INTRAMOLECULAR EFFECT OF 1-(ω-HYDROXYALKYL) GROUPS ON ALKALI DEGRADATION OF 3-METHYL-1-(ω-HYDROXYALKYL)URACILS

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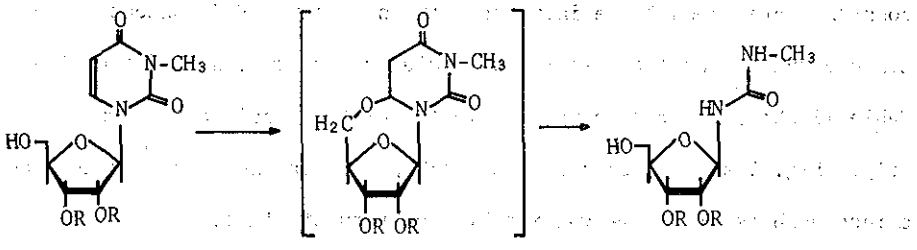
The alkali degradation of 3-methyl-1-(ω-hydroxyalkyl)uracils has been shown to involve the intramolecular acceleration by the ω-hydroxyl participation; in fact, the ω-hydroxypropyl group formed favorable six-membered intermediate 5 showed a rate enhancement. The degradation products were proved to be N-hydroxyalkyl-N'-methylureas.

The novel degradation of 3-methyluridines 1 by alkali to 3-methylurea ribosides 2 has been reported[1]. The reaction probably requires a 6,5'-cyclonucleoside as the obligatory intermediate because of quite resistance to alkali, after methylation of the 5'-hydroxyl group of 1 (Scheme 1). Herein we report an intramolecular promotive degradation of 3-methyl-1-(ω-hydroxyalkyl)uracils by alkali which would provide the possible generality of alkaline breakdown of



1a: R=H
b: R=i-Pr

2a: R=H
b: R=i-Pr

Scheme 1

3a: n=2
b: n=3
c: n=4
d: n=5
e: n=6

4a: n=2
b: n=3
c: n=4
d: n=5
e: n=6

Scheme 2

the 3-methyluridines.

3-Methyl-1-(ω-hydroxyalkyl)uracils 3a-e were prepared by reaction of uracil with chloroalkyl-*p*-nitrobenzoate followed by debenzoylation and methylation[2-5]. In a kinetic experiment, a solution of 3-methyl-1-(ω-hydroxyalkyl)uracil (2×10^{-3} mol) was incubated at various temperatures with potassium hydroxide (5 ml) of varying strength. Aliquots were withdrawn at intervals and the optical density (at 267 nm) was measured after acidification. All of the reactions followed first order kinetics. The rate constants for degradation of 3-methyl-1-(ω-hydroxyalkyl)uracils and 3-methyluridine in 0.1 *N*, 0.5 *N*, and *N* KOH solution at 55° and 37°, are given in Table I. The observed rate constants for KOH concentrations with μ=1.0 (NaCl) indicated linear functions. The rate constants are shown to be increase with increasing DMSO content[6,7] in a reaction mixture and are well correlated with dielectric constants of the mixed solvents. Table II shows the rate constants in the critical solvent composition (DMSO-H_2O, 1:1). Fig. 1 summarizes the relationship between the rate constants and the carbon-numbers of the ω-hydroxyalkyl substituents in 3.

This alkali degradation involves the competitive inter- (OH^-) and intra-nucleophilic attacks ($R\text{-}O^-$) on the C-6 position. However, since the concentration of the hydroxy ion is constant, the difference of the reaction rate can be ascribed to the nucleophilicity of the ω-hydroxyl group. Of the 3-methyl-1-(ω-hydroxyalkyl)uracils examined, 3-methyl-1-(ω-hydroxypropyl)uracil 3b showed a rate enhancement which was in accord with kinetic intramolecular

Table I. Rate Constants of Alkali Degradation of 3-Methyl-1-(ω-hydroxyalkyl)uracils in 0.1 *N*, 0.5 *N*, and *N* KOH

