

Effects of substituents on activation parameters in the reactions of carboxylic acid derivatives with anionic and neutral nucleophiles

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Changes of activation parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, with σ constants of substituents in the reactions of carboxylic acid derivatives with anionic and neutral nucleophiles in various solvents give the $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ reaction constants which are linearly related for variations of substituents in substrate and nucleophile. The dependences obtained, $\delta\Delta H^\ddagger$ vs. $\delta\Delta S^\ddagger$, allow estimation of the contribution of changes of the internal enthalpy, $\delta\Delta H^\ddagger_{\text{int}}$, to the enthalpy reaction constant, $\delta\Delta H^\ddagger$, which give a single linear dependence on the Hammett ρ reaction constants. The results obtained show that the substituent effects on the charge development in the transition state are governed by the magnitude of $\delta\Delta H^\ddagger_{\text{int}}$.

Introduction

As is well-known, there is considerable interest in finding correlations among chemical reactivity derived from experiments and computations with Hammett constants (σ). The Hammett plot and similar linear free energy relationships have been a key part and a preferred language in the interpretation of chemical facts in the experimental literature.¹ Studies on substituent effects in bimolecular nucleophilic reactions such as acyl-transfer reactions, S_N2 , S_NAr and others have been the subject of intense interest in recent years.²

Despite the great importance of acyl group transfer reactions in organic chemistry and biochemistry and a large number of studies in this field,^{2a-c} there are some aspects of these reactions which are not yet clear. They include the interpretation of the effects of polar substituents in the attacking nucleophile and leaving or nonleaving groups of acyl derivatives on reaction rate constants and activation parameters.³ It should also be emphasized that the nucleophilic reactions of carbonyl compounds provide a good example of the role of solvation effects.⁴ Therefore, an analysis of the influence of substituents on activation parameters in nucleophilic reactions of carboxylic acid derivatives 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.^{5,6} 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 solvent.^{6a,7,8}

Earlier the reaction constants, $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$ and $\delta\Delta G^\ddagger$, were determined from the dependence of the corresponding activation parameters on the σ substituent constants for the reactions of

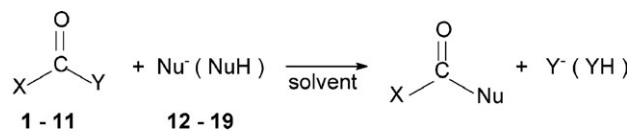
alkaline hydrolysis of esters, amides and anhydrides, by solvolysis of acyl chlorides^{6b} and *N*-acylimidazoles⁷ [eqns (1)–(3)].

$$\Delta H^\ddagger = \delta\Delta H^\ddagger\sigma + \Delta H^\ddagger_0 \quad (1)$$

$$\Delta S^\ddagger = \delta\Delta S^\ddagger\sigma + \Delta S^\ddagger_0 \quad (2)$$

$$\Delta G^\ddagger = \delta\Delta G^\ddagger\sigma + \Delta G^\ddagger_0 \quad (3)$$

However, in those papers^{6b,7} the changes of the reaction constants, $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$ and $\delta\Delta G^\ddagger$, were discussed only in the context of the individual reactions. The purpose of the present paper is a general analysis of changes in the $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$ and $\delta\Delta G^\ddagger$ values for typical acyl-transfer reactions with anionic and neutral nucleophiles in protic and aprotic solvents, the substituent being changed both in the substrate and nucleophile (Scheme 1). The results obtained provide a new insight into how the electronic effect of substituents influences changes in the internal activation enthalpy, $\delta\Delta H^\ddagger_{\text{int}}$, in



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|--|--|
| 1 - 11 | 12 - 19 |
| 1 X = RC ₆ H ₄ , Y = 4-NO ₂ C ₆ H ₄ O | 11 X = RC ₆ H ₄ , Y = RC ₆ H ₄ C(O)O |
| 2 X = RC ₆ H ₄ , Y = 2,4-(NO ₂) ₂ C ₆ H ₃ O | 12 Nu = PhSH·K ₂ CO ₃ |
| 3 X = RC ₆ H ₄ , Y = OEt | 13 Nu = RC ₆ H ₄ OH·K ₂ CO ₃ |
| 4 X = Ph, Y = RC ₆ H ₄ O | 14 Nu = OH ⁻ |
| 5 X = 4-NO ₂ C ₆ H ₄ , Y = RC ₆ H ₄ O | 15 Nu = HPO ₄ ²⁻ |
| 6 X = Me, Y = RC ₆ H ₄ O | 16 NuH = H ₂ O |
| 7 X = RC ₆ H ₄ , Y = Cl | 17 NuH = EtOH |
| 8 X = PhO, Y = Cl | 18 NuH = Imidazole |
| 9 X = RC ₆ H ₄ , Y = NH ₂ | 19 NuH = RC ₆ H ₄ NH ₂ |
| 10 X = RC ₆ H ₄ , Y = Imidazolyl | |

1 - 7, 9 - 11, 13, 19:

- | | | | | |
|--------------------------|--------------------------|-------------|--------------------------|--------------------------|
| a. R = 4-NH ₂ | d. R = 3-NH ₂ | g. R = 4-F | j. R = 3-Cl | m. R = 4-CN |
| b. R = 4-OMe | e. R = 3-Me | h. R = 4-Cl | k. R = 3-Br | n. R = 3-NO ₂ |
| c. R = 4-Me | f. R = H | i. R = 4-Br | l. R = 4-CF ₃ | o. R = 4-NO ₂ |

Scheme 1 Reactions of carboxylic acid derivatives with anionic and neutral nucleophiles.

