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THE CONFORMATION OF MACROLIDE ANTIBIOTICS. III. CIRCULAR DICHROISM AND THE CONFORMATION OF ERYTHROMYCINS

L.A. Mitscher and B.J. Slater*, Division of Natural Products Chemistry
College of Pharmacy, The Ohio State University, Columbus, Ohio 43210
and
T.J. Perun, P.H. Jones and J.R. Martin, Research Division, Abbott Laboratories
North Chicago, Illinois 60064

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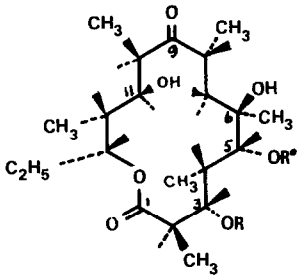
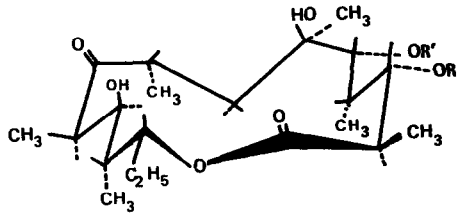
There has been considerable recent interest in the solution conformation of macrolide antibiotics based upon the reasonable expectation that this knowledge would lead to deeper insight into their chemical, physical and biological properties (1,2,3,4). Of the various possibilities put forth for erythromycin, the CD data in this note, the accompanying nmr evidence (4), and earlier X-ray measurements (5) are most consistent with conformation $I_{a,b,c,f}$ representing the molecule in dilute hydroxylic solvents.



Ia



Ib

Previous nmr studies have emphasized the relatively unanticipated conformational uniformity of erythromycin derivatives through a broad range of structural modifications (2,3,4). CD measurements strongly support this inference. The sign and relative intensities of nearly 50 members of this class have been obtained and are found to agree with one another within fairly narrow intensity limits for members of similar chromophoric type. The table contains quantitative data for selected members of the group which are representative of the whole.

The erythromycin series is specially suited for conformational analysis by CD measurements because two chromophores of different types (ketone and lactone) are situated in the molecule in

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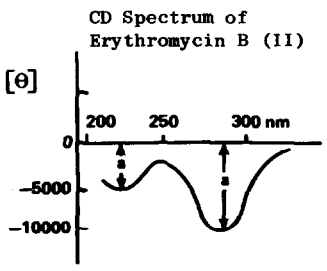
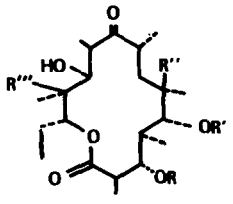
such a way that conformational alterations must be accompanied by asymmetry changes in the vicinity of one or both chromophores and appear in the spectra.

CD Spectra of Selected Erythromycin Derivatives

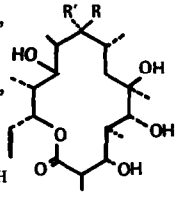
Compound			
II, Erythromycin B	288 nm ([θ]-10800, a-131.8)	210 nm ([θ]-3600, a-43.9)
III, Erythronolide B	290 nm ([θ]-12200, a-148.8)	210 nm ([θ]-4300, a-52.5)
IV, Erythromycin A	290 nm ([θ]- 6600, a- 80.5)	220 nm ([θ]-2400, a-29.3)
V, 6-Deoxyerythronolide B	290 nm ([θ]-17500, a-213.5)	215 nm ([θ]-5400, a-65.9)
VI, 3-O-Mycarosylerythronolide B	292 nm ([θ]-13500, a-164.7)	205 nm ([θ]-4200, a-51.2)
VII, 5-O-Desosaminylerythronolide B	290 nm ([θ]-13700, a-167.1)	220 nm ([θ]-5700, a-69.5)
VIII, (9S)-Dihydroerythronolide B	---	212 nm ([θ]-5990, a-73.1)
IX, (9R)-Dihydroerythronolide B	---	215 nm ([θ]-5225, a-63.7)





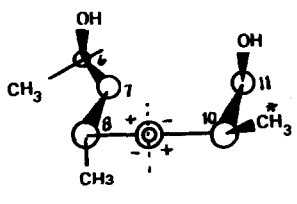
II-VII

II, R=Cladinose, R'=Desosamine, R''=OH, R'''=H
III, R=R'=R'''=H, R''=OH
IV, R=Cladinose, R'=Desosamine, R''=R'''=OH
V, R=R'=R''=R'''=H
VI, R=Mycarose, R'=R'''=H, R''=OH
VII, R'=Desosamine, R=R'''=H, R''=OH
VIII, R=OH, R'=H
IX, R=H, R'=OH

