Mechanism of Base-catalysed Hydrogen–Deuterium Exchange in Thiazolium Ion: Evidence for the Involvement of a Tetrahedral Intermediate

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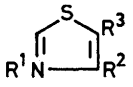
The mechanism of base-catalysed hydrogen–deuterium exchange of 2-H in the thiazolium ion has been examined by ^{1}H n.m.r. spectroscopy, using small and sterically hindered nucleophiles. Rapid H–D exchange is observed in [$^2H_6$]Me_2SO in the cases of 3,4,5-trimethyl- (1), 3-methyl-4,5-diphenyl- (2), 3,5-dimethyl-4-phenyl- (3), and 3,4-dimethyl-5-phenyl-thiazolium iodide (4), when small nucleophiles (KOD–D_2O or $KOCD_3$–$DOCD_3$; 0.016M; 25°) are employed. Utilization of a hindered nucleophile [$KOC(CD_3)_3$–$DOC(CD_3)_3$; 0.016M; 25°] however results in a slow exchange of 2-H in (1), (3), and (4), concomitant with H–D exchange of the 4- and 5-methyl protons. The rate of exchange of (1) is found to be approximately twice as rapid as that of (3) or (4). No H–D exchange of 2-H is detected in the case of (2) with the hindered nucleophile. These observations are ascribed to the formation of a tetrahedral intermediate as a prerequisite of the exchange reaction.

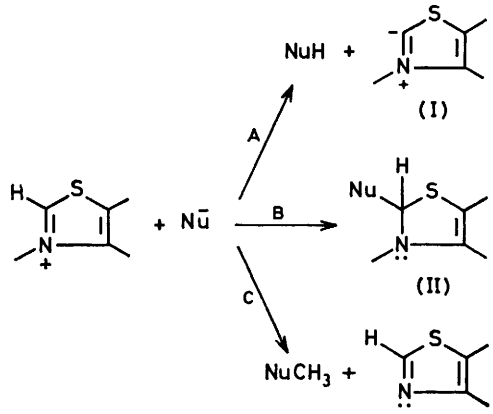
THE mechanism of H–D exchange of 2-H in thiazolium ion has received wide attention. This is mainly due to the role of thiamin (vitamin B_1) which serves to catalyse a remarkable number of diverse reactions in biological systems.[1] The pyrophosphate derivative of thiamin, co-carboxylase, is the biochemically active catalyst for such key enzymatic reactions as pyruvate decarboxylase, pyruvate dehydrogenase, α-acetolactate synthetase, transketolase, glyoxylate carboligase, and phosphoclastic reactions.[1] Recently, experimental evidence on the involvement of thiamin in the biosynthesis of irregular terpenes has been presented.[2] Apart from its importance in biochemical transformations, the value of thiazolium ion as a catalyst in synthetic organic chemistry is gaining interesting dimensions.[3]



(1) $R^1=R^2=R^3=Me$
(2) $R^1=Me$, $R^2=R^3=Ph$
(3) $R^1=R^3=Me$, $R^2=Ph$
(4) $R^1=R^2=Me$, $R^3=Ph$

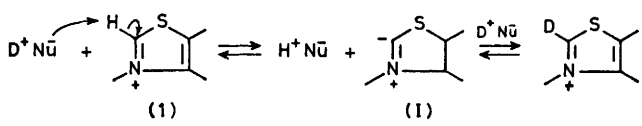
The catalytic ability of thiazolium ion originates from the unusually low pK_a of its 2-H.[4] With a pK_a of 12.6, thiazolium salts readily dissociate from 2-H, leading to the formation of a negative charge at this position. Since Breslow's proposal for the acidity of 2-H,[5] numerous diverse speculations have been forwarded for the explanation of this phenomenon.[6–14] Nevertheless, the basic structural reasons leading to the unique acidity of 2-H in thiazolium ion remain vague.

The interactions of thiazolium salts with nucleophilic bases have been noted to fall into three general routes.[15] The nucleophile may abstract one of thiazolium ring protons, among which 2-H, due to its low pK_a, is the most vulnerable candidate[5] (Scheme 1, Route A). Alternatively, the nucleophilic species may attack the aromatic ring at C-2[8,9,16–19] (Scheme 1, Route B). Steric hindrance would presumably prevent the subsequent formation of the tetrahedral intermediate (II). The third mode of interaction involves attack of the nucleophile at the *N*-alkyl moiety to displace the parent thiazole[20] (Scheme 1, Route C).



