Competitive Deprotonation of 2-Hydrogen *vs.* 8-Hydrogen in Zwitterionic Purines

By JOHN L. WONG* and JOHN H. KECK, JR.

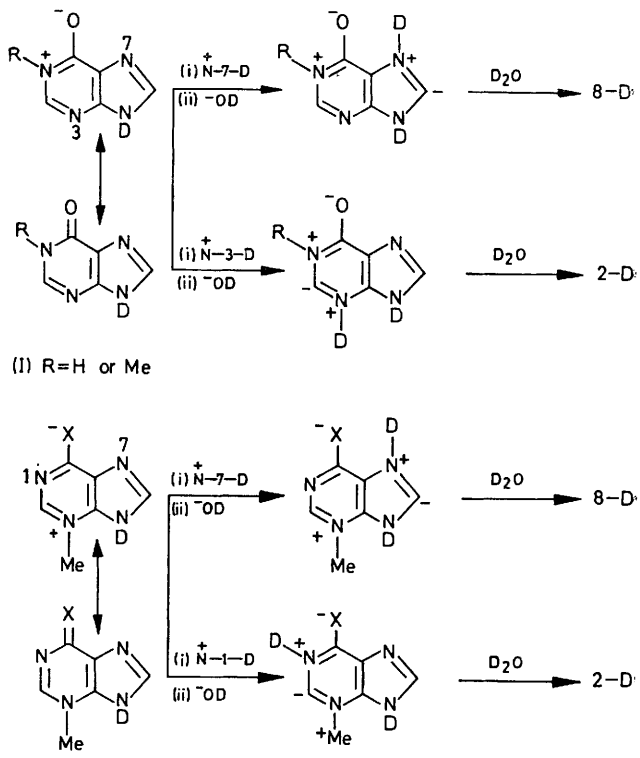
(*Department of Chemistry, University of Louisville, Louisville, Kentucky* 40208)

Summary The generality and rates of the competitive deprotonations of the 2-*vs.* the 8-hydrogen in zwitterionic purines are shown and a mechanism is proposed.

ISOTOPIC hydrogen exchange at the 8-position of purines *via* a carbanion intermediate[1] is a reaction of biological significance which indicates that C-8 is a nucleophilic centre in purine nucleosides. Thus, the report by Bergmann *et al.*[2] that only the 2-hydrogen of 3-methylhypoxanthine exchanged in D_2O at 70—85° is unique and interesting. We report now the generality of this purine 2-hydrogen deprotonation and propose a mechanism to account for the competitive exchanges of the 2- and 8-hydrogen atoms in these compounds.

Deprotonations were studied in D_2O at pD 6—7 in a sealed tube heated at 100°C, and the exchanges were followed by ^1H n.m.r. technique. The Table shows the pseudo-first-order rate constants for the 2- and 8-proton exchange in three groups of purine compounds, the hypoxanthines, 6-mercaptopurines, and adenines. The hypoxanthines were stable throughout this treatment. 6-Mercaptopurine and the 1-methyl derivative decomposed at a rate slower than that of 8-H exchange but faster than that of 2-deprotonation; hence the latter was not determined directly. Since hydrolysis of 1-methyladenine preceeded any carbon deuteriation, it is not included in the Table.

Notable conclusions are (i) deuteriation at the 2-position of a purine is significant (k_{obs} *ca.* 10^{-5} s^{-1}) only with potential zwitterionic structures, *e.g.* (I) and (II), (ii) the 1-methyl group exerts a mildly rate-enhancing effect on both the 2- and 8-deprotonation, and (iii) the 3-methyl group leads to a rapid increase of the rate of deprotonation of the 2-hydrogen with concommitant depression of that of the 8-hydrogen, thus resulting in a dramatic increase of the



SCHEME. Deprotonation mechanism of zwitterionic purines *via* a conjugate acid carbanion.

