# Use of Steric Effects in determining the Position of the Transition State for the $S_N2$ Reaction between Methyl Iodide and $\Delta^4$-Thiazoline-2-thiones

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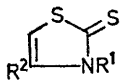
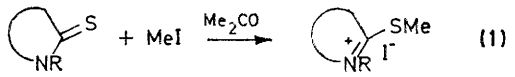
The quantitative nucleophilic reactivity of some 3-alkyl-$\Delta^4$-thiazoline-2-thiones (1) towards methyl iodide is described. Bulky alkyl groups increase the rate of *S*-alkylation and this unexpected behaviour is explained by strain release in the transition state. It is shown that the rate acceleration is closely related to the conformational state of the 3-alkyl group. Using steric effects to examine the transition state, we have shown that it is, in regard to the heterocyclic ring, 65% along the reaction co-ordinate from the initial state.

THE thiocarbonyl group of a thioamide is known to be a good nucleophile and this property has often been used



(1)

a; $R^1$ = Me, $R^2$ = H  e; $R^1$ = Me, $R^2$ = Bu$^t$
b; $R^1$ = Et, $R^2$ = H  f; $R^1$ = Et, $R^2$ = Bu$^t$
c; $R^1$ = Pr$^i$, $R^2$ = H  g; $R^1$ = Pr$^i$, $R^2$ = Bu$^t$
d; $R^1$ = Bu$^t$, $R^2$ = H  h; $R^1$ = $R^2$ = Me



(1)

for synthetic purposes in the heterocyclic field [equation (1)].[1,2] However very little quantitative work has been devoted to the factors affecting the nucleophilic reactivity.[3] This paper deals with the influence of *o*-alkyl substitution on the rate of *S*-alkylation by methyl iodide of the model compound $\Delta^4$-thiazoline-2-thione (1).

This study on the steric effect of the alkyl group gives insight into the structural modification that the nucleophile undergoes in the transition state.

## RESULTS AND DISCUSSION

Inspection of Table 1 reveals that the rate constants are almost the same for the thiocarbonyl compounds (1a—c). A significant increase in the reactivity is observed for (1d). Thus a bulky group such as Bu$^t$ leads to an acceleration of the *S*-methylation. An explanation of this unexpected behaviour [4,5] for *o*-alkyl substitution is that strain release occurs in going from the initial to the transition state.

We shall first consider the origin of the difference in reactivity between the t-butyl substituent and the three others of the Ingold set.[6] The intramolecular steric size of the isopropyl group is not very different from that of the methyl group, owing to the preferential conformation of the former in which the methine hydrogen lies in the plane of the ring on the same side as the thiocarbonyl group (Scheme 1). This conformational preference arises from the large difference in effective size between the thioxo-function in the 2-position and the hydrogen atom in the 4-position.[7] This isopropyl group behaviour is well documented in several model compounds.[8-11]

TABLE 1

Rate constants and activation parameters for the reaction MeI + (1a—h)

| Compound | M.p. (°C) | $10^6k$/l mol$^{-1}$ s$^{-1}$ 20° | 25° | 30° | $\Delta G^{\ddagger}$ 298 [b] | $\Delta H^{\ddagger}$ [b] | $\Delta S^{\ddagger}$ [b] |
|---|---|---|---|---|---|---|---|
| (1a) | 46 | 104·3 | 162·2 | 244 | 22·65 | 14·4 ± 0·3 | −27·6 ± 1 |
| (1b) | 38 | 103·5 | 159·1 | 241 | 22·65 | 14·3 ± 0·15 | −27·9 ± 0·8 |
| (1c) | 63 | 114·0 | 173·6 | 261 | 22·57 | 14·02 ± 0·4 | −28·7 ± 2·1 |
| (1d) | 56 | 188·6 | 288·6 | 435 | 22·32 | 13·8 ± 0·14 | −28·7 ± 0·7 |
| (1e) | 117 | 138·6 | 212·1 | 320 | 22·47 | 14·2 ± 0·47 | −27·8 ± 2·3 |
| (1f) | 87 | 140·6 | 214·5 | 323 | 22·45 | 14·1 ± 0·5 | −28·0 ± 2·6 |
| (1g) | 83 | 303·1 | 457·0 | 680 | 22·00 | 13·7 ± 0·5 | −27·9 ± 2·4 |
| (1h) | 119 | 172·3 | 263·0 | 396 | 22·33 | 14·1 ± 0·38 | −27·6 ± 1·8 |

[a] The rate constants were calculated at the given temperatures from the Eyring equation. [b] $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ are in kcal mol$^{-1}$, $\Delta S^{\ddagger}$ is in cal mol$^{-1}$ K$^{-1}$. The quoted errors are random errors calculated from statistical analysis (C. A. Bennett and N. L. Franklin, 'Statistical Analysis in Chemistry and the Chemical Industry,' Wiley, New York, 1954, p. 228).

