Circular Dichroism of Bufadienolides

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With the help of PMO theory a non-empirical sector rule has been derived for the $n \rightarrow \pi^*$ band CD (around 260 nm) of the pentadienolide chromophore of steroidal bufadienolides. The rule was verified by experiment using the preferred conformation for the 2-pyrene side chain found in most of the crystalline bufadienolides investigated by x-ray diffraction. Substituents in ring D do not drastically influence the Cotton effect of this transition, whereas the sign of the $\pi_4 \rightarrow \pi^*$ band Cotton effect around 300 nm is strongly dependent on such substitutions. The Cotton effect of additional carbonyl groups can in general be detected without difficulty in the CD-spectra.

INTRODUCTION

The steroidal bufadienolides are distinguished by a 5-substituted 2-pyrene ring at the 17β-position and some of these intriguing animal and plant constituents have been used from antiquity in traditional medicine, especially for their cardiac-stimulating properties. Indeed, the antineoplastic, cardiac and cell growth inhibitory properties of a variety of bufadienolides are now well established. Others have been found responsible for cotyledonosis, a neurological disorder of range animals (eating plants of the Crassulaceae family) in South Africa and some (from venom of the large toad Bufo marinus) are used in Haiti for human degradation to zombies.

Bufadienolides have a characteristic UV-absorption at 300 nm, which was used for some of the original structure studies. However, the chiroptical properties of the pentadienolide chromophore have not hitherto been investigated in detail, which may have been due to uncertainty of the side chain conformation and low signal/noise ratio of the CD-spectra. In recent years several x-ray diffraction studies of bufadienolides have become available.

* Dedicated to Professor Mihailo Lj. Mihailović on the occasion of his 60th birthday.
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and on this basis we are now able to discuss and interpret the results of our systematic studies of bufadienolide chiroptical properties. The x-ray data show⁴ that, in agreement with molecular mechanics calculations⁴, the torsional angle C(16)—C(17)—C(20)—C(21) is about +150° or —30°, if the usual 14β-β-hydroxy structure is present. However, deviations from these values are found when another substitution pattern is present in ring D.⁴

UV-SPECTRUM AND MO-S

Both 2-pyrones and its alkyl derivatives show an absorption band around 300 nm of medium intensity (ε ~ 5000) and a second band between 220 and 200 nm of similar intensity, with a pronounced minimum in between. The MOs of the chromophore can be approximated in different ways, such as by the LCBO-method or by using Streitwieser's parameters for hetero atoms.¹⁰,¹¹ We have used the latter. In the UV-spectrum only those bands corresponding to π → π* transitions can be detected. Since in the point group Cᵥ of the chromophore all π-MOs belong to the irreducible representation a¹, the excited π → π* states have A'-symmetry and are polarized in the plane of the lactone. Figure 1 shows the two frontier π-MOs (π₄ and π₄*), together with their product, which determines the direction and magnitude of the electric transition moment vector μ. With the MOs obtained in this way μ was inclined against the direction of the carbonyl C=O bond by 65° (the LCBO-approximation gave about 70°).¹² Also, in a formal sense, the n → π* transitions are electrically allowed (polarized perpendicular to the lactone plane), but due to the very weak overlap these transitions do not give rise to intense absorption bands (cf. the analogous situation for the n → π* transition of chiral conjugated enones). Otherwise these transitions are associated with a (usually strong) magnetic transition moment directed approximately along the carbonyl C=O bond.

A few calculations have appeared¹³ for the 2-pyrones and, they agree in assignment of the 300 nm band as originating mainly from the isolated n½ → π* transition; a not very strong absorption is thus predicted. The second transition, placed between 240 and 210 nm, should be mainly of n¾ → π* parentage, and the n½ → π* transition should give rise to a more intense band between 194 and 186 nm. The n → π* transition energy was not calculated with the same accuracy. The corresponding weak band was predicted to be at longer or shorter wavelengths than the first π → π* band.

