Reaction of 1,1,3,3-Tetramethylthiourea with Methyl Iodide: Kinetic and Thermodynamic Aspects

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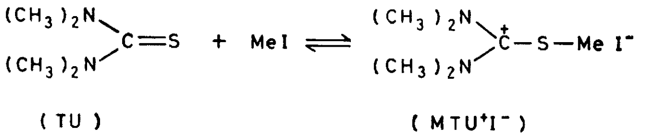
In the reaction of 1,1,3,3-tetramethylthiourea with methyl iodide limiting forms of the rate law arise in solvents in which the concentration of free ions and ion-pairs is small in comparison with higher aggregates. The solvent effects on the rate of the forward reaction were linearly correlated with those on the Menschutkin reaction. The effects were quite close to those on the pyridine–methyl iodide reaction. The value ($\Delta_2V^{\ddagger}/\Delta_2\bar{V}^{\circ}$), which is expected to be an index of the position of the transition state along the reaction co-ordinate, is *ca.* 0.27 in acetonitrile and propylene carbonate. The position of the transition state, n_T, calculated from the enthalpy term, is *ca.* 0.30 for the present reaction and for the *NN*-dimethylaniline–methyl iodide reaction. These indices of the transition state position are qualitatively in agreement with each other. The results of CNDO/2 calculations, performed for the assumed transition state structures, are in accord with the results of the experimental observations on the solvent effects on reaction rates.

THE influence of solvents upon reaction rates and equilibria has been discussed extensively in the literature, and many attempts have been made to characterize transition state properties and to correlate the effects with various aspects of solvation of the transition state of a reaction.[1-3] Parker and Abraham have carried out such analyses in terms of thermodynamic transfer quantities, on both an experimental [4,5] and a theoretical basis.[6]

In the present work we analysed the reaction of 1,1,3,3-tetramethylthiourea with methyl iodide from various kinetic and thermodynamic aspects and tried to locate the position of the transition state along the reaction co-ordinate.



EXPERIMENTAL

Materials.— Bis(dimethylamino)methylthiomethylium iodide (MTU^+I^-), prepared from 1,1,3,3-tetramethylthiourea and methyl iodide, was recrystallized five times from acetone–ethyl ether, and dried *in vacuo* over phosphorus pentaoxide at 65 °C (Calc. for $C_6H_{15}IN_2S$: H, 5.5; C, 26.3; N, 10.22. Found: H, 5.4; C, 26.2; N, 10.3%).

1,1,3,3-Tetramethylthiourea (TU) (Wako) was recrystallized three times from ethyl ether and dried over phosphorus pentaoxide at 65 °C. Solvents were purified as described elsewhere.[7,8] Kinetic measurements and density measurements were performed as described previously.[8] The apparent molal volumes were calculated by equation (1)

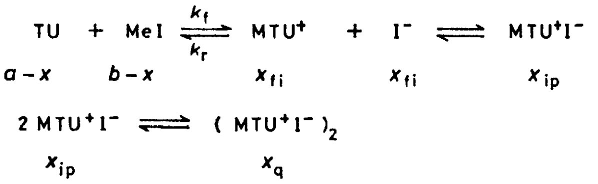
$$\phi_v = 1\,000(d_0 - d)/cd_0 + M_2/d_0 \qquad (1)$$

where the quantities have their usual meaning.

Heat of Reaction Measurements.—The heat of reaction was measured at 25 °C with a Tokyo Riko MPC-11 calorimeter used as a conduction type vessel. A methyl iodide solution (0.100M) in acetonitrile (30 ml) and tetramethylthiourea (0.218 2 g) sealed in an ampoule were placed in the calorimeter cell. After thermal equilibration, the ampoule was broken with stirring and the temperature change was recorded on a chart over 18 h. Calibration was achieved by introducing a measured quantity of thermal energy. The heat of solution of tetramethylthiourea in acetonitrile was measured with an isothermal twin calorimeter (Tokyo Riko TIC-2D) at a comparable concentration to that above (25 °C). A combination of these two data yielded a heat of reaction in acetonitrile of ΔH -16.8 ± 0.3 kcal mol^{-1}.