SCHEME 1

The generally accepted mechanism for the exchange reaction involves direct abstraction of 2-H by a weak protic base[5] (Scheme 2). This results in the formation of an ylide (I) in which C-2 of the thiazolium ring retains its sp^2 character. Whether the *d* orbitals of the adjacent sulphur atom contribute to the stability of the developed negative charge has been a subject of controversy.[11–13] In fact, earlier studies have shown that 2-H of the oxazolium analogues undergo H–D exchange at a much higher rate than their thiazolium counterparts.[12] Furthermore, CNDO/2 and Hückel theory calculations concerning charge density on C-2 have not reached convincingly uniform results.[11,14]



SCHEME 2

In view of these ambiguities, it has been of interest to us to establish the exact nature of the intermediate undergoing the exchange reaction. In a recent com-

† The reported value of 12.6 is for thiamin and has been viewed with scepticism as being too large with regard to the H–D rate of exchange of thiamin and its pH-independent reactions in biological systems.

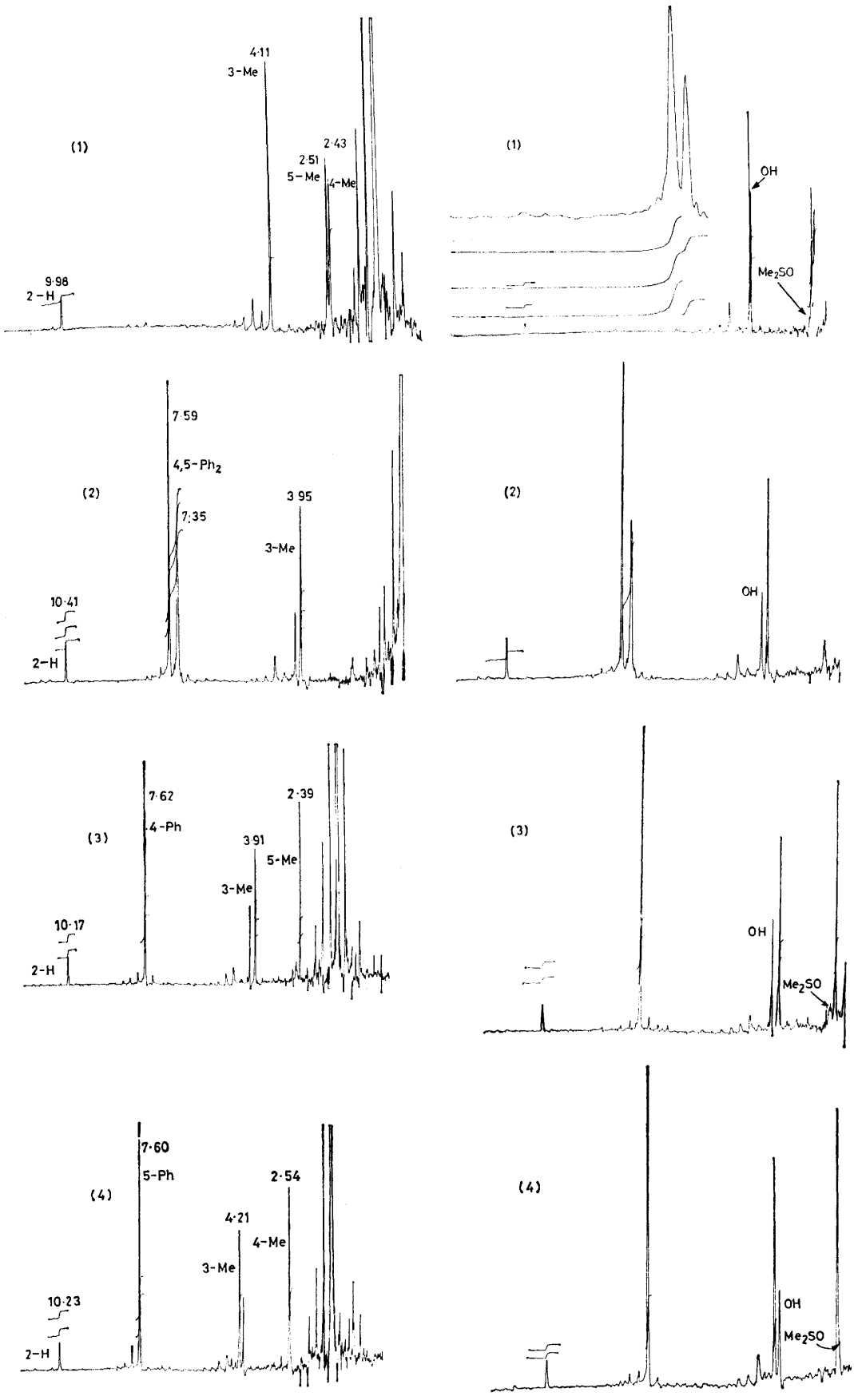


FIGURE 1 ^{1}H N.m.r. spectra of substrates (1)—(4) in [$^2H_6$]Me_2SO and in the presence of the hindered nucleophile $KOC(CD_3)_3$–$DOC(CD_3)_3$. Spectra on the left were recorded 15 min after the addition of the nucleophile. Spectra on the right were recorded 200 h after the addition of the nucleophile

munication,[21] we reported experimental evidence indicating that the formation of a tetrahedral intermediate is a prerequisite of the exchange reaction. The reported results were obtained in neutral media ($[^2H_6]Me_2SO$ or $CDCl_3$) containing potential nucleophiles of various degrees of steric hindrance [*i.e.