Relative reactivity of methyl iodide to ethyl iodide in nucleophilic substitution reactions in acetonitrile and partial desolvation accompanying activation

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Through the examination of empirical correlations involving activation parameters for nucleophilic substitution of methyl iodide and of ethyl iodide, nucleophiles have been classified into three series: (1) nucleophiles with two equivalent reaction sites, (2) nucleophiles with a chlorine atom in the *para*-position, and (3) nucleophiles with a single reaction site. Three types of partial desolvation processes accompanying activation have been deduced on the basis of these classifications. A major factor determining the relative reactivity of methyl iodide to ethyl iodide in the substitution reaction of an anionic nucleophile having a single reaction site in acetonitrile (k_{MeI}/k_{EtI}) is suggested to be partial desolvation around the nucleophilic center on going from reactant to transition-state.

Introduction

The concept of steric hindrance was developed in the 19th century and since then it has been accepted as one of the central subjects of physical organic chemistry.[1–3] However, the rationalization of the effects of steric hindrance on the rates of aliphatic nucleophilic substitution reactions has not been easy, partly because of the lack of appropriate methods for separating the observed effects into components, *i.e.*, intrinsic and solvational contributions either on experimental or on theoretical grounds. The rationalization of the effect of *ortho*-substituent on reactivities of aromatic compounds has been performed through linear free energy relationships and their extended versions with the main emphasis being laid on parameterising the effect,[4,5] in spite of the significance of solute–solvent interaction having been noticed.[3]

Recently, the importance of partial desolvation accompanying activation has been suggested as one of the major factors influencing the reactivity of nucleophilic anions in acetonitrile.[6,7] Substitution of one of the hydrogen atoms in methyl iodide by a methyl group, and introduction of a substituent into the *ortho*-position of an aromatic nucleophile, are considered to be two ways in which the solvation sphere proximate to a reaction center can be perturbed. In recent work, through the analysis of the effects induced into reaction behavior by the structural variation in a nucleophile, characteristic features of the solvation patterns at the transition state have efficiently been brought to light.[8] In the present work, the relative reactivity of methyl iodide to ethyl iodide and the effects of an *ortho*-substituent on nucleophilic substitution reactions will be determined in acetonitrile as solvent and a discussion will be presented on the significance of the solvation change on going from reactant to transition state in determining the reaction behavior in solution.

$$Nu^- + Me\text{–}I\ (Et\text{–}I) \longrightarrow Me\text{–}Nu\ (Et\text{–}Nu) + I^-$$

Results

Rate constants and activation parameters for the reaction of methyl iodide with nucleophiles in acetonitrile, specific interaction enthalpies for a relevant nucleophile, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$, and enthalpies of reaction in acetonitrile, $\Delta_r H$, are summarized in Table 1. Rate constants and activation parameters, specific interaction enthalpies for a relevant nucleophile, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$, and the enthalpies of reaction for the reaction of ethyl iodide with nucleophiles in acetonitrile are summarized in Table 2.

Enthalpies of solution, $\Delta_s H$, for tetraalkylammonium salts in acetonitrile–methanol mixtures are summarized in Table 3. Single-ion enthalpies of transfer for nucleophile, $\Delta_t H^{AN\longrightarrow mix}$, have been calculated on the basis of the tetrabutylammonium–tetrabutyl borate assumption[13] and are summarized in Table 4. These indicate a sharp minimum at a low content of methanol, which is the usually observed trend for anions in which hydrogen-bonding interactions with methanol play a significant role.[6,13] The enthalpies have been separated into their components: a physical interaction enthalpy, $\Delta_t H_{PHYS}^{AN\longrightarrow MeOH}$, which is a composite of electrostatic interaction and protophobic interaction between anion and solvents, and a specific interaction enthalpy, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$, which arises from hydrogen-bonding interaction between anion and methanol, according to eqns. (1) and (2).

$$\Delta_t H^{AN\longrightarrow mix} = \Delta_t H_{PHYS}^{AN\longrightarrow MeOH} \times x_{MeOH} \times \{1 - 1.23 \times x_{MeOH} \times (1 - x_{MeOH})\} + \Delta_t H_{SI}^{AN\longrightarrow MeOH} \times K_{se} \times x_{MeOH}/(x_{AN} + K_{se} \times x_{MeOH}) \quad (1)$$

$$\Delta_t H^{AN\longrightarrow MeOH} = \Delta_t H_{PHYS}^{AN\longrightarrow MeOH} + \Delta_t H_{SI}^{AN\longrightarrow MeOH} \quad (2)$$

Here K_{se}, x_{MeOH} and x_{AN} stand for the equilibrium constant for the solvent exchange process on the solvation site around an anion and the mole fractions of methanol and of acetonitrile, respectively,[6,10,13] and are summarized in Table 4. Observed enthalpies, $\Delta_t H^{AN\longrightarrow mix}$, could be reproduced with eqns. (1) and (2), usually with a maximum deviation of ±1.5 kJ mol^{-1}. The specific interaction enthalpies for the relevant nucleophile, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$, which have been determined in this work and also published elsewhere,[7,8,9,10] are also given in Tables 1 and 2.

