

Study of Cotton Effect of L-Mandelic Acid and its Derivatives

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Summary: Cotton effect of L-mandelic acid and its chiral derivatives L-ethylmandelate, L-ethyl chloro phenyl acetate and L-chloro phenyl acetyl chloride has been studied from their CD spectra, which shows their absolute configurations. The observed variation in the CD data has been explained as the effect of the electronic factors of substituents on the optical activity of the chiral molecules.

Introduction

With the growing awareness of the significance of molecular asymmetry in the pharmacological activity of chiral compounds the chiro - optical techniques are gaining more and more importance. Attention is now being focused world wide on new and improved means of enantioselective preparation, purification and analysis of optically active compounds [1]. Optical Rotary Dispersion (ORD) and Circular Dichroism (CD) are two chiro-optical techniques that have been successfully applied to most structural and stereochemical applications [2,3]. ORD is based on the difference of propagation velocities of left and right handed circularly polarized light through the optically active material whereas CD is based on the unequal absorption coefficients of the two circularly polarized light components in a given absorption band. In the CD method the difference in the molecular absorption coefficient (ϵ) of left and right circularly polarized light is plotted against the wavelength. After the passage of plane polarized light through optically active medium, the light becomes elliptically polarized. The angle whose tangent is equal to the ratio between the minor and the major axis of the elliptically polarized light is called "Ellipticity", denoted as θ

$$\theta = 1/4 (k_L - k_R)$$

where k_L and k_R are absorption coefficients of left and right circularly polarized light. Molar ellipticity $[\theta]$ of a substance is defined as following:

$$[\theta] = \theta / (10 Cl)$$

where C is the molar concentration of the optically active substance and l the pathlength of the cell.

The Cotton effect, which is the combined phenomenon of unequal absorption and unequal velocity of transmission of left and right circularly polarized light, provides much structural information, and is characterized by its position, sign and shape in the CD of ORD curves. In the case of a CD curve, the Cotton effect is represented by $\Delta\epsilon$ or $[\theta]$ at the maximum wavelength λ_{max} and in the case of ORD curve it is represented by the wavelengths for the peak and trough, molecular rotation and amplitude. Though ORD and CD always yield identical information in principle, they should be used selectively for the intended applications depending on their features and advantages [4,5].

The present studies of Cotton effect were carried out using the CD technique because the CD maximum nearly coincides with UV maximum with respect to the wavelength, and hence the sign of the Cotton effect can be determined exactly [5].

Results and Discussion

Measured molar ellipticities of L-mandelic acid and its derivatives are shown in Figure 1 as a function of wavelength in the range 350 - 200 nm and the CD data is summarized in Table-1.

Optical activity mainly arises due to a chiral centre, which in organic compounds, is generally, a

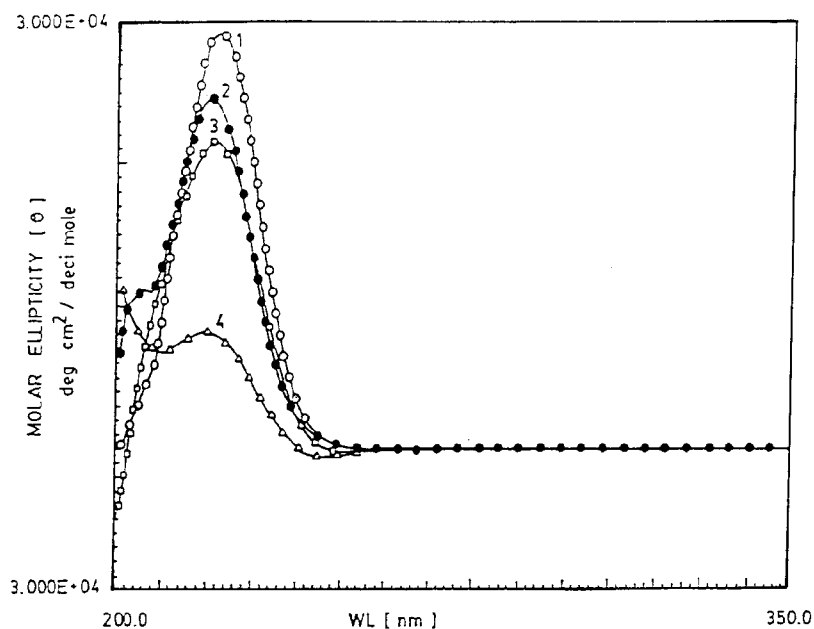


Fig. 1: CD Spectra of 1. L-Ethyl Mandelate -o- 2. L-Mandelic Acid -o- 3. L-Chlorophenyl Acetyl Chloride -o- 4. L-Ethyl-Chlorophenyl Acetate -Δ- in Ethanol.

