The Optical Rotatory Dispersion of Purine Nucleosides*

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We have previously reported that the Optical Rotatory Dispersion (ORD) curves of α-purine nucleosides give positive Cotton effects, whereas the β-anomers give negative Cotton effects (Ulbricht et al, 1964); hence purine $\underline{N}^9$-nucleosides obey Hudson's Isorotation Rules (Emerson and Ulbricht, 1964). Recently we presented preliminary results on a series of pyrimidine nucleosides, indicating that the sign and magnitude of the long wave-length Cotton effects produced by these compounds could be related to their conformation (Ulbricht et al, 1965). Further studies have confirmed these conclusions and have made it possible to propose a rule for predicting the sign of the Cotton effect in pyrimidine furanose nucleosides (Ulbricht et al, 1966). We have now examined fifty purine nucleosides, and report here our results with $\underline{N}^9$-glycosides, including cyclo-nucleosides and azapurine nucleosides. Consideration of compounds containing additional aromatic systems (e.g. p-toluoyl groups, which can influence the sign of the Cotton Effect) is excluded. In many cases, complete ORD curves are more difficult to obtain with purine than with pyrimidine nucleosides. This is because purine nucleosides absorb intensely in the ultra-violet (high ε values), necessitating the use of very dilute solutions in the region near $\lambda_{max.}$,

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[*] Optical Rotatory Dispersion of Nucleic Acid Derivatives, part V. Part IV: T.L.V. Ulbricht, R.J. Swan & A.M. Michelson, Chem. Commun., in press.

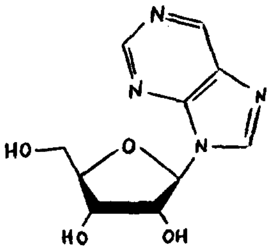
and because they have small rotations. The magnitude of the Cotton effect is noticeably lower than in pyrimidine nucleosides; for most of these purines the amplitude is in the range 50-110.

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) fixing the nucleoside in the syn-conformation by formation of a third ring (N^3,5'-cycloadenosine gives a positive Cotton effect). In the one nucleoside in which the sugar had the opposite configuration (β-L-adenosine) the Cotton effect was positive; it is probable that this relation of the sign of the Cotton effect to the optical configuration (D- or L-) of the sugar will prove to be general, since the stereochemistry at the anomeric carbon atom is the same in α-D- as in β-L-compounds.

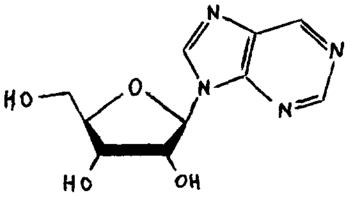
The sign is not influenced by the presence of acetyl or isopropylidene groups in the sugar ring or by replacement of the 2'-OH group by H or Cl. It is also not affected by the nature of the substituents in the purine ring, nor by substitution of N for CH at position 8 in the heterocyclic nucleus (8-azapurine nucleosides give Cotton effects like the corresponding purines). The tri-O-acetyl derivatives of adenosine and guanosine give similar curves to the parent nucleosides - suggesting, as with the pyrimidines, that hydrogen-bonding has no major influence on the Cotton effect.

The magnitude of the Cotton effect is slightly influenced by substitution in either ring but no significant differences were found between derivatives of various sugars, including ribose, 2'-deoxyribose, xylose and arabinose. In pyrimidine β-nucleosides, the amplitude of the Cotton effect is considerably higher in arabinosides than in ribosides (Ulbricht et al, 1965; Emerson et al, 1966).

If such ORD results are related to the conformation of the chromophore with reference to the asymmetry in the sugar, as suggested for pyrimidine nucleosides (Ulbricht et al, 1965, 1966), then the lower rotation and the insensitivity to the configuration at C-2' is understandable. Whereas, in pyrimidine nucleosides, steric interaction between the groups on C-2' (and, to a lesser extent, those on C-5') and substituents in position 2 of the pyrimidine ring (such as the carbonyl group) effectively prevent free rotation about the glycosidic bond, such interaction is greatly reduced or absent in purines (Donahue and Trueblood, 1960). Consequently the energy difference between the *syn* (I) and *anti* (II) forms will be small. The latter conformation will still be favoured, e.g., by electronic repulsion between N^3 and the ring oxygen atom. It is, of course, the *anti* conformation which is found in DNA, in AMP (Kraut and Jensen, 1964) and in almost all crystalline nucleosides (Sundaralingam and Jensen, 1965).