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Table 1 Rate constants and activation parameters, specific interaction enthalpies for a nucleophile, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$, and enthalpies of reaction, $\Delta_r H$, for the nucleophilic substitution of MeI in acetonitrile at 30 °C

No.	Nucleophiles	$k/10^{-2}$ dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/ J K^{-1} mol^{-1}	$\Delta_t H_{SI}^{AN\longrightarrow MeOH\,a}$/ kJ mol^{-1}	$\Delta_r H$/kJ mol^{-1}
1	I^-	7.05[b,c]	—	—	−10.0	—
2	I^- (in MeOH)	0.173[b,c]	—	—	−10.0	—
3	2,4-$(NO_2)_2$-Phenolate$^-$	3.18×10^{-3}	76.2	−79.7	−15.0	—
4	2,6-$(NO_2)_2$-Phenolate$^-$	3.27×10^{-3}	75.7	−81.2	−16.0	—
5	3,4,5,6-Cl_4-Phthalimidide$^-$	13.7	59.1	−66.6	−18.5	−114.6
6	2,4-Cl_2-6-NO_2-Phenolate$^-$	1.60×10^{-2}	72.7	−77.9	−19.0	—
7	Br^-	25.8	69.1	−28.4	−20.0	−1.23
8	Br^- (in MeOH)	1.36×10^{-2}[c]	—	—	−20.0	—
9	2,2,5-Me_3-4,6-Dioxo-1,3-dioxanide$^-$	1.71	60.4	−79.6	−24.5	—
10	3,5-$(NO_2)_2$-Benzoate$^-$	1.25	63.1	−73.5	−25.5	−54.2
11	1,3-Dimethylbarbiturate$^-$	2.98	60.5	−74.7	−26.5	—
12	4-Nitrobenzoate$^-$	4.57	66.6	−51.0	−28.0	−61.0
13	2-Nitro-5-Cl-benzoate$^-$	1.07	62.9	−75.3	−28.5	—
14	2-Nitrobenzoate$^-$	2.67	67.0	−54.2	−31.0	—
15	3,4-Cl_2-benzoate$^-$	7.37	65.2	−51.6	−31.0	−61.8
16	2,6-Cl_2-benzoate$^-$	2.74	68.2	−50.0	−31.5	−50.2
17	2-Nitro-5-CH_3O-benzoate$^-$	2.89	62.0	−70.0	−32.0	−53.2
18	4-Nitrophenolate$^-$	0.854	61.8	−80.8	−33.0	−75.7
19	Phenoxyacetate$^-$	11.1	65.2	−48.2	−34.0	−60.4
20	4-Chlorobenzoate$^-$	15.0	63.0	−53.1	−34.0	—
21	2-Chlorobenzoate$^-$	8.08	68.9	−38.7	−35.5	—

[a] Table 4 and refs. 7–10. [b] Rate constant for the reaction, $I^- + MeBr \longrightarrow MeI + Br^-$. [c] Ref. 11.

Table 2 Rate constants and activation parameters, specific interaction enthalpies for a nucleophile, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$, and enthalpies of reaction, $\Delta_r H$, for the nucleophilic substitution of EtI in acetonitrile at 30 °C

