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Circular Dichroic Properties of Flavan-3-ols†

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CD data of all four diastereoisomers of the permethylaryl ether 3-*O*-acetyl derivatives of a series of flavan-3-ols permit assignment of the absolute configuration at the stereocentres of the heterocyclic ring.

The circular dichroic (CD) method is a powerful tool for establishing the absolute configuration of mono- and oligomeric flavonoids. It has been utilized to study the absolute stereochemistry of flavanones and dihydroflavanols,[1] flavan-3-ols,[2] 4-arylflavan-3-ols[3,4] and dimeric proanthocyanidins.[5] The heterocyclic ring conformation profoundly influences the sign of the low-wavelength (220–240 nm) Cotton effects (CEs) in the CD spectra of 4-arylflavan-3-ols and dimeric proanthocyanidins.[3] Amongst these groups of compounds, the flavan-3-ols represent the constituent units of the majority of oligo- and polymeric proanthocyanidins. Since instrumental limitations previously precluded stereochemical assignments involving the CEs of the ^1L_a transition of flavan-3-ols,[2] we used our collection of natural and synthetic analogues[6] to establish the chiroptical properties of this group of monomeric flavanoids.

The flavan-3-ols comprise all four possible diastereoisomers, *i.e.* those with (2*R*,3*S*)-2,3-*trans* **1–5**, (2*S*,3*R*)-2,3-*trans* **6-10**, (2*R*,3*R*)-2,3-*cis* **11–15** and (2*S*,3*S*)-2,3-*cis* **16–20** configurations and may be divided into different ‘spheres’. The A-ring chromophore by definition forms the first sphere.[7] The heterocyclic C-ring comprises the second sphere, while the aromatic B-ring and the C-3 substituent form the third sphere. The chiral sphere closest to the chromophore (A-ring), *i.e.* the C-ring of the flavan-3-ols, determines the sign and a substantial part of the magnitude of the CE within each absorption band.

Owing to the presence of the aromatic A- and B-ring chromophores, the flavan-3-ols exhibit absorption bands in the 240 nm (^1L_a transition) and 280 nm (^1L_b transition) regions of their UV spectra. The CD data are collated in Table 1 while representative CD curves for 2,3-*trans* and 2,3-*cis* enantiomers are depicted in Figs. 1 and 2.

The ^1L_b transition

The sign of the CD band of the aromatic A-ring chromophore is determined by the chirality of the heterocyclic C-ring in a manner similar to that described for the tetralins.[8] Accordingly, the absolute configuration at C-3 will have a minor influence on the sign of the CE of this transition. Thus, the spectra of the flavan-3-ols with their chiral second sphere (C-ring) and the preference of the B-ring for an equatorial position, should be explicable in terms of the helicity rules proposed for the dihydropyran ring system.[7] *P*-Helicity of the C-ring with its preferred half-chair/C-2 sofa conformation[9] should lead to positive CE’s within the ^1L_b transition, and *M*-helicity to negative ones (Fig. 3)[7] as was recorded for a series of tetralin derivatives.[8] Flavan-3-ols with 2*R* absolute configuration, *e.g.* the catechin and epicatechin derivatives **5** and **15**, resp., will display *P*-helicity (Fig. 3) and those with 2*S* configuration, *e.g.* the *ent*-catechin and *ent*-epicatechin derivatives **10** and **20**, resp., *M*-helicity (Fig. 3).

