Substituent effects in substrates on activation parameters in the bimolecular nucleophilic reactions in solution†

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Changes of the activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, in the S_N2, S_NAr and acyl-transfer reactions with charged and neutral nucleophiles in various solvents were correlated with σ constants of the substituents in the aromatic ring of the substrates. The resultant $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ reaction constants are linearly related for variations of substituents at the substrate. Correlation of $\delta\Delta H^{\neq}$ *vs.* $\delta\Delta S^{\neq}$ allows one to estimate the contribution of changes of the internal enthalpy, $\delta\Delta H^{\neq}_{int}$, to the enthalpy reaction constant, $\delta\Delta H^{\neq}$, which gives a single linear dependence on the Hammett ρ reaction constants for all bimolecular nucleophilic reactions. The deviations from dependence of $\delta\Delta H^{\neq}_{int}$ *vs.* ρ can be interpreted in terms of changes of the transition state structure or reaction mechanism. The results obtained show that the substituent effects in the substrates and nucleophiles on the charge development in the transition state are governed by the magnitude of $\delta\Delta H^{\neq}_{int}$.

Introduction

Bimolecular nucleophilic reactions (BNRs) are of great importance for both organic chemistry[1] and biochemistry.[2] These include S_N2, S_NV, Ad_N, S_NAr and acyl-transfer reactions, *etc.*[1,2] There are a myriad experimental kinetic and theoretical studies on the mechanisms of these reactions.[2–11] Some generalizations of the changes in the enthalpy of activation ($\Delta H^{\neq}$), the entropy of activation ($\Delta S^{\neq}$) and the activation free energy ($\Delta G^{\neq}$) for BNR were made.[10,11] It was demonstrated[4,10,11] that the enthalpy and entropy of activation depend much more substantially on the reaction mechanism than the activation free energy. Hence, analysis of the main factors responsible for the ratio between the enthalpy and entropy contribution to the energy barrier for the reaction is of great importance. In this regard, studies on substituent effects in BNRs have been the subject of intense interest in recent years.[2–9,11] In most cases, substituent effects are quantified by the use of the Hammett or the Hammett-like substituent constants[12,13] for aromatic systems.[14,15]

The activation parameters are widely used for characterizing the structures of transition states.[9–11,16–18] For example, it was found that solvolysis of benzyl- and benzhydryl halides follows the S_N2 and S_N1 mechanism, respectively, as S_N2 reactions show more negative values of $\Delta S^{\neq}$.[19] In two-step nucleophilic substitution reactions of carbonyl compounds, the values of $\Delta S^{\neq}$ allow one to identify the rate-limiting step.[20–22]

For the effects of substituents on the BNRs, most studies have been on the effects of structural variations in substrate for the single kind of the S_N2,[16–18,23–41] S_NAr,[5,6,42–45] acyl-transfer reactions,[2,11,20–22,24,25,30,46–50] and relatively fewer for the S_NV,[7,11] Ad_N,[8,11] and other BNRs. Therefore, a generalized analysis of the influence of substituents in substrates on activation parameters in S_N2, S_NAr and acyl-transfer reactions in various solvents is of interest. The opportunity for such an analysis follows from separation of the effect of substituents on enthalpic and entropic contributions to the ρ reaction constant in the frameworks of the general Hammett equation.[37–39,46,49,51–55] Separate consideration of enthalpic and entropic contributions to the effects of substituents is useful for obtaining more conclusive information about the structure of the transition state, its connection with the ρ value and the interactions with the environment.[12,37–39,46,47,49,53–59] Besides, the separation of the substituent effects into enthalpic and entropic contributions is associated with the compensation effect and the isokinetic relationship.[10,11,60–64]

The reaction constants, $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$, were determined previously from the dependence of the corresponding activation parameters on the σ substituent constants for some S_N2,[37,38,46,65] S_NAr[55,66] and acyl-transfer reactions[46,47,49] [eqn (1)–(3)]. In these equations the $\Delta H^{\neq}_o$, $\Delta S^{\neq}_o$ and $\Delta G^{\neq}_o$ values are the activation parameters for the unsubstituted compounds.

$$\Delta H^{\neq} = \delta\Delta H^{\neq}\sigma + \Delta H^{\neq}_o \quad (1)$$

$$\Delta S^{\neq} = \delta\Delta S^{\neq}\sigma + \Delta S^{\neq}_o \quad (2)$$

$$\Delta G^{\neq} = \delta\Delta G^{\neq}\sigma + \Delta G^{\neq}_o \quad (3)$$

However, in the papers[49,55,65] the variations of the reaction constants, $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$, were discussed only in the context of the single kind of reaction. A question arises if the variations of the reaction constants, $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$, can be predicted for typical S_N2, S_NAr and acyl-transfer

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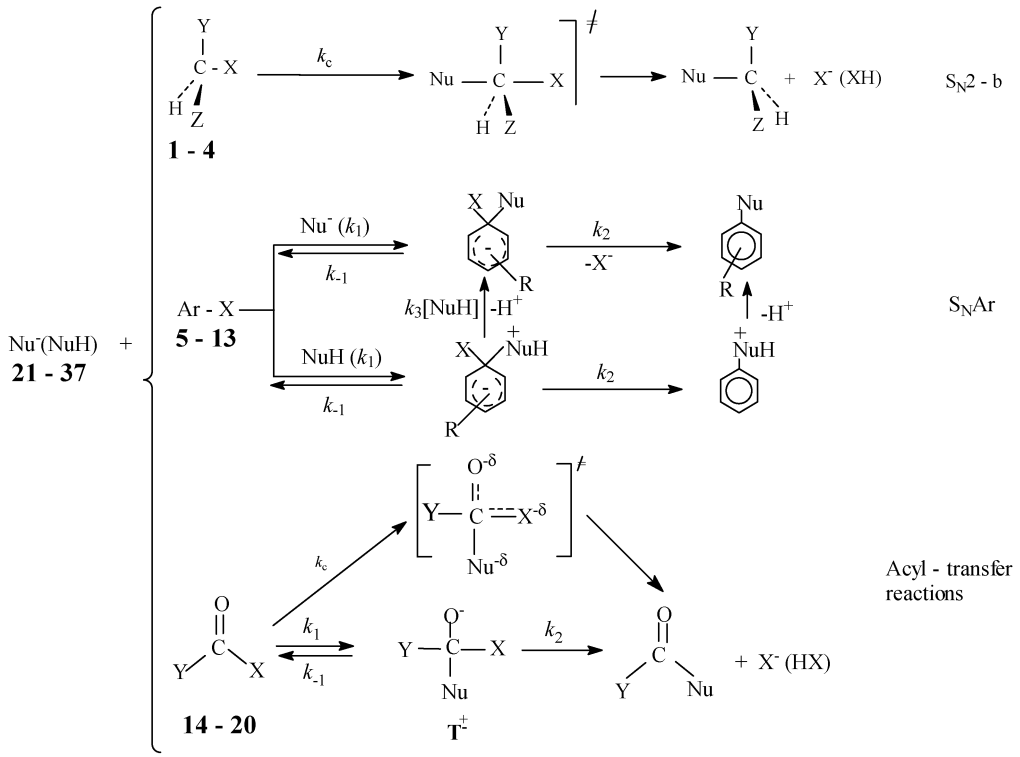
† Electronic supplementary information (ESI) available: Table S1 containing the parameters of eqn (1)–(3) for the reactions of compounds **1–20** with nucleophiles **21–37**.