No.	Nucleophiles	$k/10^{-2}$ dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/ J K^{-1} mol^{-1}	$\Delta_t H_{SI}^{AN\longrightarrow MeOH\,a}$/ kJ mol^{-1}	$\Delta_r H$/kJ mol^{-1}
1	I^-	5.93×10^{-2}[b,c]	—	—	−10.0	—
2	I^- (in MeOH)	0.205×10^{-2}[b,c]	—	—	−10.0	—
3	2,4-$(NO_2)_2$-Phenolate$^-$	1.33×10^{-3}	77.4	−83.1	−15.0	—
4	2,6-$(NO_2)_2$-Phenolate$^-$	1.84×10^{-3}	76.0	−84.9	−16.0	—
5	3,4,5,6-Cl_4-Phthalimidide$^-$	0.615[a]	66.8[a]	−67.0[a]	−18.5	−111.6[a]
6	2,4-Cl_2-6-NO_2-Phenolate$^-$	7.81×10^{-3}	77.4	−68.4	−19.0	—
7	Br^-	1.08[a]	77.4[a]	−27.2[a]	−20.0	−4.6[a]
8	Br^- (in MeOH)	0.101×10^{-2}[d]	95.0[d]	−27.2[d]	−20.0	—
9	2,2,5-Me_3-4,6-Dioxo-1,3-dioxanide$^-$	0.143[e]	67.7[e]	−76.2[e]	−24.5	—
10	3,5-$(NO_2)_2$-Benzoate$^-$	0.290[a]	68.8[a]	−66.7[a]	−25.5	−64.0[a]
11	1,3-Dimethylbarbiturate$^-$	0.180[e]	68.2[e]	−72.5[e]	−26.5	—
12	4-Nitrobenzoate$^-$	1.07[a]	68.0[a]	−58.3[a]	−28.0	−66.0[a]
13	2-Nitro-5-Cl-benzoate$^-$	0.285	68.0	−69.5	−28.5	—
14	2-Nitrobenzoate$^-$	0.608[f]	73.2[f]	−46.0[f]	−31.0	—
15	3,4-Cl_2-Benzoate$^-$	1.20[f]	69.9[f]	−51.2[f]	−31.0	−68.6
16	2,6-Cl_2-Benzoate$^-$	0.635[f]	69.9[f]	−56.6[f]	−31.5	−56.7
17	2-Nitro-5-CH_3O-benzoate$^-$	0.651	67.7	−63.6	−32.0	−61.1
18	4-Nitrophenolate$^-$	0.279[a]	68.7[a]	−67.3[a]	−33.0	−82.5[a]
19	Phenoxyacetate$^-$	2.09[a]	66.8[a]	−56.8[a]	−34.0	−67.1[a]
20	4-Chlorobenzoate$^-$	2.30	66.7	−56.5	−34.0	—
21	2-Chlorobenzoate$^-$	1.51	70.6	−47.0	−35.5	—

[a] Table 4, and refs. 7–10. [b] Rate constant and activation parameters for the reaction, $I^- + EtBr \longrightarrow EtI + Br^-$. [c] Ref. 12. [d] Ref. 13. [e] Ref. 10. [f] Ref. 8.

Discussion

The logarithmic rate for the reaction of ethyl iodide with substituted benzoate ions is related to the Hammett σ values[14] by eqn. (3).

$$\log k_{EtI} = -1.391 - 0.78\,\Sigma\sigma_i \qquad (3)$$
$$n = 8,\ r = 0.99$$

A much smaller value of the negative Hammett ρ value (0.78 by comparison to the Hammett ρ value for benzoic acid dissociation in acetonitrile, 2.41)[14] suggests early bond making between the anion and ethyl iodide in the transition state. When *ortho*-substituted benzoate ions are incorporated into the scheme with the assumption that the σ value for the *ortho*-substituent, σ_o is equal to that for the *para*-substituent, σ_p, they show significant negative deviation from the regression line [eqn. (3)]—the "*ortho*-effect" (see Fig. 1). However, the 2-nitro-5-methoxybenzoate ion reaction (no. 17) constitutes an exceptional case, that is, the rate constant does not seem to indicate any significant negative deviation.

Recently, the specific interaction enthalpy for a nucleophile, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$, has been shown to work as a relevant nucleophilic reactivity index in acetonitrile.[6,7] For non-*ortho*-substituted ion reactions, the specific interaction enthalpy also serves as a significant explanatory variable for log k_{EtI}, as indicated by eqn. (4).

$$\log k_{EtI} = -4.769 - 9.37 \times 10^{-2} \times \Delta_t H_{SI}^{AN\longrightarrow MeOH} \qquad (4)$$
$$n = 8,\ r = 0.98$$

Table 3 Enthalpies of solution, $\Delta_s H$ in acetonitrile–methanol mixtures at 25 °C (in kJ mol^{-1})[a]

x_{MeOH}	TMA 2-Cl-benzoate	TMA 4-Cl-benzoate	TMA 2-NO_2-5-CH_3O-benzoate	TMA 2-NO_2-5-Cl-benzoate	TMA 2,4-Cl_2-6-NO_2-phenolate
0.0	20.7	20.1	20.9	19.5	24.8
0.10	−8.93	−8.81	−5.43	−3.75	11.6
0.25	−12.0	−11.7	−8.32	−6.62	8.51
0.50	−10.2	−10.2	−5.40	−4.42	8.65
0.75	−7.38	−7.89	−0.743	−0.565	11.1
1.00	−1.22	−1.57	7.19	5.91	15.8

[a] x_{MeOH} = mole fraction of methanol; TMA = tetramethylammonium; 2-Cl-benzoate = 2-chlorobenzoate; 4-Cl-benzoate = 4-chlorobenzoate; 2-NO_2-5-CH_3O-benzoate = 2-nitro-5-methoxybenzoate; 2-NO_2-5-Cl-benzoate = 2-nitro-5-chlorobenzoate; 2,4-Cl_2-6-NO_2-phenolate = 2,4-dichloro-6-nitrophenolate.

