalysis is not observed [56-58]. Obviously, the formation of σ complex (rate constant k_1) and its decomposition (rate constants k_2 or k_3 [=NH]) are presumed to be rate – determined [14-17,54-61]. If in a stepwise reaction an addition of amine to the substrate (rate constant k_1 in Scheme 1) or a decomposition of intermediate (rate constant k_2) is the single rate – determining step (RDS), it can be supposed that the effect of the substituents R in the leaving group of compounds **3 – 14**, the nonleaving group of compounds **20 – 23, 25, 27, 30 – 33** and nucleophiles **36 – 38** on the changes of the reaction constants $\delta\Delta X^{\ddagger}$ ($X = H, S, G$) can be similar in according to eqns (3) and (4) for all BNRs proceeding also by concerted mechanism (*cf.* ref. 62,63). Therefore, we considered it of interest to address these questions in the present work. Furthermore, an additional focus of our interest in the properties of the RDS concerned the single RDS for the aminolysis in the multistep BNRs.

Herewith, we report on the effects of the substituents in the leaving and nonleaving groups, as well as in the nucleophiles on the variation in the $\delta\Delta X^{\ddagger}$ ($X = H, S, G$) values and on the mechanisms for the typical BNRs with neutral amines and pyridines in protic and aprotic media (Scheme 1). Our second aim

in this work was to extend the possibilities of the equations (3) and (4) for a quantitative description of the effects of the substituents in these BNRs when they can have a single RDS. This is of considerable importance since due to the presence of the single RDS in the multistep BNRs, it provides a possibilities to modify the BNRs to achieve higher or lower rates as desired. To the best of our knowledge, this has been the first comprehensive study of the mechanistic features of the aminolysis in the BNRs so far.

RESULTS AND DISCUSSION

The key results are summarized in Table 1.

Reaction Constants $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$

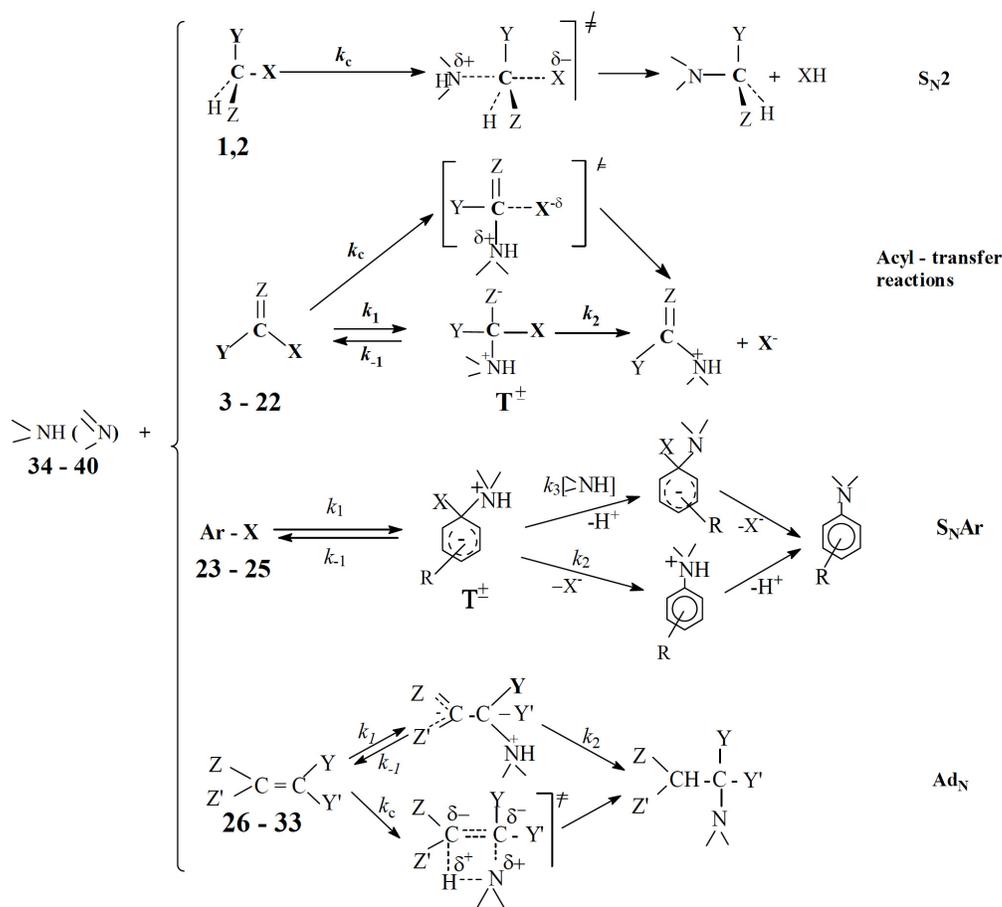
The values of the changes in the activation parameters, $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$, for the reactions of compounds **1 – 33** with amines **34 – 37, 39, 40** and pyridines **38** in various solvents (Table 1, entries 1 – 65) were obtained according to the general Hammett-like equation (1) using the Hammett's σ substituent constants (Table S1 in the supplementary data) [65].

The $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ values 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 [31-36,66,67].

