Angular *versus* Linear Transition State in Nucleophilic Reactions of Thioketones

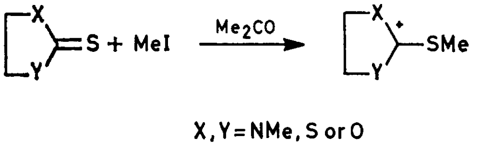
By **Michel Arbelot** and **Michel Chanon**, Ecole Normale Superieure, 43 Bd. de la Liberté, Le Bardo, Tunis, Tunisia
Roger Gallo, **Christian Roussel**, and **Jacques Metzger**,* I.P.S.O.I., Centre Universitaire St. Jérôme, Rue H. Poincaré, 13013 Marseille, France
Mikael Begtrup, Department of Organic Chemistry, Technical University of Denmark, 2800 Lyngby, Denmark

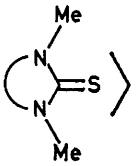
The steric effect of *o*-methyl groups is much more pronounced for *N*-alkylation with MeI, EtI, and Pr^{i}I or aza-aromatic compounds than for *S*-alkylation of heterocyclic thiones. This is explained by comparison of van der Waals interactions in the transition states of chosen homomorphic systems: an angular transition state is shown to conform with the measured kinetic constants.

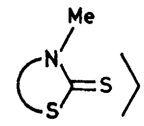
THE concept of steric hindrance is familiar[1] but it is difficult to predict the influence of steric effects on nucleophilic reactions because of insufficient knowledge of the transition states. During a study of the thiocarbonyl group[2] we uncovered evidence of specific behaviour in relation to steric effects. This paper outlines this specificity and discusses the transition state which conforms to the measured rate constants.

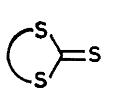
RESULTS AND DISCUSSION

During a study of the nucleophilicity of the thiocarbonyl group,[2a,b] rate constants of reactions with alkyl iodides were measured. No e.s.r. signal was detected during the course of the reactions and they closely followed second-order kinetics.[3] Results in Figure 1 show that *ortho*-substituted heterocyclic thioketones and *ortho*-substituted aza-aromatic compounds display different behaviour towards steric effects. In these series, the steric and electronic contributions to reactivity may be separated by plotting pK_a values *versus* nucleophilic reactivity; a linear relationship is obtained when steric effects are absent but this relationship no longer holds in the presence of these effects.[4] The size of the divergence is indicative of the importance of the steric interaction between the *ortho*-substituent and the electrophilic centre.[5] While bulky *ortho*-substituents markedly decrease the rate constants for aza-aromatic nucleophiles they slightly increase them for 3-alkyl-Δ^4-thiazoline-2-thione (Figure 1). This increase has been rationalised in terms of release of strain in the transition state in which the van der Waals interaction between