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[2] W. Walter and J. Voss in 'The Chemistry of Amides,' ed. J. Zabicki, Interscience, London, 1970, p. 383.

[3] M. Chanon, R. Gallo, J. Metzger, and J. M. Surzur, *Bull. Soc. chim. France*, 1968, 288; M. Arbelot, R. Gallo, M. Chanon, and J. Metzger, *Internat. J. Sulfur Chem.*, in the press.

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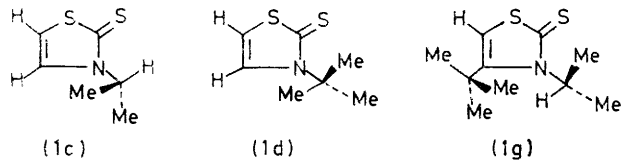
[9] A. Mannschreck and L. Enrst, *Chem. Ber.*, 1971, **104**, 228.

[10] R. J. Ouelette, B. Sinha, J. Stolfo, C. Levin, and S. Williams, *J. Amer. Chem. Soc.*, 1970, **92**, 7145.

[11] The same behaviour has been found for the dichloromethyl group, T. V. Mark and V. A. Pattison, *Chem. Comm.*, 1971, 553; B. J. Fuhr, B. W. Goodwin, H. Hutton, and T. Schaefer, *Canad. J. Chem.*, 1970, **48**, 1558.

The only acceptable conformation for a t-butyl group is the one in which two methyl groups interact with the thiocarbonyl function (Scheme 1). We think that the difference of reactivity results from this complete



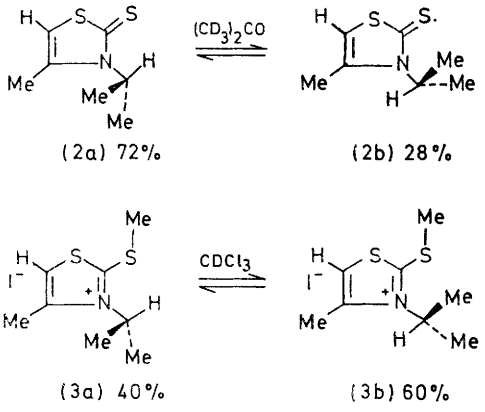
(1c) (1d) (1g)

SCHEME 1

change in the conformation of the *o*-alkyl group. This assumption is verified by a study of the reactivity of compound (1g). In this compound, the 'geared' conformation [7] of the $Bu^t$ and $Pr^i$ groups leads to a similar geometrical situation as in (1d). Inspection of Table 1 reveals that for the set of compounds (1e—g) with a $Bu^t$ group in the 4-position, a significant discontinuity in the reactivity occurs for compound (1g). The ratio $k_{(1g)}/k_{(1e)} = 2{\cdot}1$ whereas $k_{(1a)}/k_{(1d)} = 1{\cdot}73$; this difference arises mainly from a purely electronic effect of the alkyl group.

We shall now consider why this conformational preference causes a rate acceleration. Alkylation at sulphur results in large changes in geometry in going from the initial (thiocarbonyl form) to the final state (methylthio-form).[12] These changes mainly affect the thioamide system; the exocyclic C=S bond is lengthened while the ring C–N bond is shortened. Compression or expansion could result from these two opposite effects.

A study of the conformational preference of the $Pr^i$ group in the model compound (2) and in its salts (3) provides clear evidence for the expansion process (Scheme 2). We have already indicated that the




SCHEME 2

methine hydrogen of a $Pr^i$ group will preferentially lie on the same side as the more bulky group of the two flanking substituents. The observed percentages in Scheme 2 leads to the conclusion that the relative sizes of the flanking substituents in the system studied are: C=S > Me > SMe. Furthermore these percentages give an estimate of the total strain release on going from the thiocarbonyl to the methylthio-form. The maximum strain release between the initial and final states of the reaction is 0·7 kcal $mol^{-1}$ assuming that the internal strain is approximately the same in (2a) and (3a).

