Ionization Constants of Some Hydroxypyrones in Water and in 80% (w/w) Dimethyl Sulphoxide–Water at 25 °C

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The ionization constants of some hydroxypyrones have been measured spectrophotometrically at 25 °C in water and in 80% (w/w) dimethyl sulphoxide–water. A few of them are exceptionally strongly acidic. The pK_a values of these compounds are discussed in relation to their molecular structures. A plot of the pK_a in water against the corresponding pK_a in 80% (w/w) dimethyl sulphoxide–water is linear, although ΔpK_a varies from negative values for the weaker acids to positive values for the stronger acids. Possible solvent effects have been suggested.

Hydroxypyrones in aqueous solutions have significantly higher acidities than those of phenols owing to the positively charged character of the pyrone rings.[1] The formation of resonance-stabilised anions, and an interplay of electron-withdrawing effect of acetyl substituents and intramolecular hydrogen-bonding effect have been invoked to explain the observed pK_a values. To study further the structural effects on acidity, several related hydroxypyrones have been prepared and their ionization constants measured both in water and in 80% (w/w) DMSO-water. The latter solvent system has been chosen as it possesses many desirable properties.[2,3] The ionization constants of those hydroxypyrones previously measured in water have now been determined in 80% (w/w) DMSO-water for inclusion in the discussion.

Results and Discussion

The pK_a values of the compounds studied are summarised in Table 1; detailed results are given in Supplementary Publication No. 23510 (19 pp.).† The acidities of these compounds may be discussed conveniently in three groups. Compounds (1) and (2), which are 3-hydroxy-4-pyrones, are the least acidic. Compounds (3)—(8) are 4-hydroxy-2-pyrones. Although they may also exist, at least theoretically, in the tautomeric 2-hydroxy-4-pyrone forms, i.r. and u.v. spectra (Table 2) show absorptions in regions characteristic of α-pyrones. They are much more acidic than compounds (1) and (2) mainly because of resonance stabilisation of their anions and the absence of this mode of stabilisation for the anions of (1) and (2). Compounds (4)—(8) are acyl derivatives of compound (3). The electron-withdrawing effect of the acyl group at C-5 causes higher acidities of compounds (5)—(7) than compound (3). That compound (4), which is isomeric with compound (5), with the acyl group at C-3, is less acidic than compound (3), has been explained [1] by the acid-weakening effect of the very strong intramolecular hydrogen-bonding which more than counterbalances the acid-strengthening electron-withdrawing effect of the carbonyl group. Hydrogen-bonding effects in compounds (5)—(7) are comparatively weaker, as conjugate chelate rings similar to that in compound (4) are not probable owing to the lower double-bond character of the C(4)–C(5) than the C(3)–C(4) bond in an α-pyrone ring. This difference in hydrogen-bond strength is clearly reflected in the chemical shifts of the OH protons in the respective n.m.r. spectra (Table 2). The replacement of a methyl group by a phenyl group either at C-6 or in the acyl side chain apparently makes relatively small differences in the acidities of compounds (5)—(7). Compound (8), with acetyl groups at both

Table 1. pK_a of hydroxypyrones at 25 °C

Compound	pK_{H_2O} (in water)	pK_{SH} [in 80% (w/w) DMSO–water]	ΔpK_a $pK_{H_2O} - pK_{SH}$
(1)	8.21 [a]	10.94	−2.73
(2)	8.68 [a]	11.56	−2.88
(3)	4.94 [a]	6.83	−1.89
(4)	5.26 [a]	6.19	−0.93
(5)	3.93	5.30	−1.37
(6)	3.83	5.68	−1.85
(7)	4.06	5.11	−1.05
(9)	1.25 [a]	0.13	1.12
	9.21	11.72	−2.51
(10)		4.07	
(11)	1.59	1.43	0.16
(12)	1.61	1.19	0.42
(13)	0.15	−0.5 *	0.7 *

[a] K. P. Ang and S. F. Tan, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1525.

