Tetrahedron. Vol. 26, pp. 685 to 692. Pergamon Press 1970. Printed in Great Britain

AN ADDITION–ELIMINATION MECHANISM FOR C–H/C–D EXCHANGE IN THIAZOLE

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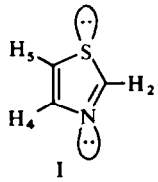
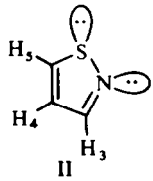
(*Received in USA* 8 *August* 1969; *Received in the UK for publication* 8 *October* 1969)

Abstract—From a study of the pH-exchange rate profile and other data, it is shown that two mechanisms are important in the substitution of deuterium for hydrogen at C_2 in thiazole in deuterio-hydroxylic solvents. These pathways are a simple base-induced proton abstraction which is important at high pH and a process involving an equilibrium protonation on nitrogen followed by a rate determining C—H ionization which is the primary exchange route at intermediate pH. It is suggested that the latter scheme has much greater generality and may even be involved in the biological activity of certain heterocyclic drugs.

SOME years ago we showed, by measuring rates of deuterium incorporation, that thiazole (I) is readily ionized by deuteroxide in D_2O or alkoxide in ROD.[1,2] De-



I



II

protonation at C_2 and C_5 in I occurs at about the same rate and proton abstraction at C_5 in isothiazole (II) is slightly faster; the other hydrogens in both compounds (H_4 in I, H_3 and H_4 in II) do not exchange even under much more drastic conditions. These observations have since been used to demonstrate the stabilization value of overlap of the forming anion with an unfilled d orbital on adjacent sulfur[2] and to suggest that a significant factor in determining the ease of any C—H ionization process is the change in total vicinal sp^2 electron pair repulsions in going from a parent heterocycle to the derived carbanion.[3] Similar C—H/C—D exchange studies on other heteroaromatic substrates have been used to evaluate the importance of inductive and coulombic effects in determining the rate of proton loss.[1–6]

Staab *et al.*[7] have reported a number of apparently similar exchange experiments (Table 1) including the replacement of H_2 in thiazole by deuterium in MeOD solution.

In view of our own experiments the results of Staab seemed to us quite extraordinary

* Abstracted in part from the Ph.D. Thesis of J. M. Landesberg, Harvard University, Oct. 1964.

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TABLE 1. RATES OF H/D EXCHANGE[a]

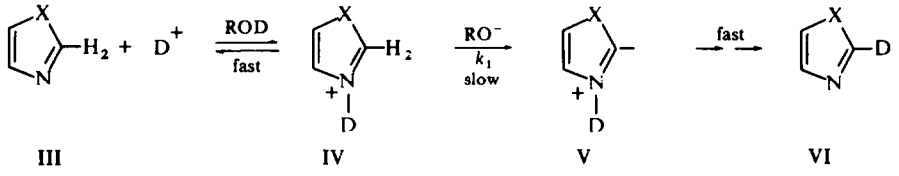
	Substrate	T(°C)	$t_{\frac{1}{2}}$ (min)
A	Oxazole	~60	600
B	4,5-Di-n-propyloxazole	60	600
C	4,5-Diphenyloxazole	69	1100
D	Benzoxazole	~60	7000
E	1-Benzylimidazole	60	110
F	Thiazole	60	800
G	Benzthiazole	60	2500

[a] Ref. 7. The numerical values reported have no quantitative significance and the relative exchange rates may not be meaningful. Staab did not report the substrate concentration used or even whether it was constant throughout the series of compounds studied. The rates do depend on substrate concentration, *vide infra*.

and even in direct contradiction with our predictions in at least four general areas. *First*, the rates in Table 1 are orders of magnitude faster than would be extrapolated from our second order rate constants [rate = k(substrate)($^-$OMe)] for the simple base induced ionization of these compounds.[2,3] *Second*, thiazole exchanged only the proton at C_2, whereas we discovered that the protons at C_2 and C_5 reacted at similar rates.[2] *Third*, we found that electron withdrawing substituents increase the exchange rate by stabilizing the forming anion.[2-6] Staab reports the opposite (A ~ B > C > D). *Fourth*, Staab showed that D and G underwent exchange very much more slowly than E while we found that N-alkylimidazoles would deprotonate much more slowly than oxazoles or thiazoles.[2-3]

Since Staab's data also could not be explained by the usual addition–elimination electrophilic substitution pathway (this would lead to deuterium exchange at C_4 or C_5 of thiazole rather than at C_2[8]) we postulated the protonation–deprotonation process outlined in Scheme I as a plausible rationalization for these results.

