Solvation and nucleophilic reactivity of conjugate-base anions of 5-methyl Meldrum's acid and of 3,3-dimethylbarbituric acid in acetonitrile–methanol

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Conjugate-base anions of 5-methyl Meldrum's acid and of 1,3-dimethylbarbituric acid give comparable nucleophilic reactivity toward ethyl iodide in acetonitrile and also have specific interaction enthalpies, $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ comparable with those of 3,5-dinitrobenzoate ion and of phthalimidide ion, while pK_a values in the aqueous phase vary significantly among the series. The results lend support to the view that nucleophilic reactivity in acetonitrile is controlled mainly by the partial desolvation of nucleophilic anions accompanying activation. Variation of the specific interaction enthalpy for the present reactions on going from the initial to the transition-state is much smaller by comparison to those for imidide ion and carboxylate ion reactions. Theoretical analysis of the enthalpy with use of MNDO/PM3 procedures indicates that the steric inhibition of the approaching solvent molecule to the carbonyl oxygen by the group coordinated to the central atom is the main factor bringing about the smaller variation.

In solution chemistry it has long been accepted that oxygen acids are more acidic than nitrogen acids and nitrogen acids are more acidic than carbon acids. Recently quantitative support has been given to this notion through equilibrium measurements in DMSO.[1] In this respect the high acidity of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and of pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (barbituric acid) *i.e.*, pK_a's in H_2O are 4.8[2] and 4.04,[3] is very intriguing since both are carbon acids although activated by geminal carbonyl groups, and attention has been paid to interpreting the high acidity from a physico-chemical viewpoint.[2–7]

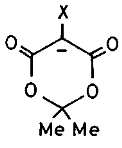
Quantitative evaluation of nucleophilic reactivity has been a long standing subject in physical organic chemistry.[8–12] Recently, empirical correlations between the logarithmic rate and the specific interaction enthalpy for a nucleophile, $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ (a measure of the hydrogen-bond accepting basicity for a nucleophile) have been documented for nucleophilic substitution reactions in acetonitrile.[13,14] From the correlations it has been concluded that the nucleophilic reactivity of anions is more influenced by a partial desolvation of the nucleophile on going from the reactant to the transition state by comparison to intrinsic properties of the nucleophile.[13,14]

Comparative studies on kinetic reactivities as well as on equilibrium reactivities for the conjugate-base anion of Meldrum's acid as a nucleophile with those for carboxylate ions and for imidide ions would be quite worthwhile for deducing essential features of nucleophilic substitution reactions in solution.

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

χ_{MeOH}	TMA MMA	TEA MA	TMA PhMA	TMA DMBarb
0	14.5	15.1	19.0	15.0
0.10	−3.96	−1.92	6.49	−5.75
0.25	−7.35	−4.10	3.13	−8.98
0.50	−5.55	−2.27	4.16	−6.12
0.75	−2.01	0.10	7.81	−1.16
1.0	4.45	6.03	14.3	6.37

TMA, tetramethylammonium; TEA, tetraethylammonium; MMA, conjugate-base anion of 5-methyl Meldrum's acid; MA, conjugate-base anion of Meldrum's acid; PhMA, conjugate-base anion of 5-phenyl Meldrum's acid; DMBarb, conjugate-base anion of 1,3-dimethylbarbituric acid; χ_{MeOH}, mole fraction of methanol.



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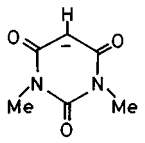


B

In this work, following the enthalpy of solution measurements for the tetraalkylammonium salts containing conjugate-base anions of Meldrum's acid and its derivatives, **A** (X = H, Me, Ph) and of 1,3-dimethylbarbituric acid, **B**, rates of reaction of the conjugate-base anion of 5-methyl Meldrum's acid and of 1,3-dimethylbarbituric acid with ethyl iodide will be determined in acetonitrile–methanol mixtures and the solvation properties will be discussed on the basis of semi-empirical molecular orbital calculations.

$$\mathrm{Nu^- + Et{-}I \longrightarrow Nu{-}Et + I^-}$$

Results

Enthalpies of solution, $\Delta_s H$ for the tetraalkylammonium salts containing the conjugate-base anion of Meldrum's acids and of 1,3-dimethylbarbituric acid have been measured in acetonitrile–methanol mixtures and are summarized in Table 1. Single-ion