* DOD, $DOCD_3$, $DOCD(CD_3)_2$, or $DOC(CD_3)_3$]. In the present communication, reactivity of thiazolium salts toward actual nucleophiles of various degrees of steric hindrance is examined in $[^2H_6]Me_2SO$. The actual nucleophiles tested include KOD–DOD, $KOCD_3$–$DOCD_3$, or $KOC(CD_3)_3$–$DOC(CD_3)_3$. The results verified our previous proposal on the intermediacy of a tetrahedral intermediate in the exchange reaction. Of particular interest is not only the difference in the rates, but also the difference in the modes of exchange of the employed substrates with the sterically hindered nucleophile utilized in this study.

RESULTS

The H–D exchange of 2-H was followed by ^1H n.m.r. spectroscopy. The decreasing 2-H signal was intergrated as a function of time with respect to a reference absorption. Since 0.1 ml of a 0.016 molar solution of deuteriated nucleophile was used for 0.1 mmol of substrate (see Experimental section), there is greater than eight-fold excess of D^+ available for the exchange reaction in each experiment.

The protonated bases [KOH–HOH, $KOCH_3$–$HOCH_3$, or $KOC(CH_3)_3$–$HOC(CH_3)_3$] associated as impurities with their respective deuteriated bases, result in the largest absorption peak in each experiment. In fact, at the normal vertical scale (v.s.) of 100, the absorption peaks of substrate, and especially of 2-H, are difficult to detect and impossibe to integrate. It was therefore necessary to increase the v.s. to 3 000. This thirty-fold increase in v.s. however, results in the appearance of a number of absorptions with considerable intensity, which at the normal v.s. of 100 lie on the base line. These absorptions include the side bands of the protonated alkyl moiety and the hydroxy-group proton of the base utilized in the experiment. The unavoidable appearance of these absorptions at a v.s. of 3 000 results in their interference with the absorption peaks of N-3 and the 4- and 5-methyl groups of the substrates (Figure 1). This interference causes no difficulty in the interpretation of results when small nucleophiles (KOD–DOD or $KOCD_3$–$DOCD_3$) are employed for the exchange reaction. In these cases, very rapid exchange of 2-H is observed with all substrates examined.

