Tetrahedron Letters Vol. 22, pp 581 - 582 0040-4039/81/0201-0581$02.00/0

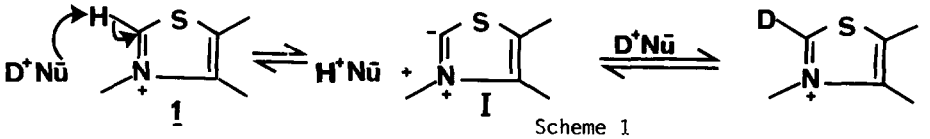
EVIDENCE FOR THE INVOLVEMENT OF A TETRAHEDRAL INTERMEDIATE IN H-D EXCHANGE OF C-2 PROTON IN THIAZOLIUM ION

K. Karimian*, I. Ganjian, and M. Askari
Institute of Biochemistry and Biophysics, University of Tehran, P.O. Box 314-1700, Tehran, Iran.

Summary: Mechanism of H-D exchange of C-2 proton of thiazolium ion has been examined by PMR spectroscopy. Involvement of a tetrahedral intermediate, prerequisite to the exchage reaction, is proposed.

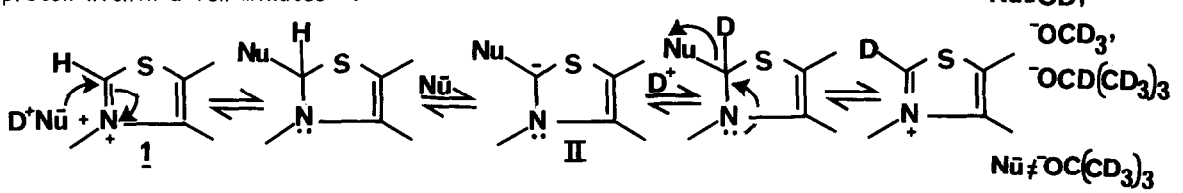
The biochemical functions of thiamin (Vitamin B_1) have been attributed to the acidity of C-2 proton in its thiazolium moiety. Since Breslow's proposal for the lability fo C-2 proton, numerous diverse speculations have been put forward for the explanation of this phenomenon[1-10].Nevertheless, the basic structural reasons leading to the unique acidity of C-2 proton in thiazolium ion still remain vague.

The currently accepted mechanism[1] for the exchange involves direct abstraction of C-2 proton by a weak protic base (Scheme 1). This leads to the formation of a ylid (I) in the transition state in which the C-2 carbon of the thiazolium ring remains an sp^2 carbon. Whether the d-orbitals of the adjacent sulfur atom contribute to the stability of the developed negative charge on C-2 carbon has been questioned[7,8]. In fact, CNDO/2 and HT (Hückel Theory) calculations regarding charge density on C-2 carbon have not reached uniform results[9].



Scheme 1

In view of these ambiguities, another rational may be considered in which the weak protic base acts as a nucleophile. Clearly, such a nucleophile can attack the C-2 position of the thiazolium ring, leading to the formation of a tetrahedral intermediate (Scheme 2). Although not isolable, the formation of the proposed intermediate enjoys strong experimental support[4,5,11,12]. The sp^3 carbon formed is now attached to three electronegative atoms and may easily lose its proton with subsequent formation of carbanion II. An analogous system is that of N,N-dialkylformamide acetals. When measured in deuterated protic solvents, these compounds exchange their formyl proton within a few minutes[13].



Scheme 2

To establish the proferred route of exchange a model thiazolium ion (1) and deuteroalcohols of increasing order of size were employed. The exchange reactions were followed by PMR spectroscopy, utilizing the decreasing CH-proton signal and increasing intensity of OH-proton signal of the alcohol formed in each experiment. Our PMR studies, summarized in Table 1, indicate that the exchange reaction does in fact involve the formation of a tetrahedral intermediat (Scheme 2). If the exchange reaction were operative through proton abstraction (Scheme 1), measurable exchange

should have been observed in the case of all deuteroalcohols examined. This is based on the fact that at low concentrations the apparent acidity of alcohols in DMSO is comparable[14,15]. Furthermore, the steric hindrance of the alcohols employed, so far as direct proton abstraction is concerned, fails to justify the lack of exchange in the case of $(CD_3)_3COD$. In fact, using $(CD_3)_3COD$, Cram[16] has reported proton abstraction in DMSO on substrates sterically more hindered than 1. Although a planar molecule, 1 did not undergo any detectable exchange with $(CD_3)_3COD$ even after 30 days.