Recent analysis of the reaction constants $\delta\Delta H^{\ddagger}$ and $\delta\Delta S^{\ddagger}$ for typical BNRs has revealed a number of compensation equations that depend on the reaction rate constants and on the differences in the effects of various substituents [31]. As can be seen from the general compensation relationship, $\delta\Delta H^{\ddagger}$ vs. $\delta\Delta S^{\ddagger}$ (Eq. 5), the slope of this equation corresponds to the

$$\delta\Delta H^{\ddagger} = \delta\Delta H_{\text{int}}^{\ddagger} + T_{\text{comp}} \delta\Delta S^{\ddagger} \quad (5)$$

compensation temperature T_{comp} and their values were tested at the $\geq 95\%$ confidence level (Table 1) [31]. Note that it is very important to test for the existence of a compensation relationship at a confidence level of $>95\%$ [68]. The compensation temperatures T_{comp} are higher than the mean experimental temperature T_{exp} excluding only entries 55-57 in Table 1 and it must be concluded that the compensation correlations are not caused by experimental errors [69]. As for the exact physical – chemical sense of the enthalpy – entropy compensation, this is still a debated question [68, 70-75]. Nevertheless, when $T_{\text{comp}} > T_{\text{exp}}$, it is necessary to



- 1 X = I, Y = Z = H
- 2 X = Br, Y = H, Z = RC₆H₄
- 3 X = RC₆H₄O, Y = 4-NO₂C₆H₄, Z = O
- 4 X = 2-NO₂-RC₆H₃O, Y = Ph, Z = O
- 5 X = 2,6-(NO₂)₂-RC₆H₃O, Y = Ph, Z = O
- 6 X = RC₆H₄O, Y = Me, Z = O
- 7 X = RC₆H₄S, Y = EtO, Z = O
- 8 X = RC₆H₄S, Y = Et, Z = O
- 9 X = RC₆H₄S, Y = PhNH, Z = O
- 10 X = RC₆H₄O, Y = *cyclo*-C₃H₅, Z = O
- 11 X = RC₆H₄O, Y = *cyclo*-C₄H₇, Z = O
- 12 X = RC₆H₄S, Y = PhCH₂, Z = S
- 13 X = RC₆H₄S, Y = Me, Z = O
- 14 X = RC₆H₄S, Y = PhCH₂, Z = O
- 15 X = Cl, Y = Ph, Z = O
- 16 X = Cl, Y = PhO, Z = O
- 17 X = Cl, Y = 2-C₄H₃OCH = CH-, Z = O
- 18 X = Cl, Y = 3-C₄H₃S-, Z = O
- 19 X = 2,4-(NO₂)₂C₆H₃O, Y = Ph, Z = O
- 20 X = CH₂Br, Y = RC₆H₄, Z = O

- 21 X = 4-NO₂C₆H₄O, Y = RC₆H₄, Z = O
- 22 X = 2,4-(NO₂)₂C₆H₃O, Y = RC₆H₄, Z = O
- 23 X = Cl, Ar = 2-NO₂-RC₆H₃
- 24 X = Cl, Ar = 2,4,6-(NO₂)₃C₆H₂
- 25 X = Cl, Ar = RC₆H₄
- 26 PhCH = C(CN)₂
- 27 (E)-RC₆H₄CH = CHNO₂
- 28 PhC ≡ C - C(O)Ph
- 29 4-NO₂C₆H₄CH = CHNO₂
- 30 RC₆H₄CH = C(CN)C₆H₄NO₂-4
- 31 RC₆H₄CH = C(Ph)NO₂
- 32 RC₆H₄CH = C(COOEt)₂
- 33 RC₆H₄CH = C(COOEt)COCH₃
- 34 Imidazole
- 35 NH₂CH₂COO⁻
- 36 R'C₆H₄CH₂NH₂
- 37 R'C₆H₄NH₂
- 38 R'C₅H₄N
- 39 NH₃
- 40 C₅H₁₀NH

2 - 14, 20 - 23, 25, 27, 30 - 33, 36 - 38:

- | | | | | | |
|--------------------------|---------------------------|----------------------------|--------------------------|--|---|
| a. R = 4-NH ₂ | f. R = 3-Me | k. R = 4-Br | p. R = 3-Br | u. R = 4-NO ₂ | z. R = 4-SO ₂ NH ₂ |
| b. R = 4-MeO | g. R = 4-NMe ₂ | l. R = 3-F | q. R = 4-CF ₃ | v. R = 3-NO ₂ | aa. R = 4-SO ₂ CF ₃ |
| c. R = 4-Me | h. R = 4-H | m. R = 3-Cl | r. R = 3-CF ₃ | w. R = 4-COOEt | |
| d. R = 3-NH ₂ | i. R = 4-F | n. R = 3,4-Cl ₂ | s. R = 4-CN | x. R = 4-SO ₂ CH ₃ | |
| e. R = 3-MeO | j. R = 4-Cl | o. R = 3,5-Cl ₂ | t. R = 3-CN | y. R = 3-SO ₂ CH ₃ | |

Scheme 1: Reactions of compounds 1 - 33 with amines 34 - 40.

Table 1: Changes in the reaction constants $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger_{\text{int}}$, $\delta\Delta H^\ddagger$, and $\delta\Delta S^\ddagger$, the experimental and compensation temperatures T_{exp} and T_{comp} , rate constants of the RDS and the Hammett ρ reaction constants in the reactions of compounds 1 - 33 with primary amines 35 - 37, 39, secondary cyclic amines 34, 40, and pyridines 38 in various solvents