Table 2 Single ion enthalpies of transfer from acetonitrile to acetonitrile–methanol mixtures, $\Delta_t H^{AN\rightarrow mix}$ and interaction parameters

χ_{MeOH}	MMA	MA	PhMA	DMBarb	TS^-(MMA)	TS^-(DMBarb)
0	0	0	0	0	0	0
0.10	−17.6	−16.6	−11.6	−19.85	−3.7	−5.65
0.25	−20.55	−18.25	−14.6	−22.7	−2.85	−7.20
0.50	−19.7	−17.0	−14.5	−20.8	0.8	−4.10
0.75	−16.8	−14.75	−11.5	−16.5	2.5	2.80
1.0	−12.75	−10.1	−7.4	−11.3	16.85	15.7
$\Delta_t H_{PHYS}{}^{AN\rightarrow MeOH}$	11.75	11.4	12.1	15.2	25.85	31.7
$\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$	−24.5	−21.5	−19.5	−26.5	−9.0	−16.0
K_{se}	30.0	42.0	18.0	40.0	18.0	12.0
Z	2.2	—	—	2.3	−0.6	1.5

β_{PHYS}'s are 395 and 445 K for MMA and DMBarb reaction. TS^-(MMA) and TS^-(DMBarb), transition-state anions for the reaction of the conjugate-base anion of 5-methyl Meldrum's acid and of 1,3-dimethylbarbituric acid.

Table 3 Rate constants and activation parameters in acetonitrile–methanol mixtures (30 °C)

	5-Methyl Meldrum's acid anion + EtI			1,3-Dimethylbarbiturate + EtI		
χ_{MeOH}	$k/10^{-6}$ dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	$k/10^{-6}$ dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
0	1.43×10^3	67.7	−76.2	1.80×10^3	68.2	−72.5
0.10	1.11×10^2	81.6	−51.6	1.42×10^2	82.4	−46.6
0.25	29.0	85.5	−49.9	40.9	83.8	−52.5
0.50	8.64	88.6	−49.7	12.9	85.3	−57.0
0.75	3.83	87.9	−58.8	5.24	88.4	−54.5
1.0	1.24	98.9	−31.9	1.73	96.8	−35.9

enthalpies of transfer from acetonitrile to mixed solvents, $\Delta_t H^{AN\rightarrow mix}$ have been calculated on the basis of the tetrabutylammonium/tetrabutyl borate (TBA/TBB) assumption[15,16] and are summarized in Table 2. All these enthalpies indicate a sharp decrease at a low methanol mole fraction, followed by a curvi-linear increase with increasing methanol mole fraction, a typically observed pattern for anions which are stabilized through hydrogen-bonding interactions with methanol.[15–17] The results are well simulated by eqns. (1) and (2), where χ_{AN}

$$\begin{aligned}\Delta_t H^{AN\rightarrow mix} &= \\ &\Delta_t H_{PHYS}{}^{AN\rightarrow MeOH} \times \chi_{MeOH} \times [1 - 1.23 \times \chi_{MeOH} \times (1 - \chi_{MeOH})] \\ &+ \Delta_t H_{SI}{}^{AN\rightarrow MeOH} \times K_{se} \times \chi_{MeOH}/(\chi_{AN} + K_{se} \times \chi_{MeOH}) \quad (1)\end{aligned}$$

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

and χ_{MeOH} stand for the mole fraction of acetonitrile and of methanol in the solvent mixtures, and K_{se} stands for the equilibrium constant for a solvent exchange process on the solvation site around an ion.[15–17] The first term on the right hand side of eqn. (1) simulates the curvi-linear increase of the enthalpy, $\Delta_t H^{AN\rightarrow mix}$ and the term, $\Delta_t H_{PHYS}{}^{AN\rightarrow MeOH}$ indicates the enthalpy of transfer from acetonitrile to methanol arising from more "physical" interactions such as electrostatic, protophobic and cavity forming interactions. The second term simulates the sharp decrease of the enthalpy at low methanol mole fractions and the term $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ indicates more "specific" or more "chemical" interactions such as hydrogen-bonding and charge-transfer interactions which are observed for a specific pair of solute and solvent.[15–17] The search for a consistent set of interaction parameters, *i.e.*, $\Delta_t H_{PHYS}{}^{AN\rightarrow MeOH}$, $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ and K_{se} has been performed through curve-fitting procedures, systematically varying $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ and K_{se}, until the optimum fit of the calculated values to the experimental one was attained. One of the most plausible sets of parameters is given in Table 2. Usually experimental results were simulated with these eqns. within the maximum deviation of ±1.6 kJ mol^{-1}. Amongst all the ions studied in this work, the conjugate-base anion of 1,3-dimethylbarbituric acid indicates the largest negative value of $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$, that is to say, is the most hydrogen-bond accepting of all (see Table 2).