From the steric point of view, the thioxo-group in the thiazoline-2-thiones (1a and d) undergoes the same steric interaction as the conformers (2a and b) (Scheme 2) respectively. Consequently, the observed change in the $\Delta G^{\ddagger}$ values for the reaction of thiazoline-2-thiones (1a and d) with methyl iodide gives an estimate of the extent of the relief of strain between the initial state and the transition state. The experimental value is 0·33 kcal $mol^{-1}$ (Table 1).

A correction for the alkyl groups' electronic contribution must be taken into account, and the expected difference should be slightly larger. Assuming that the alkyl groups' electronic effect is approximately the same in both the 3- and the 4-position in (1), the deactivation corresponding to the alkyl group change from (1a) to (1d) can be estimated from the difference between the $\Delta G^{\ddagger}$ values corresponding to the methylation of (1e and h) respectively (see Experimental section). So the corrected steric change in the $\Delta G^{\ddagger}$ value between the inital and the transition states is 0·46 kcal $mol^{-1}$.

In summary, a large part, 65%, of the total strain release has already occurred by the time the transition state is reached. This result is possible only if the reactive C=S bond is largely weakened in the transition state.

The transition state for alkylation is far from the initial state in regard to the heterocyclic ring. This does not imply the same conclusion for the bond lengths in the $S_N2$ transition state for the $S \cdots CH_3 \cdots I$ system. A 0·5 kcal $mol^{-1}$ change in the energy corresponds to a C–I bond length change of $<0{\cdot}04$ Å using a single bond force constant of 2·3 mdyn $Å^{-1}$.[13] But the fact that large changes occur in the heterocyclic systems reveals that sulphur atom hybridisation in the ground state cannot be used as a model for the approach of the incoming methyl group. A more realistic view is to consider that the sulphur atom possesses a large, spherical electron density in the transition state.

TABLE 2

$pK_a$ Values of the thiazoline-2-thiones (1a—d) in water

| Compound | (1a) | (1b) | (1c) | 1(d) |
|---|---|---|---|---|
| $pK_a$ | −3·56 | −3·54 | −3·56 | −2·97 |

The position of the transition state depends on the electronic environment of the thiocarbonyl group and in the present case the nitrogen atom has a decisive effect. We can postulate that in other thiocarbonyl systems, whether heterocyclic or not, large changes in the position of the transition state might be found depending on the stabilising ability of the surrounding groups.

*Applications.*—Strain release is also expected to affect the $pK_a$ values of the thiocarbonyl group. Some preliminary results are given in Table 2. Addition of a

[12] P. J. Weathly, *J. Chem. Soc.*, 1961, 4379; G. Pepe, personal communication.

[13] J. C. Harris and J. L. Kurz, *J. Amer. Chem. Soc.*, 1970, **92**, 349.

proton gives rises to bond lengthening which leads to an increase in the basicity of the strained compound (1d). A more detailed study of the influence of compression on $pK_a$ will be published.[14]

## EXPERIMENTAL

*Synthesis.*—The syntheses and the n.m.r. data for the thiazoline-2-thiones (1a—h) have been described previously.[15] They were recrystallised from ethanol–water twice before use. The salts used for the conductivity cell calibration were prepared by reaction of methyl iodide on the thiocarbonyl compound in a sealed tube and were washed with anhydrous diethyl ether and acetone. Their purity was established by t.l.c. and n.m.r. and u.v. spectroscopy (Table 3).

TABLE 3

Physical, u.v.,[a] and n.m.r.[b] [δ (*J*/Hz)] data for the salts derived from (1a—h) + MeI

