Nuclear Magnetic Resonance Study of the Protonation of 2,6-Dimethyl-γ-pyrone and Related Bases in Superacid Systems

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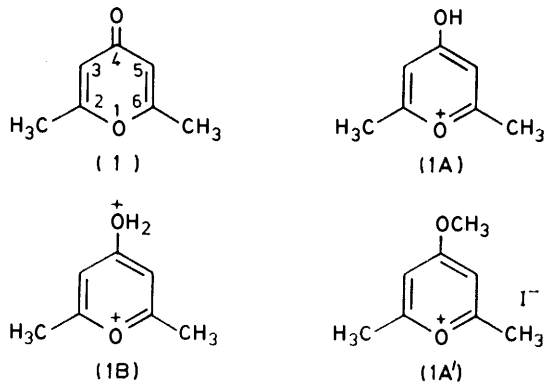
^{1}H and ^{13}C n.m.r. spectra indicate that 2,6-dimethyl-4*H*-pyran-4-one in solution in HSO_3F–SbF_5 (1 : 1) is doubly protonated at the exocyclic oxygen atom. The sulphur and nitrogen analogues, 2,6-dimethyl-4*H*-thiopyran-4-one, and 2,6-dimethyl-*N*-methyl-4-pyridone, respectively, behave similarly. Other related compounds show ^{1}H and ^{13}C n.m.r. spectra in support of our interpretation.

THE basicity and protonation behaviour of 2,6-dimethyl-4*H*-pyran-4-one (1) have been extensively studied.[1-8] The compound has been reported to be fully protonated in fluorosulphuric acid solution at room temperature.[5] Although the reported pK_a values seem to depend on the experimental method, all reports agree that (1) is a stronger base than most αβ-unsaturated ketones, with a pK_a value of *ca.* +0.3. It is generally accepted that protonation of (1) and of similar carbonyl bases takes place on the carbonyl group, with formation of pyrylium salts.[9,10]

Ketones are reported to be fully monoprotonated at the carbonyl oxygen in HSO_3F–SbF_5 solution, and it is generally possible to observe the proton signal due to the $>C=\overset{+}{O}H$ grouping in the n.m.r. spectrum.[11] It was, therefore, of interest to study the ^{1}H and ^{13}C n.m.r. spectra of



(1) in the HSO_3F–SbF_5 (1 : 1) system in order to observe the signals due to the protonated pyrone, and at the same time establish unambiguously the site of protonation in this moderately strong organic base containing two non-equivalent oxygen atoms. Since basicity and proton residence times on the protonated bases appear to be correlated for ketones,[12] it was expected that the observation of the ^{1}H n.m.r. signal of the monoprotonated carbonyl group in (1A) † should present no practical problems. However, no such proton signal due to the conjugate acids (1A or B) was observable in HSO_3F or in the HSO_3F–SO_2 system, even at temperatures down to −90°. This absence of a signal suggests that the conjugate acid undergoes fast proton exchange with the solvent acid, an unusual observation for a relatively

† The letter A after the numeral indicates that the species is the monoprotonated form of the parent, the letter B similarly refers to a diprotonated species. Primed letters refer to methylated analogues.

TABLE 1

^{1}H N.m.r. chemical shifts (δ values downfield from Me_4Si)