RESULTS AND DISCUSSION

Rate Laws.—In polar solvents the reaction followed second-order kinetics as expected,[8-10] *i.e.* first order in tetramethylthiourea and in methyl iodide. In cyclohexanone and bromobenzene the situation was rather complicated, partly because of the thermodynamic instability of the ions formed and, as a result, of the coexistence of the various kinds of aggregates in these solvents.[11,12]



SCHEME

Using the same treatment as discussed previously,[8] the Scheme was postulated. This leads to the kinetic equations (2)—(6). At equilibrium equation (7) holds

$$dx/dt = k_f(a - x)(b - x) - k_r x_{fi}^2 \qquad (2)$$

$$K = (k_f/k_r) \qquad (3)$$

$$K_{ip} = (x_{ip}/x_{fi}^2) \qquad (4)$$

$$K_q = (x_q/x_{ip}^2) \qquad (5)$$

$$x = x_{fi} + x_{ip} + 2x_q = x_{fi} + K_{ip}x_{fi}^2 + 2K_qK_{ip}^2x_{fi}^4 \qquad (6)$$

$$k_f(a - x_e)(b - x_e) = k_r x_{fi,e}^2 \qquad (7)$$

where the subscript e denotes the concentration at equilibrium.

In cyclohexanone, the stoicheiometric equilibrium constant was defined by equation (8). Combinations of equations (3), (6), (7), and (8), gives (9).

The values of K_{obs} and the corresponding values of x_e, determined analytically after keeping reaction mixtures of various initial concentrations at 30 °C for a sufficiently

$$K_{obs} \equiv \frac{x_e^2}{(a - x_e)(b - x_e)} \qquad (8)$$

long time (usually over a week), were substituted into $(K_{obs}/K)^{1/2} =$

$$1 + K_{ip}(Kx_e^2/K_{obs})^{1/2} + 2K_qK_{ip}^2(Kx_e^2/K_{obs})^{3/2} \qquad (9)$$

equation (9). The equations were solved simultaneously to give $K = 0.231$, K_{ip} 1.43×10^4 l mol^{-1}, and K_q 4.22 l mol^{-1}. The behaviour of K_{obs} as a function of x_e was well reproduced by the set of equilibrium constants as shown in Figure 1.

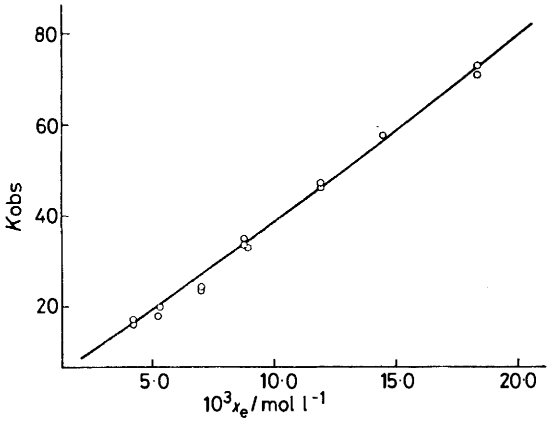


FIGURE 1 Plots of K_{obs} *versus* X_e at 30 °C: ○, experimental; —, calculated with K 0.231, K_{ip} 1.43×10^4 l mol^{-1}, K_q 4.22 l mol^{-1}

All three equilibrium constants for the present reaction are larger than those for the reaction of 3-isopropyl-4-methyl-4-thiazoline-2-thione with methyl iodide,[8] *i.e.* K 1.08×10^{-2}, K_{ip} 1.11×10^3 l mol^{-1}, K_q 3.35 l mol^{-1}, but seem to be of the correct order of magnitude. The values of x_{fi} at a given time were obtained by solving equation (6), substituted with the above set of equilibrium constants, by the Newton–Raphson method for the measured values of x.

The integration of equation (10) was carried out graphically by Simpson's method after substituting the value of x and x_{fi}. The forward rate constant thus

$$\int_0^x \frac{dx}{(a - x)(b - x) - x_{fi}^2/K} = \int_0^t k_f dt \qquad (10)$$

obtained was in agreement within experimental error with the value obtained over the initial period of the reaction, assuming irreversible second-order kinetics.