Rate constants and activation parameters for the reaction of ethyl iodide with the conjugate-base anion of 5-methyl Meldrum's acid (5-methyl Meldrum's acid anion) and with that of 1,3-dimethylbarbituric acid (1,3-dimethylbarbiturate ion) have been determined in acetonitrile–methanol mixtures and are summarized in Table 3. The rate constant shows a very significant decrease, while the activation enthalpy undergoes a sharp increase, at low methanol mole fractions, in a way that is reminiscent of the pattern observed for the single ion enthalpy of transfer for anions, $\Delta_t H^{AN\rightarrow mix}$. In contrast to these, the activation entropy goes through a maximum. These are all typically observed trends for the reactions in which the hydrogen-bonding interactions of a nucleophile with methanol play a significant role.[15,17] On the basis of a thermodynamic cycle using the enthalpies of transfer for ethyl iodide in the solvent mixtures,[16] single ion enthalpies of transfer for the transition-state anion were calculated and are summarized in Table 2. The interaction parameters for the transition-state anion were also calculated as described above and are given in Table 2. The results indicate that although specific interactions play a significant role even at the transition state, the amount of variation of the specific interaction enthalpy, $\delta\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$, on going from the reactant to the transition state, *i.e.*, 15.5 for the 5-methyl-Meldrum's acid anion and 10.5 for the 1,3-dimethylbarbiturate ion reaction, is much smaller by comparison to those for imidide ion and carboxylate ion reactions, *i.e.*, 22.9 for the former[18] and 27.2 for the latter[19] (all in kJ mol^{-1}).

Discussion

Logarithmic rates for the nucleophilic substitutions in acetonitrile have been documented to be linearly correlated with the specific interaction enthalpy for the relevant nucleophile (a scale of hydrogen-bond accepting basicity), $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$.[13] From this observation, together with the concurrent analysis of the reaction enthalpy, $\Delta_R H$, nucleophilic reactivity in acetonitrile (as log k_{AN}) is concluded to be controlled mainly by the partial desolvation of anions accompanying activation by comparison to the intrinsic properties of the central atom in

Table 4 Comparison of various reactivity parameters

Nucleophiles	$3 + \log k_{\mathrm{AN}}$	$\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$/kJ mol^{-1}	pK_a (in H_2O)	pK_a (in DMSO)	$\Delta_R H$/kJ mol^{-1}
3,5-Dinitrobenzoate	0.471[a]	−24.0[a]	2.81[b]	9.15[c]	−60.0[a]
1,3-Dimethylbarbiturate	0.252	−26.5	4.68[d]	8.4[c]	—
5-Methyl Meldrum's acid anion	0.153	−24.5	4.8[e]	7.4[f]	−110.7
Phthalimidide	1.808[a]	−26.0[a]	8.30[g]	13.7[h]	−134.7[a]

[a] Ref. 14. [b] Ref. 24. [c] Ref. 2. [d] Ref. 6. [e] The value for Meldrum's acid, ref. 2. [f] Ref. 4. [g] Ref. 25. [h] Ref. 26.

anions.[13,14] This suggests that if comparisons of reactivity are made for the reaction of nucleophiles of comparable specific interaction enthalpy, the intrinsic reactivity of the central atom could be evaluated without being modified by a solvational term. In order to critically examine the credibility of this supposition, as well as of various scales of reactivity, various scales of nucleophilic reactivity have been summarized in Table 4 for the reactions of nucleophiles which have comparable values for the enthalpy, $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$, even though they have different reaction centers.