Entry	Reactants	Solvent	$\delta\Delta G^\ddagger /$ $\text{kJ mol}^{-1} \sigma^{-1}$	$\delta\Delta H^\ddagger_{\text{int}} /$ $\text{kJ mol}^{-1} \sigma^{-1}$	$\delta\Delta H^\ddagger /$ $\text{kJ mol}^{-1} \sigma^{-1}$	$\delta\Delta S^\ddagger /$ $\text{J mol}^{-1} \text{K}^{-1} \sigma^{-1}$	$T_{\text{exp}} /$ K	$T_{\text{comp}} /$ K	Rate constant of the RDS	ρ	Ref. ^c
	Substituents R are Acyl-transfer reactions	varied on	leaving	groups							
1	4-NO ₂ C ₆ H ₄ COOC ₆ H ₄ R 3c,h,j,s,u + Imidazole 34	10vol% MeCN-H ₂ O	-9.1	-9.2	-1.1	25.4	315	320	k_1	1.56	[31, 32]
2	PhCOOC ₆ H ₃ R-NO ₂ -2 4u,v + NH ₂ CH ₂ COO ⁻ 35	60% dioxane-40% H ₂ O	-7.2	-6.5	-16.8	-32.1	298	320	k_1	1.26	[31]
3	PhCOOC ₆ H ₂ R-(NO ₂) ₂ -2,6 5h,u + NH ₂ CH ₂ COO ⁻ 35	60% dioxane-40% H ₂ O	-6.9	-6.2	-16.8	-33.1	298	320	k_1	1.24	[31]
4	MeC(O)OC ₆ H ₄ R 6j,s + 4-MeC ₆ H ₄ CH ₂ NH ₂ 36c	DMSO	-5.70	-5.48	-8.79	-10.33	298	320	k_2	1.61	-
5	MeC(O)OC ₆ H ₄ R 6j,s + 4-ClC ₆ H ₄ CH ₂ NH ₂ 36j	DMSO	-9.31	-9.19	-10.85	-5.17	298	320	k_2	1.85	-
6	EtOC(O)SC ₆ H ₄ R 7c,k + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-10.2	-9.82	-19.85	-31.35	308	320	k_c	1.63	-
7	EtOC(O)SC ₆ H ₄ R 7c,k + 4-ClC ₆ H ₄ CH ₂ NH ₂ 36j	MeCN	-8.55	-8.79	-2.1	20.92	308	320	k_c	1.37	-
8	EtC(O)SC ₆ H ₄ R 8c,m + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-12.39	-12.84	-0.70	37.94	308	320	k_2	2.12	-
9	PhNHC(O)SC ₆ H ₄ R 9c,k + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-12.20	-12.67	-3.77	27.8	303	320	k_c	2.07	-
10	PhNHC(O)SC ₆ H ₄ R 9c,k + 4-ClC ₆ H ₄ CH ₂ NH ₂ 36j	MeCN	-10.70	-11.93	11.50	73.22	303	320	k_c	1.74	-
11	<i>cyclo</i> -C ₃ H ₅ C(O)OC ₆ H ₄ R 10t,u + 4-MeC ₆ H ₄ CH ₂ NH ₂ 36c	MeCN	-15.94	-	6.55	70.70	318	-	k_2	2.47	-
12	<i>cyclo</i> -C ₃ H ₅ C(O)OC ₆ H ₄ R 10t,u + 3-ClC ₆ H ₄ CH ₂ NH ₂ 36m	MeCN	-20.45	-	-3.59	53.03	318	-	k_2	2.97	-
13	<i>cyclo</i> -C ₄ H ₇ C(O)OC ₆ H ₄ R 11t,u + 4-MeC ₆ H ₄ CH ₂ NH ₂ 36c	MeCN	-15.59	-	-0.59	47.15	318	-	k_2	2.41	-
14	<i>cyclo</i> -C ₄ H ₇ C(O)OC ₆ H ₄ R 11t,u + 3-ClC ₆ H ₄ CH ₂ NH ₂ 36m	MeCN	-17.96	-	-2.96	47.14	318	-	k_2	3.04	-
15	PhCH ₂ C(S)SC ₆ H ₄ R 12c,k + 4-MeOC ₆ H ₄ NH ₂ 37b	MeCN	-15.05	-	1.05	52.3	308	-	k_2	2.43	-

(Table 1). Continued.

