A New Approach in Exciton-Coupled Circular Dichroism (ECCD)—Insertion of an Auxiliary Stereogenic Center

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ABSTRACT There are cases in which exciton coupling between two chromophores does not occur because the two electric transition moments which should interact are coplanar. This is seen with cyclohexane-1,4-diols (both ee or ea) and a wide variety of 3-hydroxy carotenoids, 3-hydroxyretinoids, etc. A general approach to deal with such cases is to acylate one of the hydroxyl groups with a chiral allenic acid substituted with a suitable chromophore, e.g., CHROM-CH=C=CH-COOH. The allenic bond introduces a 90° twist at the italicized central carbon so that the allenic CHROM now couples with the second chromophore. This concept of introducing an allenic auxillary center should be of general applicability in other similar cases.

KEY WORDS: allene, absolute configuration, chirality, method, synthesis, resolution, chromophore, HPLC

The through-space coupling of two or more chromophores in chiral substrates gives rise to exciton-coupled circular dichroism (ECCD), which is characterized by bisignate circular dichroism (CD) curves. The signs of these "split" Cotton effects (couplets) reflect the chirality between the electric chromophores are present; this gives rise to complex and transition moments of interacting chromophores (Fig. 1). Coupling also occurs when more than two identical or different chromophores are present; this gives rise to complex and characteristic CD curves. The exciton chirality method, based on the ECCD phenomenon, nonempirically establishes, on a microscale, absolute conformations or conformations in solution. Figure 1 shows the partial structure of a steroid 2,3-bis-fl-substituted benzoate. Although the benzoate group can adopt various conformations, the most stable is the one depicted in which the ester bond is s-cis while the ester carbonyl and 3-H are eclipsed. This is supported by X-ray, MM2 calculations, and ECCD data; namely, all interpretations of the ECCD of benzoates and other acylates performed so far, including the extensive pyranose acylate library, have been based on this conformer and have proven this view to be correct.

Determination of the absolute configuration of the moiety shown in Figure 1 means determination of the absolute sense of chirality between the C(2)-O and C(3)-O bonds; this in turn is approximated by the chirality between the two longitudinal \(^1L_{\alpha}\) electric transition moments (\(\mu\)) of the benzoate chromophore, which gives rise to the main absorption band. When the chirality constitutes a clockwise turn, viewed from C(3) to C(2) or from C(2) to C(3), it is defined as positive. Such through-space coupling of transition moments leads to a bisignate CD curve centered at the absorption maximum, with positive 1st, at longer wavelengths, and negative 2nd Cotton effects, respectively. Such a couplet is defined as a positive couplet and vice versa. The distance between the peak and trough of a split CD curve is defined as the "amplitude" or \(A\) value and is expressed in \(\Delta\epsilon\). There is no exception in the relationship between the signs of transition moment chiralities and those of bisignate CD curves, positive and negative chiralities always leading to positive and negative CD couplets, respectively. Some pertinent aspects of the practical significance of ECCD are listed below:

(i) The intensity of the \(A\) value usually is such that the amount of sample required for the exciton chirality method can be far less than that required for other CD measurements, i.e., several \(\mu\)g.

(ii) Any chromophore with large \(\epsilon\) and known direction of the electric transition moment, \(\mu\), can be used.

(iii) The chromophore can be introduced by derivatization or could already be preexisting in the molecule, e.g., enone, diene, triene, etc.

(iv) In the case of cyclohexyl 1,2-bisbenzoates, the \(A\) value is maximal at a projection angle ca. 70°. There is no coupling when the projection angle is 0° or 180° (see also Fig. 3).

(v) When the two chromophores are identical, the \(A\) value is proportional to \(\epsilon^2\) and is inversely proportional to \(R^2\), where \(R\) is the interchromophoric distance.

(vi) When more than two identical chromophores are coupled, the \(A\) value is approximated by pair-wise addition of the interacting chromophores. For example, in the triad A/B/C,
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The A value is represented by the sum of respective A values of the component pairs A/B, B/C, and A/C (pair-wise additivity rule).

(ii) Chromophores with \( \lambda_{\text{max}} \) as far apart as 100 nm can still couple.

(iii) The coupling of more than two different chromophores yields a complex CD curve extending over the range covered by these chromophores. The pair-wise additivity rule holds for such complex CD curves as well, therefore giving rise to characteristic fingerprint curves. For example, the p-bromobenzoate chromophore, 245 nm \( \epsilon \) 19500 (in MeCN), and the p-methoxycinnamate chromophore, 306 nm \( \epsilon \) 23400/227 nm, \( \epsilon \) 12500 (in MeCN), esterified to the hydroxyl functions of hexopyranoses are intensely coupled and yield CD spectra which are characteristic of each substitution pattern in the range of 230-330 nm.