| Compound | M.p. of salts (°C) | $\lambda_{max.}$/nm ($\epsilon_{max.}$) | N.m.r. SMe | 5-H | 4-R | NCH | NCMe |
|---|---|---|---|---|---|---|---|
| (1a) | 154 | 285·0 (11,100) | 2·91 (3H, s) | 7·82 (1H, d) *J* 4·2 | 7·98 (1H, d) *J* 4·2 | 3·90 (3H, s) | |
| (1b) | 141 | 288·5 (10,900) | 2·90 (3H, s) | 7·86 (1H, d) *J* 4 | 8·08 (1H, d) *J* 4 | 4·31 (2H, q) *J* 7·6 | 1·48 (3H, t) *J* 7·6 |
| (1c) | 131 | 285·5 (12,500) | 2·92 (3H, s) | 7·89 (1H, 1) | 8·17 (1H, 1) | 4·80 (1H, sept) *J* 7·q | 1·54 (6H, d) *J* 7·1 |
| (1d) | 110 | 291·0 (9600) | 2·98 (3H, s) | 7·91 (1H, 1) | 8·29 (1H, 1) | | 1·85 (9H, s) |
| (1e) | 175 | 289·0 (10,900) | 2·89 (3H, s) | 7·53 (1H, s) | 1·44 (9H, s) | 4·01 (3H, s) | |
| (1f) | 136 | 291·5 (11,300) | 2·90 (3H, s) | 7·53 (1H, s) | 1·45 (9H, s) | 4·55 (2H, q) *J* 7·4 | 1·50 (3H, t) *J* 7·4 |
| (1g) | 159 | 295·0 (10,300) | 2·88 (3H, s) | 7·49 (1H, s) | 1·46 (9H, s) | 5·50 (1H, sept) *J* 7 | 1·71 (6H, d) *J* 7 |
| (1h) | 164 | 290·0 (10,400) | 2·89 (3H, s) | 7·50 (1H, q) *J* 1·3 | 2·46 (3H, d) *J* 1·3 | 3·78 (3H, s) | |

[a] The spectra were recorded for solutions in water on a Cary 14 spectrophotometer. [b] All spectra were recorded for deuterium oxide solutions on a Varian HA 100 instrument at the probe temperature.

*Conductimetric Method.*—We used a classical technique for the kinetic runs.[3,16] This method needs cell calibration by the salt. All the values obtained were within ±2% of the mean value for eight calibrations. Methyl iodide and acetone were freshly distilled.

*Correction for the Electronic Effect.*—The 3-alkyl groups' electronic effect cannot be obtained directly from the experimental data, because of an additive steric interaction with the thiocarbonyl group. This is clearly shown in (1f): the 4-butyl group forces the terminal methyl group of the ethyl substituent to be near the thiocarbonyl system, leading to an increase in the rate constant which could not come from an electronic effect alone. The change in steric requirement is nearly the same in going from (1a) to (1d) and from (1e) to (1g); however the observed change in $\Delta G^{\ddagger}$ is 0·33 in the former case and 0·47 kcal mol$^{-1}$ in the latter. These results suggest that the electronic effect of the isopropyl and t-butyl groups must be taken into account. We assumed that the purely electronic effect is approximately the same for the 3- and 4-positions. This hypothesis is based on the following experimental results: if we consider the effect of the alkyl substitution in the 4-position in (1; $R^2$ = Me), the $\Delta G^{\ddagger}$ values are 22·33 ($R^2$ = Me), 22·35 ($R^2$ = Et), 22·37 ($R^2$ = Pr$^i$), and 22·47 kcal mol$^{-1}$ ($R^2$ = Bu$^t$); thus the largest change in electronic effect is found in going from Pr$^i$ to Bu$^t$. Consequently, we have for the pure steric effect $\Delta\Delta G^{\ddagger}$ 0·47 in going from (1a) to (1d) and 0·51 kcal mol$^{-1}$ in going from (1e) to (1g).

*Results.*—The given rate constants were recalculated for given temperatures from the Eyring equation with data obtained from several runs at different temperatures (at least six) and concentrations. The confidence level was 0·9.[5] 1% Precision was obtained. In all cases the reaction is second order. Initial concentrations were in the range 1—2 × 10$^{-2}$M. Initial rate constants were determined (salt concentration 10$^{-4}$M).

*Population Determination for* (2) *and* (3).—The populations are obtained from low temperature spectra by several integrations. The percentages given in Scheme 2 are extrapolated from the percentages obtained at different temperatures. The variation for an 80° range is <2%. Conformer (2a), δ [$(CD_3)_2CO$] 6·62 (1H, s, 5-H), 5·89 (1H, sept), 2·54 (3H, s, 4-Me), and 1·49 (6H, d); conformer (2b), δ [$(CD_3)_2CO$] 6·62 (1H, s, 5-H), 4·70 (1H, sept), 2·32 (3H, s, 4-Me), and 1·81 (6H, d); conformer (3a), δ ($CDCl_3$; 100 MHz) 3·08 (3H, s, SMe), 2·76 (3H, s, 4-Me), and 1·76 (6H, d); conformer (3b), δ ($CDCl_3$; 100 MHz) 3·08 (3H, s, SMe), 2·72 (3H, s, 4-Me), and 1·81 (6H, d).

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