Tetrahedron Letters No. 36, pp 3823 - 3826, 1972. Pergamon Press. Printed in Great Britain.

DIRECT OBSERVATION OF URACIL DICATION AND RELATED DERIVATIVES[1]

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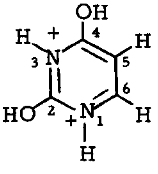
(Received in USA 28 March 1972; received in UK for publication 7 August 1972)

The structures of the mono- and dications from 2,4-dioxopyrimidines have been the focus of considerable attention.[3] It is generally agreed that the most stable monocation is protonated at O_4[3c,d,e] and the most stable dication is protonated at O_2 and O_4.[3c] However, more subtle structural details such as the stereochemistry of the protonated centers and the degree to which monoprotonation at O_4 is preferred have remained obscure. We have obtained complete ^1H NMR spectra which establish the structures of uracil dication and closely related derivatives in HSO_3F-SbF_5-SO_2. From the relative kinetic acidities of the O_2 and O_4 protons of 1,3-dimethyluracil dication, we conclude that the monocation derived from protonation at O_4 is considerably more stable than its O_2 protonated isomer.

Dications 1-5[4] were prepared by dissolving the corresponding neutral oxo and methoxy derivatives[*5] in HSO_3F-SbF_5-SO_2 at -78°. Comparisons of the ^1H spectra of 1-5 indicate only minor variations of chemical shifts



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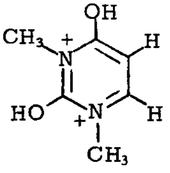

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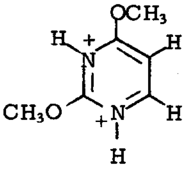

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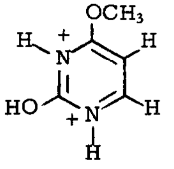

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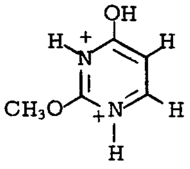


5

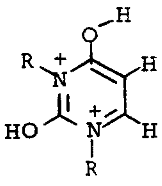
or coupling constants for protons in similar environments, suggesting that replacement of a proton attached to the oxygen or nitrogen atoms with a methyl group does not result in substantial structural changes. Assignments for protons at C_5 and C_6 were based on chemical shifts and coupling constants. The N-H resonances were easily identified because of broadening due to the ^{14}N quadrupole and coupling between the protons at N_1 and C_6. The protons attached to O_2 and O_4 appeared as sharp, low field singlets and were assigned by comparing the exchange rates between the O-H protons and solvent for 1, 2, 4 and 5 (see below).

Table I. ^{1}H NMR Spectra of Pyrimidine Dications at 60 MHz[a]

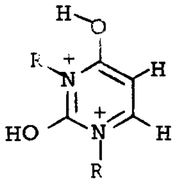
Cmpd.	Chemical Shifts (δ, ppm)						Coupling Constants (Hz)		
	N_1	O_2	N_3	O_4	C_5	C_6	$J_{1,6}$	$J_{3,5}$	$J_{5,6}$
1[b]	11.55	12.07	12.07	12.01	7.55	8.81	6.4	2.0[c]	7.6
2[d]	4.22 (4.13)[e]	12.20	4.13 (4.22)[e]	12.05	7.53	8.73	---	---	8.0
3[b]	11.85	4.77 (4.70)[e]	12.27	4.70 (4.77)[e]	7.61	8.97	6.4	2.0	7.6
4[d]	11.57	11.94	12.03	4.71	7.60	8.88	6.5	2.2	8.0
5[d]	11.73	4.79	12.22	12.14	7.51	8.83	6.5	2.2	8.0

[a] 1:1 HSO_3F-SbF_5 with added SO_2 at -60 to -80°. [b] Relative to internal CH_2Cl_2 (δ = 5.33 ppm). [c] Assigned by double resonance. [d] Relative to internal tetramethylammonium chloride (δ = 3.10 ppm). [e] Unambiguous assignments for the methyl resonances at N_1, O_2, N_3 and O_4 cannot be made.

In addition to the major resonances listed in Table I, 1 and 2 gave small singlets at 11.55 ppm (27% of the 12.01 ppm peak) and 11.53 ppm (11% of the 12.05 ppm peak), respectively. Minor peaks (within 0.2 ppm of the major resonance position) were also found for groups attached to carbon and nitrogen. Under conditions where the ^{1}H resonance of the O_4 proton in 2 is observed but the resonance at O_2 has merged with the solvent peak because rapid exchange, the minor resonance at 11.53 ppm remains sharp. However, in samples where exchange of the proton at O_4 with solvent results in a considerable broadening of the 12.05 ppm peak, the signal at 11.53 ppm disappears. In addition, the methoxy group of 4 is accompanied by a minor high field component (ca. 15%), while the methoxy group in 5 gives a single peak. The ratios of the peak intensities of major to minor components are larger for 2 than for 1. Since one would expect that introduction of a methyl group at N_3 would lower the syn-anti ratio,[6] we propose that the major peaks represent the anti isomers of 1 and 2 (where the proton at O_4 is anti to N_3) and the minor peaks result from their syn counterparts.