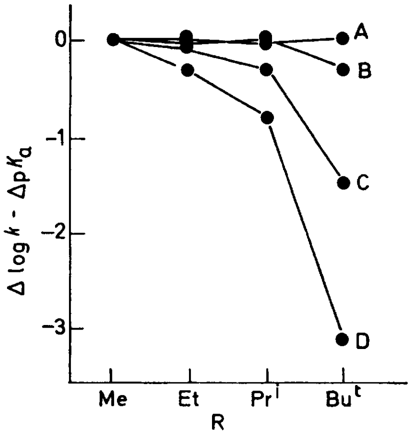


FIGURE 1 Contribution of the steric effect to the difference between the basicity and nucleophilicity of *ortho*-substituted *N*-alkylthiazoline-2-thiones and heterocyclic amines. R = *ortho*-substituent of series A—D; 10^6k/l mol^{-1} s^{-1} rate constant for the reaction between the heterocyclic compound and methyl iodide at 25 °C; $\Delta\log k = \log k_R - \log k_{Me}$; $\Delta pK_a = pK_a^R - pK_a^{Me}$. A, 4-alkylpyridines (H. C. Brown and A. Cahn, *J. Amer. Chem. Soc.*, 1955, **77**, 1715); B, *N*-alkylthiazoline-2-thiones (ref. 6 and C. Guimon, personal communication); C, 2-alkylthiazoles (ref. 5 and R. Phan Tan Luu, J. M. Surzur, J. Metzger, J. P. Aune, and C. Dupuy, *Bull. Soc. chim. France*, 1967, 3274); D, 2-alkylpyridines (ref. 4). Values of 10^6k_{298}/l mol^{-1} s^{-1}, $\Delta H^\ddagger$/kcal mol^{-1}, $\Delta S^\ddagger$/cal mol^{-1} K^{-1}, solvent in which k was measured, pK_a in water are: Me, 760, 13, --29.2, nitrobenzene, 602; Et, 777, —, —, nitrobenzene, 6.02; Pr^i, 767, —, —, nitrobenzene, 6.02; Bu^t, 757, 13, −29.0, nitrobenzene, 5.99; Me, 162, 14.4, −27.6, acetone, −3.56; Et, 159, 14.3, −27.9, acetone, −3.54; Pr^i, 173, 14.0, −28.7, acetone, −3.56; Bu^t, 288, 14.1, −27.2, acetone, −2.97; Me, 11.8, 15.1, −30.2, nitrobenzene, 3.42; Et, 9.2, 15, −31, nitrobenzene, 3.37; Pr^i, 4.3, 15.6, −30.7, nitrobenzene, 3.28; Bu^t, 0.29, 16.9, −31.7, nitrobenzene, 3.15; D, Me, 162, 13.4, −31, nitrobenzene, 5.97; Et, 76, 13.7, −31.5, nitrobenzene, 5.97; Pr^i, 24, 14.2, −32, nitrobenzene, 5.83; Bu^t, 0.08, 16.8, −34.6, nitrobenzene, 5.76

---

[1] (*a*) M. S. Newman, in ' Steric Effects in Organic Chemistry,' Wiley, New York, 1956; (*b*) E. Eliel, N. L. Allinger, S. G. Angyal, and G. A. Morrison, in ' Conformational Analysis,' Wiley, New York, 1965, p. 446.

[2] (*a*) M. Chanon, R. Gallo, J. M. Surzur, and J. Metzger, *Bull. Soc. chim. France*, 1968, 2886; (*b*) M. Arbelot, R. Gallo, M. Chanon, and J. Metzger, *Phosphorus and Sulfur*, 1976, 271; (*c*) M. Arbelot, J. Metzger, M. Chanon, C. Guimon, and G. Pfister-Guillouzo, *J. Amer. Chem. Soc.*, 1974, **96**, 6217; (*d*) D. Gonbeau and G. Pfister-Guillouzo, *Tetrahedron*, 1975, **31**, 459; (*e*) D. Gonbeau and G. Pfister-Guillouzo, *Canad. J. Chem.*, 1976, **54**, 118.

[3] H. Goldschmidt and H. K. Grini, *Z. Electrochem.*, 1913, **19**, 226.

[4] H. C. Brown, *J. Chem. Educ.*, 1959, **36**, 424.

[5] R. Gallo, M. Chanon, H. Lund, and J. Metzger, *Tetrahedron Letters*, 1972, **36**, 3857.

the thiazoline 3-alkyl group and the thiocarbonyl group is smaller than that in the initial state.[6]

A question remains: does the global effect (slight increase of rate constants) result from the algebraic sum of large steric hindrance compensated by large strain release or from compensation between small amounts of these two factors? The variation of rate constants (Figure 2) between aza-aromatic and heterocyclic thiocarbonyl compounds and increasingly sterically hindered alkyl iodides implies that the latter explanation obtains. Whereas rate constants for 2-methylpyridine (Figure 2) decrease with increasing steric hindrance at the electrophilic centre, a far smaller decrease is measured for all the heterocyclic thiones studied. This small decrease varies with the thione considered. As expected, the compound least sensitive to steric hindrance is 1,3-benzodithiole-2-thione and the most sensitive is 1,3-dimethylimidazoline-2-thione.