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acyl-transfer reactions and suggests that the development of a charge in the transition states of these reactions is mainly affected by the magnitude of $\delta\Delta H^\ddagger_{\text{int}}$ related to the Hammett ρ reaction constants.

Results and discussion

From the temperature-dependent rate data^{9–27} Eyring plots were generated by plotting $\log(k/T)$ versus $1/T$ and the enthalpy and entropy of activation, $\Delta H^\ddagger$, $\Delta S^\ddagger$, were determined for the reactions of esters **1–6**, acyl chlorides **7** and **8**, amides **9** and **10** and anhydrides **11** with the complexes of thiophenol **12** and phenols **13** with K_2CO_3 , OH^- ion **14** and HPO_4^{2-} dianion **15**, and also with uncharged nucleophiles (water **16**, ethanol **17**, imidazole **18** and anilines **19**) (Scheme 1).

Using the $\Delta H^\ddagger$, $\Delta S^\ddagger$ and $\Delta G^\ddagger$ values for the reactions of Scheme 1, the $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$ and $\delta\Delta G^\ddagger$ reaction constants were found from eqns (1)–(3) (Tables 1 and 2). Whereas the $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ (or $\text{T}\delta\Delta S^\ddagger$) values change over a very wide range, the changes in the magnitudes of $\delta\Delta G^\ddagger$ occur in a narrower range (from +14.8 to –16.4 kJ mol^{–1} σ^{–1}). It is necessary to emphasize that the $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$ and $\delta\Delta G^\ddagger$ reaction constants can be both positive and negative (Tables 1 and 2). The changes of the $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ values are strongly influenced by differences in solvation of reagents and transition states: a dominance of solvation of initial reagents leads to the positive $\delta\Delta S^\ddagger$ and small negative or positive $\delta\Delta H^\ddagger$ values on passing to electron-withdrawing substituents R (entries 3–6, 8, 11–13, 17, 19, 20, 24, 25 in Table 1 and 2).^{6b,7,15} At the same time the stronger solvation of the transition state results in the negative $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ values at the introduction of electron-withdrawing substituents R (entries 1, 2, 7, 9, 10, 14–16, 18, 21, 22, 26–28 in Table 1).^{6b,7,15,27} For the majority of reactions the absolute $\delta\Delta H^\ddagger$ values exceed the entropy component, $|\text{T}\delta\Delta S^\ddagger|$, whereas for a minority of reactions (entries 5, 8, 12, 19, 20, 26–28 in Table 2) the situation is opposite: $|\text{T}\delta\Delta S^\ddagger| > |\delta\Delta H^\ddagger|$. The latter is connected with a small change of an enthalpy component with variation of a substituent in a substrate (entries 5, 8, 12, 19, 20) or nucleophile (entries 26–28) and a larger change of activation entropy.

For the reactions subjected to a change of substituent in the leaving or nonleaving group of the carbonyl compounds (entries 1–22 in Table 2) a linear dependence between the reaction constants, $\delta\Delta H^\ddagger$ vs. $\delta\Delta S^\ddagger$, is supported [eqn (4)] (Fig. 1).

$$\delta\Delta H^\ddagger = (-10.0 \pm 0.6) + (0.31 \pm 0.01)\delta\Delta S^\ddagger$$

$$r = 0.994, s = 2.93, n = 22 \quad (4)$$

At the same time for the reactions for which a substituent is varied in the nucleophile (entries 23–28 in Table 2) the $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ values give a different linear dependence upon each other [eqn (5)] (Fig. 1).

$$\delta\Delta H^\ddagger = (12.3 \pm 1.5) + (0.45 \pm 0.05)\delta\Delta S^\ddagger$$

$$r = 0.975, s = 3.1, n = 6 \quad (5)$$

The slopes of the correlations (4) and (5) multiplied by 10³ correspond to a temperature (*cf.* ref. 5) and equal 310 K and

450 K, respectively. A higher sensitivity of $\delta\Delta H^\ddagger$ to $\delta\Delta S^\ddagger$ for reactions in which the substituent is in the nucleophiles [eqn (5) vs. eqn (4)] can indicate an enhanced influence of solvation on the activation entropy change in these reactions.