Table 4 Single ion enthalpies of transfer from acetonitrile to solvent mixtures $\Delta_t H^{AN\longrightarrow mix}$ (in kJ mol^{-1}) and interaction parameters

x_{MeOH}	2-Cl benzoate	4-Cl benzoate	2-NO_2-5-CH_3O-benzoate	2-NO_2-5-Cl-benzoate	2,4-Cl_2-6-NO_2 phenolate
0.0	0.0	0.0	0.0	0.0	0.0
0.10	−28.7	−28.0	−25.4	−22.35	−12.3
0.25	−31.4	−30.5	−27.9	−24.8	−15.0
0.50	−30.55	−29.95	−25.95	−23.6	−15.8
0.75	−28.4	−28.3	−21.9	−20.4	−14.0
1.0	−24.6	−24.4	−16.4	−16.3	−11.7
$\Delta_t H_{PHYS}^{AN\longrightarrow MeOH}$	10.9	9.60	15.6	12.2	7.3
$\Delta_t H_{SI}^{AN\longrightarrow MeOH}$	−35.5	−34.0	−32.0	−28.5	−19.0
K_{se}	45.0	58.0	50.0	45.0	20.0

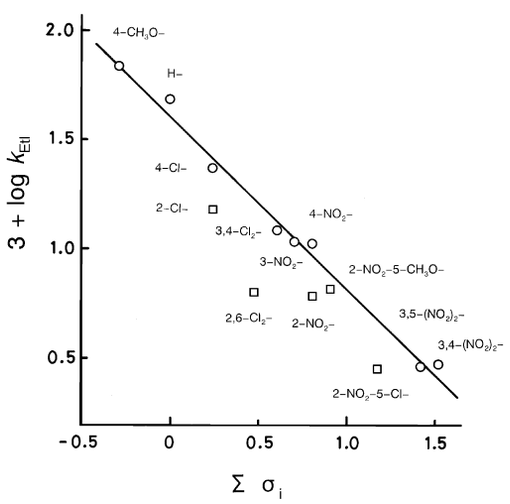

Fig. 1 Plots of logarithmic rates for the reaction of ethyl iodide with substituted benzoate ions: log (k_{EtI}) *vs.* σ value for substituent, *i*, σ_i (at 30 °C in acetonitrile). Rate constants not given in Table 2 are taken from Table 1 of ref. 7. Symbols used are: ○, experimental results for non-*ortho*-substituted benzoate ions; □, experimental results for *ortho*-substituted benzoate ions; —, calculated results from eqn. (3).

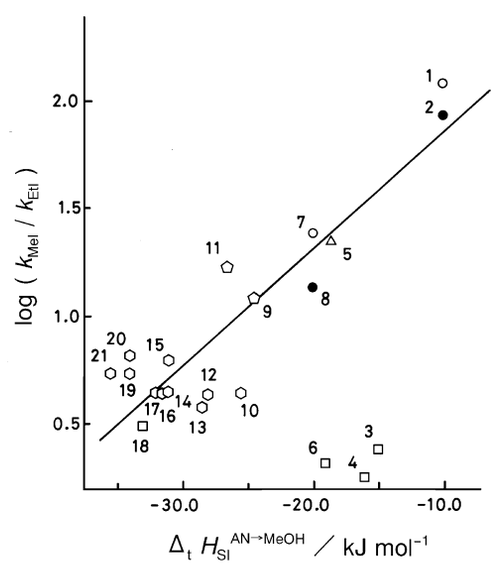

Fig. 2 Empirical correlation between the logarithmic relative rates, log (k_{MeI}/k_{EtI}), and specific interaction enthalpy of nucleophiles, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$. Rate constants in acetonitrile are taken from Tables 1 and 2. Rate constants for the iodide ion reactions are for this reaction: $I^- + MeBr\ (EtBr) \longrightarrow MeI\ (EtI) + Br^-$. Symbols used are: ○, iodide ion and bromide ion in AN; ●, iodide ion and bromide ion in MeOH; □, phenolate ions: △, tetrachlorophthalimidide ion; ⬠, conjugate-base anions of 2,2,5-trimethyl-1,3-dioxane-4,6-dione and of 1,3-dimethylbarbituric acid; ⬡, conjugate-base anions of aliphatic and aromatic carboxylates. ——, calculated results using eqn. (5). Numbers refer to Tables 1 and 2.