These nucleophiles, although phthalimidide ion has a rate that is faster by one logarithmic unit, indicate comparable reactivity as anticipated from the similar hydrogen-bond accepting basicity, $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$. p$K_a$ values in the aqueous phase and in DMSO have been suggested as scales expressing nucleophilic reactivity, but they indicate a large variation along the series, from 3,5-dinitrobenzoate to phthalimidide, *i.e.*, 5.5 pK_a units for the former and 6.3 pK_a units for the latter and the reaction enthalpy in acetonitrile, $\Delta_R H$ as well, in contrast to the much smaller variation in logarithmic rate, $3 + \log k_{\mathrm{AN}}$ and in the enthalpy, $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$. It is to be noted that the trend observed for the reaction enthalpy in acetonitrile, $\Delta_R H$ could be understood according to the principle that the weaker the acid, the more significant is the nucleophilic reactivity of the conjugate base but this applies only to the relation between the equilibrium properties, pK_a (in H_2O) and $\Delta_R H$. 1,3-Dimethylbarbituric acid has acidity comparable to diethylacetic acid in the aqueous phase, *i.e.*, pK_a's are 4.68 for the former[6] and 4.73 for the latter,[20] whereas the hydrogen-bond accepting basicity for the barbiturate ion is much weaker, *i.e.*, $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$ values are −26.0 and −48.0 kJ mol^{-1}.[14] The logarithmic rate in acetonitrile is larger by 2 units for the diethylacetate ion in comparison to the 1,3-dimethylbarbiturate ion, *i.e.*, $3 + \log k_{\mathrm{AN}}$'s are 0.252 and 2.55 for the 1,3-dimethylbarbiturate and diethylacetate ion reactions.[14] A similar situation holds for 5-methyl Meldrum's acid and pivalic acid: they have comparable aqueous pK_a values, while the hydrogen-bond accepting basicity as well as the nucleophilic reactivity for pivalate ion is much larger; relevant values for the pivalic acid and pivalate ion reactions are 5.03, −43.5 and 2.456 for pK_a,[20] $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$,[14] and $3 + \log k_{\mathrm{AN}}$,[14] respectively. It has long been accepted that O–H acids are more acidic in comparison to N–H acids, and N–H acids are more acidic in comparison to C–H acids. The results presented above are likely to give further support for the view that nucleophilic reactivity in acetonitrile is controlled mainly by the partial desolvation of anions accompanying activation and that the nucleophiles having comparable values for the enthalpy, $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$ leads to comparable nucleophilic reactivity irrespective of the intrinsic properties of the nucleophilic central atom.

Quantitative separation of the activation parameters into constituents is an essential part of an analysis for the understanding of reaction behaviors in mixed solvents. Variation of activation parameters in solvent mixtures is brought about by differential responses of two constituent interactions to solvent composition, *i.e.*, more "physical" and specific interactions, as well as differential contributions for the transition-state anion from those at nucleophiles and is expressed by eqn (3), where Y stands for relevant thermodynamic quantities. Reconstruction of activation parameters, which is guided by the solvent exchange model with the use of the interaction parameters derived above, can be carried out through the following procedures.[21,22]

$$\delta\Delta Y^{\ddagger} = \delta\Delta Y^{\ddagger}_{\mathrm{PHYS}} + \Delta_t Y_{\mathrm{SI}}^{\mathrm{AN\to mix}}(\mathrm{TS}^-) - \Delta_t Y_{\mathrm{SI}}^{\mathrm{AN\to mix}}(\mathrm{Nu}^-) \qquad (3)$$

1. Activation enthalpies arising from "more physical" interactions can be derived through eqn. (4), substituting the relevant values given in Table 2 and enthalpies of transfer for ethyl iodide[15] into eqn. (4).

$$\delta\Delta H^{\ddagger}_{\mathrm{PHYS}} = [\Delta_t H_{\mathrm{PHYS}}^{\mathrm{AN\to MeOH}}(\mathrm{TS}^-) - \Delta_t H_{\mathrm{PHYS}}^{\mathrm{AN\to MeOH}}(\mathrm{Nu}^-)] \times \chi_{\mathrm{MeOH}} \times [1 - 1.23 \times \chi_{\mathrm{MeOH}} \times (1 - \chi_{\mathrm{MeOH}})] - \Delta_t H^{\mathrm{AN\to mix}}(\mathrm{EtI}) \qquad (4)$$

