Ring Opening and Closing in Heterocyclic Compounds. Kinetic Studies on Solvent Effects in the Reaction between 6-Nitrobenzothiazole and Methoxide ion at 25 °C

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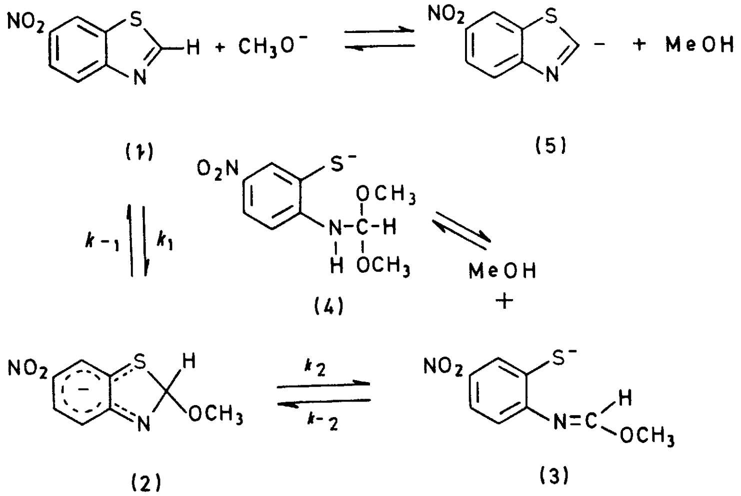
Kinetic studies on the ring opening reaction between 6-nitrobenzothiazole and methoxide ion in DMSO–MeOH at 25 °C are reported. The results demonstrate that dipolar aprotic solvents increase the equilibrium constant between reagents and the Meisenheimer-like adduct (2). The equilibrium constant between anion (2) and 2-methoxymethyleneamino-5-nitrobenzenethiolate (3) is lowered by this solvent mixture. The net effect of these counteracting influences is such that the DMSO favours the ring opening process.

In recent years there has been considerable interest on the chemistry of σ-anionic complexes,[1] which are formed from nitro-activated heterocyclic substrates and strong bases. Their precise structures, stabilities, and rates of formation and decomposition have been investigated for thiophen,[2] pyridine,[3] and pyrimidine [4] systems. Recent studies from our laboratory,[5] carried out on benzothiazole substrate, showed (see Scheme) that the action of methoxide ion on the 6-nitro-derivative (1) in DMSO–MeOH led to the formation of significant amounts of a σ-anionic complex (2) in the initial phase of reaction; this metastable intermediate yields large amounts of open anionic adducts (3) and (4).



Scheme

In addition, evidence has been found for the existence

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[1] M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667 and references cited therein.

[2] D. Spinelli, V. Armanino, and A. Corrao, *J. Heterocyclic Chem.*, 1970, 1441; G. Doddi, G. Illuminati, and F. Stegel, *J. Org. Chem.*, 1971, **36**, 1918; G. Paulmier, M. Simonnin, A. Chartrousse, and F. Terrier, *Tetrahedron Letters*, 1973, 1123.

[3] P. Bemporad, G. Illuminati, and F. Stegel, *J. Amer. Chem. Soc.*, 1969, **91**, 6742; C. Abbolito, C. Iavarrone, G. Illuminati, F Stegel, and A. Vazzoler, *ibid.*, p. 6746; G. B. Bressan, I. Giardi, G. Illuminati, P. Linda, and S. Sleiter, *J. Chem. Soc.* (*B*), 1971, 225.

[4] M. E. C. Biffin, J. Miller, A. G. Moritz, and D. B. Paul, *Austral. J. Chem.*, 1969, **22**, 2561.

[5] G. Bartoli, F. Ciminale, and P. E. Todesco, *J.C.S. Perkin II*, 1975, 1472.

of a side equilibrium process between reagents and anion (5), which is formed by base-promoted abstraction of hydrogen in position 2; its concentration is, however, always considerably lower than that of all other species throughout the reaction. The present study was undertaken to investigate the influence of the protic nature of the medium on the relative stabilities of complexes (2) and (3). Kinetic studies on their rates of formation and decomposition are reported for three DMSO–MeOH mixtures at 25 °C. The results provide conclusive evidence for the mechanism of reaction. The dependence of rate of formation of adduct (4) on base concentration has also been studied.

