BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 1246—1247(1972)

Hydrogen-Deuterium Exchange in 1,4,5- and 1,3,5-Trimethyltetrazolium Iodides

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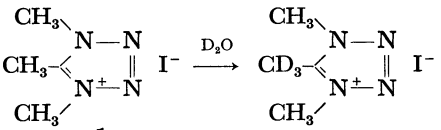
(Received August 25, 1971)

Considerable attentions are directed to the C–H/C–D exchange reaction of ring protons in azoles such as thiazoles,[1] thiazolium salt,[2] pyrazolium, and imidazolium salts,[3] 1,4-,[3–5] 1,3-,[6] and 2,3-disubstituted tetrazolium salts.[3] These investigations were focused on C–H bond which is sp^2 hybridized at carbon. The most acidic 1,4-disubstituted tetrazolium salt undergoes rapid hydrogen-deuterium exchange on the 5-carbon even in 2N-DCl *via* ylide formation.[3,5] As for the deuterium exchange of methyl protons of substituted azoles where C–H bonds are sp^3 hybridized at carbon, there has been a report concerning with 3- or 5-methylisothiazole.[7] This paper presents the C–H/C–D exchange of methyl protons of 1,4,5- and 1,3,5-trimethyltetrazolium iodides[8] in basic D_2O solutions containing pD buffer mixtures.

On standing a deuterium oxide solution of 1,4,5-trimethyltetrazolium iodide (**1**) at room temperature, deuterium exchange of the 5-methyl protons occurred slowly and the hydrogen was completely replaced by deuterium in a week. When the H/D exchange was carried out in D_2O at pD 8.40, 9.34, and 10.50, the rate of deuterium incorporation increased under more basic conditions; $t_{1/2}$ 50 min at pD 8.40, $t_{1/2}$ 15 min at pD 9.34, $t_{1/2}$ 12 min at pD 10.50. The half-life, $t_{1/2}$, of the exchange was measured by following the disappearance of the peak at δ 2.95 ppm in the NMR spectrum. There was found no exchange of the *N*-methyl protons of **1** under the above conditions.



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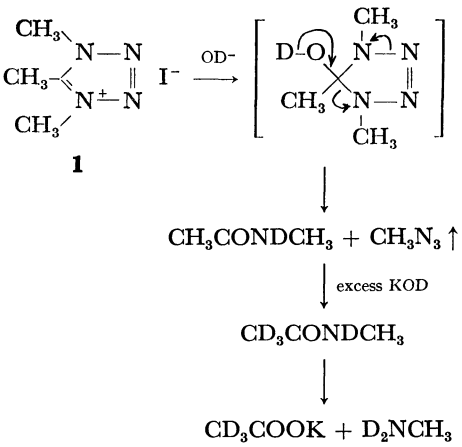
Under more basic condition (pD 13.50) the 1,4,5-trimethyl salt **1** underwent rapid decomposition with vigorous gas evolution. The gas was determined to be methylazide by the mass spectrum; a parent ion at *m/e* 57. When **1** was dissolved in deuterium oxide containing less than one-equivalent of potassium deuteroxide in an NMR tube, there appeared a couple of single peaks at δ 2.01 and 2.73 ppm assigned to acetyl and *N*-methyl protons of *N*-d_1-methylacetamide at the expense of the peaks at δ 2.95 and 4.27 ppm associated with **1**, and some amount of the original peaks at δ 2.95 and 4.27 ppm still remained maintaining the starting integral ratio of 1 : 2, respectively. This showed that the rapid hydrolytic decomposition occurred before H/D exchange. In the presence of excess potassium deuteroxide, the original peaks at δ 2.95 and 4.27 ppm disappeared showing complete decomposition of **1** into *N*-d_1-methylacetamide. On standing overnight, the acetyl protons of *N*-methylacetamide were exchanged with deuterium, which was displayed by the disappearance of the peak at δ 2.01 ppm associated with the acetyl protons, and further hydrolysis of the deuterated *N*-methylacetamide occurred slowly to give potassium d_3-acetate and *N*-d_2-methylamine whose peak was found at δ 2.30 ppm. This hydrolysis was also confirmed by following the change in the NMR spectrum of the authentic *N*-methylacetamide in potassium deuteroxide solution. These results showed that the reaction proceeded as follows:



Duffin[9] reported the analogous hydrolytic decomposition of 1,5-dimethyl-4-phenyltetrazolium iodide in an aqueous 50% potassium hydroxide solution yielding phenylazide and methylamine.

