Base-catalysed Hydrogen–Deuterium Exchange in Some 2-Substituted Thiazoles: Reactivity in the 5-Position

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Kinetic data on the base-catalysed hydrogen deuterium exchange at the 5-position of some 2-substituted thiazoles in [$^2H_6$]DMSO–CD_3OD (1 : 1 v/v) are reported. The reaction probably occurs *via* an anionic intermediate. Substituent effects give (using σ_m) a high ρ value (5.7). Only 2-*NN*-dimethylamino-3-methylthiazolium iodide shows an appreciable exchange reaction at the 4-position. The reactivity order for the three thiazole positions (5 ≥ 2 ≫ 4) is related to inductive effects and the presence of sulphur. The tautomerism of some 2-aminothiazoles is discussed.

MANY workers have studied the thiazole ring system because of its biological and chemical interest. Recently we have attempted to determine the relative reactivity of the three carbon atoms in the thiazole ring. Usually

position 2 is accepted as the most reactive towards both electrophilic and nucleophilic reagents,[1] but positions 4 and 5 may also be considered to have similar reactivity to that of position 2 towards most nucleophiles.[1,2] The thiazole system can be considered as an electron deficient aromatic heterocycle (because of the presence of the 'aza' group) or an electron rich system (because of the presence of six electrons in five-centred molecular orbitals). Furthermore, variation of the substituents bonded to the carbon atoms can cause large changes in its chemical behaviour, because the small ring is very sensitive to substituent electronic effects, as shown by the high ρ values usually observed.[3-5] Some unexpected chemical behaviour of thiazole derivatives can probably be explained by reference to this.

Hydrogen–deuterium exchange was studied for position 2.[6] Position 5 was shown by Olofson and his co-workers[6] to be less reactive than position 2 in neutral medium, and both had similar reactivity at pD 13.4. Position 4 is usually considered to be unreactive and the presence of the sulphur atom explains the difference in reactivity between the three positions.

RESULTS

The exchange reactions were performed at 30.5 °C by n.m.r. analysis (see Experimental section) in [$^2H_6$]DMSO–CD_3OD (1 : 1 v/v) and in the presence of the appropriate amount of $CD_3O^-Na^+$. The solvent was chosen on consideration of the reactivity requirements of the substrates. All the kinetic runs followed a first-order kinetic law, and first-order rate constants were calculated by using the correction recommended by Sachs.[7] From these values second-order rate constants are obtained by dividing by the base concentration. The results are reported in Table 1.

To avoid complications arising from nucleophilic substitution reactions, we did not use good leaving groups (*e.g.* NO_2, halogen, SO_2R). In all cases, only hydrogen–deuterium exchange was observed. In order to obtain information on the mobility of 4-H under our reaction conditions, we used a more active substrate, such as 2-*NN*-dimethylamino-3-methylthiazolium iodide, for which we observed not only a fast exchange reaction at C-5, but also exchange at C-4. Kinetic data for positions 4 and 5 were obtained from independent runs.

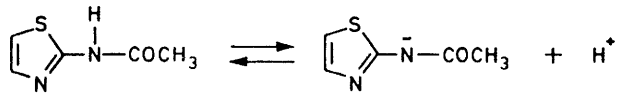
TABLE 1

H–D exchange reactions in positions 5 of some 2-substituted thiazoles, at 30.5 °C, in [$^2H_6$]DMSO–CD_3OD (1 : 1 v/v) and in the presence of $CD_3O^-Na^+$

Substrate	k/l mol^{-1} s^{-1}
Thiazole	5.17×10^{-4} (4.19×10^{-4}) [a]
2-*NN*-Dimethylaminothiazole	3.96×10^{-5}
2-Dideuterioaminothiazole	5.75×10^{-5}
2-*N*-Benzylaminothiazole	1.55×10^{-4}
2-Phenylsulphinylthiazole	5.0×10^{-1}
Ethyl thiazole-2-carboxylate	1.2×10^{-1}
2-Phenylthiothiazole	6.5×10^{-3}
2-*N*-Phenylaminothiazole	2.8×10^{-4}
2-*NN*-Dimethylamino-3-methylthiazolium iodide	1.2×10^{-1} (4.2×10^{-4}) [b]

[a] Rate of exchange at position 2. [b] Rate of exchange at position 4.

2-Acetylaminothiazole gave no appreciable exchange in both 4 and 5 positions, even for long reaction times. The acetylamino group is electron withdrawing (σ_m 0.21) so that 2-acetylaminothiazole should be more reactive than thiazole.