Base	Protons	$CDCl_3$	HSO_3F–SbF_5	Δδ *
(1)	CH_3	2.25	2.74	0.49
			(2.1 †)	(−0.1 †)
	3,5	6.05	7.04	0.99
			(6.5 †)	(0.45 †)
	$-\overset{+}{O}H_2$		9.69	
			(*ca.* 9.6 †)	
	T/K	Ambient	253 (233 †)	
(4)	CH_3	2.35	2.90	0.55
	3,5	6.71	7.66	0.95
	$-\overset{+}{O}H_2$		9.71	
	T/K	Ambient	263	
(5)	C–CH_3	2.31	2.91	0.60
	3,5	6.17	7.60	1.43
	N–CH_3	3.48	4.10	0.62
	$-\overset{+}{O}H_2$		9.67	
	T/K	Ambient	253	
(6)	CH_3	2.23	2.80	0.57
	3,5	6.93	7.80	0.87
	−SH		9.7	
	T/K	Ambient	253	
(7A')	C–CH_3	2.62	2.94 †	0.32
	3,5	7.29	7.43 †	0.14
	N–CH_3	3.55	2.91 (d) †	0.60
			(*J* 5.4 Hz)	
	$-\overset{+}{N}H$ Solvent acid		Unresolved	
	T/K	Ambient	233	
(1A')	C–CH_3	2.93		
	3,5	7.89		
	O–CH_3	4.47		
	T/K	Ambient		
(2)	CH_3	1.32	1.31 † (d)	
		(d, *J* 6.2 Hz)	(*J* 5.9 Hz)	
	2,6	*ca.* 3.7 (m)	4.82 † (m)	
	3,5	*ca.* 2.3 (m)	*ca.* 3.18 † (m)	
	$=\overset{+}{O}H$		14.85 †	
	$\overset{+}{O}H$		10.19 †	
	T/K	Ambient	233	
(3)	CH_3	2.57 (d)	1.135 (d) †	
		(*J* 6.3 Hz)	(*J* 6.3 Hz)	
	2,4,6,OH	*ca.* 5.0 (m)	4.0—4.7 (m) †	
	3,5	*ca.* 3.27	1.6—2.2 (m) †	
		(m, dd?)		
	$-\overset{+}{O}H_2$		9.77 (d) †	
			(*J* 2.9 Hz)	
	$\overset{+}{O}H$		8.64 (s) †	
	T/K	Ambient	233	

* Δδ = δ (in HSO_3F–SbF_5) − δ (in $CDCl_3$). † Sample diluted with sulphur dioxide.

TABLE 2

^{13}C N.m.r. chemical shifts [δ (p.p.m.) values downfield from Me_4Si]

Base	Solvent	C-2, -6	C-3, -5	C-4	C–CH_3		T/K
(1)	$CDCl_3$	165.13	113.23	179.67	19.30		Ambient
	HSO_3F–SbF_5	179.69	109.27	177.58	19.49		253
	Δδ *	14.55	−3.96	−2.09	0.18		
(4)	$CDCl_3$	150.35	127.78	181.84	22.11		Ambient
	HSO_3F–SbF_5	172.77	122.93	173.42	22.19		263
	Δδ *	22.42	−4.84	−8.42	0.08		
						NCH_3	
(5)	$CDCl_3$	148.61	117.47	178.22	20.60	34.62	Ambient
	HSO_3F–SbF_5	159.64	114.19	161.39	20.84	38.67	253
	Δδ *	11.03	−3.28	−16.83	0.24	4.05	
(6)	$CDCl_3$	158.74	124.20	201.54	19.00		Ambient
	HSO_3F–SbF_5	172.13	116.24	177.11	19.96		233
	Δδ *	13.39	−7.96	−24.43	0.96		
(7A′)	$CDCl_3$	158.91	103.91	169.00	20.64	42.75	Ambient
	HSO_3F–SbF_5	162.39	114.48	187.61	21.08	47.11	283
	Δδ *	3.48	10.57	18.61	0.44	4.36	
						OCH_3	
(1A′)	$CDCl_3$	177.56	109.77	178.44	21.58	61.40	Ambient
(2)	$CDCl_3$	73.12	49.07	207.34	22.10		Ambient
	HSO_3F–SbF_5 †	86.20	43.48	238.19	17.66		233
	Δδ *	13.08	−5.59	30.85	−4.44		

*,† See footnotes to Table 1.

