

# Menschutkin Reactions of Bicyclic Aliphatic Amines and of Pyridine Derivatives with Methyl Iodide. Extended Brönsted Treatments and Isokinetic Relationships in Acetonitrile–Methanol

Yasuhiko Kondo,\* Ryōichi Uematsu, Yoshinobu Nakamura, and Shigekazu Kusabayashi  
*Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan*

The rate constants, activation parameters for the Menschutkin reactions for five bases with methyl iodide, and the enthalpies of solution for the relevant species of the reactions have been determined in acetonitrile–methanol. The bases are quinuclidine, 1,4-diazabicyclo[2.2.2]octane, and 4-cyano-, 4-*t*-butyl-, and 4-dimethylamino-pyridine. The coefficients of empirical energy correlations defined in terms of 'more physical' energies, extended Brönsted treatments,  $\alpha_{\text{phys}}$  and isokinetic temperatures,  $\beta_{\text{phys}}$  have been determined for these reactions. Discussion is provided on the physical meaning of these coefficients in relation to the characteristics of the activated complex.

The Menschutkin reaction is historically the prototype of reactions in which neutral reactants lead to ionic products.<sup>1–3</sup> Through quantitative treatment of solvent effects on reaction rates, together with other thermodynamic procedures for deducing transition state characteristics, the early nature of the transition state along the reaction co-ordinate seems to have been confirmed.<sup>1,4–7</sup>

Recently there has been much dispute over the credibility of the reactivity–selectivity principle as regards more sophisticated versions, selecting the Menschutkin reaction as a model.<sup>8–13</sup> As one of the fundamental tools in physical organic chemistry, much attention has been given to the quantitative form of rate–equilibrium relationships, extended Brönsted relationships, and elaborated versions.<sup>13–16</sup> Apart from the theoretical interest, great care needs to be taken over the practical application of these quantitative formulae to mechanistic studies; various examples have been given.<sup>7,17–20</sup>

In previous work theoretical procedures have been developed for extended Brönsted treatments, all types of solute–solvent interactions being taken into account.<sup>17,18</sup> In this work these procedures are applied to the Menschutkin reactions of bicyclic aliphatic amines and of pyridine derivatives with methyl iodide in acetonitrile–methanol. Discussion is provided on the results in relation to the characteristics of the activated complex.

## Experimental

**Materials.**—Quinuclidine was recrystallized three times from acetone and dried over silica gel which was stored over phosphorus pentoxide prior to use. 1,4-Diazabicyclo[2.2.2]octane, recrystallized three times from acetone, was dried over silica gel treated as described above. 4-Cyanopyridine was recrystallized three times from anhydrous ethanol and dried (silica gel dried over P<sub>2</sub>O<sub>5</sub>). 4-*t*-Butylpyridine was stored over calcium hydride overnight and distilled three times under reduced pressure. 4-Dimethylaminopyridine was recrystallized three times from benzene and dried (silica gel dried over P<sub>2</sub>O<sub>5</sub>). 1-Methyl-1,4-diazabicyclo[2.2.2]octyl iodide, prepared from 1,4-diazabicyclo[2.2.2]octane and methyl iodide in acetonitrile, was recrystallized three times from acetone–methanol–diethyl ether, and dried (P<sub>2</sub>O<sub>5</sub>) (Found: H, 6.1; C, 32.9; N, 11.1; I, 50.0. Calc. for C<sub>7</sub>H<sub>15</sub>IN<sub>2</sub>: H, 5.95; C, 33.1; N, 11.0; I, 49.9%). Other materials were treated as described elsewhere.<sup>17,20</sup>

**Kinetic Measurements.**—Reactions were followed by measur-

ing the iodide ion produced in the reaction with potentiometric titration using silver nitrate solution and rate constants were determined at four of the following temperatures, 0.0, 10.0, 20.0, 30.0, 40.0, and 50.0 °C. Experimental errors were estimated to be ca. 2%.<sup>17–19</sup>

**Heat of Solution Measurements.**—Heats of solution were measured with a Tokyo Riko twin isoperibol calorimeter (TIC-2D) as described elsewhere,<sup>17–19</sup> and the final concentration ranges were 1.1–1.3 × 10<sup>−2</sup> mol dm<sup>−3</sup> for bases and salt. Experimental errors were estimated to be ca. 2% from duplicate or triplicate runs.<sup>17–20</sup>

## Results

Rate constants (at 30 °C) and activation parameters (calculated at 25 °C) are summarized in Table 1. Logarithmic rate constants for three reactions of strong amines with methyl iodide, *i.e.*, quinuclidine, 1,4-diazabicyclo[2.2.2]octane (DABCO), and 4-dimethylaminopyridine, indicate negative deviation from the line linking the values determined in pure solvents, *i.e.*,  $x_1 \ln k_1 + x_4 \ln k_4$  (subscript 1 refers to methanol and 4 to acetonitrile hereafter). This fact is in contrast to the behaviour anticipated from that observed for the triethylamine plus methyl iodide reaction, *i.e.*, rather linear changes over whole range of solvent composition. In other words, the similarity in base strength as judged from pK<sub>a</sub> values determined in water does not necessarily lead to any definite predictions for rate behaviour in non-aqueous mixed solvents, *viz.*, pK<sub>a</sub> values are 10.9, 10.8, 8.8, and 9.6 for quinuclidine,<sup>21</sup> triethylamine,<sup>21</sup> DABCO,<sup>21</sup> and 4-dimethylaminopyridine.<sup>22</sup>

Activation enthalpies for the reactions of three strong amines with methyl iodide indicate large positive deviations from the line linking the values in pure solvents, those for the 4-*t*-butylpyridine reaction have a small positive deviation, and those for the 4-cyanopyridine reaction have a small negative deviation at high methanol content.