16	PhCH ₂ C(S)SC ₆ H ₄ R 12c,k + 4-ClC ₆ H ₄ NH ₂ 37m	MeCN	-16.95	- (-17.34)	-7.30	31.37	308	-	k ₂	3.31	-
17	MeC(O)SC ₆ H ₄ R 13c,k + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-30.02	- (-31.15)	-1.02	94.15	308	-	k ₂	5.00	-
18	MeC(O)SC ₆ H ₄ R 13c,k + 4-ClC ₆ H ₄ CH ₂ NH ₂ 36j	MeCN	-30.10	- (-31.37)	2.10	104.60	308	-	k ₂	5.42	-
19	PhCH ₂ C(O)SC ₆ H ₄ R 14c,k + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-9.31	-9.42	7.32	52.30	318	320	k ₂	1.42	-
20	PhCH ₂ C(O)SC ₆ H ₄ R 14c,k + 3-ClC ₆ H ₄ CH ₂ NH ₂ 36m	MeCN	-13.0	-13.17	13.60	83.67	318	320	k ₂	1.79	-
	Substituents R are varied on	varied on	nucleophiles								
21	R'C ₆ H ₄ N 38h,m,o,p,s + MeI 1	MeCN	13.1	13.9	9.9	-10.7	298	370	k _c	-2.27	[31, 33,34]
22	R'C ₆ H ₄ NH ₂ 37c,f,h,j,k,m,n + PhCH ₂ Br 2h	EtOH	5.6	5.1	8.0	7.9	303	370	k _c	-0.89	[31, 33,34]
	Acyl-transfer reactions										
23	R'C ₆ H ₄ NH ₂ 37c,h,j,u,v + PhC(O)Cl 15	C ₆ H ₆	14.7	14.7	14.7	0	298	370	k ₁	-2.90	[31, 32,34]
24	R'C ₆ H ₄ NH ₂ 37h,m,v + PhOC(O)Cl 16h	MeCN	11.8	11.0	15.3	11.6	298	370	k ₁	-2.22	[31, 32,34]
25	R'C ₆ H ₄ NH ₂ + 37c,f,h,j,m,v 2-C ₄ H ₉ O-CH=CHC(O)Cl 17	C ₆ H ₆	18.1	18.6	16.2	-6.4	298	370	k ₁	-2.86	[31, 34]
26	R'C ₆ H ₄ NH ₂ + 37b,c,f,h,j,m,v 3-C ₄ H ₉ S-C(O)Cl 18	C ₆ H ₆	18.1	18.2	17.5	-2.0	298	370	k ₁	-3.21	[31, 34]
27	R'C ₆ H ₄ N 38f,g + PhC(O)OC ₆ H ₃ (NO ₂) ₂ -2,4 19	44wt% EtOH – H ₂ O	25.61	18.48	57.87	106.47	303	370	k ₂	-5.26	[36, 64]
28	MeC(O)OC ₆ H ₄ Cl-4 6j + R'C ₆ H ₄ CH ₂ NH ₂ 36c,j	DMSO	5.20	- (6.69)	-1.05	-20.92	298	-	k ₂	-1.05	-
29	MeC(O)OC ₆ H ₄ CN-4 6s + R'C ₆ H ₄ CH ₂ NH ₂ 36c,j	DMSO	-2.12	- (-1.35)	-5.22	-10.47	298	-	k ₂	-0.56	-
30	PhNHC(O)SC ₆ H ₄ Me-4 9c + R'C ₆ H ₄ CH ₂ NH ₂ 36b,j	MeCN	7.62	10.85	-7.06	-48.4	303	370	k _c	-1.30	-
31	PhNHC(O)SC ₆ H ₄ Br-4 9k + R'C ₆ H ₄ CH ₂ NH ₂ 36b,j	MeCN	8.82	9.62	5.16	-12.06	303	370	k _c	-1.54	-
32	cyclo-C ₃ H ₅ C(O)OC ₆ H ₄ CN-3 10t + R'C ₆ H ₄ CH ₂ NH ₂ 36c,m	MeCN	12.83	13.64	7.91	-15.50	318	370	k ₂	-2.10	-

(Table 1). Continued.

33	<i>cyclo</i> -C ₃ H ₅ C(O)OC ₆ H ₄ NO ₂ -4 10u + R'C ₆ H ₄ CH ₂ NH ₂ 36c,m	MeCN	6.91	8.91	-5.42	-38.74	318	370	k ₂	-1.36	-
34	<i>cyclo</i> -C ₄ H ₇ C(O)OC ₆ H ₄ CN-3 11t + R'C ₆ H ₄ CH ₂ NH ₂ 36c,m	MeCN	12.68	13.49	7.76	-15.48	318	370	k ₂	-2.08	-
35	<i>cyclo</i> -C ₄ H ₇ C(O)OC ₆ H ₄ NO ₂ -4 11u + R'C ₆ H ₄ CH ₂ NH ₂ 36c,m	MeCN	9.57	10.38	4.65	-15.5	318	370	k ₂	-1.36	-
36	MeC(O)SC ₆ H ₄ Me-4 13c + R'C ₆ H ₄ CH ₂ NH ₂ 36b,j	MeCN	8.42	8.95	5.86	-8.36	308	370	k ₂	-1.65	-
37	MeC(O)SC ₆ H ₄ Br-4 13k + R'C ₆ H ₄ CH ₂ NH ₂ 36b,j	MeCN	8.36	8.36	8.36	0	308	370	k ₂	-1.25	-
38	PhCH ₂ C(O)SC ₆ H ₄ Me-4 14c + R'C ₆ H ₄ CH ₂ NH ₂ 36b,m	MeCN	9.21	11.25	-3.26	-39.22	318	370	k ₂	-1.54	-
39	PhCH ₂ C(O)SC ₆ H ₄ Br-4 14k + R'C ₆ H ₄ CH ₂ NH ₂ 36b,m	MeCN	6.89	7.92	0.66	-19.61	318	370	k ₂	-1.44	-
S_NAr reactions											
40	R'C ₆ H ₄ NH ₂ 37f,h,j,k,m,p + 2,4-(NO ₂) ₂ C ₆ H ₃ Cl 23u	EtOH	18.4	15.4	37.7	60.4	318	370	k ₁	-3.06	[31, 34]
41	R'C ₆ H ₄ NH ₂ 37h,j,m + 2,4,6-(NO ₂) ₃ C ₆ H ₂ Cl 24	C ₆ H ₆	27.6	27.7	27.0	-2.0	298	370	k ₁	-4.79	[31, 34]
Ad_N reactions											
42	R'C ₆ H ₄ CH ₂ NH ₂ 36b-f, h-m,q,v + PhCH = C(CN) ₂ 26	MeCN	7.5	3.7	21.8	48.8	293	370	k ₁	-0.99	[31, 34]
43	R'C ₆ H ₄ NH ₂ 37b-f, h,j,k,m,p-v + (E)-PhCH = CHNO ₂ 27h	MeCN	10.6	9.3	16.0	18.1	298	370	k ₁	-1.88	[31, 34]
44	R'C ₆ H ₄ NH ₂ 37a-f, h,j,k + PhCH ≡ C(O)Ph 28	95% EtOH	10.6	13.1	-3.4	-44.7	313	370	k ₁	-2.18	[31, 34]
45	R'C ₆ H ₄ CH ₂ NH ₂ 36b,j + 4-NO ₂ C ₆ H ₄ CH = CHNO ₂ 29	MeCN	8.38	10.13	0.84	-25.1	298	370	k _c	-1.55	-
46	R'C ₆ H ₄ CH ₂ NH ₂ 36b,j + 4-BrC ₆ H ₄ CH = C(CN)- C ₆ H ₄ NO ₂ -4 30k	MeCN	8.32	8.96	5.86	-8.38	298	370	k _c	-1.30	-
47	R'C ₆ H ₄ CH ₂ NH ₂ 36b,j + 4-MeOC ₆ H ₄ CH = C(CN)- C ₆ H ₄ NO ₂ -4 30b	MeCN	6.52	8.45	-0.84	-25.1	298	370	k _c	-0.95	-

(Table 1). Continued.

