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CIRCULAR DICHROISM—XLVII[1]
INFLUENCE OF SUBSTITUTION PATTERN ON THE BENZENE ^1L_b-BAND COTTON EFFECT

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Abstract—The signs of the second and third sphere contributions to the ^1L_b-band Cotton effect in a family of homochiral compounds depends on the substitution pattern of the benzene ring. This change of signs can be explained by making use of simplified spectroscopic moments for the different substituents.

RECENTLY[1] we published a refinement of our earlier treatment of the chiroptical properties of the benzene chromophore. This is based on two assumptions:

(1) That the chiral sphere which is nearest to the chromophore determines in general the sign of the Cotton effect, and

(2) Sector rules are built up from the nodal planes of the corresponding polarization diagram[2] of the respective transitions ($^1B_{2u} = {}^1L_b$ and $^1B_{1u} = {}^1L_a$), the plane of the ring and additional planes, if the local symmetry of the compounds investigated requires them.

The influence of substituents on the intensity of the benzene UV-bands has been treated theoretically by Platt[3] by making use of the "spectroscopic moments", whose signs and magnitudes have been investigated in more details by Petruska.[4] The importance of the spectroscopic moments for the calculation of CD-spectra of differently substituted aromatic compounds (paracyclophanes) has been demonstrated.[5]

For a detailed treatment of the chiroptical properties of ring-substituted benzene derivatives one has to take into account not only the signs but also the magnitudes of the spectroscopic moments. As, however, Platt's[3] and Petruska's[4] values are not always proportional to each other, and Petruska[4] has pointed out that quantitative relationships cannot be obtained for groups with a monoshift of more than 1500 cm^{-1} in his calculations (the important RO-group belongs to this class), we in a first approximation assign identical magnitudes to all moments, and apply this simple treatment to the ^1L_b-band CD. Furthermore it is not known whether these moments have the same magnitude *e.g.* for a group CH_2X "freely" rotating and CHX confined to one single conformation by incorporation into a ring.

The chiral third sphere

Fig. 1 shows the polarization diagram for the ^1L_b-band (A) and the signs for the third sphere contributions to the Cotton effect in the upper sectors for a chirally monosubstituted phenyl compound (B) and in a tetralin (C). One has to differentiate

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strictly between the signs in a polarization diagram and in a sector rule for the CD: in the first case only their pattern is important, not their absolute value, in the second on the contrary we need the absolute values. To make this difference better discernible in the figures we use throughout this paper simple + and − signs for the polarization diagrams, ⊕ and ⊖ for the sector diagrams. The spectroscopic moment vector of a substituent at any C-atom of the benzene ring is perpendicular to the corresponding nodal plane through this atom and we can direct it, *e.g.*, from a positive to a negative sector (Fig. 2A). This choice is arbitrary, but we have to use it then always in the same way. Fig. 2B gives a schematic drawing of such a chirally monosubstituted benzene derivative together with the signs of the sector rule.[1] If we assign the polarization diagram signs as in Fig. 2A. then the moment vector points into a positive upper sector of Fig. 2B. In a more substituted benzene derivative we have now just to determine the direction of the over-all spectroscopic moment vector, starting from

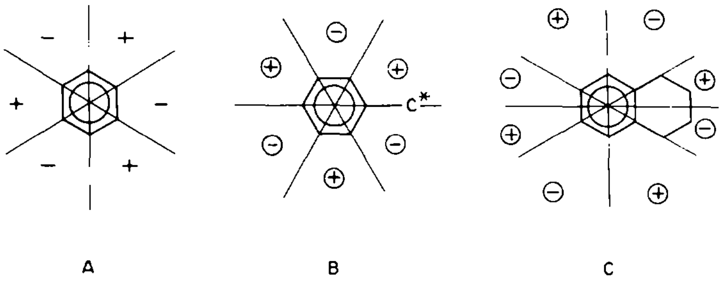


FIG 1. Polarization diagram (A) of the benzene ^1L_b-band and signs for the third sphere contributions to the CD within this band in upper sectors of a chirally monosubstituted benzene (B) and a tetralin (C)

