Hydrogen Bonding in 3,4-Disubstituted 5-Hydroxyfuran-2(5*H*)-ones

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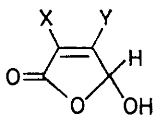
An abnormally strong self-association of 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones in solution has been observed. All measurements reveal that in these compounds dimeric association is dominant. The association constants have been determined over the temperature range 23—55 °C, from which the enthalpies, $-\Delta H^0$, and entropies, $-\Delta S^0$, have been calculated.

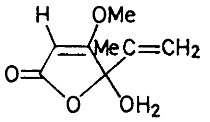
PREVIOUSLY [1] we reported strong self-association of penicillic acid (VI) in solution. Unusually persistent self-association in solution occurring for concentrations >1 mM is already well known for certain classes of compounds such as carboxylic acids, oximes, dimedone derivatives,[2] and cyclohexane-1,3-diols,[3] labdane-8α,15-diol,[4] 5β-B-norcholestan-3α,6α-diol,[5] rosololactone derivatives,[6] steroidal hydroxy-esters,[7] dihydroxy- and trihydroxy-5β-steroids,[8,9] *meta*- and *ortho*-substituted phenols [10-12] and 3-substituted benzo-[*b*]thiophens.[13]

We have sought other compounds which might be expected to behave in a similar way. We have examined five 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones, whose self-association is comparable to that of penicillic acid (VI).[1]



(A)

(I) X = H, Y = Cl
(II) X = Cl, Y = Cl
(III) X = Br, Y = Br
(IV) X = Cl, Y = SEt
(V) X = SEt, Y = SEt



(B)
(VI)

EXPERIMENTAL

Measurements.—I.r. spectra were recorded with a Unicam SP 100 double beam instrument equipped with an SP 130 NaCl prism-grating monochromator. The calibration was checked against the spectrum of water and polystyrene film of 25 μm thickness after each group of measurements. Wavenumbers for the free and bonded OH and CO groups are accurate to ±1 cm^{-1}. The apparent half band-widths, $\Delta\nu_{\frac{1}{2}}$, are quoted to the nearest integer; where necessary they were determined by reflection of the unperturbed side of the unsymmetrical bands. Intensities are given as apparent molar absorptivities, ε, rounded to the nearest integer.

To obtain the thermodynamic quantities, measurements were carried out for 5 mM solutions in carbon tetrachloride at room and several other temperatures up to 55 °C, in 10·0 mm cells. The temperature was measured by a calibrated thermometer inserted in the cell which was heated by water from an ultrathermostat. Variation in the thickness of the cells with temperatures was neglected. The molar absorptivities of the free O–H stretching mode were plotted against concentration at each temperature and extrapolated to obtain the molar absorptivity at infinite dilution.

Association constants, $K = [\text{dimer}]/[\text{monomer}]^2$, were calculated from the equation $K = (1 - a)/ca^2$ where a is the value of the ratio of the apparent molar absorptivity of the free OH band at concentration c relative to its value at infinite dilution. Enthalpies ($-\Delta H^0$) and entropies ($-\Delta S^0$) were calculated from plots of log K against $1/T$. Linear correlation parameters were calculated from statistical relationships [14] by use of a Gier digital computer.

Materials.—AnalaR CCl_4 was used directly. AnalaR $CHCl_3$ was dried several times by passage through a column of silica gel and used directly. The compounds used in the investigation were chromatographically pure and their preparation has been described elsewhere.[15-17]

RESULTS AND DISCUSSION

Results are in Tables 1 and 2. All compounds investigated show the presence of three hydroxy-absorptions for solution in CCl_4. Following the results obtained for penicillic acid (VI) [1] we assign the bands at higher wavenumbers to the free OH stretching absorption. The broad, concentration-dependent band at 3347—3392 cm^{-1} is assigned to a closed ring of hydrogen bonds resulting from dimeric association.[1,8,9,12]

The stretching absorptions of free and bonded OH were shifted downfield on changing from CCl_4 to $CHCl_3$ solution, as expected. Monohydroxy-compounds that

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we have examined show strong self-association involving a carbonyl group. In the carbonyl region, two concentration-dependent bands are observed and this confirms that the C=O group is participating in hydrogen bonding.

The centre of the absorption band of the associated hydroxy-groups in compounds (I) and (IV)—(VI) and free hydroxy-groups in compounds (I) and (VI) shifts slightly to higher wavenumbers as the concentration is decreased (Table 1). A change in the half-width of *ca.* 5 cm^{-1} occurs for all compounds over the range of concentration used, except for compound (V) where it is larger ($\Delta\nu_{\frac{1}{2}}$, 47 ⟶ 24 cm^{-1}).