1 X = Cl, Y = $RC_6H_4NHC(O)$, Z = H
2 X = Br, Y = RC_6H_4, Z = H
3 X = Cl, Y = RC_6H_4, Z = H
4 X = Br, Y = RC_6H_4, Z = Me
5 X = F, Ar = RC_6H_4
6 X = Cl, Ar = RC_6H_4
7 X = Cl, Ar = 2-ClC_6H_3R
8 X = Cl, Ar = 2-$CF_3C_6H_3R$
9 X = F, Ar = RC_6F_4
10 X = F, Ar = 5-$NO_2C_6H_3R$
11 X = Cl, Ar = 2-$NO_2C_6H_3R$
12 X = I, Ar = 2-$NO_2C_6H_3R$
13 X = F, Ar = 2-$NO_2C_6H_3R$
14 X = 4-$NO_2C_6H_4O$, Y = RC_6H_4
15 X = 2,4 –$(NO_2)_2C_6H_3O$, Y = RC_6H_4
16 X = OEt, Y = RC_6H_4
17 X = Cl, Y = RC_6H_4
18 X = NH_2, Y = RC_6H_4
19 X = Imidazolyl, Y = RC_6H_4
20 X = $RC_6H_4C(O)O$, Y = RC_6H_4
21 Nu = $PhNMe_2$
22 NuH = $PhNH_2$
23 Nu = C_5H_5N
24 NuH = $C_5H_{10}NH$
25 NuH = NH_3
26 NuH = Imidazole
27 NuH = H_2O
28 NuH = EtOH
29 Nu = PhSLi
30 Nu = LiBr
31 Nu = MeONa
32 Nu = NaN_3
33 Nu = MeSNa
34 Nu = PhSH· K_2CO_3
35 Nu = 4-Cl C_6H_4OH · K_2CO_3
36 Nu = Na_2HPO_4
37 Nu$^-$ = OH$^-$

1 – 20:

a. R = 4-OMe **b.** R = 4-Me **c.** R = 4-NH_2 **d.** R = 3-Me **e.** R = H **f.** R = 4-F **g.** R = 4-Cl **h.** R = 4-Br **i.** R = 3-F **j.** R = 3-Cl **k.** R = 3-Br **l.** R = 4-COO$^-$ **m.** R = 4- CF_3 **n.** R = 4-COOEt **o.** R = 4-CN **p.** R = 3-NO_2 **q.** R = 4-NO_2 **r.** R = 3-CF_3 **s.** R = 4-$COCH_3$ **t.** R = 4-SO_2CH_3 **u.** R = 3-SO_2CH_3 **v.** R = 3-$COCH_3$ **w.** R = 4- SO_2NH_2 **x.** R = 4-SO_2CF_3 **y.** R = 3,4-Me_2 **z.** R = CHO

Scheme 1 Reactions of compounds **1–20** with ionic and neutral nucleophiles **21–37**.

reactions on the basis of the single equation, the substituent being changed in the substrate (Scheme 1).

This scheme shows the main mechanisms of S_N2,[3,4] S_NAr[5,6] and acyl-transfer reactions.[2] These reactions can proceed both by concerted (S_N2 and acyl-transfer reactions) and stepwise pathways (S_NAr and acyl-transfer reactions). If in stepwise reactions an addition of the nucleophile to the substrate is the rate-determining step (RDS) (rate constant k_1 in Scheme 1), it can be supposed that the effect of the substituents R in the substrates **1–20** on the changes of the reaction constants $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$ can be similar for all BNRs proceeding also by concerted mechanism (*cf.* ref. 67).

The purpose of the present work was to study the substituent effects in the substrate on the variations in the

$\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$ values for the generalized set of typical BNRs with anionic and neutral nucleophiles in protic and aprotic media (Scheme 1).

Methods

From the temperature-dependent rate data[16,23,26–28,42,45–47,68–118] the Eyring plots were generated by plotting $\log(k/T)$ *versus* $1/T$ and the enthalpy and entropy of activation, $\Delta H^{\neq}$, $\Delta S^{\neq}$, were determined for the reactions of alkyl halides **1–4**, aryl halides **5–13**, esters **14–16**, acyl chloride **17**, amides **18**, **19** and anhydride **20** with charged **29–37** and uncharged nucleophiles **21–28** (Scheme 1). The $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$ activation parameters obtained were used by eqn (1)–(3) to establish the $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$ reaction constants (Table 1). All details of the statistical parameters of these equations for the reactions of compounds **1–20** with nucleophiles **21–37** are given in Table S1 of the ESI.† The rate constants and the ρ values were published earlier.[16,23,26–28,42,45–47,68–118]

Results and discussion

Reaction constants $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$

The key results are summarized in Table 1. The $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$ reaction constants calculated by eqn (1)–(3) reflect the sensitivity of activation parameters to substituent nature in the substrate. It is seen that the $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ (or $T\delta\Delta S^{\neq}$) values change over a very wide range. The range of variations of $\delta\Delta G^{\neq}$ is fairly narrow for S_N2 and acyl-transfer reactions (entries 1–11, 27–43 in Table 1) and wide for S_NAr reactions (entries 12–26). The $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ values strongly depend on solvation of reagents and transition states.[46,47,49,55,65,66] The enhanced influence of solvation on the activation parameter change is characteristic of acyl-transfer reactions (entries 27–43 in Table 1).