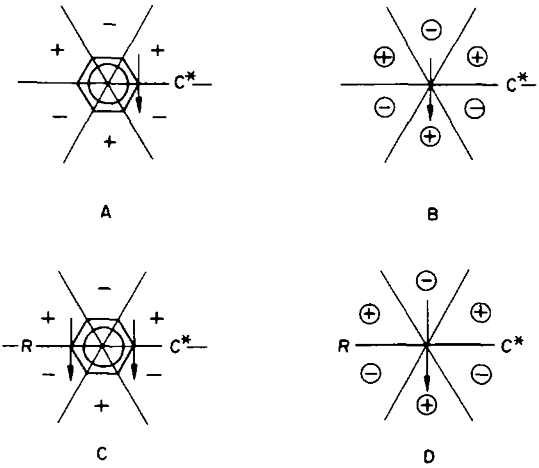


FIG 2. Polarization diagrams of the ^1L_b-band for a chirally mono substituted benzene derivative (A, signs are chosen arbitrarily) and its *p*-substituted analogue (C) and signs for the third sphere contributions to the CD within this band in upper sectors for the two compounds (B and D). For details see text.

the same sign pattern relative to the chiral substituent as in Fig. 2A, and obtain the corresponding sector rule by adjusting the CD-signs so that the tip of the vector is in a positive sector.

For a *p*-disubstituted benzene (R is an achiral substituent with a positive spectroscopic moment in our examples) Fig. 2C shows that the two individual spectroscopic moment vectors are parallel; the sum vector has, therefore, the same relative position with respect to the Ar-C* bond (Fig. 2D) as in case of the monosubstituted compound (Fig. 2B) and the pattern of sectors is the same. For a *m*- or *o*-disubstituted benzene on the other hand the sum vector has been rotated relative to its position in the monosubstituted compound in such a way, that a sign inversion takes place (Fig. 3). We expect, therefore, that in a homochiral family of compounds the parent compound and its *p*-substituted derivative have the same sign of the Cotton effect within the ^1L_b-band, whereas sign inversion takes place for the *m*- and *o*-isomers.

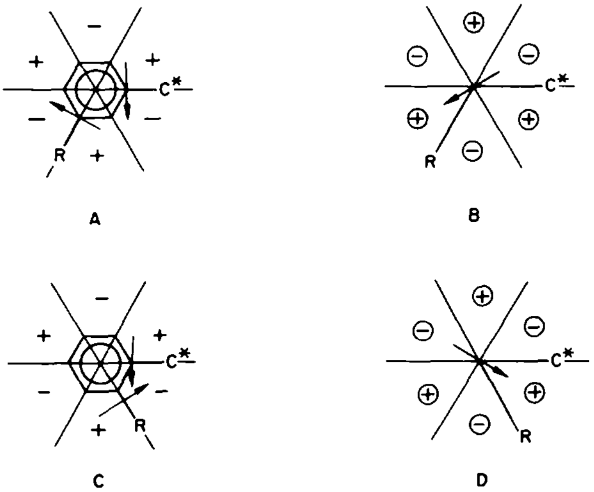
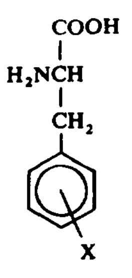
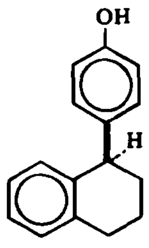


Fig 3. Polarization diagrams of the ^1L_b-band for a *m*- (A) and *o*-substituted (C) analogue of a chirally substituted benzene (signs chosen as in Fig. 2A) and signs for the third sphere contributions to the CD within this band in the upper sectors for the two compounds (B and D). For details see text.