strong base with pK_a +0.3. Our previous studies [12] with a series of weak organic oxygen bases of different strengths had led to the conclusion that a fully resolved resonance for $=\overset{+}{O}-H$ is associated with a very low equilibrium concentration of free base in solution. To achieve even more complete protonation of (1) we therefore moved on to the stronger acid system HSO_3F–SbF_5 (1 : 1) in order to detect a fully resolved ^1H n.m.r. signal due to the conjugate acid. In this solvent a new sharp signal did appear but was found to be due to double protonation of the exocyclic oxygen atom to produce the species (1B). It is a singlet at δ 9.69 with a peak integral corresponding to two protons and is observable over the temperature range +30 to −60°. All other proton signals are displaced downfield relative to their position for solutions of (1) in $CDCl_3$ (Figure 1). Above +30° the spectrum shows fast exchange of the 2H singlet at δ 9.69 with the acid peak (at δ *ca.* 11.2), whereas below −60° viscosity broadening takes over. The position of the acid peak moves upfield as the concentration of added base is increased, but the positions of other peaks (including that of the 2H singlet at δ *ca.* 9.7) do not change with concentration.

Dilution of the solutions with sulphur dioxide was found useful to reduce the viscosity of some solutions at low temperatures but, in general, was not found necessary for the observation of sharp spectra.

The identification of the observed species (1B), indicated by the proton integrals, is also supported by the chemical shifts observed in ^1H and ^{13}C n.m.r. spectra, by comparisons with spectra of structurally related species. The unusual protonation behaviour is linked with the production of an aromatic system, with a cationic charge essentially located on the ring oxygen atom. As a result, a quasi-phenolic hydroxy-group is produced which is susceptible to further protonation in HSO_3F–SbF_5. A parallel for this behaviour is to be found in the protonation of *p*-cresol and of other phenols in superacid media [13,14] (although it is also known that the protonation site in phenols is strongly dependent on temperature and on the precise nature of the acidic medium).[13] The difference in this respect from other ketones is clearly shown by the difference in the ^{13}C chemical shifts of the carbonyl atom between the spectra of (1) taken in chloroform and in HSO_3F–SbF_5 (Figure 2). In acid this resonance shifts 2.1 p.p.m. *upfield*, relative to the position in $CDCl_3$ whereas in other ketones there is a larger *downfield* shift.

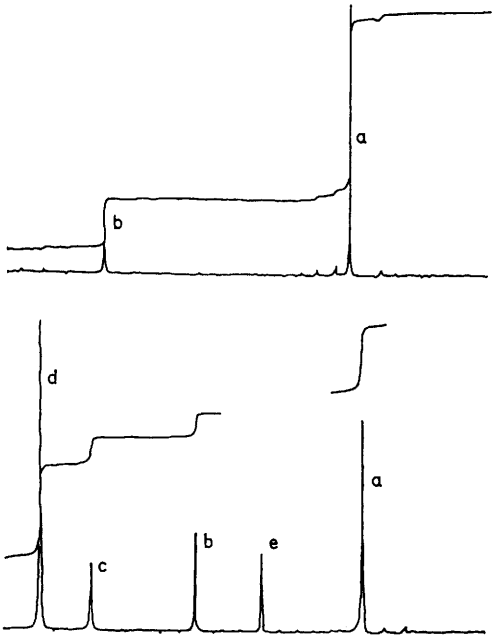


FIGURE 1 ^1H N.m.r. spectra of 2,6-dimethyl-γ-pyrone. Upper spectrum: in $CDCl_3$. Lower spectrum: in HSO_3F–SbF_5. a, CH_3; b, 3-, 5-positions; c, $\overset{+}{O}H_2$; d, solvent acid; e, lock signal

