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Intra- and intermolecular hydrogen bonding in 3-hydroxy- and 5-hydroxychromone

Nursen Binbuga [a], Tor P. Schultz [b], William P. Henry [a,*]

[a] Department of Chemistry, Mississippi State University, Box 9573, Mississippi State, MS 39762, United States
[b] Forest Products Laboratory, FWRC, Mississippi State University, Mississippi State, MS 39762, United States

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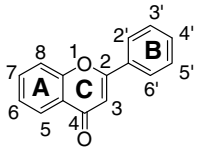
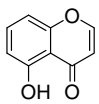
ABSTRACT

The crystal structures for 3-hydroxychromone and 5-hydroxychromone have been obtained. Both molecules exhibit intramolecular hydrogen bonding between the hydroxy group and the ketone oxygen atom. However, only the 3-hydroxy derivative contains hydrogen bonds between molecules. By comparing the current results with those obtained for the corresponding flavone derivatives, the effect of the B phenyl group on hydrogen bonding is inferred.

Flavones (**1**), specifically the hydroxy-substituted derivatives, are naturally occurring compounds that show extensive health benefits.[1] Numerous studies attempting to relate reactivity with this pharmacology have been reported.[2–11] Some of these compounds are also present in the heartwood of a tree resistant to fungal decay.[12] The mechanism by which these compounds prevent fungal decay from occurring has been the subject of investigations in these laboratories.[13,14] To determine the importance of the B phenyl ring, 5-hydroxychromone (**2a**) and 3-hydroxychromone (**3**) were synthesized, and their reactivities of possible importance in wood protection were compared with the related hydroxyflavone compounds **4a** and **5a**, respectively.[15,16]

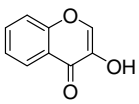


1



2

a, unsubstituted
b, 7-OH, 6,8-Me



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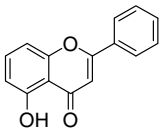
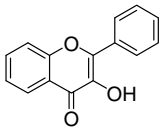


4

a, unsubstituted
b, 4'-Br
c, 4',6,7-OMe
d, 7-OMe
e, 4',7-OMe
f, 2',7,8-OMe



5

a, unsubstituted
b, 2'-Me
c, 3'-Me
d, 7-OMe
e, 6-OMe
f, 2',4'-OMe
g, 3'-OMe

Some surprising results were obtained when the binding of the hydroxychromones and -flavones with Al^{3+} in methanol was investigated (Eq. 1).[15] The 5-hydroxy derivatives have essentially the same chelation properties with the aluminum ion. However, 3-hydroxychromone has markedly lower binding affinity toward this metal ion than flavonol. The significant difference between the 3-hydroxy and 5-hydroxy pairs was unexpected based on the cinnamoyl resonance form invoked to stabilize the binding of the hydroxyflavones with Al^{3+}.[17]

$$xHL + Al^{3+} \rightleftharpoons [Al(L)_x]^{(3-x)+} + xH^+ \qquad HL = \mathbf{5a};\quad x = 2 \qquad HL = \mathbf{4a}, \mathbf{2a}, \mathbf{3};\quad x = 1 \tag{1}$$

In light of these results, it was of interest to know whether there is a significant difference in the hydrogen bonding characteristics between the hydroxychromone and -flavone derivatives in the solid state. Particularly intriguing are the hydrogen bonding parameters in the 3-hydroxychromone because of the interesting observations of Etter.[18] She noted that the hydrogen bonding distances varied as the angle of the B phenyl ring to the C heterocyclic

* Corresponding author. Tel.: +1 662 325 7606; fax: +1 662 325 1684.
E-mail address: wph1@ra.msstate.edu (W. P. Henry).

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ring in a series of flavonols. As the B ring rotated out of conjugation with the C ring, the parameters indicated that the hydrogen bond strength decreased.