Enthalpy–entropy compensation

For the S_N2 (entries 1–11 in Table 1) and acyl-transfer reactions (entries 27–43) involving a change of substituent in the substrate the linear dependences between the reaction constants, $\delta\Delta H^{\neq}$ *vs.* $\delta\Delta S^{\neq}$, are supported [eqn (4) and (5)] (lines I and IV, respectively in Fig. 1).

$$\delta\Delta H^{\neq} = (-1.5 \pm 1.4) + (0.38 \pm 0.03)\delta\Delta S^{\neq}; \quad r = 0.973,\ s = 4.3,\ n = 11 \qquad (4)$$

$$\delta\Delta H^{\neq} = (-10.4 \pm 0.08) + (0.31 \pm 0.01)\delta\Delta S^{\neq}; \quad r = 0.995,\ s = 3.1,\ n = 17 \qquad (5)$$

For the S_NAr reactions there are the two linear dependences between the $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ values: relative weak activated arenes (entries 12–18 in Table 1) fit eqn (6) and highly reactive substrates (entries 20–26) give the different equation (7) (lines II and III, respectively in Fig. 1).[55]

$$\delta\Delta H^{\neq} = (-37.7 \pm 0.9) + (0.45 \pm 0.03)\,\delta\Delta S^{\neq}; \quad r = 0.988,\ s = 2.3,\ n = 7 \qquad (6)$$

$$\delta\Delta H^{\neq} = (-21.7 \pm 0.8) + (0.33 \pm 0.06)\,\delta\Delta S^{\neq}; \quad r = 0.931,\ s = 2.1,\ n = 7 \qquad (7)$$

Fig. 1 shows one deviation from eqn (6) depicting reactions of compounds **6r**,**q**,**t**,**w** with ammonia in water (entry 19 in Table 1, Fig. 1). These reactions are characterized by very low rate constants,[45,89] so that the corresponding $|\delta\Delta H^{\neq}|$ value is negative and large. It should be noted that the arrangement of lines I–IV in Fig. 1 reflects the difference of the effects of substituents in the substrate on the rate constants of BNRs. At the same time for all BNRs for which a substituent is varied in the nucleophile the $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ values give a single linear dependence upon each other. The latter means that the effects of substituents in the nucleophile on the rate constants of BNRs are similar.[120,121]

The slopes of correlations (4)–(7) multiplied by 10^3 correspond to compensation temperatures (*cf.* ref. 51 and 52) equaling 380, 310, 450 and 330 K, respectively. The compensation temperature is the temperature in which the $\Delta H^{\neq}$ value is determined by the solvation effects only. A higher sensitivity of $\Delta H^{\neq}$ *vs.* $\Delta S^{\neq}$ in S_NAr reactions with weakly activated arenes [eqn (6) *vs.* eqn (4), (5) and (7)] can indicate an enhanced solvation effect on the activation entropy change in these reactions.

Recent analysis of the activation parameters $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$ for typical BNRs has revealed a number of $\Delta H^{\neq}$ *vs.* $\Delta S^{\neq}$ compensation equations which depend on the reaction rate constants.[11] The chemical nature of the observed compensation relations was confirmed by the fact that the observed compensation temperatures appreciably differed from the experimental temperatures. In addition, linear relationships between $\Delta H^{\neq}$ and $\Delta G^{\neq}$ were found for the BNRs.[122] The comparison of compensation temperatures from eqn (4)–(7) with experimental ones shows a significant difference between them. The plot of $\delta\Delta H^{\neq}$ *vs.* $\delta\Delta G^{\neq}$ (Fig. 2) shows that all BNRs can be divided into several reaction groups, in which greater negative values of $\delta\Delta G^{\neq}$ belong particularly to S_NAr reactions (*cf.* ref. 63). These data might be expected as an additional support to the chemical nature of the compensation relationships (4)–(7).[60–64,122–125]

According to the recently developed theory on the enthalpy–entropy compensation,[126] eqn (4)–(7) in which the intercepts are not zero may be regarded as related to a general enthalpy–entropy compensation. In these cases, the intercepts in eqn (4)–(7) divided by the compensation temperatures (380, 310, 450 and 330 K, respectively) correspond to the genuine entropy reaction constants $\delta\Delta S^{\neq}_{\text{hidden}}$ (−3.9, −33.5, −83.8 and −65.6 J mol^{-1} K$^{-1}\sigma^{-1}$) for the hidden processes of the microphase transitions from the initial compounds to the corresponding transition states.[126] At the same time, the enthalpic effects of the hidden processes will be equal to $\delta\Delta H^{\neq}_{\text{hidden}}$ = −3.0, −20.8, −75.4 and −43.4 kJ mol^{-1} σ^{-1} for the compensation relationships (4)–(7), respectively. Along this line, the increase of the $\delta\Delta S^{\neq}$ values for the reactions of entries 4–7, 9–11, 13–26 and 29–43 in Table 1 relative to the corresponding $\delta\Delta S^{\neq}_{\text{hidden}}$ values indicates more ordered structure of hydrated initial compounds compared to the corresponding transition states due to the formation of solvation shells around hydrophilic and hydrophobic groups in solvents. However, the decrease in the $\delta\Delta S^{\neq}$ values for the reactions of entries 1–3, 8, 12, 27, 28 in Table 1 in comparison with the corresponding $\delta\Delta S^{\neq}_{\text{hidden}}$ values suggests a transition to a more

Table 1 Substituent effects in substrates **1–20** on activation parameters in their reactions with nucleophiles **21–37**