CD-SPECTRA: NON-EMPirical TREATMENT

In most cases a distinct Cotton effect is observed around 300 nm, which corresponds to the π₄ → π₄* transition. A second Cotton effect, often seen only as a shoulder, appears between 270 to 250 nm (where the UV-spectrum shows a broad minimum) and one or two Cotton effects can be found at still shorter wavelengths. Therefore, this second CD-band must be associated with the n → π₄* transition of the 2-pyrones chromophore. For conjugated unsaturated lactones this band appears between 260 and 240 nm,¹⁷ and for the related isocoumarones we have recently identified it in the same wavelength range.¹₈
Figure 1. Schematic drawings of the \( \pi \)-HOMO (\( \pi_0 \), top left), and the LUMO (\( \pi_0^* \), top right) as well as their formal product (bottom), together with the direction of the corresponding electric transition moment.

For the usual 14/8-hydroxy-bufadienolides both the first and the second Cotton effects are negative, the third is positive, the fourth, if observed at all, again negative.

Since the 2-pyrone chromophore is connected to the steroid nucleus by a single bond, it seems appropriate to discuss these CD-bands with the help of a sector rule. In accordance with the general treatment by Schellman, the symmetry-determined sector rule is a quadrant rule in the \( C_{nv} \) approximation, and reduces to a hemisphere rule for \( C_{s} \)-symmetry. Also, in the latter case we have to assume at least a quadrant rule, as orbitaldetermined nodal surfaces have to be taken into account in developing such sector rules, too. These nodal surfaces of the involved \( \pi \)-MOs might be bent; however, within the usual approximations it suffices instead to work with planes. For the \( \pi_0 \rightarrow \pi_0^* \) transition such an additional nodal plane should lie approximately perpendicular to \( \mu \) as can be derived from Figure 1 and is denoted \( Z_1 \) in Figure 2.

The \( n \rightarrow \pi^* \) transition is mainly associated with a magnetic transition moment of \( a' \)-symmetry along the \( O=C \) bond. Thus, the missing in-plane electric transition moment can be taken from any \( \pi \rightarrow \pi^* \) transition. The
energetically unfavoured combination of coulombic interaction potentials must be used if this $\mu$ comes from the energetically nearest $\pi \rightarrow \pi^*$ state, which is the $\pi_4 \rightarrow \pi_5^*$ transition.\textsuperscript{29} The interaction has to be taken between the $\pi_4 \rightarrow \pi_5^*$ transition dipole and the quadrupole associated with the $n \rightarrow \pi_5^*$ transition and it does not matter whether one uses a positive or negative test charge to work out this perturbation.\textsuperscript{30} By moving this test charge around the chromophore we find three different surfaces (approximated in the following by planes) for the dipole ($\mathcal{E}_2$) and the quadrupole ($\mathcal{E}_3$ and the plane of the chromophore). These surfaces separate spaces where the charge/multipole interaction is either attractive or repulsive, giving four upper and four

Figure 2. CD sector rule for the $n \rightarrow \pi_5^*$-band CD. According to our general procedure\textsuperscript{30} the energetically unfavoured interaction of a test charge (here deliberately chosen as positive) and the quadrupole associated with the magnetic transition moment of the $n \rightarrow \pi_5^*$-transition has to be chosen, if the favourable one has been taken between this same charge and the electric transition dipole stolen from the $\pi_4 \rightarrow \pi_5^*$-transition. For the sector in which the test charge has been positioned the angle between $\mu$ and the $\mathbf{m}$ along the C=O bond is acute and contributions to the rotational strength in that sector are positive. For the correlation between the sign pattern in the quadrupole $Q$ and the direction of $\mathbf{m}$ cf. ref.\textsuperscript{29}. Charges and signs refer to the hemisphere above the plane of the lactone ring ($\Sigma_1$).
lower sectors which are pairwise small or wide. If the charge/dipole inter-
action is deliberately chosen to be attractive, then the charge/quadrupole
interaction has to be taken as repulsive. By this procedure the relative
phasing of $\mu$ and $m$ was obtained in a manner similar to derivation of
the famous octant rule for saturated ketones. The signs for contributions to the
Cotton effect of groups in the upper sectors obtained in this way are shown
in Figure 2.