Table 1. Nucleophile size dependent H-D exchange of C-2 proton in 1.

Catalyst	Solvent	Time	% Exchange
D_2O	DMSO-d_6*	14 Min.	100
	$CDCl_3$**	14 Min.	100
CD_3OD	DMSO-d_6	2 Days	66
	$CDCl_3$	6 Days	75
$(CD_3)_2CDOD$	DMSO-d_6	2 Days	39
	$CDCl_3$	6 Days	25
$(CD_3)_3COD$	DMSO-d_6	30 Days	Not observed
	$CDCl_3$	30 Days	Not observed

PMRS were recorded on a Varian FT-80 NMR Spectrometer. All experiments were carried out at 25°C.
* 10 mg substrate in 0.4 ml DMSO-$_{d6}$ and four equivalent moles of D_2O or deuteroalcohol.
** 4 mg substrate in 0.4 ml $CDCl_3$ and ten equivalent moles of D_2O or deuteroalcohol.

On the other hand, the question of steric hindrance of the employed deuteroalcohols becomes of paramount importance if the formation of a tetrahedral intermediate is a prerequisite to the exchange reaction. Clearly , the formation of such an intermediate becomes increasingly more difficult as the nucleophile employed becomes progressively more hindered. This rationale is in fact in accord with our experimental results. Furthermore, our initial CNDO calculations[17] indicate that the proposed carbanion (II) has a lower energy (>5 K Cal mole^{-1}) than the previously proposed ylid (I).

A detailed report on the H-D exchange of thiazolium ion and some related heteroaromatic systems (oxazolium and imidazolium ions) will be provided in a full paper.

This research was supported by Grant No. 36-426 form the University of Tehran.

References

1. R. Breslow, and E. McNelis, J. Am. Chem. Soc., 81, 3080, (1959).
2. H.W. Wanzlick, Angew. Chem. Int. Ed. Eng., 1, 75, (1962).
3. H. Balli, ibid, 3, 809, (1964).
4. G.E. Risinger, E.J. Breaux, and H.H. Hsieh, J. Chem. Soc. Chem. Comm., 841, (1968).
5. P. Haake, and J.M. Duclos, Tetrahedron Lett, 461, (1970).
6. R.A. Olofson, W.R. Thompson, and J.S. Michelson, J. Am. Chem. Soc., 86, 1865, (1964).
7. Bernardi, I.G. Csizmadia, A. Mongini, H.B. Schlegel, M.H. Wangbo, and S. Wolf, ibid, 97, 2209, (1975).
8. P. Haake, W.B. Miller, and L.P. Bausher, ibid, 91, 1113, (1969).
9. F. Jordan, ibid, 96, 3625, (1974).
10. P. Haake, and C.P. Bausher, J. Phy. Chem., 72, 2213, (1968).
11. A.O. Irvespa, Helv. Chem. Acta, 51, 1723, (1965).
12. A. McKillop, T.S.B. Sayer, and G.C. Bellinger, J. Org. Chem. 41, 1328, (1976).
13. G. Simchen, S. Rebsdat, and W. Kantlehner, Angew. Chem. Int. Ed. Eng., 6, 875, (1967).
14. R.G. Pearson, and R.L. Dillon, J. Am. Chem. Soc., 75, 2439, (1953).
15. E.C. Steiner, and J.M. Gilbert, ibid, 87, 382, (1965).
16. D.J. Cram, B. Rickborn, C.A. Kingsburg, and P. Haberfield, ibid, 83, 3678, (1961).
17. Theoretical results will be included in a forthcoming full report.

(Received in UK 19 November 1980)