RESULTS AND DISCUSSION

Because of their strong absorbance in the visible region, the anionic adducts (2)—(4) can be distinguished from the starting materials; kinetic studies were performed by following their appearance by means of appropriate spectrophotometric techniques: wavelengths of 460, 485, and 550 nm were selected.

TABLE 1

Reaction between 6-nitrobenzothiazole and potassium methoxide in various DMSO–MeOH mixtures at 25 °C: dependence of first-order rate constant ($k_{1,\mathrm{obs}}$) for adduct (2) formation on the excess concentration of 6-nitrobenzothiazole [a]

Solvent composition DMSO–MeOH (v/v)	$k_{1,\mathrm{obs}}$/s^{-1}	[(1)]$_0$/M
90 : 10	5.8	0.034 6
	4.9	0.027 7
	3.5	0.017 3
	3.0	0.013 8
	2.04	0.006 9
80 : 20	7.5	0.070 0
	6.7	0.056 0
	5.7	0.035 0
	5.2	0.023 0
	4.8	0.014 0
70 : 30	13.0	0.069 0
	12.8	0.062 1
	12.4	0.051 8
	12.0	0.028 0

[a] [MeO$^-$] = 5×10^{-4} M.

TABLE 3

Rate and equilibrium constants for reaction between 6-nitrobenzothiazole and potassium methoxide in DMSO–MeOH mixtures at 25 °C.

DMSO–MeOH (v/v)	k_1/ l mol^{-1} s^{-1}	k_{-1}/s^{-1}	K_1/l mol^{-1}	10^2k_2/s^{-1}	10^3k_{-2}/s^{-1}	K_2	K_1K_2/ l mol^{-1}
90 : 10	136 ± 1	1.13 ± 0.03	120 ± 4	1.79 ± 0.08	6.1 ± 0.1	3.0 ± 0.2	361 ± 36
80 : 20	48 ± 1	4.1 ± 0.1	11.7 ± 0.5	4.9 ± 0.3	3.7 ± 0.4	13 ± 2	150 ± 30
70 : 30	30 ± 1	11.00 ± 0.07	2.77 ± 0.06	12.7 ± 0.4	3.3 ± 0.1	38 ± 2	104 ± 7

Measurements of rate constants were carried out under pseudo-first-order conditions with a large excess of 6-nitrobenzothiazole. We shall return to the reasons for this choice of experimental conditions later.

Rates of Formation and Decomposition of Adduct (2).—In agreement with our previous ^{1}H n.m.r. studies, preliminary stopped flow experiments showed that the rate of formation of (2) is considerably greater than that of all subsequent reactions. Thus the observed rate constant ($k_{1,\mathrm{obs}}$) for attainment of equilibrium is given by equation (1) where k_1 is the second-order rate constant

$$k_{1,\mathrm{obs}} = k_{-1} + k_1\,[(1)]_0 \qquad (1)$$

for formation of (2), k_{-1} the rate constant of its decomposition, $[(1)]_0$ represents the excess of 6-nitrobenzothiazole. Experimental $k_{1,\mathrm{obs}}$ values for different DMSO–MeOH mixtures are reported in Table 1. By plotting $k_{1,\mathrm{obs}}$ against $[(1)]_0$ the best fit gives straight lines whose slopes and intercepts are k_1 and k_{-1} respectively (see Figure 1). Values for k_1, k_{-1}, and K_1 are listed in Table 3.