2. In the reactions for which an isokinetic relationship holds between the activation parameters arising from "more physical" interactions, eqn. (5) holds. Thus, activation entropies arising from "more physical" interactions can be derived through the division of the enthalpies calculated above by an assumed value for the isokinetic temperature due to "more physical" interactions, β_{PHYS}.

$$\delta\Delta S^{\ddagger}_{\mathrm{PHYS}} = \delta\Delta H^{\ddagger}_{\mathrm{PHYS}}/\beta_{\mathrm{PHYS}} \qquad (5)$$

3. Single ion enthalpies of transfer arising from specific interactions can be calculated through the substitution of the relevant quantities given in Table 2 into eqn. (6).

$$\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to mix}} = \Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}} \times K_{\mathrm{se}} \times \chi_{\mathrm{MeOH}}/(\chi_{\mathrm{AN}} + K_{\mathrm{se}} \times \chi_{\mathrm{MeOH}}) \qquad (6)$$

4. According to the solvent exchange model the quantity $\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}}$ can be separated into components, the number of methanol molecules participating in specific interactions with the relevant solute, Z, and the enthalpy of the solvent exchange process on the solvation site around the anion, ΔH_{se}, according to eqn. (7). Single ion entropies of transfer arising from specific interactions can be derived through eqn. (8) by substituting the relevant quantities given in Table 2, together with the assumed values of Z and ΔH_{se} into eqn. (8).

$$\Delta_t H_{\mathrm{SI}}^{\mathrm{AN\to MeOH}} = Z\Delta H_{\mathrm{se}} \qquad (7)$$

$$\Delta_t S_{\mathrm{SI}}^{\mathrm{AN\to mix}} = (Z\Delta H_{\mathrm{se}}/T) \times (K_{\mathrm{se}}\chi_{\mathrm{MeOH}})/(\chi_{\mathrm{AN}} + K_{\mathrm{se}}\chi_{\mathrm{MeOH}}) + ZR\ln(\chi_{\mathrm{AN}} + K_{\mathrm{se}}\chi_{\mathrm{MeOH}}) \qquad (8)$$

5. Substitution of these derived quantities into eqn. (3) gives the desired thermodynamic quantities. The procedures 1–5 were repeated until optimum fits between the calculated and experimental values were attained. One of the most plausible sets of parameters, solvation numbers Z for nucleophilic anions and for the transition state anions are also given in Table 2; the final values of β_{PHYS} are 395 and 445 K for the reaction of 5-methyl Meldrum's acid anion and for the reaction of 1,3-dimethylbarbiturate ion.

General trends observed for the activation parameters (*S*-shaped character of $\delta\Delta H^{\ddagger}$ *vs.* $\delta\Delta S^{\ddagger}$ correlation) could be reproduced by the procedures as described above (see Fig. 1).

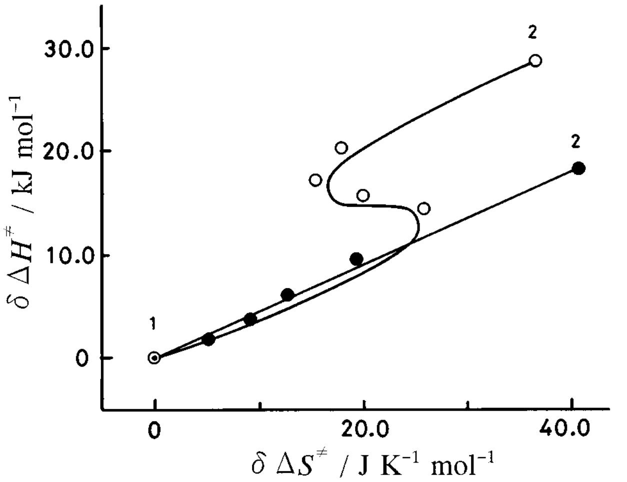


Fig. 1 Activation enthalpy *vs.* activation entropy correlations for the reaction of 1,3-dimethylbarbiturate ion plus ethyl iodide in acetonitrile–methanol mixtures: ○, overall quantity; ●, "more physical" interaction quantity; curve, calculated values (see text). 1, Acetonitrile; 2, methanol.