Table 1 CD data of 2,3-*trans*- and 2,3-*cis*-flavan-3-ol permethylaryl ether acetates **1–20**

Entry	Compound	Configuration	^1L_a(*ca.* 240 nm)($\lambda \times 10^3$)	^1L_b(*ca.* 280 nm)($\lambda \times 10^3$)
1		2,3-*trans*:2*R*,3*S*	236.7(+8.1)	272.2(−6.9)
2	guibourtinidol	2,3-*trans*:2*R*,3*S*	238.8(+16.5)	284.0(−10.3)
3	fisetinidol	2,3-*trans*:2*R*,3*S*	240.6(+7.0)	285.5(−14.4)
4	afzelechin	2,3-*trans*:2*R*,3*S*	240.4(+4.9)	277.0(−3.0)
5	catechin	2,3-*trans*:2*R*,3*S*	242.1(+4.0)	279.8(−5.3)
6		2,3-*trans*:2*S*,3*R*	236.7(−7.8)	272.2(+6.8)
7	*ent*-guibourtinidol	2,3-*trans*:2*S*,3*R*	238.0(−14.9)	283.2(+9.6)
8	*ent*-fisetinidol	2,3-*trans*:2*S*,3*R*	241.1(−7.3)	286.6(+15.3)
9	*ent*-afzelechin	2,3-*trans*:2*S*,3*R*	240.1(−5.2)	277.1(+3.1)
10	*ent*-catechin	2,3-*trans*:2*S*,3*R*	243.1(−3.9)	279.1(+5.5)
11		2,3-*cis*:2*R*,3*R*	235.6(+5.1)	275.3(−6.2)
12	epiguibourtinidol	2,3-*cis*:2*R*,3*R*	236.1(−2.9)	274.4(−3.1)
13	epifisetinidol	2,3-*cis*:2*R*,3*R*	237.7(−8.8)	282.27(−2.7)
14	epiafzelechin	2,3-*cis*:2*R*,3*S*	236.8(−3.9)	275.7(−2.9)
15	epicatechin	2,3-*cis*:2*R*,3*S*	237.6(−10.6)	275.9(−2.0)
16		2,3-*cis*:2*S*,3*S*	236.2(−4.4)	275.4 (+6.8)
17	*ent*-epiguibourtinidol	2,3-*cis*:2*S*,3*S*	235.6(+3.2)	274.0 (+2.9)
18	*ent*-epifiisetinidol	2,3-*cis*:2*S*,3*S*	236.0(+9.1)	282.1 (+2.1)
19	*ent*-epiafzelechin	2,3-*cis*:2*S*,3*S*	235.9(+4.4)	275.1 (+2.4)
20	*ent*-epicatechin	2,3-*cis*:2*S*,3*S*	238.2(+10.9)	275.2(+2.1)

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

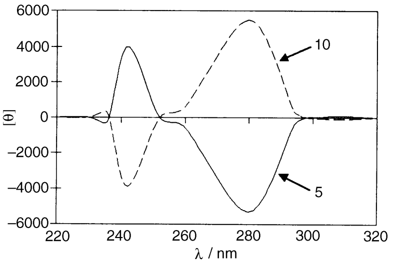


Fig. 1 CD curves of (2*R*,3*S*)-**5** and 2*S*,3*R*)-**10** flavan-3-ols

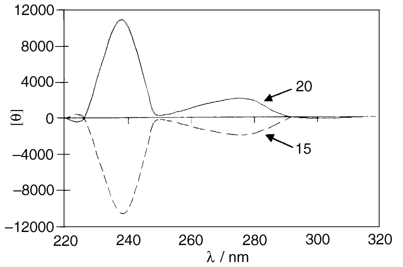


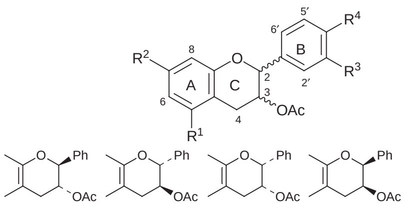
Fig. 2 CD curves of (2*R*,3*R*)-**15** and (2*S*,3*S*)-**20** flavan-3-ols