In bromobenzene, the ions are expected to exist as higher aggregates,[11,12] and the assumption $x_q \gg x_{fi}$ and x_{ip} seems plausible. Then, equation (6) simplifies to (11). In bromobenzene the overall equilibrium constant

$$x \approx 2x_q = 2K_qK_{ip}^2x_{fi}^4 \qquad (11)$$

K_{obs} was defined by the left-hand side of equation (12), and from combination of equations (3), (7), and (11), the

$$K_{obs} \equiv \frac{x_e^{1/2}}{(a - x_e)(b - x_e)} = K(2K_qK_{ip}^2)^{1/2} \qquad (12)$$

left-hand side leads to the right-hand side of equation (12). Under these conditions, equation (2) simplifies to (13).

$$dx/dt = k_f[(a - x)(b - x) - K_{obs}^{-1}x^{1/2}] \qquad (13)$$

$$\int_0^x \frac{dx}{(a - x)(b - x) - K_{obs}^{-1}x^{1/2}} = \int_0^t k_f dt \qquad (14)$$

The values of k_f and K_{obs} were calculated in two ways. First, graphical integration of the left-hand side of equation (14) was carried out by Simpson's method for an assumed value of K_{obs}. The procedure was repeated until a constant value of k_f was obtained throughout the run. Secondly for assumed values of k_f and K_{obs} the graphical integration by Simpson's method was repeated until the calculated set of x *versus* t data agreed with the experimental values. The best set of K_{obs} and k_f were 4.40×10^3 l$^{1/2}$ mol$^{-1/2}$ and 7.20×10^{-4} l mol^{-1} s^{-1}, respectively. The overall equilibrium constant obtained analytically after keeping the reaction mixture at 30 °C for a sufficiently long time (over two weeks), 4.68×10^3 l$^{1/2}$ mol$^{-1/2}$, thus agreed well with the value calculated above from the kinetic measurements.

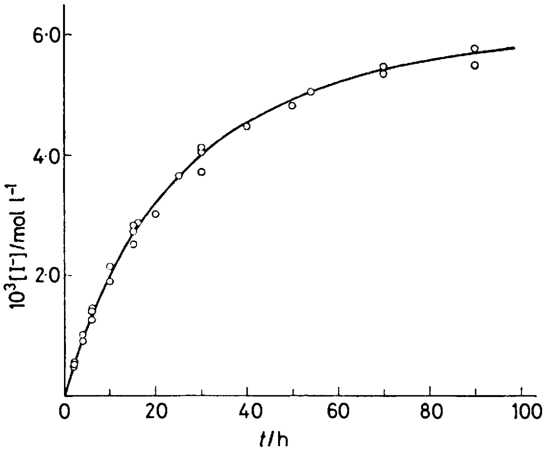


FIGURE 2 Plots of [I$^-$] *versus* t at 30 °C in bromobenzene: ○, experimental; —, calculated with K_{obs} 4.4×10^3 l$^{1/2}$ mol$^{-1/2}$, k_f 7.20 10^{-4} l mol^{-1} s^{-1}, $a = b = 1.03 \times 10^{-2}$ mol l^{-1}

In toluene and benzene the rate behaviour was expected to follow the same pattern as observed in bromobenzene. However, partly because of the slow rate the reaction could be followed only over the initial period, so that more detailed analysis was impossible. The rate followed second-order kinetics over the initial period.

Solvent Effects on the Rate Constant k_f.—The rate constants k_f are summarized in Table 1, where k_x denotes the rate constant expressed in mole fraction units as calculated from the rate constant k_f and the

TABLE 1

Comparison of rate constant k_f at 30 °C

Solvent	$10^4k_f/$ l mol^{-1} s^{-1}	10^3k_x/s^{-1}
Propylene carbonate	98.2	114.9
Acetonitrile	38.4	72.1
Nitrobenzene	50.1	48.5
Cyclohexanone	29.3	28.0
Bromobenzene	7.20	6.79
Benzene	1.37	1.52
Toluene	0.964	0.898
Methanol	7.47	18.2
Propan-2-ol	4.71	6.09

molar volume of the solvent V_s/l by the equation $k_x = k_f V_s^{-1}$.