In the case of the hindered nucleophile [$KOC(CD_3)_3$–$DOC(CD_3)_3$], 2-H exchange is brought about *via* proton abstraction from the 4- and/or 5-methyl groups (see Discusssion section). Unfortunately, however, a definite analysis of the rates of exchange of the 4- and/or 5-methyl group protons is complicated by a number of factors. First, the side-band absorptions of the alkyl moiety of $KOC(CD_3)_3$–$DOC(CD_3)_3$ affect the absorption intensity of the 4- and/or 5-methyl groups (Figure 1). Secondly, being the most intense peak, the methyl groups of $KOC(CH_3)_3$–$HOC(CH_3)_3$ cause slight phase deformations in the proximity of their position of absorption, which cannot be totally corrected for. This in turn affects the intensity of absorption, and hence the integral value, of the 4- and/or 5-methyl groups. Finally, the protonated impurity of $[^2H_6]Me_2SO$ resonates at δ 2.43, which is in the region of absorption of the 4-methyl group.

A combination of the foregoing inherent difficulties makes the establishment of a detailed correlation between the rates of exchange of C-2 and the 4- and/or 5-methyl group protons impossible. It is of interest to note, however, that an empirical correlation between the rates of disappearance of C-2 and the -4 and/or -5 methyl group protons does exist in the case of (1), (3), and (4). This correlation is especially pronounced in the case of (1) in which a 15% decrease in the intensity of absorption of the 4- and 5-methyl groups is observed after 48 h.

Another source of interference is the hydroxy-group absorption of $HOC(CH_3)_3$, which is present in the exchange media as an impurity. As shown in Figure 1, at the particular concentration used (see Experimental section), this proton absorbs in the vicinity of the absorption of 3-methyl group [(1), δ 4.11; (2), 3.95; (3), 3.91; (4), 4.21]. In the case of (2)—(4) there is enough separation between these absorptions so that a reasonable integral of the 3-methyl group may be obtained. In the case of (1), due to the close proximity of the hydroxy-proton and the 3-methyl absorptions, it became necessary to expand the spectra so that the 3-methyl group could be integrated independently (Figure 1).

Calculations.—The rate of disappearance of 2-H was measured for each substrate as a function of time relative to a reference absorption. In the case of (1), the reference absorption was the 3-methyl group, whereas for (2)—(4) the phenyl groups were chosen as the reference. It should be emphasized that since no measurable exchange of the 3-methyl group protons was observed, they may be substituted for the phenyl groups as the reference absorption. This in fact results in a similar percentage exchange–time profile as shown in Figure 2.

Small Nucleophiles (KOD–DOD *or* $KOCD_3$–$DOCD_3$).—Very rapid exchange of 2-H was observed for all the substrates under examination. Total H–D exchange was observed for all substrates in 10 min with KOD–DOD. In the case of $KOCD_3$–$DOCD_3$ the required time for 80% exchange was 6 h, and total exchange 28 h.

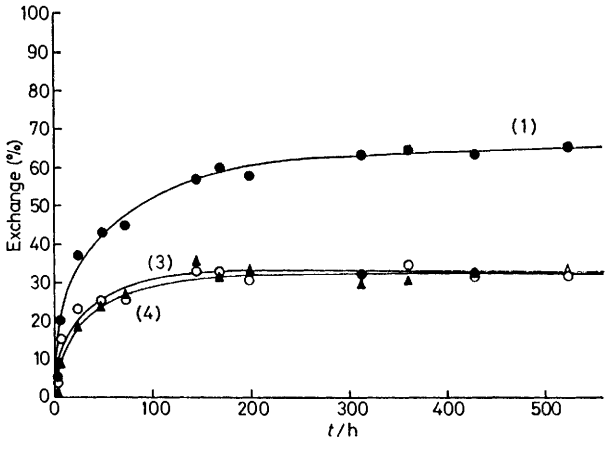


FIGURE 2 H–D exchange of 2-H of substrates (1), (3), and (4) as a function of time in $[^2H_6]Me_2SO$ and in the presence of the hindered nucleophile $KOC(CD_3)_3$–$DOC(CD_3)_3$

Hindered Nucleophile [$KOC(CD_3)_3$–$DOC(CD_3)_3$].—As shown in Figure 2, slow rates of exchange were observed for