When the *ortho*-effect is defined by the term, the ratio of observed rate to calculated rate (k_{obs}/k_{calc}), with k_{calc} being estimated by substituting the relevant specific interaction enthalpy into eqn. (4), we obtain the following *ortho*-effects. For substituted nitrobenzoate ion reactions, the *ortho*-effects are 0.455 for 2-nitrobenzoate, 0.358 for 2-nitro-5-chlorobenzoate and 0.384 for 2-nitro-5-methoxybenzoate. When the *ortho*-effects were estimated by the use of σ values, an exceptional case was observed as mentioned above. However when the quantity $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$ was used, the estimated *ortho*-effects were all comparable. This means that the value of $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$ serves as a relevant explanatory variable incorporating multi-substituted benzoate ion nucleophiles, and the relevancy would reside in the fact that $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$ is a directly determined quantity for a particular system, while the σ value has been determined by recourse to a reference system.

The relative reactivity of methyl iodide to ethyl iodide (k_{MeI}/k_{EtI}) does not stay constant but varies according to the nature of the nucleophile. A general trend is expressed by eqn. (5) (see Fig. 2).

$$\log (k_{MeI}/k_{EtI}) = 2.39 + 5.41 \times 10^{-2} \times \Delta_t H_{SI}^{AN\longrightarrow MeOH} \quad (5)$$
$$n = 18,\ r = 0.91$$

The results of the reactions of 2,4- and 2,6-dinitrophenolate ions and of 2,4-dichloro-6-nitrophenolate ion (no. 3, 4 and 6, *i.e.*, □'s in lower right corner of Fig. 2) indicate a significant downward deviation from the regression line, and are not included in the correlation.

Two types of empirical correlations, *i.e.*, activation enthalpy for methyl iodide reaction *vs.* that for ethyl iodide reaction, $\Delta H^{\ddagger}_{MeI}$ *vs.* $\Delta H^{\ddagger}_{EtI}$, and the differential activation entropy between the methyl iodide and ethyl iodide reaction *vs.* the specific interaction enthalpy for the relevant nucleophile, $(\Delta S^{\ddagger}_{MeI} - \Delta S^{\ddagger}_{EtI})$ *vs.* $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$ are compared in Figs. 3 and 4.

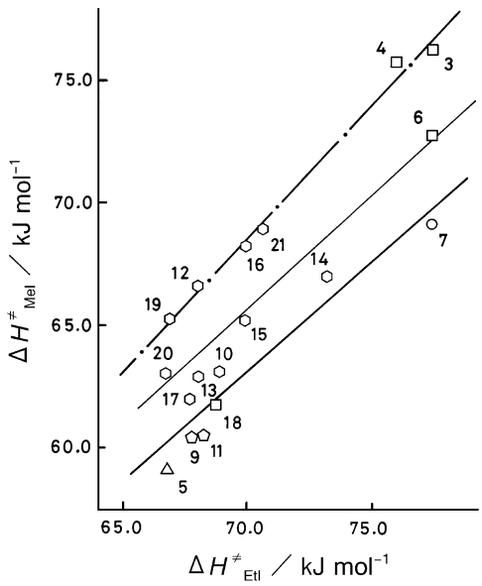

Fig. 3 Empirical correlations between the activation enthalpies for methyl iodide reaction in acetonitrile, $\Delta H^{\ddagger}_{MeI}$, and those for ethyl iodide reaction, $\Delta H^{\ddagger}_{EtI}$. - · -, calculated results for the reactions of the first series of nucleophiles using eqn. (6); —, calculated results for the reactions of the second series of nucleophiles using eqn. (8); ——, calculated results for the third series of nucleophiles using eqn. (10). Symbols refer to those used in Fig. 2 and numbers to those in Tables 1 and 2.

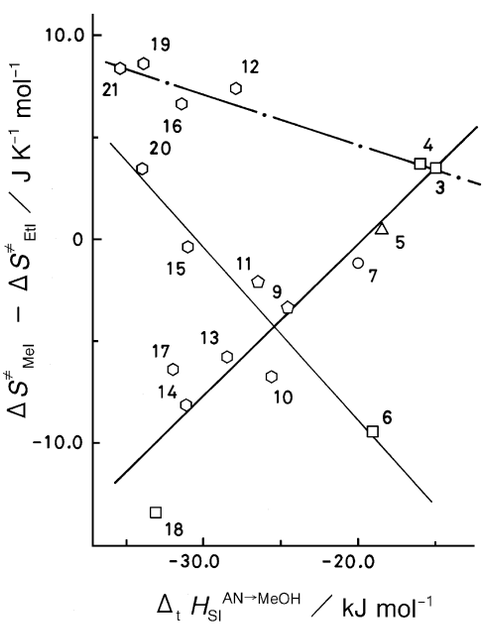

Fig. 4 Empirical correlations between the difference in activation entropy, $(\Delta S^{\ddagger}_{MeI} - \Delta S^{\ddagger}_{EtI})$ and the specific interaction enthalpy, $\Delta_t H_{SI}^{AN\longrightarrow MeOH}$. - · -, calculated results for the first series of nucleophiles using eqn. (7); —, calculated results for the second series of nucleophiles using eqn. (9); ——, calculated results for the third series of nucleophiles using eqn. (11). Symbols refer to those in Fig. 2 and numbers to those given in Tables 1 and 2.