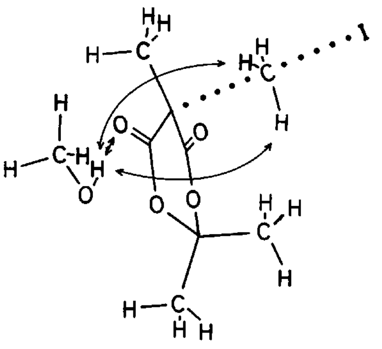
These are other examples which indicate that the linear enthalpy *vs.* entropy correlation does not necessarily hold for observed overall quantities, even when it holds between particular constituent quantities, *i.e.*, "more physical" interaction quantities.

Statistical analysis on specific interaction enthalpies with respect to the number of solvent molecules which participate in specific interaction, Z, leads to eqn. (9). This implies that the

$$\Delta_t H_{SI}{}^{AN\rightarrow MeOH} = -2.2 - 10.2 \times Z \qquad (9)$$
$$n = 4, r = 0.99$$

enthalpy change for the solvent exchange process on the solvation site, ΔH_{se} for relevant anions studied here, -10.2 kJ mol^{-1} is fairly close to those for imidide ion and for carboxylate ion reactions, -11.6 for the former[22] and -12.9 for the latter[23] reactions. The result is insufficient to provide a satisfactory interpretation of the smaller differential specific interaction enthalpy on going from the initial to the transition states for the present reactions, $\delta\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ by comparison to those for imidide ion and carboxylate ion reactions.

In order to explore solvation effects on reactions in solution, information on molecular properties for relevant species in the gas phase is indispensable. Semi-empirical molecular orbital calculations were performed for nucleophilic anions as well as for transition-state anions with MNDO/PM3 procedures.[27] For the reactions of the present study, methyl iodide, the electrophile approaches the central carbon from the direction expected for sp^3-hybridization at the central carbon atom (see Scheme 1). Using the calculated results, various correlations were tried empirically. One of the seemingly successful correlations is the one between the specific interaction enthalpy for the nucleophilic anion, $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ and the atomic charge on the carbonyl oxygen as shown in Fig. 2.



Scheme 1

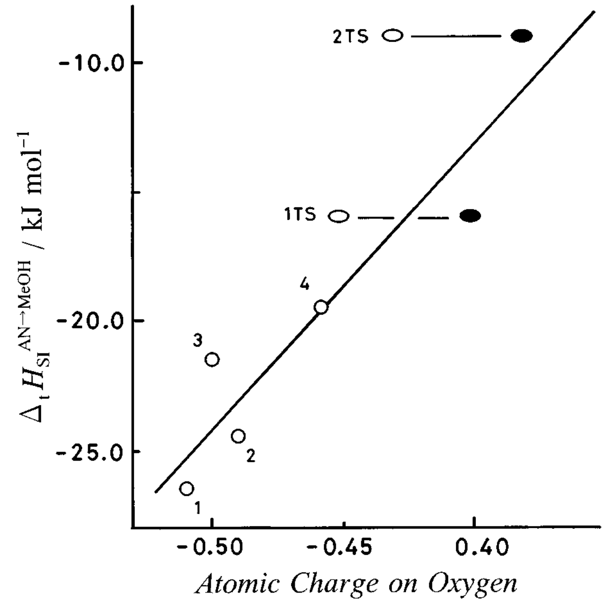


Fig. 2 Empirical correlation between the specific interaction enthalpy, $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$ and the atomic charge on carbonyl oxygen: ○, nucleophilic anions; ⬭, transition-state anions; ⬬, effective atomic charge on carbonyl oxygen in transition-state anions. 1, 1,3-dimethylbarbiturate ion; 2, conjugate-base anion of 5-methyl Meldrum's acid; 3, conjugate-base anion of Meldrum's acid; 4, conjugate-base anion of 5-phenyl Meldrum's acid; 1TS, transition-state anion of 1,3-dimethylbarbiturate ion reaction; 2TS, transition-state anion of 5-methyl Meldrum's acid anion reaction.

In this correlation the enthalpies for the transition state anion (⬭) are likely to indicate an upward deviation from the regression line as had been observed for the imidide ion and the carboxylate ion reactions.[22,23] In order to allow for the effects of the methyl group in the incoming methyl iodide, the geometry was optimized for the transition-state anion complexed with methanol, with C (reaction center of nucleophilic anion)–C (in methyl iodide) and C (in methyl iodide)–I distances being fixed at the values which have been optimized in advance for uncomplexed transition-state anions. One example of optimized structures, *i.e.*, the transition-state anion for 5-methyl Meldrum's acid anion reaction is shown in Scheme 1.