1: X = H
2: X = *p*-OH
3: X = *m*-OH
4: X = *o*-OH



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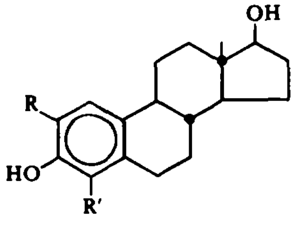


6: R = R′ = H
7: R = Me, R′ = H
8: R = H, R′ = Me

Experimentally this has indeed been found. L-Phenylalanine[6,7] (1) gives a positive CD at about 260 nm, as does its *p*-hydroxy derivative L-tyrosine[6,8] (2), whereas L-*m*-tyrosine [8](3) and L-*o*-tyrosine [8](4) show negative CD-bands in the same area. Korver[9] recently in a series of ring-substituted mandelic acids found other results: the *p*- and the *o*-disubstituted derivatives showed sign inversion. In his case the chiral center is, however, next to the benzene ring and one may reasonably assume that the population of different rotamers is changed by introduction of a substituent. This may be due, *e.g.*: to a different ability of the ring for hyperconjugation depending on the substituent position. Chiral center and benzene ring are separated by a CH_2-group in case of the phenylalanine-tyrosine group of amino acids, so that no such conformational changes are probable. In their theoretical calculations Hooker and Schellman[8] neglected the spectroscopic moment of the alkyl side-chain and treated the tyrosines as phenols. By this they also got a correct prediction for the found signs of the CD within the ${}^1L_b$-band, the sign difference between 6 and 7 (see later) can be explained, however, only by taking into consideration also the moment of the methyl group.

The chiral second sphere

In tetralins and tetrahydroisoquinolines the helicity of the non-aromatic ring determines the sign of the Cotton effect.[1] Fig. 4 shows the correlation between the

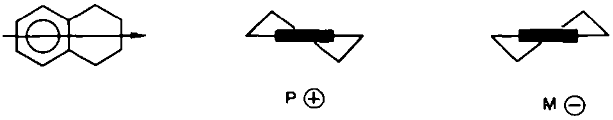


FIG 4. Sign of the second sphere contribution of a tetralin to the ${}^1L_b$-band CD. The arrow indicates the direction of projection, P and M refer to the helicity of the non-aromatic ring.

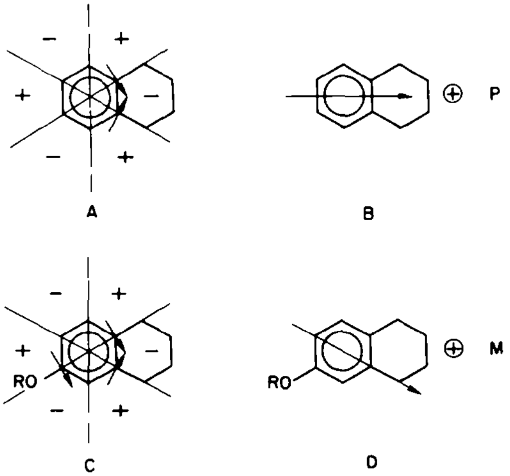
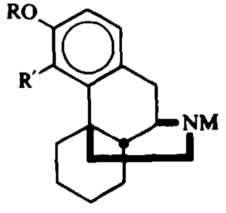


FIG 5. Polarization diagrams of the ${}^1L_b$-band for a tetralin (A, signs chosen arbitrarily) and its 6-substituted analogue (C, R = H or Alkyl) and direction of the over-all spectroscopic moment vector for these compounds (B and D). A positive sign of the CD within this band indicates a (*P*)-helicity for A and a (*M*)-helicity for C

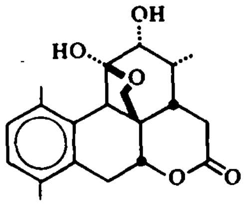
sign of the ${}^1L_b$-band CD and this helicity for a tetralin (or tetrahydroisoquinoline) not further substituted in the benzene ring: a (*P*)-helicity of the cyclohexene (or piperideine) ring gives rise to a positive, a (*M*)-helicity to a negative sign. This rule was first checked by us[1] with a rigid *trans*-1,2,3,4,4a,9,9a,10-octahydroanthracene. A further good example is compound **5** which gives a positive Cotton effect within the ${}^1L_b$-band absorption.[10] X-ray data for a derivative of **5** proved[10] that in the crystalline state the substituent adopts a pseudoequatorial conformation giving rise to a (*P*)-helicity of the cyclohexene ring.