SCHEME 1



In accord with this hypothesis are the following arguments: (1) The protonated bases (IV) would be expected to undergo rapid deprotonation at C_2 under the reaction conditions. When X is sulfur and the D in IV is replaced by ethyl, $t_{\frac{1}{2}}$ for exchange at C_2 is ca. 7 seconds (extrap) at pD 7 and 31°.[5] (2) N-D-Thiazolium[2] cation (IV, X = S) should exchange H_2 several powers of ten more rapidly than H_5 in analogy with the N-alkylthiazolium cations.[5] (3) Electron withdrawing substituents, by reducing the base strength of the substrate would drive the initial equilibrium (III ⇌ IV) to the left and, by diminishing the concentration of IV, reduce the rate.

(4) A similar argument (electronegativities: O > N > S) together with the d-σ overlap effect responsible for the special rate enhancement in the sulfur systems,[2, 3, 5] would serve to rationalize the observed order: E ≫ D ~ G.

For Scheme I (with X = sulfur) the following rate expression holds:

$$\text{Exchange rate} = k_1[^-\text{OR}][\text{IV}]$$

Let K_a be the acid dissociation constant of protonated thiazole,

$$K_a = \frac{[\text{III}][\text{D}^+]}{[\text{IV}]}$$

and $[Th]$ be the total concentration of all thiazole species (a constant)

$$[Th] = [\text{III}] + [\text{IV}].$$

Then:
$$K_a = \frac{([Th] - [\text{IV}])[\text{D}^+]}{[\text{IV}]}$$

Rearranging:
$$[\text{IV}] = \frac{[Th][\text{D}^+]}{K_a + [\text{D}^+]}$$

Substituting for [IV] in the rate equation:

$$\text{Rate} = \frac{k_1[^-\text{OR}][Th][\text{D}^+]}{K_a + [\text{D}^+]}$$

But $[\text{D}^+][^-\text{OR}] = K_w$, the dissociation constant of the hydroxylic solvent. Therefore:

$$\text{Rate} = \frac{k_1 K_w[Th]}{K_a + [\text{D}^+]} \quad \text{or} \quad \frac{k_1 K_w([\text{III}] + [\text{IV}])}{K_a + [\text{D}^+]} \qquad \textit{Equation A}$$

Equation A predicts that the exchange rate should be constant at high basicity (when $K_a \gg [\text{D}^+]$), but should decrease in acid media as a function of the concentration of [III]. As a consequence of this analysis we began a study of the rate of exchange of thiazole as a function of the pH of the medium.

RESULTS AND DISCUSSION

The experimentally determined rates for the C—H → C—D exchange at C_2 of thiazole in deuteriomethanol and in heavy water solutions are presented in Tables 2 and 3 respectively. Since K_a for the thiazolium cation is known ($K_a = 3{\cdot}0 \times 10^{-3}$ at 20° in water[10]) the predicted rates in D_2O were compared with the observed values assuming the reaction follows Scheme I and Equation A. From Fig. 1 it is seen that between pD 0 and pD 11 the theoretical curve follows the experimental points (runs 19–33) with gratifying exactness. At higher base concentration the simple ionization mechanism reported earlier[2] (Scheme II) becomes predominant, the rate suddenly increases very rapidly and becomes first order in both thiazole and deuteroxide concentrations (Equation B).

