# Circular dichroism and absolute conformation of Δ⁴-uronate derivatives: a semi-empirical rule for inherent chiral α-alkoxy acrylates

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**The theoretical basis for using CD spectroscopy to predict the conformation of Δ⁴-uronates is reported.**

As part of ongoing research into the chemistry of glycosaminoglycans, our laboratory has been exploring the use of Δ⁴-uronate derivatives as building blocks for the synthesis of heparin. Circular dichroism (CD) spectroscopy was used to study the conformation of these Δ⁴-uronate derivatives in an effort to better understand differences in their reactivity.[1]

Qualitative molecular orbital (MO) theory, frequently used to explain molecular properties (*e.g.* geometry,[2] photoelectron spectra[3] or reactivity[4]) can also help in better understanding CD spectra. Rotational strength (*R*),[5] a substance property, can be defined as the area under a CD band multiplied by a factor [eqn. (1)].

$$R = 0.229 \times 10^{-38} \int (\Delta\varepsilon/\lambda \mathrm{d}\lambda \qquad (1)$$

*R* is theoretically given by the scalar product of the electronic ($\mu$) and the magnetic (*m*) transition moments for the absorption observed [eqn. (2)].

$$R = \mu m = |\mu|\ |m| \cos\beta \qquad (2)$$

When light is absorbed by the electron cloud of a molecule, electron charge can be shifted in the direction of the electric field vector of the light wave, and it may also be rotated. This first phenomenon corresponds to $\mu$, the latter to *m*. The values of $\mu$ and *m* can be determined by identifying the molecular orbitals (MOs) at which the electron excitation mainly occurs. From the cosine term of eqn. (2) it follows that the CD is positive if the angle between $\mu$ and *m* is acute ($0 < \beta < 90°$), and negative if the angle is obtuse ($90 < \beta < 180°$). In limited cases the vectors $\mu$ and *m* are prependicular to each other, so the scalar product is zero ($\cos 90 = 0$) and the Cotton effect vanishes.

Qualitatively $\mu$ and *m* can be determined by multiplying together the two MOs between which the transition occurs (Snatzke MO recipe).[6] The absolute directions of $\mu$ and *m* depend on the arbitrary choice of the orbital phases and have no physical meaning.[7] However, their relative orientation determines the sign of the CD. This single CD argument only gives information about the absolute conformation of a molecule (*i.e.* the sign of a torsion angle around a bond) and not about the absolute configuration. A second method is required to correlate the absolute conformation with the determined absolute configuration.

The Δ⁴-uronate derivatives as shown in Fig. 1(*a*) are formally α-alkoxy acrylates. Their C=C–O moiety is locked into the chiral conformation of the dihydropyran ring, making this chromophore inherently chiral[8] [Fig. 1(*b*)]. We propose a semi-empirical rule for predicting the absolute conformation of cyclic α-alkoxy acrylates based on the sign of the Cotton effect. Snatzke has already suggested such a semi-empirical rule for chiral dihydropyrans incorporating an enol ether chromophore, present, for example, in glycals and in many iridoids.[6,7,9]

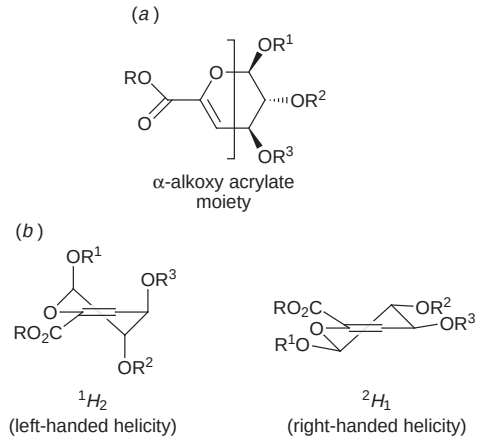
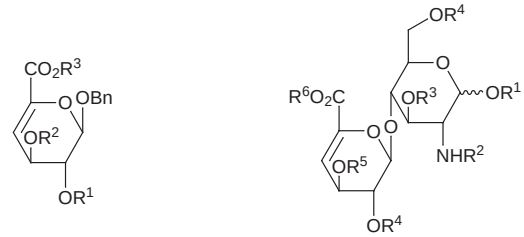



**Fig. 1** The structure of (*a*) the α-alkoxyacrylate moiety in Δ⁴-uronate derivatives and (*b*) the half-chair conformers of the Δ⁴-uronate derivatives

The CD spectra of the Δ⁴-uronates (Fig. 2) show a Cotton effect around 235–240 nm. This band is negative for the compounds **1**–**5**, and positive for compounds **6** and **7**. Since this



**1** $R^1 = R^2 = H$, $R^3 = Me$
**2** $R^1 = R^2 = Piv$, $R^3 = Me$
**3** $R^1 = R^2 = R^3 = Bn$
**4** $R^1 = R^2 = TBDMS$, $R^3 = Me$
**5** $R^1$–$R^2 = (Pr^i_2Si)O(Pr^i_2Si)$
**6** $R^1 = R^3 = R^5 = R^6 = H$, $R^2 = R^4 = SO_3H$
**7** $R^1 = R^3 = R^4 = R^5 = R^6 = H$, $R^2 = Ac$