On the basis of the solvation theory developed by Hepler⁵ values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are divided into internal ($\Delta H^\ddagger_{\text{int}}$, $\Delta S^\ddagger_{\text{int}}$) and external ($\Delta H^\ddagger_{\text{ext}}$, $\Delta S^\ddagger_{\text{ext}}$) terms, referring to the chemical reactions and the solvation process, respectively. In the same way the $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ reaction constants of this paper can be divided also into internal and external parts [eqns (6) and (7)].^{5,6}

$$\delta\Delta H^\ddagger = \delta\Delta H^\ddagger_{\text{int}} + \delta\Delta H^\ddagger_{\text{ext}} \quad (6)$$

$$\delta\Delta S^\ddagger = \delta\Delta S^\ddagger_{\text{int}} + \delta\Delta S^\ddagger_{\text{ext}} \quad (7)$$

The changes in the $\delta\Delta S^\ddagger$ values caused by the substituent variation in a substrate and a nucleophile result from the changes in solvation (external term $\delta\Delta S^\ddagger_{\text{ext}}$) and, therefore, it is possible to believe, that in the eqn (7) the internal part of the activation entropy is independent of the substituent in the absence of a steric effects ($\delta\Delta S^\ddagger_{\text{int}} \approx 0$) and $\delta\Delta S^\ddagger \approx \delta\Delta S^\ddagger_{\text{ext}}$.^{5,29}

The magnitude of $\delta\Delta H^\ddagger_{\text{ext}}$ can be calculated by the eqn (8).^{5,6b}

$$\delta\Delta H^\ddagger_{\text{ext}} = \beta_{\text{ext}}\delta\Delta S^\ddagger \quad (8)$$

In this equation the β_{ext} value corresponds to a constant temperature equal to 310 K and 450 K for reactions, described by the eqns (4) and (5), respectively. The values of $\delta\Delta H^\ddagger_{\text{ext}}$ and $\delta\Delta H^\ddagger_{\text{int}}$ calculated from eqns (8) and (6) are given in Table 2. From comparison of these values it is seen that $|\delta\Delta H^\ddagger_{\text{ext}}| > |\delta\Delta H^\ddagger_{\text{int}}|$ for reactions with dominant solvation of transition states (entries 1, 2, 10, 14, 15, 26–28 in Table 2), and for the reactions with stronger solvation of initial reagents (entries 19, 20 in Table 2). In the case of the rest of the reactions changes of internal activation enthalpy exceed changes of external activation enthalpy, $|\delta\Delta H^\ddagger_{\text{int}}| > |\delta\Delta H^\ddagger_{\text{ext}}|$. Values $\delta\Delta H^\ddagger_{\text{int}}$ are always negative for reactions involving a change of the substituent in a substrate (entries 1–22 in Table 2) and positive for reactions where variation of the substituent is in the nucleophile (entries 23–28 in Table 2); this is caused by a reduction or increase of activation enthalpy $\Delta H^\ddagger$ on passing to electron-withdrawing substituents R in substrate or nucleophile, respectively.

The sign of $\delta\Delta H^\ddagger_{\text{ext}}$ depends on the difference in solvation of initial reagents and transition states, as well as on $\delta\Delta S^\ddagger_{\text{ext}}$ or $\delta\Delta S^\ddagger$: if $\delta\Delta H^\ddagger_{\text{ext}} > 0$ (entries 3–6, 8, 11–13, 17, 19, 20, 24, 25 in Table 2), stronger solvation of initial reagents on passing to electron-withdrawing substituents R leads to increase in the magnitudes of $\delta\Delta H^\ddagger_{\text{ext}}$ (*cf.* refs. 6b, 7 and 15). Negative values of $\delta\Delta H^\ddagger_{\text{ext}}$ imply increased solvation of a transition states and a reduction in the magnitudes of $\delta\Delta H^\ddagger_{\text{ext}}$ upon introduction of electron withdrawing substituents R (entries 1, 2, 7, 9, 10, 14–16, 18, 21, 22, 26–28 in Table 2) (*cf.* refs. 6b, 7 and 15).

As implied by the data of Table 2 the reaction constant $\delta\Delta G^\ddagger$ becomes approximately equal to $\delta\Delta H^\ddagger_{\text{int}}$ provided that the experimental temperature T approaches β_{ext} (entries 1–25) [eqn (9)] (*cf.* refs. 6b and 29).

$$\delta\Delta H^\ddagger_{\text{int}} = (-0.5 \pm 0.2) + (0.96 \pm 0.02)\delta\Delta G^\ddagger$$

$$r = 0.996, s = 0.76, n = 25 \quad (9)$$

Table 1 Parameters of equations $\Delta H^\ddagger = \delta\Delta H^\ddagger\sigma + \Delta H^\ddagger_0$, $\Delta S^\ddagger = \delta\Delta S^\ddagger\sigma + \Delta S^\ddagger_0$, and $\Delta G^\ddagger = \delta\Delta G^\ddagger\sigma + \Delta G^\ddagger_0$ for the reactions of compounds **1–11** with nucleophiles **12–19**

