Reaction enthalpy of nucleophilic substitution of ethyl iodide in acetonitrile and its mechanistic significance

Yasuhiko Kondo,* Tamio Tsukamoto and Naoko Kimura

Department of Natural Science, Osaka Women's University, Sakai, Osaka 590, Japan

Enthalpies of reaction for nucleophilic substitution of ethyl iodide have systematically been determined in acetonitrile. Through the concurrent analysis of empirical correlations between the reaction enthalpies and the specific interaction enthalpies for relevant anions with those between the logarithmic rates and the specific interaction enthalpies, partial desolvation accompanying activation has been deduced to be the major contributor to activation thermodynamic parameters, while the propensity of the reacting central atom in the nucleophilic anion plays a crucial role in determining reaction thermodynamic parameters. Semi-empirical molecular orbital calculations have supported these ideas. The application of the Marcus equation to the analysis of reaction characteristics in these reactions is discussed.

Empirical correlations between activation and reaction thermodynamic parameters have long been used as one of the fundamental procedures for deducting important information about the character of chemical reactions based on experimental results.[1–4] Various models and theoretical approaches have been developed and used to rationalize or critically examine the intuitive notions derived through these correlations.[1–13]

Except for proton transfer reactions, the low rate of most organic reactions in non-aqueous solvents prevents the accurate and concurrent determination of the activation and reaction thermodynamic parameters required for mechanistic investigations of fundamentally important organic reactions.[14,15]

For reactions in solution, solvation of the participating species plays a crucial role in the reaction mechanism. Considering the difficulties in determining thermodynamic parameters of solvation at relevant experimental conditions, exploration of any other easily determined thermodynamic parameters that are closely related to the solvation of the participating species, especially of ionic species which play an important role in the reaction, has been eagerly awaited in order to understand the mechanistic character of a chemical reaction from the point of view of solute–solvent interactions.

In previous work, the specific interaction enthalpy for a nucleophilic anion, $\Delta_t H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}$, the enthalpy of transfer of a single ion from acetonitrile to methanol, which provides a scale of chemical interactions such as hydrogen-bonding between the nucleophilic anion and methanol, has been found to serve as a reactivity scale for the nucleophilic anion.[16] In this work reaction enthalpies for the nucleophilic substitution of ethyl iodide in acetonitrile [reaction (a)] are systematically determined, the

$$\mathrm{Nu}^- + \mathrm{EtI} \longrightarrow \mathrm{EtNu} + \mathrm{I}^- \qquad \text{(a)}$$

physical significance of empirical correlations involving reaction enthalpies from the view of solute–solvent interactions is discussed and some of these ideas are examined through semi-empirical molecular orbital calculations.

Results

The enthalpies of reaction, $\Delta_r H$, are summarized in Table 1. The rate constants, activation parameters and the specific interaction enthalpies for the nucleophilic anion, $\Delta_t H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}$ which have been published elsewhere[17–26] are also included in the table to allow comprehensive discussion.

The rate constants cover the range of two orders of magnitude with some overlap between the reaction groups, and the reactions can be roughly classified into three groups according to the value of the reaction enthalpy, *i.e.* the halide ion group ($\Delta_r H > -13.0$ kJ mol^{-1}), the oxygen anion group ($\Delta_r H$, -60.0–-87.0 kJ mol^{-1}) and the nitrogen anion group ($\Delta_r H$, -112.0–-143.0 kJ mol^{-1}).

Discussion

Statistical analysis of the logarithm of the rate with respect to the specific interaction enthalpy for the nucleophilic anion led to eqns. (1) and (2).[16]

For carboxylate ion reactions:

$$3 + \log k = -1.53 - 8.76 \times 10^{-2} \times \Delta_t H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}} \qquad (1)$$

$$r = -0.97, n = 13$$

For imidide ion reactions:

$$3 + \log k = -0.42 - 7.23 \times 10^{-2} \times \Delta_t H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}} \qquad (2)$$

$$r = -0.95, n = 10$$

From eqns. (1) and (2), and the observation that the activation enthalpies for the carboxylate ion reactions are large in comparison to those for imidide ion reactions, when compared at the same value of the interaction enthalpy, $\Delta_t H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}$, it is concluded that the partial desolvation at the transition state is more pronounced for carboxylate ion reactions in comparison to that for imidide ion reactions.[16]

The same conclusion can be reached by the following analysis of activation parameters. Statistical analyses of the activation enthalpy with respect to the logarithmic rate give eqns. (3) and (4).