Entry	Reactants	Solvent	N^a	T^b/K	$\delta\Delta H^{\neq c,d}$/ kJ mol^{-1} $\sigma^{-1}(r)$	$\delta\Delta S^{\neq c,d}$/ J mol^{-1} K^{-1} $\sigma^{-1}(r)$	$T\,\delta\Delta S^{\neq}$/ kJ mol^{-1} σ^{-1}	$\delta\Delta G^{\neq c,d}$/ kJ mol^{-1} σ^{-1} (r)	$\delta\Delta H^{\neq e}_{ext}$/ kJ mol^{-1} σ^{-1}	$\delta\Delta H^{\neq f}_{int}$/ kJ mol^{-1} σ^{-1}	ρ^c	Ref.
	S_N2 reactions											
1	$RC_6H_4NHC(O)–CH_2Cl$ **1a,b,d,e,h,p,q,s,y** + $PhNMe_2$ **21**	*n*-Octanol	9	440	−34.9 (0.984)	−69.0 (0.988)	−30.4	−4.5	−26.9	−8.0	1.71[g]	68
2	$RC_6H_4CH_2Br$ **2b,e,g,j,q** + $PhNH_2$ **22**	MeCN	5	308	−2.0	−17.3[h] (0.999)	−5.3	3.3 (0.987)	−6.7	4.7	−0.55	23
3	$RC_6H_4CH_2Cl$ **3b,e,g,j,q** + $PhNH_2$ **22**	MeCN	5	318	0.0	−9.6 (0.993)	−3.1	3.1 (0.994)	−3.7	3.7	−0.51	23
4	$RC_6H_4CH_2Br$ **2b,e,q** + C_5H_5N **23**	MeOH	3	298	17.5 (0.999)	50.2 (0.999)	15.0	2.5 (0.999)	19.6	−2.1	−0.66	26
5	$RC_6H_4CH_2Br$ **2b,e,q** + C_5H_5N **23**	DMF	3	298	9.5 (0.996)	25.8 (0.986)	7.7	1.8 (0.965)	10.1	−0.6	−0.31	26
6	$RC_6H_4CH_2Cl$ **3b,e,q** + C_5H_5N **23**	MeOH	3	298	31.2 (0.994)	89.3 (0.997)	26.6	4.6	34.8	−3.6	−0.78	26
7	$RC_6H_4CH_2Cl$ **3b,e,q** + C_5H_5N **23**	DMF	3	298	19.4 (0.998)	56.8 (0.986)	16.9	2.5	22.1	−2.7	−0.49	26
8	$RC_6H_4CH_2Cl$ **3a,b,e,g,q** + PhS^-Li^+ **29**	MeOH	5	293	−11.6	−22.2[i] (0.916)	−6.5	−5.1[i] (0.944)	−8.6	−3.0	1.15[i]	16
9	$RC_6H_4CH(Me)Br$ **4b,e,h,q,y** + LiBr **30**	Acetone	5	303	14.1 (0.892)	55.6 (0.953)	16.8	−2.7	21.1	−7.0	1.13[j]	27
10	$RC_6H_4CH_2Br$ **2a,b,d,e,g,n,q** + C_5H_5N **23**	MeCN	7	290	12.6[k] (0.976)	36.8	10.7	1.9[i] (0.962)	14.0	−1.4	−0.32[i]	28
11	$RC_6H_4CH_2Br$ **2a,b,d,e,g,n,q** + C_5H_5N **23**	IL[l]	7	290	7.3[m] (0.998)	13.1	3.8	3.5[n] (0.954)	5.0	2.3	−0.56[i]	28
	S_NAr reactions											
12	RC_6H_4F **5e,p,q** + MeONa **31**	MeOH	3	373	−54.5 (0.999)	−34.3	−12.8	−41.7 (0.998)	−15.4	−39.1	7.0[g]	42, 45, 69–75
13	RC_6H_4Cl **6g,j,m,q,r,t** + MeONa **31**	MeOH	6	373	−44.6 (0.999)	−12.4 (0.999)	−4.7	−39.9 (0.999)	−5.6	−39.0	6.6[g]	45, 76–78
14	1,2-$Cl_2C_6H_3R$ **7e,j,q** + MeONa **31**	MeOH	3	373	−39.8 (0.999)	−7.3 (0.999)	−2.7	−37.1 (0.999)	−3.3	−36.5	*6.2*[g]	45, 79, 80
15	1-Cl-2-$CF_3C_6H_3R$ **8e,m,r,q** + MeONa **31**	MeOH	4	393	−27.9 (0.999)	15.1 (0.999)	5.9	−33.8 (0.999)	6.8	−34.7	*5.3*[g]	45, 81, 82
16	RC_6F_5 **9e,f,g,m,q,r** + MeONa **31**	MeOH	6	323	−27.5 (0.999)	18.3 (0.999)	5.9	−33.4 (0.999)	8.2	−35.7	5.4	45, 83–85
17	RC_6F_5 **9e,f,g,s** + $C_5H_{10}NH$ **24**	Dioxane	4	323	−13.4 (0.981)	54.2	17.5	−30.9 (0.982)	24.4	−37.8	5.6[o]	45, 86, 87
18	1-F-3-R-5-$NO_2C_6H_3$ **10e,i,j,k,p,r,u,v** + MeONa **31**	MeOH	8	373	−24.2 (0.999)	36.7 (0.999)	13.7	−37.9 (0.999)	16.5	−40.7	5.8[g]	45, 72, 88
19	RC_6H_4Cl **6r,q,t,w** + NH_3 **25**	H_2O	4	473	−43.4 (0.999)	31.0 (0.999)	14.7	−58.1 (0.999)	6.8[p]	−58.0[q]	8.6[g]	45, 89
20	1-Cl-2-$NO_2C_6H_3R$ **11e,r,q,t,x** + NH_3 **25**	MeOH	5	423	−30.6 (0.999)	−22.6 (0.999)	−9.6	−21.0 (0.999)	−7.5	−23.1	3.8[g]	45, 90, 91
21	1-Cl-2-$NO_2C_6H_3R$ **11e,g,h,j,k,m,n,o,q** + $C_5H_{10}NH$ **24**	C_6H_6	9	373	−23.6 (0.999)	−3.8 (0.999)	−1.4	−22.2 (0.999)	−1.2	−22.4	3.6[g]	45, 92
22	1-I-2-$NO_2C_6H_3R$ **12e,o,q,z** + NaN_3 **32**	MeOH	4	323	−20.2 (0.999)	−5.2 (0.999)	−1.7	−18.5 (0.999)	−1.7	−18.5	3.0	45, 75, 93
23	1-Cl-2-$NO_2C_6H_3R$ **11e,q,r,u,x** + $C_5H_{10}NH$ **24**	MeOH	5	373	−20.9 (0.999)	5.3 (0.999)	2.0	−22.9 (0.999)	1.7	−22.6	3.6[g]	45, 94–97
24	1-F-2-$NO_2C_6H_3R$ **13e,l,q** + MeONa **31**	MeOH	3	323	−19.1 (0.999)	13.7 (0.999)	4.4	−23.5 (0.999)	4.5	−23.6	3.8	45, 72, 75, 98
25	1-Cl-2-$NO_2C_6H_3R$ **11e,n,q** + MeSNa **33**	MeOH	3	323	−15.7 (0.999)	12.8 (0.999)	4.1	−19.8 (0.999)	4.2	−19.9	3.2	45, 79
26	1-Cl-2-$NO_2C_6H_3R$ **11e,f,g,h,m,o,q,s,t,x,z** + MeONa **31**	MeOH	11	323	−16.0 (0.999)	19.2 (0.999)	6.2	−22.2 (0.999)	6.3	−22.3	3.6	45, 72, 76–78, 90, 91, 100–104
	Acyl-transfer reactions											
27	$RC_6H_4C(O)OC_6H_4NO_2$-4 **14a,b,e h,k,m** + $PhSH{\cdot}K_2CO_3$ **34**	DMF	6	299	−108.5 (0.992)	−332.0 (0.987)	−99.3	−9.2	−101.6	−6.9	1.10	105
28	$RC_6H_4C(O)OC_6H_4NO_2$-4 **14a,b,e,h,j, p,q** + 4-ClC_6H_4 $OH{\cdot}K_2CO_3$ **35**	DMF	7	313	−76.4 (0.990)	−192.0 (0.983)	−60.0	−16.4	−58.8	−17.6	3.43	106
29	$RC_6H_4C(O)OC_6H_4NO_2$-4 **14b,e,g,o,q** + Imidazole **26**	10 vol% MeCN–H_2O	5	308	−5.6 (0.972)	3.9	1.2	−6.8 (0.996)	1.2	−6.8	1.10	107
30	$RC_6H_4C(O)OC_6H_3$ $(NO_2)_2$-2,4 **15b,e,g,o,q** + Na_2HPO_4 **36**	10 vol% MeCN–H_2O	5	313	−10.2 (0.986)	10.2	3.2	−13.4 (0.998)	3.1	−13.3	2.20	108
31	$RC_6H_4C(O)OC_6H_3$ $(NO_2)_2$-2,4 **15b,e,g,o,q** + Imidazole **26**	10 vol% MeCN–H_2O	5	298	−2.9	23.7 (0.956)	7.1	−10.0 (0.999)	7.3	−10.2	1.74	107