CD band corresponds to a strong UV absorption, it must come from a $\pi \rightarrow \pi^*$ transition and not from a forbidden $n \rightarrow \pi^*$ transition. Application of the Snatzke MO recipe to such an α-alkoxy acrylate chromophore is shown in Fig. 3. Here the relevant MOs approximate the two possible HOMOs and the LUMO of the isoelectronic 2,3-dimethylbutadiene dianion, although the LCAO coefficients are not identical. The terminal AOs are twisted to reflect the chirality (left-handed twist chosen). The formal multiplications $\pi_a\pi^*$ and $\pi_b\pi^*$ reveal the generation of an electronic transition moment $\mu$. For the $\pi_a \rightarrow \pi^*$ transition, $\mu$ is localized nearly exclusively in the achiral part of the chromophore, so this excitation cannot correspond to the strong Cotton effect measured. The latter must then come from the $\pi_b \rightarrow \pi^*$ transition. The translation of charge during the $\pi_b \rightarrow \pi^*$ excitation generates $\mu$. Part of the charge is transferred

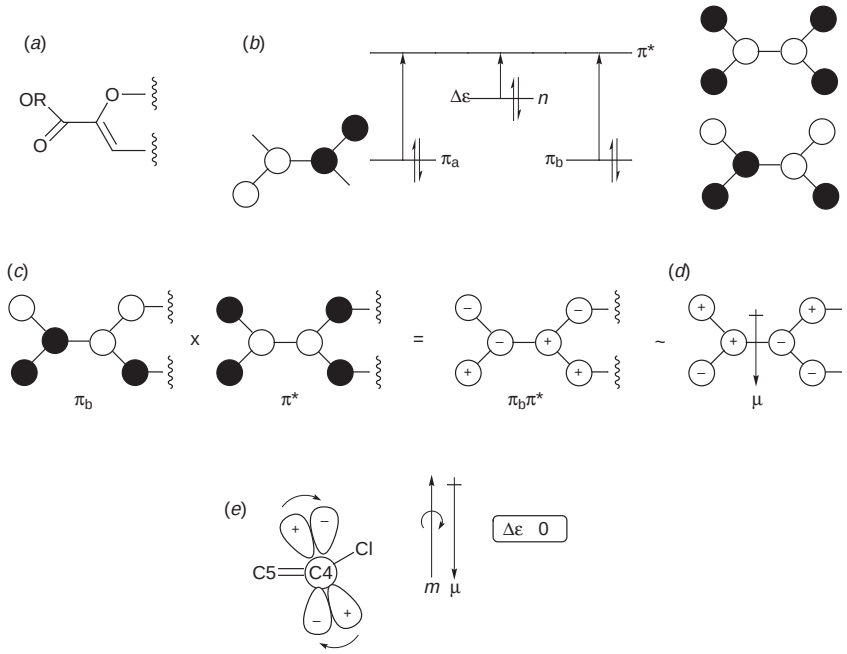



**Fig. 3** Application of Snatzke MO formalism to Δ⁴-uronates: (*a*) chiral α-alkoxy acrylate chromophore (absolute conformation of the dehydropyran ring is chosen as $^1H_2$; (*b*) relevant MOs of the isoelectronic 2,3-dimethylbutadiene dianion; (*c*) formal multiplication of $\pi_b$ and $\pi^*$ giving the electron density; (*d*) charge translation and $\mu$; (*e*) concomitant charge rotation and *m*

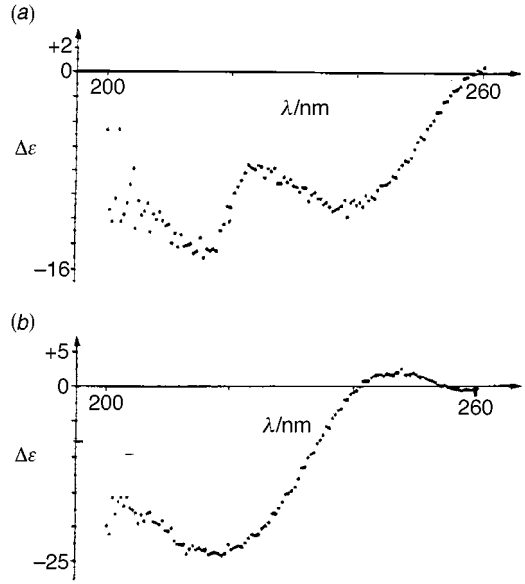



**Fig. 2** Superposition of CD curves with (*a*) negative (**1**–**5**) and (*b*) positive Cotton effects (**6** and **7**). These compounds show a single absorption peak at 235–240 nm.

within the dihydropyran ring and this is done for the absolute conformation $^1H_2$ chosen on a left-handed helical path. Such rotation of charge along the line connecting C4–$O_{ring}$ generates *m* which, by the right-hand rule, is oriented antiparallel to $\mu$. The resulting Cotton effect is, therefore, negative and the absolute conformation of the dihydropyran ring in compounds **1**–**5** is $^1H_2$.

For compounds **6** and **7** (a positive Cotton effect measured) the charge is transferred on a right-handed helical trajectory, thus predicting a $^2H_1$ absolute conformation for their ring systems.

The $^1$H NMR data for the compounds are in full agreement with the prediction of their absolute conformation concluded from this new semi-empirical rule. CD spectroscopy provides the absolute conformation, information that is simply not obtainable using NMR analysis.

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## Notes and References

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