For carboxylate ion reactions:

$$\Delta H^\ddagger = 71.5 - 4.42 \times (3.0 + \log k) \qquad (3)$$

$$r = 0.86, n = 13$$

For imidide ion reactions:

$$\Delta H^\ddagger = 71.8 - 5.86 \times (3.0 + \log k) \qquad (4)$$

$$r = 0.92, n = 9$$

Eqns. (3) and (4) indicate that for the carboxylate ion reactions 76% of the total effect on the activation free energy, induced by varying the structure of the nucleophile, originates in the activation enthalpies and the remaining 24% in the

Table 1 Rate constants and activation parameters for reaction (a) in acetonitrile at 30 °C, and specific interaction enthalpies for the nucleophilic anion, $\Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}$ and the reaction enthalpies, $\Delta_{\mathrm{r}}H$ at 25 °C

Nucleophile	$10^2\ k_{\mathbf{AN}}/\mathrm{dm^3\ mol^{-1}\ s^{-1}}$	$\Delta H^{\ddagger}{}_{\mathbf{AN}}/\mathrm{kJ\ mol^{-1}}$	$\Delta S^{\ddagger}{}_{\mathbf{AN}}/\mathrm{J\ K^{-1}\ mol^{-1}}$	$\Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}/\mathrm{kJ\ mol^{-1}}$	$\Delta_{\mathrm{r}}H/\mathrm{kJ\ mol^{-1}}$
Chloride ion	1.24[a]	79.1[a]	−20.6[a]	−31.0[a]	−12.7
Bromide ion	1.08[b]	77.4[b]	−27.2[b]	−20.0[b]	−4.6
4-Nitro-3-cresolate ion	0.550[c]	67.0[c]	−67.3[c]	−33.0[c]	−85.9
4-Nitrophenolate ion	0.279[c]	68.7[c]	−67.3[c]	−33.0[c]	−82.5
Adamantane-1-carboxylate ion	38.0[d]	56.5[d]	−66.7[d]	−49.5[e]	−76.7
Diethylacetate ion	35.6[f]	60.8[f]	−53.1[f]	−48.0[g]	−82.4
Pivalate ion	28.6[d]	63.2[d]	−47.0[d]	−43.5[e]	−86.5[h]
4-Biphenylacetate ion	10.2[i]	62.5[i]	−57.9[i]	−38.0[i]	−75.6
2-Chlorophenylacetate ion	6.86[i]	61.6[i]	−64.1[i]	−37.0[i]	−74.4
Diphenylacetate ion	6.74[f]	63.1[f]	−59.3[f]	−35.5[f]	−72.8
Phenoxyacetate ion	2.09[i]	66.8[i]	−56.8[i]	−34.0[i]	−67.1
4-Methoxybenzoate ion	6.76[f]	66.8[f]	−47.1[f]	−39.0[g]	−78.3
Benzoate ion	4.78[d]	61.9[d]	−66.0[d]	−36.0[e]	−74.2[h]
3-Nitrobenzoate ion	1.08[i]	67.4[i]	−60.4[i]	−29.0[g]	−69.0
4-Nitrobenzoate ion	1.07[d]	68.0[d]	−58.3[d]	−28.0[e]	−66.0
3,5-Dinitrobenzoate ion	0.290[i]	68.8[i]	−66.7[i]	−25.5[g]	−64.0
3,4-Dinitrobenzoate ion	0.296[i]	68.4[i]	−67.8[i]	−24.0[e]	−60.0
3,3-Dimethylglutarimide ion	148.0[j]	51.0[j]	−73.6[j]	−49.0[k]	−135.1
cis-Hexahydrophthalimide ion	28.2[i]	56.6[i]	−68.9[i]	−37.0[k]	−142.4
cis-1,2,3,6-Tetrahydrophthalimide ion	21.1[i]	62.0[i]	−53.5[i]	−35.0[i]	−139.8
Succinimide ion	16.5[h]	58.4[h]	−67.4[h]	−37.0[h]	−138.3[h]
1-Methylhydantoin anion	10.5[j]	60.6[j]	−63.9[j]	−40.0[k]	−139.6
Phthalimide ion	6.43[h]	62.6[h]	−61.4[h]	−26.0[h]	−134.7[h]
2,3-Naphthalimide ion	5.74[i]	61.4[i]	−66.3[i]	−29.5[k]	−136.2
4-Nitrophthalimide ion	1.54[j]	56.7[j]	−92.7[j]	−22.5[k]	−127.8
3-Nitrophthalimide ion	1.14[j]	63.9[j]	−71.5[j]	−23.0[k]	−130.9
3,4,5,6-Tetrachlorophthalimide ion	0.615[j]	66.8[j]	−67.0[j]	−18.5[k]	−111.6