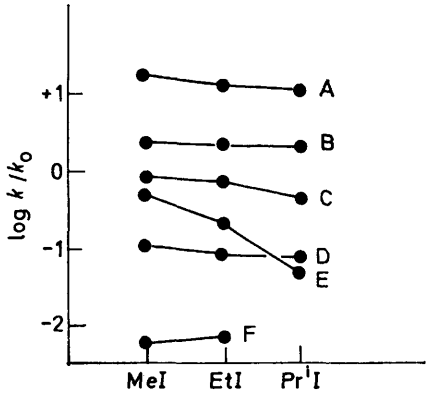
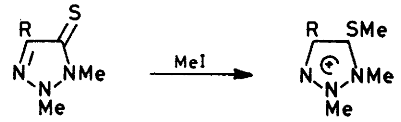


FIGURE 2 Variations of the rate constants for the reaction between various heterocyclic compounds and alkyl iodides for alkyl = Me, Et, or $\mathrm{Pr^i}$. k/l $\mathrm{mol^{-1}\ s^{-1}}$ rate constant at 25 °C; k_0/l $\mathrm{mol^{-1}\ s^{-1}}$ = rate constant at 25 °C between MeI, EtI, or $\mathrm{Pr^iI}$ and the nucleophile taken as reference (pyridine for sets B and E and *N*-methylthiazoline-2-thione for sets A, C, D, and F). A, 1,3-dimethylimidazoline-2-thione; B, 4-methylpyridine; C, 1,3-dimethylbenzimidazoline-2-thione; D, 3-methylbenzothiazoline-2-thione; E, 2-methylpyridine; F, 1,3-benzodithiole-2-thione. Values of 10^6k_{298}/l $\mathrm{mol^{-1}\ s^{-1}}$, $\Delta H^{\ddagger}$/kcal $\mathrm{mol^{-1}}$, $\Delta S^{\ddagger}$/cal $\mathrm{mol^{-1}\ K^{-1}}$, solvent in which k was measured are: A, MeI, 3 198, 11.8, −30.5, acetone; EtI, 169, —, —, acetone; $\mathrm{Pr^iI}$, 2.94, 15.9, −30.5, acetone; B, MeI, 760, 13, −29.2, nitrobenzene; EtI, 41.9, 15.1, −28.3, nitrobenzene; $\mathrm{Pr^iI}$, 1.99, 16.5, −29, nitrobenzene; C, MeI, 144, 14.2, −28.6, acetone; EtI, 10.2, —, —, acetone; $\mathrm{Pr^iI}$, 0.1, —, —, acetone; D, MeI, 17.1, 14.8, −30.6, acetone; EtI, 1.01, —, —, acetone; $\mathrm{Pr^iI}$, 0.019, —, —, acetone; E, MeI, 162, 13.4, −31, nitrobenzene; EtI, 4.27, 15.8, −30.2, nitrobenzene; $\mathrm{Pr^iI}$, 0.05, 18.5, −29.8, nitrobenzene; F, MeI, 1.01, 16.1, −31.6, acetone; EtI, 0.076, —, —, acetone; $\mathrm{Pr^i}$, reactivity too low to give precise results. For the two reference compounds: pyridine, MeI, 343, 13.3, −29.8, nitrobenzene; EtI, 18.3, 15.4, −28.8, nitrobenzene; $\mathrm{Pr^iI}$, 0.94, 16.9, −29.5, nitrobenzene; *N*-methylthiazoline-2-thione, MeI, 160, 14.4, −27.6, acetone; EtI, 12.3, —, —, acetone; $\mathrm{Pr^iI}$, 0.22, 16.6, −33.1, acetone