TABLE 1

Hydroxy and carbonyl stretching absorptions of 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones in carbon tetrachloride solution

			O–H										C=O					
		Cell paths	Free						Bonded			Cell paths	Free			Bonded		
Compound	Conc. (mM)	(mm)	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ε[a]	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ε[a]	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ε[a]	(mm)	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ε[a]	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ε[a]
(I)	5·0	5·276	3603	29	80	3573	33	62	3382	230	50	0·964	1805	12	835	1769	20	35
	2·5	20·0	3605	29	90	3577	32	75	3387	240	35	0·964	1805	11	880	1770		30
	0·5	50·0	3605	31	100	3577	31	80	3392		(10)	5·276	1805	10	910	1772		15
(II)	0·5	50·0	3599	29	115	3570	36	90	3387	150	20	5·276	1821		30	1803	21	560
(III)	0·5	50·0	3599	32	110	3571	26	100	3387	180	20	5·276	1806	12	870			
(IV)	50·0	0·964	3600	32	40	3572	31	50	3387	230	80	0·1	1783		390	1764		350
	10·0	2·736	3600	33	75	3572	38	80	3387	205	40	0·474	1785	17	590			
	5·0	9·66	3600	27	90	3574	23	95	3387	210	25	0·964	1785	16	655			
	0·5	50·0	3602	33	100	3575	26	100	3387		(10)	5·276	1785	15	730			
(V)	50·0	2·736	3585	47	20	3571	35	25	3347	300	50	0·474	1775		200	1747		120
	10·0	5·276	3587	35	30	3571	35	35	3347	310	40	0·964	1777	22	245			
	1·0	50·0	3590	24	40	3572	30	55	3347		(15)	5·276	1777	17	270			
(VI)[b]	8·0	5·0	3589	26	50				3302	226	80	0·5	1777	(23)	250	1746	28	480
	0·8	20·0	3592	25	120				3345		(15)	5·0	1779	20	675	1752		(75)

[a] ν and $\Delta\nu_{\frac{1}{2}}$ are in cm^{-1}, ε is l mol^{-1} cm^{-1}; values in parentheses are approximate: [b] Values for penicillic acid (VI) taken from ref. 1 are included for comparison.

TABLE 2

Stretching absorptions of 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones in chloroform solution

			O-H										C=O						C=C		
		Cell paths	Free						Bonded			Cell paths	Free			Bonded					
Compound	Conc. (M)	(mm)	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ϵ[a]	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ϵ[a]	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ϵ[a]	(mm)	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ϵ[a]	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ϵ[a]	ν	$\Delta\nu_{\frac{1}{2}}$[a]	ϵ[a]
(I)	0·1	0·474	3593	(52)	45	3569	(52)	45	3251	345	105	0·1	1798	19	335	1769	22	570	1624	10	270
	0·05	0·474	3595	(51)	45	3569	(51)	45	3253	330	105	0·1	1797	20	370	1770	21	630	1624	10	280
	0·01	0·964	3595		55	3567		55	3251		110	0·474	1797	19	375	1769	21	630	1624	9	275
(II)	0·1	0·474	3591	(53)	40	3569	(53)	40	3229	350	100	0·1	1816		80	1787	23	690	1614	11	230
	0·05	0·474	3593	(50)	45	3567	(50)	45	3227	355	115	0·1	1816		90	1788	21	745	1640	12	250
	0·02	0·964	3593	(50)	50	3596	(50)	50	3227	357	115	0·474	1816		85	1787	22	730	1641	11	245
(III)	0·1	0·474	3591	(53)	40	3569	(53)	40	3229	350	105	0·1	1798	27	340	1777	21	660	1619	12	200
	0·05	0·474	3591	(51)	45	3567	(51)	45	3230	350	110	0·1	1798	28	350	1777	19	700	1619	12	220
	0·02	0·964	3594	(52)	50	3567	(52)	50	3227	355	115	0·474	1798	30	350	1778	20	700	1620	13	220
(IV)	0·1	0·474	3591	(47)	45	3564	(47)	45	3256	320	95	0·1				1773	24	625	1604	18	145
	0·05	0·474	3591	(46)	50	3566	(46)	50	3256	320	110	0·1				1772	24	650	1604	17	145
	0·01	0·964	3594	(48)	50	3566	(46)	50	3256	325	115	0·474				1773	23	660	1605	19	145
(V)	0·2	0·474				3569	100	30	3270	350	65	0·1				1761	35	460			
	0·05	0·964				3569	100	35	3270	360	60	0·1				1760	36	500			
	0·02	0·964				3569	100	35	3270	360	65	0·474				1762	34	500			
(VI)[b]	0·08	0·51				3574	42	75	3342	260	40	0·11	1768	33	640				1645	13	1080
	0·02	2·0				3574	40	95	3342		20	0·11	1767	27	725				1644	13	1090
	0·01	2·0				3573	41	100	3342		(15)	0·11	1766	25	735				1644	13	1090

[a] See note *a* of Table 1. [b] Data from ref. 1.

