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CIRCULAR DICHROISM—LXVIII[1] COMPOUNDS FROM VALERIAN—XII.[2]

ON THE CHIROPTICAL PROPERTIES OF VALEPOTRIATES AND RELATED COMPOUNDS

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Abstract—The CD of saturated iridoids containing a 2,9-dioxatricyclo[4.3.1.$0^{3,7}$] decan skeleton derived from valepotriates is determined by the acetal chromophore. For the less symmetric ring system of 1,6-anhydro hexapyranoses the sign of this CD is predictable. The vicinal effect for enones and diketones in this series is appreciable. A new rule for the correlation between the CD around 190–205 nm of enol ethers and their absolute conformation is given; the same reasoning is applicable to explain the known rules for cisoid and transoid vinyl cyclo-propanes.

Recently the relative[3] and absolute[2] configuration of several Iridoids isolated from *Valeriana* species as well as of many of their degradation products has been described. In this paper we discuss the chiroptical properties of several of these compounds with 2,9-dioxatricyclo[4.3.1.$0^{3,7}$] decan and cyclopentano[c]pyran skeleton containing chromophores like C=O, C=C, C=C–O and –O–C–O–.

2,9-*Dioxatricyclo*[4.3.1.$0^{3,7}$]*decans*

Our compounds with this ring system (**1–10**, **12–20**) contain two acetal groupings which have one O atom in common, another of these oxygens is present as an –O–alkyl moiety. Though the chiroptical data of a few acetals have been published (e.g. [4–7]) calculations and band assignment have been given only for the UV absorption of ethers.[8,9] In the gas spectra several Rydberg transitions have been identified (n_0 to 3s, 3p and 3d MO), in condensed phase we have to consider, however, mainly valence shell transitions. For dimethyl ether the HOMO is calculated[9a] to be the n-orbital (p-type) on oxygen, the LUMO is totally symmetric[9a] (Fig. 1). According to this the valence shell transition of lowest energy is electrically dipol allowed ($A_1 \rightarrow B_1$) and polarized perpendicular to the plane of the ether grouping. Its ϵ is small (approx. 1000) because of weak orbital overlap.

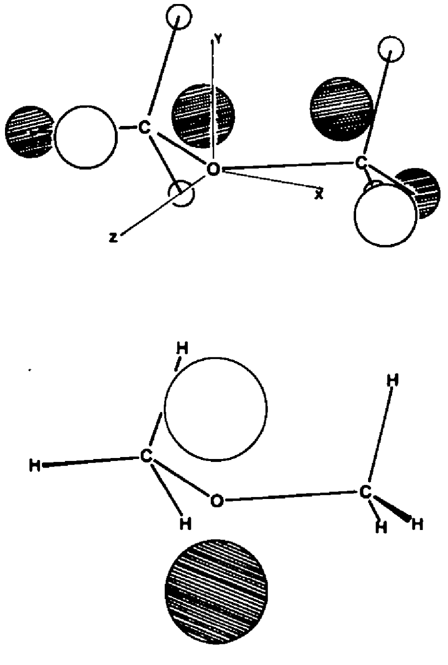

Fig. 1. HOMO and LUMO for dimethyl ether.[9a]

In an acetal of fixed and chiral conformation the interaction between these two "ether" transitions will determine its chiroptical properties. Figure 2 shows the arrangements of these two transition dipol moment vectors for the skeleton of a 1,6-anhydro-D-pyranose; the conformation is known from X-ray measurements.[10] According to exciton theory (cf. e.g. [11]) this interaction leads to a negative CD-couplet,[12] and indeed negative (plain) ORD curves have been described for such products (e.g. multistriatin **11** and its stereoisomers[13]). The dioxabicyclo[2.2.2]octan moiety of **1** and its derivatives is, however, achiral and will thus not lead to such a couplet. For the combination of the common "ether" function with the OMe group chiral situations are possible, but as several rotamers may be present in equilibrium their inherently chiral CD will compensate to a great extent. The CD will then be governed mainly by the perturbation of the chromophore by the chirally arranged