This hypothesis of weak steric hindrance is confirmed by the reactivity of 1,2,3-triazoline-5-thiones. Thus, 1,2-dimethyl-1,2,3-triazoline-5-thione reacts 1.57 times faster with methyl iodide than does its 4-methyl derivative. The steric hindrance exerted by this group produces a 2.5 fold decrease ($\Delta\Delta G^{\ddagger}$ *ca.* 550 cal $\mathrm{mol^{-1}}$) as the electronic effect alone would enhance the rate 1.6 times.[2a] For a homomorphic[7] pair of thiazole derivatives (2-methyl- and 2-t-butyl-thiazole) the same increase in steric hindrance gives a 32-fold decrease in rate ($\Delta\Delta G^{\ddagger}$ *ca.* 2 050 cal $\mathrm{mol^{-1}}$).[5] A homomorphic pair of pyridines (2-methyl- and 2-t-butyl-pyridine) displays an even larger sensitivity to steric hindrance ($k_{\mathrm{Me}}/k_{\mathrm{Bu^t}}$ 2 000; $\Delta\Delta G^{\ddagger}$ *ca.* 5 460 cal. $\mathrm{mol^{-1}}$).[4] So steric hindrance plays a more important role in aza-aromatic systems than in their homomorphic heterocyclic thione counterparts. The reason for this specific behaviour must be sought in the transition state geometries. The transition state for the alkylation of thiones may be either linear (*a*) or angular (*b*).

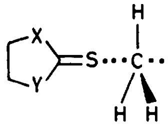


R = H or Me

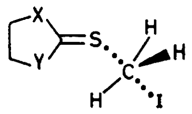
There is no steric hindrance in a linear transition state. This absence of interaction does not fit the small but significant hindrance observed in this work (Figure 2). A contribution from an angular transition state must therefore be introduced in the description of this reaction in accord with the CNDO calculations of Gonbeau *et al.*[2d] which predict that the least energetic direction of approach of methyl chloride to thiourea in the absence of steric effects corresponds to a $\mathrm{CSCH_3}$ angle of 108° to the plane of thiourea. The transition state related to thiazole and other aza-aromatic compounds corresponds to the geometry allowing the better overlap between the nitrogen lone pair and the lowest unoccupied molecular orbital of methyl halide.

An important indeterminacy is the length of bonds being formed (see Experimental section). However, the

(*a*)



(*b*)



calculation of van der Waals interactions in the transition state (Table) of the three systems with different geometries all give a decreasing order of steric strain energies: 2-t-butylpyridine > 2-t-butylthiazole > 1,2,4-trimethyl-1,2,3-triazoline-5-thione. This agrees with the experimental order of steric sensitivity. The semi-quantitative treatment derived from the homomorphic concept is sufficient to explain the weak steric sensitivity of the thiocarbonyl group. Thus the transition state for nucleophilic reaction of the thiocarbonyl group with an electrophile is angular. This result can probably be ex-

---

[6] C. Roussel, R. Gallo, M. Chanon, and J. Metzger, *J.C.S. Perkin II*, 1974, 1304.

[7] H. C. Brown, *J. Chem. Soc.*, 1956, 1248.

tended to carbonyl analogues where such transition states are found in enzymic catalysis. Subtler differences require a more complete treatment,[8] *i.e.* van der Waals strain is mainly released by enlargement of the bond angle. This factor may even account for a small part of the differences between the three homomorphic systems studied here if it is supposed that, in the transition state, the force constants of angular deformation for the C–S and C–N bonds being formed are significantly different. This possibility is not supported by the ratio of angular deformation constants (k_{CNC}/k_{CSC} 1.04) measured for stable compounds.[9]

Calculated[a] van der Waals interactions in the transition states of the three homomorphic systems 2-t-butylpyridine,[b] 2-t-butylthiazole, and 1,2,4-trimethyl-1,2,3-triazoline-5-thione