KOH Conc	Comp	Temp 55° k (sec^{-1})	KOH Conc	Comp	Temp 55° k (sec^{-1})
0.1 *N*	1a	8.12×10^{-5}	0.5 *N*	1a	2.98×10^{-4}
	3a	4.90×10^{-6}		3a	3.91×10^{-5}
	3b	1.31×10^{-5}		3b	6.87×10^{-5}
	3c	3.83×10^{-6}		3c	2.16×10^{-5}
	3d	1.40×10^{-6}		3d	1.55×10^{-5}
	3e	—*		3e	1.15×10^{-5}
KOH Conc	Comp	Temp 55° k (sec^{-1})	KOH Conc	Comp	Temp 37° k (sec^{-1})
N	1a	6.52×10^{-4}	*N*	1a	4.23×10^{-4}
	3a	9.37×10^{-5}		3a	4.65×10^{-5}
	3b	1.67×10^{-4}		3b	1.10×10^{-4}
	3c	3.25×10^{-5}		3c	1.07×10^{-5}
	3d	2.70×10^{-5}		3d	7.59×10^{-6}
	3e	2.36×10^{-5}		3e	5.63×10^{-6}

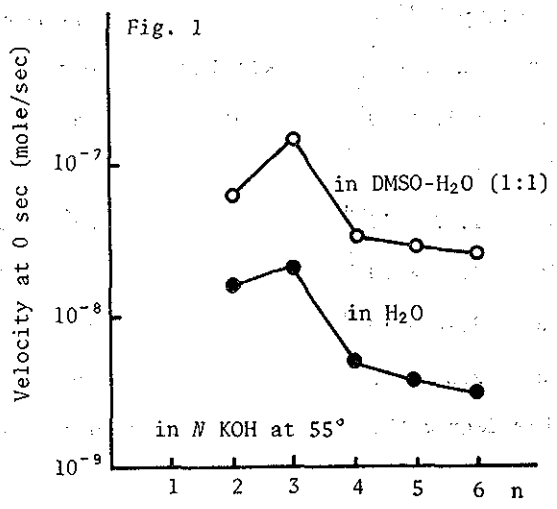
* No measurable degradation observed after as long as 120 min.

Table II. Rate Constants of Alkali Degradation of 3-Methyl-1-(ω-hydroxyalkyl)uracils in *N* KOH DMSO-H_2O

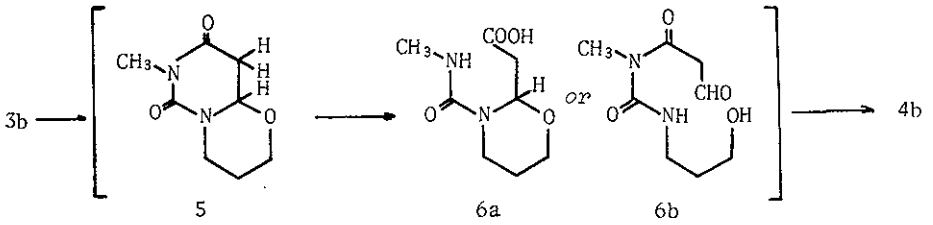
Temp	Comp	k (sec^{-1})
55°	1a	2.79×10^{-3}
	3a	3.74×10^{-4}
	3b	6.63×10^{-4}
	3c	2.47×10^{-4}
	3d	2.12×10^{-4}
	3e	2.00×10^{-4}

participation of the ω-hydroxyl group to form the six-membered intermediate 5. The fact agrees with the result of calculation of the activation energies of 3 in which the energy for 3b is the lowest value, about 4.5 Kcal/mol comparable to the value of 1a.

In general, the 5,6-dihydrouracil nucleosides are sensitive to alkali, giving the γ-ureidopropionic acid derivatives as the sole end-product[8]. On the contrast with the 5,6-dihydrouracil derivatives, 6-hydroxy-5,6-dihydrouridine



undergoes more deep degradation by alkali to give ribosylurea in addition to other products[9]. Thus, in analogy with 6-hydroxy-5,6-dihydrouridine, the cyclic intermediate 5 proceeds the concomitant ring-opening of the dihydrouracil nucleus (6a or 6b) followed by second-rupture to ureido derivative 4 (Scheme 3). Attempts to isolate the three-carbon fragment failed when 3b was incubated with 1-0.5 *N* KOH. In a preparative scale, the degradation product of 3b was identical with N-hydroxypropyl-N'-methylurea[5] 4b, mp 105-108°, which was finally evidenced by separate synthesis.



Scheme 3

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