	Substituents R are varied on	S_N2 reactions	nonleaving groups								
48	RC ₆ H ₄ CH ₂ Br 2h,j,u + PhNH ₂ 37h	MeCN	3.3	4.7	-2.0	-17.3	308	380	k_c	-0.55	[31, 33,35]
49	RC ₆ H ₄ CH ₂ Br 2c,h,u + C ₅ H ₅ N 38h	DMF	1.8	-0.6	9.5	25.8	298	380	k_c	-0.31	[31, 33,35]
Acyl-transfer reactions											
50	RC ₆ H ₄ OC(O)Cl 16b,u + C ₅ H ₅ N 38h	MeCN	-5.92	-6.21	1.20	23.89	288	310 °	k_1	1.03	[36]
51	RC ₆ H ₄ C(O)CH ₂ Br 20b,u + 3-MeC ₅ H ₄ N 38f	MeCN	-1.89	-	-11.03	-28.74	318	-	k_1	0.28	[36]
52	RC ₆ H ₄ C(O)CH ₂ Br 20b,u + 3-CNC ₅ H ₄ N 38t	MeCN	-3.12	-	-4.89	-5.57	318	-	k_2	0.54	[36]
53	RC ₆ H ₄ COOC ₆ H ₄ NO ₂ -4 21c,h,j,s,u + Imidazole 34	10 vol% MeCN – H ₂ O	-6.8	-6.8	-5.6	3.9	308	310 °	k_1	1.10	[31, 32]
54	RC ₆ H ₄ C(O)OC ₆ H ₃ (NO ₂) ₂ -2,4 22c,h,j,s,u + Imidazole 34	10 vol% MeCN – H ₂ O	-10.0	-10.2	-2.9	23.7	298	310 °	k_1	1.74	[31, 32]
S_NAr reactions											
55	RC ₆ H ₄ Cl 25r,u,x,z + NH ₃ 39	H ₂ O	-58.1	-58.0	-43.4	31.0	473	450	k_1	8.6	[31, 35]
56	1-Cl-2-NO ₂ C ₆ H ₃ R 23h,r,u + NH ₃ 39	MeOH	-21.0	-23.1	-30.6	-22.6	423	330	k_1	3.8	[31, 35]
57	1-Cl-2-NO ₂ C ₆ H ₃ R 23h,j,k,m,p,q,s,u,w + C ₅ H ₁₀ NH 40	C ₆ H ₆	-22.2	-22.4	-23.6	-3.8	373	330	k_1	3.6	[31, 35]
58	1-Cl-2-NO ₂ C ₆ H ₃ R 23h,r,u,y,aa + C ₅ H ₁₀ NH 40	MeOH	-22.9	-22.6	-20.9	5.3	373	330	k_1	3.6	[31, 35]
Ad_N reactions											
59	RC ₆ H ₄ CH=C(Ph)NO ₂ 31b,k + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-6.38	-6.94	0.84	25.1	298	310	k_c^d	1.46	-
60	RC ₆ H ₄ CH=C(Ph)NO ₂ 31b,k + 4-ClC ₆ H ₄ CH ₂ NH ₂ 36j	MeCN	-6.38	-6.64	-1.66	16.72	298	310	k_c^d	1.19	-
61	RC ₆ H ₄ CH=CHNO ₂ 27c,u + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-10.13	-10.53	1.76	39.64	288	310	k_c^d	1.82	-
62	RC ₆ H ₄ CH=C(CN)- C ₆ H ₄ NO ₂ - 4 30b,k + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-6.58	-6.87	-1.68	16.74	298	310	k_c^d	1.19	-
63	RC ₆ H ₄ CH=C(CN)- C ₆ H ₄ NO ₂ - 4 30b,k + 4-ClC ₆ H ₄ CH ₂ NH ₂ 36j	MeCN	-4.78	-5.35	5.02	33.46	298	310	k_c^d	0.84	-

(Table 1). Continued.

64	RC ₆ H ₄ CH=C(COOEt) ₂ 32b,k + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-7.30	-7.85	2.52	33.48	293	310	k _c ^d	1.24	-
65	RC ₆ H ₄ CH=C(COOEt)COCH ₃ 33b,j + 4-MeOC ₆ H ₄ CH ₂ NH ₂ 36b	MeCN	-6.30	-7.04	3.34	33.48	288	310	k _c ^d	1.03	-

^aValues in parentheses were calculated by Eq. 8. ^bValues are taken from the reference [31]. ^cThe references relate to the values of $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger_{\text{int}}$, $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$, T_{exp} , the rate constants of the RDS, and ρ ; if the reference is not indicated, these values are taken from Tables 1S and 2S in the supplementary data. ^dValue of $T_{\text{comp}} = 310$ (entries 50, 53, 54 and 59 – 65) is calculated by the compensation equation $\delta\Delta H^\ddagger = (-9.21 \pm 0.53) + (0.31 \pm 0.02) \delta\Delta S^\ddagger$ ($r = 0.975$, $s = 3.0$, $n = 23$ at the 97% confidence limits), where the $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ are taken from [31] and this Table.

accept the existence of a real correlation between the values of $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ [69].