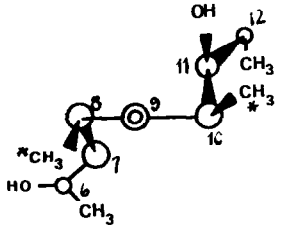


VIII-IX

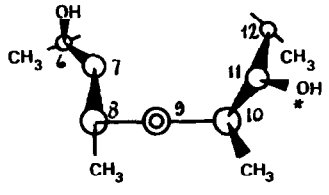
Erythromycins as Ketones: Using the well known octant rule (6) as modified for moderately twisted systems (7), the Perun model (I) (2,4) leads to a correct prediction of negative ketone peaks, with the axial C-8 methyl group being the dominant influence, and the moderately high molecular amplitudes are evidence for some twisting of the ring system (Ic). The 6β-hydroxyl group stands in a positive octant and would be expected to diminish the negativity of the ketone



Ic



Id



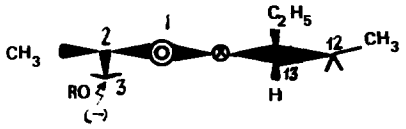
Ie

* = atoms at or very near nodal planes

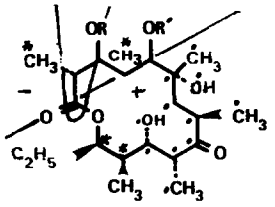
transition (12). Removal of this function (V) does result in increased negative molecular amplitude (Table). The 11β-hydroxyl group is in a negative octant and increasing its bulk by acetylation should also increase the negative amplitude of the 290 nm band. In fact, 11-acetylerythronolide B (X) shows a_{292}-218.1 or an increase of -69.3 amplitude units over III. The Celmer model (Id) is inconsistent with the spectrum of V and the Demarco model (Ic) is inconsistent with the spectrum of X. Analogous treatment of similar systems is discussed by Crabbé (8). This analysis is

pertinent when twisting is insufficiently severe as to override the effect of asymmetry changes near the chromophore.

Erythromycins as Lactones: The Perun model (If,g) leads to correct prediction of a negative trough for the lactone chromophore based either on chirality rules (C-3 is below the plane of the ring) (9) or upon the modified lactone sector rule (10). It must be emphasized, however, that no previous CD spectra have been recorded involving lactone rings large enough to exist in the energetically favored S-anti geometry (11).



If

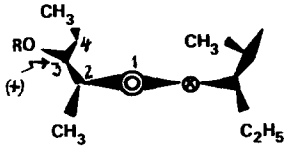


Ig

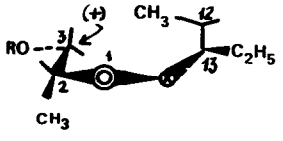
* In xy node

In lower (reversed sign) sectors

The Celmer model (Ih) would lead to positive peak prediction based upon chirality rules, while the lactone sector views are difficult to represent in two dimensions because virtually the whole of the molecule projects upward from the plane of the lactone moiety. Nevertheless, the significant atoms are predominantly in positive sectors.



Ih



Ii

The Demarco model (Ii) involves a lactone region similar to the Celmer model although the chromophore is seriously twisted even in the ground state and the energetically preferable S-anti arrangement has been abandoned (3, but see 13). There is no readily discernible overriding steric interaction which would cause such drastic twisting to occur and to persevere through the series. The chromophore could not possibly present a normal $n \rightarrow \pi^*$ UV absorption because of the drastically altered electronic overlap. This is not the case experimentally for the peak positions and intensities are not abnormal. In addition, chirality analysis predicts positive peaks and one cannot even apply the lactone sector analysis because lack of planarity of the chromophore does not allow one to define the sector boundaries at all.

Thus, the Perun conformational model ($I_{a,b,c,f}$) best satisfies all currently available data from X-ray (5), nmr (2,3,4) and CD studies. The slight but significant opening of the ring as compared with the Celmer model can be ascribed to avoidance of 1,3-steric interactions between substituents on C_4 and C_6; and C_3 and C_5.

Use of this three dimensional model allows a simple rationalization of a number of chemical reactions of antibiotics in this group which are otherwise somewhat unobvious. This and several additional subtilities encoded in the CD and nmr spectra will be discussed in a full paper in preparation.

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11. W.D. Closson, P.J. Orenski and B.M. Goldschmidt, J. Org. Chem., 32, 3160 (1967).

12. Similar amplitude differences are noted in other 4-hydroxyketones such as are described in: W. Klyne and W. Robertson, Experientia, 18, 413 (1962); C. Djerassi and W. Klyne, J. Chem. Soc., 4929 (1962); and on p. 109, 110 in reference 8. The proximity of the ketone and hydroxyl groups is also clear from the rapid (< 1 min) loss of carbonyl character (> 90%) for 6-hydroxy derivatives in methanol-acid while the 6-deoxy compounds are unchanged (> 120 min). See C. Djerassi, B.J. Mitscher and L.A. Mitscher, J. Am. Chem. Soc., 81, 947 (1959).

13. After completion of this manuscript a full account (14) of Demarco's work (3) appeared in which a somewhat modified conformation is presented. This will be discussed in our full paper.

14. P.V. Demarco, Journal of Antibiotics Japan, 22A, 327 (1969).