TABLE 2

Reaction between 6-nitrobenzothiazole and potassium methoxide in various DMSO–MeOH mixtures at 25 °C: dependence of first-order rate constants ($k_{2,\mathrm{obs}}$) for adduct (3) formation on the excess concentration of 6-nitrobenzothiazole [a]

Solvent composition DMSO–MeOH (v/v)	$10^2k_{2,\mathrm{obs}}$/s^{-1}	[(1)]$_0$/M
90 : 10	1.80	0.016 7
	1.64	0.011 2
	1.50	0.008 3
	1.40	0.006 7
	1.33	0.005 6
80 : 20	2.60	0.070 0
	2.30	0.056 0
	1.75	0.035 0
	1.60	0.028 0
	1.07	0.014 0
70 : 30	2.40	0.069 9
	2.10	0.058 7
	1.70	0.044 0
	1.07	0.022 0
	0.91	0.017 6

[a] [MeO$^-$] = 5×10^{-4} M.

The rate constants in DMSO–MeOH (70 : 30 v/v) were determined several times for each value of $[(1)]_0$ over a wide range of concentrations. This was done to minimize the experimental error in slope determination due to the small increment produced in the ordinate over the maximum range of variation in the abscissa allowed by the solubility of (1).

Rates of Formation and Decomposition of Adduct (3).—An accurate kinetic investigation of the equilibrium between anions (2) and (3) can be performed, if the rate of its attainment is considerably greater than that of the subsequent reaction of (3) with methanol. The relative rate of these two processes is in turn dependent on experimental conditions. The addition of methanol to the C=N double bond of (3) was found to be base catalysed; in the presence of large amounts of free methoxide ion this reaction would predominate over that of formation of (3) from (2). These findings rule out the possibility of carrying out kinetic studies under pseudo-monomolecular conditions with an excess of methoxide ion.

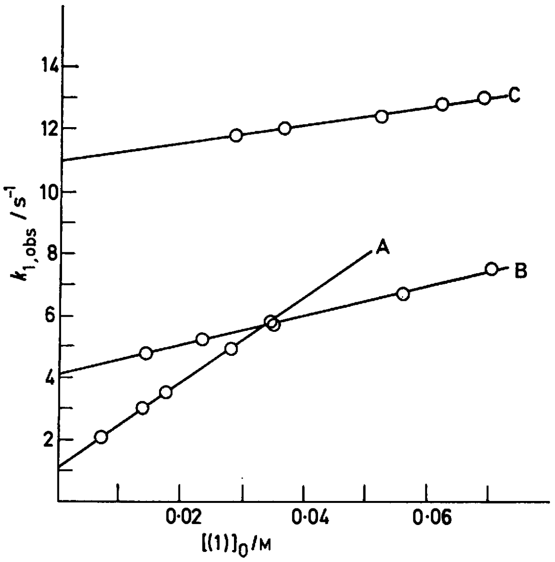

FIGURE 1 Plots of $k_{1,obs}$ *versus* excess concentration of 6-nitrobenzothiazole: A, DMSO–MeOH (v/v 90 : 10); B, (80 : 20); C, (70 : 30)

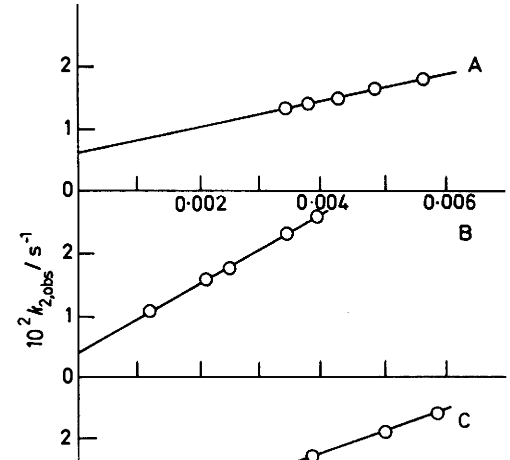

FIGURE 2 Plots of $k_{2,obs}$ *versus* [(1)]/{1 + K_1[(1)]} (see text): A, DMSO–MeOH (v/v 90 : 10); B, (80 : 20); C, (70 : 30)

When the reactions are carried out with an excess of 6-nitrobenzothiazole and with an initial concentration of MeO$^-$ of *ca.* 5×10^{-4}M the formation of (4) is considerably slowed. In this case we can assume that the attainment of equilibrium between (2) and (3) occurs before the latter reacts with methanol.