Enthalpies of solution for these amines and for 1-methyl-1,4-diazabicyclo[2.2.2]octyl iodide (1-Me-DABCO<sup>+</sup>I<sup>−</sup>) are summarized in Table 2. There are observed analogies in the behaviours of the two types of enthalpy in the sense that the large decrease in enthalpy of solution is associated with a marked increase in activation enthalpy, on going from acetonitrile to mixed solvent.

On the basis of a thermodynamic cycle,<sup>17,18</sup> transfer enthalpies for the activated complex for these reactions are calculated and summarized in Table 3. The steady increase in

**Table 1.** Rate constants (30.0 °C) and activation parameters (25.0 °C) in acetonitrile–methanol mixtures

$X_{\text{MeOH}}$	Quinuclidine + MeI			DABCO + MeI			4-Cyanopyridine + MeI		
	$10^2 k$ $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger$ $\text{kJ mol}^{-1}$	$\Delta S^\ddagger$ $\text{J K}^{-1} \text{mol}^{-1}$	$10^2 k$ $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger$ $\text{kJ mol}^{-1}$	$\Delta S^\ddagger$ $\text{J K}^{-1} \text{mol}^{-1}$	$10^6 k$ $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger$ $\text{kJ mol}^{-1}$	$\Delta S^\ddagger$ $\text{J K}^{-1} \text{mol}^{-1}$
0	331.5	28.7	-140.5	204.5	32.1	-133.1	25.2	57.9	-142.3
0.1	98.0	45.3	-95.7	63.75	47.2	-93.0	22.9	59.0	-139.3
0.25	36.2	48.4	-93.55	25.1	50.9	-88.8	20.1	61.0	-133.75
0.50	14.05	51.2	-92.3	9.72	53.0	-89.7	14.0	62.6	-131.5
0.75	6.105	52.1	-96.4	4.21	54.5	-91.8	8.35	65.0	-127.9
1.0	1.97	55.5	-94.6	1.37	59.8	-83.5	3.155	68.7	-123.6

$X_{\text{MeOH}}$	4-t-Butylpyridine + MeI			4-Dimethylaminopyridine + MeI		
	$10^5 k$ $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger$ $\text{kJ mol}^{-1}$	$\Delta S^\ddagger$ $\text{J K}^{-1} \text{mol}^{-1}$	$10^4 k$ $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$	$\Delta H^\ddagger$ $\text{kJ mol}^{-1}$	$\Delta S^\ddagger$ $\text{J K}^{-1} \text{mol}^{-1}$
0	115.5	51.1	-132.8	138.1	47.9	-122.7
0.1	77.9	56.1	-119.5	55.05	57.35	-99.1
0.25	48.5	59.3	-112.8	25.65	59.5	-98.45
0.50	25.3	62.3	-108.3	11.2	64.0	-90.4
0.75	13.3	67.0	-98.2	5.23	67.0	-87.0
1.0	4.75	72.6	-88.5	1.83	71.7	-80.2

 $X_{\text{MeOH}}$  = mole fraction of methanol.**Table 2.** Enthalpies (in  $\text{kJ mol}^{-1}$ ) of solution and interaction parameters in acetonitrile–methanol mixtures (25.0 °C)

$X_{\text{MeOH}}$	Quinuclidine	DABCO	4-Cyanopyridine	4-t-Butylpyridine	4-Dimethylamino- pyridine	1-Me-DABCO <sup>+</sup> 1 <sup>-</sup>
0	10.1	17.7	18.7	3.60	23.5	3.75
0.1	-3.71	0.29	18.1	-0.078	14.8	-0.06
0.25	-7.16	-6.10	17.7	-2.55	11.9	0.68
0.50	-7.95	-7.62	17.9	-4.05	11.3	4.87
0.75	-7.72	-6.63	18.8	-4.58	11.8	10.7
1.0	-6.99	-4.05	20.5	-5.05	12.1	21.15
$\Delta H_{\text{t,phys}}^{\text{AN} \rightarrow \text{MeOH}}$	4.9	13.75	6.8	0.35	4.1	3.4 <sup>a</sup> + 10.3 <sup>b</sup>
$\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}}$	-22.0	-35.5	-5.0	-9.0	-15.5	-10.0 <sup>c</sup>
$K_{\text{se}}$	16.0	10.0	3.5	6.5	13.0	1.8
Z	2		1	1	1	