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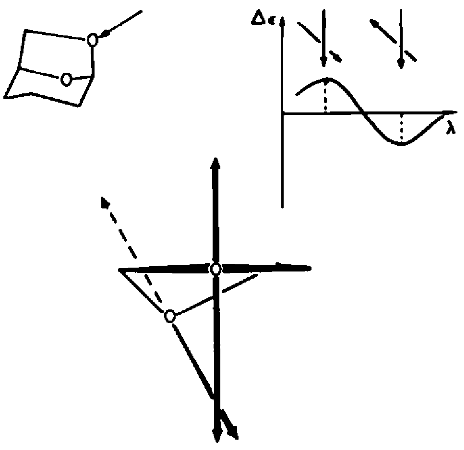
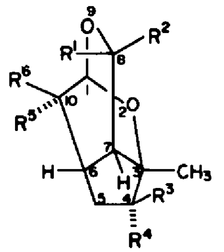


Fig. 2. Chiroptical properties of the acetal chromophore of 1,6-anhydro-D-hexapyranoses. *Top left*: absolute configuration of the ring system. *Middle*: The directions of the two transition moment vectors of the individual ether oxygens in the fivemembered ring (direction of projection as indicated by the arrow in the formula). *Top right*: The two possible coupling modes giving rise to a positive CD at higher energies and a negative CD at lower ones.

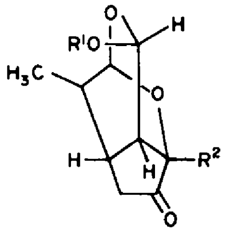
C-4/C-5 bridge and indeed regardless of the configuration at the glycosidic C-8 the CD of 1-3 is strongly negative below 190 nm. If one treats the acetyl moiety in the skeleton as one single chromophore then from symmetry considerations[14,15] a planar rule is expected. Regardless of the configuration at C-8 the OMe group will always be on the same side of this nodal plane and such a planar rule is also in agreement with the identical CD signs for 1 and 2 vs 3.

The dominating chromophore in the compounds 4-6 is the CO group. In the region of the n→π*-band a bisignated CD curve is found, at 189 nm a stronger negative Cotton effect appears. This latter CD band may in part come from the aforementioned acetal chromophore but can also be due to the second CO transition (most probably n→σ*) which is known to give a Cotton effect in this region of the spectrum.[17] The size of the alkyl group within the -OR moiety at C-8 is virtually of no influence upon the CD. The CD of the acid 7 deviates somewhat from that of the others, but mainly in the short wavelength region where the carboxylic group itself gives rise to a Cotton effect.[18] Bisignated CD curves may have different reasons, as e.g. presence of several species (conformers, solvated and non-solvated molecules, etc.), vibronic coupling ("allowed-character" and "forbidden-character" series[19,20]), appearance of hot bands, band splitting because of interaction of molecular orbitals (as e.g. exciton splitting or weak interaction through bonds), etc. From molecular models it appears unlikely that the ring system is very flexible, furthermore 6 did not show great changes of the CD curve with change of the solvent, so solute-solvent interaction is not very probable as the cause of this bisignated appearance of the Cotton effect. Vibronic coupling must therefore be the reason, and the band at longer wavelengths should be characteristic for the absolute configuration, whereas the shorter-wavelength wing is mainly vibrationally determined.[19,20] The CO chromophore is incorporated at the same time into two chiral second spheres (5-membered and 7-membered ring), and according to general experience[21] the smaller of these two determines the sign of the CD. A negative CD is thus predicted[21,22] in accordance with the experimental finding. O atom 2 with respect to the CO group is in such a conformation as in α-axial hydroxy ketones and this explains the strong bathochromic shift of the CD band(s),[23] its contribution to the CD depends on the orientation of its p-type lone pair and cannot yet be predicted.[21,24,25]

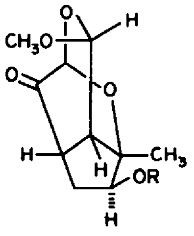
Compounds 8 and 9 with two ether oxygens in α-position to the CO show only a negative CD with some fine structure within the n-π* band, again shifted to the