If we assume that, owing to the large difference in rates between formation of (2) and of (3), the anionic adduct (2) is in instantaneous equilibrium with (1) and MeO$^-$ during formation of (3), the rate equation again gives a pseudo-first-order relationship. The observed first-order rate constant ($k_{2,obs}$) is expressed by equation (2) (see Experimental section) where k_2 and k_{-2} are the first-

$$k_{2,obs} = k_{-2} + k_2K_1[(1)]_0/\{1 + K_1[(1)]_0\} \qquad (2)$$

order rate constants for formation and decomposition of (3) respectively; K_1 is available from Table 3. Experimental $k_{2,obs}$ values are reported in Table 2. In plotting $k_{2,obs}$ against $[(1)]_0/\{1 + K_1[(1)]_0\}$ the best fit is given by straight lines whose slopes are given by k_2K_1 and intercepts by k_{-2}. Values for k_2, k_{-2}, and K_2 are shown in Table 3. The slower formation of (4) does not interfere with determination of $k_{2,obs}$ at higher concentrations of (1); since at lower concentrations there is slight interference; $k_{2,obs}$ values were calculated in these circumstances from recorder absorption curves by the same extrapolation procedure proposed by Bernasconi [6] for equilibrium reactions of this kind

Solvent Effects.—There is a large increase in the equilibrium constant K_1 with increasing proportions of dimethyl sulphoxide in the reaction mixture, due to an increase in the rate constant of formation k_1 and a simultaneous decrease in the rate constant of decomposition k_{-1}. These results can be taken as conclusive evidence that this process is associated with Meisenheimer-like adduct formation. In fact in previous work [5] formation of a Meisenheimer adduct could not be demonstrated with any certainty by ^{1}H n.m.r. analysis, since owing to the rapid interconversion between (1) and (2) coalescence of all the proton signals was observed. We assumed that (2) is formed, by assuming that anion (5) or a radical species is not involved in producing the characteristic spectra. Crampton and Gold [7] examined the effect of solvent on tritium–hydrogen exchange in a homocyclic nitro-activated compound; increasing proportions of DMSO in the medium do not influence equilibria involving carbanions of type (5), while they do influence strongly equilibria involving σ-anionic adducts. Thus the present findings that this process is extremely sensitive to the stabilizing action of the dipolar aprotic solvent, as observed for homocyclic systems,[8] supports our previous interpretation.

The solvent effect on the stability of adduct (3) relative to that of (2) is opposite to that described for the formation of (2). In fact there is an appreciable fall in the equilibrium constant K_2 with increasing amounts of DMSO, due to an appreciable decrease in k_2 and a slight increase in k_{-2}. These results can be accounted for by the action of methanol in facilitating cleavage of the C–S bond in adduct (2); the solvation effects of the protic solvent will stabilize the thiolate ion yielded by the

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[6] C. F. Bernasconi, *J. Amer. Chem. Soc.*, 1971, **93**, 6975.

[7] M. R. Crampton and V. Gold, *J. Chem. Soc.* (*B*), 1966, 498.

[8] J. H. Fendler and J. W. Larsen, *J. Org. Chem.*, 1972, **37**, 2608; E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *ibid.*, 1970, **35**, 287; J. W. Larsen, K. Amin, S. Ewing, and L. L. Magid, *ibid.*, 1972, **37**, 3857; F Terrier, A. P. Chartrousse, and R. Schaal, *ibid.*, 1972, **37**, 3010.

reaction. This phenomenon is analogous to the rise in pK_a values of benzenethioles in dipolar aprotic solvents.[9]

In order fully to evaluate solvent effects on ring opening, we need to examine the stability of adduct (3) relative to the reactants. This relationship is expressed by formula (3) where K^* is equal to K_1K_2. Values for

$$K^* = [(3)]/[(1)]_0[\mathrm{MeO^-}] \qquad (3)$$

K_1K_2 are reported in Table 3. K^* Increases with increasing proportions of DMSO in the medium, due to the fact that the increment in K_1 is larger than the fall in K_2. This means that the positive influence on the first equilibrium over-rides the counteracting effect on the second. Thus we conclude that dipolar aprotic solvents favour ring opening, which is dependent upon formation of a σ-anionic complex.