Entry	Reactants	N^a	$\delta\Delta H^\ddagger_{bc}/$ $\text{kJ mol}^{-1} \sigma^{-1}$	$\Delta H^\ddagger_0/\text{kJ mol}^{-1}$	r/s	$\delta\Delta S^\ddagger_{bc}/$ $\text{J mol}^{-1} \text{K}^{-1} \sigma^{-1}$	$\Delta S^\ddagger_0/\text{J mol}^{-1} \text{K}^{-1}$	r/s	$\delta\Delta G^\ddagger_{bc}/\text{kJ mol}^{-1} \sigma^{-1}$	$\Delta G^\ddagger_0/\text{kJ mol}^{-1}$	r/s	Ref.
1	1b,c,fi,k,l + 12	6	-108.5 ± 7.0	-5.3 ± 2.2 ^d	0.992 (5.0)	-332.0 ± 26.8	-20.0 ± 8.5 ^d	0.987 (19.2)	-9.2	0 ^d	—	9
2	1b,c,fi,j,n,o + 13h	7	-76.4 ± 4.9	-9.8 ± 2.3 ^d	0.990 (5.07)	-192.0 ± 15.8	-30.9 ± 7.5 ^d	0.983 (16.5)	-16.4	0 ^d	—	10
3	1c,f,h,m,o + 18	5	-5.6 ± 0.8	39.8 ± 0.4	0.972 (0.64)	3.9	-148	—	-6.8 ± 0.3	84.4 ± 0.3	0.996 (0.27)	11
4	2c,f,h,m,o + 15	5	-10.2 ± 1.0	67.7 ± 0.5	0.986 (0.84)	10.2	-93.2	—	-13.4 ± 0.5 (0.998)	95.0 ± 0.2	0.998 (0.41)	12
5	2c,f,h,m,o + 18	5	-2.9	37.2	—	23.7 ± 4.2	-123.6 ± 2.6	0.956 (3.71)	-13.4 ± 0.5	74.9 ± 0.1	0.999 (0.19)	11
6	3a,c-f,n,o + 14	7	-11.9 ± 0.4	58.9 ± 0.2	0.997 (0.50)	5.4	-96.6	—	-13.5 ± 0.3	87.0 ± 0.3	0.998 (0.41)	13
7	3a-c,f,h,i,o + 14	7	-15.9 ± 0.4	71.0 ± 0.2	0.998 (0.43)	-4.5	-67.3	—	-14.5 ± 0.3	92.0 ± 0.3	0.999 (0.33)	14
8	3a-c,f,i,o + 14	6	-6.2 ± 0.7	72.5 ± 0.3	0.975 (0.59)	21.2	-66.1	—	-12.5 ± 0.4	91.5 ± 0.1	0.998 (0.31)	6b
9	4c,f,g,j,n,o + 14	6	-24.9 ± 3.1 ^e	63.6 ± 1.5	0.971 (2.49)	-39.0	-53.1	—	-13.0 ± 0.5 ^e	79.7 ± 0.2	0.997 (0.38)	15
10	4d-g,j,n,o + 14	7	-21.3 ± 2.3 ^e	38.0 ± 1.0	0.972 (2.1)	-36.9	-109.9	—	-10.3 ± 0.6 ^e	70.0 ± 0.2	0.993 (0.52)	16
11	4d-g,j,n,o + 14	7	-3.8 ± 0.7 ^e	42.7 ± 0.3	0.927 (0.63)	6.1	-106.7	—	-5.7 ± 0.5 ^e	76.9 ± 0.2	0.981 (0.46)	17
12	5c,f,h,m,o + 18	5	-1.1	38.9	—	25.4 ± 3.5	-172.0 ± 2.5	0.973 (4.45)	-9.1 ± 0.1	90.5 ± 0.1	0.999 (0.16)	11