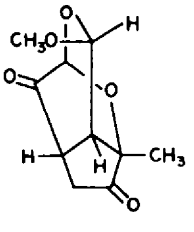
1: $R^1 = OCH_3$, $R^2 = R^4 = R^6 = H$, $R^3 = OH$, $R^5 = CH_3$
2: $R^1 = OCH_3$, $R^2 = R^3 = R^6 = H$, $R^4 = OH$, $R^5 = CH_3$
3: $R^1 = R^3 = R^6 = H$, $R^2 = OCH_3$, $R^4 = OH$, $R^5 = CH_3$



4: $R^1 = R^2 = CH_3$
5: $R^1 = C_2H_5$, $R^2 = CH_3$
6: $R^1 = n\text{-}C_4H_9$, $R^2 = CH_3$
7: $R^1 = CH_3$, $R^2 = COOH$



8: R = H
9: R = Ac



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red.[23] Assuming also here an achiral dioxabicyclooctan skeleton the only contributions to the Cotton effect are from the OMe group, C-4, C-5 and the OR at C-4. The first lies nearly in the vertical nodal plane and may adopt several conformations, so its contribution to the CD will be negligable. C-5 according to the octant rule gives a positive contribution,[26] C-4 is close to the vertical nodal plane and should give sign inversion, i.e. a negative CD,[26,27] the contribution of the OR should be positive again. Overall one would thus expect a positive Cotton effect. On the other hand fusion of this dioxabicyclooctan system containing an sp^2-carbon to a 5-membered ring leads to a deviation from the high symmetry as suggested by molecular models. According to the projection (Fig. 3B) the negative contribution of the twisted ring (1–2–3–7–6–3) to the CD must be bigger than the positive one of ring (1–9–8–7–6–3), predicting a negative Cotton effect from second-sphere chirality. We take the found negative CD as an indication that indeed such a twisted system is present.

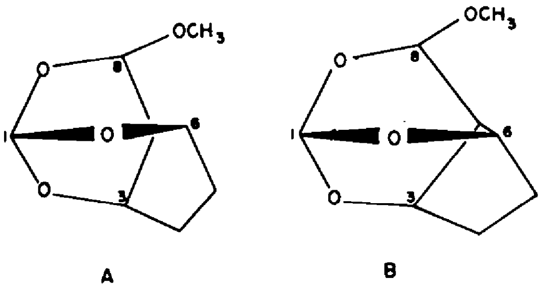
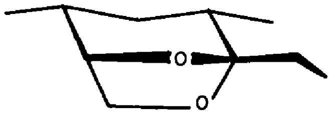


Fig. 3. Projection of the ring system of **8** from O to C of carbonyl C-4. *A*: achiral conformation of the bicyclo[2.2.2]skeleton; *B*: chiral conformation of the bicyclo[2.2.2]skeleton.

The diketone **10** gives a positive CD at about 310–330 nm, and a negative one of approximately equal rotational strength at 220 nm. This latter band position is at too long wavelengths to be attributed to the n-σ^* transition, furthermore in the UV spectrum the absorption is negligable at this wavelength. This CD must be caused by the interaction between the two CO groups; around 300 nm the sum of the CD's of 4-ketone **4** and of 10-ketone **8** is very weak and bisignated, and positive at 210 nm. In these molecules no CO lies in one of the nodal planes of the second, so according to our generalization[28] for such γ-diketones appreciable vicinal effects are expected.