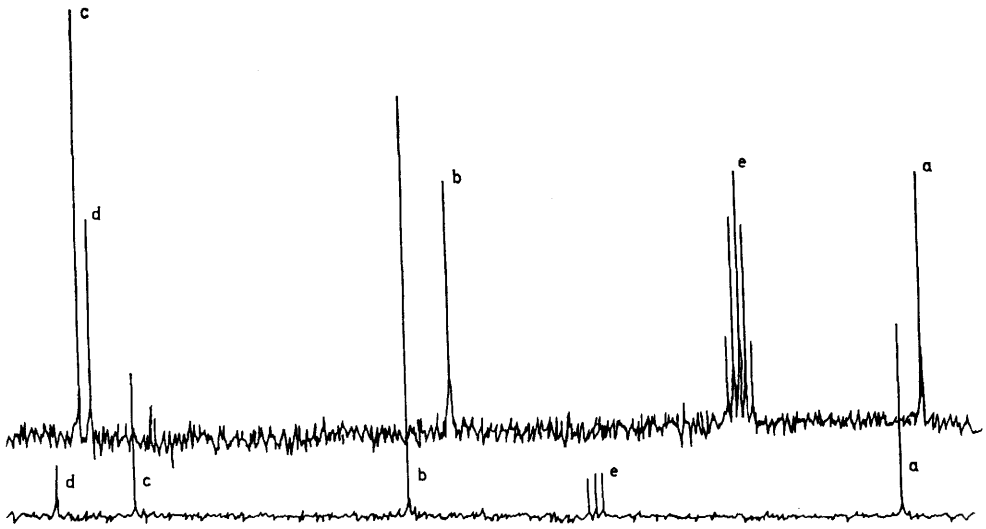
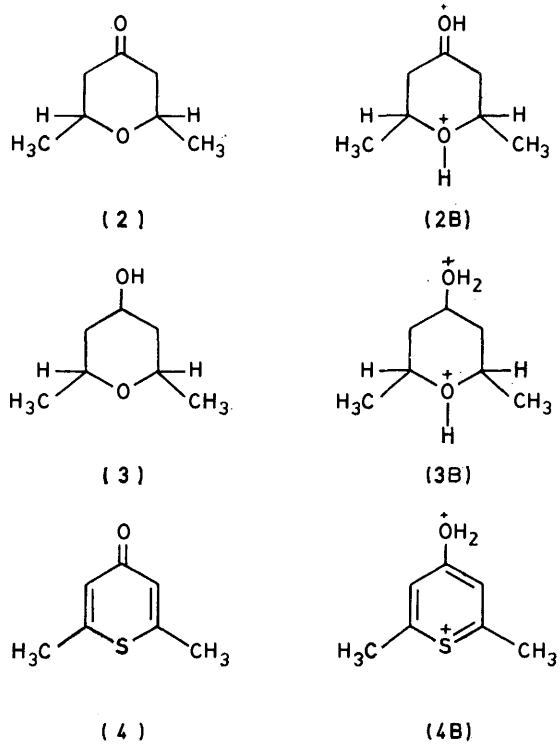


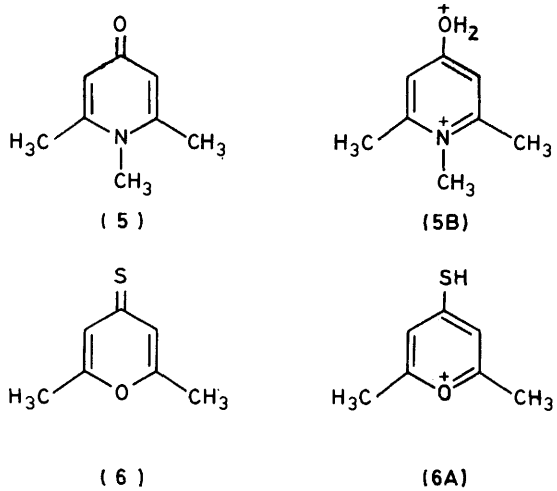
FIGURE 2 ^{13}C N.m.r. spectrum of 2,6-dimethyl-γ-pyrone. Upper spectrum: in HSO_3F–SbF_5. Lower spectrum: in $CDCl_3$. a, CH_3; b, C-3, -5; c, C-2, -6; d, C=O; e, lock signal

For example, 2,6-dimethyltetrahydropyran-4-one (2), the ring-saturated analogue of (1), also undergoes double protonation, forming (2B). Correspondingly, the resonance of the 4-carbon moves downfield by over 30 p.p.m. The ^1H spectrum of the corresponding saturated alcohol (3) also shows it to be protonated on both oxygen atoms [giving (3B)], with a hydroxy-resonance at the expected positions for a protonated alcohol.