Table 1 (*continued*)

Entry	Reactants	Solvent	N^a	T^b/K	$\delta\Delta H^{\neq c,d}$/ kJ mol^{-1} $\sigma^{-1}(r)$	$\delta\Delta S^{\neq c,d}$/ J mol^{-1} K^{-1} $\sigma^{-1}(r)$	$T\,\delta\Delta S^{\neq}$/ kJ mol^{-1} σ^{-1}	$\delta\Delta G^{\neq c,d}$/ kJ mol^{-1} σ^{-1} (r)	$\delta\Delta H_{ext}^{\neq e}$/ kJ mol^{-1} σ^{-1}	$\delta\Delta H_{int}^{\neq f}$/ kJ mol^{-1} σ^{-1}	ρ^c	Ref.
32	$RC_6H_4C(O)OEt$ **16b,c,d,e,p,q** + OH^- **37**	60 vol% Me_2CO–H_2O	7[r]	298	−11.9 (0.997)	5.4	1.6	−13.5 (0.998)	1.7	−13.6	2.38	109
33	$RC_6H_4C(O)OEt$ **16a,b,c,e,g,h,q** + OH^- **37**	85 wt% EtOH–H_2O	7	308	−15.9 (0.998)	−4.5	−1.4	−14.5 (0.999)	−1.4	−14.5	2.55	110
34	$RC_6H_4C(O)OEt$ **16a,b,c,e,h,q** + OH^- **37**	71.2 wt% MeOH–H_2O	6	298	−6.2 (0.975)	21.2	6.3	−12.5 (0.998)	6.5	−12.7	2.19	46
35	$RC_6H_4C(O)Cl$ **17b,e,h,q** + H_2O **27**	95 vol% Me_2CO–H_2O	4	298	−25.8 (0.983)	−48.0 (0.959)	−14.3	−11.5	−14.7	−11.1	1.77	111
36	$RC_6H_4C(O)Cl$ **17b,e,f,g,h,q** + EtOH **28**	60 vol% Et_2O–EtOH	6	285	−20.2 (0.986)	−37.2	−10.6	−9.6 (0.996)	−11.4	−8.8	1.52	112
37	$RC_6H_4C(O)Cl$ **17b,e,f,g,h,q** + EtOH **28**	EtOH	6	298	−15.4 (0.989)	−22.0	−6.6	−8.8 (0.988)	−6.7	−8.7	1.54	46
38	$RC_6H_4C(O)Cl$ **17b,e,g,q** + $PhNH_2$ **22**	C_6H_6	4	298	−8.2 (0.998)	3.0	0.9	−9.1 (0.954)	0.9	−9.1	1.22	113
39	$RC_6H_4C(O)NH_2$ **18b,e,g,o** + OH^- **37**	60 vol% Et_2O–EtOH	4	347	−12.9 (0.991)	−14.1	−4.9	−8.0 (0.997)	−4.3	−8.6	1.14	114
40	$RC_6H_4C(O)Z^s$ **19b,e,g,q** + OH^- **37**	10 vol% MeCN–H_2O	4	298	27.4	119.9 (0.966)	35.7	−8.3 (0.999)	36.7	−9.3	1.47	47, 115, 116
41	$RC_6H_4C(O)Z^s$ **19b,e,g,q** + H_2O **27**	10 vol% MeCN–H_2O	4	298	9.4	58.9 (0.973)	17.5	−8.1 (0.999)	18.0	−8.6	1.41	47, 115, 116
42	$RC_6H_4C(O)Z^s$ **19b,e,g,o,q** + H_2O **27**	10 vol% MeCN–H_2O^t	5	313	−10.8 (0.999)	−10.9	−3.4	−7.4 (0.997)	−3.3	−7.5	1.25	47, 117
43	$[RC_6H_4C(O)]_2O$ **20a,b,e,g,p,q,o** + H_2O **27**	75 vol% dioxane–H_2O	7[r]	331	−16.6[u] (0.980)	−19.8[u]	−6.6[u]	−10.0[u] (0.999)	−6.1[u]	−10.5[u]	1.59[u]	118