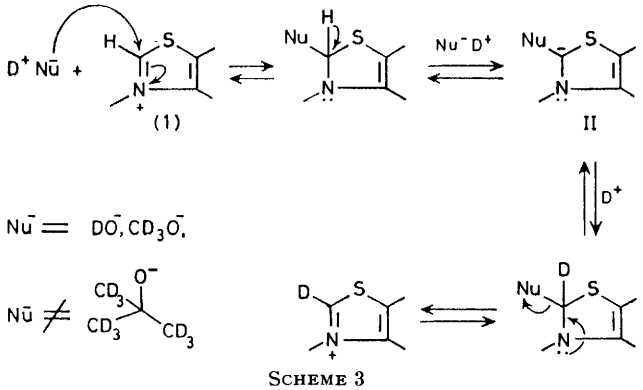
(1), (3), and (4). In the case of (2), no H–D exchange could be detected even after 500 h. Of special interest is the fact that the rate of exchange of 2-H in (1) is approximately twice as rapid as in (3) or (4).

DISCUSSION

Two important features may be noted by comparison of the rates of exchange of (1)—(4) with the employed nucleophiles. First, the rates of exchange for small nucleophiles KOD–DOD or $KOCD_3$–$DOCD_3$ are much faster compared with that for the sterically hindered nucleophile $KOC(CD_3)_3$–$DOC(CD_3)_3$. Secondly, whereas the small nucleophiles catalyse the exchange reaction equally well with all substrates, the hindered nucleophile (a) results in no detectable exchange in the case of (2), and (b) the rate of exchange of (1) is approximately twice that of (3) or (4) (Figure 2).

An explanation of the results is not easily realized on the basis of the currently accepted mechanism [5] for the H–D exchange reaction of thiazolium salts (Scheme 2). If the exchange reactions were operative through direct proton abstraction, measurable exchange should have been observed in the cases of all catalysts utilized in this study. The question of steric hindrance of $KOC(CD_3)_3$–$DOC(CD_3)_3$, so far as direct proton abstraction is concerned, fails to justify the lack of measurable exchange in the case of (2). In fact, using $KOC(CD_3)_3$–$DOC(CD_3)_3$ as catalyst, Cram [22] has reported H–D exchange in dimethyl sulphoxide on protons sterically more hindered, and of much higher pK_a values than the 2-H of (2). Although a planar molecule, (2) did not undergo any detectable exchange even after 500 h.

In view of the aforementioned ambiguities another rationale may be considered which involves nucleophilic attack of the base on the 2-position of the thiazolium ring (Scheme 3). Although not isolable, the formation of the proposed tetrahedral addition intermediate enjoys strong experimental support.[8,9,16,17] The sp^3 carbon formed is attached to three electronegative atoms

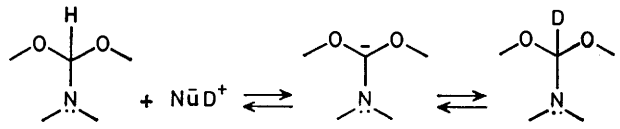


SCHEME 3

and may easily lose its proton with the subsequent formation of carbanion (II) (Scheme 3).

An analogous system is that of *NN*-dialkylformamide acetals. When measured in deuteriated protic solvents, these compounds exchange their formyl proton within a few minutes [23] (Scheme 4).

The question of steric hindrance of the employed nucleophiles becomes of paramount importance if the formation of a tetrahedral addition intermediate is a prerequisite of the exchange reaction. Clearly, ready formation of this species would be expected with the small nucleophiles (KOD–DOD or $KOCD_3$–$DOCD_3$). This in turn may explain the rapid exchange observed in the cases of these nucleophiles. On the other hand, the steric hindrance of $KOC(CD_3)_3$–$DOC(CD_3)_3$ is a