The pattern of the effect of protonation on the ^{13}C shifts at the 2-, 3-, and 4-positions of (1) (downfield at the 2-position, upfield at the others) parallels the protonation shifts at these positions in pyridine, which is consistent with the idea that in both cases a positive charge is located on the cyclic heteroatom at position 1. However, the upfield shift in (1) (2 p.p.m.) is much less than that in pyridine (12 p.p.m.), which is expected if the group attached to the 4-position is also protonated [as in (1B)].

The change in the spectra of two hetero-analogues of (1), *viz.* 2,6-dimethyl-4*H*-thiopyran-4-one (4) and 2,6,*N*-trimethyl-4-pyridone (5), on transfer of the compounds to HSO_3F–SbF_5, closely parallels that of (1). The protonation is accordingly inferred to be analogous, leading to species that are diprotonated on exocyclic oxygen [(4B) and (5B)]. 2,6-Dimethyl-4*H*-pyran-4-



thione (6), on the other hand, is only singly protonated at the exocyclic sulphur atom to give (6A). As expected, the basicity of the thiol group is evidently much lower than that of a hydroxy-group, and a second protonation does not, therefore, occur in HSO_3F–SbF_5. Correspondingly, the ^{13}C resonance for position 4 experiences a

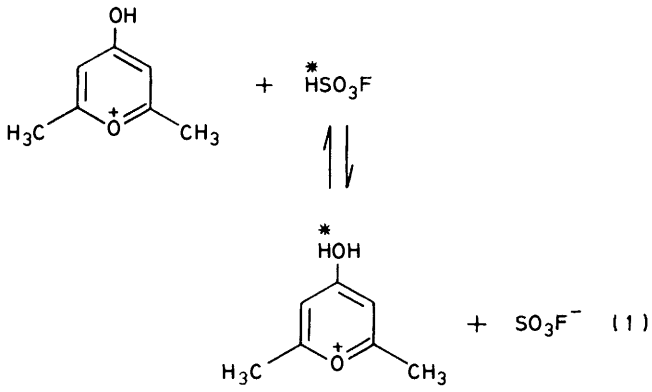
much larger *upfield* shift in the acid than the doubly protonated oxygen analogue (1).

The proton spectra of (1) and (6) in chloroform solution have previously been reported,[15,16] with chemical shifts in fair agreement with our measurements. Brown and Bladon [16] also observed spectra of these compounds in trifluoroacetic acid solutions. The proton chemical shifts at the 3,5-positions and the methyl groups [δ 7.14 and 2.73, respectively, for (1) and δ 7.71 and 2.81, respectively, for (6)] are remarkably similar to the values given for solutions of these compounds in HSO_3F–SbF_5. It would therefore appear that similar protonation occurs in these two acidic solvents despite their great difference in acid strength, *viz.* formation of (1B) and of (6A) in both solvents. Brown and Bladon [16] make no mention of the appearance of a peak ascribable to an oxygen-bound hydrogen in the protonated base in trifluoroacetic acid solution. We infer from this the occurrence of rapid exchange between such protons and the solvent, as in fluorosulphuric acid solution without the addition of antimony pentafluoride.

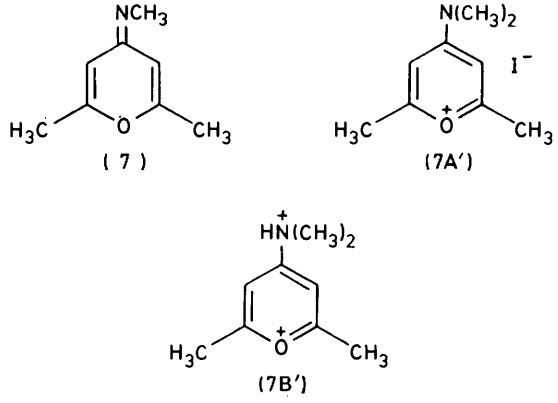
The dimethylpyrylium ion (7A′) may be regarded as a derivative of the iminopyran (7), a nitrogen analogue of (1), with (7A′) being the analogue of (1A). We find that (7A′) is readily protonated to give a di-cation (7B′) analogous to (1B). The proton spectrum of the di-cation (in a solution diluted with sulphur dioxide) shows a doublet (6H) centred at δ *ca.* 2.9 corresponding to the six protons of the dimethylamino-group split by the added proton. We attribute its upfield shift (relative to the position in $CDCl_3$) to the dilution of the sample with sulphur dioxide. [Analogous effects are exhibited by compounds (1) and (3); see Table 1.]