In the same manner one should be able to derive a rule for the $\pi_1 \rightarrow \pi_1^{*}$
band CD. If the same two transition moments are considered relevant, its
sign is predicted to be opposite to that of the $n \rightarrow \pi_1^{*}$ band CD. The $\pi_1 \rightarrow \pi_1^{*}$
transition is also associated with a magnetic transition moment vector perpen-
dicular to the plane of the ring and the corresponding $\mu$ has to be taken from a
$\pi \rightarrow \sigma^{*}$ or $\sigma \rightarrow \pi^{*}$ transition. Furthermore, the in-plane electric transition
moment has a reasonably strong component perpendicular to the direction
of the O=C bond and the $n \rightarrow \pi_1^{*}$ transition cannot contribute any $m$. Since
so many terms contribute to this Cotton effect, a straightforward prediction
of the sign by a qualitative treatment does not seem possible. Very often the
first two Cotton effects have the same signs. Thus, it is only for the second
one that a correlation between its sign and the absolute conformation of
the bufadienolide can be predicted.

**CD-spectra: Experimental Values**

Pyrone 1\textsuperscript{22} gives a pronounced negative $n \rightarrow \pi^{*}$-band CD at 267. The
$\pi_1 \rightarrow \pi_1^{*}$ band Cotton effect is also negative and appears only as a shoulder.
With pyrone 1 we expected to be able to «calibrate» our rule, but a molecular
model showed that rings A and B are very flexible and it could not be
deduced whether the bulk of the atoms of rings C and D are in upper or
lower sectors. Bufadienolides\textsuperscript{5, 8, 22} to 4 all have a negative $n \rightarrow \pi^{*}$ band CD
which is in full agreement with the above rule, arrived at by the non-
empirical treatment (cf. Figure 2). A projection from oxygen to carbon along
the carbonyl group shows that most of the atoms contributing to the Cotton
effect are in a «negative» sector (cf. Figure 2 of Ref. 12 for a projection of
bufalin). Substituents at C(5), C(11), or C(15) have no influence upon the
CD, and no sterie interactions with the side chain are expected from such
groups. Also, $6\beta$, $7\beta$, and even $12\beta$-hydroxy groups do not influence the
CD-spectra, nor does unsaturation at D\textsuperscript{1} of the scillarenine-type compounds
(5, 6, cf. Figure 3).\textsuperscript{2, 23} While a 16β-substituent is known to influence the
conformation of a 17β-side chain (at least with the C/D-trans compounds),\textsuperscript{24}
the x-ray crystal structure studies\textsuperscript{4} prove that even the 16β-acetoxy group
reduces the otherwise preferred torsional angle only by $5^\circ$ to $125^\circ$. In one
case\textsuperscript{25} the x-ray structure of cinobufagin ($8, R^1 = R^2 = H, R^3 = Ac$) reveals
the torsional angle as $131^\circ$. Thus, the $n \rightarrow \pi^{*}$ band CD retains its negative
sign (7), but the first $\pi \rightarrow \pi^{*}$ Cotton effect becomes positive (cf. Figure 3).
Probably this sign inversion does not come from the small change of the
torsional angle C(16)—C(17)—C(20)—C(21). Instead, we prefer to ascribe it to
an orbital interaction between $\pi$-systems of the pentadienolide and acetate
chromophores, e.g. of the exciton type.\textsuperscript{26} Such a view is supported by the
3a: \( R^1 = \alpha-L\text{-rhamnose}, \quad R^2 = R^3 = H \) (proscillariden-A)

b: \( R^1 = H, \quad R^2 = \text{OH} \)

c: \( R^1 = R^2 = H, \quad R^3 = \text{OH} \), (scilliphaoasidin)

