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# A new exciton-coupled circular dichroism method for assigning the absolute configuration in acyclic α- and β-hydroxy carboxylic acids

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***Abstract:*** A new exciton-coupled circular dichroism (ECCD) method is described for the configurational assignment of α- and β-hydroxy carboxylic acids. Using the chromophoric combination 2-naphthoate/9-methylanthryl group, the absolute stereochemistry of α- and β-hydroxy carboxylic acids can be deduced easily from a single CD measurement. The developed microscale method is also useful for chiral amino acids and natural products containing carboxyl groups. © 1997, Elsevier Science Ltd. All rights reserved.

The exciton-coupled circular dichroism (ECCD) is a nonempirical microscale method to determine the absolute configuration and conformation of organic molecules and has been widely used in the field of natural products.[1] ECCD is based on the through space coupling of two or more chromophores in chiral substrates giving rise to a bisignate circular dichroism (CD) curve. The interacting chromophores include those preexisting in the molecule and/or those introduced through O- or N-acylation. The signs of the resulting split Cotton effects (couplets) establish the absolute sense of twist of the electric transition moments in a nonempirical manner.[1] Recent studies have focused on extending the applicability of ECCD to unexplored areas by developing (i) chromophores with red shifted absorption maxima;[2] (ii) chromophores with intense absorptions resulting in strong interactions over a large distance e.g. porphyrins with $\epsilon$=350 000;[3] and (iii) chromophores which are useful for induced chirality.[4] The methods developed so far are most commonly applied to compounds bearing two or more hydroxyl or amino groups that may be derivatized with an exciton-coupling chromophore. However, to date no ECCD method has been established to determine the stereochemistry in molecules containing carboxyl groups.

Chiral α-hydroxy acids are important building blocks for the synthesis of optically active glycols,[5a] halo esters,[5b] epoxides[5c] and amino acids.[5d] Several enzymatic[6] and chemical[7] methods have been employed for the synthesis of α-hydroxy funtionalized carboxylic acids. Nevertheless, a general method for the stereochemical assignment of the synthesized α-hydroxy acids is still lacking. In the following, we describe a new ECCD method for the configurational assignment of α- and β-hydroxy carboxylic acids, exemplified by 2-hydroxypropanoic acid **1** and 3-hydroxybutanoic acid **2**.

The application of ECCD to α- or β-hydroxy carboxylic acids requires two chromophores suitable for exciton coupling. The 'bichromophoric' ECCD method utilizes two different types of chromophores which are selectively introduced at two different types of hydroxyls or other functional groups.[8] Using 9-anthryldiazomethane **5** carboxyl groups can be selectively derivatized to the corresponding 9-methylanthryl esters (Figure 1c). The fluorescent chromophore 9-anthryldiazomethane **5** was developed as fluorescent marker for the HPLC analysis of fatty acids:[9] it can be easily synthesized from 9-anthraldehyde hydrazone[9c] by oxidation with HgO[9a] to yield 80–90%,[11] stored for several months and used whenever needed. Since the 9-methylanthryl group may be introduced selectively to carboxyl groups, the remaining secondary hydroxyl group in position 2 or 3 can be derivatized with the 2-naphthoate chromophore. Subsequent treatment of the methylanthrylesters with 2-napthoyltriazole[10] **6** finally gave 9′-methylanthryl 2-(2″-naphthoate)propanoates **3** and 9′-methylanthryl 3-(2″-naphthoate)butanoates

