Mechanism for the Photohydration of Pyrimidines

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A ZWITTERIONIC structure (D_2) was suggested[1] to explain the photoinduced unidirectional 1,4-addition of water to uracil derivatives (A) and is consistent with observed polar mechanisms.[2,3] We now report the studies of the effects of substitution on the rates of photohydration, as measured by spectral decrease in the 260—270 mμ region,[3] which implicate quaternary N(1) and N(3) mesomeric species as intermediates in these reactions.

The Table records that the rates of hydration of all N(1)-substituted uracils at neutral pH are higher than those of uracil, while N(3)-substituted uracils are lower. Also, the rates increase 4—10-fold as the N(1)-substituents become more electron withdrawing. While a similar effect is expected to be exerted on N(3), the rates of hydration, nevertheless, decrease 14—46% with N(3)-substituents. One possible explanation is that N-substituents tend to promote the formation of quaternary N(1) and N(3) mesomeric species, D_1 and D_3, as intermediates which then undergo water addition as shown in the Scheme. While D_3 forms a stable product C, D_1 forms an unstable product B, which reverts readily to the starting material A. This competing process becomes more important when N(3) is substituted and would result in the observed slower rates for N(3)-substituted uracils. Steric hindrance at the reaction site is suggested by the slower hydration rates of 6-methyluracil and 1,3,6-trimethyluracil, which are seven times less than those of uracil and 1,3-dimethyluracil, respectively.

Effect of substitution and pH[b] on the rate of hydration of ***uracil*** *derivatives*

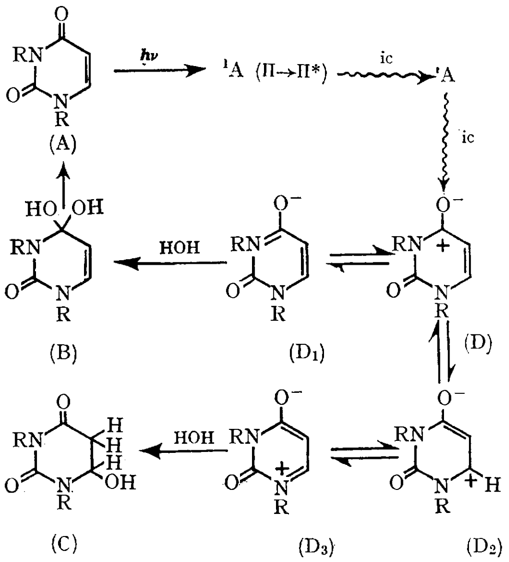
Uracils[a]	Rate[c] (10^3/min.) H$_2$O	pH 2	pH 4	pH 6	pH 7	pH 8	Relative rate pH 2
6-Me	1·74	4·1[d]	3·7	1·7	2·1	1·8	[d]
1,3,6-Me$_3$	6·1	[b]	4·2	5·9	5·7	5·4	[d]
3-Me	8·1	61	18	8·1	8·8	6·0	0·95
Uracil	12·2	64	29	11·5	11·5	11	1·0
1-Me	51·3	52	51	51	51	42	0·80
1-CH$_2$CO$_2$H	64·4	87	62	61	56	52	1·36
1-[CH$_2$]·CO$_2$H	66	84	70	64	55	50	1·30
1-CH$_2$CONH$_2$	70	72	70	70	62	58	1·14
1-CH$_2$·CO$_2$Et	83	83·5	83	82	74	68	1·30
Ethyl-1-propionate	82·5	81	83	72	71	63	1·29
1-Acetamide	86	91	88·7	86	83	80	1·42
Diethyl-1-malonate	98	106	105	123	—	120	1·65
Uridine	121	126	123	121	122	117	2·0
Uridylate	126	130	126	125	126	120	2·0
1,3-Me$_2$	44	[d]	[e]	44	44	41	[d]
Diethyl 1,3-di-malonate	66	[e]	[e]	66	89	[e]	[e]

[a] These compounds and hydration products (over 86% yields) were identified by elemental analyses, i.r. and n.m.r.
[b] Phosphate buffer system (0·01M) with KCl added to keep [Cl$^-$] constant. pH 2 buffer was HCl–KCl system.
[c] Precision within 1·8%.
[d] Hydration product is unstable at pH 2.
[e] No determination was made.

At pH 2, where protonated quaternary N(1) is favoured, the hydration rates for uracil and 3-methyluracil approach those of N(1)-substituted uracils and were six and eight times greater than at pH 7, respectively. Also, the relative rates are in good agreement with the electron donating and withdrawing abilities of the N(1)-substituents.

The insensitivity of hydration rates to oxygen,[4] photosensitizers,[5] quenchers,[6] and wavelength variation from 240 to 280 mμ,[7] suggests that reaction is initiated in the lowest singlet (S_1) rather than triplet (T_1) excited state.[8] Excimer mechanisms are not important since rate constants increase as initial concentrations decrease,[3] and the presence of associated dimers of uracil and uridine is minimal in dilute aqueous solutions.[9] Plots of dD/dt *vs.* $(1—10^{-D})$ are nonlinear,[10,11] while a great number of uracil derivatives show perfect first-order plots from 10 to 0·4 optical density units for more than 75% reaction. In the absence of marked dependence of hydration rates on pH, the observed decreases in rates in D$_2$O, compared to H$_2$O,[11] are probably not due to acid–base reactions of excited states.[12]

The ease with which the hydration products revert to starting materials in acid or base, or upon heating,† and the fact that *dark* hydration has not been observed under any conditions suggest that the photohydration intermediates are high-energy species, either in the electronically excited singlet or upper vibrationally excited ground-state. The observed substituent, pH, and isotopic effects[13] and the first-order plots (at optical density > 2) in the absence of excimer mechanisms suggest that intermediates D$_1$ and D$_3$ may be vibrationally excited species formed by internal-conversion processes from the S_1 state. Such processes are important in the S_1 and T_1 states of these pyrimidines whose N–H protons are held more firmly in



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† The kinetics of dehydration reaction has been studied and will be included in the full pape

the S_1 state than in the ground state,[14] very much in agreement with our results of pH and D_2O effects.[5]

The treatment of uracils as urea derivatives of $\alpha\beta$-unsaturated ketones is justified by the fact that partial or fully aromatic alkoxy-pyrimidines do not undergo photohydration.[11] This is consistent with MO calculations[15] and ground-state reactions of uracil derivatives.[16] We tentatively suggest that irradiation of uracils results in populating D and D_2 species which are then stabilized[17] to form D_1 and D_3. D_1 and D_3 should contribute significantly to the observed reactivity of these nascent vibrationally excited species with the solvent molecules.

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