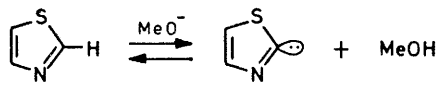
SCHEME 1

However in basic medium the equilibrium is shifted to the right (Scheme 1) as shown by u.v. spectra.[8] In the n.m.r. spectrum the addition of a solution of $CD_3O^-Na^+$ to 2-acetylaminothiazole in [$^2H_6$]DMSO gives a shift (*ca.* 0.4 p.p.m.) of the ring proton signals towards higher field, as expected for passing from 2-acetylaminothiazole to the anion which is obviously deactivated towards base-catalysed exchange in position 5.

DISCUSSION

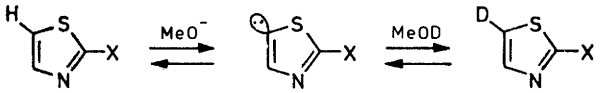
We have reported previously that the reactivity of 2- and 5-halogenothiazoles towards nucleophilic reagents is similar in a polar protic solvent (methanol) and with anionic nucleophiles (sodium methoxide and sodium benzenethiolate).[1] The reactivity of 4-halogenothiazoles towards nucleophiles is complicated by super-

position of some medium (solvent–nucleophile) effects.[2] However, for the three halogenothiazole isomers we observed the reactivity order 5 > 2 > 4 (in MeOH with MeO^-). Consideration of the H–D exchange reaction for unsubstituted thiazole shows the same reactivity order (5 ⩾ 2 ⩾ 4) in our reaction conditions and those used by Olofson.[6,9] Base-catalysed H–D exchange reaction in position 2 is regarded [6] as preceding by a carbonium anion mechanism (Scheme 2). We think that the same mechanism also operates for position 5. The substituent effect supports this hypothesis, because electron-withdrawing substituents enhance the reactivity which is depressed by electron-donating substituents (see Table 1). The differences are notably higher than



SCHEME 2

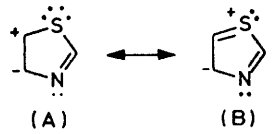
experimental error. The rate enhancement on going from 2-*NN*-dimethylamino- to 2-phenylsulphonyl-thiazole is 1.5×10^4. Hammett treatment of the data gives the best linear correlation when σ_m values are used (ρ 5.72 ± 0.2, r 0.996). This is expected for the formation of a negative charge in an sp^2 orbital which is more sensitive to substituent inductive than mesomeric effects. Therefore, we think that the rate-determining step is proton abstraction by base catalysis, as represented in Scheme 3. We observed appreciable H–D



SCHEME 3

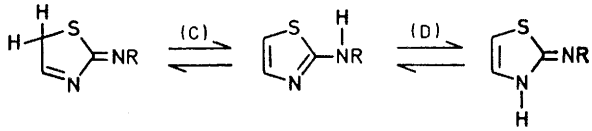
exchange in position 4 for 2-*NN*-dimethylamino-3-methylthiazolium iodide only. The ratio of the exchange rate in position 5 ($k_{2\text{-}NN\text{-dimethylamino-3-methylthiazolium iodide}}$: $k_{2\text{-}NN\text{-dimethylaminothiazole}}$) is 3×10^3. The electron-withdrawing effect of the ring nitrogen is considerably enhanced by the positive charge. However position 5 is also more reactive than position 4 (k_5/k_4 3×10^2) for this compound.

Several explanations are possible for this behaviour. First, the inductive effect which is higher for nitrogen than for sulphur may be important. In this case the importance of the inductive effect is emphasized by the use of σ_m, by the high ρ value obtained, and by the reactivity of the positively charged thiazole. Secondly, there is the possibility of negative charge stabilization by the sulphur atom (which certainly operates more in position 5 than in position 4) as discussed in detail by Haake [10] and by Olofson.[6,9] This stabilization is probably from polarization of the electronic distribution.[11] In order to explain the difference in reactivity between positions 5 and 4 the previous arguments need to be partially reversed. We think that the reactivity of position 4 is depressed by the presence of sulphur which exerts an electron-releasing effect, as for the thiophen ring. Thiophen is unreactive even in more drastic conditions than those used here.[9] Tentatively we consider the structures (A) and (B) which participate together with the other mesomeric structures (with charge separation) to be reasonably probable.



In other words the C-4–C-5 π bond is polarized towards the more electronegative nitrogen. This situation is in agreement with MO calculations [12] which indicate that C-4 is the most negative carbon atom, and with the lack of reactivity (under similar experimental conditions) of 3-H in isothiazole and 1,2,3-thiadiazole systems,[9] and of 4-H in oxazole.[13] The observed reactivity order is probably derived from superposition of the effects discussed which are difficult to separate. These results confirm our previous estimates of the electron density at C-5 of thiazole which is very close to that usually accepted for C-2. Nevertheless we consider it scarcely realistic to put forward a hypothesis on the electron density of the three carbon atoms of the thiazole ring. In fact the reaction data used for this purpose result from particular requirements which should involve some properties of the heteroatoms (or of the substituents) which would hardly apply in different situations. For example, our conclusions apparently do not agree with reports on the nitration of thiazole derivatives [14] which show that positions 4 and 5 have similar reactivity.