Data from: [a] Ref. 17. [b] Ref. 18. [c] Ref. 19. [d] Ref. 20. [e] Ref. 21. [f] Ref. 22. [g] Ref. 23. [h] Ref. 24. [i] Ref. 16. [j] Ref. 25. [k] Ref. 26.

activation entropies, *i.e.* in the $T\Delta S^{\ddagger}$ term, while for the imidide ion reactions nearly 100% of the effect originates in the activation enthalpies and only a negligible amount in the activation entropies, *i.e.* the activation entropy is not altered by a change in the structure of the nucleophile. As anticipated from eqns. (1) and (2), the more reactive nucleophiles are the stronger hydrogen-bond accepting anions. For carboxylate ion reactions, as the hydrogen-bond accepting capacity increases, larger amounts of solvent molecules are believed to be released from the solvation shell around the nucleophilic anion on going from the initial to the transition state, resulting in the increasing value of the activation entropy with increasing nucleophilic reactivity of the anion.

Statistical analyses of reaction enthalpy, $\Delta_{\mathrm{r}}H$ with respect to the enthalpy, $\Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}$ led to eqns. (5)–(7).

For halide ion reactions, with the relation, $\Delta_{\mathrm{r}}H = 0$ for the identity reaction between the iodide ion and ethyl iodide being taken into account:

$$\Delta_{\mathrm{r}}H = 6.57 + 0.607 \times \Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}} \qquad (5)$$
$$r = 0.99,\ n = 3$$

For carboxylate ion reactions:

$$\Delta_{\mathrm{r}}H = -37.2 + 1.01 \times \Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}} \qquad (6)$$
$$r = 0.94,\ n = 12$$

For imidide ion reactions:

$$\Delta_{\mathrm{r}}H = -115.9 + 0.651 \times \Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}} \qquad (7)$$
$$r = 0.91,\ n = 8$$

The adamantane-1-carboxylate ion reaction was supposed to fall into the regression equation (6), and the 3,3-dimethylglutarimidide ion and 3,4,5,6-tetrachlorophtalimidide ion reactions were supposed to fall into the regression equation (7), since in the former analyses the adamantane-1-carboxylate ion reaction was grouped into eqn. (1), and the 3,3-dimethylglutarimidide ion and 3,4,5,6-tetrachlorophtalimidide ion reactions were into eqn. (2). However, this was not the case. One point to note is that all three reactions which have been eliminated from the above analyses are grouped together in log *k vs.* $\Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}$ correlations.[16] The specific interaction enthalpy has its molecular mechanistic origin in hydrogen-bonding *i.e.* partial bonding between the nucleophilic anion and methanol, while the enthalpy of reaction is a differential enthalpy between the reactants and products. The enthalpy of reaction being composed of such large quantities as bond-dissociation energy, electron affinity and energy of solvation. When non-concordant perturbations are induced in the constituent terms through seemingly regular structural variation, the perturbations could not effectively be compensated for and as a result the sum of these effects might not successfully be simulated by parameters pertinent to the structural perturbation in the reactants, such as the enthalpy, $\Delta_{\mathrm{t}}H_{\mathbf{SI}}^{\mathbf{AN}\rightarrow\mathrm{MeOH}}$.