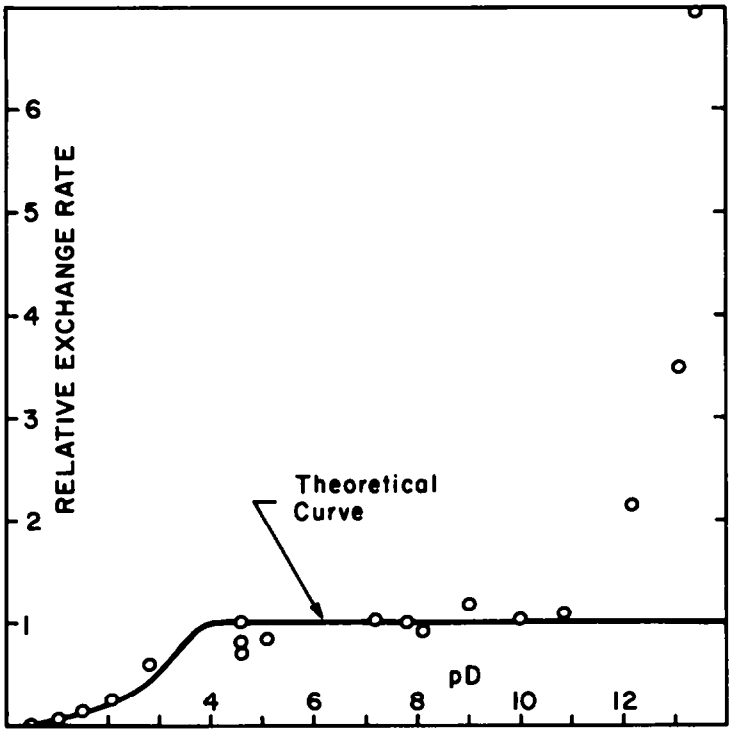


FIG. 1 Rate C—H_2 → C—D_2 exchange of thiazole vs. pD at 60·7°.

TABLE 2. EXCHANGE OF THIAZOLE AT C_2 IN MeOD AT 60·7°

Run No.	Thiazole Molarity	Addend	$t_{\frac{1}{2}}$ (min)
1	0·10	—	760
2	0·55	—	800
3	1·05	—	860
4	1·47	—	975
5	2·07	—	1020
6	2·50	—	1260
7	3·20	—	1350
8	1·01	piperidine (1·0M)	1140
9	1·05	piperidine (0·4M)	990
10	1·00	citric acid (0·2M)	930
11	1·00	DCl (2·1M)[a]	$>10^5$ [a]
12[b]	1·00	—	820[b]
13[c]	1·00	—	[c]

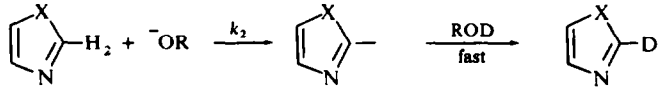
[a] Less than 2% exchange in 20 hr; could not use CF_3CO_2D solutions for intermediate acidity because of esterification problems. [b] Exchange of thiazole-2D in MeOH; $k_{H(MeOD)}/k_{D(MeOH)} \sim 1·0$. [c] Reaction in t-BuOD as solvent; no detectable exchange at 100° over a 36 hr period.

TABLE 3. EXCHANGE OF THIAZOLE AT C_2 IN D_2O AT 60·7°

Run No.	Thiazole molarity	pD[a]	Buffer	$t_{\frac{1}{2}}$ (min)	Rel. Rate
14	1·00	—	—	160	1·000
15	1·10	—	—	174	0·92
16	1·68	—	—	206	0·78
17	2·16	—	—	230	0·70
18	1·15	—	$NaClO_4$ (1M)	180	0·89
19	1·00	0·50	D_2SO_4	7920	0·020
20	1·06	1·00	D_2SO_4	2560	0·062
21	1·00	1·52	D_2SO_4	1260	0·127
22	1·00	2·06	D_2SO_4–Na_2SO_4	620	0·26
23	1·07	2·80	D_2SO_4–Na_2SO_4	275	0·58
24	1·00	4·6	DOAc–NaOAc (0·1M)	160	1·00
25	1·03	4·6	DOAc–NaOAc (0·3 M)	205	0·78
26	0·97	4·6	DOAc–NaOAc (1M)	225	0·71
27	1·18	5·1	DOAc–NaOAc (1M)	225	0·71
28	1·08	9·0	Na_2DPO_4 (0·25M)	135	1·19
29	1·01	10·0	$NaDCO_3$–Na_2CO_3 (0·25)	155	1·03
30	1·05	10·85	Na_2DPO_4–Na_3PO_4 (0·1M)	150	1·07
31	1·00	12·20	Na_2DPO_4–Na_3PO_4 (0·1M)	75 (930)[b]	2·14 (0·172)[b]
32	1·07	13·10	NaOD–$NaClO_4$ (1M)	46 (107)[b]	3·48 (1·50)[b]
33	1·05	13·40	NaOD–$NaClO_4$ (1M)	23 (42)[b]	7·0 (4·0)[b]
34[c]	1·00	—	—	660[c]	0·24
35[c]	1·00	—	—	25[c]	6·4
36[d]	1·00	—	—	430[d]	0·37[d]

