ULTRAVIOLET ABSORPTION OF FLAVONOIDS

III. IONIZATION CONSTANTS OF THE 5-HYDROXY GROUP IN 5,x-DIHYDROXYFLAVONES

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We have shown previously that phenolic hydroxy groups in positions 7 and 4' of the flavone molecule possess fairly strong acid properties [1]. A hydroxy group in position 5 differs substantially in its properties from 7- and 4'-hydroxy groups because in the peri position with respect to it there is a proton-accepting carbonyl group capable of forming an intramolecular hydrogen bond [2]. Consequently, a 5-hydroxy group, unlike other hydroxyls, does not undergo methylation in chromanones and flavanones [3], and 5-hydroxyflavanone does not undergo ring-opening under the action of alkali [4]. The existence of an intramolecular hydrogen bond is confirmed by the fact that the signals of the protons of the 5-hydroxy group in the NMR spectra of a number of flavonoid compounds appear in a very weak field (12.0-13.0 ppm).

By making use of the spectrophotometric method of determining ionization constants, we have found that for the hydroxy group of 5-hydroxyflavone pK = 11.56 ± 0.03 (Table 1), while the pK value of the hydroxyl in 7-hydroxyflavone is 8.12 ± 0.05 and in 4'-hydroxyflavone it is 9.14 ± 0.06 [1]. The substantial difference in the acidities of these groups is a consequence of intramolecular hydrogen bonding.

TABLE 1. Values of the Constants K for a Series of Flavones Calculated by the Numerical Method

Compound	λ, nm	pK_{av}	Mean-square error (S)	No. of degrees of freedom (f)	$pK_{av} \pm \Delta X$	K
5-Hydroxyflavone	240	11,57	0,07	22	11,56±0,03	$2{,}75 \cdot 10^{-12}$
	285	11,55				
	310	11,59				
	335	11,57				
	390	11,55				
4',5-Dihydroxyflavone	270	8,82	0,075	11	8,74±0,05	$1{,}82 \cdot 10^{-9}$
	320	8,74				
	330	8,74				
	385	8,62				
	270	12,71	0,08	10	12,72±0,05	$1{,}9 \cdot 10^{-13}$
	320	12,74				
	330	12,72				
	385	12,67				
3-Hydroxy-5-methoxyflavone	250	10,27	0,08	10	10,20±0,05	$6{,}31 \cdot 10^{-11}$
	360	10,21				
	400	10,19				
	405	10,14				
5-Hydroxy-7-methoxyflavanone	245	10,95	0,09	11	10,94±0,06	$1{,}15 \cdot 10^{-11}$
	300	10,87				
	360	10,99				

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TABLE 2. Values of D and of the pH Used for the Calculation of K_1 and K_2 of 3,5-Dihydroxyflavone

λ, nm	D in experiment							
	1	2	3	4	5	6	7	8
365	0,350	0,320	—	0,209	0,186	0,163	—	0,131
410	0,032	0,070	0,224	0,225	0,310	—	0,351	0,385
420	0,020	0,058	0,221	—	0,313	—	0,358	0,390
pH	8,12	8,24	8,64	8,68	9,40	9,62	9,68	9,90

It appeared of interest to study the influence on the state of acidity of a 5-OH group of nucleophilic substituents (in our case, OH groups) introduced into the 5-hydroxyflavone molecule in positions which, as the result of the transfer of conjugation, act directly on the carbonyl group and, consequently, on the intramolecular hydrogen bonding with the 5-OH group. Such points in the molecule are, above all, positions 4', 3, and 7.

The ionization constants have been obtained for 4',5-dihydroxyflavone (see Table 1). The higher of them depends on the ionization of the 4'-hydroxy group, since its magnitude is comparable with the ionization constant of this group in 4'-hydroxyflavone [1]. A fall in the acidity of the 5-hydroxy group in the 4',5'-disubstituted molecule as compared with 5-hydroxyflavone may be connected with the increase in the nucleophilicity of the oxygen atom of the carbonyl group and to the strengthening of the hydrogen bond as a consequence of an increase in the nucleophilicity of the lateral phenyl ring.

In 3,5-dihydroxyflavone, less difference is observed in the acidities of the two groups than in 4',5-dihydroxyflavone, and in this case the question of the sequence of ionization requires special consideration. On the basis of the fact that the hydroxy group in 3-hydroxyflavone is more acidic (pK 9.6 ± 0.1) [1] than in 5-hydroxyflavone (pK 11.56 ± 0.03) (see Table 1), it may be assumed that the same sequence of acidities is retained in 3,5-dihydroxyflavone. A 3-hydroxy group in a flavone also forms an intramolecular hydrogen bond with the carbonyl group, but this bond is considerably weaker than that of a 5-hydroxy group. What has been said is confirmed by the fact that in the NMR spectrum of 5-hydroxy-substituted flavonoids the signal of the proton of the 5-OH group is found in a weaker field than the signal of the proton of the hydroxyl in 3-hydroxyflavone (9.55 ppm). The simultaneous participation of the carbonyl group in intramolecular hydrogen bonding with the 5- and 3-hydroxy groups leads to the situation that the capacity for ionization of both groups becomes greater than in the case of the corresponding monohydroxy-substituted flavones. Also in agreement with this is the fact that in 3-hydroxy-5-methoxyflavone the ionization constant of the 3-OH group is somewhat lower than in 3-hydroxyflavone.