If we assign arbitrarily the signs for the polarization diagram of a tetralin as given in Fig. 5A, then Fig. 5B shows the direction of the over-all spectroscopic moment vector. Thus, if this vector lies in the direction of the C_2-axis of the tetralin, (*P*)-helicity leads to a positive ${}^1L_b$-band Cotton effect. As there is a simple relationship between the helicity of the ring and the signs of the third-sphere contributions[1] (Fig. 1C) we can predict that for a substitution pattern of the benzene ring which leaves this direction unchanged (or reverses it) the same correlation of Fig. 4 will hold. If this vector is rotated, however, then it depends on the angle of this rotation whether we get the same correlation or the opposite one within a family of homochiral compounds. According to Fig. 1C a rotation of approximately 30° should lead to sign inversion, for other angles we must resort to experiment.

Fig. 5C and D show the diagrams for a substitution pattern as in the oestrogenic hormones (3-hydroxysteroids with ring A aromatic). The vector is rotated around 30° and the expected sign inversion is indeed found. In a steroid with aromatic ring A and normal stereochemistry (8β, 9α) ring B has to adopt a (*P*)-helix and the sign of the ${}^1L_b$-band Cotton effect according to Fig. 5C, D should be negative. Indeed a negative CD was found[0] for oestradiol (**6**). The same is true for levorphanol[11] (**9**) if we assume that the smaller of the two rings forming second spheres determined the CD (*c.f.* the discussion of this point in ref.[1]).



9: R = R' = H
10: R = Me, R' = OH



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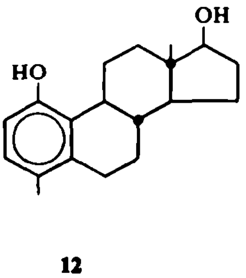

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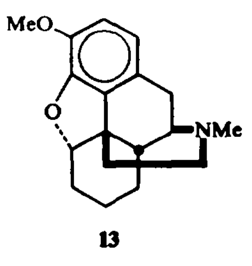

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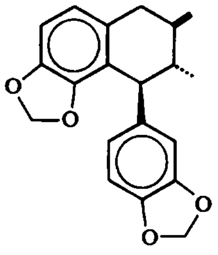

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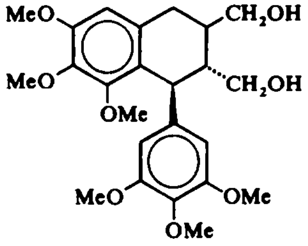

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The CD of three types of disubstituted compounds is available in the literature. 6,7-Dioxygenated tetrahydroisoquinolines are present in most of the aromatic alkaloids investigated (*e.g.* Amaryllidaceae alkaloids,[12,13] tetrahydroberberine alkaloids,[6,14] argemonine[1,15,16] etc.), and 6,7-dioxygenated tetralines are found in many of the 4-aryltetralin type lignans.[17–19] In all these cases (*P*)-helicity leads to a positive ${}^1L_b$-band CD, which is expected according to Fig. 6 A, B. The same holds for 2-methyloestradiol (7).[6]