Table-1

Compound	Wave-length (nm)	Ellipticity θ (m deg)	Molar Ellipticity $[\theta]$ (deg. cm ² /decimole)	Sign of Cotton Effect
L-Mandelic acid	202	75	2.59×10^4	Positive
L-ethyl mandelate	223	96.94	3.07×10^4	Positive
L-Ethyl chloro phenyl acetate	219	28.98	8.23×10^4	Positive
L-chloro phenyl acetyl chloride	222	73.03	2.15×10^4	Positive

central carbon atom having different polarities of all four bonds due to different substituents [6]. Optical activity is associated with electronic transitions occurring in a chiral environment such that the scalar product of the electric and magnetic transition dipole moment is non-zero [7]. In case of a molecule of L-mandelic acid the chiral centre is directly attached with a hydrogen atom which has negligible influence on polarity, a phenyl group which is an electron donating group, a carbonyl group which is mildly electron withdrawing and a hydroxyl group which is strongly electron withdrawing. The net polarization is therefore towards the hydroxyl group as shown in Figure 2. A careful comparison of the CD data of all the chiral derivatives of L-mandelic acid reveal some important effects of electronic factors of the substituents on the observed molar ellipticities of the compound which can be discussed as following under separate headings.

Effect of substituents on molar ellipticity

Esterification

When L-mandelic acid is esterified to L-ethyl mandelate the molar ellipticity increases by 4800 deg. cm²/decimole because of hyperconjugation of ethyl group in L-ethyl mandelate. Electron polarization is more towards the hydroxyl group than that in L-mandelic acid, which causes an increase in bond polarity and ultimately in $[\theta]$.

Substitution of -OH with -Cl

When L-ethyl mandelate is chlorinated to L-ethyl α -chloro phenyl acetate the molar ellipticity decreases by 22468 deg. cm²/decimole. As -Cl is less electron withdrawing than -OH, the net polarity is decreased and hence a decrease in $[\theta]$ is observed.

Comparison of esterification and chlorination

In the case of L-mandelic acid, esterification increase the $[\theta]$ value by 4800 units while chlorination decreases $[\theta]$ value by 22468 units. Thus the difference of inductive effect between -OH and -Cl is far greater than that between acid and ethyl group.

