Kinetics and Mechanism of the Transalkylation between Some Alkyl Heterocyclic Ethers and Thiophenol

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The transalkylation between some ring-nitrogen activated alkyl heterocyclic ethers and thiophenol has been studied quantitatively for alkoxy-1-methylbenzimidazoles. The influence of structural changes of the alkoxy-moiety and of the benzene nucleus on the basicity and reactivity of the system has been investigated. The results are consistent with a reaction mechanism where a rapid acid–base equilibrium between thiol and ether was established, followed by an S_N2 attack by ArS^- at the ether saturated carbon atom. 1-Methyl-2-methylthiobenzimidazole did not react with thiophenol: this fact was interpreted in terms of the low electron-donating ability of the sulphur atom of the sulphide.

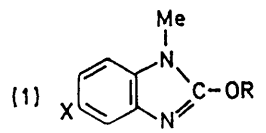
DEALKYLATIONS of aliphatic and alkyl aromatic ethers with a variety of substrates are well known,[1] but have not been extensively studied for heterocyclic compounds from the mechanistic point of view. Zoltewicz and his co-workers [2] reported a kinetic study of the methoxy-dealkylation of methoxypyridines. The transfer of alkyl groups from alkylated systems to thiol substrates, which is of biological interest,[3] has not been quantitatively investigated. We have now studied quantitatively the transalkylations which take place between some heteroaromatic alkoxy-derivatives and thiophenol.

RESULTS AND DISCUSSION

Methyl ethers of some heterocyclic compounds are quantitatively demethylated by thiophenol in carbon tetrachloride solution according to the stoicheiometry (1).

$$\text{Het–OMe} + \text{ArSH} \longrightarrow \text{Het–OH} + \text{ArSMe} \quad (1)$$

Such a reaction is characteristic of ring-nitrogen activated alkoxy-heteroaromatic derivatives, in which the heterocyclic moiety is sufficiently basic. Indeed, the reaction is observed for 6-methoxy-2,4-lutidine ($pK_b = 8{\cdot}85$), 2-methoxyquinoline [4] ($pK_b = 10{\cdot}84$), and 2-methoxy-1-methylbenzimidazole ($pK_b = 9{\cdot}93$), whereas it is known that 2-ethoxybenzo-thiazole and -oxazole show analogous behaviour under more drastic conditions.[5]



(1)

(a) X = H; R = Me
(b) X = H; R = Et
(c) X = H; R = Pr^i
(d) X = H; R = Bu^s
(e) X = H; R = CH_2Ph
(f) X = NO_2; R = Me

Such a reaction has been studied in detail for 2-alkoxy-1-methylbenzimidazoles (1) in CCl_4 solution at 55 °C. The reactions follow clean second-order kinetics, first-order in each reactant, up to high conversions (80—90%). Some representative second-order rate coefficients are reported in Table 1.

TABLE 1

Second-order rate coefficients for the reactions of 2-isopropyloxy-1-methylbenzimidazole (1c) and of the corresponding 2-benzyloxy-derivative (1e) with thiophenol at different initial concentrations of reactants; solvent CCl_4 at 55 ± 0·05 °C

10^2[1c]/M	6·24	4·60	7·91	11·5	2·31	9·29
10^2[ArSH]/M	6·02	1·00	14·7	1·99	7·50	2·62
10^7k/l mol^{-1} s^{-1}	1·10	1·12	1·14	1·12	1·11	1·13
10^2[1e]/M	7·22	5·14	15·1	5·03	4·19	2·81
10^2[ArSH]/M	1·00	4·88	3·93	25·7	22·4	0·90
10^5k/l mol^{-1} s^{-1}	2·96	3·02	3·01	3·03	3·08	2·99

The nature of the alkyl group and nitro-substitution at the benzene nucleus alter the basicity of the pyridine nitrogen of the ethers † (1) as shown from the following values of pK_b; (1a), 9·93; (1b), 9·63; (1c), 9·54; (1d), 9·50; (1f), 11·9. These structural changes also affect the reactivity of the system according to the sequence (Table 2) $CH_2Ph \gg Me > Et > Pr^i > Bu^s$, whereas in

TABLE 2

Specific rate coefficients for the reactions between 2-alkoxy-1-methylbenzimidazoles (1a)—(1e) (2·8—15 × 10^{-2}M) and thiophenol (0·9—26 × 10^{-2}M) in CCl_4 at 55 ± 0·05 °C

R	Me	Et	Pr^i	Bu^s	CH_2Ph
10^7k/l mol^{-1} s^{-1}	9·43	4·07	1·12	0·89	302

the case of the nitrobenzimidazole ether (1f) no reaction occurred even under more drastic conditions. These results can be rationalized according to the Scheme, which consists of a rapid acid–base equilibrium between thiophenol and benzimidazole ether ‡ followed by a nucleophilic attack of thiophenoxy-anion on the saturated carbon atom α to the ether oxygen atom. According to the Scheme, assuming $k_{-1} \gg k_2$, the kinetic

† It was not possible to determine pK_b of the 2-benzyloxy-derivative because of its instability in strongly basic or acid solutions.