* Approximate value.

Table 2. U.v. absorption maxima and chemical shifts of hydroxy protons of hydroxyprones

	$\lambda_{max.}$/nm			
Compd.	In 80% (w/w) DMSO–water	In water	In $CHCl_3$	δ_{OH} In $CDCl_3$
(1)	268	265	270	* 8.9br
(2)	275	273	276	* 8.3br
(3)	285	282	284	* 11.2br
(4)	310	305	310	16.68
(5)	260	223	268	12.31
	290 (sh)	257 (sh)	295 (sh)	
		285 (sh)		
(6)	258	257	260	10.35
	275 (sh)	280 (sh)	275 (sh)	
(7)	256	232	266	11.65
	310	254 (sh)	315	
		305 (sh)		
(8)	268	230	311	17.9
	305 (sh)	270 (sh)		
(9)	270	271	268	16.4br
	320	314	310	19.1
(10)	345	340	245	
		228		
(11)	278	275	312	~16v br
	347	342		
(12)	275	275	312	~14v br
	350	342		
(13)	281	282	322	16.3
	361	355		(at 0 °C)

* In [$^2H_6$]DMSO.

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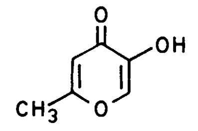
† For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, Index Issue.



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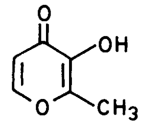

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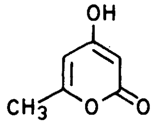

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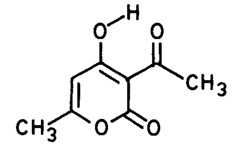

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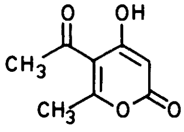

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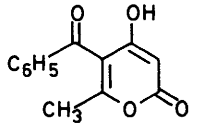

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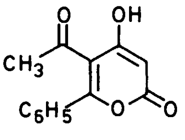

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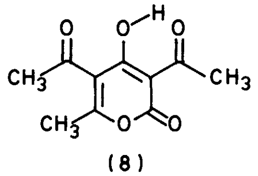

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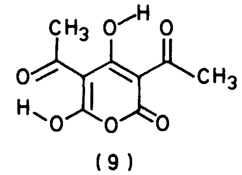

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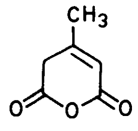

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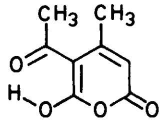

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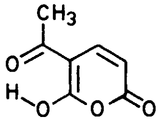

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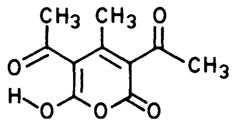
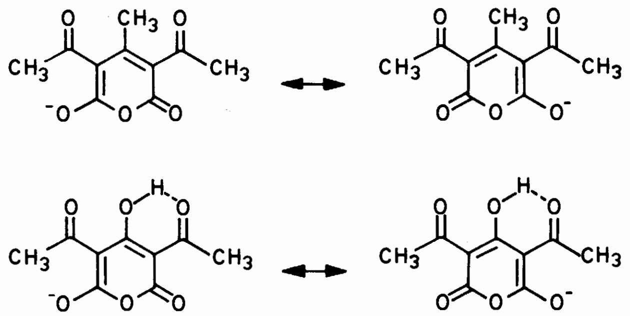


(13)

C-3 and -5, shows a very low field OH in its n.m.r. spectrum. pK_a measurement of this compound by a spectrophotometric method is however complicated by changes which take place in its electronic spectra in solution. Its $\lambda_{max.}$ in non-polar solvents occurs around 311 nm but shifts in more polar solvents to shorter wavelengths and in 80% (w/w) DMSO–water it occurs at 268 nm. Moreover, in the last mentioned solvent, the absorption intensity decreases slowly with time, reaching a steady value after a few hours. Such changes suggest a possible tautomeric change from the predominance of the α-pyrone form in the solid state and in non-polar solvents to the γ-pyrone form in the more polar solvents, although the anion derived from either form should be the same. All the other compounds currently studied do not show changes in their electronic spectra within the time taken for pK_a measurements.

