THE OPTICAL ROTATORY DISPERSION OF PYRIMIDINE NUCLEOSIDES*

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Although the optical rotatory dispersion (ORD) of polynucleotides has been studied intensively in the last six years, little work has been done on their monomeric components (Yang and Samejima, 1963; Ulbricht et al, 1964). We have previously reported that the ORD curves of α-pyrimidine nucleosides give negative Cotton effects, whereas the β-anomers give positive Cotton effects (Ulbricht et al, 1964); hence pyrimidine $\underline{N}^3$-nucleosides do not obey Hudson's Isorotation Rules (Emerson & Ulbricht, 1964). In order to find what factors affect the sign and magnitude of the long wave-length Cotton effect produced by these compounds, a series of about forty such nucleosides have been examined. These include numerous derivatives of uracil, cytosine and thymine, as well as *cyclo*nucleosides, azapyrimidine nucleosides and pseudouridines.

We find that the *sign* of the Cotton effect is influenced by the following factors: 1) the anomeric configuration at C-1', as already noted; 2) the position of substitution of the glycoside residue on the pyrimidine ring (e.g., β-pseudouridine, which is a $\underline{C}^5$-glycoside, gives a small *negative* Cotton effect); 3) substitution of N for CH in the heterocyclic nucleus (in 4-azauridines and 4-azacytidines the sign of the Cotton effect is reversed); 4) formation of a third ring, between C-5' and O-2 ($\underline{O}^2$,5'-*cyclo*uridine gives a negative Cotton effect).

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*Optical Rotatory Dispersion of Nucleic Acid Derivatives, Part III.

The following observations were noted for the series of β-nucleosides. The sign of the Cotton effect is not influenced by the nature of the substituents in the sugar ring or on the nitrogen-heterocyclic ring. The fact that the magnitude of the Cotton effect is little influenced by acetylation of the sugar hydroxyls (uridine and uridine triacetate give very similar curves, as do azauridine and azauridine triacetate) indicates that hydrogen-bonding is not involved.

The magnitude of the Cotton effect is only slightly influenced by substitution in either ring, but is sensitive to the configuration at C-2' in the sugar. For example, arabinosides (spongouridine, a = +294*; cytosine arabinoside) give larger Cotton effects than ribosides (uridine, +117; cytidine), as do O^2,2'-*cyclo*nucleosides (O^2,2'-*cyclo*uridine, a = +266) (see Figure 1).

It seems reasonable to assume that the ORD results must be related to the conformation of the chromophore with reference to the asymmetry in the sugar. Of particular relevance, therefore, are the results obtained with *cyclo*nucleosides, in which the conformation is fixed by formation of a third ring. Whereas O^2,2'-*cyclo*uridines and O^4,5'-*cyclo*-4-hydroxyuridine (a = +490) show similar Cotton effects (though of a larger amplitude) to that shown by uridine, the sign of the Cotton effect in O^2,5'-*cyclo*uridines and -thymidines is reversed (see Figure 1). We suggest, therefore, that in a nucleoside like uridine (I), although rotation about the *N*-*C*1' bond is theoretically possible, a preferred conformation is adopted in which the oxygen atom on C-2 is directed away from the sugar ring, as shown. Formation of additional rings, either between O-2 and C-2' or between a hydroxyl on C-4 and C-5' would change this conformation very little. However, to form an O^2,5'-*cyclo*nucleoside,

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*Amplitude a (molecular rotation at first extremum minus molecular rotation at second extremum) is divided by 100 (Djerassi and Klyne, 1963).

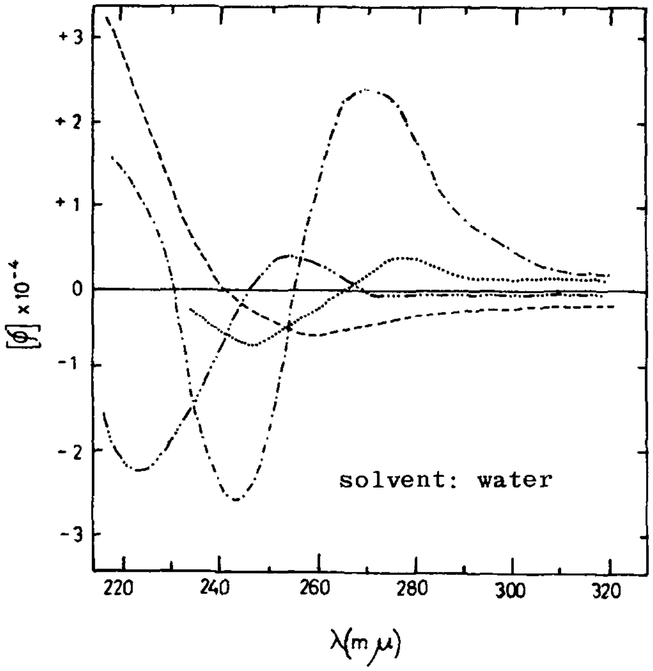
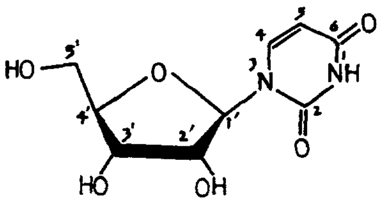


Fig.1. ORD curves of uridine (·····); O^2,2'-cyclouridine (-···-); O^2,5'-cyclothymidine (- - -) and O^2,5'-cyclo-4-hydroxyuridine (-·-·).

a rotation of about 180° about the N-C1' bond is required. In making a comparison between the *cyclo*- and non *cyclo*-uridines it is assumed that although the chromophores may differ (as their U.V. data indicate) this factor does not in itself lead to any drastic alteration of their ORD behaviour.



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ORD measurements were made with the Bellingham and Stanley/ Bendix-Ericsson Spectropolarimeter "Polarmatic '62" at room-temperature on aqueous (and a few methanolic) solutions (with an optical density at $\lambda_{max.}$ of not more than 2).

It is hoped to publish full details of these and other results elsewhere, together with a consideration of the recent interpretation of U.V. data (Clark and Tinoco, 1965), and an acknowledgement to the many kind individuals who have supplied us with compounds.

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