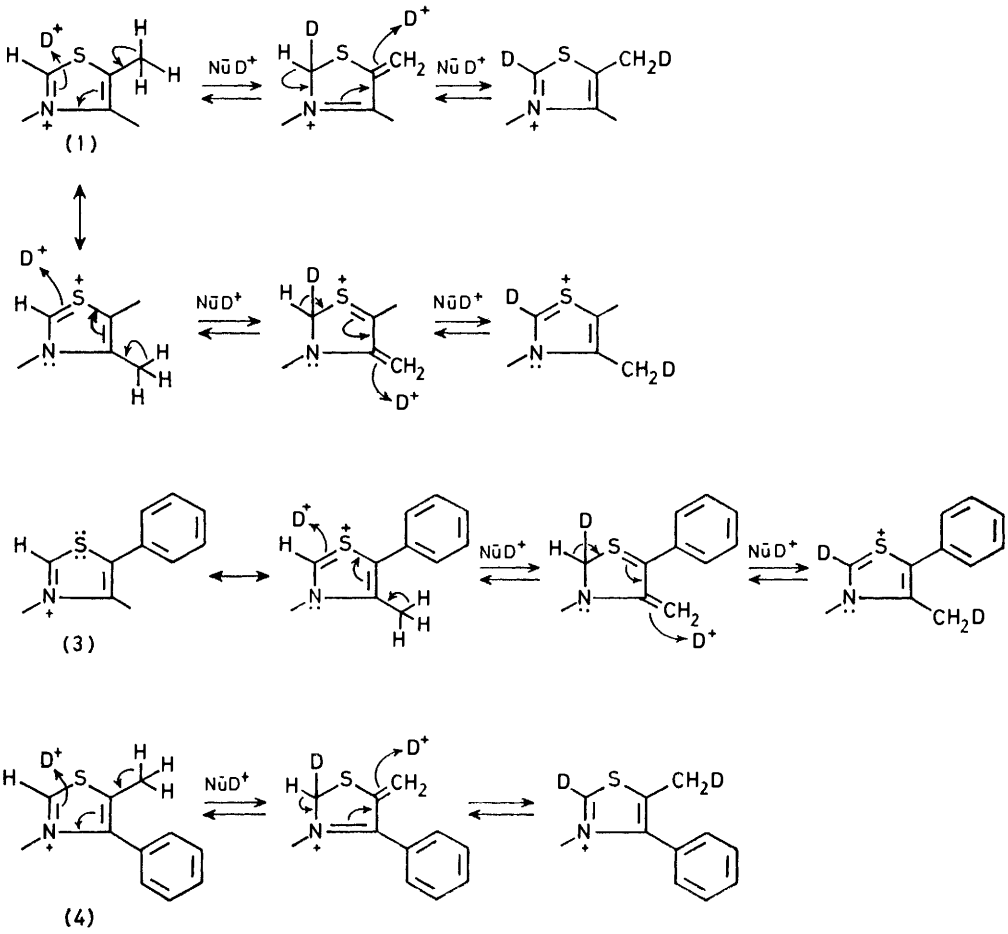
SCHEME 4

formidable obstacle to the formation of the tetrahedral intermediate. This argument is in fact in accord with our experimental results which show slow rates of disappearance of 2-H in the cases of (1), (3), and (4) with the hindered nucleophile.

Considering the impediments to the formation of the tetrahedral addition intermediate with $KOC(CD_3)_3$–$DOC(CD_3)_3$, a rationale may be forwarded that explains not only the lack of exchange in the case of (2), but also the fact that the rate of exchange of (1) is twice that of (3) or (4). An explanation of the differences in the rates of exchange of the substrates employed with the hindered nucleophile may be realized by considering proton abstraction from the 4- and/or 5-methyl groups (Scheme 5).

The resonance structures of the thiazolium ring provide the possibility that both the 4- and 5-methyl groups undergo proton abstraction, as depicted in Scheme 5. The number of such vulnerable methyl groups in (1) is twice that of (3) or (4), and accordingly the rate of exchange of 2-H is twice as rapid. On the other hand, with phenyl groups at the 4- and 5-positions, (2) is incapable of undergoing H–D exchange in the manner of (1), (3), or (4). This hypothesis requires that a direct correlation between the rates of disappearance of 2-H and the 4- and/or 5-methyl group should exist in the cases of (1), (3), and (4). Although a decrease in the intensity of absorption of these methyl groups is observable as a function of time, due to the inherent experimental difficulties, direct and accurate measurement of their rates of exchange is not possible (see Results section).