[a] Number of compounds. [b] Temperature of experiments. [c] σ constants[13] were used in the correlation equations $\Delta H^{\neq} = \delta\Delta H^{\neq}\sigma + \Delta H_0^{\neq}$, $\Delta S^{\neq} = \delta\Delta S^{\neq}\sigma + \Delta S_0^{\neq}$ and $\Delta G^{\neq} = \delta\Delta G^{\neq}\sigma + \Delta G_0^{\neq}$, $\log k = \rho\sigma + \log k_0$ for reactions of entries 1–11 and 27–43; σ^- constants[13] were used in these equations for reactions of entries 12–26; standard errors of the $\delta\Delta H^{\neq}$, $\delta\Delta S^{\neq}$ and $\delta\Delta G^{\neq}$ reaction constants are estimated to be less than 8%, 11% and 5%, respectively. [d] Values given without correlation coefficient are calculated by the equation $\delta\Delta G^{\neq} = \delta\Delta H^{\neq} - T\delta\Delta S^{\neq}$. [e] Values are calculated by the equation $\delta\Delta H_{ext}^{\neq} = T_{comp}\delta\Delta S^{\neq}$, where T_{comp} = 380 K (entries 1–11), 450 K (entries 12–18), 330 K (entries 20–26) and 310 K (entries 27–43). [f] $\delta\Delta H_{int}^{\neq} = \delta\Delta H^{\neq} - \delta\Delta H_{ext}^{\neq}$. [g] Value ρ is calculated at 323 K. [h] Value is calculated for compounds **2e,g,q**. [i] Value is calculated by the Yukawa–Tsuno equation.[119] [j] Value ρ is calculated by eqn (13). [k] Value is calculated for compounds **2a,b,d,e,g,n**. [l] IL is the ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide. [m] Value is calculated for compounds **2a,b,e,g,n**. [n] Value is calculated for compounds **2b,d,e,g,n,q**. [o] Value is calculated for compounds **9e,f,g,m**. [p] $\delta\Delta H_{ext}^{\neq} = \delta\Delta H^{\neq} - \delta\Delta H_{int}^{\neq}$. [q] Value $\delta\Delta H_{int}^{\neq}$ is calculated by eqn (12). [r] The substituent R = 3-NH_2 is added.[13] [s] Z is Imidazolyl. [t] Imidazole was used as a buffer.[47,117] [u] Value is halved due to the two carbonyl groups are available for attack in compound **20**.[118]

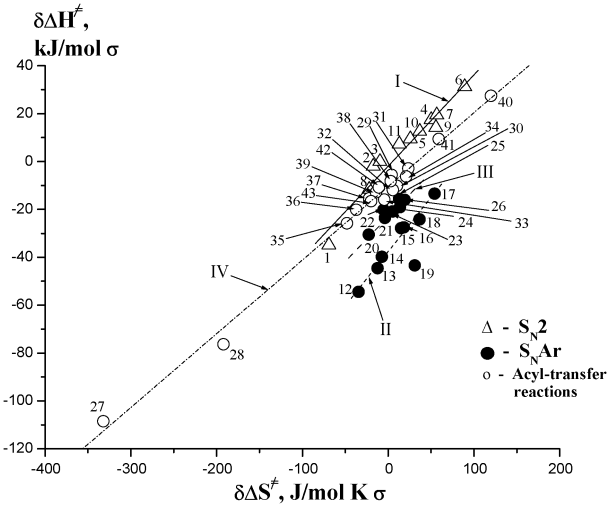


Fig. 1 Plot of $\delta\Delta H^{\neq}$ *vs.* $\delta S^{\neq}$ for the S_N2, S_NAr and acyl-transfer reactions of compounds **1–20** with anionic and neutral nucleophiles **21–37** in various solvents; the identity of the numbers is the entry number in Table 1.

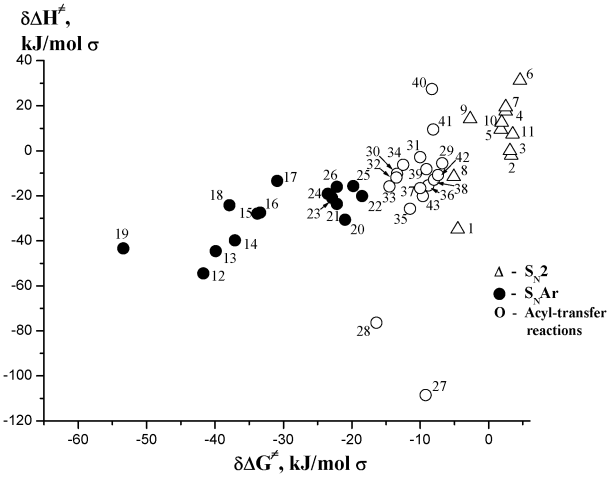


Fig. 2 Plot of $\delta\Delta H^{\neq}$ *vs.* $\delta\Delta G^{\neq}$ for the S_N2, S_NAr and acyl-transfer reactions of compounds **1–20** with anionic and neutral nucleophiles **21–37** in various solvents; the identity of the numbers is the entry number in Table 1.

ordered structure of the corresponding transition states. This transition is owed to the formation of solvation shells around hydrophobic groups in various media. One of the main differences between the reactions of entries 4–7, 9–11, 13–26, 29–43 and 1–3, 8, 12, 27, 28 (Table 1) lies in the total charges on the initial compounds and corresponding transition states. These charges could favour the onset of microphase transitions between different hidden structures of solvents.[126]

Separation of enthalpy and entropy contributions to the substituent effects

In keeping with the Hepler solvation theory,[51,52] values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are divided into internal (ΔH_{int}, ΔS_{int}) and external (ΔH_{ext}, ΔS_{ext}) terms, referring to the chemical reactions and the solvation processes, respectively.[51,52] Likewise, the $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ reaction constants of this paper can also be divided into internal and external parts [eqn (8) and (9)].[37–39,46,49,53–55,65,66]

$$\delta\Delta H^{\neq} = \delta\Delta H^{\neq}_{int} + \delta\Delta H^{\neq}_{ext} \quad (8)$$

$$\delta\Delta S^{\neq} = \delta\Delta S^{\neq}_{int} + \delta\Delta S^{\neq}_{ext} \quad (9)$$