‡ A similar situation has been found for the reaction of 2-halogenobenzimidazoles with thiols.[6]

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[3] J. S. Fruton and S. Simmonds, 'General Biochemistry,' J. Wiley and Sons, New York, 1963.

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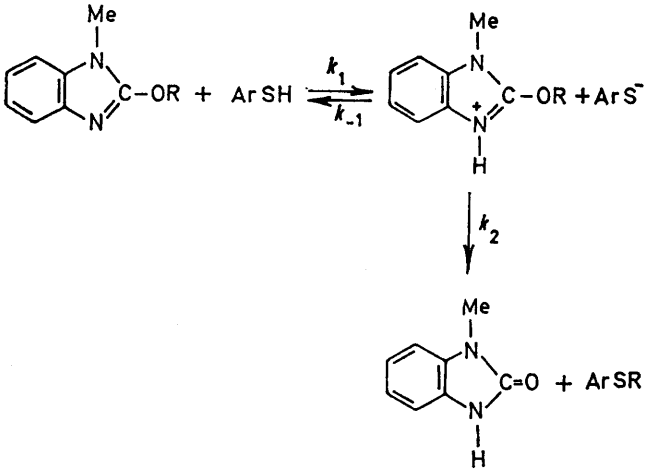
[6] A. Ricci and P. Vivarelli, *J. Chem. Soc.* (*B*), 1968, 1280.

equation has the form (2) (B stands for alkyl benzimidazolyl ether) in accordance with the observed second-order kinetics if we set $k_{obs} = (k_1/k_{-1}) \times k_2$. Substituent

$$\text{Rate} = (k_1/k_{-1}) \times k_2[\text{B}][\text{ArSH}] \qquad (2)$$

modifications at the alkoxy-carbon atom influence, as shown above, the basicity of the system and therefore



SCHEME

modify k_1/k_{-1} in respect to the methoxybenzimidazole (1a). On the other hand, substituents are effective also in the second elementary step (k_2) by electronic and steric interactions. Therefore the reactivity of the system is a balance of such effects in agreement with the suggested mechanism.

The observed reactivity sequence is that expected for an aliphatic S_N2 reaction in agreement with the kinetic form found in every case.[7] The fact that such a mechanism is operative also for the 2-benzyloxy-derivative (1e) may be attributed to the use of a particular solvent [7] whose low solvating power is known.[8]

The Scheme also accounts for the fact that the overall process is characteristic of aza-activated alkyl heterocyclic ethers with good basicity, for which the acid–base equilibrium between the substrate and the thiol is possible. Accordingly, the nitro-derivative (1f) does not react in line with the lack of protonation of the system which makes k_1/k_{-1} negligible.

The suggested mechanism does not include a competitive dealkylation of the system by the thiol, which, in the undissociated form, is much less nucleophilic than the thiophenoxy-anion.[9] Further, the latter is certainly present, in CCl_4 solution, as an ion-pair associated with the protonated benzimidazole ether and therefore in a condition highly favourable to the reaction. From this it may be concluded that the ArS^- anion is the only nucleophile responsible for the observed dealkylation.

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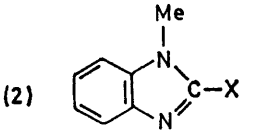
This interpretation is in agreement with the fact that unchanged thiophenol is recovered from the interaction of (1a) with equivalent amounts of thiol and trifluoroacetic acid in CCl_4: the stronger trifluoroacetic acid protonates the base which reacts with the sole anion present to yield 1-methylbenzimidazol-2(3*H*)-one and methyltrifluoroacetate.

Indeed, that the heterocyclic base is present in the protonated form in these conditions is shown by i.r. spectroscopy of a solution of (1a) ($3{\cdot}4 \times 10^{-2}$M) in CCl_4 in the presence of $CF_3{\cdot}CO_2H$ ($3{\cdot}4 \times 10^{-2}$M) which shows the absorption band (at *ca.* 2500 cm^{-1}) characteristic of the $-\overset{+}{N}H=$ group and identical to that observed, in the same experimental conditions, with 2-chloro-1-methylbenzimidazole (2a). 1-Methyl-2-methylthiobenzimidazole (2b) having pK_b 9·48, *i.e.*, of the same magnitude as, or larger than, that of the other bases, does not react



(a) X = Cl
(b) X = SMe

with thiophenol in our experimental conditions. The fact was not completely unexpected considering the poor electron-releasing properties of a side-chain sulphur atom [10] which may reduce the delocalization of the negative charge introduced by the thiolate anion in the transition state.

This situation may prevent the formation of a sulphur–heterocyclic carbon atom double bond, followed by the breaking of the S–C linkage between the sulphur and saturated carbon atom; consequently no reaction between 1-methyl-2-methylthiobenzimidazole (2b) and thiophenol should be expected, as observed.