[a] See experimental for discussion. [b] Second number is exchange of H_5; k_{H_2}/k_{H_5} is 12·4 at pD 12·2; 2·3 at pD 13·1; 1·8 at pD 13·4. [c] Run 34 at 46·0°; run 35 at 82·0°, $E_a = -20·7$ kcal/mole. [d] Exchange of thiazole-2D in H_2O; $k_{H(D_2O)}/k_{D(H_2O)} = 2·7$.

SCHEME II



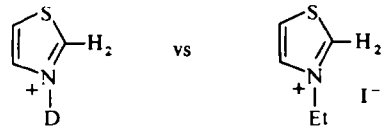
III VI

$$\text{Exchange rate} = k_2[^-OR][III] \qquad \textit{Equation B}$$

Also at high basicity the proton at C_5 begins to exchange (runs 31–33) and the ratio k_{H_2}/k_{H_5} decreases from 12·4 at pD 12·2 to 1·8 at pD 13·4 as anticipated.[2]

Some additional correlations are available from Tables 2 and 3: (A) rate in D_2O (run 14) > rate in MeOD (run 3) ≫ rate in t-BuOD (run 13); (B) $E_a = -20·7$ kcal/mole in D_2O (runs 14, 34, 35); (C) $k_{H(MeOD)}/k_{D(MeOH)}$ 1·0 (run 12); $k_{H(D_2O)}/k_{D(H_2O)} = 2·7$ (runs 14, 36); (D) there is little salt effect (note especially run 15 *vs* 18 and 24–26); (E) the rate decreases as the thiazole concentration increases (runs 1–7 and 14–17).

If the mechanism postulated in Scheme I for the exchange of thiazole is correct it should be possible to correlate these new values with the known exchange rate for 3-ethylthiazolium iodide (VII): $k_2 = 9·8 \times 10^5$ l/mole sec at 31° in D_2O. From



IV VII

the ΔH plot, *vide supra*, we estimate the rate of exchange of thiazole in D_2O at 31° to be $4{\cdot}3 \times 10^{-6}$ sec^{-1}. Since for pD's > 4:

$$k_{obs}[\text{III}] = k_1 \frac{K_w}{K_a}[\text{III}] \quad \text{or} \quad k_1 = k_{obs}\frac{K_a}{K_w} \qquad \textit{Equation C}$$

$$K_{w(D_2O)} = \frac{2{\cdot}4 \times 10^{-14}}{6{\cdot}5} \quad \text{and} \quad K_a = \frac{3{\cdot}0 \times 10^{-3}\,\dagger}{3}$$

Therefore: $$k_1 = 4{\cdot}3 \times 10^{-6}\frac{(1{\cdot}0 \times 10^{-3})}{(3{\cdot}7 \times 10^{-15})} = 1 \times 10^6 \text{ l/mole sec}$$

in excellent though somewhat fortuitously close agreement with k_2 for VII.* Though Scheme I would also be valid if protonation occurred on sulfur, the above comparison indicates that IV is indeed the active intermediate in this addition–elimination mechanism for thiazole exchange.