Although the exciton chirality method is an extremely versatile microscale technique applicable to a wide variety of compounds, it cannot be applied to cases shown in Figure 2 because the amplitudes of the CD curves are extremely weak or nil (unpublished observations). The conditions for the absence or presence of coupling between two transition dipoles are illustrated in Figure 3.

In Figure 3I, if A, B, C, and D are all in the same plane, there is no coupling. This is exemplified in Figure 2 by the 3β,7β-bisbenzoate of an A/B trans-steroid, 3α,7α-bisbenzoates of an A/B cis-steroid, and the 2,4-bisbenzoate of glucose.

In Figure 3II, (a subset of I), if any three points, e.g., A, B, C, are collinear, D must form a plane with them and there is no coupling. Many 3-hydroxy-carotenoids and retinoids are known (Fig. 2), but despite the extensive CD studies performed by Noak, Liaen-Jensen, and others a nonempirical method to determine the configuration of the 3-hydroxy function is lacking.

In Figure 3III, the occurrence of exciton coupling requires A, B, C, and D to be noncoplanar. The 3-acylates of 3-hydroxyretinoids and 3-hydroxycarotenoids belong to category II and show only weak coupling (Fig. 2). The \( \beta \)-dimethylamino-benzoate chromophore (dmaBz), with its quite intense absorption, \( \lambda_{\text{max}} \) (EtOH) 309 nm (\( \epsilon \) 30400), is used widely in ECCD. In the 3-\( \beta \)-dimethylaminobenzoate of (3R)-3-hydroxy-\( \beta \)-ion-one, (3R)-IVc, it couples with the ionone chromophore, \( \lambda_{\text{max}} \) (hexane) 280 nm (\( \epsilon \) 8200) to give a negative split CD of low intensity (Fig. 4), UV (hexane) 300 nm (\( \epsilon \) 33900); CD (hexane) 303 nm (−5.3), 273 nm (+3.0). This negative CD shows that the electric transition moments of the benzoate and the dienone constitute a negative chirality. However, this is an interesting case where we cannot assign the configuration at C-3 despite the negative couplet. There are several reasons for this:

(i) as evidenced by the nuclear Overhauser effect (NOE) observed between both 7-H/8-H and the 1,1-gemdimethyl and 5-methyl groups, the side-chain is fluctuating; then, depending on the side-chain conformation, its chirality with 3-benzoate becomes slightly positive or slightly negative; (ii) the cyclohexene conformation is also flexible; (iii) however, the overriding cause is that the two chromophores are in a “para” position with respect to the cyclohexene ring (Fig. 2), and this makes this bichromophoric system fall closely into category II. The negative couplet in Figure 4 simply represents the overall chirality of a mixture of various conformers and cannot be used to assign the 3-hydroxy configuration. The amplitude is influenced by both the solvent and the nature of the 3-acylate. Attempts to assign configurations to 3-hydroxylated carotenoids by introducing appropriate chromophores, e.g., retinoates (Fig. 2), also failed because of weak or nil coupling (unpublished observations).

A general approach to cope with such cases would be to incorporate an auxiliary chiral moiety that induces exciton coupling into the molecule. One such approach is to derivatize one of the hydroxyl groups with a chiral allenic acid substituted with a suitable chromophore, e.g., CHROM–CH=CH=C=COOH. The allenic bond introduces a 90° twist at the italicized central carbon so that the allenic CHROM now couples with the chromophore in the parent compound. In the case of 3-hydroxyretinoids or carotenoids, the chirality becomes clearly defined irrespective of side-chain and/or cyclohexenyl ring conformation. This concept of intro-

![Fig. 1. The exciton chirality method nonempirically determines the absolute configurations of molecules in solution. A positive chirality between the electric transition dipoles gives a bisignate CD curve with a positive first Cotton effect. This is exemplified by the longitudinal \( \Delta \lambda \) transition dipoles of \( \beta \)-substituted benzoates.](image-url)
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**Fig. 2.** Systems where the exciton chirality method cannot be applied because no characteristic exciton split CD curve is observed due to unfavorable alignment of the two chromophores.

**Fig. 3.** The existence of ECCD can be determined from the relative positions of the four points (A, B, C, and D) that define the two transition dipoles.