TABLE. Rates of deuteration at 100°

	δ[a]		k/s^{-1}		
	2-H	8-H	2-Position	8-Position	k(2-H)/k(8-H)
Hypoxanthine[b,f]	8·42	8·51	$9·75 \times 10^{-6}$	$2·80 \times 10^{-4}$	0·035
1-Methylhypoxanthine[b]	8·60	8·50	$1·16 \times 10^{-5}$	$3·72 \times 10^{-4}$	0·031
3-Methylhypoxanthine[b]	8·67	8·57	$2·22 \times 10^{-3}$	$2·04 \times 10^{-5}$	109·0
6-Methoxypurine 3-oxide[b]	8·86	8·64	$6·85 \times 10^{-6}$	$1·08 \times 10^{-5}$	0·635
6-Mercaptopurine[c]	8·28	8·43	$<1·13 \times 10^{-6}$[e]	$1·30 \times 10^{-5}$	<0·09
1-Methyl-6-mercaptopurine[c]	8·63	8·43	$<1·30 \times 10^{-7}$[e]	$1·38 \times 10^{-5}$	<0·01
3-Methyl-6-mercaptopurine[c]	9·32	8·60	$2·20 \times 10^{-4}$	$6·48 \times 10^{-7}$	340·0
Adenine[d]	8·20	8·17	$1·72 \times 10^{-7}$	$1·10 \times 10^{-4}$	0·001
3-Methyladenine[b]	8·30	8·07	$2·51 \times 10^{-5}$	$5·58 \times 10^{-7}$	45·0

[a] From internal sodium 3-(trimethylsilyl)propanesulphonate. Assignments are made according to J. R. Fox, Ph.D. Thesis, University of Illinois, Urbana, Illinois, 1965. [b] 0·1M Solution of the purine compound in D_2O. pD of all solutions are in the range 6—7. [c] In $(CD_3)_2SO$–D_2O (2:1). [d] J. A. Elvidge, J. R. Jones, and C. O'Brien, *Chem. Comm.*, 1971, 394, extrapolated from k (detritiation; 85°) using $E = 22·3$ kcal mol^{-1}. [e] Rate of decomposition, hence the rate of exchange is less than this rate. [f] In $(CD_3)_2SO$–D_2O (2:1) solution at 100°, k/s^{-1} for the 2- and 8-position are respectively $6·95 \times 10^{-7}$ and $1·84 \times 10^{-5}$, k (2-H)/k (8-H) = 0·038.

relative rate of 2-*vs.* 8-deprotonation by many orders of magnitude.

We[3a] and others[3b] have shown that deuteriation of the 2-, 4-, and 5-position of imidazoles in D_2O (pD 0—12) proceeds *via* a carbanionic mechanism occurring on the conjugate acid species. The same mechanism has been proposed for the 8-exchange of several 6-substituted purines by Maeda *et al.*[1a] and Olson *et al.*[1b] The Scheme illustrates this deprotonation mechanism for the 2- and 8-hydrogen of the zwitterionic purines. Similar zwitterionic structures have been postulated by Beak *et al.*[4] to explain the hydrogen deuterium exchange at the 2-position of an *N*-methyl-4-pyrimidone and a 1,3-dimethyl-4-pyrimidonium salt. Thus, N-3 or N-7 deuteriation leads to the respective conjugate acid species for 2- and 8-deprotonation of (I). Since the basicity of N-7 and N-3 of (I) is enhanced when R is Me rather than H, the greater facility of forming the necessary conjugate acid species should yield a higher k_{obs} of exchange of 1-methylhypoxanthine than that of hypoxanthine. In comparing the 3-methylhypoxanthine zwitterionic form (IIa) with (I), the basicity of N-7 in (IIa), on account of the direct attachment of the quaternized N-3 to the imidazole ring, must be significantly depressed relative to N-7 in (I). Conversely, N-1 in (IIa), being adjacent to the 6-oxy anion, should be much more basic than N-3 of (I). The combined effects of the N-3-quaternized structure (IIa) are that the k_{obs} of 2-deprotonation is enhanced while that of 8-deprotonation is depressed. Similar mechanisms appear to prevail for the deprotonation of the 3-methyl derivatives of 6-mercaptopurine (IIb) and adenine (IIc). For 6-methoxypurine *N*-oxide, the *N*-oxide deactivation of N-7 is expected to be less than for a genuine quaternary N-3. However, the activation of N-1 due to the more remote and less basic *N*-3-oxide anion is also less pronounced, hence a more subdued relative rate was obtained.

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