Compounds **2a** and **3** were synthesized according to literature procedures.[19–21] Crystals of **3** suitable for diffraction studies were obtained by crystallization from a methanol solution. Crystals of **2b** were obtained from the reaction mixture after the unsuccessful methylation of the hydroxy group in acetone. The crystal structures were obtained at room temperature on a Bruker SMART 1000 diffractometer using the SHELX package for structure refinement.[22,23] Figure 1a shows the thermal ellipsoid diagram for individual molecules of **2a** while that for **3** is given in Figure 2a. Packing diagrams are shown in Figures 1b and 2b, respectively.

The hydroxy group in 5-hydroxychromone forms the expected intramolecular hydrogen bond with the 4-keto oxygen atom. The hydrogen atom of this interaction is coplanar with the rest of the molecule. In this crystal, there is only the intramolecular O–H···O hydrogen bond. The shortest intermolecular distance in the structure is between an adjacent 4-keto oxygen atom and the hydrogen atom (position not refined) at C3 [C–H: 0.93 Å; H···O4{symmetry: $-x+1$, $-y+1$, $z+0.5$}: 2.65 Å; C···O: 3.547(4) Å; <CHO: 163°]. A comparison of the intramolecular hydrogen bond parameters in **2a** and **2b**[26] with those for selected 5-hydroxyflavones[27–32] is given in Table 1. Perusal of this table suggests that the removal of the B phenyl ring from the flavone derivatives has very little effect on the hydrogen bonding characteristics. This is consistent with the similar binding affinities of the 5-hydroxy compounds with Al^{3+}.[15]

However, in the case of the 3-hydroxy derivatives, there is a significant difference in the hydrogen bonding characteristics between the flavone and chromone compounds. Table 2 summarizes the hydrogen bonding parameters for **3** and **5a**[18] and some other 3-hydroxyflavone derivatives.[18,33–36] Notice that for the intramolecular hydrogen bond, the carbonyl oxygen atom to the hydroxy hydrogen atom distance is significantly longer for **3** than **5a** indicative of a weaker interaction. In fact, the chromone derivative has a weaker hydrogen bond than any of the flavones (**5a**–**c**) considered in Etter's paper.[18]

Unlike the 5-hydroxychromone, intermolecular O–H···O hydrogen bonds occur in the solid state for **3**. The molecules form stacks with the molecules alternating such that the benzene ring of one chromone is above the pyrone ring of the next chromone (Fig. 2b). A 3-hydroxychromone molecule then forms a hydrogen-bonded dimer with another molecule in an adjacent stack (**A**). The dimeric hydrogen bonding motif also occurs for most of the 3-hydroxyflavones considered here (**5b**, **5c**, **5e**, **5f**, and **5g**). However, 3-hydroxyflavones can also adopt a hydrogen bonding geometry where the OH serves as a hydrogen bond donor to one molecule, while a different molecule serves as the donor for the keto oxygen atom acceptor. Thus, hydrogen-bonded polymeric structures are formed (**B**). **5a** and **5d** adopt this motif which may be the reason for the longer O–H distance in these molecules. Either motif involves bifurcated hydrogen bonding. The intermolecular O–H···O hydrogen bond parameters are compiled in Table 3. Again, this intermolecular hydrogen bonding interaction is generally weaker in **3** than in the corresponding flavonols.

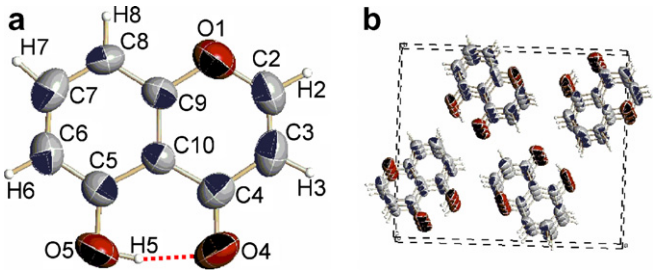


Figure 1. (a) Thermal ellipsoid diagram for **2a**. (b) Packing diagram for **2a**.