<sup>a</sup>  $\Delta H_{\text{t}}^{\text{AN} \rightarrow \text{MeOH}}$  (1-Me-Quinuc<sup>+</sup>) = 3.4, a reference cation.<sup>20</sup> <sup>b</sup>  $\Delta H_{\text{t,phys}}^{\text{AN} \rightarrow \text{MeOH}}$ . <sup>c</sup>  $\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}}$  for a differential quantity (see text). The single ion enthalpy of transfer for 1-Me-DABCO<sup>+</sup> ion,  $\Delta H_{\text{t}}^{\text{AN} \rightarrow \text{MeOH}}$  (1-Me-DABCO<sup>+</sup>) =  $\Delta H_{\text{t}}^{\text{AN} \rightarrow \text{MeOH}}$  (1-Me-DABCO<sup>+</sup>1<sup>-</sup>) -  $\Delta H_{\text{t}}^{\text{AN} \rightarrow \text{MeOH}}$  (1<sup>-</sup>) = 17.4 - 13.7 = 3.7, can be separated into three constituents given in the Table, 3.4, 10.3, and -10.0.

**Table 3.** Enthalpies (in  $\text{kJ mol}^{-1}$ ) of transfer for the activated complexes and interaction parameters in acetonitrile–methanol mixtures (25.0 °C)

$X_{\text{MeOH}}$	Quinuclidine + MeI	DABCO + MeI	4-Cyanopyridine + MeI	4-t-Butylpyridine + MeI	4-Dimethylaminopyridine + MeI
0.00	0	0	0	0	0
0.1	2.8	-2.3	0.5	1.3	0.75
0.25	2.4	-5.0	2.1	2.0	0.0
0.50	4.25	-4.6	3.7	3.35	3.7
0.75	5.1	-2.4	6.7	7.2	6.9
1.0	8.7	4.95	11.6	11.8	11.4
$\Delta H_{\text{t,phys}}^{\text{AN} \rightarrow \text{MeOH}}$	8.7	8.9 <sup>a</sup> + 13.85 <sup>b</sup>	11.6	11.8	11.8 <sup>c</sup> + 3.6 <sup>b</sup>
$\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}}$		-17.8			-4.0
$K_{\text{se}}$		5.0			3.0
Z		2			1

<sup>a</sup>  $\Delta H_{\text{t}}^{\text{AN} \rightarrow \text{MeOH}}$  for the activated complex of the triethylamine plus methyl iodide reaction, a reference compound.<sup>18</sup> <sup>b</sup>  $\Delta H_{\text{t,phys}}^{\text{AN} \rightarrow \text{MeOH}}$  for a differential quantity. <sup>c</sup>  $\Delta H_{\text{t}}^{\text{AN} \rightarrow \text{MeOH}}$  for the activated complex of the 4-t-butylpyridine plus methyl iodide reaction, a reference compound.

the transfer enthalpy with increasing methanol content is a generally observed pattern of behaviour throughout, except for the cases of two activated complexes, *i.e.*, negative values for the DABCO plus methyl iodide reaction and a less significant increase over the region of low methanol content, though followed by a steady increase at higher methanol content, for the 4-dimethylaminopyridine plus methyl iodide reaction.

## Discussion

*Solute–Solvent Interaction at Initial State, Final State, and Transition State.*—The enthalpy change on transferring bases from acetonitrile to mixed solvents follows the same pattern of behaviour observed for the transfer of pyridine and triethylamine, *i.e.*, a sharp decrease over the region of low methanol content followed by a rather mild increase or decrease

over a region of high methanol content. This behaviour was ascribed to the combined results of a specific interaction between methanol and a base molecule (in these cases a specific interaction corresponds to a hydrogen-bonding interaction) and a 'more physical' interaction such as van der Waals and dipole-dipole interactions.<sup>17,18</sup> For these bases transfer enthalpies could be well reproduced by equations (1) and (2),

$$\Delta H_t^{\text{AN} \rightarrow \text{MeOH}} = \Delta H_{t,\text{phys}}^{\text{AN} \rightarrow \text{MeOH}} + \Delta H_{t,\text{SI}}^{\text{AN} \rightarrow \text{MeOH}} \quad (1)$$

$$\Delta H_t^{\text{AN} \rightarrow \text{mix}} = \Delta H_{t,\text{phys}}^{\text{AN} \rightarrow \text{MeOH}} \cdot x_1 + \frac{\Delta H_{t,\text{SI}}^{\text{AN} \rightarrow \text{MeOH}} K_{\text{se}} x_1}{(x_4 + K_{\text{se}} x_1)} \quad (2)$$

$$\therefore \Delta H_{t,\text{SI}}^{\text{AN} \rightarrow \text{MeOH}} = z \Delta H_{\text{se}}$$

which were derived on the basis of a solvent exchange model on the solvation site around a solute.<sup>17,18</sup>

In these equations,  $z$ ,  $\Delta H_{\text{se}}$ , and  $K_{\text{se}}$  are the number of solvation sites, the enthalpy change, and the equilibrium constant of the solvent exchange process. Transfer enthalpies determined in this work could also be reproduced well by these equations. The parameters derived are summarized in Table 2.