Finally, we suggest that the rate decrease with increasing substrate concentration (runs 1–7, 14–17) is caused by a medium effect due to decreasing dielectric constant of the solvent with added heterocycle. Consider the consequence of this effect using Equation C; K_a should not change appreciably since it involves ions on both sides of the equilibrium, k_1 should undergo a small increase and K_w a large decrease; the overall effect would be the observed moderate rate decrease. In accord with this analysis is the large change in K_w as dioxane is added to water; there is a linear correlation of ΔpK_w with mole fraction dioxane with a slope of 12.[12] If a similar correlation holds with added thiazole, for two molar thiazole (mole fraction 0·04) the effect on pK_w would be 0·5, which translates into a rate decrease of three fold. The strongest argument that we are observing a medium effect is found in the MeOD rates. The rate decrease is proportional to the molar concentration of added species, regardless of its nature: 2M thiazole (run 5) gives the same rate as 1M thiazole plus 1M piperidine (run 8), 1·5M thiazole (run 4) gives approximately the same rate as 1M thiazole plus 0·4M piperidine (run 9). Note that the absence of a large salt effect in water does not exclude this explanation. Although K_w increases with added salt at low salt concentrations, at high salt concentrations (ca. 1M) it returns nearly to the value observed at zero ionic strength.[13]

* This numerical agreement together with the reverse substitution positional preference referred to earlier is considered definitive evidence against an unusual though kinetically indistinguishable (with the present substrate) protonation on carbon followed by elimination electrophilic substitution mechanism in which H^+ or ROH_2^+ acts as the proton source while ^-OR functions as the hydrogen abstracting agent. Identification of this latter mechanism will be considered in greater detail in a future paper in this series.

† Corrections in K_w and K_a for shift to D_2O (correction for K_a should be about half as large as that for K_w).[11]

The addition–elimination pathway diagrammed in Scheme I constitutes a new and alternative mechanism for accomplishing what is formally an electrophilic substitution reaction. Since we presented our initial results in this area,[14] others have postulated similar processes in diverse systems. For example, Harris and Randall[15] have used this pathway in sorting out the conflicting data in the literature on imidazole exchanges; others have recently postulated analogous ylidic intermediates to account for the ready C—H exchange of N,N-dimethylformamide acetals,[16] pyridines,[17] 4-aminopyridines,[18] and pyrazoles,[19] and even the exchange of 4-pyrimidones[20] has been formulated in terms of an initial protonation followed by nuclear deprotonation.[21] In addition to the Staab exchanges described above, we suspect other known reactions are best interpreted as examples of Scheme I. Among these are the ready exchange at C_8 in purines (complete exchange in 10–20 min at 90–100° in D_2O[22]), and of the ring proton in nitronyl nitroxides (pH independent $k = 3{\cdot}3 \times 10^{-3}$ sec^{-1} at 23° in D_2O;[23] in this system protonation should take place at the exocyclic oxygen) and possibly even some of the electrophilic substitution reactions in mesoionic systems. In conclusion it might be noted that several heterocyclic drugs may undergo ring deprotonation by this mechanism under physiological conditions, and that the result of this process is the liberation of a nucleophilic species which might react irreversibly with a specific electrophilic site in the body and thus be responsible for the pharmacological activity of the drug. In future papers we shall examine this hyposthesis further and also present still another mechanism for electrophilic substitution in heterocycles.[24]

EXPERIMENTAL

Materials. Thiazole was prepared by the method of McLean[9] from 2-aminothiazole (Aldrich) and purified by distillation on a spinning-band column, b.p.$_{760\,mm}$ 117–118° (lit.[9] 117°). Thiazole-2D (>98% D by NMR) was obtained by exchange of thiazole in D_2O and isolated by extraction and distillation. The heavy water had an isotopic purity >99·5% D, the MeOD > 99% D, and the D_2SO_4 > 98% D. The NaOD and NaOMe solutions were prepared by reacting sodium metal with D_2O and MeOD respectively and standardizing the solutions with 0·100N HCl. Any proton bearing inorganic salt used in the buffers was first exchanged with deuterium by dissolving the salt in D_2O and then evaporating to dryness.

