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A RULE FOR PREDICTING THE SIGN OF THE COTTON EFFECT IN PYRIMIDINE FURANOSE NUCLEOSIDES[1]

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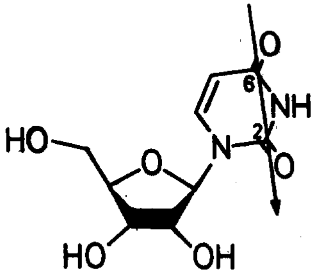
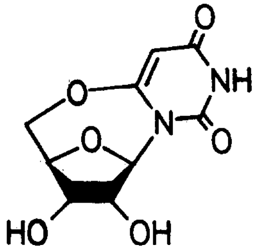
A recent paper on the optical rotatory dispersion (O.R.D.) of uracil and thymine nucleosides[2] confirms our results regarding the sign of the Cotton effect (C.E.) in these compounds[3]. However, Frič *et al.*[2] do not seem to be aware of our other publications on this subject[4,5]. In a paper published early last year[5] we related the sign and magnitude of the C.E. in pyrimidine nucleosides to their conformation. We concluded that a positive C.E. in pyrimidine nucleosides containing a carbonyl group at position 2 (uracil, thymine, cytosine) was due to restricted rotation about the glycosidic bond (hence the amplitude is higher in β-arabinosides than in β-ribosides[5], as Frič *et al.* have also found), and to a preferred conformation in which the

2-carbonyl group is directed away from the sugar (e.g. uridine, I).



I



II

As a result of further studies we are now able to propose a rule for predicting the sign of the C.E. in pyrimidine furanose nucleosides. Its basis is the well-known concept, recently restated[6], that correlation of the sign of the Cotton effect to the absolute configuration at the nearest anomeric centre requires that the rotameric composition about single bonds within the chromophore moiety itself be more or less fixed. It also makes use of the fact that the B_{2u} absorption band in uracil derivatives is polarised along the line joining the two keto groups[7] (see arrow in I).

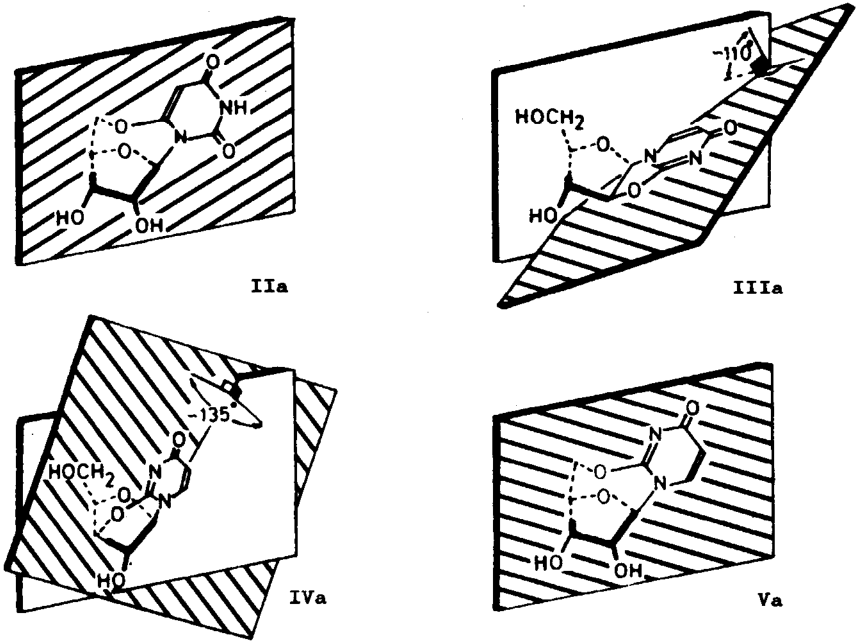
The proposed rule is:

The sign of the C.E. will be positive if 1) the nucleoside has a preferred conformation owing to restricted rotation about the $N-C^1$ bond and 2) a line from the $C^6{=}O$ group passing through the C^2=O group passes from above to below the plane of the furanose ring, provided that the chromophore is not twisted to such an extent that the line passes through $C^{5'}$. ("Above" is defined as the same side of the furanose ring as $C^{5'}$).

This rule is obeyed by all pyrimidine nucleosides of this structure which we have examined - twenty-six uracil and thymine pentofuranosides, and eleven cytosine pentofuranosides. (In the case of cytosine nucleosides the line is from C^6-NH_2 to C^2=O. The direction of polarisation has not been determined.) The recent results of Frič et al.[2] are also in agreement.

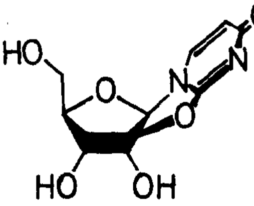
The following examples illustrate the rule:

Simple pentofuranosides of uracil, thymine, and cytosine, and cyclonucleosides such as O^4,5'-cyclo-4-hydroxyuridine (II), O^2,2'- and O^2,3-cyclouridine (II and III) fulfil the conditions of the rule and give positive C.E.'s. In O^2,5'-cyclouridine (V) the line passes through $C^{5'}$ and the C.E. is negative. In α-anomers and in β-pseudouridine the line passes from below to above the

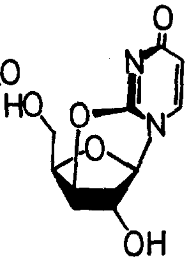


Stereochemical drawings of the cyclo-nucleosides (II-V). The plane of the chromophore is shaded, and the reference plane is unshaded. Thick lines are in front of the planes, broken lines behind them, and plain lines are in the reference plane.

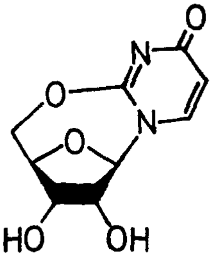
plane of the furanose ring; the C.E.'s are negative.



III



IV



V

The effect of changes in the conformation can be seen particularly clearly by comparing the cyclonucleosides (II-V), the stereochemistry of which is shown in figures IIa-Va. If the plane in which the pyrimidine ring lies in II is taken as the reference plane, the angle that the pyrimidine ring makes with this reference plane in compounds II-V varies from 0° to 180° (see table I), and as it does so, the positive C.E. is reduced in amplitude and finally becomes negative. (The hypothetical reference plane is chosen for convenience, as it demonstrates the point most simply; it is related to the real plane of the ribose ring.)

TABLE I

Compound	Angle of pyrimidine ring with reference plane	$a \times 10^{-2}$
II	0	+490
III	∽110°	+266
IV	∽135°	+ 43
V	180°	-371 !*

*! Second extremum not reached.

In purine nucleosides, rotation about the glycosidic bond is much freer, and the C.E.s are smaller[8]. It may be possible to suggest a similar kind of rule for these compounds.

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