Finally, the *N*-methyl group, at least in theory, could provide vulnerable protons for H–D exchange. Earlier studies have shown, however, that these protons, even when assisted by the stabilizing effect of an adjacent pyrimidine ring (*i.e.* thiamin), do not readily undergo H–D exchange.[24] Furthermore, if such H–D exchange were operative, it would have been concomitant with H–D exchange of 2-H *via* simple tautomerism of the



SCHEME 5

developed negative charge on the *N*-methyl group. No H–D exchange of 2-H, however, could be detected in (2). It is possible that much stronger anions than potassium t-butoxide are required for abstraction of these protons.[25]

In conclusion, it should be stated that central to the understanding of the mechanism of H–D exchange in thiazolium salts is the question of formation of a tetrahedral addition intermediate at the 2-position. In this and a previous communication [21] we have presented experimental evidence for the validity of this proposal. To complement our studies of H–D exchange of thiazolium salts, we have recently examined its related heteroaromatic systems, the oxazolium and imidazolium salts. Our preliminary experimental investigations indicate that these heteroaromatic systems also undergo H–D exchange at the 2-position *via* the intermediacy of a tetrahedral addition species. A detailed report on H–D exchange of oxazolium and imidazolium salts will be provided.

EXPERIMENTAL

M.p.s were determined on an Electrothermal m.p. apparatus and are uncorrected. ^{1}H N.m.r. spectra were recorded on a Varian FT80 spectrometer in [$^2H_6$]Me_2SO with Me_4Si as internal reference. I.r. spectra were taken on a Perkin-Elmer 267 spectrophotometer and u.v. spectra were obtained in ethanol solution on a Varian Cary 14 spectrophotometer. T.l.c. was performed on silica gel (Macerey-Nagel Co.; Plygram Sil G/uv 254). All n.m.r. solvents used were Aldrich Gold Label and were dried as described.

3,4,5-Trimethylthiazolium Iodide (1).—The procedure reported by Schwarts [26] for synthesis of thiazoles was employed with slight modifications. To a 50 ml two-neck round-bottom flask, equipped with a reflux condenser, an addition funnel, and a calcium chloride drying tube, were added dry benzene (7.4 ml), phosphorus pentasulphide (7.45 g, 33 mmol), and formamide (8.56 g, 0.19 mol). The flask was then immersed in an oil-bath at 90° with stirring. A solution of 3-bromobutanone (32.6 g, 0.215 mol) in dry benzene (30 ml) was added dropwise during 1 h. After the addition of a few ml of the halogenated ketone, the flask was removed from the oil-bath and the reaction allowed to proceed for 48 h. The mixture was then transferred to a separatory funnel and water (50 ml) was added. The aqueous layer was recovered and its pH adjusted to 10 by 5N-sodium hydroxide. Extraction with ether (5 × 50 ml), followed by work-up gave a brown oil which was distilled (144—147°) to afford 4,5-dimethylthiazole (9.3 g, 41%). To the thiazole (1.0 g, 9.0 mmol) was added butanone (15 ml) and methyl iodide (2.76 ml, 5 mol. equiv.) The mixture was refluxed overnight and light yellow crystals precipitated

on cooling. The crude product was crystallized five times from chloroform–acetone and the crystals (1.71 g, 73%) were dried (P_2O_5); R_F (acetic acid–water, 80 : 20) 0.25, (acetonitrile–water, 70 : 30) 0.24, m.p. 228—230°, δ ([$^2H_6$]Me_2SO) 9.98 (1 H, s), 4.11 (3 H, s), 2.51 (3 H, s), and 2.43 (3 H, s), $\nu_{max.}$ (Nujol) 2 945, 1 610, and 1 395 cm^{-1}, $\lambda_{max.}$ (95% EtOH) 273 nm (ε 455).

