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# Features of electronic circular dichroism and tips for its use in determining absolute configuration

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Dedicated to the memory of Dr. Howard Flack

A B S T R A C T

This review focuses on the general features of electronic circular dichroism (ECD) as applied in determining the absolute configuration of organic compounds. The high sensitivity and straightforward spectral interpretation of the exciton chirality method makes this approach very useful, and complementary to X-ray crystallography. A brief tutorial is provided on ECD, with precautions and tips for using it, especially the exciton chirality method. The spectroscopic ECD of several examples are analyzed.

## 1. Introduction

Nowadays, electronic circular dichroism (ECD) has become a powerful technique for establishing the absolute configuration of organic compounds, of both natural and synthetic origin. Since the 1960s, ECD has been displacing optical rotatory dispersion (ORD),[1–3] another useful technique for structural, stereochemical and conformational studies in organic chemistry.

This review is not intended to give an large number of recent references, but gives selected examples to illustrate theoretical and practical features and applications of ECD[4–8] in determining the absolute configuration of organic compounds. Optical activity is the result of the different indices of refraction for left and right plane-polarized light when it travels through chiral structures, such as small organic molecules (sugars, natural products, peptides) or macromolecules (proteins).[9–11] Normally the rotation occurs for the strongest yellow band of sodium light, called the D-line, at 589 nm. The variation of this optical activity with wavelength gives rise to an optical rotatory dispersion curve (ORD) (not a spectrum, since electronic transitions are not necessarily involved).

There are two types of ORD curves, those called plain or normal curves, and Cotton-effect curves. The former result from chiral organic molecules without an absorption band (chromophore or light-absorbing group) within the spectral range under analysis, while the Cotton-effect curves derive from those chiral molecules that display a maximum or a minimum, or both, in the region under study. This is because of abnormal behavior of the rotatory power at the wavelength of an absorption band (chromophore). It was named the Cotton effect after the person who first observed this phenomenon. It is said to be a positive or negative Cotton-effect curve, depending on the sign of the first extremum observed at the longer wavelength (Fig. 1).

Unlike ORD, circular dichroism (ECD) is observed for those chiral molecules that absorb light in the region under study. Thus, ECD is the difference in the absorption of left-handed circularly polarized light and right-handed circularly polarized light. Therefore, ECD is a spectroscopic technique, since there is light-absorption, and yields spectra instead of curves, although they are usually called curves.

Since ECD requires optically active chromophores, the following classification is very useful (Fig. 2):

- Non-chiral chromophores and molecules, which lead to non-active ECD.
- Chiral molecules without chromophores, which also lead to non-active ECD, but can become ECD-active by introducing a chromophore. For instance, the chemical transformation of an alcohol into a *p*-substituted benzoate.
- Chiral chromophores and molecules (inherently chiral chromophores). This type of chromophore (type 1) exhibits strong ECD.
- Non-chiral chromophores located in chiral molecules (inherently achiral but chirally-perturbed chromophores). This type of chromophore (type 2) shows weak ECD.

Different types of ECD spectra can be expected; (i) those with a *single* (positive or negative) *Cotton effect*; (ii) those with *multiple Cotton effects*, where two or more Cotton effects of equal or different signs are observed (Fig. 3); and (iii) those called *split* or *exciton ECD spectra.* This last is based on the through space interaction of the electric transition moment of two chromophores, which gives

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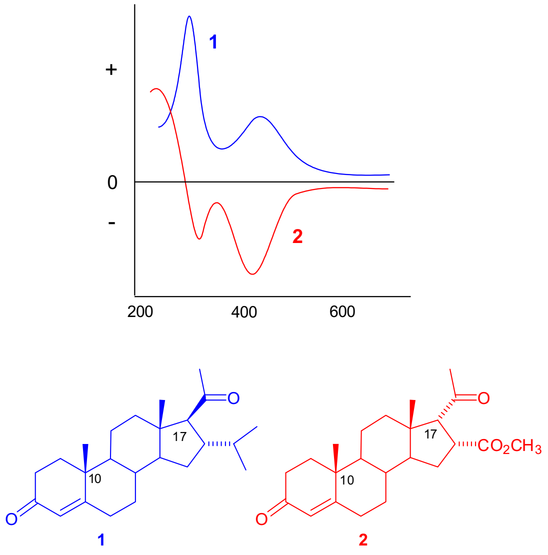

**Figure 1.** ORD curves of compounds **1** (positive, blue) and **2** (negative, red).

rise to an excited state split into two energy levels (*exciton chirality method*).