An empirical linear correlation is found between the log k_x values for the present reaction (Table 1) and log k_x values for the pyridine–benzyl bromide reaction (Figure 3). The slope of the plot, 0.84, is very close to that for the reaction of pyridine with methyl iodide and is larger than that for the corresponding reaction of 4-thiazoline-2-thione with methyl iodide.[8] The present reaction proceeds 2—5 times faster than the corresponding reaction of 4-thiazoline-2-thione with methyl iodide. This possibly explains the larger equilibrium constants found for the present reaction.

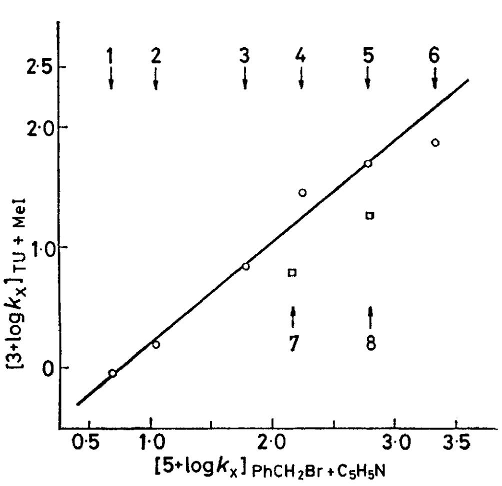


FIGURE 3 Empirical correlations for the rate constants. Ordinate, present system; abscissa, pyridine + benzyl bromide. 1, Toluene; 2, benzene; 3, bromobenzene; 4, cyclohexanone; 5, nitrobenzene; 6, acetonitrile; 7, propan-2-ol; 8, methanol

Pressure Effects and the Volume Change of Reaction.— Activation volumes and their pressure derivatives were determined by the least-squares method after expanding the rate constants into power series of pressure as given by equations (15)—(17) and summarized in Table 3.

The apparent molal volumes of the solute ϕ_v and the overall volume change in the reaction $\Delta\phi_v$ are summarized in Table 4. In acetonitrile and propylene carbonate, the values of $\Delta\phi_v$ in Table 4 are approximately equal to the volume change of the reaction $\Delta\bar{V}^0$ since under the experimental conditions (concentration *ca.* 5×10^{-2}M) the salt is expected to be largely dissociated.[13,14]

TABLE 2

Comparison of slopes for various reactions

Reaction	$\Delta \log k_x/(\Delta \log k_x)_{PhCH_2Br + C_5H_5N}$
Benzyl bromide + pyridine	1.0
Methyl iodide + pyridine	0.82[8]
Methyl iodide + 1,1,3,3-tetramethyl-2-thiourea	0.84
Methyl iodide + 4-thiazoline-2-thione	0.51[8]

$\Delta V_0^\ddagger$ has been regarded as consisting of two terms, *i.e.*

$$\ln k_p = \ln k_0 + Bp + Cp^2 \qquad (15)$$

$$\Delta V_0^\ddagger = (-1)BRT \qquad (16)$$

$$(\partial \Delta V^\ddagger/\partial p)_0 = (-2)CRT \qquad (17)$$

$\Delta_1 V^\ddagger$ and $\Delta_2 V^\ddagger$. The first term expresses the volume change of the reactant molecules as they form a transition state, while the latter expresses the contribution due to the volume change in the surrounding solvent. A similar dissection of $\Delta\bar{V}^0$ can be made in terms of $\Delta_1\bar{V}^0$ and $\Delta_2\bar{V}^0$. Stewart and Weale[15] concluded that $\Delta_1\bar{V}^0$ is *ca.* 0 for the Menschutkin reaction, using the cylinder model, and essentially the same conclusion can be drawn if model solutes are used to estimate the various $\bar{V}_1^0$ terms for reactants and products. We know already that $V_m = 67.1$ cm^3 mol^{-1} for methyl iodide, and if we take acetone (V_m 73.5 cm^3 mol^{-1}) as a model for tetramethylthiourea, 1-methylethyl methyl ether (V_m 102.4 cm^3 mol^{-1}) as a model for the *S*-methylated cation, and liquid xenon[16] (V_m 37.3 cm^3 mol^{-1}) as a model for iodide ion we find that $\Delta_1\bar{V}^0 = 102.4 + 37.3 - 73.5 - 67.1 = -0.9$ cm^3 mol^{-1}. Thus the major contribution to the observed $\Delta\phi_v$ value must come from the $\Delta_2\bar{V}^0$ term.