13	6c,e,f,n,o + 14	5	-8.2 ± 0.5	50.4 ± 0.2	0.994 (0.46)	0.4	-80.7	—	-8.3 ± 0.3	72.3 ± 0.1	0.998 (0.26)	13
14	7c,fi,o + 16	4	-25.8 ± 3.5	46.5 ± 1.5	0.983 (2.5)	-48.0 ± 10.0	-177.2 ± 4.1	0.959 (7.2)	-11.5	99.6	—	18
15	7c,f-i,o + 17	6	-20.2 ± 1.7	59.5 ± 0.6	0.986 (1.23)	-37.2	-126.4	—	-9.6 ± 0.4	93.9 ± 0.2	0.996 (0.37)	19
16	7c,f-i,o + 17	6	-15.4 ± 1.2	61.5 ± 0.5	0.989 (0.94)	-22.0	-98.7	—	-8.8 ± 0.1	90.9 ± 0.3	0.988 (0.56)	6b
17	7c,f,h,o + 19f	4	-8.2 ± 0.4	28.6 ± 0.2	0.998 (0.26)	3.0	-172.1	—	-9.1 ± 2.0	81.0 ± 0.8	0.954 (1.46)	20
18	9c,f,h,m + 14	4	-12.9 ± 1.2	74.3 ± 0.5	0.991 (0.89)	-14.1	-112.0	—	-8.0 ± 0.4	114.3 ± 0.2	0.997 (0.29)	21
19	10c,f,h,o + 14	4	27.4	32.5	—	119.9 ± 22.6	-165.8 ± 9.4	0.966 (16.2)	-8.3 ± 0.3	82.0 ± 0.1	0.999 (0.19)	7, 22
20	10c,f,h,o + 16	4	9.4	36.5	—	58.9 ± 13.8	-175.2 ± 6.6	0.973 (9.3)	-8.1 ± 0.1	97.5 ± 0.1	0.999 (0.09)	7, 22
21	10c,f,h,m,o + 16	5	-10.8 ± 0.3	41.6 ± 0.1	0.999 (0.23)	-10.9	-158	—	-7.4 ± 0.3	88.4 ± 0.2	0.997 (0.28)	7, 23
22	11b-d,f,h,n,o + 16	7	-16.6 ± 0.7	34.2 ± 1.5	0.980 (1.6)	-19.8	-77.3	—	-10.0 ± 0.2	67.8 ± 0.1	0.999 (0.17)	24
23	7f + 19c,f,h,n,o	5	14.7 ± 1.5 ^f	28.6 ± 1.0	0.986 (1.9)	0	-166.1	—	14.7 ± 1.2 ^f	80.0 ± 0.8	0.992 (1.42)	20, 25
24	7f + 19f,h,n,o	4	19.1 ± 0.5 ^f	22.9 ± 0.3	0.999 (0.45)	14.4	-181.8	—	14.8 ± 1.2 ^f	78.1 ± 0.9	0.994 (1.16)	25
25	8 + 19f,j,n	3	15.3 ± 4.0	20.5 ± 1.7	0.937 (2.1)	11.6	-154.7	—	11.8 ± 0.4	67.9 ± 0.2	0.999 (0.18)	26
26	2f + 13b,c,e	3	-0.25 ± 0.03	1.71 ± 0.01 ^d	0.993 (0.01)	-34.0 ± 1.2	3.09 ± 0.22 ^d	0.999 (1.15)	9.7	0 ^d	—	27
27	2f + 13h,k,n	3	-10.2 ± 0.3	1.06 ± 0.13 ^d	0.999 (0.10)	-40.1 ± 0.9	17.7 ± 0.4 ^d	0.999 (0.32)	1.5	0 ^d	—	27
28	2f + 13m,n,o	3	-7.0 ± 0.04	-1.25 ± 0.04 ^d	0.999 (0.02)	-45.5 ± 0.2	21.5 ± 0.2 ^d	0.999 (0.09)	6.3	0 ^d	—	27