At low temperatures (*ca* −185 °C) there are two CD bands in the ^1L_b region, *i.e.* at longer (*ca.* 290 nm) and at shorter (*ca.* 270 nm) wavelengths which were attributed to the A- and B-ring aromatic chromophores, resp.[2] Our measurements at *ca.* 25 °C revealed a single CD band in the ^1L_b region. The data in Table 1 confirmed the observations[2] that 2*R* and 2*S* absolute configurations are compatible with negative and positive CEs, resp., for the A-ring chromophore in the ^1L_b region. This is opposite to the relationship found in the tetralins which conforms to the helicity rules. Such a deviation presumably results from the fact that the C_{2v} symmetry of the tetralin chromophore is absent in the chroman chromophore. Additionally, an n → π* transition from the p_z-orbital of the heterocyclic oxygen to the π* orbital of the A-ring might be involved.[2]

A conspicuous feature of the pairs of CD curves of *e.g.* the catechin/*ent*-catechin (Fig. 1) and epicatechin/*ent*-epicatechin (Fig. 2) derivatives is the reduced amplitude of the long wavelength CEs of the latter pair. This presumably results from the aptitude of 2,3-*cis*-flavan-3-ols for an A-conformation,[9] the conformational itinerary then including a considerable proportion of an inversed half-chair/C-2 sofa conformation exhibiting *M*- as opposed to the *P*-helicity of the 'normal' conformations. The negative CEs in the 280 nm regions for analogues with both 2*R*,3*S* and 2*R*,3*R* absolute configurations and the positive CEs in the same region for derivatives with both 2*S*,3*R* and 2*S*,3*S* configurations, confirm the negligible influence of the C-3 stereocentre on the sign of the CE of the ^1L_b transition.

The ^1L_a transition

The sign of the CE of the ^1L_b transition at about 240 nm (Table 1) is opposite to that at long wavelength for the derivatives of both the (2*R*,3*S*)- and (2*S*,3*R*)-2,3-*trans* enantiomers, *e.g.* the catechin derivatives **5** and **10** (Fig. 1) and the same for the (2*R*,3*R*)- and (2*S*,3*S*)-2,3-*cis* enantiomers, *e.g.* the epicatechin derivatives **15** and **20** (Fig. 2). Positive and negative CEs in the 240 nm region seem to indicate 3*S* and 3*R* absolute configurations, resp. The only exception is the reversal of the sign of the CE of the ^1L_a transition for 2,3-*cis* derivatives, **11** and **16** which are devoid of A-ring hydroxylation. Such a change in the A-ring substitution pattern may indeed reverse the sign of the Cotton effect.[7] Notable from Table 1 are the small discrepancies in the magnitude of the CEs of enantiomers. These probably result from concentration differences and the presence of minor impurities.



2*R*, 3*S*	2*S*, 3*R*	2*R*, 3*R*	2*S*, 3*S*
1	**6**	**11**	**16** $R^1 = R^2 = R^3 = H, R^4 = OMe$
2	**7**	**12**	**17** $R^1 = R^3 = H, R^2 = R^4 = OMe$
3	**8**	**13**	**18** $R^1 = H, R^2 = R^3 = R^4 = OMe$
4	**9**	**14**	**19** $R^3 = H, R^1 = R^2 = R^4 = OMe$
5	**10**	**15**	**20** $R^1 = R^2 = R^3 = R^4 = OMe$

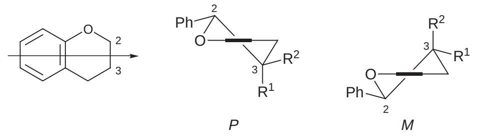


Fig. 3 *P*- and *M*-helicity of the dihydropyran C-ring (projection in the direction of arrow, wedge represents the plane of the benzenoid A-ring)

The CD data in Table 1 and the curves depicted in Figs. 1 and 2 should find useful application for the straightforward and unequivocal establishment of the absolute configuration of flavan-3-ols. Naturally occurring analogues may be derivatized to facilitate comparison with the data in Table 1.

Experimental

CD data were recorded in MeOH (*ca.* 1 mg/10 ml MeOH) on a Jasco-J710 spectrometer; scan parameters: band width (2.0 nm), sensitivity (10 mdeg), response (4 s), scan speed (50 nm min^{-1}), step resolution (0.1 nm).

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