TABLE 3

Activation volumes and the pressure derivatives (30 °C)

Solvent	$\Delta V_0^\ddagger$/cm^3 mol^{-1}	$(\partial\Delta V^\ddagger/\partial p)_0$/ cm^5 mol^{-1} kg^{-1}
Acetonitrile	−22.0	0.008 30
Propylene carbonate	−17.4	0.006 31

In order to obtain the corresponding $\Delta_2 V^\ddagger$ term, it is necessary to estimate the $\Delta_1 V^\ddagger$ value. Now the previous estimate of $\Delta_1 V^\ddagger = -6.4$ cm^3 mol^{-1} for the forward Menschutkin reaction was obtained using van der Waals radii.[15] It is known that the experimentally determined molal volume of a solute V_M is larger than the van der Waals volume V_w by a factor of 1.3—2.2 because of the existence of empty volume in the liquid.[17,18] The estimated value, −6.5 cm^3 mol^{-1}, must be multiplied by this factor to yield a corrected $\Delta_1 V^\ddagger$ value of −11.7 cm^3 mol^{-1} which can be used in conjunction with other values obtained from molar volumes. Then using $\Delta V_0^\ddagger = -22.0$ (see Table 4) we calculate that $\Delta_2 V^\ddagger =$

TABLE 4

Apparent molal volumes ϕ_v and the volume change of the reaction at 30 °C

Solvent	ϕ_v/cm^3 mol^{-1} TU	MeI	MTU$^+$I$^-$	$\Delta\phi_v$	$\Delta V_0^\ddagger$	$(\Delta_2 V^\ddagger/\Delta_2\bar{V}^0)$
Acetonitrile	127.4	67.1[8]	157.1	−37.4	−22.0	0.27
Propylene carbonate	131.0	65.1[8]	175.0	−21.1	−17.4	0.27

-10.3 cm^3 mol^{-1} and hence that $(\Delta_2V^{\ddagger}/\Delta_2\bar{V}^0) \approx (\Delta_2V^{\ddagger}/\Delta\phi_v) = 0.27$; this value is very close to those previously observed for the Menschutkin reaction and for the *S*-methylation of 4-thiazoline-2-thione with methyl iodide, *i.e.* 0.26—0.29.[8] In principle the procedure would give a means of estimating an index which locates the position of the transition state along the reaction co-ordinate on the basis of the electrostrictive view, though at this stage the value of 0.27 is subject to some uncertainties.

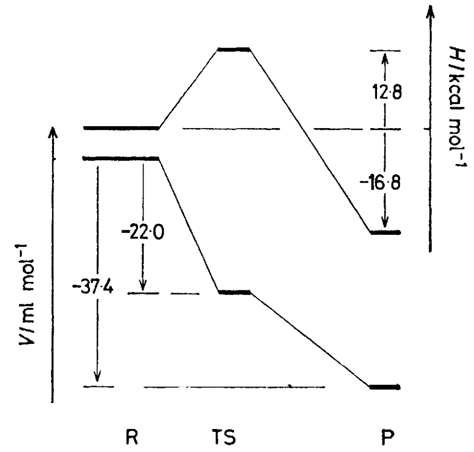


FIGURE 4 Volume and enthalpy *versus* reaction co-ordinate profile

Activation Enthalpy $\Delta H^{\ddagger}$ and Heat of Reaction $\Delta\bar{H}^0$.—Recently theoretical methods have been developed to locate the position of the energy barrier along the reaction co-ordinate.[19-21] Agmon[20] and Miller[21] have independently derived the same analytical relationship which determines the position of the transition state as (18) where E_a and ΔE stand for the activation energy and

$$n_T = E_a/(2E_a - \Delta E) \qquad (18)$$

the energy change of the reaction. Data in Table 5 suggest that the enthalpies and, therefore, the position of the transition state is of similar magnitude for the two slow reactions. The two indices which give the position of the transition state are in agreement with each other.