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 (external term $\delta\Delta S^{\neq}_{ext}$). Therefore, it may be presumed that the internal part of the activation entropy, $\delta\Delta S^{\neq}_{int}$, in eqn (9) is independent of the substituent provided that steric effects are absent, *i.e.* $\delta\Delta S^{\neq}_{int} \approx 0$ and $\delta\Delta S^{\neq} \approx \delta\Delta S^{\neq}_{ext}$.[51,52,60,64] In this case, the magnitude of $\delta\Delta H^{\neq}_{ext}$ can be calculated by eqn (10).[51,52,60,64]

$$\delta\Delta H^{\neq}_{ext} = T_{comp}\delta\Delta S^{\neq} \quad (10)$$

In this equation, the T_{comp} value corresponds to the compensation temperature[60,64] amounting to 380, 310, 450 and 330 K for the reactions described by eqn (4)–(7), respectively. It should be noted that the intercept in eqn (4)–(7) is the $\delta\Delta H^{\neq}_{int}$ value for the given reaction series which varies only very slightly with the remote substituents on the aromatic ring. The values of $\delta\Delta H^{\neq}_{ext}$ and $\delta\Delta H^{\neq}_{int}$ calculated from eqn (10) and (8) are given in Table 1. Values of $\delta\Delta H^{\neq}_{int}$ are always negative for all reactions excluding the S_N2 reactions of entries 2, 3 and 11 in Table 1. In these cases, values of $\delta\Delta H^{\neq}_{int}$ are positive and rather small.

The sign of $\delta\Delta H^{\neq}_{ext}$ depends on the difference in solvation of initial reagents and corresponding transition states, as well as on $\delta\Delta S^{\neq}_{ext}$ or $\delta\Delta S^{\neq}$: positive $\delta\Delta H^{\neq}_{ext}$ values (entries 4–7, 9–11,15–19, 23–26, 29–32, 34, 38, 40, 41 in Table 1) correspond to stronger solvation of initial reagents in going to electron-withdrawing substituents R. Negative values of $\delta\Delta H^{\neq}_{ext}$ reflect enhanced solvation of the corresponding transition states and a reduction in the magnitudes of $\delta\Delta H^{\neq}_{ext}$ upon introduction of electron-withdrawing substituents R (entries 1–3, 8, 12–14, 20–22, 27, 28, 35–37, 39, 42, 43 in Table 1) (*cf.* ref. 46, 47, 49, 55 and 65).

Relationships between the reaction constants, $\delta\Delta H^{\neq}_{int}$, $\delta\Delta G^{\neq}$ and ρ

As follows from the data in Fig. 2, the reaction constant $\delta\Delta G^{\neq}$ according to the equation $\delta\Delta G^{\neq} = -2.303RT\rho$ reflects a substituent effect in the substrate: the larger negative values of $\delta\Delta G^{\neq}$ are obtained for the reactions at the larger positive magnitudes of ρ (entries 12–19 in Table 1; Fig. 2). Whereas the $\delta\Delta G^{\neq}$ values are always negative for S_NAr and acyl-transfer reactions, the changes in these magnitudes for S_N2 reactions can be both positive and negative (Table 1; Fig. 2). A correlation (11) between $\delta\Delta G^{\neq}$ and ρ for the reactions of entries 1–43 (Table 1) has been developed. The intercept in eqn (11) is connected with a small change of the ρ constant with variation of a solvation and close to zero.

$$\delta\Delta G^{\neq} = (0.1 \pm 0.4) - (6.0 \pm 0.1)\rho; \quad r = 0.991,\ s = 1.7,\ n = 43 \quad (11)$$

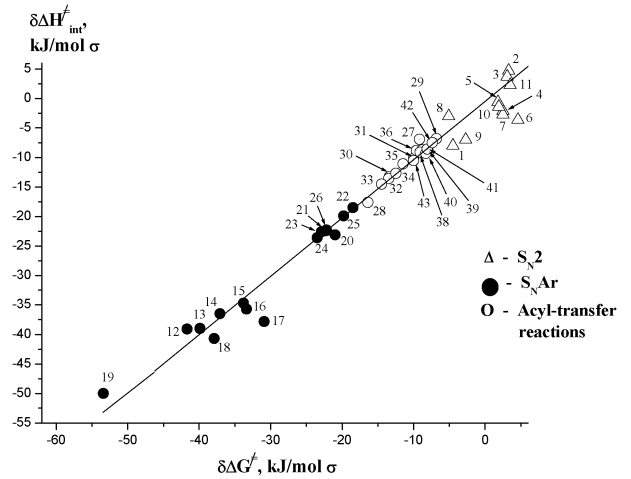


Fig. 3 Plots of $\delta\Delta H^{\neq}_{int}$ *vs.* $\delta\Delta G^{\neq}$ for the S_N2, S_NAr and acyl-transfer reactions of compounds **1–20** with anionic and neutral nucleophiles **21–37** in various solvents; the identity of the numbers is the entry number in Table 1.

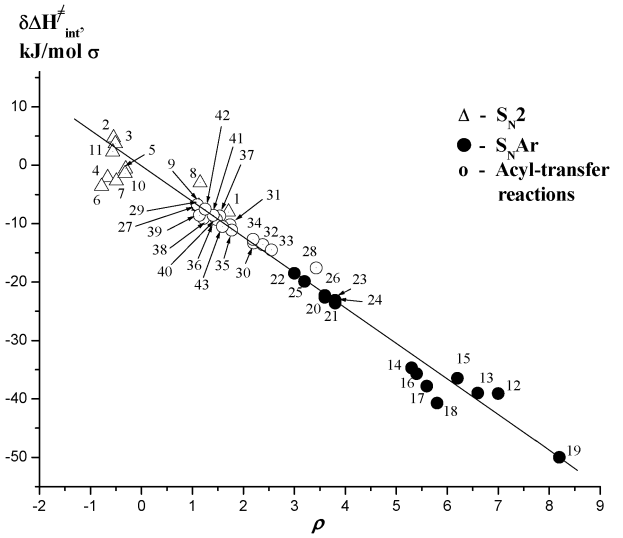


Fig. 4 Plots of $\delta\Delta H^{\neq}_{int}$ *vs.* ρ for the S_N2, S_NAr and acyl-transfer reactions of compounds **1–20** with anionic and neutral nucleophiles **21–37** in various solvents; the identity of the numbers is the entry number in Table 1.