Throughout the correlations shown in Figs. 3 and 4, six reactions, *i.e.*, no. 3, 4, 12, 16, 19 and 21, are suggested to conform to one series of reactions and are correlated by eqns. (6) and (7).

$$\Delta H^{\ddagger}_{MeI} = -7.36 + 1.085 \times \Delta H^{\ddagger}_{EtI} \quad (6)$$
$$n = 6,\ r = 0.99$$

$$(\Delta S^{\ddagger}_{MeI} - \Delta S^{\ddagger}_{EtI}) = -0.165 - 0.243 \times \Delta_t H_{SI}^{AN\longrightarrow MeOH} \quad (7)$$
$$n = 6,\ r = 0.97$$

When the correlation shown in Fig. 3 is the only one available, it is not possible to identify the three reactions, *i.e.*, no. 6, 15 and 20, as a separate series. However, consideration of the correlations shown in Figs. 3 and 4 side by side leads to the conclusion that the three reactions, *i.e.*, no. 6, 15 and 20, conform to one series [eqns. (8) and (9)]. This series will be referred to as the second series.

$$\Delta H^{\ddagger}_{MeI} = 1.11 + 0.923 \times \Delta H^{\ddagger}_{EtI} \quad (8)$$
$$n = 3,\ r = 0.99$$

$$(\Delta S^{\ddagger}_{MeI} - \Delta S^{\ddagger}_{EtI}) = -25.4 - 0.831 \times \Delta_t H_{SI}^{AN\longrightarrow MeOH} \quad (9)$$
$$n = 3,\ r = 0.99$$

Finally, the remaining reactions, *i.e.*, no. 5, 7, 9, 10, 11, 13, 14, 17 and 18, are suggested to form another series [eqns. (10) and (11)] and this will be referred to as the third series.

$$\Delta H^{\ddagger}_{MeI} = 0.913 + 0.890 \times \Delta H^{\ddagger}_{EtI} \quad (10)$$
$$n = 9,\ r = 0.95$$

$$(\Delta S^{\ddagger}_{MeI} - \Delta S^{\ddagger}_{EtI}) = 14.8 + 0.749 \times \Delta_t H_{SI}^{AN\longrightarrow MeOH} \quad (11)$$
$$n = 11,\ r = 0.93$$

It should be noted that nucleophiles having a variety of atoms in the reaction center, *i.e.*, carbon, nitrogen, oxygen and bromine, are included in this third series, although the correlation coefficients are a little lower by comparison to the former correlations.

There are hints that each series of reactions derives mainly from certain structural features in the nucleophile. In most of the first series reactions, the nucleophiles are carboxylate ions, in which two reaction centers are available for reaction. The second series consists of nucleophiles substituted by a chlorine atom at the *para*-position. In nucleophiles classified as belonging to the third series, a single site is available for reaction. Because of steric repulsion, carboxylate and nitro groups in the *o*-nitrobenzoate ions are twisted out of the plane of the phenyl ring. The approach of electrophiles and solvent molecules to one of the oxygen atoms in the carboxylate group is thus limited by the partial overlap of the carboxylate group with the nitro group. In acetonitrile–methanol mixtures, the reaction of the *o*-nitrobenzoate ion with ethyl iodide indicates a quite different pattern of activation enthalpy *vs.* activation entropy correlation, $\delta\Delta H^{\ddagger}$ *vs.* $\delta\Delta S^{\ddagger}$, from those for the reactions of the *p*-nitrobenzoate and 2,6-dichlorobenzoate ions with ethyl iodide.[8] The steric inhibition of reaction and of solvation to one of the oxygen atoms in the carboxylate group has been suggested to be the major cause.[8] Thus, the different classification of the three *o*-nitrobenzoates, no. 13, 14 and 17, from the four carboxylate ions, no. 12, 16, 19 and 21, is supported by molecular mechanistic considerations.

Modern gas phase kinetic studies indicate that the activation enthalpy of ethyl iodide reaction is larger by comparison to that of methyl iodide reaction toward the same nucleophile, while the activation entropy of ethyl iodide reaction is smaller by comparison to that of the methyl iodide reaction.[15,16] Theoretical calculations support this trend.[17] Conventionally this has been accepted as the expected trend for a reaction in which steric crowding at the transition state is the major factor influencing reactivity. For the reactions of the third series, the

activation enthalpy follows such a trend, while the trend in activation entropy is reversed. Furthermore, the differential activation entropy, ($\Delta S^{\ddagger}_{MeI} - \Delta S^{\ddagger}_{EtI}$) increases with increasing specific interaction enthalpy of the nucleophile, $\Delta_t H_{SI}^{AN \longrightarrow MeOH}$ [eqn. (11)].