*ORD versus ECD:* The Cotton effects observed in the ORD curves of compounds **1** and **2** (Fig. 1) are the result of the interactions between plane-polarized light and each stereogenic carbon in the molecules, in addition to the anomalous interactions with the chromophores present. Therefore, a correlation between the ORD curves and the stereochemistry of these compounds is difficult.

However, the ECD spectra of compounds **1** and **2** (Fig. 3) are almost superimposable except for the region just below 300 nm ($n \rightarrow \pi^*$ transition of the keto chromophore) which are of opposite signs. The Cotton effects above 300 and around 240 nm correspond to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of the α,β-unsaturated ketone, respectively. Therefore, the correlation and interpretation of the ECD data with the stereochemistry of these molecules is simpler. The different sign of the Cotton effect below 300 nm reveals the opposite absolute configuration at carbon 17, the nearest to the keto group, while the similarity of the rest of the spectra confirm the same absolute configuration for those stereogenic carbons near the α,β-unsaturated ketone, mainly carbon 10.

The ease of interpretation of the ECD spectra means this technique has been shifting the ORD. Hence herein we will concentrate on ECD (electronic circular dichroism).

Tip 1. There is a straightforward correlation between the wavelength of a Cotton effect in the ECD spectra and the wavelength of its UV absorption transition.

Tip 2. Enantiomers exhibit identical ECD spectra but of opposite signs.

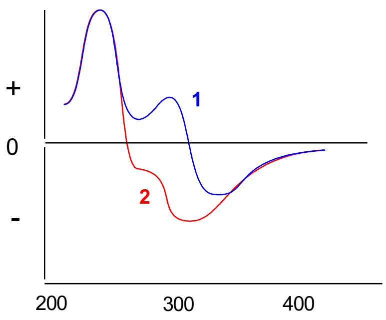

**Figure 3.** ECD spectra of compounds **1** (negative, blue) and **2** (negative, red).

Tip 3. The sign of a Cotton effect depends mainly on the absolute configuration of the nearest stereogenic carbon to the corresponding absorption band.

Many effective empirical rules[1–4,6–8] have been proposed, by researchers such as Djerassi, Crabeé, and Snatzke and are very useful for establishing the absolute configurations of organic compounds. Further developments came with the *exciton chirality method*,[5] mainly through the seminal scientific contribution of Harada and Nakanishi. This method is a non-empirical one, so comparison with any other compound or its ECD data is not necessary. This powerful and sensitive technique allows the absolute configuration of organic compounds to be determined by non-empirical means, via a straightforward spectroscopic interpretation.

ECD can also be applied in conformational analysis in general, to small to medium size molecules in solution,[12] as well as macromolecules, especially proteins.[10]

In practice, this information is obtained by:

1. Spectra comparison with samples possessing very similar structures with known absolute configurations. For example, the analysis already mentioned of compounds **1** and **2**.
2. Using empirical rules.[1–4,6–8] There are many effective empirical rules for olefins, dienes,[13] allylic alcohols and esters, saturated ketones (Octant Rule),[14] aldehydes, sulfoxides,[15] and so on. Due to the empirical character of these rules, they are not dealt with herein.
3. The *exciton chirality method* (non-empirical method).[5,6,16] This requires the presence of at least two chromophores with high molar extinction coefficients (ε).

Before continuing it is important to clarify some basic ideas. Figure 4 shows how the sign of the ECD spectrum of 3-methylcyclohexanone changes with the conformation of the chair (for a fixed absolute configuration) or conversely with the absolute configuration (for a fixed conformation). In this case, the widely known Octant Rule[1–4,14] can easily correlate the experimental sign

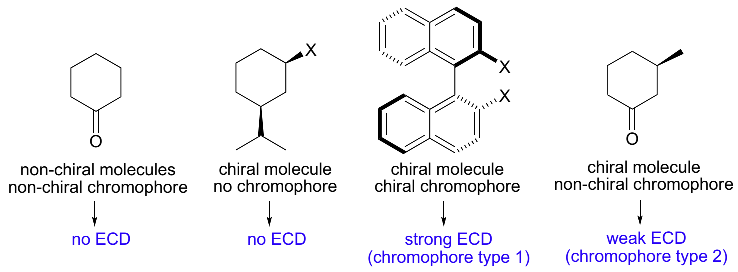

**Figure 2.** Classification of optically active chromophores.