3-*Methyl*-4,5-*diphenylthiazolium Iodide* (2).—α-Chlorobenzyl phenyl ketone was prepared by exchanging the hydroxy-group of benzoin with chlorine, using thionyl chloride. The procedure employed for the synthesis of (1) was utilized with phosphorus pentasulphide (2.0 g, 9 mmol), formamide (2.28 g, 50 mmol), α-chlorobenzyl phenyl ketone (11.83 g, 57 mmol), and dry benzene (30 ml). The reaction was allowed to reflux for four days. Substituting dichloromethane for ether, the previously described work-up procedure was carried out. The crude 4,5-diphenylthiazole was then applied to a silica gel column (Merck Kieselgel 60) and eluted with benzene (300 ml), followed by 90 : 10, 80 : 20, 70 : 30, 50 : 50, and 25 : 75 benzene–chloroform (each 100 ml), and finally chloroform (100 ml). The fractions affording a single spot on t.l.c. in ether (R_F 0.63) were combined (3.2 g, 23%). *N*-Methylation of 4,5-diphenylthiazole (1.0 g, 4.2 mmol), followed by crystallization afforded (2) (1.1 g, 69%), R_F (acetic acid–water, 80 : 20) 0.51, (acetonitrile–water, 70 : 30) 0.59, m.p. 191—193°, δ ([$^2H_6$]Me_2SO) 10.41 (1 H, s), 7.47 (10 H, m), and 3.95 (3 H, s), $\nu_{max.}$ (Nujol) 2 950, 1 515, and 1 170 cm^{-1}, $\lambda_{max.}$ (95% EtOH) 280 nm (ε 6 997).

3,5-*Dimethyl*-4-*phenylthiazolium Iodide* (3).—The procedure described for the synthesis of (1) was employed using phosphorus pentasulphide (4.0 g, 18 mmol), formamide (4.5 g, 0.1 mol), 2-bromo-1-phenylpropan-1-one (21.0 g, 0.1 mol), and dry benzene (4 ml). Distillation of the product (87—91° at 1 mmHg) afforded 4-phenyl-5-methylthiazole (7.5 g, 43%). *N*-Methylation of the product (1.75 g, 10 mmol), followed by crystallization, gave (3) (2.5 g, 79%), R_F (acetic acid–water, 80 : 20) 0.44, (acetonitrile–water, 70 : 30) 0.34, m.p. 204—207°, δ ([$^2H_6$]Me_2SO) 10.17 (1 H, s), 7.62 (5 H, s), 3.91 (3 H, s), and 2.39 (3 H, s), $\nu_{max.}$ (Nujol) 2 917, 1 427, and 1 370 cm^{-1}; $\lambda_{max.}$ (95% EtOH) 290 nm (ε 2 577).

3,4-*Dimethyl*-5-*phenylthiazolium Iodide* (4).—Using the procedure for synthesis of (1) with phosphorus pentasulphide (1.61 g, 7 mmol), formamide, (1.85 g, 40 mmol), 1-bromo-1-phenylpropan-2-one (8.6 g, 40 mmol), and dry benzene (5 ml), a brown oil was obtained which upon distillation (143—147° at 10 mmHg) afforded 4-methyl-5-phenylthiazole (3.2 g, 45%). *N*-Methylation of product (1.75 g, 10 mmol), followed by crystallization yielded (4) (2.6 g, 82%), R_F (acetic acid–water, 80 : 20) 0.44 (acetonitrile–water, 70 : 30) 0.34, m.p. 189—191°, δ ([$^2H_6$]Me_2SO) 10.23 (1 H s,), 7.6 (5 H, s), 4.21 (3 H, s), and 2.54 (3 H, s), $\nu_{max.}$ (Nujol) 2 920, 1 460, and 1 375 cm^{-1}, $\lambda_{max.}$ (95% EtOH) 285 nm (ε 6 503).

Preparation of Nucleophiles.—Aldrich Gold Label D_2O, $DOCD_3$, and $DOC(CD_3)_3$ were used. The alcohols were dried by the procedure of Cram.[22] In all cases a 0.016 molar solution of the base was prepared by weighing freshly cut potassium (6.3 mg) transferring the metal to a 10-ml volumetric flask which contained a few ml of the appropriate deuterioalcohol. The metal was allowed to dissolve and the solution was made up to 10 ml. All transfers and solvent additions were carried out in a dry box u nder nitrogen.

Preparation of N.M.R. Samples.—Triplicate samples of each thiazolium salt were prepared by weighing the compound (0.1 mmol) in predried n.m.r. tubes, followed by the addition of dry [22] [$^2H_6$]Me_2SO (0.4 ml). At this point, solution (0.1 ml) of base [KOD–DOD, $KOCD_3$–$DOCD_3$, or $KOC(CD_3)_3$–$DOC(CD_3)_3$] was added to each sample tube. Utmost care was exercized to prevent water absorption from atmosphere.

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