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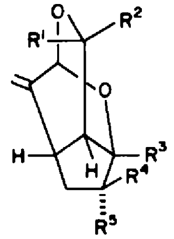
Compounds **12–18** contain a methylene group at C-10 which gives rise to a very strong positive Cotton effect at 184–189 nm. This double bond is exocyclic to two chiral second spheres, and the existing rules do not cover this case unequivocally. On both sides of the sp^2-atom of the ring two alike atoms (oxygens and carbons) are approximately symmetrically disposed with respect to the plane of the C=C, so Yogev's rule[29] as well as Burgstahler's rule[30,31] cannot be applied; Scott's rule[32] has many exceptions, especially in case of methylene compounds.[33] We have expressed the view[15] that second sphere chirality will also be of importance in explaining the sign of the CD of olefins and the data obtained for **12–17** can easily be rationalized in this way. The compounds with an OR group at C-4 in exo-position (with respect to the 5-membered ring) (**14**, **15**) show only one strong positive CD ($\Delta\epsilon = +23$), whereas for the others with the OR in endo-position (**12**, **13**, **16**, **17**) $\Delta\epsilon$ is somewhat smaller and a small negative Cotton effect appears above 200 nm. Taking into account the known[34] flexibility of the bicyclooctan skeleton, in case of an sp^2-atom at C-10 an endo-substituent at C-4 will tend to force the bicyclooctan skeleton into a more symmetric conformation, whereas an exo-substituent will cause a deviation from this geometry. In the latter case (**14**, **15**) the CD should, therefore, be stronger, and compensate fully the Cotton effect of the acetal system; for the other compounds (**12**, **13**, **16**, **17**) the olefin-CD is expected to be smaller and the onset of the negative acetal-CD is already observable. The CD of **18** is consistent with this, and shows the additional Cotton effect of the thiocyanate chromophore at 245 nm.[35]

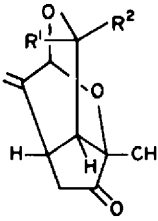
The olefine ketones **19** and **20** show a bisignated CD within the n-π^* region similar to their saturated analogue **4**; three more CD bands could be detected at shorter wavelengths showing the complex interaction of the transitions of the several chromophores present.

Cyclopentane[c]pyrans

Compounds **21–24** contain the enol ether chromophore which is isoelectronic with the allyl anion and has thus similar HOMO and LUMO.[9b] Incorporation into a ring renders the C–O–C=C–C moiety chiral (cf. e.g. the X-ray structure of a steroidal dihydropyran[36]) and the cor-



12: $R^1 = OCH_3$, $R^2 = R^5 = H$, $R^3 = CH_3$, $R^4 = OH$
13: $R^1 = OCH_3$, $R^2 = R^5 = H$, $R^3 = CH_3$, $R^4 = OAc$
14: $R^1 = OCH_3$, $R^2 = R^4 = H$, $R^3 = CH_3$, $R^5 = OH$
15: $R^1 = OCH_3$, $R^2 = R^4 = H$, $R^3 = CH_3$, $R^5 = OAc$
16: $R^1 = R^5 = H$, $R^2 = OCH_3$, $R^3 = CH_3$, $R^4 = OH$
17: $R^1 = R^5 = H$, $R^2 = OCH_3$, $R^3 = CH_3$, $R^4 = OAc$
18: $R^1 = OCH_3$, $R^2 = R^5 = H$, $R^3 = CH_2SCN$, $R^4 = OAc$



19: $R^1 = OCH_3$, $R^2 = H$
20: $R^1 = H$, $R^2 = OCH_3$

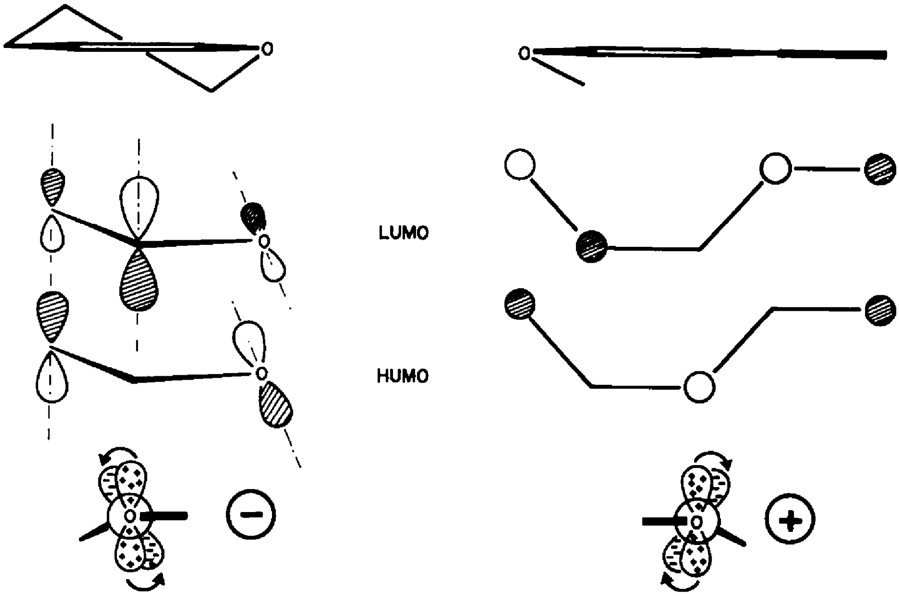
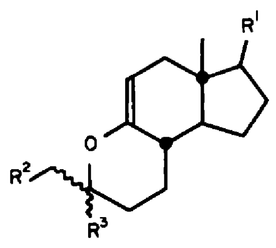