**Fig. 4.** CD spectrum of coupled (3R)-3-hydroxy-β-ionyl 4'-dimethylaminobenzoate [(3R)-IVc] (dmaBz = dimethylaminobenzoate).

**MATERIALS AND METHODS**

**General Experimental Procedures**

Melting points are uncorrected. $^1$H and $^{13}$C-NMR spectra were recorded on a Varian (Walnut Creek, CA) VXR-400, 300 or 200 MHz spectrometers as noted. Electron impact (EI), chemical ionization (CI), and high resolution (HR)-EI mass spectra were measured on NERMAG (Paris, France) R1010 and JEOL (Tokyo, Japan) JMS-DX303 HF mass spectrometers, respectively. Ultraviolet-visible (UV/vis) and CD spectra were recorded in hexane or acetonitrile solution on a Perkin-Elmer (Norwalk, CT) Lambda 4B UV/vis spectrometer and a Jasco J-720 spectropolarimeter, respectively. Intra-
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Scheme 1. Synthesis of biphenylallenic acid esters (S)-Ia and (R)-Ib.

Synthesis of Biphenylallenic Acid (Scheme 1)

Ethyl 4-biphenyl-2-methylbuta-2,3-dienoate [(R, S)-I] 4-Biphenylacetic acid (212 mg, 1.00 mmol) was dissolved in thionyl chloride (10 ml) and refluxed for 3 h. The excess thionyl chloride was evaporated under reduced pressure. To a solution of acid chloride in CH₂Cl₂ (2 ml), a solution of triethylamine (280 ml, 2.0 mmol) and [I-carboethoxyethanoltriphenyl-phosphorane (362 mg, 1.00 mmol) in CH₂Cl₂ (10 ml) was added and stirred overnight under argon atmosphere. The solvent was removed under reduced pressure and the solid residue was extracted with pentane. The pentane was evaporated and the crude product purified by flash chromatography (silica gel, CH₂Cl₂) to give the racemic biphenylallenic ethyl ester [(R,S)-I] (122 mg, 44%). White powder, mp 94°-97°C (from pentane), 400 MHz ¹H-NMR (CDCl₃) δ 1.70 (t, 3H, J = 7 Hz, O-CH₂CH₃), 2.07 (6.56 (9, lH, J = 3 Hz, 4-H), 7.3-7.7 (m, 9H). 75 MHz ¹³C-NMR (CDCl₃): δ 14.2, 15.0, 61.0, 96.8, 99.4, 126.8, 127.3, 127.4, 127.6, 127.7, 131.5, 140.5, 140.5, 166.9, 212.5. IR (KBr) 3020, 3010, 2986, 1946, 1708, 1268, 1116 cm⁻¹. HR-EI calculated for C₁₉H₁₈O₂ 278.1307, found 278.1310.

Resolution of ethyl 4-biphenyl-2-methylbuta-2,3-dienoate [(R,S)-I] Resolution of the allenic enantiomers was achieved by chiral HPLC using a Chiralcel OD 250 mm x 20 mm column. Baseline separation (Fig. 5) was possible for injections up to 10 μl at a concentration of 0.22 mg/μl. Once a sufficient quantity of each enantiomer was isolated, the respective absolute stereochemistries could be determined by CD (see “Discussion”).

UV (hexane) 276 nm (ε 28300), 210 (38800). CD (hexane) [(S)-Ia] 274 nm (Δε +11.4), 226 nm (Δε +6.9), 208 nm (Δε +8.0); [(R)-Ib] 277 nm (Δε -11.3), 226 nm (Δε -6.7), 209 nm (Δε -8.0).

4-Biphenyl-2-methylbuta-2,3-dienoic acid [(R,S)-II] (Scheme 2) 4-Biphenylallenic acid ester [(R,S)-I] (291 mg, 1.05 mmol) in 1,2-dimethoxylethane (DME, 10 ml) was treated with aqueous solution of potassium hydroxide (0.5 M, 10 ml). The solution was stirred at room temperature for 2 h, concentrated under reduced pressure, diluted with water (50 ml), and extracted with ether (50 ml) to remove any remaining ester. The aqueous phase was adjusted to pH = 1 with 1 M HCl and extracted with CH₂Cl₂ (2 x 50 ml). The combined organic extracts were washed with brine (100 ml), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1%
acetic acid, 2% ethyl acetate/CH₂Cl₂ to afford the racemic
acid ([R,S]-II) (224 mg, 86%) as white powder.