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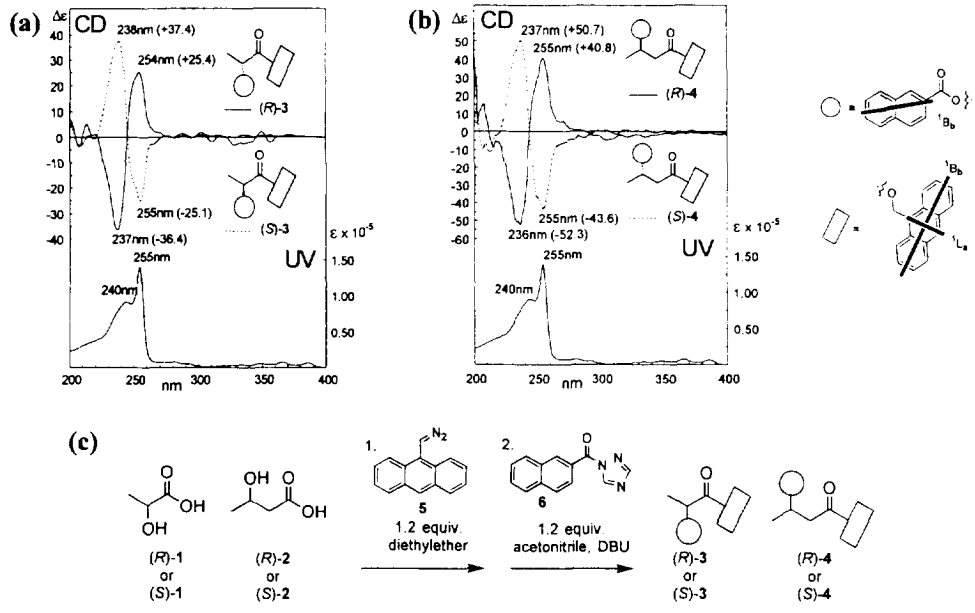


**Figure 1.** (a and b) UV and CD spectra of bichromophoric derivatives (*R*)-**3**, (*S*)-**3**, (*R*)-**4** and (*S*)-**4** in MeCN (1 cm cell). (c) Derivatization of α- and β-hydroxy carboxylic acids **1** and **2** to the corresponding bichromophoric derivatives **3** and **4** (— — transition dipoles).

**4** (Figure 1c).[11] The bichromophoric derivatives **3** and **4** are highly fluorescent, facilitating easy purification on small scale. The CD and UV[12] spectra of **3** and **4** are shown in Figure 1.[13]

In 9′-methylanthryl 2(*R*)-(2″-naphthoate)propanoate (*R*)-**3** the long axis $^1B_b$ transition (Figure 1) of the 9-methylanthryl chromophore with its quite intense absorption couples with the $^1B_b$ band of the 2-naphthoate chromophore to give a positive split CD curve with extrema at 254 nm ($\Delta\epsilon$=+25.4) and 237 nm ($\Delta\epsilon$=−36.4) and an amplitude *A* of +61.8. This positive CD shows that the electric transition dipoles ($^1B_b$) of the 9-methylanthryl chromophore and the 2-naphthoate constitute a positive chirality. The corresponding optical antipode (*S*)-**3** exhibits an opposite bisignate CD curve with a negative Cotton effect at 255 nm ($\Delta\epsilon$=−25.1) and a positive CE at 236 nm ($\Delta\epsilon$=+37.4), amplitude *A*=−62.5. The methylanthryl/2-naphthoate couplings in 3-hydroxybutanoic acid derivatives (*R*)-**4** and (*S*)-**4** are shown in Figure 1b. The CD coupling in 9′-methylanthryl 3(*R*)-(2″-naphthoate)butanoate (*R*)-**4** between the two chromophores give rise to a positive split CD curve with CEs at 255 ($\Delta\epsilon$=+40.8) and 236 nm ($\Delta\epsilon$=−52.3), *A*=+93.1. The corresponding (*S*)-**4** enantiomer shows a similar CD curve with the same shape but opposite sign of Cotton effects at 255 ($\Delta\epsilon$=−43.6) and 237 nm ($\Delta\epsilon$=+50.7), with an *A* value of −94.3. Thus the absolute stereochemistry of α- and β-carboxylic acids can be deduced from a single CD measurement without any further understanding of the exciton coupling involved. In addition, our data are in agreement with predictions based on MM2 calculations using MacroModel 5.0.[14] The amplitudes of split Cotton effects are inversely proportional to the square of interchromophoric distance and proportional to the square of extinction coefficients.[1] Furthermore, the amplitude is dependent on the torsion angle between the electric transition dipoles of the chromophores.[1] There is no coupling, if the projection angle is 0° or 180°, whereas coupling is maximal for a torsion angle of ca 70°. Due to the closer distance of the two chromophores in α-hydroxy acids **3** we would expect a stronger coupling (or *A*-value) compared to **4**. However, as shown in Figure 1b, the amplitudes of the β-hydroxy carboxylic acids derivatives (*R*)-**4** and (*S*)-**4** are stronger than the *A* values of the corresponding α-hydroxy acids (*R*)-**3** and (*S*)-**3** (Figure 1). This can be explained by the conformational difference between **3** and **4**. Whereas the interchromophoric distance in **4** is due to the free rotation of the methylanthryl group,