Electrostatic energy, ESE for the four atom systems shown by arrows in Scheme 1 can be expressed by eqn. (10), where Q_i and

$$\mathrm{ESE} = Q_O Q_{H'}/r_{O\text{–}H'} + \Sigma\ Q_{H'}Q_H/r_{H'\text{–}H}$$
$$= (Q_{H'}/r_{O\text{–}H'})\ [Q_O + \Sigma\ Q_H/(r_{H'\text{–}H}/r_{O\text{–}H'})] \qquad (10)$$

$r_{i\text{–}j}$ stand for the atomic charge on atom i, and the distance between atom i and atom j, and the suffixes O, H, and H′ stand for the carbonyl oxygen, the hydrogen atoms in the incoming methyl group and the hydroxy hydrogen in methanol. The second term in the square bracket goes to zero, when the distance $r_{H'\text{–}H}$ becomes infinity, that is, at the initial state, and the term in the square bracket would be taken as an effective atomic charge on carbonyl oxygen being sensed by the hydrogen atom in methanol. When the effects of the two hydrogen atoms nearest to the carbonyl oxygen are taken into account, effective atomic charges on oxygen shift to the position denoted by (⬬) in Fig. 2. The regression equation is given by eqn. (11).

$$\Delta_t H_{SI}{}^{AN\rightarrow MeOH} =$$
$$31.0 + 110.7 \times\ [Q_O + \Sigma Q_H/(r_{H'\text{–}H}/r_{O\text{–}H'})] \qquad (11)$$
$$n = 6, r = 0.94$$

The eqn. (11) predicts that the enthalpy, $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$

Table 5 Solvents for recrystallization and elementary analysis

	Solvents	Obs.(%) C	Obs.(%) H	Obs.(%) N	Formula	Calc.(%) C	Calc.(%) H	Calc.(%) N
Tetramethylammonium 5-methyl Meldrum's acid anion	Acetone	57.2	9.01	6.14	$C_{11}H_{21}NO_4$	57.1	9.15	6.06
Tetraethylammonium Meldrum's acid anion	Acetonitrile	60.4	9.88	5.03	$C_{14}H_{27}NO_4$	61.5	9.96	5.12
Tetramethylammonium 5-phenyl Meldrum's acid anion	Acetonitrile	65.3	7.94	4.83	$C_{16}H_{23}NO_4$	65.5	7.90	4.77
Tetramethylammonium 1,3-dimethylbarbiturate	Acetonitrile–THF	51.8	8.32	18.1	$C_{10}H_{19}N_3O_3$	52.4	8.35	18.3

becomes zero at effective atomic charge = -0.280. The value is very close to the charge on the carbonyl oxygen of uncharged compounds for which the effect of hydrogen-bonding interactions cannot usually be detected through enthalpy of transfer analysis.[28] The slope value, 110.7 is *ca.* one-third of those for imidide and carboxylate ion reactions, *i.e.*, 369.2 for the former[22] and 333.8 for the latter[23] reactions. This means that for the reactions in the present study molecular properties such as atomic charges on the carbonyl oxygen are not effectively reflected in solute–solvent interactions.

In carboxylate and imidide ions, three and two lone pair orbitals at the reaction center are open for reaction as well as for molecular interactions and these do not prohibit the approach of solvent molecules to an adjacent carbonyl oxygen. In contrast, in charge-delocalized carbanions as studied in this work, three σ orbitals at the reaction center are used for bonding with three atoms, only the lone pair p orbital is free for molecular interaction, and the groups coordinated to the central carbon, *i.e.*, hydrogen atom, methyl and phenyl groups, are likely to hinder the approach of solvent to an adjacent carbonyl oxygen, that is, only part of the surface of the carbonyl oxygen remains free for solute–solvent interactions. The transition-state anion for the charge-delocalized carbanion reaction is coordinated with four atoms, leading to further limited surface being open. Thus, even when the atomic charge on carbonyl oxygen varies significantly on going from reactant to transition-state anion as indicated by quantum-mechanical calculations (see the abscissa of Fig. 2), the effects would not effectively be transmitted to surrounding solvents, resulting in the rather minor changes in $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$. Thus, the rather smaller variation in the specific interaction enthalpy on going from the reactant to the transition-state as well as the smaller coefficient in the correlation, eqn. (11), for the present reactions in comparison to those for carboxylate and imidide ion reactions would be described as resulting from steric inhibition of solvation by the coordinated atom and group at the central carbon.