2a: \( R^1 = R^2 = R^3 = R^5 = H, \quad R^4 = \text{OH} \) (bufalin)

b: \( R^1 = \text{Ac}, \quad R^2 = R^3 = R^5 = H, \quad R^4 = \text{OH} \)

c: \( R^1 = \text{CO(CH}_2\text{_6)_2COOR}, \quad R^2 = R^3 = R^5 = H, \quad R^4 = \text{OH}, \quad R^6 = \text{H or Me} \)

d: \( R^1 = \text{Cl} \)

3a: \( R^1 = R^2 = R^5 = H, \quad R^3 = \text{OH} \) (telocinobufagin)

b: \( R^1 = \text{Ac}, \quad R^2 = R^5 = H, \quad R^3 = \text{OH} \)

c: \( R^1 = \text{CO(CH}_2\text{_6)_2COOMe}, \quad R^2 = R^3 = \text{H}, \quad R^4 = \text{OH} \)

d: \( R^1 = \text{Cl} \)

5a: \( R^1 = \alpha-L\text{-rhamnose}, \quad R^2 = R^3 = H \) (proscillariden-A)

b: \( R^1 = R^3 = H, \quad R^2 = \text{OH} \)

c: \( R^1 = R^2 = H, \quad R^3 = \text{OH} \), (scilliphaoasidin)

6a: \( R^1 = \text{OH}, \quad R^2 = R^3 = H \)

b: \( R^1 = R^3 = H, \quad R^2 = \text{OH} \)

c: \( R^1 = R^2 = H, \quad R^3 = \text{OH} \)
CD-spectra of the 16\(\beta\)-substituted 14\(\beta\),15\(\beta\)-epoxy-bufadienolides\(^{2,29}\) 8 to 10. The bulk of the atoms contributing to the \(n\rightarrow\pi^*\) band CD lie in the usual negative sector (cf. Figure 4) and regardless of whether or not a 16\(\beta\)-hydroxyl or its acetate is present, both of the first Cotton effects are negative. Obviously, interaction between the chromophores is a function of small differences in the torsional angles of the 16\(\beta\)-acetoxy group. In all these compounds the position of the \(n\rightarrow\pi^*\) band CD is at somewhat shorter wavelengths than usual. The very small Cotton effect around 340 nm of 8a and 9 could be detected only with the newer instrumentation. We have checked in a few cases that it is not a general feature of all pentadienolide CD-spectra.

With inversion of the epoxide configuration to 14\(\alpha\), 15\(\alpha\) (11) the sign of the first Cotton effect is also inverted, whereas the second Cotton effect still seems to be negative although it can be detected only as a positive
minimum instead of the usual negative maximum. No x-ray data are available to correlate these chiroptical data with the preferred conformation of the side chain. Interestingly, here the 16β-acetoxy substitution product has the usual features of the CD-spectra (12). With Δ14-anhydro-bufadienolides the crystal conformation has the bulk of the atoms in a positive sector (Figure 5), mainly due to the changed shape of ring D. In the CD-spectra the n → π* Cotton effect is bisignate, with positive rotational strength above 253 nm and negative below that wavelength. This might indicate the presence of a mixture of side-chain rotamers in solution. The first π → π* Cotton effect
Figure 4. Projection from O to C of the lactone C=O of the 16-O-acetate of 9.55
Figure 5. Projection from O to C of the lactone C=O of 13.8

is positive, and this could be caused by direct (exciton like) interaction of the lactone chromophore with the 14-ene system (13, 14).

