OPTICAL PROPERTIES AND CONFORMATION OF PYRIMIDINE NUCLEOSIDES IN SOLUTION **

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SUMMARY: A modified empirical rule relating the sign of the long wave-length Cotton effect in the ORD of pyrimidine nucleosides to their conformation is given, and illustrated by means of a novel projection diagram.

Our studies of the optical rotatory dispersion (ORD) of pyrimidine nucleosides (see ref. 1 for references) established that:

1. The sign of the long wave-length Cotton effect is determined by the optical configuration (D or L) of the sugar, and the anomeric configuration at C - 1'; thus the simple pyrimidine β-D-nucleosides found in DNA and RNA (thymidine, deoxycytidine, uridine and cytidine) give positive Cotton effects, whereas the corresponding β-L- and α-D- compounds give negative Cotton effects;

2. the sign and magnitude of the Cotton effect is also goverened by the nucleoside conformation, i.e., the orientation of the sugar relative to the transition dipole moment associated with the optical transition of the base. A positive Cotton effect is associated with the *anti* conformation and β-D-nucleosides which for steric reasons have the *syn* conformation give a negative Cotton effect.

Since then, n.m.r.[2-6], X-ray diffraction[7] and C.D. studies[8] have confirmed the above conclusions. It is now generally

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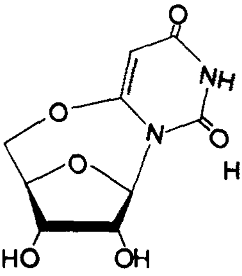
** Optical Rotatory Dispersion of Nucleic Acid Derivatives, Part X. Part IX: Rogers, G.T., Ulbricht, T.L.V. and Szer, W., Biochem. Biophys. Res. Comm. 27, 372 (1967).

agreed that except when special steric factors supervene, pyrimidine nucleosides and mononucleotides have the anti conformation in solution.



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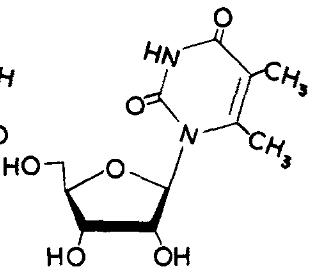

II

On the basis of our results we formulated an empirical rule for predicting the sign of the long wave-length Cotton effect in the ORD of pyrimidine D-nucleosides[9]. This has been slightly modified in the light of experience;[10,11] the sign of the Cotton effect will be positive if the following conditions are fulfilled:

1. The nucleoside has a preferred conformation due to restricted rotation about the glycosidic bond such that the sugar-base torsion angle ϕ_{CN} is in the range -75° through 0° to +105°, and

2. A line from the $C^4 = O$ (or $C^4 - NH_2$) group through the $C^2 = O$ group passes from above to below the plane of the furanose ring.

The rule is illustrated for β-D-compounds in a projection diagram (Fig. 1).[10,11] The glycosidic bond is at right angles to the plane of the page, at the centre of the circle. The pyrimidine ring is above the plane of the page. The sugar ring is below the plane of the page, at an angle to it, and held in such a position that the projection of the $C^{1'} - O$ bond onto the plane of the page is in the position shown (heavy line). If the pyrimidine ring is now rotated while the sugar ring is held fixed, the pyrimidine $C^2 = O$ group describes a circle. Different points on this circle represent different nucleoside conformations, as shown.

The sugar-base torsion angle, ϕ_{CN} is the angle formed by the trace of the plane of the base with the projection of the $C^{1'}$ - O bond.[12] The line dividing the circle into positive and negative halves corresponds to ϕ_{CN} = -75° and +105°. Compounds with a conformation such that the C^2 = O group is in the positive half of the circle, give positive Cotton effects in the O.R.D.; and those in which the C^2 = O group is in the other half, negative Cotton effects. In Fig. 1, the amplitude of the Cotton effect is given in each case. The value ϕ_{CN} = -60° for ordinary β-D-nucleosides[7] corresponds to a positive Cotton effect, as shown.

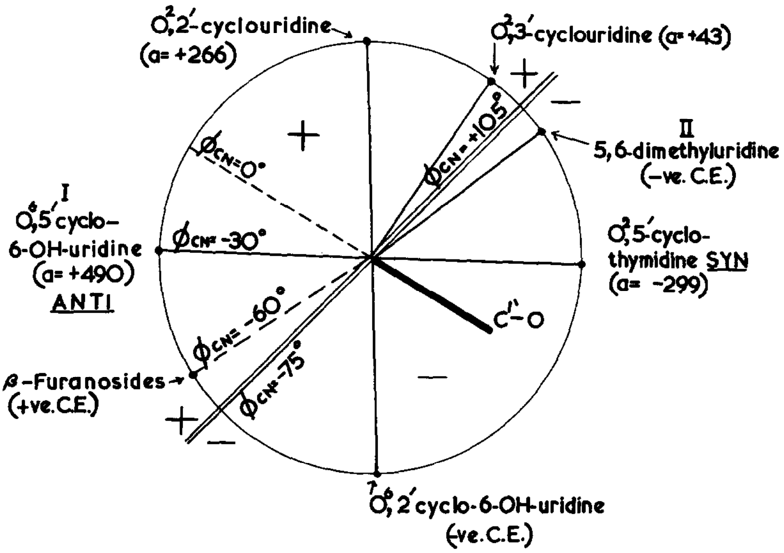

FIG. 1. RELATIONSHIP BETWEEN ϕ_{CN} AND THE SIGN OF THE COTTON EFFECT IN PYRIMIDINE NUCLEOSIDES

The rule will not apply to compounds containing additional chromophores since these may fundamentally alter the optical properties of the pyrimidine nucleoside.

It was assumed previously[13] that although the chromophores of cyclo- and non-cyclo-nucleosides may differ somewhat (as their U.V. data indicated) this factor does not in itself lead to any drastic alteration of their O.R.D. behaviour. C.D.

studies[8] have meanwhile shown that the observed long wave-length Cotton effect in the ORD of pyrimidine cyclo-nucleosides is due to two separate Cotton effects. It was suggested that the small long wave-length Cotton effect was due to the B_{2u} transition, although no evidence for this was presented.[8] Recently it has been shown that this Cotton effect (at 270-280 mμ in non-polar solvents) is in fact due to an $n-\pi^*$ transition,[14] which has also been observed in some azapyrimidine nucleosides.[15] The major Cotton effect in the C.D. of pyrimidine cyclo-nucleosides is due to the B_{2u} transition (or an overlap of the B_{1u} and B_{2u} transitions) and has the same sign as the previously observed Cotton effect in the ORD. This work[14] confirms our rule, which may now be regarded as applying specifically to the B_{2u} Cotton effect.

The rule is most readily understood by reference to two compounds. O^6,5'-Cyclo-6-hydroxyuridine (I) has the <u>anti</u> conformation and gives a very large positive Cotton effect. This compound has a chromophore very similar to uridine and establishes the relationship between a positive Cotton effect and <u>anti</u> conformation in pyrimidine β-D-nucleosides.

5,6-Dimethyluridine (II) which because of the steric effect of the 6-methyl group cannot have the <u>anti</u> conformation, gives a negative Cotton effect, as expected (See Fig. 1).

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