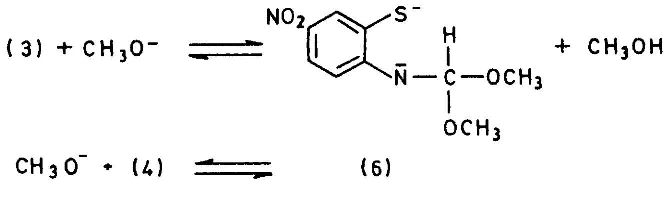
Dependence of Rate of Formation of Adduct (4) *on Base Concentration.*—When reactions were carried out under pseudo-first-order conditions with concentrations of methoxide ion in excess of 6×10^{-2}M formation of (3) is almost completely obscured by that of (4). These results were confirmed by ^{1}H n.m.r. studies: a rapid scan of the reaction performed under similar experimental conditions (MeOK; substrate mole ratio 2 : 1) showed an immediate appearance of proton signals for species (4) only. Previous spectroscopic studies [10] on reaction carried out with an excess of substrate revealed the formation of (3) prior to that of (4). First-order rate constants for formation of (4) under these experimental conditions can be calculated approximately (Table 4); they depend on base concentration by an exponential factor ranging from 1 to 2 units. These findings strongly support the hypothesis that this equilibrium is reached through a base-catalysed process analogous to that proposed by Ogata [11] for addition of alcohols to substituted benzylideneanilines. These authors suggested a mechanism involving an anionic adduct formed between $\mathrm{MeO^-}$ and Schiff's bases.

TABLE 4

Reaction[a] of 6-nitrobenzothiazole with methoxide ion in DMSO–MeOH (80 : 20 v/v) mixture at 25 °C: dependence of first-order rate constants[b] ($k_{3,\mathrm{obs}}$) for formation of adduct (4) on the excess concentration of methoxide ion

$10^3k_{3,\mathrm{obs}}/\mathrm{s}^{-1}$	$[\mathrm{MeO^-}]_0$/M
2.7	0.060
3.4	0.074
5.8	0.10
10.3	0.12

[a] $[(1)]$ 2×10^{-4}M. [b] Approximately calculated by excluding from calculation the first part of recorder absorption curves in which formation of (4) and that of (3) overlap.



More recently [12] we have reported ^{1}H n.m.r. evidence on the formation of a stable anion of the type proposed by Ogata; this anion is produced by interaction between methoxide ion and the *S*-methyl derivative of (3) at room temperature in DMSO. In the present case nucleophilic attack by $\mathrm{MeO^-}$ is directed against a carbon atom of anion (3) distant from the thiolate ion and *para* to the nitro-group; thus, it is very likely that the reaction proceeds *via* a dianion of type (6).

EXPERIMENTAL

Visible spectra were recorded with a Perkin-Elmer 402 spectrophotometer.

Materials.—6-Nitrobenzothiazole was prepared by nitration of benzothiazole as described by Ward.[13] Methanol (reagent grade) was purified by refluxing and distilling over magnesium. Dimethyl sulphoxide was dried by refluxing over calcium hydride and distilling twice over 4A molecular sieves.

Stock solutions of potassium methoxide were prepared by dissolving freshly cut potassium metal in methanol and then by adding the appropriate amount of DMSO. Solvent mixtures were prepared by mixing thermostatted amounts of the pure solvents. In all operations care was taken to remove atmospheric CO_2 and moisture by a stream of nitrogen.

Rate Measurements.—Rate measurements for formation of (2) were performed by a Durrum–Gibson stopped-flow spectrometer. The $k_{1,\mathrm{obs}}$ values of Table 1 represent average values of 3–4 determinations. In the case of DMSO–MeOH (70 : 30 v/v) rate determinations were repeated 8—10 times. Measurements of the rate of formation of (2) and (4) were performed by a Gilford 2400 S instrument. In order to avoid carbonation, the cell compartment was kept under nitrogen. The $k_{2,\mathrm{obs}}$ values of Table 2 represent average values of 4—5 determinations.