Compounds (9)—(13) are exceptionally strong acids. They differ from the other compounds in being the enolized forms of cyclic anhydrides, that is, 6-hydroxy-2-pyrones. Whereas compounds (9) and (11)—(13) are completely enolised in the solid state as well as in solutions as shown by i.r., u.v., and n.m.r. spectra, compound (10) appears to enolise only in polar solvents. Compound (9) has previously been studied.[1] The high acidities of compounds (10)—(13), which are substituted glutaconic anhydrides, reinforce the previous assignment of the first pK_a of compound (9) to 6-OH rather than to the 4-OH. Consistent with this, compound (10) is isomeric with but more acidic than compound (3), while compound (11) is isomeric with but more acidic than compounds (4) and (5). The anions formed from 6-hydroxy-2-pyrones have greater symmetry and have more extensively delocalised negative charges than the anions from 4-hydroxy-2-pyrones. The pK_a values of compounds (11) and (12) are comparable showing that the methyl substituent at C-4 has little effect on acidity. Compound (13) is the strongest acid among the ones currently studied. U.v. spectra indicate that it is fully ionized in solution; $\lambda_{max.}$ and $\varepsilon_{max.}$ of compound (13) in DMSO–water remaining unchanged upon the addition of alkali. Conductance measurements in 80% (w/w) DMSO–water further support this view. Molar conductance of solutions of compound (13), hydrochloric acid, and picric acid of similar concentration are found to be comparable. At a concentration of 10^{-4}M, Λ_m of compound (13) (33.41 Ω^{-1} cm^2 mol^{-1}) is slightly lower than that of hydrochloric acid (38.75 Ω^{-1} cm^2 mol^{-1}) probably owing to the larger size of its anion, but slightly higher than that of picric acid (26.12 Ω^{-1} cm^2 mol^{-1}). That its pK_a is even lower than pK_1 of compound (9) could possibly be interpreted as due to contribution from two highly symmetrical and equivalent structures to its resonance-stabilised anion. The anion of compound (9) is slightly less symmetrical due to the presence of a strong intramolecularly hydrogen-bonded ring between 4-OH and 3-acetyl group, as confirmed by the n.m.r. spectrum of its mono-sodium salt in [$^2H_6$]DMSO (δ_{OH} 17.32).

ΔpK_a is *ca.* 0.6 between compounds (3) and (4), and 1.5 between (3) and (5) in 80% (w/w) DMSO–water solvent; the difference being due to the introduction of the electron-withdrawing acetyl group. ΔpK_a between compounds (10)



and (11), is, however, much larger, *ca.* 2.6 units. Allowing for the absence of an acetyl group, compound (10) still seems to be less acidic than expected probably owing to incomplete enolization of the 6-carbonyl group, whereas the 5-acetyl group in compound (11) promotes complete enolization. A comparison of u.v. spectra of (10) in $CHCl_3$, ethanol, water, and 80% (w/w) DMSO–water shows that enolization, while absent in chloroform, is not complete in the latter three more polar solvents.