An attempt to extend this type of analogy to the protonation of the corresponding methoxy-compound [2,6-dimethyl-4-methoxypyrylium iodide, (1A′)] proved unsuccessful. The compound readily undergoes demethylation in solution, with formation of (1B) in HSO_3F–SbF_5.

Finally, we return to the question of why a proton resonance signal could not be observed for the $=\overset{+}{O}H$ grouping due to (1A) in fluorosulphuric acid solution, under conditions where other evidence points to complete protonation of the carbonyl group. Under such conditions, diprotonation evidently takes place to a sufficient extent for proton life-times on oxygen to be shortened by the occurrence of exchange according to route (1). The equilibrium constants for the first and second protonation of (1) seem to differ by an unusually small factor, arising from the large separation between the charges in the di-cation. It is thus intelligible why the $=\overset{+}{O}H$ proton in (1A), the conjugate acid of a moderately strong organic base, appears to have a short residence time even when the concentration of (1) in equilibrium with (1A) is minute. On recording the ^{13}C n.m.r. spectrum of a solution containing equimolar proportions of (1) and of HSO_3F (with SbF_5), we obtained only the spectrum of (1B), without any indication of the presence of (1A). We conclude that, under the conditions of our experiment, half the added pyrone (1) is diprotonated, the other



half remaining undissolved. It has not been established whether this is a kinetic effect, due to the large rate of



second protonation relative to the rate of solution, or a thermodynamic effect favouring the right-hand side of equilibrium (2) in HSO_3F–SbF_5.

$$2\ (1A) \rightleftharpoons (1)\ (\text{solid}) + (1B) \qquad (2)$$

EXPERIMENTAL

HSO_3F (Aldrich) acid was twice distilled under nitrogen, and both HSO_3F and SbF_5 (Aldrich) were stored in a dry atmosphere. Throughout this paper the description HSO_3F–SbF_5 refers to an equimolar (1 : 1) mixture.

2,6-Dimethyl-4*H*-pyran-4-one (1) was commercially available (Aldrich). 2,6-Dimethyl-4*H*-thiopyran-4-one (4),[17] 2,6,*N*-trimethyl-4-pyridone (5),[18] 2,6-dimethyltetrahydropyran-4-one (2),[19] 2,6-dimethyltetrahydropyran-4-ol (3),[19] 2,6-dimethyl-4*H*-pyran-4-thione (6),[20] 2,6-dimethyl-4-dimethylaminopyrylium iodide (7A′),[9b,21] and 2,6-dimethyl-4-methoxypyrylium iodide (1A′) [9b] were prepared according to literature methods. In the case of (5) an improved yield was obtained by heating (1) in a sealed tube, with 40% aqueous dimethylamine solution. The preparation of the iodide salt (7A) from the iodide salt (1A′) followed the procedure previously described for the corresponding perchlorates.[9b]

Solutions in HSO_3F–SbF_5 or in HSO_3F were prepared by first cooling the acid to −78°, and then adding to it the calculated amount [usually 1 mol base to 7—10 mol HSO_3F–

SbF_5 (1 : 1)], quickly and under a stream of dry nitrogen. For proton spectra the sample was then quickly transferred to a Wilmad co-axial n.m.r. tube with CD_2Cl_2 (containing some $CDHCl_2$) as 'external standard' and as deuterium lock, in the outer tube. For ^{13}C n.m.r. a Wilmad 5-mm n.m.r. tube was used for the sample, and a 10-mm tube for CD_2Cl_2.

All n.m.r. spectra were recorded on a Bruker HFX90 Fourier-transform instrument.

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