Specific interaction enthalpy, $\Delta_t H_{SI}^{AN \longrightarrow MeOH}$, was originally introduced to characterize the nucleophile–methanol interaction, arising mainly from hydrogen-bonding interactions, with acetonitrile being used as a reference.[13] Acetonitrile as a solvent possesses a definite hydrogen-bond donor acidity *i.e.* $\alpha = 0.19$,[18] although not as significant as for methanol, $\alpha = 0.93$.[18] In accord with this, the single ion enthalpy of transfer for halide ions from acetonitrile to amides, which do not have any hydrogen-bond donor acidity, *i.e.*, $\alpha = 0$,[18] are all positive.[19] These facts suggest that hydrogen-bonding interactions between acetonitrile and the anion do make a finite contribution to the specific interaction enthalpy, $\Delta_t H_{SI}^{AN \longrightarrow MeOH}$. Recently, partial desolvation around a nucleophilic central atom accompanying activation has been suggested as the major factor determining nucleophilic reactivity in acetonitrile.[6,7] Analysis of kinetic isotope effects on nucleophilic substitution reactions suggest that the nucleophile–α-carbon bond distance is crucial in influencing reaction behavior, including kinetic isotope effects.[20] As the approach of a nucleophile to the reaction center in the alkyl iodide becomes more unfavorable, by substituting one of the α-hydrogen atoms in methyl iodide by a methyl group, partial desolvation around the nucleophilic center is more significant. That is to say, a larger number of solvent molecules will have to be squeezed out of the solvation sphere around the nucleophilic center. This led us to expect that activation enthalpy as well as activation entropy for the ethyl iodide reaction should become larger by comparison to those of the methyl iodide reaction, and, as a result, the difference, $\Delta S^{\ddagger}_{MeI} - \Delta S^{\ddagger}_{EtI}$, should become more negative as the nucleophile is more solvated. According to this line of argument, the empirical correlations, eqns. (10) and (11), would be rationalized as the result of partial desolvation of the solvation sphere around the nucleophilic center for the third series, *i.e.*, nucleophiles with a single reaction site. Empirical correlations eqns. (5) and (11) could be transformed into common units (kJ mol^{-1}), with the former being multiplied by 2.3 RT and the latter by T. The value of the slope reduce to 0.31 for the former and to 0.23 for the latter. This indicates that *ca.* 75% (~0.23/0.31) of the relative reactivity of methyl iodide to ethyl iodide is determined by the partial desolvation discussed above.

In the reaction of carboxylate ions, two types of partial desolvation are taking place. The first is that proceeding around a reacting oxygen, the same type as the one discussed above, and the second is that proceeding around non-reacting oxygen atoms. Characteristic features of methyl iodide reactions which are compared with those of ethyl iodide reactions, are summarized as follows: the activation enthalpy in acetonitrile, is a little smaller, by *ca.* 1.5 kJ mol^{-1}, the reaction enthalpy in acetonitrile is less exothermic by *ca.* 6 kJ mol^{-1}, and the dissociation energy is larger by *ca.* 4 kJ mol^{-1}.[21] Consideration of these results on the basis of such non-linear energy correlations as the Marcus equation[22] would lead us to conclude that the transition state is located a little later along the reaction coordinate for the methyl iodide reaction by comparison to that for the ethyl iodide reaction. This is supported by the larger negative value of the Hammett ρ for the methyl iodide reaction [eqn. (12)] by

$$\log k_{MeI} = -0.592 - 0.92\,\Sigma\sigma_i \qquad (12)$$
$$n = 4,\ r = 0.99$$

comparison to that for the ethyl iodide reaction [eqn. (3)] −0.92 (±0.02) *vs.* −0.78 (±0.03). (The number in parenthesis gives the standard error for a respective ρ value.)

The partial desolvation around the non-reacting oxygen is supposed to proceed further for the methyl iodide reaction, overcompensating the effects brought about around the reacting oxygen atom, resulting in the small negative slope value of eqn. (7). The larger activation enthalpy for the reaction of methyl iodide with the first series nucleophiles by comparison to the activation enthalpy for the third series nucleophiles, *ca.* 5 kJ mol^{-1} (see Fig. 3) would be rationalized as the extra enthalpy that is required for more advanced partial desolvation around a non-reacting oxygen. Eqns. (7) and (11) cross each other at the specific interaction enthalpy, $\Delta_t H_{SI}^{AN \longrightarrow MeOH} = -15.0$ kJ mol^{-1}. This suggests that in the benzoate ion reaction, the contribution from the partial desolvation around the non-reacting oxygen atom becomes negligible at this enthalpy.