The transfer enthalpy of the reaction product, a quaternary ammonium iodide, is a composite quantity from cationic and anionic enthalpies. For iodide ion, the transfer enthalpy has already been dissected into its constituents, *i.e.* 'more physical' and specific interaction enthalpy.<sup>17,18</sup> Constituent analysis on transfer enthalpies for quaternary ammonium ions indicated that electrostatic interactions between ion and solvent such as ion-solvent dipole and dipole-dipole interactions are the major contributing effects, while the contribution from such specific interactions as dipole-dipole or acid-base associations, although conceivable, could not be evaluated.<sup>20</sup> 1-Methyl-1,4-diazabicyclo[2.2.2]octyl iodide (1-Me-DABCO<sup>+</sup>I<sup>-</sup>) is an exceptional case, since in the salt the interaction at the tertiary amine centre still unreacted should make an extra contribution to the transfer enthalpy, in addition to the normal term arising from quaternary ammonium iodide transfer. Quantitative analysis on the transfer enthalpy could be carried out in two steps, first making a differential quantity from a relevant reference compound, in this case 1-methylquinuclidinium iodide (1-Me-Quinuc<sup>+</sup>I<sup>-</sup>),  $\delta_R \Delta H_t^{\text{AN} \rightarrow \text{mix}}$ , according to equation (3),

$$\delta_R \Delta H_t^{\text{AN} \rightarrow \text{mix}} = \Delta H_t^{\text{AN} \rightarrow \text{mix}}(1\text{-Me-DABCO}^+\text{I}^-) - \Delta H_t^{\text{AN} \rightarrow \text{mix}}(1\text{-Me-Quinuc}^+\text{I}^-) \quad (3)$$

secondly, carrying out a quantitative analysis of the differential quantity on the basis of equations (1) and (2). Parameters derived are given in Table 2.

The transfer enthalpy of an activated complex generally indicates a steady increase with increasing content of methanol; this is the expected pattern of behaviour if the dipole-dipole interaction is the leading term for a solute-solvent interaction in the dipolar transition state, *i.e.*, average polarity of the mixed solvent, defined in terms of dipole moment, decreases with increasing content of methanol.<sup>20</sup>

Here the activated complex for the DABCO reaction is an exceptional case; the transfer enthalpy is negative throughout the mixed solvent. The solute-solvent interaction at the transition state should be a composite quantity including a dipole-dipole interaction around the incipient cationic as well as anionic moiety, together with a mainly specific interaction at tertiary amine centres remaining unreacted. We have two reference compounds for calculating the differential quantity, *i.e.*, the activated complex for the triethylamine plus methyl iodide reaction determined in previous work<sup>18</sup> and that for the quinuclidine plus methyl iodide reaction determined above. The

**Table 4.** Coefficients of extended Brønsted treatments,  $\alpha_{\text{phys}}$ , and isokinetic temperatures,  $\beta_{\text{phys}}$ , in acetonitrile-methanol mixtures

Reaction	$\alpha_{\text{phys}}$	$\beta_{\text{phys}}/\text{K}$
Quinuclidine + MeI	0.22	(163)
Triethylamine <sup>a</sup> + MeI	0.35	150
DABCO + MeI	0.45	
4-Cyanopyridine + MeI	0.22	(300)
Pyridine <sup>a</sup> + MeI	0.38	393
4-t-Butylpyridine + MeI	0.53	380
4-Dimethylaminopyridine + MeI	0.64	965

<sup>a</sup> Ref. 18.

argument is as follows. (i) The differential enthalpy was calculated under the assumption that triethylamine reaction serves as the reference. (ii) The differential enthalpy as calculated above was better reproduced by equations (1) and (2) than the enthalpy calculated under the assumption that quinuclidine reaction serves as reference. This is probably a reflection of the fact that charge development in the transition state for the triethylamine reaction is closer to that for the DABCO reaction than that for the quinuclidine reaction, and as a result compensation is more effective for the triethylamine reaction (see Table 4). The parameters derived are given in Table 3.

Comparison of the specific interaction enthalpy per one nitrogen atom and of equilibrium constants for a solvent exchange process, *i.e.*,  $-35.5/2:-17.8:-10.0$  (kJ mol<sup>-1</sup>) and 10.0:5.0:1.8 for DABCO, the activated complex and 1-Me-DABCO<sup>+</sup> ion, indicates that as the reaction proceeds from reactants, through the transition state, to products, the perturbation effected by developing positive charge at a reacting nitrogen atom manifests itself first on the equilibrium constant for the specific interaction of the non-reacting nitrogen atom with methanol in the transition state and then both on the equilibrium constant and on the enthalpy change in the final state, in other words entropy is likely to provide a more stringent probe for detecting a variation in a weak interaction between solute and solvent than enthalpy.