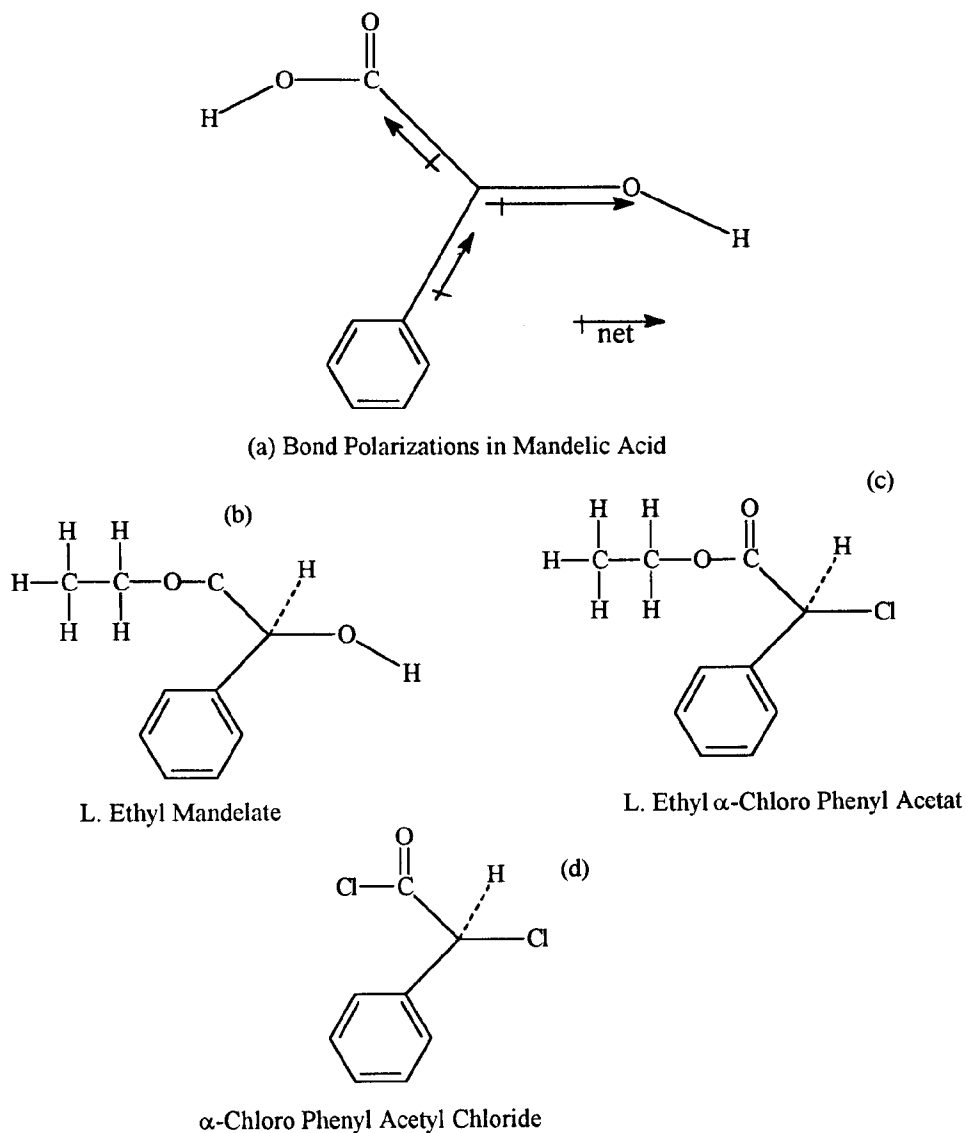


Fig. 2: (a) Bond Polarizations in Mandelic Acid, (b) Ethyl Mandelate (c) L-Ethyl α -Chloro Phenyl Acetate, (d) a Chloro Phenyl Acetyl Chloride

Comparison of ester and acyl chloride

Switching from L-ethyl α -chloro phenyl acetate to L- α -chloro phenyl acetyl chloride, the molar ellipticity value increases by 13268 deg. cm²/decimole. In the acyl chloride, the chloro group is less electro-negative than the oxygen of an ester group, but hyperconjugation of the ethyl group of the ester decreased its electron withdrawing ability and hence becomes slightly more or comparable to the acyl

chloride. However, increase of $[\theta]$ value is far greater suggesting some contribution of the electron pair of -Cl in resonance with an associated decrease in the electron withdrawing ability of the acyl chloride group and an increase in net polarity, hence a large increase in $[\theta]$ value.

Effect of distance from chiral centre

Chlorination of L-mandelic acid to L-chlorophenylacetyl chloride decreased molar

ellipticity by 4400 deg.cm²/decimole. Here two -OH groups are substituted by -Cl, one is directly attached to a chiral centre, while the other one is one carbon away. Had there been equal effect of the two substituents on the asymmetry of the molecule at the chiral centre, we would not have observed any change in the molar ellipticity value. On the contrary, the observed decrease in $[\theta]$ value of the chlorinated compound is suggestive of a net decrease in the polarity of the molecule, resulting from a relatively larger contribution of the effect of substitution at the chiral centre as compared to a similar substitution one carbon atom away. This demonstrates the effect of distance of the substituent from the chiral centre on the optical activity of the molecule.

Experimental

Synthesis [8]

Synthesis of *L*-ethyl mandelate

L-Mandelic acid (3.04 gms) dissolved in absolute ethanol (4 ml) was mixed with a solution of anhydrous hydrogen chloride (0.2 gms) in absolute ethanol (2 ml), and refluxed for 5 hours on a steam bath before being added to cold water and neutralized by a solution of sodium bicarbonate. The reaction mixture was then extracted with two portions of dry ether (6 ml each), washed with water and dried over anhydrous sodium sulphate (1 gm) and ether evaporated. Yield (2.94 - 3.08 gms) b.p. = 114 - 145°C.

Synthesis of *L*-ethyl α -chloro phenyl acetate

L-ethyl mandelate (2.7 gms) was allowed to stand over night in thionyl chloride (1.18 ml) in round bottomed flask equipped with reflux condenser capped with a drying tube. It was then refluxed for 30 minutes on steam bath and added to cold water and extracted with dry ether twice (5 ml each). The extract was washed twice with saturated aqueous solution of sodium bicarbonate (5 ml each) and once with water dried over anhydrous sodium sulphate and allowed to evaporate. Yield 2.42-2.52 gms. b.p. = 134 - 135°C, $n_D^{20} = 1.5149$, $[\alpha]_D^{16.4} = -64.0^\circ$.

Synthesis of *L*- α -ethyl chloro phenyl acetyl chloride

To *L*-mandelic acid (3.04 gms) was added thionyl chloride (4.76 gms) in a round bottomed

flask equipped with reflux condenser and drying tube and allowed to stand overnight, then added to cold water and extracted with two portions of dry ether (6 ml each). The extract was washed with water and dried over anhydrous sodium sulphate and the ether was allowed to evaporate b.p. = 120C/23 mm.

CD measurements

CD measurements were carried out on J 710 Spectropolarimeter (Japan Spectroscopic Co. (JASCO) Ltd., Tokyo Japan) in the wavelength range 400-200 nm. Improved signal to noise ratio was achieved by averaging at least four spectra in each case. Dry nitrogen gas was continuously purged through the spectrometer at a rate of 2l/min to avoid ozone gas generation from the xenon lamp. All measurements were made by dissolving the sample in ethanol with concentration typically in the range 10^{-3} - 10^{-4} M and pathlengths of the cells varied from 0.1-1.0 cm.

Conclusion

Above experiments and studies have proved that by collecting CD data on a large number of compounds, and considering the capability of the substituents as electron donors and the probable mechanism of the electron promotion, the type and position of the substituents can be related to the sign of the rotational strength induced by each substitution in the transition examined.

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