White powder, mp 171-172°C (from CH₂Cl₂), 400 MHz
¹H-NMR (acetone-δ) δ 1.96 (d, 3H, J = 3 Hz, 2-Me), 6.69
(q, 1H, J = 3 Hz, 4-H), 7.35 (br. t, 1H, J = 8 Hz, ArH), 7.44
(4H, ArH), 7.65 (4H, ArH), 10.95 (br. s, 1H, CO₂H). IR
(KBr) 2977, 2671, 2554, 1944, 1681, 1488, 1420, 1293, 1136
cm⁻¹. HR-EI calculated for C₁₇H₁₄O₂ 250.0993, found
99.7, 127.5, 128.1, 128.3, 128.6, 129.7, 131.2 or 132.8,

To a solution of acid

and stirred for 3 h at room temperature. The solvent and
excess thionyl chloride was evaporated under reduced pres-
esure. To a solution of acid chloride and (3R)-3-hydroxy-
P-ionone (3R)-3-hydroxy-P-ionyl

Scheme 2. Formation of diastereomeric biphenylallenic (S)-3-hydroxy-β-ionone esters ([S,3R]-IIIa and (R,3R)-IIIb).
ids. Furthermore, a comparison of calculated and experimental UV and CD data for this type of chiral allene revealed a useful correlation between the sign of long axis B1 sub aromatic Cotton effect and the absolute configuration; namely, all studied phenylalene carboxylic acids of S configuration consistently exhibit a positive CD band ca. 240-250 nm and vice versa.

As expected, in biphenylallenic ethyl esters Ia and Ib (Fig. 6) the longitudinal aromatic transition is shifted bathochromically in comparison to the long axis B1 sub band of phenylalene esters and appears as a UV band at 276 nm (ε 28300, hexane). The corresponding CD spectra of Ia and Ib in hexane exhibit a positive CD Cotton effect (274 nm, Δε + 11.4) and negative Cotton effect (277 nm, Δε -11.3), respectively. In view of these experimental data and the above-mentioned correlation, the biphenylalene ester Ia is of S configuration, while the ester Ib should be of R configuration.

S-cis and S-trans Isomerization

The asymmetry present in the allene chromophore provides a complication absent in symmetrical chromophores such as benzoate. The single bond between the ester carbonyl and the allene unit can exist in the s-cis or s-trans conformation. Studies have shown that the s-trans conformation is preferred in the crystalline state while the s-cis is only slightly preferred in solution. Clearly the s-cis and s-trans conformations will both exist in solution, so it is important to understand how this should affect the observed CD data.

When a chiral allene, R-biphenylalene acid [(R)-Ib] for example, is attached to a chiral alcohol, such as (3R)-3-hydroxy-p-ionone [(3R)-IVa], two conformers are possible (Fig. 7). Examination of the relationship between the two chromophore transition dipoles shows that the nature of the allene chromophore causes both s-cis and s-trans conformers to have negative chiralities between the two respective chromophores. Thus both the s-cis and s-trans conformers of the R-allene p-ionone [(R,3R)-IIIb] are predicted to give the same negative first Cotton effect.

It should be noted here that the S-biphenylalene p-ionone ester [(S,3R)-IIIa] (Scheme 2) also has two similar conformers with positive chiralities. Models show, however, that the dipole alignment in both of the S conformers suggests much weaker exciton coupling than either of the R conformers, leading to a smaller Δε.

Preparation and Purification of Coupled p-Ionone and Biphenylalene Acid

Hydrolysis of the allenic acid ethyl ester [(R,S)-I] (Scheme 1) was achieved with potassium hydroxide in water and DME. When methanol was used as cosolvent in the hydrolysis reaction, a methanol adduct to a center carbon atom of allene function was obtained. Moreover, when the chiral ethyl esters (S)-Ia or (R)-Ib were hydrolyzed, racemization of the chiral allene function was observed, presumably via an equilibrium between the allene and propyne functions. Therefore, the racemic acid [(R,S)-II] was used for the next esterification
CONCLUSION

The use of allene as a chiral auxiliary induces clear-cut chirality leading to useful CD couplets in molecules where conventional usage of chromophores gives no couplets or to inconclusive interpretations of the couplets because the transition dipole chiralities are geometrically ambiguous. This concept of induced CD expands ECCD to molecules exemplified in Figure 2, where the exciton chirality method was not previously applicable. While the concept of the chiral auxiliary chromophore has been shown to work experimentally, the first chromophore to be used, the biphenylallene chromophore, presented many difficulties in its handling. Studies with other auxiliary chromophores are in progress.

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LITERATURE CITED