An analysis of the $\delta\Delta H^{\neq}_{int}$ and $\delta\Delta G^{\neq}$ values from Table 1 shows that these values are close for the majority of reaction series. A linear relationship (12) between $\delta\Delta H^{\neq}_{int}$ and $\delta\Delta G^{\neq}$ for the reactions of entries 1–3, 5, 8, 10–16, 18 and 20–43 has been developed (Fig. 3).

$$\delta\Delta H^{\neq}_{int} = (-0.5 \pm 0.4) + (0.99 \pm 0.02)\delta\Delta G^{\neq}; \quad r = 0.994,\ s = 1.4,\ n = 37 \qquad (12)$$

The intercept in eqn (12) is the $\delta\Delta G^{\neq}_{ext}$ value and close to zero: $\delta\Delta G^{\neq}_{ext} = \delta\Delta H^{\neq}_{ext} - T\delta\Delta S^{\neq}_{ext} \approx 0$.[37–39,46,53,54,64] The latter means that the dependence of the free energy of activation is governed mainly by the changes in the internal enthalpy of activation of the chemical reaction: $\delta\Delta G^{\neq} \approx \delta\Delta H^{\neq}_{int}$.[12,37–39,46,53,54,64] It is obvious that realisation of dependence (12) becomes possible, as the substituent effects on the changes of the $\delta\Delta H^{\neq}_{int}$ values are similar for the BNRs for which the k_c (entries 1–3, 5, 8, 10,11, 35–38) or k_1 (entries 12–16, 18, 20–34, 39–43) step is presumed to be rate-determined (Scheme 1).

However, some concerted S_N2 (entries 4, 6, 7, 9 in Table 1) and S_NAr reactions (entry 17) noticeably deviate from the dependence (12). A probable reason is an appreciable increase of the $\delta\Delta G^{\neq}$ constants for these reactions. The latter is connected with a larger increase of the $\delta\Delta S^{\neq}$ values at formation of a transition state in comparison with the other S_N2 and S_NAr reactions. The stronger solvation of the initial reagents results in the large positive $\delta\Delta S^{\neq}$ values at the introduction of electron-withdrawing substituents R (Table 1) (*cf.* ref. 55 and 65). Earlier, proposal steps of mechanism for S_N2 reactions of entries 4, 6, 7 and 9 were discussed in some detail.[65]

It should be noted that eqn (12) and (8) make it possible to estimate the $\delta\Delta H^{\neq}_{int}$ and $\delta\Delta H^{\neq}_{ext}$ values for S_NAr reactions of entry 19 for which the nucleophile attack is the rate-determining step (Table 1).[45,89]

Considering eqn (11) and (12), a correlation (13) between $\delta\Delta H^{\neq}_{int}$ and ρ for the reactions of entries 1–3, 5, 8, 10–18 and 20–43 (for which the k_c or k_1 step is presumed to be rate-determining) has been developed as shown in Table 1 and Fig. 4.

$$\delta\Delta H^{\neq}_{int} = (-0.1 \pm 0.5) - (6.1 \pm 0.2)\rho; \quad r = 0.989,\ s = 1.9,\ n = 38 \qquad (13)$$

The intercept in eqn (13) is close to zero and the slope reflects a sensitivity of $\delta\Delta H^{\neq}_{int}$ to a change of ρ equaling approximately $2.303RT$ at T = 313–323 K. Therefore, for reactions of entries 1, 12–15, 18–21 and 23 carried out at higher temperatures the values of $\rho(k_1)$ have been calculated at 323 K (Table 1).

Realisation of dependence (13) becomes possible, as magnitudes of $\rho(k_c)$ or $\rho(k_1)$ for these reactions characterise charge development at the transition state of the concerted and stepwise processes (Scheme 1).[10,12,47,56–59] Therefore, for S_N2 reactions of entry 9 the value of $\rho(k_c)$ has been calculated by eqn (13) using the $\delta\Delta H^{\neq}_{int}$ value (Table 1; Fig. 4).

It is obvious from eqn (13) that the $\delta\Delta H^{\neq}_{int}$ reaction constant, as well as the reaction constant ρ from the Hammett equation,[10,12,47,56–59] characterizes the degree of developing negative charge in the transition states (rate constants k_c or k_1 in Scheme 1). The large positive values of $\delta\Delta H^{\neq}_{int}$ indicate essential charge development in the transition state of S_NAr reactions of entries 12–19 (Table 1; Fig. 4).

The deviations of the ρ values from eqn (13) for the dissociative S_N2 reactions of entries 4, 6 and 7 ($\rho < 0$[23–25]) (Fig. 4) are, possibly, connected with a change in the geometry of the trigonal-bipyramidal transition states.[39,65] Though the correlation dependence (13) describes normal S_N2 reactions in a solution proceeding on concerted and backside attack S_N2-b mechanism (Scheme 1), the deviations from it give a possibility of offering alternative ways for these reactions.

Recently, a correlation (14) between $\delta\Delta H^{\neq}_{int}$ and ρ for the BNR involving a change of substituent in the nucleophile has been developed.[120]

$$\delta\Delta H^{\neq}_{int} = (-0.7 \pm 0.8) - (6.1 \pm 0.3)\rho; \quad r = 0.971,\ s = 1.6,\ n = 24 \qquad (14)$$

The comparison of eqn (13) and (14) shows that both equations coincide practically. It is obvious from these relationships that the electronic effects of substituents in the substrate and nucleophile which are kinetic and thermodynamic in nature, respectively, are described by the single Hammett-like equation for all BNR.

Conclusions

Determining the compensation dependence between the $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ values in the S_N2, S_NAr and acyl-transfer reactions for variations of substituents at the substrates gives a straightforward way for estimating T_{comp} and obtaining $\delta\Delta H^{\neq}_{int}$.

The $\delta\Delta H^{\neq}_{int}$ values give a single linear dependence with the values of ρ from the Hammett equation for all BNRs proceeding both by a concerted mechanism and a stepwise mechanism through an intermediate with its formation being the rate-determining step.

The single linear dependence of $\delta\Delta H^{\neq}_{int}$ *vs.* ρ for all BNRs involving a change of substituent in the substrate and nucleophile gives an opportunity to describe a very wide range of the Hammett ρ values using the $\delta\Delta H^{\neq}_{int}$ reaction constants.

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