^a Number of compounds. ^b σ constants²⁸ were used in the correlations; standard errors of the $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$ and $\delta\Delta G^\ddagger$ reaction constants are estimated to be less than 8%, 11% and 5%, respectively. ^c Values given without correlation coefficient are calculated by the equation $\delta\Delta G^\ddagger = \delta\Delta H^\ddagger - T\delta\Delta S^\ddagger$. ^d The differences in the activation parameters $\Delta\Delta H^\ddagger_0 = \Delta H^\ddagger_0(\text{R}) - \Delta H^\ddagger_0(\text{H})$, $\Delta\Delta S^\ddagger_0 = \Delta S^\ddagger_0(\text{R}) - \Delta S^\ddagger_0(\text{H})$, and $\Delta\Delta G^\ddagger_0 = \Delta G^\ddagger_0(\text{R}) - \Delta G^\ddagger_0(\text{H})$, respectively. ^e σ^+ constants¹⁵ were used in correlations. ^f σ^- constants²⁸ were used in correlations.

Table 2 Effect of substituents in compounds **1–11** on activation parameters in their reactions with nucleophiles **12–19**

Entry	Reactants	Solvent	N^a	T/K^b	$\delta\Delta H^{tsd}/$ $\text{kJ mol}^{-1} \sigma^{-1} (r)$	$\delta\Delta S^{tsd}/$ $\text{J mol}^{-1} \text{K}^{-1} \sigma^{-1} (r)$	$T\delta\Delta S^\ddagger/$ $\text{kJ mol}^{-1} \sigma^{-1} (r)$	$\delta\Delta G^{tsd}/$ $\text{kJ mol}^{-1} \sigma^{-1} (r)$	$\delta\Delta H_{\text{ext}}^\ddagger/$ $\text{kJ mol}^{-1} \sigma^{-1}$	$\delta\Delta H_{\text{int}}^\ddagger/$ $\text{kJ mol}^{-1} \sigma^{-1}$	ρ^c
1	1b,c,f,i,k,l + 12	DMF	6	299	-108.5 (0.992)	-332.0 (0.987)	-99.3	-9.2	-101.6	-6.9	1.10
2	1b,c,f,i,j,n,o + 13h	DMF	7	313	-76.4 (0.990)	-192.0 (0.983)	-60.0	-16.4	-58.8	-17.6	3.43
3	1c,f,h,m,o + 18	10 vol% MeCN-H ₂ O	5	308	-5.6 (0.972)	3.9	1.2	-6.8 (0.996)	1.2	-6.8	1.10
4	2c,f,h,m,o + 15	10 vol% MeCN-H ₂ O	5	313	-10.2 (0.986)	10.2	3.2	-13.4 (0.988)	3.1	-13.3	2.20
5	2c,f,h,m,o + 18	10 vol% MeCN-H ₂ O	5	298	-2.9	23.7 (0.956)	7.1	-10.0 (0.999)	7.3	-10.2	1.74
6	3a,c-f,n,o + 14	60 vol% Me ₂ CO-H ₂ O	7	298	-11.9 (0.997)	5.4	1.6	-13.5 (0.988)	1.7	-13.6	2.38
7	3a-c,f,h,i,o + 14	85 wt% EtOH-H ₂ O	7	308	-15.9 (0.998)	-4.5	-1.4	-14.5 (0.999)	-1.4	-14.5	2.55
8	3a-c,f,i,o + 14	71.2 wt% MeOH-H ₂ O	6	298	-6.2 (0.975)	21.2	6.3	-12.5 (0.988)	6.5	-12.7	2.19
9	4e,f,g,j,n,o + 14	2.25M Bu ₄ NBr in H ₂ O	6	305	-24.9 (0.971) ^g	-39.0	-11.9	-13.0 (0.997) ^g	-11.9	-13.0	2.31 ^g
10	4d-g,j,n,o + 14	80 vol% DMSO	7	298	-21.3 (0.972) ^g	-36.9	-11.0	-10.3 (0.993) ^g	-11.0	-10.3	1.79 ^g
11	4d-g,j,n,o + 14	H ₂ O	7	313	-3.8 (0.927) ^g	6.1	1.9	-5.7 (0.981) ^g	1.9	-5.7	1.01 ^g
12	5c,f,h,m,o + 18	10 vol% MeCN-H ₂ O	5	315	-1.1	25.4 (0.973) ^h	8.0	-9.1 (0.999) ^h	7.8	-8.9	1.56 ^h
13	6c,e,f,n,o + 14	60 vol% Me ₂ CO-H ₂ O	5	273	-8.2 (0.994)	0.4	0.1	-8.3 (0.998)	0.1	-8.3	1.59
14	7c,f,i,o + 16	95 vol% Me ₂ CO-H ₂ O	4	298	-25.8 (0.983)	-48.0 (0.959)	-14.3	-11.5	-14.7	-11.1	1.77
15	7c,f-i,o + 17	60 vol% Et ₂ O-EtOH	6	285	-20.2 (0.986)	-37.2	-10.6	-9.6 (0.996)	-11.4	-8.8	1.52
16	7c,f-i,o + 17	EtOH	6	298	-15.4 (0.989)	-22.0	-6.6	-8.8 (0.988)	-6.7	-8.7	1.54
17	7c,f,h,o + 19f	C ₆ H ₆	4	298	-8.2 (0.998)	3.0	0.9	-9.1 (0.954)	0.9	-9.1	1.22
18	9c,f,h,m + 14	60 vol% Et ₂ O-EtOH	4	347	-12.9 (0.991)	-14.1	-4.9	-8.0 (0.997)	-4.3	-8.6	1.14
19	10c,f,h,o + 14	10 vol% MeCN-H ₂ O	4	298	27.4	119.9 (0.966)	35.7	-8.3 (0.999)	36.7	-9.3	1.47
20	10c,f,h,o + 16	10 vol% MeCN-H ₂ O	4	298	9.4	58.9 (0.973)	17.5	-8.1 (0.999)	18.0	-8.6	1.41
21	10c,f,h,m,o + 16	10 vol% MeCN-H ₂ O ⁱ	5	313	-10.8 (0.999)	-10.9	-3.4	-7.4 (0.997)	-3.3	-7.5	1.25
22	11b-d,f,h,n,o + 16	75 vol% dioxane-H ₂ O	7	331	-16.6 (0.980) ^j	-19.8 ^j	-6.6 ^j	-10.0 (0.999) ^j	-6.1 ^j	-10.5 ^j	1.59 ^j
23	7f + 19c,f,h,n,o	C ₆ H ₆	5	298	14.7 (0.986) ^h	0	0	14.7 (0.992) ^h	0	14.7	-2.90
24	7f + 19f,h,n,o	Et ₂ O	4	298	19.1 (0.999) ^h	14.4	4.3	14.8 (0.994) ^h	6.5	12.6	-2.84
25	8 + 19f,j,n	MeCN	3	298	15.3 (0.937)	11.6	3.5	11.8 (0.999)	5.2	10.1	-2.22
26	2f + 13b,c,e	DMF	3	293	-0.25 (0.993)	-34.0 (0.999)	-10.0	9.7	-15.3	15.0	-3.21 ^k
27	2f + 13h,k,n	DMF	3	293	-10.2 (0.999)	-40.1 (0.999)	-11.7	1.5	-18.0	7.8	(-1.72)
28	2f + 13m,n,o	DMF	3	293	-7.0 (0.999)	-45.5 (0.999)	-13.3	6.3	-20.5	13.5	(-0.36)
											(-1.14)