Further interesting observations can be made from reactivity data on 2-aminothiazoles for which it is accepted that the presence of tautomeric processes in Scheme 4 is possible: [15] these are responsible for the



SCHEME 4

chemical behaviour of some 2-aminothiazoles derivatives.[16,17] The very similar reactivity of 2-aminothiazole and of 2-*NN*-dimethylaminothiazole (for which tautomerism is not possible) makes equilibrium (C) improbable. Hence our previous reports [16] on the reactivity of 5-halogeno-2-aminothiazoles with nucleophiles probably indicate the existence of equilibrium (D). Only 2-*N*-benzylaminothiazole deviates from Hammett plot (its reactivity is higher than expected) but this deviation is so small than it represents only a feeble indication of the presence of equilibrium (C).

EXPERIMENTAL

Materials.—Thiazole derivatives were prepared and purified by the usual methods. Physical properties and ^1H

TABLE 2

Physical properties and n.m.r. data of some thiazole derivatives

Substrate	M.p. (°C) (solvent)	Chemical shift (δ from Me_4Si) 5-H	4-H	Substituent
Thiazole	93—94 [a]	7.76 (1 H, d) [b]	7.95 (1 H, d)	9.16 (1 H, d) [c]
2-Aminothiazole	93—94 ($CHCl_3$)	6.55 (1 H, d) [b]	6.95 (1 H, d)	
2-*NN*-Dimethylaminothiazole	83—84 (20) [a]	6.81 (1 H, d) [d]	7.33 (1 H, d)	3.18 (6 H, s) [e]
2-Acetylaminothiazole	206—207 (H_2O)	7.33 (1 H, d) [b]	7.60 (1 H, d)	2.18 (3 H, s) [f]
2-Phenylthiothiazole	145 (3) [a]	7.65 (1 H, d) [b]	7.80 (1 H, d)	7.5 (5 H, m) [g]
2-Phenylsulphinylthiazole	68—69 (light petroleum)	7.93 (2 H, s) [h]		7.6 (5 H, m) [g]
Ethyl thiazole-2-carboxylate	119—121 (15) [a]	8.15 (2 H, s) [b]		1.29 (3 H, t), [i] 4.41 (2 H, q) [i]
2-*N*-Phenylaminothiazole	128—129 (CCl_4)	6.96 (1 H, d) [i]	7.35 (1 H, d)	7.5 (5 H, m) [g]
2-*N*-Benzylaminothiazole	131—132 (CCl_4)	6.65 (1 H, d) [i]	7.07 (1 H, d)	7.35 (5 H, s), [g] 4.31 (2 H, s) [m]
2-*NN*-Dimethylamino-3-methylthiazolium iodide	204—206	7.43 (1 H, d) [d]	7.62 (1 H, d)	3.55 (6 H, s), [e] 4.13 (3 H, s) [n]

[a] B.p. (*p*/mmHg). [b] In $(CD_3)_2SO$. [c] 2-H. [d] In CD_3OD. [e] 2-NCH_3. [f] $COCH_3$. [g] Ph. [h] In $(CD_3)SO$–CD_3OD (3 : 1 v/v). [i] Et.[1] [l] In $(CD_3)_2SO$–CD_3OD (2 : 1 v/v). [m] CH_2Ph. [n] NCH_3.

n.m.r. data are reported in Table 2 (m.p.s and b.p.s are uncorrected). 2-Dideuterioaminothiazole was obtained by dissolving 2-aminothiazole in MeOD and evaporating the solvent (four times) [extent of deuteriation ⩾97% (n.m.r. and i.r.)]. CD_3OD and [$^2H_6$]DMSO (Fluka) were used without purification. $CD_3O^-Na^+$ solutions were prepared from CD_3OD and Na. The amount of CD_3O^- was determined by titration with 0.01N-H_2SO_4.

Kinetics.—Appropriate thiazole derivative solutions (0.4—0.05M) in [$^2H_6$] DMSO—CD_3OD (1 : 1 v/v) were added to $CD_3O^-Na^+$ solutions in CD_3OD. The exchange reactions were monitored by 60 Hz ^1H n.m.r. with temperature control (±0.3 °C). When possible, the 4-H peak was used as internal standard reference. From the analytical data the first-order rate constant was calculated by using the method of ref. 7. The infinite time measurements were calculated as recommended by Sachs,[7] to avoid curvature in the log (peak area)–time plots. All the reactions were first order in thiazole up to high percentages of exchange (50—70%). Data reproducibility was *ca.* 10%.

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