When the regression eqns. (1) and (2) are expressed in terms of energy by multiplying by $2.303RT$ (in kJ $\mathrm{mol^{-1}}$), the coefficients reduce to 0.508 for eqn. (1) and 0.419 for eqn. (2). These coefficients, smaller in comparison to those in eqns. (6) and (7), indicate that structural perturbations introduced into the nucleophiles are reflected less in the activation free energy than in the reaction enthalpy. The ratio of the coefficients, 0.50 (0.508/1.01) for carboxylate ion reactions and 0.64 (0.419/0.651) for imidide ion reactions, are comparable to the value of the slope of a plot of log *k vs.* log $K_{\mathbf{eq}}$, *i.e.* 0.61 for the arenesulfonate ion and methyl arenesulfonate reaction and 0.38 for phenyl selenide ion and aryl methyl selenide reaction in sulfolane.[27,28] For the reactions whose behaviour can be predicted by such non-linear kinetic *vs.* thermodynamic correlations as typified by Marcus and related theory,[5–10] the coefficients of extended Brønsted treatment decrease as the reaction becomes more exothermic. The observation of ratios of comparable range, 0.5 ± 0.1, as described above *i.e.* 0.61 and 0.38 for the reactions of which are nearly thermoneutral[27,28] and 0.50 and 0.64 for those which have high exothermicity, suggests that $\mathrm{S_N2}$ reactions in solution are too complicated to be explained by these theories.

In order to evaluate the contribution of terms intrinsic to the reaction in solution, kinetic barriers (or logarithmic rates) for reactions that have a comparable range of solvational terms will have to be estimated and compared. Substitution of the enthalpy, $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN}\rightarrow\mathrm{MeOH}}$, for the iodide ion into eqns. (1) and (2) gives the logarithmic rates for the reactions of the hypothetical carboxylate and imidide ions which have the same specific interactions as the iodide ion. The difference between the two reactions amounts to 0.96 (5.5 kJ mol^{-1} when multiplied by 2.303RT) with the imidide ion reaction being the more reactive. Furthermore, in the correlations, the bromide ion reaction falls in the imidide ion reaction series and the chloride ion reaction into the carboxylate ion reaction series.[16] Accordingly, the maximum difference between the three reaction series, halide ion, carboxylate ion and imidide ion, is 5.5 kJ mol^{-1}. The same procedures applied to eqns. (5)–(7), led to the enthalpy changes $\Delta_{\mathrm{r,h}}H$ for the hypothetical reactions mentioned above, *i.e.* 0.5, −47.3 and −122.4 kJ mol^{-1} for the halide ion, carboxylate ion and imidide ion reactions, respectively. A much larger difference in the enthalpy $\Delta_{\mathrm{r,h}}H$ between the three reaction series is seen in comparison with the smaller difference in activation free energy, 5.5 kJ mol^{-1}, with the imidide ion reaction being more reactive. The results all indicate that the character of the reacting central atom in the nucleophilic anion is not fully reflected in the activation free energy, and give support to the idea that activation parameters are controlled more by partial desolvation of the nucleophilic anion than by partial bond-making and bond-breaking between reacting atoms. Although recent high level *ab initio* molecular orbital calculations indicate that intrinsic barriers in the gas phase are linearly correlated with the electron affinities of nucleophilic anions,[29] in solution these effects would be overcompensated by solvational effects resulting in the two empirical correlations, eqns. (1) and (2).

