STABILITY OF METAL-CHELATE COMPOUNDS OF BENZOPYRONE DERIVATIVES

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THE benzo-γ-pyrone derivatives—chromones, flavones, isoflavones and xanthones—constitute a group of closely related compounds that occur extensively in nature. In each of these sub-groups, chemical evidence based on low acid-dissociation and difficulty of methylation of the hydroxyl group and ferric chloride reaction, indicates the existence of hydrogen bonds between the carbonyl group and the hydroxyl group in the 5- and 3-positions of the chromone ring. Following the procedure suggested by Bate-Smith and Westall,[1] Simpson and Garden[2] have found by chromatography that chelation with the 5-hydroxyl group is much stronger than that with the 3-hydroxyl group. But no quantitative information is available regarding the variations in the stabilities of this bond depending on structural features of the different groups of compounds.

No systematic work seems to have been done for the utilisation of benzopyrone derivatives in analytical chemistry. The formation of an ether-soluble highly fluorescent complex with boric acid and citric acid has been considered specific for flavonols[3] and the formation of zirconium complexes with flavones and flavonols has been recorded by Horhammer[4, 5] and the reactions of flavonoids with copper, cadmium and titanium[6] and heavy metals[7] have also been described. However, only two compounds have so far been put to actual analytical use. Morin has been employed for the detection of aluminium,[8] tin,[9] titanium and zirconium[10] and for the determination of tin,[11] thorium[12] and uranium.[13] Quercetin has been used for the detection of iron and uranium[14] and for the determination of germanium[15] and zirconium.[16]

As a preliminary to a systematic study of the analytical uses of benzopyrone derivatives, a comparison of the stability of metal chelates formed by typical members has been undertaken. To avoid complications, only monohydroxy compounds have been chosen and the free hydroxyl group is left in the 5- or the 3-position of flavones and chromones, 5-position of isoflavones and diphenyl chromones and 1-position of xanthones. In certain cases methoxyl groups are introduced in the 7-position (3-position in xanthone) since this position is invariably substituted in natural flavonoids and such substituted compounds are also easier to prepare; it may be significant to note that the 5-hydroxyl group which is the most active in chelation is most difficult to methylate and 5-hydroxy-7-methoxy compounds of flavonoids are readily made by partial methylation of 5: 7-dihydroxy derivatives. The list of compounds examined is given in Table I arranged according to the strength of the metal chelate bond.

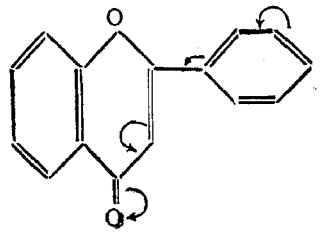
For the determination of the degree of formation of the complex (n) the method of Calvin and Wilson[17] has been adopted. Copper ions have been used as the standard and the formation constants of this metal ion with each of the benzopyrone derivatives as ligand have been determined in aqueous dioxan medium (2 vol. water: 1 vol. dioxan) potentiometrically. These authors have shown that this titration can be done without entailing serious error using a glass electrode over the whole pH range. In view of the limited objective of our experiments minor interferences have not been taken into account. M/100 Solutions of the ligands in dioxan have been titrated in the presence of excess of aqueous perchloric acid with normal alkali solution both in the presence and absence of cupric ions. Since preliminary experiments showed that there was no chelation in the presence of sulphate ions (see also Burkin[17a]), copper nitrate solution has been employed. For the determination of stability constants the method of Irving and Rossotti[18] has been employed. Since the values of $\bar{n}$, the degree of formation, are considerably below 1·5 in each case, only the value of K_1 could be determined. It would appear, therefore, that the higher complex CuL_2 has little stability. The values of log K_1 are given in Table I.

TABLE I

		log K_1	pK_a
1.	1-Hydroxy-3-methoxy xanthone	4·80	10·72
2.	1-Hydroxy xanthone	4·70	10·72
3.	5-Hydroxy-7-methoxy flavone	3·45	8·10
4.	5-Hydroxy flavone	3·40	8·10
5.	3-Hydroxy-7-methoxy flavone	3·01	7·90
6.	3-Hydroxy flavone	3·00	7·90
7.	2-Methyl-5-hydroxy-7-methoxy chromone	2·57	7·85
8.	2-Methyl-5-hydroxy chromone	2·50	7·90
9.	2-Methyl-3-hydroxy-7-methoxy chromone	2·30	7·86
10.	2: 3-Diphenyl-5-hydroxy-7-methoxy chromone	2·10	8·05
11.	5-Hydroxy-7-methoxy isoflavone	2·00	8·10

The results show that the metal-chelate ring in xanthone is the strongest. Next in order of stability are the 5-hydroxy flavones followed by 3-hydroxy flavones. In metal-chelation, isoflavones are weaker than even the chromones and 2:3-diphenyl chromones come in between them. Obviously, the position of the phenyl group plays an important part. The 2-position is highly favourable (*cf.* flavones and chromones). It should also be pointed out that the presence of a methoxyl group in the 3-position in xanthones or the 7-position in chromones, flavones and isoflavones exerts a favourable influence, though not very marked.

The observations seem to be in agreement with expectations based on the structure of chelate bonds and the influence of substituents on them. The two participants in the chelate bond are (*a*) the carbonyl donor group, C = O and (*b*) the hydrogen atom of the hydroxyl group (or the metal ion). The electron-availability at the donor oxygen atom is increased by a phenyl group present in conjugation with the carbonyl group in flavones (I) and the bond formed is thus much stronger than it is in chromones. In a similar manner, the fused benzene ring in xanthone also augments electron-availability at the carbonyl group (II).