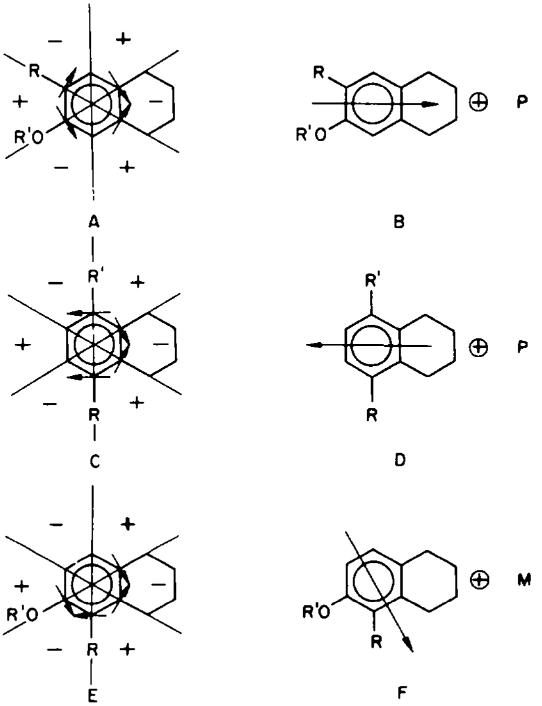

FIG 6. Polarization diagrams of the ${}^1L_b$-band for a 6,7-disubstituted (A, R = OH, OAlkyl or Alkyl, R' = H or Alkyl), 5,8-disubstituted (C, R' = Alkyl or R = Alkyl, R'' = OH) and 5,6-disubstituted tetralin (E, R = O, OAlkyl or Alkyl, R' = H or Alkyl) and direction of over-all spectroscopic moment vector for these compounds (B, D and F). A positive sign of the CD within this band indicates a (*P*)-helicity in the first two cases (A, C), a (*M*)-helicity, however, in the last (E), The signs in the polarization diagrams are chosen as in Fig. 5A

5,8-Disubstitution according to Fig. 6 C, D also must lead to the same correlation as that given in Fig. 4. Indeed for chaparrol[20] (**11**) (R = R' = Me in Fig. 6 C, D) and in the dienone-phenol-rearrangement product **12**[6] (R = Me, R' = OH in Fig. 6 C, D), both with (*P*)-helicity of the cyclohexene ring, a positive CD was found.

For a 5,6-disubstituted tetralin or tetrahydroisoquinoline on the contrary the spectroscopic moment vector is rotated around 60° (Fig. 6 E, F) compared to the situation in Fig. 4. The experimental values found with tetrahydroberberine alkaloids,[14] 4-methyloestradiol[6] (**8**) and morphine type alkaloids[21] [as *e.g.* dihydrodeoxycodeine D (**13**) or tetrahydrodeoxycodeine (**10**)] all gave the same result, *viz*: that for this type (taking into account again only the smaller second sphere) (*P*)-helicity leads to a negative $^{1}L_{b}$-band CD. Rotation of the spectroscopic moment vector around 60° leads, therefore, also to sign inversion. On the basis of these results one has then to conclude that the absolute configuration of otobain is that given in formula **14**. This is opposite to that which has been derived[17, 19] on the assumption that the substitution pattern of the benzene ring does not influence the sign of the Cotton effect.

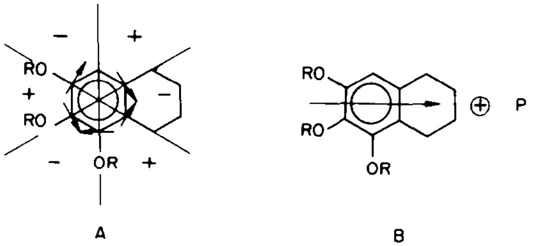

FIG 7. Polarization diagram of the $^{1}L_{b}$-band for a 5,6,7-trisubstituted tetralin (A, R = H or Alkyl) and direction of the over-all spectroscopic moment vector (B). A positive sign of the CD within this band indicates a (*P*)-helicity. The signs in the polarization diagram are chosen as in Fig. 5A

Finally for 5,6,7-trisubstituted tetralins and tetrahydroisoquinolines according to Fig. 7 A, B the direction of the spectroscopic moment vector. indicates the *same* relationship between the sign of the $^{1}L_{b}$-band CD and the helicity of the non-aromatic ring as in the unsubstituted case (Fig. 4). This has indeed been found for Amaryllidaceae alkaloids,[12, 13] tetrahydroberberine alkaloids[14] and some lignans, as *e.g.* lyoniresinol dimethyl ether (**15**).[17, 19]

Although this treatment of the $^{1}L_{b}$-band Cotton effect of ring-substituted benzene derivatives is very crude because of the fact that we used the same length for all spectroscopic moment vectors, it leads nevertheless to a correct description of the observed conservation or change of CD-signs within several families of homochiral compounds. At present we are preparing model compounds with different substitution patterns in the benzene ring to test and refine this treatment further.

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