In the hypothetical reaction enthalphy, $\Delta_{\mathrm{r,h}}H$, the contribution from the differential solvation between nucleophilic anion and leaving anion is likely to be mostly compensated for and the contribution from the character of the central atom in the nucleophile would be greater. One way to evaluate this possibility is to estimate the enthalpy changes using electron affinity and bond-dissociation energy. The electron affinities of the relevant anions are 295.1, 303.9 and 151.5 kJ mol^{-1} for the iodide ion, propionate ion and N-methylanilide ion (as a model compound for the imidide ion) respectively.[30] Bond-dissociation energies are 205.0, 238.0 and 254.0 kJ mol^{-1} for C–I, C–O and C–N bond respectively.[31] The estimated energy changes are 0, −24.2 and −192.6 kJ mol^{-1} for the iodide ion, carboxylate ion and imidide ion reactions, respectively and are comparable to the hypothetical reaction enthalpy, $\Delta_{\mathrm{r,h}}H$ for the respective reactions as derived above. This suggests that the reaction enthalpy for the nucleophilic substitution in acetonitrile, $\Delta_r H$, is controlled mainly by the character of the central atom in the nucleophile.

As a mean of deducing the characteristic features of a reaction from an experimental view point, empirical correlation between activation and thermodynamic quantities has long been taken into account and the Marcus equation has often been invoked to give theoretical support for such procedures.[5–10] However, experimental difficulties usually only allowed thermodynamic quantities to be determined over a limited range, $\Delta G^\circ \sim 0$. In order to critically examine the credibility of the deductions made using procedures, the concurrent determination of kinetic and equilibrium parameters over fairly wide ranges is desirable. Activation enthalpies for the forward reaction, $\Delta_{\mathrm{for}}H^\ddagger$ (by definition equal to the observed activation enthalpy, $\Delta H^\ddagger$) are plotted against the observed enthalpy of the reaction, $\Delta_r H$, in the left half of Fig. 1.

$$\mathrm{Nu^- + EtI \underset{\Delta_{rev}H^\ddagger}{\overset{\Delta_{for}H^\ddagger}{\rightleftharpoons}} EtNu + I^-}$$

Activation enthalpies for the reverse reaction, $\Delta_{\mathrm{rev}}H^\ddagger$ have been calculated from experimental values of activation and reaction enthalpies on the basis of eqn. (8) and are plotted

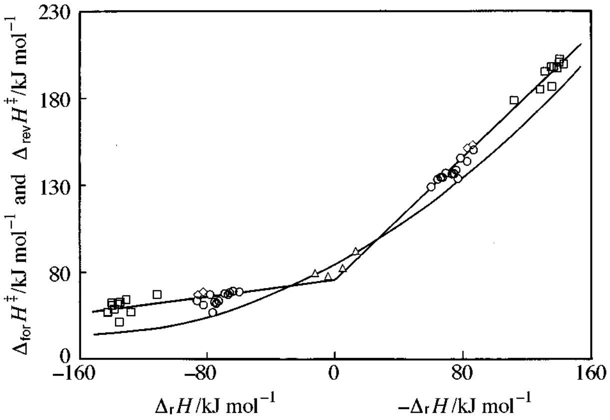

Fig. 1 Empirical correlations between activation and reaction enthalpies. The left half of the figure shows the observed activation enthalpies plotted against the observed reaction enthalpies ($\Delta_r H$) either for reaction (a) in acetonitrile. The right half of the figure shows the activation enthalpies for the reverse reaction as calculated by eqn. (8) plotted against the reaction enthalpies for the reverse direction ($-\Delta_r H$) (see text). △, halide ions; ◇, phenolate ions; ○, carboxylate ions; □, imidide ions. The straight line plot shows calculated values by eqns. (9) and (10); the curved plot shows calculated values according to eqn. (11) with $w = 44.0$ and $\Delta H^\ddagger_0 = 40.0$ (both in kJ mol^{-1}).

$$\Delta_{\mathrm{rev}}H^\ddagger = \Delta H^\ddagger - \Delta_r H \qquad (8)$$

against the negative of the observed reaction enthalpy ($-\Delta_r H$) in the right half of Fig. 1. Regression analyses of the activation enthalpy with respect to the reaction enthalpy leads to eqns. (9) and (10) and regression lines are also shown in Fig. 1.

$$\Delta_{\mathrm{for}}H^\ddagger = 75.1 + 0.121\Delta_r H \qquad (9)$$
$$r = 0.76,\ n = 27$$

$$\Delta_{\mathrm{rev}}H^\ddagger = 75.1 + 0.878(-\Delta_r H) \qquad (10)$$
$$r = 0.99,\ n = 27$$

Theoretical values of activation enthalpy were calculated according to Marcus theory which has been simplified with the assumption that the work term is equal to w for both forward and reverse reactions,[5–10] and which has been transformed into enthalpy, eqn. (11) with the assumption, $w = 44.0$ and

$$\Delta H^\ddagger = w + \Delta H_0^\ddagger[1 + \Delta_r H/(4\Delta H_0^\ddagger)]^2 \qquad (11)$$

$\Delta H_0^\ddagger = 40.0$ (in kJ mol^{-1}) and are also shown in Fig. 1 for comparison.

