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CIRCULAR DICHROISM PROPERTIES OF (3S,5R)-CIS- and (3S,5S)-TRANS-3,5-DIMETHYLVALEROLACTONES[1]

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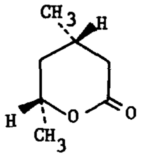
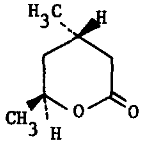
The relationship between the sign of the Cotton effect of optically active lactones and absolute configuration is a subject of current interest. Klyne has formulated a sector rule which predicts the Cotton effect exhibited by many optically active lactones.[2] However, Wolf has shown that the sign of the Cotton effect of δ-lactones is more generally correlated with the conformation of the 6-membered ring.[3,4] This relationship between the Cotton effect of δ-lactones and chirality of the ring has been related to the torsion angle along the C-C-C=O system of the lactone ring.[5,6]

Recently we reported[7] the syntheses of racemic cis and trans-3,5-dimethylvalerolactones and reported an analysis of their NMR and IR spectral properties.[8] We now describe a study of the circular dichroism (CD) properties of optically pure (3S,5R)-cis and (3S,5S)-trans-3,5-dimethylvalerolactones (I and II respectively).* Since the absolute configuration of the lactones I and II are known[**,8,9] and since these lactones differ only in their absolute configuration at C-5 of the lactone ring, the CD properties of these structures were of particular interest. The CD spectra of both lactones show a negative Cotton effect (-CE) for the


I


II

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[*] These lactones were prepared from 3-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]glutarimide (actidione). The synthesis of these lactones, and their conversion to 5-alkyl-5-(3'-hydroxy-1'-methylbutyl)-barbituric acids of known absolute configuration, will be reported elsewhere.

[**] The absolute configuration of actidione, the starting material for the lactones, has been determined (ref. 9).

lactone $n-\pi^*$ transition. Lactone I shows a negative minimum at 226 nm ([Θ] = -1760) and lactone II shows a negative minimum at lower wavelength (214 nm) but with larger molecular ellipticity ([Θ] = -5169) (see Figure 1).