In the case of 1,3,5-trimethyltetrazolium iodide (**2**), much slower H/D exchange was found even under fairly basic condition; $t_{1/2}$ 3115 min at pD 11.05. This is compatible with the easier deuterium exchange of the ring proton of 1,4-dimethyltetrazolium salt than the 1,3-dimethyl isomer.[6] When **2** was dissolved in more basic deuterium oxide, pD 13.50, there occurred no hydrolytic decomposition of **2**, but an additional H/D exchange of the 3-protons, $t_{1/2}$ 26 min, as well

1) R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966).

2) R. A. Olofson and J. M. Landesberg, *ibid.*, **88**, 4263 (1966).

3) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *ibid.*, **86**, 1866 (1964).

4) T. J. Curphey, *ibid.*, **87**, 2064 (1965).

5) A. C. Rochat and R. A. Olofson, *Tetrahedron Lett.*, 3377 (1969).

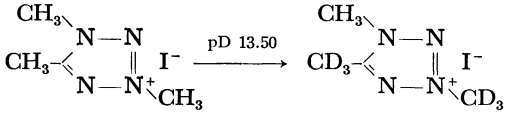
6) W. P. Norris and R. A. Henry, *ibid.*, 1213 (1965).

7) J. A. White and R. C. Anderson, *J. Heterocycl. Chem.*, **6**, 199 (1969).

8) T. Isida, S. Kozima, S. Fujimori, and K. Sisido, This Bulletin to be published.

9) G. F. Duffin, *Chem. Ind.* (London), **1955** 1355.

as the rapid exchange of the 5-methyl protons (too fast to be measured). It must be notable that there was no exchange of the 1-methyl protons of **2** even under the strongly basic condition. Analogous selective deuterium exchange of the 3-methyl protons of 1,3-dimethyltetrazolium chloride was found by Norris and Henry.[6] The inertness of the 1-methyl protons of **2** as well as **1** could be attributed to the lower acidity of the 1-methyl protons than the 3-methyl ones. This might be brought about by the electron donation from the adjacent 5-carbon atom and the 5-methyl group into the 1-nitrogen atom, whereas, there might be comparatively less electron donation from the 2- and 4-nitrogen atoms to the 3-nitrogen atom.



2

Experimental

1,4,5- and 1,3,5-Trimethyltetrazolium iodides were prepared by the reaction of 5-methyltetrazole with methyl iodide.[8]

The kinetics were run by following the changes in the NMR spectra at 23°C. The NMR spectra were determined at 60 MHz with a JEOL C-60HL spectrometer. The integral ratios were referred to an external standard acetonitrile kept in a capillary. The exchange was nicely first order over two half-lives, the substrate concentration was approximately 0.5 molar, and little rate variation was observed between 0.27—0.82M. D_2O buffer solutions of pD 8.40, 9.34, and 10.50 were made from Atkins-Pantin buffer mixture[10] (KCl–Na_2CO_3–H_3BO_3), and that of pD 11.05 from Menzel one[11] ($NaHCO_3$–Na_2CO_3). Measured pD values were uncorrected for differance between pH and pD. The buffer capacities were sufficient to maintain the same pD value on addition of the substrate. The mass spectrum was measured by Hitachi RMS-4 Mass Spectrometer.

10) W. R. G. Atkins and C. F. A. Pantin, *Biochem. J.*, **20**, 102 (1926).

11) H. Menzel, *Z. Phys. Chem.*, **100**, 276 (1921).