		Energy of interaction (kcal mol^{-1})	
θ_1[c] (°)	θ_2[c] (°)	2-t-Butylthiazole	1,2,4-Trimethyl-1,2,3-triazoline-5-thione
75	45	34	25
75	60	36	25
90	30	30	24
90	45	15	9
90	60	28	19
105	30	15	10
105	45	8	3
105	60	14	8
120	30	30	22
120	45	15	9
120	60	8	3
120	75	15	9
120	90	30	22
135	60	14	8
135	75	8	3
135	90	15	10
150	60	28	19
150	75	15	9
150	90	30	24
165	60	36	25
165	75	34	25

[a] The energies are calculated for each pair of θ_1 and θ_2 values. The relation used is $E_{NB} = Ae^{-\mu r} - Br^{-6}$ with *A* and *B* in kcal mol^{-1} and μ in Å^{-1} (S–H, *A* 127 000, *B* 532, μ −4.1; H–H, *A* 65 000, *B* 150, μ −4.8; C–H, *A* 30 000, *B* 140, μ −4.17; N–H: *A* 61 500, *B* 141, μ −4.55). [b] For this compound the calculated values are not reported: steric interactions are too high and the data have no significance. [c] In the Scheme atoms 1—5 are in the same plane P. θ_1 is defined as the angle formed by the bond C(5)–H(6) and P and θ_2 as the angle formed by C(1)–H(9) and P. The length of bonds being formed are taken as 1.5 times those of formed bonds.

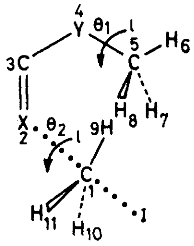
EXPERIMENTAL

The preparation of 3-alkylthiazoline-2-thiones,[10] 1,3-dimethylimidazoline-2-thione,[2b] 1,3-dimethylbenzimidazoline-2-thione,[10] 3-methylbenzothiazoline-2-thione,[11] and 1,3-benzodithiole-2-thione [12] have been described elsewhere.[2b] 1,2,3-Triazoline-5-thiones were prepared by thiation of the corresponding triazolium salts by sulphur and sodium hydride in dimethylformamide.[13,14]

Rate constants and activation parameters were determined by conductimetric measurements at five temperatures using the statistical treatment previously reported.[15,16] The k_{298}, $\Delta H^‡$, and $\Delta S^‡$ values are accurate to ±3, ±3, and ±5%, respectively (Fischer *t* 2.776). The rate constants and activation parameters associated with the reaction between methyl iodide and 1,2-dimethyl- or 1,2,4-trimethyl-1,2,3-triazoline-5-thione in acetone are respectively k_{298} 2.4×10^{-2} and 1.5×10^{-2} l mol^{-1} s^{-1}, $\Delta H^‡$ 11.4 and 11.4 kcal mol^{-1}, and $\Delta S^‡$ −27.5 and −28.5 cal mol^{-1} K^{-1}.

The geometries used for the calculations of van der Waals interactions in the transition state (Table) are either experimental (pyridine,[17] thiazole [18]) or inferred from geometries determined for analogous compounds [19,20] (1,2,3-triazoline-2-thione).

The bond lengths in the transition states, for which experimental data are lacking, are provided by an *ab initio* approach. Dedieu and Veillard [21] calculated the length of the H–C and F–C bonds formed when the nucleophiles H$^-$ and F$^-$ attack CH_3F. The calculated values for H–C and F–C bonds in the transition state are respectively 1.8 and 1.3 times longer than the values measured in the ground state. In the hard and soft acids and bases approach,[22] the nucleophiles H$^-$ and F$^-$ are classified respectively as typically 'soft' and 'hard'. Thus the probable range of lengths for the C–S and C–N bonds being formed is between 1.3 and 1.8 times the values in the ground state. The calculations of van der Waals interactions in the transition state are therefore performed with bond lengths in this range (Table).