It should be noted that the intercept in Eq. 5 is the internal enthalpy constant $\delta\Delta H^\ddagger_{\text{int}}$ for the given reaction series. The latter were calculated by Eqs. 5 and 6 where the the external enthalpy constant $\delta\Delta H^\ddagger_{\text{ext}}$ depends only on the solvation effects [31,37,38].

$$\delta\Delta H^\ddagger_{\text{ext}} = T_{\text{comp}} \delta\Delta S^\ddagger \quad (6)$$

However, there are the deviations from Eq. 5 for the acyl-transfer reactions (entries 11-18, 28, 29, 51 and 52 in Table 1). Obviously, in these cases $\delta\Delta H^\ddagger_{\text{int}}$ values cannot be calculated by Eqs. 5 and 6; therefore, they were calculated by Eq. 8.

Reaction Constants $\delta\Delta G^\ddagger$ and $\delta\Delta H^\ddagger_{\text{int}}$

The changes in the free energy of activation reaction constant, $\delta\Delta G^\ddagger$, reflect a substituent effect in the leaving groups, nucleophiles, and nonleaving groups. The values of $\delta\Delta G^\ddagger$ are negative for the reaction series in which the substituents R are varied in the leaving and nonleaving groups (entries 1 – 20 and 50 – 65 in Table 1) excluding entries 48 and 49 for S_N2 reactions of substituted benzyl bromide with aniline and pyridine, respectively [9,20,31]. On the other hand, reaction series in which change is only made to substituent R' in the nucleophile (entries 21 – 47) are characterized by positive value of $\delta\Delta G^\ddagger$. Such variation in the signs of the $\delta\Delta G^\ddagger$ values is common for the BNRs [31-36] according to the Hammett-like equation $\delta\Delta G^\ddagger = -2.303RT_{\text{exp}}\rho$ [66].

The dependence $\delta\Delta G^\ddagger$ vs. ρ has been developed for these reactions (Eq. 7) [31]. However, Eq. 7 does not speak about peculiarities of the mechanisms of the BNRs because the Hammett ρ values may depend on the contributions of each step in a stepwise process and the TS structure in the concerted reaction (Scheme 1) [31].

$$\delta\Delta G^\ddagger = 0.04 - 6.04 \rho \quad (7)$$

$$r = 0.995, s = 1.56, n = 98$$

As follows from the data in Table 1, the reaction constants $\delta\Delta H^\ddagger_{\text{int}}$ and $\delta\Delta G^\ddagger$ are close for the majority of reaction series, that is, $\delta\Delta G^\ddagger \approx \delta\Delta H^\ddagger_{\text{int}}$ (cf. ref. 25). A single linear relationship between $\delta\Delta H^\ddagger_{\text{int}}$ and $\delta\Delta G^\ddagger$ for the BNRs (entries 1 – 10, 19-26, 30 – 50, 53-65 in Table 1) has been developed (Eq. 8) (Figure 1).

$$\delta\Delta H^\ddagger_{\text{int}} = (0.05 \pm 0.17) + (1.01 \pm 0.01) \delta\Delta G^\ddagger \quad (8)$$

$$r = 0.996, s = 1.25, n = 52$$

The intercept in Eq. 8 corresponds to the $\delta\Delta G^\ddagger_{\text{ext}}$ value and $\delta\Delta G^\ddagger_{\text{ext}} = \delta\Delta H^\ddagger_{\text{ext}} - T_{\text{ext}} \delta\Delta S^\ddagger_{\text{ext}} \approx 0$ [31,66,76]. It is noteworthy that Eq. 8 coincides practically with the similar Eq. 3 relating to the BNRs for which the k_c and k_1 steps were rate-determining (Scheme 1) [31]. Therefore, a single Hammett-like linear Eq. 8 between the $\delta\Delta H^\ddagger_{\text{int}}$ and $\delta\Delta G^\ddagger$ values for the BNRs can be feasible provided that steps with k_c , k_1 and k_2 (Scheme 1) are presumed to be single rate-determining. In this case, Eq. 8 can be taken as an evidence for a shift of the RDS in the multistep BNRs.

There is the one deviation from the dependence depicted in Eq. 8 for the reactions of entry 27 in Table 1. This deviation can be explained by a larger change of activation entropy due to the stronger difference in solvation of TS forming at a breakdown of T[‡] for acyl-transfer reactions (step k_2 in Scheme 1) [36,64].

Mechanistic Criteria for the Aminolysis in the BNRs

To determine the single RDS for the aminolysis in the BNRs discussed (entries 1 – 65 in Table 1) the analysis of the kinetic data was made on the basis of the Brønsted and Hammett equations (Table 2S in the supplementary data) [40-53,64,77-88]. It should be noted that the biphasic Brønsted plots found for the aminolysis of compounds **6**, **8**, **10** – **14**, **19**, **20** (entries 4, 5, 8, 11 – 20, 27 – 29, 32 – 39, 52 in Tables 1 and