Kinetics. At high thiazole concentrations the kinetics were monitored by NMR on a Varian A-60 spectrometer. Aliquots were taken at appropriate intervals from the reaction soln which was kept in a constant temp bath (±0·1°). The exchange was quenched by cooling, and the amount of substitution determined by comparing the ratio of H areas at the reacting positions with the area for the non-exchanging H_4. At low thiazole concentrations (0·1–0·6M) the kinetics were followed by determining the isotope ratio for each point (from aliquots after quenching and isolation of the partially exchanged thiazole by *in vacuo* evaporation of the solvent) on a Consolidated Engineering Corp. Type 21-103C mass spectrometer. The reactions were all nicely first order in thiazole concentration over at least two half lives; the reproducibility was about 10%. The pD was measured on a pH scale at 25° using a Radiometer pH meter 4 and is not corrected to give the true pD. Pure D_2O gave an observed pD of 6·9 while 1 to 2M thiazole solutions gave values ranging from 7·5–8·1. The measured pD always varied by less than 0·08 units from the beginning to the end of a run; the final pD was used in the calculations.

Acknowledgement—We wish to thank the U.S. Public Health Service for a grant (GM-13980) to support this research.

REFERENCES

[1] R. A. Olofson, J. M. Landesberg, and R. O. Berry, Abs. of the 144*th Meeting of the ACS* p. 45M. Los Angeles, Apr. (1963).

[2] R. A. Olofson, J. M. Landesberg and K. N. Houk, *J. Am. Chem. Soc.* **88**, 4265 (1966).

[3] R. A. Olofson, R. V. Kendall, A. C. Rochat, J. M. Landesberg, W. R. Thompson and J. S. Michelman, *Symposium on the Properties of Anions, Abs. of the 153rd Meeting of the ACS* p. Q34. Miami, Apr. (1967).
[4] R. A. Olofson, W. R. Thompson and J. S. Michelman, *J. Am. Chem. Soc.* **86**, 1865 (1964).
[5] R. A. Olofson and J. M. Landesberg, *Ibid.* **88**, 4263 (1966).
[6] A. C. Rochat and R. A. Olofson, *Tetrahedron Letters* 3377 (1969).
[7] H. A. Staab, M.-Th. Wu, A. Mannschreck and G. Schwalbach, *Ibid.* 845 (1964).
[8] J. M. Sprague and A. H. Land, *Heterocyclic Compounds* (Edited by R. C. Elderfield), Vol. 5, p. 484. Wiley N.Y. (1957).
[9] J. McLean and G. D. Muir, *J. Chem. Soc.* 383 (1942).
[10] A. Albert, R. Goldacre and J. Phillips, *Ibid.* 2240 (1948).
[11] R. P. Bell, *The Proton in Chemistry, Cornell University Press* p. 188. Ithaca, N.Y. (1959).
[12] H. S. Harned and B. B. Owen, *The Physical Chemistry of Electrolytic Solutions* (3rd edition) p. 662. Reinhold, N.Y. (1958).
[13] See graph, Ref. 12, p. 640.
[14] R. A. Olofson, *Lecture.* Gordon Research Conference in Heterocyclic Chemistry, August (1964).
[15] T. M. Harris and J. C. Randall, *Chem. & Ind.* 1728 (1965).
[16] G. Simchen, S. Rebsdat and W. Kantlehner, *Angew. Chem.* Internat. Edit. **6**, 875 (1967).
[17] J. A. Zoltewicz and C. L. Smith, *J. Am. Chem. Soc.* **89**, 3358 (1957).
[18] J. A. Zoltewicz and J. D. Meyer, *Tetrahedron Letters* 421 (1968).
[19] E. Chung Wu and J. D. Vaughan, *J. Org. Chem.* in press.
[20] G. E. Wright, L. Bauer and C. L. Bell, *J. Heterocyclic Chem.* **3**, 440 (1966).
[21] P. Beak and E. McL. Moore, *J. Org. Chem.* **34**, 589 (1969).
[22] F. J. Bullock and O. Jardetzky, *Ibid.*, **29**, 1988 (1964); M. P. Schweizer, S. I. Chan, G. K. Helmkamp and P. O. P. Ts'o, *J. Am. Chem. Soc.* **86**, 696 (1964).
[23] D. G. Boocock, R. Darcy and E. F. Ullman, *Ibid.* **90**, 5945 (1968).
[24] H. L. Kohn, S. J. Benkovic and R. A. Olofson, unpublished results.