A rather small range of variation in transfer enthalpy for the activated complex for the 4-dimethylaminopyridine plus methyl iodide reaction, especially in the region of low methanol content, compared with that for other pyridine derivatives suggests the presence of a specific interaction in the transition state, presumably arising from the electrophilic assistance to leaving iodide ion by methanol. Substitution of the parameters for 4-dimethylaminopyridine summarized in Table 2 into equation (9) predicts the presence of a minimum at  $x_{\text{MeOH}}$  0.48 in the transfer entropy-solvent composition profile, which should result in the presence of the maximum in the activation entropy-solvent composition profile for the 4-dimethylaminopyridine plus methyl iodide reaction, if other compensating factors do not bring in significant effects. This does not seem to be the case (see Table 1). Along the same line of treatment as described above, constituent analysis was carried out for the differential quantity which has been derived by selecting the activated complex for the pyridine or 4-t-butylpyridine plus methyl iodide reaction as a reference system, and the parameters derived are summarized in Table 3. The results indicate that the electrophilic assistance to leaving iodide ion, although weak, becomes experimentally observable when there is such large charge development at transition state,  $\alpha_{\text{phys}}$  0.64 (see Table 4).

*Extended Brønsted Treatments and Entropy-Enthalpy Compensations.*—In order for the transition state characteristics to

be derived from empirical energy correlations, quantities which are supposed to give a monotonic change along a reaction coordinate should be used in these correlations.<sup>17,18</sup> In our systems the relevant quantity corresponds to 'more physical' interaction energies; the contribution from specific interactions has to be subtracted from the observed quantities.<sup>18</sup>

According to a thermodynamic cycle<sup>17,18</sup> and discussions given above, solvent effects on activation enthalpy due to a 'more physical' interaction can be calculated by substituting the relevant parameters given in Tables 2 and 3 into equation (4),

$$\delta\Delta H_{\text{phys}}^{\ddagger} = \Delta H_{\text{obs}}^{\ddagger} - \left\{ \left[ \frac{\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}} K_{\text{se}} x_1}{(x_4 + K_{\text{se}} x_1)} \right]_{\text{AC}} - \left[ \frac{\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}} K_{\text{se}} x_1}{(x_4 + K_{\text{se}} x_1)} \right]_{\text{B}} \right\} \quad (4)$$

where the suffices AC and B stand for an activated complex and a base. According to the same line of treatment, solvent effects on the reaction enthalpy due to 'more physical' interaction can be given by equation (5), where the suffix PC stands for a product cation.

$$\delta\Delta H_{\text{phys}}^{\circ} = \Delta H_{\text{obs}}^{\circ} - \left\{ \Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{mix}}(\text{I}^-) + \left[ \frac{\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}} K_{\text{se}} x_1}{(x_4 + K_{\text{se}} x_1)} \right]_{\text{PC}} - \left[ \frac{\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}} K_{\text{se}} x_1}{(x_4 + K_{\text{se}} x_1)} \right]_{\text{B}} \right\} \quad (5)$$

Except for these systems for which the parameters are summarized in Tables 2 and 3, unity and zero should be substituted into the parameters,  $K_{\text{se}}$  and  $\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}}$ , respectively, which means no preferential solvation of methanol over acetonitrile and zero specific interaction enthalpy.

Extended Brønsted treatments carried out on the basis of two different definitions, *i.e.* a 'more physical' quantity against an overall quantity, are compared in Figures 1 and 2, and the slopes of the correlations defined using the 'more physical' quantity,  $\alpha_{\text{phys}}$ , are summarized in Table 4.

The free energy and entropy of transfer due to a specific interaction are given by equations (6) and (9).<sup>18</sup>

$$\Delta G_{\text{t,SI}}^{\text{AN} \rightarrow \text{mix}} = -RT \ln (x_4 + K_{\text{se}} x_1)^z \quad (6)$$

$$\Delta S_{\text{t,SI}}^{\text{AN} \rightarrow \text{mix}} = \left( \frac{z\Delta H_{\text{se}}}{T} \right) \left( \frac{K_{\text{se}} x_1}{x_4 + K_{\text{se}} x_1} \right) + R \ln (x_4 + K_{\text{se}} x_1)^z \quad (7)$$

The free energy of activation due to 'more physical' interaction can be calculated by equation (8), according to the same

$$\delta\Delta G_{\text{phys}}^{\ddagger} = \delta\Delta G_{\text{obs}}^{\ddagger} - \left\{ [-RT \ln (x_4 + K_{\text{se}} x_1)^z]_{\text{AC}} - [-RT \ln (x_4 + K_{\text{se}} x_1)^z]_{\text{B}} \right\} \quad (8)$$

line of argument. In order for the entropy and free energy to be calculated according to equations (6)–(8), the solvation number  $z$  has to be determined; it is evaluated as follows. First,

$$x_{1,\text{min}} = \frac{(-1)}{(K_{\text{se}} - 1)} \left[ \left( \frac{\Delta H_{\text{se}}}{RT} \right) \frac{K_{\text{se}}}{(K_{\text{se}} - 1)} + 1 \right] \quad (9)$$

the entropy of transfer, equation (7), has the minimum at solvent composition  $x_{1,\text{min}}$ .<sup>18</sup> The required parameter,  $\Delta H_{\text{se}}$ , can be given through the division of the parameter,  $\Delta H_{\text{t,SI}}^{\text{AN} \rightarrow \text{MeOH}}$  ( $= z\Delta H_{\text{se}}$  and given in Table 2) by an assumed value of  $z$ , and the value,  $K_{\text{se}}$ , is summarized in Table 2. With respect to