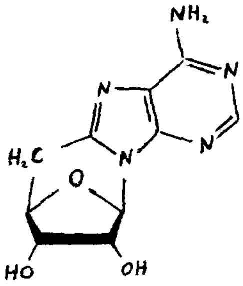


I

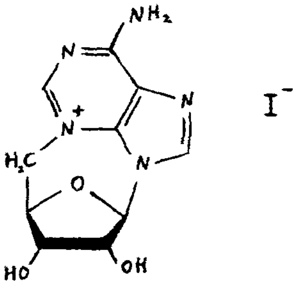


II

The results obtained with *cyclo*nucleosides, in which the conformation is fixed by formation of a third ring, are of particular interest. Thus 8,5'-cycloadenosine (III) ($\lambda_{max.}$, 264 mμ), in which the *anti* conformation is fixed by a ring linking C-5' of the sugar to C-8 in the imidazole ring, has a negative Cotton effect like other purine β-nucleosides, but of larger amplitude (a = -183). On the other hand, 2',3'-isopropylidene-*N*^{3},5'-cycloadenosine iodide (IV) ($\lambda_{max.}$, 272 mμ), which necessarily has the *syn* conformation, has a small *positive* Cotton effect (a = +34) (see Figure 1). From other examples we know that the isopropylidene group has no effect on the sign of the ORD, and it should also be noted that the $\lambda_{max.}$ of both cyclonucleosides falls within the range of the compounds studied (248-279 mμ). However, in the case of the *N*^{3},5'-cyclonucleoside, the possibility that a change in the chromophore is responsible for the change in sign cannot be excluded.



III



IV

The interpretation of the curves given by glycosides of unsubstituted purine (see fig. 2) is made difficult by the fact that the first peak in the ORD curve occurs at a wave-length very close to the $\lambda_{max.}$ (265 mμ). This suggests that this maximum in the U.V. is due to an overlap of the absorption due to two transitions, only one of which is optically active. If the optically active transition were at a wave-length lower than $\lambda_{max.}$, the first Cotton effect would be positive; if it were at a wave-length higher than $\lambda_{max.}$, the first Cotton effect would be negative. The latter would be in accord with the results for substituted purine β-nucleosides, but since the direction of the transition moment may be different, the sign of the Cotton effect will not necessarily be the same. The absence of a real trough before the first peak is reached suggests that the first Cotton effect may be positive.

It will be noted that these unsubstituted purine nucleosides have two Cotton effects, the second being negative. We have observed one or both extrema of this second Cotton effect in a number of other

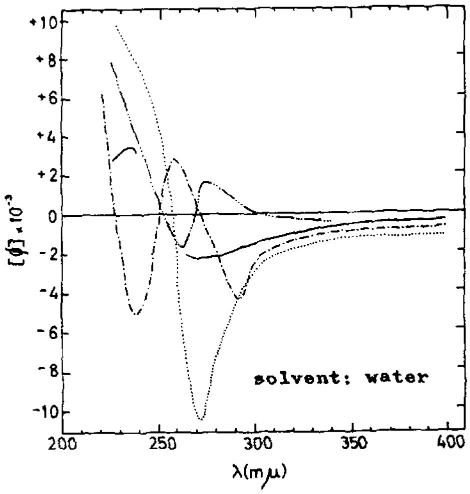


Fig. 1. ORD curves of adenosine (——); 8-azaadenosine (— · —·); 8,5'-cycloadenosine (······); 2',3'-isopropylidene-N^3,5'-cycloadenosine iodide (— ··· — ···).

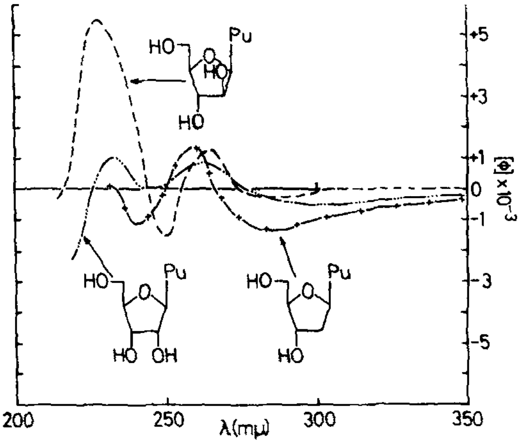


Fig. 2. ORD curves of the β-riboside, 2'-deoxyriboside and arabinoside of unsubstituted purine.

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nucleosides in which measurements were satisfactorily extended to low wave-lengths, e.g. 8-azaadenosine (fig. 1), and various derivatives of 6-chloropurine. The sign of the second Cotton effect appears to be always negative in β-anomers (it has not been observed in the α-anomers so far available).

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 full acknowledgement to the many kind individuals who have supplied us with compounds. Many were the gift of Drs. L. Goodman, W.W. Lee and E.M. Acton and their associates at Stanford Research Institute, to whom we are particularly indebted.

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