Conclusion

In the nucleophilic substitution of ethyl iodide by the conjugate-base anion of 5-methyl Meldrum's acid and of 1,3-dimethylbarbituric acid, the effects of solvent composition on activation enthalpies are less marked by comparison to those of imidide ion and carboxylate ion reactions. The origin of the effects has been ascribed to the steric inhibition of solvation by the groups coordinated to the reaction center. Even for these more complicated systems, the specific interaction enthalpy for nucleophilic anion, $\Delta_t H_{SI}{}^{AN\rightarrow MeOH}$, seems to be a very useful scale for molecular mechanistic calculations.

Experimental

Materials

Tetraalkylammonium salts containing the conjugate-base anions of Meldrum's acid and of 1,3-dimethylbarbituric acid were prepared from tetraalkylammonium hydroxide and a relevant acid in methanol as described previously[29] and recrystallized three times from the solvents shown in Table 5. The results of elementary analysis are also shown in Table 5. Other materials were treated as described elsewhere.[15,17]

Enthalpy of solution measurements

Enthalpies of solution, $\Delta_s H$ for tetraalkylammonium salts were measured at 25.0 ± 0.1 °C with a Tokyo Riko twin isoperibol calorimeter.[15,16] Final concentration ranges were $(0.4\text{–}1.5) \times 10^{-2}$ mol dm^{-3} and the experimental errors were *ca.* 0.7 kJ mol^{-1}. The enthalpies of reaction, $\Delta_R H$ have also been determined with the calorimeter as described elsewhere.[14]

$\Delta_R H$'s are -101.9 kJ mol^{-1} and -110.7 kJ mol^{-1} for Meldrum's acid and 5-methyl Meldrum's acid anion reactions and experimental errors are *ca.* 5 kJ mol^{-1}.

Product analysis and kinetic procedures

Stock solutions of ethyl iodide and of the relevant tetraalkylammonium salt were mixed in a round bottomed flask and kept overnight. After near completion of the reaction, the reaction mixtures were carefully evaporated to dryness and solid precipitates were washed several times with several portions of ether. The solvent, ether, was evaporated to near dryness and the uncharged reaction product was dissolved in chloroform. ^{1}H NMR spectra of the uncharged reaction product for the 5-methyl Meldrum's acid anion reaction agreed with that of 2,2-dimethyl-5-ethyl-1,3-dioxane-4,6-dione. ^{1}H NMR spectra of the uncharged reaction product of the 1,3-dimethylbarbituric acid anion reaction agreed with that of tautomeric mixtures of 1,3-dimethyl-5-ethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (trioxo form) and 1,3-dimethyl-5-ethylpyrimidine-2,4(1*H*,3*H*)-dion-6-ol (dioxo-monoenol form). Thus ethylation reactions seem to proceed at the carbon atom for both the Meldrum's acid anion reaction and for the 1,3-dimethylbarbituric acid anion reaction, as far as can be detected. Reaction rates were calculated through the determination of iodide ion formed by potentiometric titration using silver nitrate solution[21,23] and rates were measured at four of the following temperatures, 0.0, 20.0, 30.0, 40.0, 50.0 and 60.0 °C. Experimental errors were estimated to be *ca.* 2%, 0.5–1.0 kJ mol^{-1} and 1.7–3.0 J K^{-1} mol^{-1} for rate constants, activation enthalpies and activation entropies, respectively.

Calculations

Semi-empirical molecular orbital calculations were carried out using the MNDO/PM3 method with most of the parameters kept at the default values.[27] In order to shorten the computation time, the following restrictions were imposed; the frameworks of the anion were assumed to have C_s symmetry, the methyl group to have C_{3v} symmetry and in the calculation methyl iodide was used as an electrophile instead of ethyl iodide which was used in experiments. The structures of the transition state anion hydrogen bonded with methanol were optimized with C–C and C–I bond distances being fixed at the values which had in advance been determined for uncomplexed transition structure optimizations.

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