The pK_a values of compounds (1)—(8) measured in 80% (w/w) DMSO–water are higher than those measured in water, the ΔpK_a being larger for the less acidic compounds. Although the effects of solvent changes on acidities especially in mixed solvents could be complex, the above observed trend may be qualitatively expected from the lower dielectric constant and poorer solvating power of DMSO for anions compared to water. However, it is interesting to note that for the strongly acidic compounds (9)—(13), the pK_a values in 80% (w/w) DMSO–water are slightly lower than those obtained in aqueous solution. It is possible that for these compounds differences in solvation effect on the very extensively delocalised anions are less important while the greater basicity of DMSO than water could contribute towards the observed decrease in pK_a in the DMSO–water mixture. A plot of the pK_a values in 80% (w/w) DMSO–water against the corresponding values in water is linear with a slope of 1.4. A similar linear relationship with a slope of 1.48 has been observed for phenols.[4]

Experimental

Materials.—Compound (4) was commercially available. Compounds (12) and (13) were prepared as described below. The rest were synthesized according to literature procedures [5-7] and characterized by i.r. and ^{1}H n.m.r. spectra. All compounds were purified by repeated crystallization. Triply distilled water and spectrophotometric grade dimethyl sulphoxide were used for preparing the solvent mixture. Buffer solutions were prepared from carbonate-free sodium hydroxide solution. Indicators were purified according to the method of Baughman and Kreevoy.[2]

3-*Acetylglutaconic Anhydride* (12).—Glutaconic anhydride (320 mg), fused sodium acetate (350 mg), and freshly distilled acetic anhydride (1 ml) were mixed and left to stand for 10—15 min. The dark red precipitate obtained was filtered and dissolved in the minimum amount of water. The solution was neutralised with concentrated HCl and extracted several times with $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and evaporated to yield a sticky solid which was recrystallized repeatedly from $CHCl_3$–n-hexane to give pale beige needles of 3-*acetylglutaconic anhydride*, m.p. 105 °C (Found: C, 54.35; H, 4.15. $C_7H_6O_4$ requires C, 54.55; H, 3.9%).

3,5-*Diacetyl-4-methylglutaconic Anhydride* (13).—β-Methylglutaconic anhydride (3.2 g) was refluxed with acetic anhydride (8 ml) and fused sodium acetate (3.7 g) for *ca.* 1 h on the water bath. The red solid that formed on cooling was filtered, and dissolved in the minimum amount of water and neutralised with concentrated HCl. The cream solid that separated was filtered and washed with a little water. Recrystallization from $CHCl_3$–n-hexane yielded pale beige needles of 3,5-*diacetyl-4-methylglutaconic anhydride*, m.p. 120 °C (Found: C, 57.0; H, 4.75. $C_{10}H_{10}O_5$ requires C, 57.15; H, 4.75%).

Spectrophotometric Measurements.—Measurements were made with a Perkin-Elmer spectrophotometer 551 on triplicate solutions at 25 °C using matched 1 cm silica cells. The experimental details and methods of calculation of the pK_a values are described in refs. 1 and 8. The stability of all the compounds was checked by recording the u.v. spectra at regular intervals. The pK_a value for compound (13) in 80% (w/w) DMSO–water is approximate since very strong acid solutions were used to determine pK_a. The approximate pK_a value, marked with an asterisk, is included in Table 1 for the purposes of discussion. For compounds (1)—(3), (5), (6), (9) (second pK_a), and (10), the pK_a values in 80% (w/w) DMSO–water were measured using suitable indicators. In other cases, appropriate buffers or HCl solutions were used. Activity coefficients were calculated using the Davies equation.[9] Each pK_a value was corrected for the influence of the ionization of the pyrone or the indicator on the pH of the solution. Compounds (11) and (13) were unstable in very strong acids. Hence D_1 for these compounds was determined by plotting $(D - D_2)/[H^+]$ as a function of D according to equation (1) where D, D_1, and D_2 have the usual meaning.[1]

$$D = D_1 - K(D - D_2)/[H^+] \qquad (1)$$

Conductance Measurements in 80% (w/w) *DMSO–Water*.—Conductances of a number of solutions of hydrochloric acid, compound (13), and picric acid of similar concentrations (in the range 10^{-3}—10^{-4}M) were measured at 25 °C using a Wayne Kerr autobalance universal bridge B642. The solutions were thermostatted at 25 °C for a minimum of 30 min before taking readings.

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