TABLE 5

Reaction	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta\bar{H}^0$/ kcal mol^{-1}	n_T	Method for determining ΔH
Tetramethylthiourea + MeI [a]	12.8	-16.8	0.30	Calorimetry
NN-Dimethylaniline + MeI [b]	11.4 [22]	-15.4 [22]	0.30	Second law

[a] In acetonitrile. [b] In nitrobenzene.

Abraham estimated the extent of charge separation in the transition state as 0.37—0.45 for the Menschutkin reaction from a correlation of the transfer free energies.[23] These values were estimated by referring to the ion pair as product.[5,23] In contrast, our values of n_T were calculated with respect to the product dissociated pair of ions. For going from the dissociated pair of ions to ion pair, ΔV^0 has been reported to be *ca.* $+17$ cm^3 mol^{-1} for Et_4NI in acetone.[24] Assuming that the same value applies to the present reaction products, the reaction index which refers to the ion pair product would be given by $-10.3/(-37.4 + 17) \approx 0.50$, which is very close to the n_T values estimated from the work of Abraham.[23,*] At the present stage of sophistication the indices have only the accuracy suggested by the fact that the slope of the plot of $\delta \log k$ against $\delta \log K$ is *ca.* 0.4,[25] while the n_T value in Table 5 is 0.3, for the same *NN*-dimethylaniline–methyl iodide reaction.

CNDO/2 *Calculations.*—CNDO/2 Calculations[26] were carried out for the estimated structures of the transition state using model compounds. In order to save time

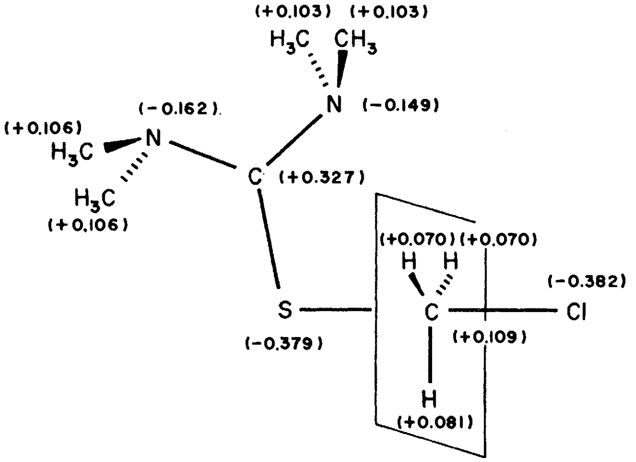


FIGURE 5 Charge distribution for minimized structure: r_{C-S} 1.83 Å; r_{C-Cl} 1.81 Å; μ 7.76 D

the following assumptions were made: tetramethylthiourea has C_s symmetry, $C\hat{S}C = 101°$, and the central CH_3 group is planar. Calculations were repeated until a minimum total energy was reached, by changing the value of Δr using $r_{S-C} = 1.80 + \Delta r$ and $r_{C-Cl} = 1.78 + \Delta r$, where the numerals indicate the normal bond distances of model compounds,[27] assuming normal bond lengths and angles except as mentioned above.[26]

TABLE 6

Experimental and CNDO/2 results

Reaction	$\Delta \log k/(\Delta \log k)_{PhCH_2Br + C_5H_5N}$	Charge on Cl	μ/D
1,1,3,3-Tetramethyl-2-thiourea + MeI	0.84	-0.382	7.76
4-Thiazoline-2-thione + MeI	0.51	-0.338 [8]	6.74 [8]

For the minimized structures, both the charge on chlorine and the dipole moments are larger than the corresponding values of the *S*-methylation reaction of 4-thiazoline-2-thione. The facts are intuitively in agreement with the kinetic behaviour, *i.e.* the larger the negative charge density on chlorine, the more sensitive the rate to solvent change. The dipole moment thus obtained seems to be of the correct order.[8,23] These

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[*] We thank a referee for this suggestion.

model calculations seem to have some, though limited, use in estimating solvent effects on reaction rates.

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