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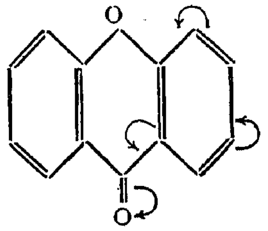
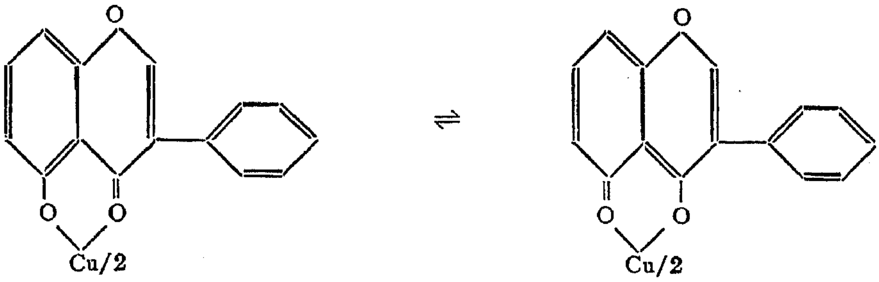


II

The difference in the stability of the five-membered and six-membered chelate rings is evident from the stability constants of 5-hydroxy- and 3-hydroxy-flavones and chromones.

The abnormally low values of K_1 obtained for isoflavone complexes require explanation. In isoflavones, the phenyl group is not in conjugation with the carbonyl group and hence electron-availability should be the same as for the corresponding chromone. However, as was pointed out by Calvin and Wilson,[17] the stability of metal-chelate bond is governed by two factors: (1) electron-availability and (ii) resonance of the type indicated by formulæ (III) and (IV). The presence of phenyl group in the 3-position hinders the resonance. As a matter of fact, in molecular models it could be seen that the 3-phenyl group makes it difficult to produce planar copper complex (IV). It may be pointed out, however, that this weakening of the chelate ring in isoflavones is operative only in metal-chelate formation and not in hydrogen bond formation. This can readily be seen from the pK_a values of 2-methyl-5-hydroxy-7-methoxy chromone and 5-hydroxy-7-methoxy isoflavone, being 7·85 and 8·1 respectively.



III IV

From the above reasoning it will be clear that in 2: 3-diphenyl chromones two opposing factors play their part. As a consequence these compounds have a slightly higher log K_1 value than the simpler isoflavones.

The effect of methoxyl substituent in the 3-position in xanthones and in the 7-position of chromones becomes explicable since it will increase electron-availability at the carbonyl group by electromeric effect and thus facilitate chelation.

Preparation of the reagents:

2-*Methyl*-5-*hydroxy chromone* and 5-*hydroxy flavone* have been prepared from γ-resacetophenone by heating with sodium acetate and acetic anhydride in the case of the former[19] and sodium benzoate and benzoic anhydride in the case of the latter.[20] Employing phloracetophenone in a similar manner and effecting partial methylation, 2-*methyl*-5-*hydroxy*-7-*methoxy chromone*[21] and 5-*hydroxy*-7-*methoxyflavone* have been obtained.[22] Allan-Robinson condensation of 2: 4: 6-trihydroxy-phenyl-benzyl ketone with sodium benzoate and benzoic anhydride yielded 2: 3-diphenyl-5: 7-dihydroxy-chromone.[23] It is more convenient to use for this preparation Baker-Venkataraman reaction recently reported by Gupta and Seshadri.[24] Subsequent partial methylation with dimethyl sulphate (1·1 mole) and dry potassium carbonate in dry acetone solution yielded the 7-methyl ether.

5-*Hydroxy*-7-*methoxyisoflavone* has been made by the ethyl formate method using 2-hydroxy-4: 6-dimethoxy-phenyl-benzyl ketone and subsequent partial demethylation of the dimethyl ether with hydriodic acid using mild conditions.[25]

The most convenient procedure for preparing 3-*hydroxy*-7-*methoxy flavone* is the partial demethylation of 3: 7-dimethoxy flavone using aluminium chloride and nitrobenzene.[26] A similar method has been used for the preparation of 2-methyl-3-hydroxy-7-methoxy chromone. The substance crystallised from methanol as colourless rectangular prisms, m.p. 220–21° (decomp.) (Found: C, 64·4, H, 4·4; $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%).

For the preparation of 3-*hydroxy flavone* the method of nuclear reduction has been employed. For this purpose, 3-methoxy-7-hydroxy flavone[27] was tosylated and subjected to reduction in the presence of Raney nickel.[28] The product was 3-methoxy flavone, which was then demethylated with hydriodic acid.[28]

1-*Hydroxy xanthone and* 1-*hydroxy*-3-*methoxy xanthone* have been prepared by condensation of salicylic acid with resorcinol[29] and phloroglucinol dimethyl ether[30] respectively in the presence of fused zinc chloride.

SUMMARY

A comparative study of hydroxy-benzopyrone derivatives has been made with reference to their capacity to form chelate combinations with metals. Based on the determination of stability constants it could be concluded that 1-hydroxy xanthone forms the most stable complex. Addition of a methoxyl group in the 3-position has a favourable influence. Among the flavones a hydroxyl group in the 5-position forms definitely a stronger complex as compared with the 3-hydroxyl group. Here also addition of a methoxyl group in the 7-position is an advantage. Similar results are obtained with the chromones though their complexes are comparatively weaker. Isoflavone derivatives unexpectedly form the weakest complexes and in this case steric factors seem to be involved. The presence of this factor could be noticed in the case of 2: 3-diphenyl chromones also which also have abnormally weak complexes.

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