The introduction of a nucleophilic methoxy group ($\sigma_{p\text{-}OCH_3} = -0.27$ [5]) into position 7 of 5-hydroxyflavone [6] scarcely changes the acidity of the 5-OH group as compared with 5-hydroxyflavone. However, the replacement of the methoxy group by a hydroxy group which is easily ionized in position 7 ($\sigma_{p\text{-}O^-} = -0.52$ [5]) leads to a considerable increase in the acidity of the 5-OH group (pK 9.2 ± 0.3) in 5,7-dihydroxyflavone [6]. The 7-OH group in 5,7-dihydroxyflavone becomes more acidic than in 7-hydroxyflavone (pK 7.3 ± 0.3 and 8.12 ± 0.05, respectively) [1, 6].

Consequently, under the influence of the introduction of further hydroxy groups in position 4', 3, or 7 of the 5-hydroxyflavone molecule the acid properties of the 5-hydroxy group change significantly (pK range 12.72 ± 0.5 to 9.2 ± 0.3).

We have measured the ionization constant of the 5-hydroxy group in a hydrogenation analog of tectochrysin – pinostrobin. While in 5-hydroxy-7-methoxyflavone (tectochrysin), the pK value of the hydroxy group is 11.63 ± 0.08 [6], in the corresponding flavanone the acidity of the 5-OH group has risen somewhat (pK 10.97 ± 0.09) (see Table 1). This is probably explained by some weakening of the intramolecular hydrogen bonding in the flavanone molecule, which is also reflected in the NMR spectra. Thus, the signal of the proton of the 5-OH group of tectochrysin appears at 12.8 ppm, while in pinostrobin it is at 12.1 ppm.

EXPERIMENTAL

The NMR-spectroscopic figures used in the paper were given to us by V. I. Lutskii. The NMR spectra were taken on a Varian A-60 instrument in dimethyl sulfoxide (with hexamethyldisiloxane as internal standard). The analyses of all the compounds corresponded to the calculated figures.

5-Hydroxyflavone, mp 157°C (from petroleum ether). Literature data: 155-156°C [7]. It was obtained from 2,6-dihydroxyacetophenone and benzoic anhydride by the method of Allan and Robinson [8].

3-Hydroxy-5-methoxyflavone, mp 170-172°C (from ethyl acetate). Literature data: 170-171°C [10].

3,5-Dihydroxyflavone, mp 144-146°C (from ethanol). Literature data: 144°C [9]. It was synthesized from 2-hydroxy-6-methoxyacetophenone and benzaldehyde by Seshadri's method as modified by Looker [9].

TABLE 3. Values of K_1 and K_2 Calculated for 3,5-Dihydroxyflavone by Means of the Komar' Equation and from the Figures in Table 2.

Experiment	λ, nm	Constant	Experiment	λ, nm	Constant
		$K_1 \cdot 10^{-9}$			$K_2 \cdot 10^{-10}$
1, 2, 4	365	4,22	5, 6, 8	365	1,86
1, 2, 3	410	2,28	5, 7, 8	410	1,80
		1,69	5, 7, 8	420	1,44
1, 2, 4	420	1,34			
1, 2, 3		1,82			

$K_1=2,29 \cdot 10^{-9}$
$pK_1=8,7 \pm 0,2$
for $P=0,95$
$f=4$ $s=0,19$

$K_2=1,7 \cdot 10^{-10}$
$pK_2=9,8 \pm 0,15$
for $P=0,95$
$f=2$ $s=0,12$

4',5-Dihydroxyflavone,* mp 246-248°C (from ethyl acetate). Literature data: 237-240°C [11]. Obtained by a modified Baker–Venkataraman method [12] from 2,6-dihydroxyacetophenone and anisoyl chloride.

5-Hydroxy-7-methoxyflavanone (pinostrobin) was isolated by V. I. Lutskii by column chromatography on polyamide from an acetone extract of the wood of the Siberian pine [13].

The ionization constants were determined by the method described previously [6] at 21 ± 1°C. The concentrations of the substances studied and their ionic strengths corresponded to the figures given in our previous paper [1].

The ionization constants of 5-hydroxy- and 4',5-dihydroxyflavones and 5-hydroxy-7-methoxyflavanone were calculated numerically by the method given by Albert and Serjeant [14] (see Table 1), and that for 3,5-dihydroxyflavone was calculated by the Komar' method [15] (Tables 2 and 3). For each compound the mean-square error and the confidence range of the mean value for 95% probability were calculated from the values of the ionization constants obtained [16].

SUMMARY

The ionization constants of the hydroxy groups in 5-hydroxy-, 3,5- and 4',5-dihydroxy- and 3-hydroxy-5-methoxyflavones and in 5-hydroxy-7-methoxyflavanone have been determined. It has been shown that because of intramolecular hydrogen bonding the 5-hydroxy group has a reduced acidity. However, the capacity for ionization of the 5-hydroxy group changes under the influence of hydroxy groups introduced into the 3, 4', or 7 positions, and also on passing to the flavanone series.

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*The synthesis was performed by N. G. Devyatko.