Except for the compounds above and bufadienolide 25c all the other compounds investigated contained at least one carbonyl function that gave rise to a Cotton effect in the same wavelength range as the pentadienolide π₁→π₅* band. The CD of a 5β-3-oxo-system is weakly negative,52 and 3-dehydro-bufalin (15) displays a Cotton effect band around 300 nm, slightly broader and more negative than that of the parent compound 2a (cf. Figure 6). The CD around 300 nm of 3-dehydro-resibufogenin (16) was of similar
appearance. Unfortunately, no sample of resibufogenin was available for direct comparison. With deacetyl cinobufagone (17) it was possible to make a direct comparison, and the difference CD-spectrum leads as expected to a negative Cotton effect. Again with 14-anhydro-bufalone (18) direct comparison was completed and we clearly identified just above 300 nm the negative CD of the 3-oxo chromophore, followed by the positive Cotton effect of the side chain chromophore noted for the parent compound 13 and the negative one for the n → π* band. The 11α-hydroxy-12-oxo system present in arenobufagin (19) has its counterpart in the cardenolide series in sinogenin and a medium strong positive Cotton effect has been recorded for sinogenin acetate. We observed the same for acetate derivative 19b for which the positive CD of the 12-ketone completely obliterated the negative first Cotton effect and the negative n → π* band was seen as a positive minimum. The
free hydroxyl group of 19a can form a hydrogen bond with the carbonyl, and in this way retains the positive Cotton effect with a pronounced blue-shift (usual for such a situation). The negative $\pi_s \rightarrow \pi^*_{C=O}$-CD for alcohol 19a (cf. Figure 6) can just be recognized as a small band.

The x-ray crystal structure of 14β-artebufogenin 3-acetate (20b) has been completed \(^{39}\) and the relevant torsional angle (+136°) is again not too different from that in 14β-hydroxy-bufadienolides, so the Cotton effect within the $n \rightarrow \pi^*$ band is negative. Since the Cotton effect of the 14β-H-15-oxo group is negative, \(^{38}\) a strong negative CD is observed for these two products as the sum for both Cotton effects. On the other hand, the carbonyl CD is strongly positive for the 14α-configuration, \(^{38}\) and this positive Cotton effect overrides completely the smaller negative one of the pentadienolide chromo-
Compound 23 contains an epoxy-ketone chromophore that should exhibit a strong negative Cotton effect, as expected from the corresponding rule, and this was found in the spectrum. Hellebrigenin (24) gave a CD curve similar to that of the analogous bufadienolides lacking the aldehyde group. The aldehyde does only introduce a small additional negative Cotton effect. A similar weak negative Cotton effect has been described for the corresponding cardenolide k-strophanthidin.
Finally, for resibufagin (25a) and its oxime 25c the »usual« CD-features of bufadienolides were found. But in the spectrum of its acetate (25b) the $n \rightarrow \pi^*$ band CD must have been shifted somewhat bathochromically, as we observed a crossover point with the lambda-axis instead of the negative Cotton effect.

In summary, even in the presence of other chromophores the pentadie-nolide chromophore of the bufadienolides with an undistorted side chain conformation can be identified in the CD-spectra. For correlation with the absolute conformation only the $n \rightarrow \pi^*$ band Cotton effect can be used in agreement with the situation observed in similar cases.
### Table I

**CD-Data of Pentadienolides**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_{	ext{max}}$ ($\lambda_{	ext{max}}$)</th>
<th>solvent</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>285sh (--1.45), 262(--1.98), positive below 230 nm.</td>
<td>AN</td>
</tr>
<tr>
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<td>AN</td>
</tr>
<tr>
<td>2b</td>
<td>294(--1.37), 254(--0.99), 214(+ -4.4).</td>
<td>AN</td>
</tr>
<tr>
<td>2c</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>2f</td>
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</tr>
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<td>310sh(--1.67), 292(--2.16), 250sh(--0.58), 215(+5.0).</td>
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<td>25c</td>
<td>315sh(--0.89), 290(--1.60), 250sh(--0.71), 216(+3.8).</td>
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* AN = acetonitril, DN = dioxan
EXPERIMENTAL

CD-data were measured (at room temperature and concentrations of appr. 3-5 mg/ml) with the dichrograph models 185 and Mark III from ISA-Jobin-Yvon-Jouan. In a few cases data were smoothed by the Golay-Savitzky algorithm with the help of a PDP/8-e computer.

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IZVOD

Cirkularni dihroizam bufadienolida

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