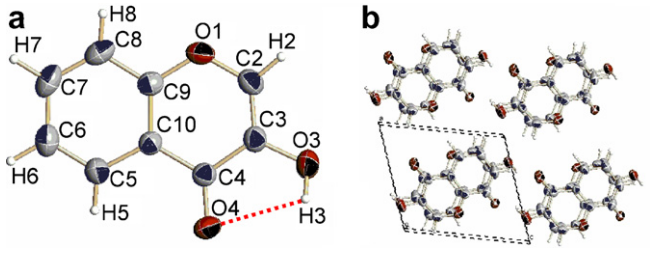


Figure 2. (a) Thermal ellipsoid diagram for **3**. (b) Packing diagram for **3**.

Table 1
Intramolecular hydrogen bond parameters for **2a**, **2b** and selected 5-hydroxyflavones

Compound	O5-H (Å)	H···O4 (Å)	O5···O4 (Å)	<O5HO4 (°)	Ref.
2a	0.91 (5)	1.70 (5)	2.579 (4)	162 (4)	This work
4a	1.02[a]	1.68	2.596[a]	148[a]	27
4b	1.06	1.54	2.574[a]	163	28
4c	0.82[b]	1.84[b]	2.574	148[b]	30
4d	0.80[a]	1.90[a]	2.586[a]	142[a]	31
4e	0.82[b]	1.83[b]	2.571	149[b]	29
4f	0.95	1.69	2.586	156	32
2b	0.84[a,b]	1.83[a,b]	2.587[a]	149[a,b]	26

[a] Obtained from structure deposited in Cambridge Structural Database[24] using Mercury.[25]
[b] Hydrogen atom positions not refined.

Table 2
Intramolecular hydrogen bond parameters for **3** and selected 3-hydroxyflavones

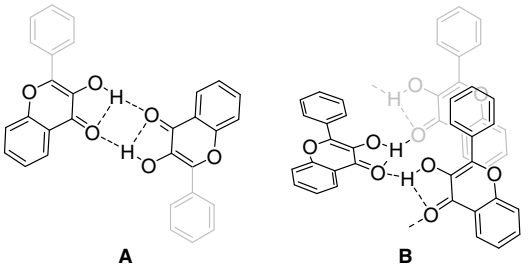
Compound	B–C Torsion (°)	O3-H (Å)	H···O4 (Å)	O3···O4 (Å)	<C4O4H (°)	<O3HO4 (°)	<HO3C3 (°)	Ref.
3		0.86 (2)	2.43 (2)	2.768 (1)	76.7 (5)	104 (2)	111 (1)	This work
5g	72.2[a]	0.68[b]	2.45	2.764[b]	74.3[b]	111[b]	114[b]	34
5f	67.0[c]	0.80[b]	2.31	2.748[b]	76.2[b]	115[b]	107[b]	35
5b	60.5[d]	0.89	2.39	2.765	78.8	106	114	18
5c	23.1[d]	0.86	2.30	2.72	79.1	111	112	18
5e	11.3[e]	0.87[b]	2.25	2.700[b]	79.8[b]	112[b]	111[b]	36
5a	5.5[d]	0.96	2.20	2.677	82.5	110	109	18
5d	1.2[e]	1.01[b]	2.48	2.681[b]	82.9[b]	89.7[b]	121[b]	33

[a] C3–C2–C1′–C2′ torsion angle.
[b] Obtained from structure deposited in Cambridge Structural Database[24] using Mercury.[25]
[c] 180° - C3–C2–C1′–C2′ torsion angle.
[d] Dihedral angle between least squares planes for B phenyl ring and AC rings.
[e] C6′–C1′–C2–C3 torsion angle.

Table 3
Intermolecular O–H···O hydrogen bond parameters for **3** and selected 3-hydroxy flavones

Compound	O3–H (Å)	H···O4 (Å)	O3···O4 (Å)	<O3HO4 (°)	Ref.
3	0.86 (2)	1.94 (2)	2.739 (1)	154 (2)	This work
5g	0.68[a]	2.09	2.723[a]	156[a]	34
5f	0.80[a]	2.05	2.784[a]	151[a]	35
5b	0.89	1.86[a]	2.688[a]	155[a]	18
5c	0.86	1.92	2.713	154	18
5e	0.87[a]	1.96	2.732[a]	147[a]	36
5a	0.96	1.88	2.734	146	18
5d	1.01[a]	1.87	2.739[a]	143[a]	33