In CHCl$_3$ solution where some interaction with the solvent is to be expected, the absorption bands (Table 2) broaden and shift to lower wavenumber and the amount of interbonding is reduced.

The presence of two absorption bands assigned to the stretching of the free OH absorption suggests that two conformers may be in equilibrium. Thus, for CCl$_4$ solution we suggest conformer (A) with the ' free ' hydroxy-group (3605 cm^{-1}) directed towards the π bond of the lactone ring; and conformer (B) with the ' free ' hydroxy-group (3573 cm^{-1}) directed towards the oxygen of the lactone ring.

In CCl$_4$ conformation (B) of compounds (IV) and (V) is more favoured as can be seen by the increased intensity of the band at 3571 cm^{-1}. This may be

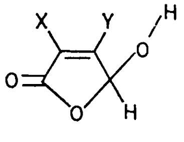
TABLE 3

Thermodynamic quantities for 3,4-disubstituted 5-hydroxyfuran-2(5*H*)-ones calculated from i.r. measurements in carbon tetrachloride

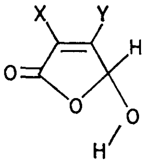
Compound	t/°C	O–H Free ν [a]	ε [a]	ν [a]	ε [a]	O–H Bonded ν [a]	ε [a]	K/l mol^{-1}	$-\Delta H^0$/$-\Delta S^0$ [a]
(I)	29·6	3603	82	3575	66	3383	46	80·6	
	35·8	3605	86	3576	70	3387	37	57·9	
	40·2	3605	90	3577	72	3395	32	47·0	4·37 ±0·15
	45·0	3605	92	3577	74	3397	27	37·0	10·11 ±1·19
	50·0	3605	94	3577	75	3397	23	30·3	
	55·0	3605	94	3577	75	3397	20	26·3	
(IV)	23·0	3599	88	3572	92	3388	31	39·6	
	31·0	3600	92	3572	95	3392	26	31·8	3·82 ±0·27
	35·0	3600	92	3573	94	3398	20	23·2	9·21 ±2·11
	40·2	3601	96	3574	96	3398	17	19·4	
	45·1	3602	98	3574	98	3406	15	16·0	
	50·0	3602	97	3574	97	3406	13	14·2	
(V)	26·6	3591	34	3573	43	3367	30	106·9	
	31·5	3592	36	3573	45	3377	26	82·7	
	35·4	3592	37	3573	47	3377	23	70·4	3·83 ±0·17
	39·7	3592	38	3574	47	3377	20	59·2	8·17 ±1·31
	44·5	3592	40	3575	48	3377	18	48·8	
	49·6	3591	40	3575	49	3377	16	42·9	
(VI)	28·5	3586	59			3307	76	583·7	
	31·5	3587	63			3307	69	463·1	6·52 ±0·39
	35·4	3588	70			3327	59	311·4	15·33 ±3·05
	39·8	3589	76			3327	53	235·0	
	44·5	3589	79			3347	45	193·6	
	49·5	3589	84			3347	40	138·7	

[a] See note *a* in Table 1, $-\Delta H^0$ in kcal mol^{-1}, $-\Delta S^0$ in cal mol^{-1} K^{-1}.

explained by the presence of the bulky SEt group attached to the C=C bond.



(A)



(B)

Support for this assignment is adduced from the presence of only one free OH band in the spectrum of penicillic acid (VI) in which the bulky CH_2=CMe– group is attached to the same carbon atom as the OH group (Tables 1 and 2).

Examination of Dreiding models of the compounds investigated shows that there is no steric hindrance for intermolecular hydrogen bonding of the cyclic ' dimeric ' type. The interacting OH and CO groups in the two conformes of this compound can approach within bonding distance (O · · · O, *ca.* 3 Å). The assumption that dimer formation is dominant seems to be reasonable because at the low concentration used (<10 mM) polymeric association is negligible.

The fact that a plot of log K against $1/T$ gave a straight line supports the occurrence of this equilibrium. Limits of accuracy were found to be *ca.* ±6% for $-\Delta H^0$ and ±20% for $-\Delta S^0$.

For the systems studied the largest K value was observed for compound (V) which might be explained by a steric effect [hydrogen bonding is less influenced by the nature of the solvent in (V) than in compounds (I)—(IV)]. Similar values for the thermodynamic quantities for compounds (I)—(V) suggest that the nature of substituents attached to the C=C bond does not play any significant role.

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