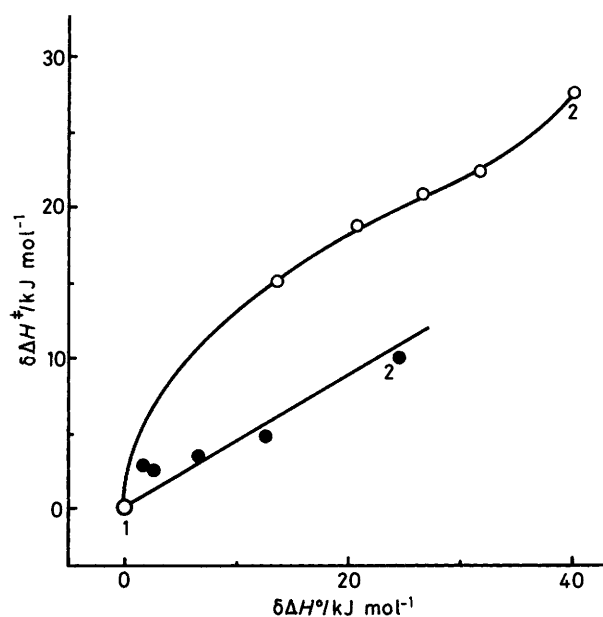


Figure 1. Correlation between activation enthalpy and reaction enthalpy for the DABCO plus methyl iodide reaction in acetonitrile-methanol mixtures: ○, overall quantity; ●, quantity due to 'more physical' interaction; 1, acetonitrile; 2, methanol

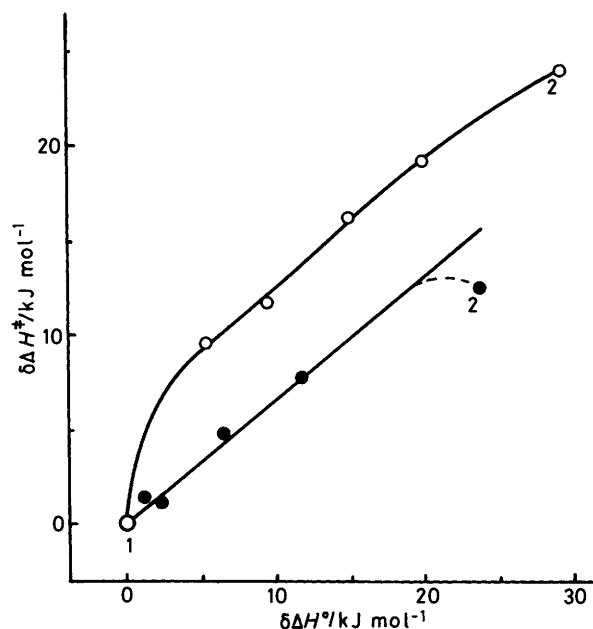


Figure 2. Correlation between activation enthalpy and reaction enthalpy for the 4-dimethylaminopyridine plus methyl iodide reaction in acetonitrile-methanol mixtures: ○, overall quantity; ●, quantity due to 'more physical' interaction; 1, acetonitrile; 2, methanol

the transfer of quinuclidine the entropy minimum should be observed at  $x_{\text{MeOH}} 0.22$  for  $z 2$  and at  $x_{\text{MeOH}} 0.52$  for  $z 1$ . Activation entropy *versus* solvent composition profiles lead one to suspect that the minimum should exist at  $x_{\text{MeOH}} \lesssim 0.5$  (see Table 1). This supposition agrees with the view that  $z = 2$  for quinuclidine solvation by methanol and this view has an analogy with the result that  $z = 2$  for triethylamine solvation with methanol.<sup>18</sup>

However, these criteria cannot be applied to the 4-dimethylaminopyridine plus methyl iodide reaction as described above.

Secondly, for an assumed value of  $z$ , the entropy of transfer from acetonitrile to methanol can be given by substituting the required parameters, *i.e.*,  $\Delta H_{se} = \Delta H_{1,SI}^{AN \rightarrow MeOH}/z$  and  $K_{se}$ , and  $x_1 = 1.0$ , into equation (7). Quite interestingly, the substitution of  $z = 2$  throughout for aliphatic amines and  $z = 1$  for 4-dimethylaminopyridine together with the parameters given in Tables 2 and 3 leads to nearly the same range of entropy changes throughout for the strong bases of similar  $pK_a$  values, *i.e.*,  $-27.7$ ,  $-32.5$ ,  $-32.9$ , and  $-30.7$  at  $25^\circ\text{C}$  (all in  $\text{J K}^{-1} \text{mol}^{-1}$ ) for quinuclidine, triethylamine, activated complex for DABCO plus methyl iodide reaction, and 4-dimethylaminopyridine, respectively. Experimental estimates of the corresponding entropy change by Abraham leads to  $-21 \text{ J K}^{-1} \text{mol}^{-1}$  for triethylamine transfer from acetonitrile to methanol.<sup>23</sup> The value  $z = 1$  for the 4-dimethylaminopyridine-methanol interaction has an analogy with  $z = 1$  for pyridine-methanol interaction derived previously.<sup>18</sup>

Activation enthalpy *versus* activation free energy correlations were carried out for two different quantities, *i.e.*, a 'more physical' quantity against an overall quantity, and comparisons are exemplified in Figures 3 and 4.