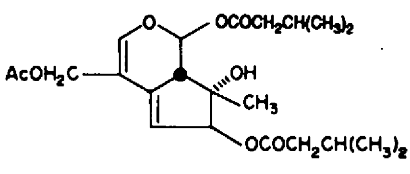
Fig. 4. Sign of the first CD-band of inherently chiral enol ethers and dienol ethers. *Left*: Absolute conformation of the dihydropyran ring of D-glucal; HOMO and LUMO for the 3π-system, and (bottom) charge distribution in the excited state. This leads to a lefthanded helical path for the charge delocalization during excitation, i.e. to a negative CD. *Right*: Absolute conformation of the dienol ether moiety of 26–29, LUMO and HOMO for the 5π-system (projection from above, only upper halves of the p-lobes), and (bottom) charge delocalization in the excited state (right handed helical path) leading to a positive CD.

relation between the sign of the CD and absolute conformation of this chromophore can easily be derived (Fig. 4). Formally multiplying the MOs of HOMO and LUMO gives the charge displacement during excitation.[11,14,37] For the conformation deliberately shown in Fig. 4 this displacement follows a left-handed helical path giving thus rise to a negative CD. This rule explains correctly the strong negative CD of glycals[38] of hexapyranoses around 200 nm and of enol ether 25 of same chirality of the C–O–C=C–C moiety ($\Delta\epsilon < -6$ below 195 nm).[39] The same derivation is also valid in predicting the sign of the first CD band of cisoid and transoid vinyl cyclopropanes[37,40] if one uses Walsh-orbitals instead of the lone pair orbital on oxygen.

According to molecular models the ring system of 21–24 seems to be quite flexible, detailed interpretation of the IR and NMR spectra[3] showed, however, that the dihydropyran ring is preferred in a conformation with quasiaxial O-acyl grouping at C-1, which is also favoured by the anomeric effect. In such a conformation the O–C=C–C chromophore adopts the geometry shown in Fig. 4 which must then lead to a strong negative CD. Such a Cotton effect is indeed found regardless whether the geminal methyl hydroxy compounds 21 and 22 or the oxido compounds 23 and 24 are investigated.



25 R¹ = R³ = OAc, R² = COOEt



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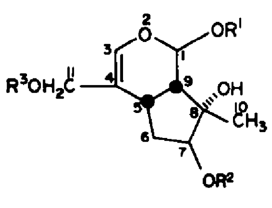
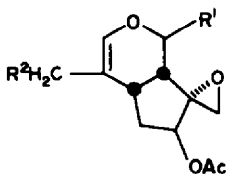
The diene 26 shows a strong positive CD in the range of the π→π*-absorption at 225 nm, a shoulder with fine structure around 220 nm, and a negative CD at 195 nm. The conformation of the bicyclic system is known from NMR-data;[3] in these molecules the acyloxy moiety at C-1 is quasi equatorially arranged. This conformation leads to a small negative torsion angle for the transoid diene system, and applying



21: R¹ = COCH₂CH(CH₃)₂, R² = H, R³ = -β-D-glucose
22: R¹ = R³ = COCH₂CH(CH₃)₂, R² = Ac