SCHEME

The pair 2-methyl- and 2-t-butyl-pyridine has been chosen as the homomorphic counterpart of the pair 1,2-dimethyl- and 1,2,4-trimethyl-1,2,3-triazoline-5-thione because the *o*-t-butyl group may be considered as approximately representative of a blocked ethyl group with the methyl oriented toward the nitrogen. The uncertainty in this hypothesis is obtained from a comparison of the rate constant ratio for the reaction of the following aza-aromatic compounds with methyl iodide: $k_{2\text{-methylpyridine}} : k_{2\text{-t-butylpyridine}}$ 2 000, $\Delta\Delta G^‡$

---

[8] M. H. Abraham, P. L. Grellier, and M. Hogarth, *J.C.S. Perkin II*, 1974, 1613; 1975, 1365.

[9] N. T. Forel and G. Garrigou-Lagrange, *J. chim. Phys.*, 1971, **68**, 1329.

[10] C. Roussel, A. Babadjamian, M. Chanon, and J. Metzger, *Bull. Soc. chim. France*, 1971, 1902.

[11] A. Chambonnet, Thesis, Marseille, 1962.

[12] A. Samat and R. Guglielmetti, personal communication.

[13] M. Begtrup, *Acta Chem. Scand.*, 1975, **B29**, 141.

[14] M. Begtrup, to be published.

[15] R. Cottet, R. Gallo, and J. Metzger, *Bull. Soc. chim. France*, 1967, 4499.

[16] M. Chanon, R. Gallo, J. M. Surzur, and J. Metzger, *Bull. Soc. chim. France*, 1968, 2881.

[17] A. Almenningen, O. Bastansen, and L. Hansen, *Acta Chem. Scand.*, 1955, **9**, 1306.

[18] B. Bak, L. Nygaard, E. J. Pedersen, and J. Rastrup-Andersen, *J. Mol. Spectroscopy*, 1966, **19**, 283.

[19] G. B. Ansell, D. M. Forkey, and D. W. Moore, *Chem. Comm.*, 1970, 56.

[20] B. Bak, L. Hansen, and J. Rastrup-Andersen, *J. Chem. Phys.*, 1954, **22**, 2013.

[21] A. Dedieu and A. Veillard, *J. Amer. Chem. Soc.*, 1972, **94**, 6730.

[22] R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, 1967, **89**, 1827.

4.50 kcal mol^{-1}; $k_{\text{quinoline}}:k_{\text{8-methylquinoline}}$ 1 800; $\Delta\Delta G^{\ddagger}$ 4.43 kcal mol^{-1}.[23]

The geometries adopted for the van der Waals calculations (Table) are the following: 2-t-butylpyridine (X = N, Y = CH_2) 1–2 2.01 Å, 2–3 1.34 Å, 3–4 1.51 Å, 4–5 1.54 Å, 5–6, 5–7, 5–8, 1–9, 1–10, 1–11 1.09 Å, 9–1–2 90°, 1–2–3 122°, 2–3–4 115°, 3–4–5, 4–5–8 111°; 2-t-butylthiazole 1–2 2.01 Å, 2–3 1.30 Å, 3–4 1.51 Å, 4–5 1.54 Å, 5–6, 5–7, 5–8, 1–9, 1–10, 1–11 1.09 Å, 9–1–2 90°, 1–2–3 127.5°, 2–3–4 123.6°, 3–4–5 111°, 4–5–8 111°; 1,2,4-trimethyl-1,2,3-triazoline-5-thione (X = S, Y = N) 1–2 2.55 Å, 2–3 1.7 Å, 3–4 1.42 Å, 4–5 1.51 Å, 5–6, 5–7, 5–8, 1–9, 1–10, 1–11 1.09 Å, 9–1–2 90°, 1–2–3 110°, 2–3–4 128°, 3–4–5 126°, 4–5–8 111°. θ_1 and θ_2 were varied by steps of 15°, with $\theta_1 = \theta_2 = 0$ in the Scheme. The Table summarizes the van der Waals interactions in the transition state: only the lowest values are reported.

[5/2164 *Received, 6th November,* 1975]

---

[23] J. Packer, J. Vaughan, and E. Wong, *J. Amer. Chem. Soc.*, 1958, **80**, 905.