Isokinetic temperatures due to a 'more physical' interaction,  $\beta_{\text{phys}}$ , were calculated from two types of correlations, *i.e.*, activation enthalpy *versus* activation free energy correlations, and activation enthalpy *versus* activation entropy correlations, and the average values are summarized in Table 4. With respect to the quinuclidine plus methyl iodide and to the 4-cyanopyridine plus methyl iodide reactions, the range of variations for  $\delta\Delta H_{\text{phys}}^\ddagger$  is rather narrow, as partly inferred from the low values of  $\alpha_{\text{phys}}$ , and the slope values derived using these values, *i.e.*,  $\beta_{\text{phys}}$ , contain large uncertainties and are indicated in parentheses.

**Characteristics of an Activated Complex.**—In activation enthalpy *versus* reaction enthalpy correlation with the variation in substrate clearly indicates that aliphatic amines form a different reaction series from that of aromatic amines,<sup>19</sup> *i.e.*, the reaction series is determined by a family-dependent property. With respect to the aliphatic amines, the rising trend in the coefficient  $\alpha_{\text{phys}}$  (quinuclidine < triethylamine < DABCO) does not agree with the trend of increasing reactivity as judged from the activation enthalpy in acetonitrile (triethylamine < DABCO < quinuclidine) while for aromatic amines both trends follow the order of electron-donating power of the substituents (4-cyanopyridine < pyridine < 4-t-butylpyridine < 4-dimethylaminopyridine). Furthermore, the isokinetic temperatures,  $\beta_{\text{phys}}$  for the aromatic amine reactions indicate systematically higher values than room temperature, while those for the aliphatic amine reactions are lower than room temperature. Within the aliphatic amine series, substrate variation is usually accompanied by a significant geometrical change around the reaction centre with multiple effects being introduced into the reactivity as well as the transition state index itself. However, within the aromatic amine series, substituent effects are transmitted to a reaction centre through simultaneous internal as well as external polarizations from a remote site of substitution. Thus probes detecting either internal or external variations induced by substituents would be subjected to a parallel response.

At the transition state of the quinuclidine reaction the rear side of the reacting nitrogen is protected by the hydrocarbon skeleton from the approach of solvent, while in the triethylamine reaction the rear side is open to approaching solvent and polarization in the transition state seems to be assisted by electrostatic solvation at the rear side of a reacting nitrogen atom. From photoelectron spectroscopic studies, strong evidence has been given for a through-space interaction between lone pair electrons on the nitrogen atoms located at the opposite

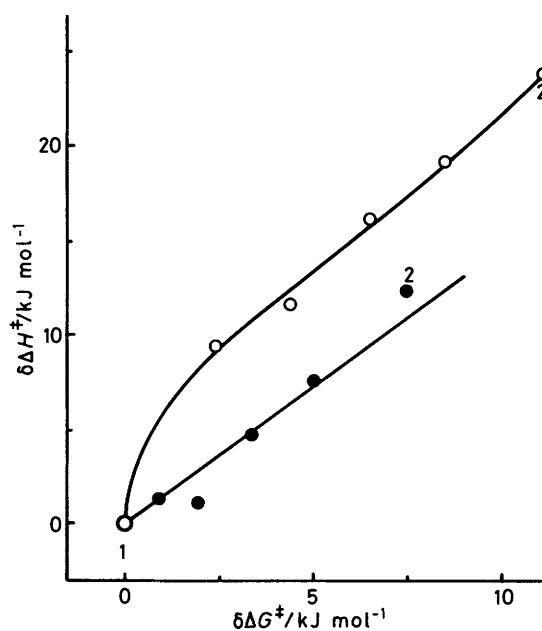


Figure 3. Correlation between activation enthalpy and activation free energy for the 4-dimethylaminopyridine plus methyl iodide reaction in acetonitrile-methanol mixtures:  $\circ$ , overall quantity;  $\bullet$ , quantity due to 'more physical' interaction; 1, acetonitrile; 2, methanol