The relatively large work term, w, in comparison to the intrinsic barrier, $\Delta H_0^\ddagger$, may agree with the notion deduced from the empirical analysis that a significant contribution to the activation enthalpy is made by the partial desolvation accompanying activation. When the Marcus equation appropriately simulates the reaction behaviour, the value of the slope should be 0.5 over the narrow region $\Delta_r H \sim 0$ and the correlation line should be curved as shown in Fig. 1.

In this work forward reactions are downhill by definition over the series and activation parameters have been found to be more affected by the partial desolvation of the nucleophilic anion on going from the initial to the transition state, while in the reaction enthalpy contributions from the solvation exchange accompanying the reaction are minor. The major part of the enthalpy contributions is presumed to be determined by the character of the reacting central atom in the nucleophilic anion as can be clearly seen by grouping of the reaction

Table 2 Enthalpies of formation and of solvation calculated through MNDO/PM3 and MNDO/PM3/COSMO procedures, $\Delta_f H_{calc}$, and $\Delta_{solv} H_{calc}$, and comparison of the calculated activation and reaction enthalpies, $\Delta H^{\ddagger}_{calc}$ and ΔH°_{calc}, with experimental values, $\Delta H^{\ddagger}_{exp}$ and $\Delta_r H$ (in kJ mol^{-1})

	$\Delta_f H_{calc}$					$\Delta H^{\ddagger}$ and ΔH°			
	Nu^-	CH_3I	TS^-	NuMe	I^-	$\Delta H^{\ddagger}_{calc}$	ΔH°_{calc}	$\Delta H^{\ddagger}_{exp}$	$\Delta_r H$
Phenoxyacetate + methyl iodide reaction									
Gas	−544.3	39.5	−501.6	−388.6	−270.4 (−188[a])	3.2	−154.2 (−71.8)	—	—
Acetonitrile	−891.7	27.9	−779.7	−440.8	−599.8(−517.4)	84.1	−176.8 (−94.4)	66.8[d]	−67.1[d]
$\Delta_{solv} H_{calc}$	−347.4	−11.6	−278.1	−52.2	−329.4	80.9[b]	−22.6[c]		
Phthalimide + methyl iodide reaction									
Gas	−309.1	39.5	−268.7	−191.9	−270.4 (−188[a])	0.9	−192.7 (−110.3)	—	—
Acetonitrile	−658.5	27.9	−541.5	−248.6	−599.8 (−517.4)	89.1	−217.8 (−135.4)	62.6[d]	−134.7[d]
$\Delta_{solv} H_{calc}$	−349.4	−11.6	−272.8	−56.7	−329.4	88.2[b]	−25.1[c]		

[a] Ref. 30. [b] Differential solvation enthalpies between transition-state anion and reactants. [c] Differential solvation enthalpies between products and reactants. [d] Experimental results for reaction (a).

enthalpies into three series (see Fig. 1). This is responsible for a smaller slope value, 0.121, and the lower correlation coefficient in eqn. (9). In contrast, the reverse reactions are uphill over the series and reaction enthalpy forms the major contribution the activation enthalpy [see eqn. (8)]. This is reflected in a larger slope value, 0.878, and the higher correlation coefficient in eqn. (10). When the reaction systems are varied from downhill to uphill, the empirical correlations, eqns. (9) and (10) introduce a discontinuous change in the slope value from 0.121 to 0.878 at the boundary $\Delta_r H = 0$ while the Marcus eqn. (11) changes continuously. On inspection it is not easy to decide whether the correlation is curved or not, and which of the two correlations more appropriately simulates the reaction behaviour. For methyl transfer reactions the contribution of the Marcus quadratic term has been documented as not being a major component of the calculated rate.[27,28] The results shown in Fig. 1 demonstrate.