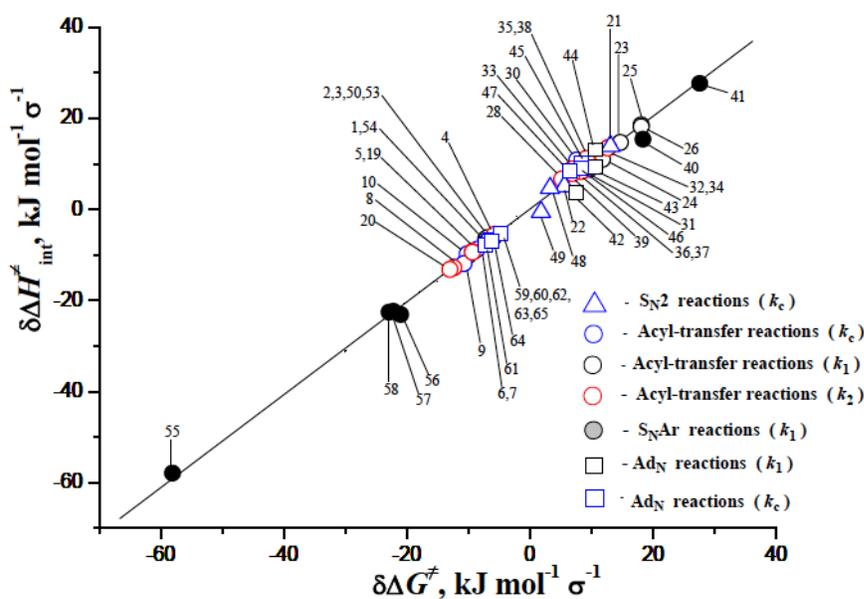


Figure 1: Plot of $\delta\Delta H_{\text{int}}^{\ddagger}$ vs. $\delta\Delta G^{\ddagger}$ for the S_N2 , acyl-transfer, S_NAr and Ad_N reactions of compounds **1** – **33** with neutral amines **34** – **40** in various solvents; the identity of the numbers is the entry number in Table 1.

2S) can be explained by the existence of the zwitterionic tetrahedral intermediate T^{\ddagger} on the reaction pathway and a change in the RDS from formation of T^{\ddagger} (step k_1 in Scheme 1) to its breakdown to products of T^{\ddagger} (step k_2 in Scheme 1), as the amine basicity decreases [44-53,59,60,64,77-109]. The low Brønsted slopes β correspond to the formation of T^{\ddagger} (the step k_1 is the RDS) whereas the high ones determine the RDS with k_2 [44-53,59,60,64,77-109]. The middle value of the Brønsted slope β is characteristic of the concerted mechanism in the aminolysis reactions [40,41,44,45]. In these cases, the Brønsted plot does not show a break [40-45,88]. In other words, a concerted mechanism has often been expected to give a straight-line because a curved Brønsted plot can arise from a variable transition state [27].

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 aminolysis reactions (Eq. 9) [40-53].

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

It was found that the cross-interaction constants $\rho_{RR'}$ are greater for the RDS with k_2 than the one with k_1 or k_c (entries 4 – 20, 27 – 39, 45 – 47, 50 – 52, 59 – 65 in Table 2S of the supplementary data (Scheme 1) [10].

So, the analysis of the kinetic data on the basis of the Brønsted and Hammett-like equations gave an

opportunity to determine the single RDS for the reactions of compounds **1** – **33** with neutral amines **34** – **40** in solution (entries 1 – 65 in Table 1). At the same time, the determination of the k_1 , k_2 or k_c reaction rate constants as the single RDS makes it possible to estimate the role of the Eq. 8 for understanding the reaction mechanism.

It is obvious that the contribution of any step into the rate constant of the aminolysis with neutral amines in the BNRs can be determining. Therefore, the Eq. 8 has the more general character for the interpretation of the mechanistic features of these reactions. In particular, this dependence underlines the importance of the RDS operating on these BNRs. Furthermore, the dependence $\delta\Delta H_{\text{int}}^{\ddagger}$ vs. $\delta\Delta G^{\ddagger}$ gives a possibility to elucidate the changes of the internal enthalpy $\delta\Delta H_{\text{int}}^{\ddagger}$ on the basis of the single reaction rate constants.

Relationships between the Reaction Constants, $\delta\Delta H_{\text{int}}^{\ddagger}$ vs. ρ

Considering Eqs. 7 and 8, a correlation between $\delta\Delta H_{\text{int}}^{\ddagger}$ and ρ for the reactions of entries 1 – 5, 8, 19, 20, 23 – 26, 32 – 44, 50, 53 – 58 in Table 1, for which the k_1 or k_2 step is presumed to be rate-determining, has been developed as shown by Eq. 10 (Figure 2). The Eq. 10 includes also the reactions of entries 6, 7, 9, 10, 21, 22, 30, 31, 45 – 49, 59 – 65 with the rate constants k_c .

$$\delta\Delta H_{\text{int}}^{\ddagger} = (-0.07 \pm 0.24) - (6.16 \pm 0.10) \rho \quad (10)$$