almost the same as in **3**,[14] the torsion angle between the transition dipoles of the chromophores is very small in the case of the α-hydroxy acids (*R*)-**3** and (*S*)-**3**, compared to (*R*)-**4** and (*S*)-**4**;[14] therefore we obtain a stronger amplitude in **4**.

The above data clearly demonstrate that the two-step derivatization using the 9-methylanthryl- and the 2-naphthoate chromophore provides a general microscale method for absolute configurational assignments of α- and β-hydroxy carboxylic acids. This ECCD method opens a new field of applications to chiral amino acids as well as many natural products containing carboxyl groups, e.g. fumonisins. Further studies and applications are currently under investigation.

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11. The two step derivatization: to a solution of hydroxy acid (0.25 mmol) in dry diethyl ether (2.5 mL) a solution of 9-anthryldiazomethan (0.3 mmol) in dry diethyl ether (2.5 mL) was added dropwise. The reaction mixture was stirred at RT for 30 min, concentrated under reduced pressure and the product purified by prep TLC (silica gel 60 $F_{254}$, 2 mm, E. Merck). Solvent system: diethyl ether, yield 80–90%. The anthrylmethylester (0.025 mmol) was then treated with 2-naphthoyltriazole

(0.03 mmol) and a catalytic amount of DBU in acetonitrile (1 mL) at RT for 10 h. The reaction mixture was concentrated and purified by prep TLC as described above (yield 90%). Solvent system: diethyl ether/pentane (1:1).

12. UV of methylanthryl chromophore (1cm cell): $\epsilon_{254}$=140 000 $M^{-1}$ $cm^{-1}$.
13. Partial $^1H$ NMR data (400 MHz, $CDCl_3$): (a) (*S*)-**3** and (*R*)-**3**: δ 1.59 (d, J=7.0 Hz, 3H, $CH_3$), 5.41 (q, J=7.0 Hz, 1H, CH), 6.27 (dd, J=33.0/12.5 Hz, 2H, $CH_2$), 7.50 (m, 6H, Ar), 7.87 (m, 3H, Ar), 8.02 (m, 3H, Ar), 8.33 (d, J=8.6 Hz, 2H, Ar), 8.51 (s, 1H, Ar), 8.58 (s, 1H, Ar). (b) (*S*)-**4** and (*R*)-**4**: δ 1.41 (d, J=6.3 Hz, 3H, $CH_3$), 2.73 (dd, J=5.0/15.4 Hz, 1H, $CH_2$a), 2.87 (dd, J=8.4/15.4 Hz, 1H, $CH_2$b), 5.55 (m, 1H, CH), 6.16 (s, 2H, $CH_2$), 7.40 (m, 4H, Ar), 7.56 (m, 2H, Ar), 7.81 (m, 6H, Ar), 8.25 (d, J=8.4 Hz, 2H, Ar), 8.33 (s, 1H, Ar), 8.34 (s, 1H, Ar).
14. This conclusions are based on preferred torsion angles for interacting transition dipoles obtained by computer analysis with MacroModel 5.0 using the modified Allinger MM2 force field.

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