Semi-empirical molecular orbital (MNDO/PM3 and MNDO/PM3/COSMO)[32] calculations give quantitative supports for some of the ideas deduced through empirical procedures. For the two reactions shown in Table 2 calculated activation enthalpies are, although somewhat larger, comparable to the experimental values. When the enthalpy of formation of the iodide ion in the gas phase is replaced by the experimental value (the value in parentheses) as described previously,[16] the calculated enthalpy of reaction for the imidide ion reaction (the value in parentheses) is very close to the experimental value, and for the carboxylate ion reaction, although slightly more exothermic, comparable to the experimental value. The more exothermic character of imidide ion reaction in comparison to the carboxylate ion reaction could also successfully be simulated by these procedures. Differential solvation energies between a transition-state anion and a pair of reactants, although somewhat larger, are comparable to the experimental activation enthalpies. This supports the notion that partial desolvation accompanying activation is dominant in determining the activation thermodynamic parameters. Differential solvation enthalpies between a pair of reactants and a pair of products contribute to the observed enthalpies of reaction by *ca.* one-third for the carboxylate ion reaction and by much less for the imidide ion reaction (see Table 2). This supports the view that the reaction enthalpy is mainly controlled by molecular characteristics in the gas phase, since solvational terms are largely compensated for between a pair of products and of reactants.

Conclusion

The specific interaction enthalpy for a nucleophilic anion, $\Delta_t H_{SI}^{AN \rightarrow MeOH}$, is very valuable for deducing characteristic features of nucleophilic reactions through empirical correlation with logarithmic rates and with reaction enthalpies. Some of the conclusions arrived at through empirical analysis have been given theoretical support through semi-empirical molecular orbital calculations. These are that partial desolvation accompanying activation is dominant in determining activation thermodynamic parameters, while molecular characteristics in the gas phase are the major factor for determining reaction parameters, since solvational terms are cancelled out in these quantities. A combination of empirical analysis with theoretical procedures is indispensable for molecular mechanistic studies on chemical reactions.

Experimental

Materials

Tetraalkylammonium salts containing a nucleophilic anion were prepared from tetraalkylammonium hydroxide and the relevant conjugate acid in methanol and purified as described elsewhere.[16–26] Other materials were treated as described elsewhere.[16–26]

Enthalpy of reaction measurements

Enthalpies of reaction were measured in acetonitrile by either of the two methods given below using a twin isoperibol calorimeter (Tokyo Riko TIC-2D).[16–26] The half-life of the reaction was controlled to be *ca.* 2 min by adjusting the excess concentration of ethyl iodide. Experimental errors were estimated to be less than ±3 kJ mol^{-1} from three to six determinations.

Method 1. A solution of ethyl iodide in acetonitrile (usually 100 cm^3) and the tetraalkylammonium salt containing the relevant nucleophilic anion sealed in an ampoule were kept in a calorimeter cell. After thermal equilibration, the ampoule was broken and the heat evolved was measured. After correcting for the enthalpy of solution of the tetraalkylammonium salt in acetonitrile, the enthalpy of reaction was calculated.

Method 2. A solution of the tetraalkylammonium salt containing the relevant nucleophilic anion (usually 100 cm^3) and a solution of ethyl iodide in acetonitrile sealed in an ampoule were kept in a calorimeter cell. After thermal equilibration, the ampoule was broken and the heat evolved was measured. After correction for enthalpy of dilution for ethyl iodide in acetonitrile, the enthalpy of reaction was calculated.

Theoretical calculations

Semi-empirical molecular orbital calculations in the gas phase were performed with MNDO/PM3 procedures[32] with options being kept as defaults and in acetonitrile MNDO/PM3/COSMO procedures were used[32] using 35.94 as the relative permittivity for acetonitrile with other options being kept as defaults. In order to shorten the computation time, methyl iodide was used as the substrate in place of ethyl iodide.

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