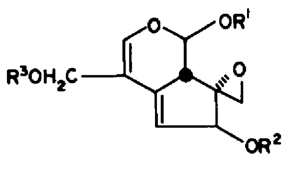
23: R¹ = OCOCH₂CH(CH₃)₂, R² = H
24: R¹ = R² = OCOCH₂CH(CH₃)₂

Table 1. Circular dichroism

Compound	Solvent[a]	CD – maxima given as λ_{max} ($\Delta\varepsilon$)[b]
1[43]	A	negative below 210 nm
2[43]	A	negative below 205 nm
3[42]	A	negative below 205 nm
4[43]	A	336(-0.16), 303(+0.69), 189(-7.58)
5[43]	A	334(-0.15), 303(+0.56), 189(-6.35)
	I	339(-0.25), 329sh(-0.15), 301(+0.36), 189(-7.57)
	E	334(-0.19), 300(+0.60), negative below 191 nm
6[43]	A	335(-0.21), 302(+0.58), 189(-7.10)
7[42]	A	338(-0.03), 303(+0.64), 218(+0.34), negative below 209 nm
8[42]	A	316sh(-0.41), 309(-0.49), 204(+1.28), negative below 193 nm
	E	318sh(-0.32), 309(-0.51), 204(+1.27)
9[42]	A	320sh(-0.34), 317sh(-0.34), 310(-0.40), 224(-0.07), 198(+1.06), negative below 189 nm
10[42]	A	325sh(+0.36), 315sh(+0.71), 306(+0.78), 218(-0.93)
	C	331sh(+0.48), 319(+0.83), 309(+0.75), 220(-1.28)
12[43,44]	A	209(-0.15), 189(+16.08)
13[44]	A	220(-0.02), 186(+21.59)
14[44]	A	190(+23.88)
15[3]	A	189(+22.65)
16[43,44]	A	204(-2.52), 188(+13.40)
17[44]	A	202(-1.20), 184(+17.15)
18[44]	A	245(-0.31), 216(-0.48), 185(+21.21)
19[43,44]	A	336(-0.09), 303(+0.64), 216(-0.86), 199(+3.28), 189(-2.83)
20[44]	A	337(0.27), 328sh(-0.19), 301(+0.30), 214(-1.80), 200(+1.59), 190(-3.54)
21[3,43]	A	190(-15.33)
22[2]	A	193(-11.51)
23[2]	A	188(-13.95)
24[2]	A	193(-14.71)
25[2]	A	255(+13.88), 228sh(+4.20), 220sh(+3.52), 195(-6.35)
26[2]	A	255(+6.77), 217(+4.03), 194(-3.85)
27[45]	A	256(+7.30), 214(+3.28), 193(-6.11)
28[45]	A	254(+7.95), 212(+7.52), 193(-2.30)

a) A : acetonitril, I : isooctan, C : cyclohexan, E : ethanol

b) sh indicates a shoulder



27: $R^1 = R^2 = COCH_2CH(CH_3)_2$, $R^3 = H$
28: $R^1 = R^2 = COCH_2CH(CH_3)_2$, $R^3 = Ac$
29: $R^1 = R^3 = COCH_2CH(CH_3)_2$, $R^2 = Ac$

the known rule[41] would lead to a negative CD. The situation is, however, similar to the case of the enol ethers: the isoelectronic chromophore is the pentadienyl anion, and the sign of the CD for the band at longest wavelengths can again be obtained from the formal multiplication procedure of the HOMO and the LUMO (Fig. 4). For the conformation given the sense of helicity is positive (right handed screw) and this is in best agreement with the positive Cotton effect measured. Also in this series the replacement of the geminal methyl hydroxy groupings by the epoxide ring does not grossly change the chiroptical properties, but the second CD-band about 215 nm is now detectable much better and increases with the bulkiness of the ester group at C–11.

EXPERIMENTAL

All CD spectra were recorded with the Dichrograph III (Jobin-Yvon) at 20° in cells of thickness 0.01–1.00 cm and concentrations of about 0.2–1 mg/g. All compounds besides 3, 7, 8, 9, 10[42] have been described in former publications.[2,3,43–45]

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