EXPERIMENTAL

Thiophenol and carbon tetrachloride (commercial) were purified by described methods.[11] Compounds (1c)—(1e) were prepared by heating 2-chloro-1-methylbenzimidazole [12a] (2a) with the appropriate sodium or potassium alkoxide in the corresponding alcohols under the conditions described [12a] for the preparation of (1a). Compound (1f) was obtained by the same procedure from 2-chloro-1-methyl-5-nitrobenzimidazole.[12b] The ethoxy-derivative (1b) was prepared as described by Takahashi and Kano [13] for the syntheses of other 2-substituted benzimidazoles. Compound (2b) was obtained by the literature method.[14] For analyses *etc.* see Table 3.

6-*Methoxy*-2,4-*lutidine*.—This was obtained by heating a methanol solution of 6-chloro-2,4-lutidine [15] (0·1 mol) and sodium methoxide (0·5 mol) at 150—160 °C during 4 h, followed by evaporation of the alcohol, addition of water,

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[15] E. Aston and J. N. Collie, *J. Chem. Soc.*, 1897, **71**, 653.

and ether extraction. Vacuum distillation gave a liquid, b.p. 69—70° at 15 mm (90%). Its *picrate* had m.p. 147—148° (from ethanol) (Found: C, 46·2; H, 3·9; N, 15·2. $C_{14}H_{14}N_4O_8$ requires C, 45·9; H, 3·9; N, 15·3%). 2-Methoxyquinoline was prepared by literature method.[16]

Reaction Products.—The products from the reaction of the alkylheterocyclic ethers (0·01 mol) and thiophenol (0·06 mol) were isolated for all cases in the conditions used for the kinetic experiments. When the reaction was complete, the mixture was evaporated to dryness and the residue was carefully washed with ether. 1-Methylbenzimidazol-2(3*H*)-one [17] [m.p. 192—193° (from ethanol)], 2-hydroxyquinoline [18] [m.p. 199—200° (from ethanol)], and 6-hydroxy-2,4-lutidine [19] [m.p. 170—171° (from water)] were obtained in nearly quantitative yields from the benzimidazole ethers (1a)—(1e), 2-methoxyquinoline, and 6-methoxy-2,4-lutidine respectively. Agreement of properties with the same compounds prepared by independent routes [17-19] was satisfactory. The ether filtrate was washed with aqueous sodium hydroxide and water and dried, and the solvent was evaporated. The corresponding sulphides were separated and their i.r. spectra found to be identical with those of authentic materials obtained by independent syntheses.[20-23] Their yield always averaged above 90%.

Reaction of 2-Methoxy-1-methylbenzimidazole (1a) *with Trifluoroacetic Acid with Added Thiophenol.*—The title compounds in the molar ratio 1 : 1 : 1 were kept in CCl_4 at 55 °C. At the end of the reaction, dilution with light petroleum and cooling to −20 °C caused the separation of 1-methylbenzimidazol-2(3*H*)-one (88%). The solution was washed with aqueous sodium hydroxide and dried. The solution contained methyl trifluoroacetate (g.l.c.; 90%) which was separated and identified by comparison with the i.r. spectrum of a commercial sample. Acidification of the aqueous solution and ether extraction allowed the unchanged thiophenol to be recovered nearly quantitatively.

Determination of pK_b *Values.*—These were determined spectrophotometrically [24] at 25 °C in aqueous solution with 2% methanol at constant (0·5M) ionic strength (NaCl).

TABLE 3

Compound	Yield (%)	M.p. (°C)	Solvent for crystn.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(1b)	70	60—61	n-Heptane	$C_{10}H_{12}N_2O$	67·7	6·9	15·6	68·2	6·87	15·9
(1c)	80	*a*		$C_{11}H_{14}N_2O$	68·9	7·5	14·8	69·4	7·4	14·7
(1d)	70	*b*		$C_{12}H_{16}N_2O$	70·4	7·9	13·6	70·6	7·9	13·7
(1e)	60	66—67	Ligroin	$C_{15}H_{14}N_2O$	75·7	6·0	11·9	75·6	5·9	11·8
(1f)	90	192—193	Ethanol	$C_9H_9N_3O_3$	51·9	4·4	20·2	52·2	4·4	20·3

[a] B.p. 97—98° at 0·2 mm. [b] B.p. 104—105° at 0·3 mm.

The solutions were stable during the time of the measurements. The pH values of buffered solutions were determined with a Radiometer 26 pH-meter with glass and calomel electrodes.

Kinetics.—Known volumes of thermostatted solutions of benzimidazoles and thiophenol in CCl_4 were mixed, at zero time, in a flask fitted with a Teflon cap. Samples were taken at intervals and analysed spectrophotometrically at 294 nm [λ_{max} of 1-methylbenzimidazol-2(3*H*)-one]. By the end of a run no appreciable variation of the concentration of a blank of thiophenol solution was apparent. By means of integrated second-order equation the analytical data were plotted in order to evaluate the rate coefficients.[25] The reported kinetic data are the average of three or more independent runs with deviations not larger than 2% from the average. I.r. and u.v. spectra were recorded respectively with Perkin-Elmer 257 and 224 instruments.

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