^a Number of compounds. ^b Temperature of experiments. ^c σ constants²⁸ were used in the correlation equations $\Delta H^\ddagger = \delta\Delta H^\ddagger\sigma + \Delta H^\ddagger_0$, $\Delta S^\ddagger = \delta\Delta S^\ddagger\sigma + \Delta S^\ddagger_0$ and $\Delta G^\ddagger = \delta\Delta G^\ddagger\sigma + \Delta G^\ddagger_0$, $\log k = \rho\sigma + \log k_0$; standard errors of the $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$, and $\delta\Delta G^\ddagger$ reaction constants are estimated to be less than 8%, 11% and 5%, respectively; ρ values were taken from the works.⁹⁻²⁷ ^d Values given without correlation coefficient are calculated by the equation $\delta\Delta H^\ddagger = \delta\Delta H^\ddagger - T\delta\Delta S^\ddagger$. ^e Values are calculated by the equation $\delta\Delta H^\ddagger_{\text{ext}} = \beta_{\text{ext}}\delta\Delta S^\ddagger$, where $\beta_{\text{ext}} = 310$ K (entries 1–22) and 450 K (entries 23–28). ^f $\delta\Delta H^\ddagger_{\text{int}} = \delta\Delta H^\ddagger - \delta\Delta H^\ddagger_{\text{ext}}$. ^g σ^0 constants¹⁵ were used in correlations. ^h σ^- constants²⁸ were used in correlations. ⁱ Imidazole was used as a buffer. ^j σ^- constants²⁸ were used in correlations. ^k Value ρ_1 is calculated by the eqn (11); the data in the parentheses are the ρ values.²⁷

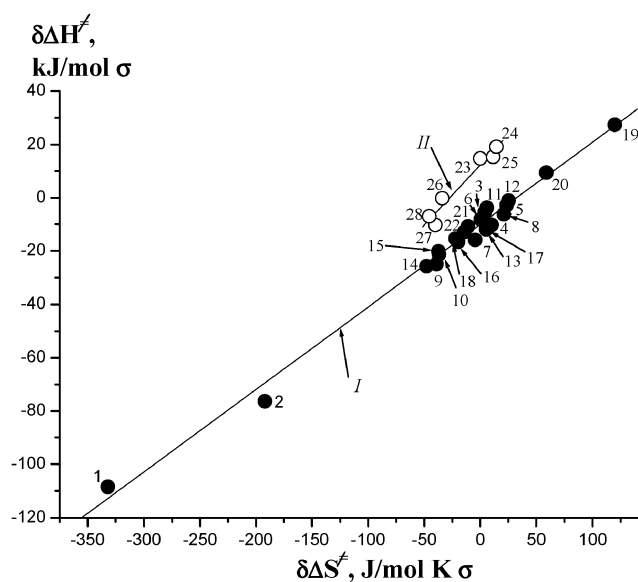
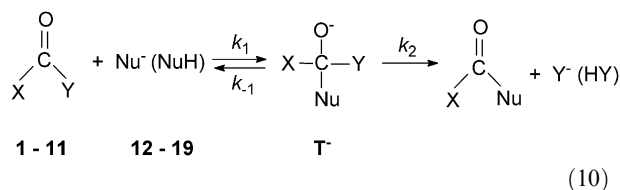


Fig. 1 Plots of $\delta\Delta H^\ddagger$ vs. $\delta\Delta S^\ddagger$ for the reactions of carboxylic acid derivatives **1–11** with anionic and neutral nucleophiles **12–19** in various solvents; lines I and II are for the reactions involving a change of substituents in substrates and nucleophiles, respectively; the identity of the numbers is the entry number in Table 2.

However, some reactions in which the substituent is changed in the nucleophiles (entries 26–28 in Table 2) noticeably deviate from the dependence (9). The reason for this deviation, possibly, is an appreciable reduction of the $\delta\Delta G^\ddagger$ constants for these reactions, because $\delta\Delta G^\ddagger$ represents the reaction constants of a two-step reaction involving nucleophile addition to ester **2f** (rate constant k_1) and a departure of leaving group from a tetrahedral intermediate T^- (rate constant k_2) when $k_{-1} > k_2$ and $k = (k_1/k_{-1})k_2$ [eqn (10)].²⁷



Taking into account the fact that according to the Hammett equation the $\delta\Delta G^\ddagger$ reaction constant can be determined as $\delta\Delta G^\ddagger = -2.303RT\rho^{6b,30}$ and considering the relationship of eqn (9), a correlation (11) between $\delta\Delta H^\ddagger_{\text{int}}$ and ρ for the reactions of entries 1–25 (for which the k_1 step is presumed to be rate-determining) has been developed as shown in Table 2 and Fig. 2.

$$\begin{aligned}
 \delta\Delta H^\ddagger_{\text{int}} &= (-1.32 \pm 0.19) - (5.13 \pm 0.092)\rho \\
 r &= 0.996, s = 0.75, n = 25
 \end{aligned}
 \quad (11)$$