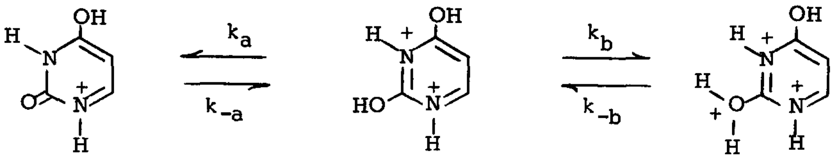
anti



syn

As a solution of 2 in 1:1 HSO_3F-SbF_5 is warmed from -60 to -20°, the low field O-H resonance broadens and merges with the solvent peak, while the high field O-H peak remains sharp.[7] The OH proton of 4 exhibited a temperature dependence similar to that of the low field resonance of 2; whereas, the sharp peak due to the proton at O_4 in 5 did not broaden between -60 and -20°. Thus, we conclude that proton exchange occurs more readily at O_2 in dications 1 and 2. In 1:1 HSO_3F-SbF_5 at -60° the barrier for exchange ($\Delta F^{\ddagger}$) at O_2 is 13.5 kcal/mol.[8]

Two limiting mechanisms which could account for proton exchange at O_2 are shown below.



1a 1 1b

If one makes the reasonable assumption that k_{-a} is large with respect to k_a, then the rate at which 1a is formed is directly proportional to the relative equilibrium populations of 1 and 1a. The same argument can be applied to exchange by path b. Since 1, 1a and 1b differ in the degree of protonation, a reduction in acid strength should increase the equilibrium concentration of 1a with respect to 1 and produce a concurrent decrease in the equilibrium concentration 1b.[9] Therefore, if exchange occurs by deprotonation-protonation (path a), the observed rate should be inversely proportional to solvent acidity. Although a precise acidity scale for mixtures of HSO_3F and SbF_5 is not known,[10] the acidity of HSO_3F ($H_o \cong -14.5$)[10] is greatly enhanced upon addition of SbF_5 (estimated $H_o \cong -17.5$ for 1:1 HSO_3F-SbF_5).[11] Thus, the data in Table II support a deprotonation-protonation mechanism for proton exchange at O_2.

Table II. Rates of Proton Exchange in 1,3-Dimethyluracil

HSO_3F : SbF_5	T, °C	k(sec^{-1}) O_2	k(sec^{-1}) O_4
1:1[a]	-60	.05[b]	c
1:1[a]	-41	1.4	c
1:1[a]	-30	6.3	c
1:1[a]	-25	11	c
1:1[a]	-21	36	c
1:1[d]	-16.5	2300	c
1:0.75[e]	-60	2.4	c
1:0.50[e]	-60	95	c
1:0.25[e]	-60	f	10
1:0.0	-60	f	f

[a] 6.8 mol of HSO_3F/mol of 2. [b] Extrapolated from rates at -21 to -41°. [c] Too slow to measure. [d] 3.8 mol of HSO_3F/mol of 2. [e] >6 mol of HSO_3F/mol of 2. [f] Too fast to measure.

When the molar ratio of SbF_5 to HSO_3F is lowered to 0.25, a broadening of the O_4 proton resonance suggests that exchange with solvent has also become rapid *via* a deprotonation mechanism involving proton loss at O_4 instead of O_2. Although we have not yet obtained accurate rate data for exchange at O_2 and O_4 in a common solvent, the kinetic acidity of the proton at O_2 is at least 2000 times that of the O_4 proton.[12] If the rates of protonation at O_2 and O_4 are similar, then monocation **1a** is at least 3.9 kcal/mol more stable than its O_2 protonated isomer in 1:1 HSO_3F-SbF_5.

References

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1. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and PHS Grant RR07092 for support of this work.

2. University of Utah Research Fellow.

3. (a) W. E. Cohn in E. Chargaff and J. N. Davidson, "The Nucleic Acids," Vol. I, Academic Press, 1955, p. 217; (b) R. Shapiro and M. Danzig, *Biochem.*, 11, 23 (1972); (c) von R. Wagner and W. von Philipsborn, *Helv. Chim. Acta*, **53**, 299 (1970); (d) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1540 (1962); (e) H. M. Sobell and K. Tomita, *Acta Cryst.*, 122 (1964); (f) E. P. Parry, D. H. Hern and J. G. Burr, *Biochim. Biophys. Acta*, 182, 570 (1969); (g) O. Jardetzky, P. Pappas and N. G. Wade, *J. Amer. Chem. Soc.*, **85**, 1657 (1963); (h) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 3046 (1963).

4. Only one of several possible resonance structures are shown for each mono- and dication.

5. J. L. Wong and D. S. Fuchs, *J. Org. Chem.*, **35**, 3786 (1970).

6. This assumes that the two isomers are at equilibrium although a kinetic controlled protonation should show a similar trend.

7. A similar phenomenon was noticed for **1** but the N-H resonances complicated analysis of the exchange rates.

8. Calculated from the rate constant at -60° in 1:1 HSO_3F-SbF_5 listed in Table II. M. Saunders, *Tetrahedron Letters*, 1699 (1963).

9. One could also envision exchange at O_2 which proceeds through a transition state similar to **1b**; however, the arguments presented against **1b** would apply to a "triprotonated" transition state as well.

10. R. J. Gillespie, T. E. Peel and E. A. Robinson, *J. Amer. Chem. Soc.*, **93**, 5083 (1971).

11. G. C. Levy, J. D. Cargioli and W. Racela, *ibid.*, **92**, 6238 (1970).

12. We should be able to detect exchange with a rate constant as low as 1 sec^{-1}.