$r = 0.993, s = 1.73, n = 52$

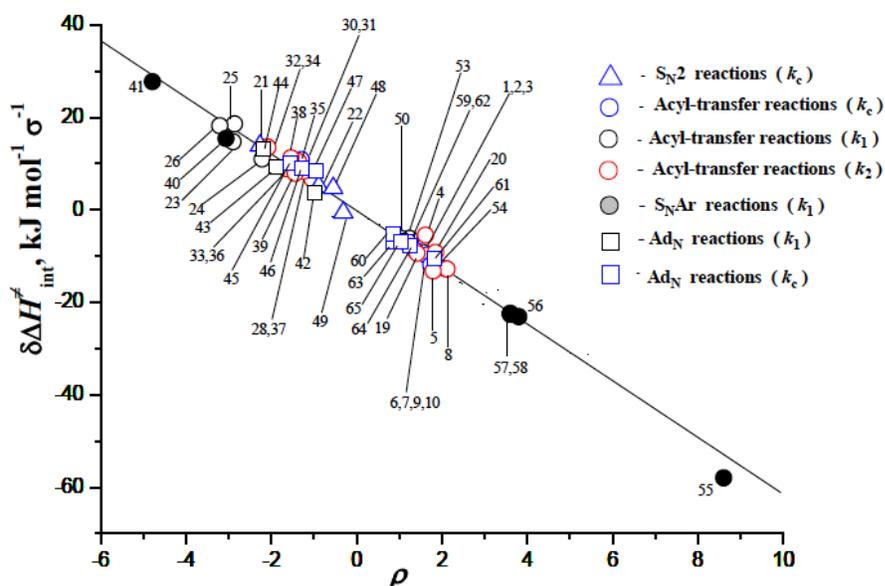


Figure 2: Plot of $\delta\Delta H_{\text{int}}^{\ddagger}$ vs. ρ for the S_N2 , acyl-transfer, S_NAr and Ad_N reactions of compounds 1 – 33 with neutral amines 34 – 40 in various solvents; the identity of the numbers is the entry number in Table 1.

The intercept in Eq. 10 is close to zero and the slope reflects a sensitivity of $\delta\Delta H_{\text{int}}^{\ddagger}$ to a change of ρ equaling approximately $2.303RT = -6.0$ at $T_{\text{exp}} = 310 - 317$ K. The single deviation from Eq. 10 for the reaction of entry 27 in Table 1 (Figure 2) is connected with an appreciable reduction of the $\delta\Delta H_{\text{int}}^{\ddagger}$ reaction constant. Such reduction in the $\delta\Delta H_{\text{int}}^{\ddagger}$ value is due to a larger positive change of an entropy component determined by the solvation influence of TS in protic solvent (see above) [64]. It is noteworthy that the calculated values of the $\delta\Delta H_{\text{int}}^{\ddagger}$ reaction constants by Eq. 8 for entries 11 – 18, 28, 29, 51 and 52 in Table 1 coincide with the same values calculated by Eq. 10.

Realization of Eq. 10 becomes possible, as magnitude of $\rho(k_1)$, $\rho(k_2)$ or $\rho(k_c)$ for BNRs characterize charge development at the TS of the stepwise and concerted processes [23-26,67,110-113]. The $\delta\Delta H_{\text{int}}^{\ddagger}$ reaction constants characterize also the degree of developing charge in the TSs (rate constants k_1 , k_2 or k_c in Scheme 1). The large positive and negative values of $\delta\Delta H_{\text{int}}^{\ddagger}$ indicate essential charge development in the TSs of S_NAr reactions (entries 40, 41 and 55 in Table 1) [31] and acyl-transfer ones (entries 25 and 26) (Figure 2). It is obvious that the electronic effects of substituents R and R' in the leaving and nonleaving groups and nucleophiles are described by the single Hammett-like Eq. 10 for all BNRs with the rate constants k_1 , k_2 or k_c when the rate constants k_1 or k_2 are rate-determining. The linearity over a wide range of the ρ furthermore supports the assumption that there is no change in the mechanisms in this case. Therefore,

the deviations from Eq. 10 can give a possibility to elucidate a reaction series in which a change of TS structure or reaction mechanism takes place.

CONCLUSIONS

The use of the parameters from the Brønsted and Hammett-like equations providing mechanistic criteria for the aminolysis in the BNRs has allowed us to determinate the single RDS in the mechanism of these reactions.

The reaction constants $\delta\Delta H_{\text{int}}^{\ddagger}$ give rise to two linear dependences with the values of the reaction constants $\delta\Delta G^{\ddagger}$ or the Hammett values of ρ for the BNRs proceeding by a concerted mechanism and a stepwise mechanism through an intermediate with its formation or breakdown being the RDS. Furthermore, the different deviations from these dependences could have significant impact on the TS structures and mechanisms of the BNRs on the ground of their activation parameter variations.

The single linear dependence of $\delta\Delta H_{\text{int}}^{\ddagger}$ vs. ρ for all BNRs involving a change of substituent in the leaving and nonleaving groups and nucleophiles gives an opportunity to describe a very wide range of the Hammett ρ values using the $\delta\Delta H_{\text{int}}^{\ddagger}$ reaction constants.

METHODS

Eyring plots were generated by plotting $\log(k/T)$ versus $1/T$ using temperature-dependent rate data [40-

53,64], and the enthalpies and entropies of activation, ΔH^\ddagger , ΔS^\ddagger , were determined for the BNRs of compound **1** – **33** with neutral amines **34** – **40** (Scheme 1). The activation parameters ΔH^\ddagger , ΔS^\ddagger , and ΔG^\ddagger obtained were used by Eq. 1 to establish the reaction constants $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$, and $\delta\Delta G^\ddagger$ (entries 4 – 20, 28 – 39, 45 – 47, 50 – 52, 59 – 65 in Tables 1 and 1S in the supplementary data). These constants were then used in Eq. 2, 5 and 6 to determine the internal reaction constants $\delta\Delta H^\ddagger_{\text{int}}$ when $\delta\Delta S^\ddagger_{\text{ext}} \approx 0$ and $\delta\Delta S^\ddagger \approx \delta\Delta S^\ddagger_{\text{ext}}$ (Table 1) [31-36]. The compensation Eq. 5 was tested at the $\geq 95\%$ confidence level for all reaction series [31].

The quantitative data from the Brønsted and Hammett equations characterizing the aminolysis reactions of compounds **1** – **33** are collected in Table 1S (in the supplementary data) to provide mechanistic criteria for these reactions [40-53,64].

SUPPLEMENTAL DATA

The supplemental data can be downloaded from the journal website along with the article.

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