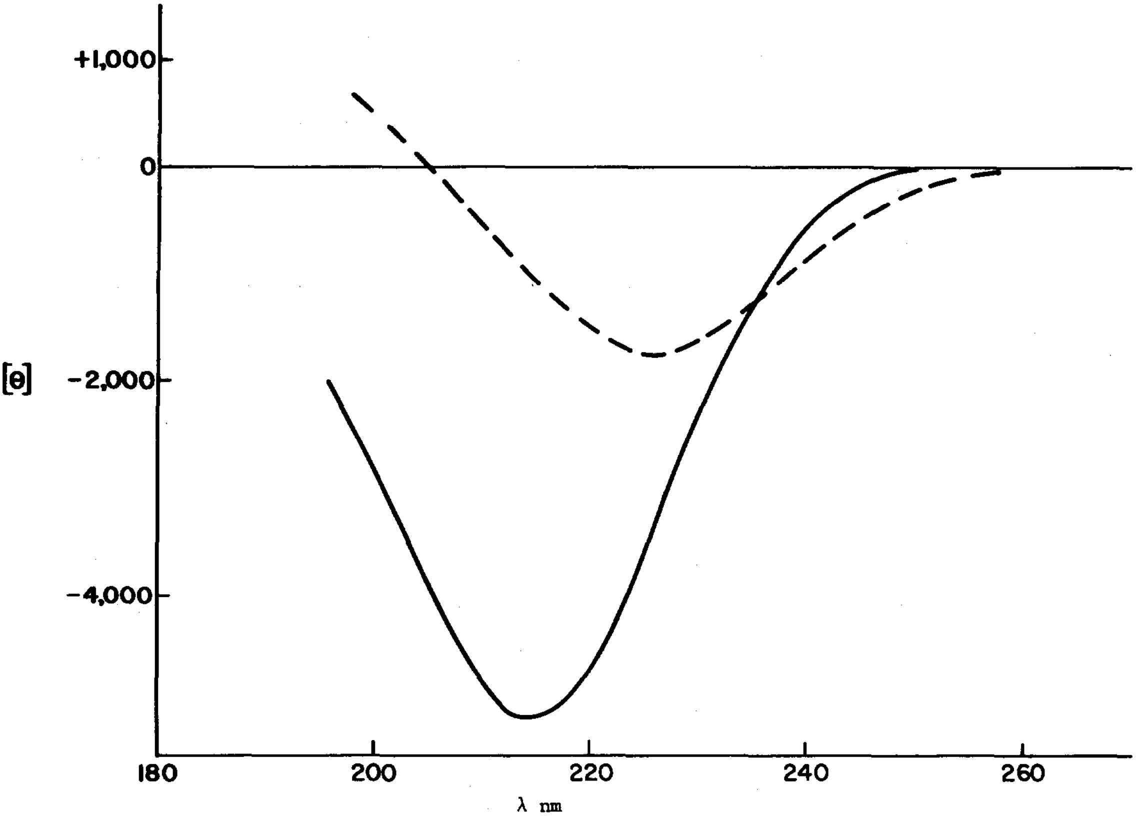

Figure 1: Circular dichroism spectra of I (-----) and II (———) in methanol

Examination of octant and sector diagrams of lactones I and II show that the sector rule[2] predicts a positive CE for both of these lactones, in disagreement with the experimental spectra. Therefore we have interpreted the CD properties of the cis- and trans-lactones I and II respectively in relation to the chirality of the lactone ring. Inspection of Dreiding models shows that a half-chair conformation of IA which has the two methyl groups in equatorial positions predicts a -CE for lactone I in agreement with the experimental CD spectra. A boat conformation (IB) which has the 3-methyl group equatorial and the 5-methyl axial also predicts a -CE for this lactone. However, this conformation is less stable than IA and is not supported by the NMR and IR data.[8] Legrand and Bucourt rules on ring chirality allow the sign of a CE to be predicted for conformations other than half-chair and half-boat forms.[6] According to the rules of these authors the sign of the $n-\pi^*$ band of nonplaner lactones is opposite to the sign of the torsion angle between bonds C_1-O and C_2-C_3 when a Newman projection is viewed along bond C_2-C_1 with the lactone ring to the right.[*] Chart I shows Newman projections of lactone I in the half-chair conformation (IA) and lactone II in a conformation (IIA) where the torsion angle is approximately +20°. The conformation IIA, which is intermediate between a half-chair and half-boat conformation, predicts a -CE for lactone II. In addition this conformation, which has a larger torsion angle than IA could account for the larger CE minimum of lactone II and for the observed vicinal and geminal coupling constants of the C_3-H and the C_2-methylene protons in the NMR spectrum.[**,8] The -CE of lactone II could also be accounted for by the half-chair conformation (IIB) or the half-boat conformation (IIC). However, the chair form IIB does not account for the 12 nm difference in the CD minimum of I and II, the boat form IIC does not account for its IR carbonyl absorption at 1736 cm^{-1} and neither IIB or IIC is consistent with the NMR data.[8,+,++]

The following conclusions can be drawn from the CD spectra of I and II: a) the lactone ring chirality rules, but not the sector rule, can be used to explain both the sign and magnitude of the CE of I and II, b) the CD spectra of I and II support the conformation previously reported on the basis of IR and NMR data,[8] c) a comparison of the CE of I and II allows a more accurate description of the latter lactone, d) caution should be used in the assignment

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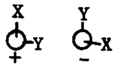
[*] The torsion angle is considered positive or negative according as the bond to the front atom X requires to be rotated to the right or left respectively, in order that its direction coincide with that of the rear atom y 

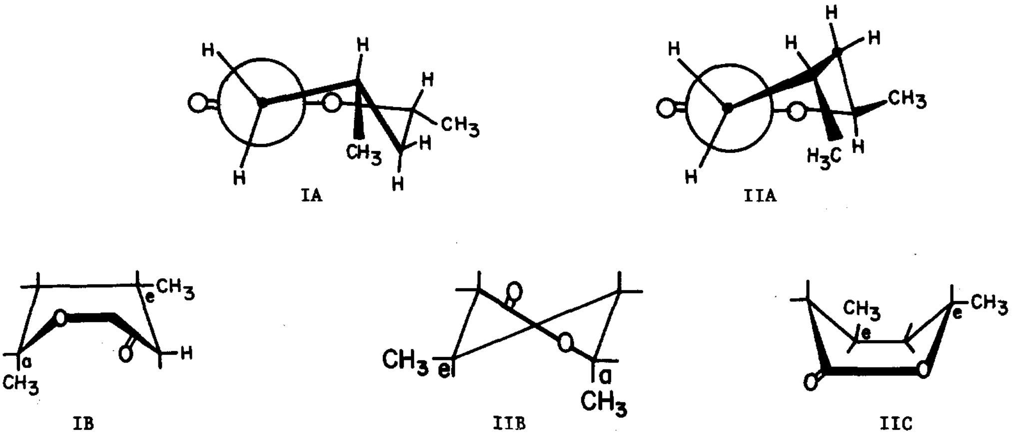
. See IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, J. Org. Chem. 35, 2849 (1970).

[**] It is recognized that caution is necessary in any exact interpretation of the NMR data in terms of the Karplus theory, however, conformation IIA fits the observed coupling constants better than the half-chair or half-boat form.

[+] Half-boat conformations are reported to show absorption at 1758-1765 cm^{-1} (ref. 10). The position of carbonyl absorption in the IR spectrum is not reported for conformations such as IIA. However, conformation IIA is not too different from that of a half-chair conformation and it seems reasonable that its carbonyl absorption would be similar to that of a half-chair conformation.

[++] Wolf has shown that the CD minimum of a half-chair conformation usually lies at longer wavelength than that of the corresponding half-boat form (ref. 4). The CD minimum of a conformation such as IIA relative to a half-chair or half-boat conformation has not been reported.

of conformation to nonrigid δ-lactones based solely on CD and/or ORD properties.



IA IIA

IB IIB IIC

Chart I

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1. This work was carried out under Contract PH43-65-1057 of the National Institutes of General Medical Sciences, National Institutes of Health, Bethesda, Maryland.
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