Because of the large size and large polarizability of the chlorine atom, a large number of solvent molecules surrounding the chlorine atom substituted at the *para*-position are supposed to sense the variation of charge accompanying activation. The extent of solvent expulsion around the chlorine atom is supposed to be more prominent for a stronger hydrogen-bond accepting anion and for the methyl iodide reaction. This results in the larger negative slope in eqn. (9).

Concluding remarks

Partial desolvation accompanying activation proceeds at various sites in anionic nucleophiles, and every site exerts individual effects on the activation parameters. At least two types of partial desolvation must be taken into account. Firstly, solvent molecules surrounding the nucleophilic center have to be squeezed out of the solvation sphere by the approach of the nucleophile to the electrophile, and the contribution to the activation parameters for the ethyl iodide reaction exceeds that for the methyl iodide reaction. Secondly, accompanying the partial shift of anionic charge from nucleophile to leaving group, solvent molecules surrounding a non-reacting oxygen atom in the carboxylate anion will have to be released; the contribution for the methyl iodide reaction exceeds that for the ethyl iodide reaction, since the transition state is located later. The concept of steric effects in a conventional sense has to be revised, in order to include the fact that partial desolvation accompanying activation becomes more significant, the more unfavorable steric crowding is in the transition state. In order to unravel the molecular mechanistic features operating in solution, examination of both enthalpic and entropic effects is necessary, because enthalpy is a relevant thermodynamic function for probing strong interactions in solution, whilst entropic effects are more related to weak interactions.

Experimental

Materials

Tetramethylammonium salts containing the conjugate base anion of a weak acid were prepared from tetramethylammonium hydroxide and the corresponding acid in methanol according to the procedures described elsewhere.[23] Solvents for recrystallization and the results of elementary analysis are summarized in Table 5. Other compounds were treated as described elsewhere.[24,25]

Product analysis and kinetic measurements

Analysis of reaction products was performed by large scale experiments under the same reaction condition as the kinetic measurements, as described elsewhere.[10] Reaction rates were determined by measuring the concentration of iodide ion that was produced by the reaction, by potentiometric titration using silver nitrate solution,[6,10] at four of the following temperatures: 0.0, 20.0, 30.0, 40.0, 50.0 and 60.0 °C. Experimental errors were estimated from duplicate or triplicate runs to be *ca.* 2% for rate constants, 0.8 kJ mol^{-1} for $\Delta H^{\ddagger}$ and 2.5 J K^{-1} mol^{-1} for $\Delta S^{\ddagger}$.

Table 5 Solvents for recrystallization and elementary analysis

	Solvents	Obs. (%)			Formula	Calc. (%)		
		C	H	N		C	H	N
Tetramethylammonium 2-chlorobenzoate	Acetonitrile	57.2	6.83	6.10	$C_{11}H_{16}NO_2Cl$	57.5	7.02	6.10
Tetramethylammonium 4-chlorobenzoate	Acetonitrile	58.0	6.96	6.21	$C_{11}H_{16}NO_2Cl$	57.5	7.02	6.10
Tetramethylammonium 2-NO_2-5-chlorobenzoate	Acetonitrile	48.0	5.47	10.4	$C_{11}H_{15}N_2O_4Cl$	48.1	5.50	10.2
Tetramethylammonium 2-NO_2-5-CH_3O-benzoate	Acetonitrile	53.3	6.72	10.45	$C_{12}H_{18}N_2O_5$	53.3	6.71	10.4
Tetramethylammonium 2,4-dichloro-6-nitrophenolate	Butan-2-one	42.7	4.76	9.93	$C_{10}H_{14}N_2O_3Cl_2$	42.7	5.03	9.97

Enthalpy of solution measurements

Enthalpies of solution for tetramethylammonium salts, Δ_sH, were measured with a Tokyo Riko twin isoperibol calorimeter and the final concentration range of the salts was *ca.* (0.4–1.5) × 10^{-2} mol dm^{-3}.[6,13] Experimental errors were estimated to be *ca.* 1 kJ mol^{-1}.

Enthalpy of reaction measurements

Enthalpies of reaction, Δ_rH, were measured with a Tokyo Riko twin isoperibol calorimeter, by dissolving the relevant salt, sealed into an ampoule, in an acetonitrile solution containing a large excess of methyl iodide (or ethyl iodide) over the relevant salt and by measuring the heat evolved.[7] The contribution from the enthalpy of solution of the relevant salt into acetonitrile was corrected afterwards. Experimental errors were estimated from usually four to six determinations to be *ca.* 2 kJ mol^{-1}.

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