Realisation of this dependence becomes possible, as magnitudes of $\rho(k_1)$ for these reactions characterise charge development at the transition state before formation of intermediate T^- at $k_2 \gg k_{-1}$ (cf. refs. 7, 8a,b, 30 and 31). Therefore, for reactions of entries 26–28 in Table 2 the values of $\rho_1(k_1)$ have been calculated by the eqn (11) for the reaction

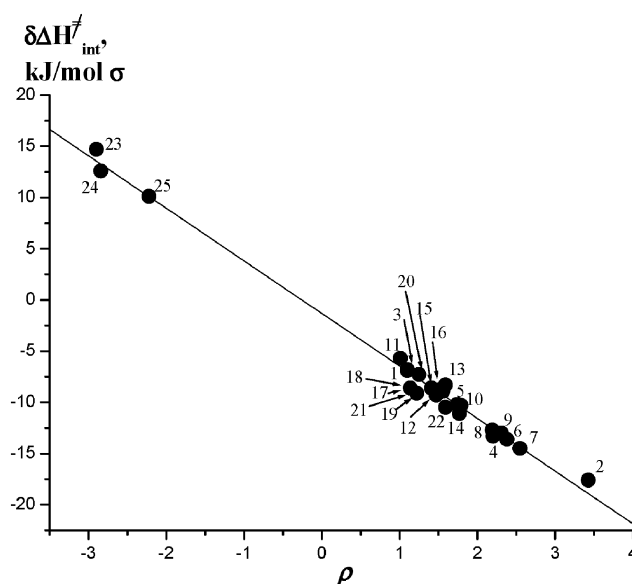


Fig. 2 Plot of $\delta\Delta H^\ddagger_{\text{int}}$ vs. ρ for the reactions of carboxylic acid derivatives **1–11** with anionic and neutral nucleophiles **12–19** in various solvents; the identity of the numbers is the entry number in Table 2.

step forming the intermediate T^- using the $\delta\Delta H^\ddagger_{\text{int}}$ values. The calculated values of $\rho_1(k_1)$ differ significantly from values $\rho = \rho_1(k_1) + \rho_2(k_2/k_{-1})$, obtained by the Hammett equation with the use of observable rate constants for these reactions.²⁷ At the same time the magnitudes of $\rho_2(k_2/k_{-1})$ for the step corresponding to decomposition of intermediate T^- are positive and equal to 1.5, 1.4 and 1.8 for reactions of entries 26–28 in Table 2, respectively. It is obvious from the relationship of eq (11), that the $\delta\Delta H^\ddagger_{\text{int}}$ reaction constant, as well as the reaction constant ρ from the Hammett equation,^{7,8a,b,30,31} characterizes the degree of developing negative charge in the transition state (rate constants k_1), and the larger absolute values of $|\delta\Delta H^\ddagger_{\text{int}}|$ are obtained for reactions at rather small absolute values of $|\delta\Delta H^\ddagger_{\text{ext}}|$ (entries 2, 4, 6–9, 23–25 in Table 2; Fig. 2) because of reduction of the solvation contribution into change of the $\delta\Delta H^\ddagger$ activation enthalpy constant for these reactions.

It is believed that with the increase in facility of nucleophilic replacement of leaving group in carboxylic acid derivatives the mechanism in acyl group transfer reactions changes from stepwise [eqn (10)] to concerted.^{2b,d,g} Therefore, we suggest that solvolysis and aminolysis of acyl chlorides **7** and **8** (entries 14–17, 23–25 in Table 2) may proceed also by concerted mechanism.^{26,32} In this case, the ρ values are positive for variation of substituents in a substrate ($\rho_x = +1.22$ up to $+1.77$)³³ and negative for changes of substituents in nucleophile ($\rho_{\text{nuc}} = -2.22$ up to -2.90),³⁴ which is characteristic for reactions involving partial development of charge with a low degree of bond cleavage in the transition state.²⁶ Though the ρ values for reactions of acyl chlorides **7** and **8** with nucleophiles **16**, **17** and **19** cannot provide a basis for assignment of a stepwise or concerted reaction mechanism, nevertheless, correlation dependence (11) equally well describes those reactions, which proceed on both mechanisms.

Conclusions

The enthalpy and entropy reaction constants, $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$, playing a significant role in determining the substituent influence on the solvation change in the acyl-transfer reactions change in very wide range.

Determining the compensation dependences between the $\delta\Delta H^\ddagger$ and $\delta\Delta S^\ddagger$ values in acyl-transfer reactions gives a straightforward way of estimating β_{ext} and obtaining $\delta\Delta H^\ddagger_{\text{int}}$.

Both negative and positive values of $\delta\Delta H^\ddagger_{\text{int}}$ give a single linear dependence with the corresponding positive and negative values of ρ . The large absolute values of $\delta\Delta H^\ddagger_{\text{int}}$ indicate essential charge development in the transition state of acyl-transfer reactions. It is evident that the deviations from dependence of $\delta\Delta H^\ddagger_{\text{int}}$ vs. ρ can be interpreted in terms of a change of reaction mechanism.

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