Derivation of Equation (2).—The rate equation for attainment of equilibrium between (2) and (3) is given by (4) since

$$\mathrm{d}[(3)]/\mathrm{d}t = k_2[(2)] - k_{-2}[(3)] = k_2([(2)][(3)]_\mathrm{E} - [(2)]_\mathrm{E}[(3)])/[(3)]_\mathrm{E} \qquad (4)$$

$k_{-2} = k_2[(2)]_\mathrm{E}/[(3)]_\mathrm{E}$, where $[(2)]_\mathrm{E}$ and $[(3)]_\mathrm{E}$ are concentrations at equilibrium of (2) and (3) respectively. With reference to the Scheme, we adopt the following assumptions. (i) The concentration of (5) is negligible by comparison with that of all other species. (ii) Adduct (2) is in instantaneous equilibrium with (1) and $\mathrm{MeO^-}$ during formation of (3) (see Discussion section). It follows under the pseudomonomolecular conditions given by an excess of 6-nitrobenzothiazole, that equations (5) and (6) apply at any

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[9] P. De Maria, personal communication.

[10] See ref. 5.

[11] Y. Ogata and A. Kawasaki, *J. Org. Chem.*, 1974, **39**, 1058.

[12] G. Bartoli, F. Ciminale, and P. E. Todesco, *Tetrahedron Letters*, 1975, 1785.

[13] E. R. Ward and W. H. Poesche, *J. Chem. Soc.*, 1961, 2825.

time, where $[\mathrm{MeO}^-]_0$ and $[(1)]_0$ are the initial concentrations of methoxide ion and 6-nitrobenzothiazole, respectively.

$$K_1 = [(2)]/[\mathrm{MeO}^-][(1)]_0 \qquad (5)$$

$$[\mathrm{MeO}^-]_0 = [(2)] + [(3)] + [\mathrm{MeO}^-] \qquad (6)$$

When (3) has reached equilibrium with (2), the concentrations at equilibrium of the various species are linked by equations (7)—(9). By combining equation (5) with (6),

$$K_1 = [(2)]_{\mathrm{E}}/[\mathrm{MeO}^-]_{\mathrm{E}}[(1)]_0 \qquad (7)$$

$$K_2 = [(3)]_{\mathrm{E}}/[(2)]_{\mathrm{E}} \qquad (8)$$

$$[\mathrm{MeO}^-]_0 = [(2)]_{\mathrm{E}} + [(3)]_{\mathrm{E}} + [\mathrm{MeO}^-]_{\mathrm{E}} \qquad (9)$$

(7) with (8), and (7) with (8) and (9) the $[(2)]$, $[(2)]_{\mathrm{E}}$, and $1/[(3)]_{\mathrm{E}}$ terms are given respectively by equations (10)—(12).

$$[(2)] = \frac{([\mathrm{MeO}^-]_0 - [(3)])K_1[(1)]_0}{1 + K_1[(1)]_0} \qquad (10)$$

$$[(2)]_{\mathrm{E}} = \frac{([\mathrm{MeO}^-]_0 - [(3)]_{\mathrm{E}})K_1[(1)]_0}{1 + \mathrm{K}_1[(1)]_0} \qquad (11)$$

$$\frac{1}{[(3)]_{\mathrm{E}}} = \frac{1 + K_1[(1)]_0 + K_1K_2[(1)]_0}{K_1K_2[\mathrm{MeO}^-]_0} \qquad (12)$$

Substitution of these equations into (4) yields (13). Integration of equation (13) gives a first-order relationship, in

$$\frac{d}{\mathrm{d}t}[(3)] = \left(k_{-2} + \frac{k_2K_1[(1)]_0}{1 + K_1[(1)]}\right)([(3)]_{\mathrm{E}} - [(3)]) \qquad (13)$$

which the observed first-order rate constant ($k_{2,\mathrm{obs}}$) is given by equation (2).

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