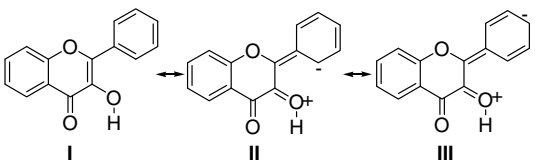
[a] obtained from structure deposited in Cambridge Structural Database[24] using Mercury.[25]



Therefore, the hydrogen bonding in **3** follows the trend identified by Etter, where the removal of the B phenyl ring is an extreme case of complete deconjugation of the ring.[18] In addition, the relative bonding of **3** and **5a** with Al^{3+} in methanol[15] is reflected in the relative strength of the hydrogen bonding in these compounds. However, very little difference in either hydrogen bonding strength or aluminum ion binding ability exists between **2a** and **4a**.

In addition to intermolecular O–H···O hydrogen bonding, there are also intermolecular C–H···O interactions in the solid state for **3**. The hydrogen atoms at carbons 2, 5, and 6 interact with oxygen atoms on adjacent chromone molecules. The interactions are C2–H2···O4 [C–H: 0.93(2) Å; H···O4{symmetry: $x+1$, y, z}: 2.56(2) Å; C···O: 3.423(2) Å; <CHO: 155(2)°], C5–H5···O1 [C–H: 0.92(2) Å; H···O1{symmetry: $x-1$, y, z}: 2.61(2) Å; C···O: 3.504(2) Å; <CHO: 164(1)°], and C6–H6···O3 [C–H: 0.98(2) Å; H···O3{symmetry: $x-1$, y, $z-1$}: 2.54(2) Å; C···O: 3.465(2) Å; <CHO: 158(2)°]. Interactions of this nature are common in the crystal structures of flavones.[18,29]

Attempts to explain the hydrogen bonding and metal binding observations using a simplistic approach are difficult. The hydrogen bonding behavior suggests that with full conjugation of the B phenyl ring, the 4-carbonyl group is a better hydrogen bond acceptor, the 3-hydroxy group is a better hydrogen bond donor or both are true. It is possible to rationalize the enhanced hydrogen bond donor ability of the 3-hydroxy group with conjugation of the B phenyl ring. When coplanar with the C ring, this phenyl group can resonance stabilize the electron density on the oxygen atom (resonance forms **II** and **III**). This will have the effect of making the oxygen–hydrogen bond more polarized resulting in a better hydrogen bond donor.



In conclusion, the present work serves to confirm that the removal of the B phenyl group from flavonol has a dramatic effect on the intra- and intermolecular hydrogen bonding characteristics of the 3-hydroxy group. In contrast, very little effect on this interaction is shown when this phenyl group is removed from 5-hydroxyflavone. These results are in accord with the Al^{3+} binding affinities of the compounds. Theoretical studies to understand these effects are underway.

Acknowledgement

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23. *Crystallographic data for* **2a**: orthorhombic, $Pna2_1$, $a = 15.014(2)$ Å, $b = 12.833(2)$ Å, $c = 3.7679(6)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 726.0(2)$ Å^3, $Z = 4$, $D_c = 1.483$ Mg/m^3, $T = 297$ K, $\mu = 0.113$ mm^{-1}, GOF on $F^2 = 1.034$, $R = 0.0474$, $wR = 0.1415$ [$I > 2\sigma(I)$]. Crystallographic data for **3**: triclinic, $P\bar{1}$, $a = 6.8463(16)$ Å, $b = 7.1284(15)$ Å, $c = 8.3695(16)$ Å, $\alpha = 109.205(3)°$, $\beta = 106.402(2)°$, $\gamma = 96.128(3)°$, $V = 360.93(13)$ Å^3, $Z = 2$, $D_c = 1.492$ Mg/m^3, $T = 298$ K, $\mu = 0.113$ mm^{-1}, GOF on $F^2 = 1.074$, $R = 0.0436$, $wR = 0.1277$ [$I > 2\sigma(I)$]. More complete crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 689349 (**2a**) and CCDC 689348 (**3**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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