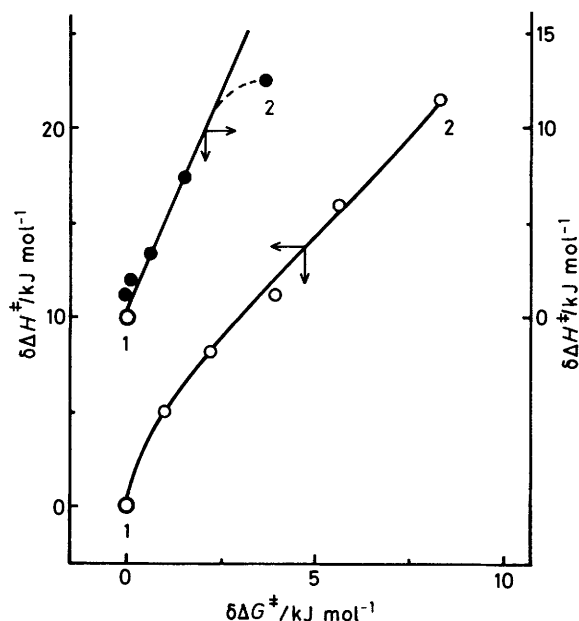


Figure 4. Correlation between activation enthalpy and activation free energy for the 4-t-butylpyridine plus methyl iodide reaction in acetonitrile-methanol mixtures:  $\circ$ , overall quantity;  $\bullet$ , quantity due to 'more physical' interaction; 1, acetonitrile; 2, methanol

side of the bridgehead in DABCO.<sup>24</sup> The activated complex for the DABCO reaction, although also protected from the approach of solvent as for the quinuclidine reaction, seems to be effectively polarized due to assistance from the lone pair electrons at the opposite side to the reacting nitrogen atoms. Within the aliphatic amine series, partly because of the low polarizability of the hydrocarbon skeleton, polarization at transition state could be affected by seemingly unexpected factors incorporated into the relevant system.

Within the aromatic amine series, an increasing isokinetic temperature,  $\beta_{\text{phys}}$ , is accompanied by an increasing charge development in the transition state as given by the value  $\alpha_{\text{phys}}$ . The value  $\beta_{\text{phys}}$  expresses the relative significance of enthalpy over entropy in the free energy. These trends are accommodated by the view that as the polarization proceeds further, the solute-solvent interaction shifts from an entropy-dominated free energy to an enthalpy-dominated one, *i.e.*, entropy provides a more sensitive probe for detecting weaker interactions.

There are two seemingly conflicting pieces of evidence from kinetic isotope effect studies on the pyridine plus methyl iodide reaction series.  $\alpha$ -Deuterium kinetic isotope effects ( $k_{\text{CH}_3}/k_{\text{CD}_3}$ ) ( $\alpha$ -D k.i.e.) indicate that the better the nucleophile, the less crowded becomes the activated complex.<sup>11</sup> On the other hand, an entering group kinetic isotope effect, ( $k_{\text{I}^{15}\text{N}}/k_{\text{I}^{14}\text{N}}$ ), may indicate that as the nucleophile becomes better, N-C bond making in the transition state proceeds further.<sup>12</sup>

A hydrogen-bonded complex between base and HX,  $\text{B} \cdots \text{H}-\text{X}$ , is a conceptually analogous to the activated complex of the Menschutkin reaction, since in either complex partial bond-making and partial bond-breaking processes proceed simultaneously along a bond linking three atoms. In fact, the activation enthalpy for the Menschutkin reaction in acetonitrile and the enthalpy of hydrogen-bond formation as given by the quantity  $\Delta H_{\text{I,SI}}^{\text{AN-MeOH}}$  indicate analogous responses to varying basicity of the relevant amines.<sup>25</sup> Recent work on the rotational spectra for the hydrogen-bonded complex between base and hydrogen fluoride indicates that lengthening of the H-F bond increases with increasing hydrogen-bond strength.<sup>26</sup>

These conclusions derived from two types of kinetic isotope effect studies, the spectroscopic studies, and the present work on solvent effects can be unified into one suggestion that as the nucleophile becomes better, N-C bond-making proceeds further with accompanying efficient C-I bond-breaking; this results in more charge development on the incipient cationic as well as on the anionic centre in the transition state. Stated otherwise, as the nucleophile becomes better, the transition state shifts in a more product-like direction, although the slope of the  $\Delta H^\ddagger$  versus  $\Delta H^\circ$  correlation due to substrate variation remains constant at 0.23 throughout the series.<sup>10,19</sup>

An alternative interpretation can be given in terms of two-dimensional potential energy surfaces, partly modified version of More O'Ferrall diagrams.<sup>27</sup> The coefficient,  $\alpha_{\text{phys}}$ , can be taken as a measure of developing negative charge on the leaving iodine atom,<sup>18</sup> in a way similar to C-I bond-breaking, while the  $\alpha$ -D k.i.e. gives the extent of relative crowding at the transition state, a perpendicular positioning to a reaction co-ordinate.<sup>11</sup> The substituent effects on the coefficient  $\alpha_{\text{phys}}$  combined with those on  $\alpha$ -D k.i.e. lead to the suggestion that as the nucleophile becomes better, the transition state shifts its character from a tight and less charge-developed structure to a loose and more charge-developed one. These interpretations are plausible in a sense but are not sophisticated enough to incorporate all the information derived through various transition state probes into one scheme.

A variation in substrate induces multiple effects into transition state characteristics with accompanying variations in intramolecular as well as in intermolecular solvation, while solvent and isotope effect studies provide a probe for detecting more specific properties. This is crucial for the observations; reactions, although belonging to a particular Brønsted series according to substrate variation,<sup>19</sup> *i.e.*, aliphatic or aromatic amines, manifest individual isotope and solvent effects.

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