

## Unexpected Mobility of the Halogen in some 4-Halogenothiazoles and 5-Halogenothiazoles

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**Summary** In contrast with previous reports, it has been found that 4-halogenothiazoles and 5-halogenothiazoles react with methoxide ion at rates comparable to that of the isomeric 2-halogenothiazole.

It is a textbook notion that aza-activated halogeno-hetero-aromatic derivatives react with nucleophiles at appreciable rates especially when the halogen is in a position from which conjugation is possible with the aza-activating group, as has been well demonstrated in the case of six-membered rings.<sup>1</sup> In five-membered rings, 4- and 5-halogeno-thiazoles are described as unreactive as compared with 2-halogeno-thiazoles.<sup>2</sup>

We have found that this statement is incorrect. In fact, 4-halogenothiazoles (halogen = Cl, Br) and 5-halogenothiazoles react with methoxide ion in methanol under the same experimental conditions used for the corresponding 2-isomers yielding almost quantitatively the expected 4-methoxythiazole and 5-methoxythiazole.

Recently Metzger also reported similar results for the reaction of 4-chlorothiazole with ethoxide ion.<sup>3</sup>

The second-order kinetic constants at 50° ( $10^5k$  in  $s^{-1} \text{ mol}^{-1}$ ), and for some cases, the Arrhenius parameters  $E_{\text{Att}}$  in  $\text{kcal.mol}^{-1}$   $\Delta S^\ddagger$  in  $\text{cal mol}^{-1}\text{deg}^{-1}$  are as follows: 2-Cl 0.81; 18.4, -27.1; 2-Br 1.05, —, —; 4-Cl 0.060, 25.5, -10.1; 4-Br 0.13, —, —; 5-Cl 1.9, 22.8, -11.6; 5-Br 2.3, —, —.

The reactivity order for the different isomers in the case of chloro- and bromo-derivatives is  $5 > 2 > 4$ . All the data are included within a factor of less than 30. The small "element effect" [e.g.,  $k(4\text{-Br})/k(4\text{-Cl}) \approx 2$ ] indicates that carbon-halogen bond breaking is not involved in the transition state. In principle, as far as the reactions of 4-halogenothiazoles are concerned, an elimination-addition mechanism (*via* hetaryne)<sup>4</sup> could be considered as a likely candidate on the basis of the ready hydrogen exchange at the 5-position observed by Olofson in the reaction of the simple thiazole<sup>5</sup> with alkoxides (the 4-hydrogen does not exchange at all).

However, we have found that 4-chloro-5-phenylthiazole reacts with methoxide ion at a rate comparable with that of 4-chlorothiazole. Even when *t*-butoxide in *t*-butyl alcohol, which strongly favours 'elimination reactions'<sup>6</sup>, is used as a nucleophile, similar  $k$  values are found (at 50°  $10^5k$   $s^{-1} \text{ mol}^{-1}$ ): 4-chloro-5-phenylthiazole 21.9, 4-chlorothiazole 25.2). These results rule out the above mechanistic possibility.

A discussion of the possible mechanism involved will be given in the full paper.

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<sup>2</sup> J. M. Sprague and A. H. Land, in R. G. Elderfield, "Heterocyclic Compounds", Wiley, New York, 1957, vol. 5, p. 545; M. H. Palmer, "The Structure and Reactivity of Heterocyclic Compounds", Arnold, London, 1967, p. 377; A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry", Methuen, London, 1967, p. 155.

<sup>3</sup> J. Metzger "Recherches recentes dans la serie du thiazole 1.3", invited lecture at the 2ème Congres International de Chimie Heterocyclique, Montpellier 7—11 July, 1969.

<sup>4</sup> R. W. Hoffman "Dehydrobenzene and Cycloalkynes", Academic Press, London, 1967, p. 275; T. Kauffmann and F. P. Boettcher, *Chem. Ber.*, 1962, **95**, 1528; R. J. Martens and H. J. Den Hertog, *Tetrahedron Letters*, 1962, 643.

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<sup>6</sup> G. Modena, *Accounts Chem. Res.*, 1971, **4**, 73; D. V. Banthorpe, "Elimination Reactions", Elsevier, London, 1962, p. 30.