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Preliminary communication

A circular dichroism rule for glycosyl-pyrimidines and -purines

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The circular dichroism (c. d.) of pyrimidine and purine nucleosides has been extensively studied. It has been shown that dipole–dipole coupling between the strong, near-ultraviolet bands of the chromophore and the far-ultraviolet bands of the sugar produces a significant, coupled-oscillator contribution to the optical activity of the aromatic chromophore[1]. The c. d. spectra of pyrimidine and purine nucleosides show multiple Cotton effects, and it is believed that the longer-wavelength envelope, at ~270 nm, is due in part to $n \rightarrow \pi^*$ transitions[2]. Several rules have been proposed for correlating the sign of the Cotton effect with the conformation of the nucleosides and, more specifically, with the angle between the plane of the heterocyclic ring and the direction of the C-1′→O bond[1,3,4]. Attempts have also been made[4] to compute the magnitude of the Cotton effect by using as variables (*a*) the unit vector in the direction of the electric dipole moment, $\vec{e}_B$, (*b*) the unit vector in the direction of the principal axis of polarizability of the D-ribosyl group, $\vec{e}_S$, and (*c*) the distance vector, $\overrightarrow{R_{BS}}$.

We have now used similar parameters to develop an empirical rule that predicts the sign of the Cotton effect of glycosyl-pyrimidines and -purines having glycosyl groups attached to naturally occurring bases. This rule is not restricted to pentofuranosyl groups linked to N-1 of pyrimidines and N-9 of purines, but can be applied to cyclic and acyclic sugars linked to any of the possible positions on these bases.

In developing a general, Cotton-effect rule, it was important to assign to each base the proper orientation in the *x,y* plane. The dipole-moment vector, $\vec{e}_B$, as determined by DeVoe and Tinoco[5] was arbitrarily placed along the *x* axis with the negative end of the dipole pointing in the negative direction. The positive and negative sense of the distance vector, $\overrightarrow{R_{BS}}$, along the *y* axis was arbitrarily assigned for each class of nucleoside by so turning the ring about the *x* axis that a nucleoside existing in a known conformation would give the correct sign when rules 1–3, given later, were applied[6–11]. Interestingly, most of the hetero-atoms capable of $n \rightarrow \pi^*$ transitions were concentrated in the same half of the molecule for the various bases; this is not surprising, as $n \rightarrow \pi^*$ transitions affect the sign of the Cotton effect of the longer-wavelength absorption (at ~270 nm). The orientation

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of the glycosyl group with respect to the base was described by the direction of the C-1′→O bond, which corresponds roughly to the *syn* and *anti* orientations. Thus, $\vec{e}_S$ was arbitrarily assigned along this bond with the vector pointing towards the oxygen atom.

Fig. 1 shows the proper orientation in the *x,y* plane of uracil, cytosine, thymine, adenine, and guanine residues attached to glycosyl groups through the various atoms in the heterocyclic ring. The orientation of the glycosyl group with respect to the base is depicted by the C-1′→O bonds in the *syn* and *anti* orientations, and the sign of the Cotton effect predicted for any given conformation is shown. A study of the data for the known compounds led to the generalizations given, which predict the sign of the Cotton effect of the as-yet-unknown glycosyl-pyrimidines and -purines shown in Fig. 1.

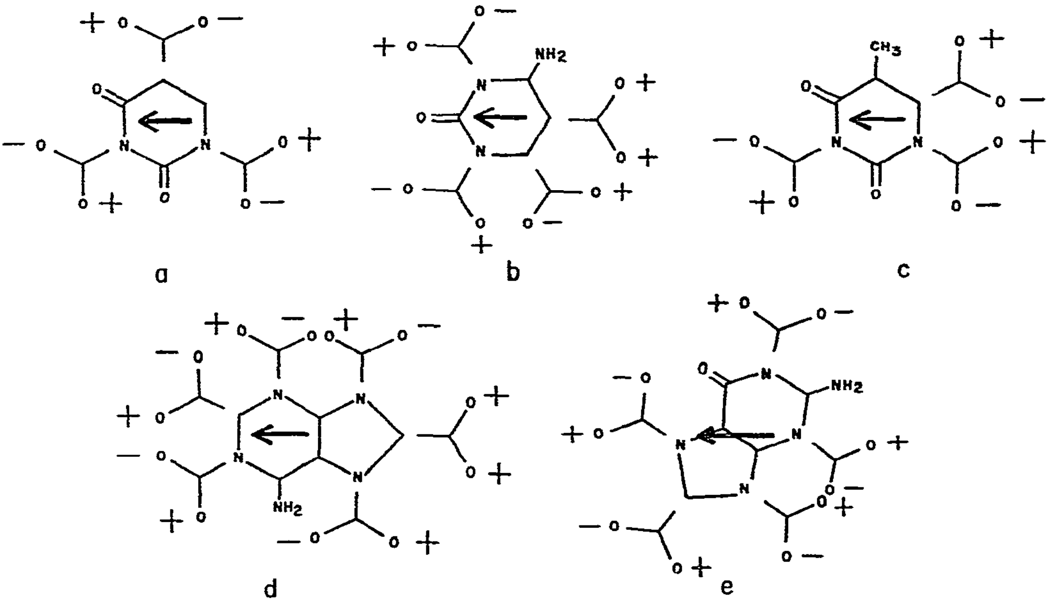

Fig.1. Orientation, in the *x,y* plane, of a residue of (a) uracil, (b) cytosine, (c) thymine, (d) adenine, and (e) guanine attached to a glycosyl group.

1. For a nucleoside having C-1′ of the glycosyl group in the *R* configuration, such as a β-D-ribofuranosyl group, and having $\overrightarrow{R_{BS}}$ negative in the *y* direction (the glycosyl group lying below the base), the sign of the Cotton effect will be negative if the *x* components of $\vec{e}_S$ (roughly represented by the C-1′→O bond) and $\vec{e}_B$ point in the same direction The sign of the Cotton effect will be positive if these two vectors point in opposite directions.

2. If the $\overrightarrow{R_{BS}}$ vector is positive in the *y* direction, the glycosyl group lying above the base, the sign of the Cotton effect will be positive when the *x* components of $\vec{e}_S$ and $\vec{e}_B$ are in the same direction, and it will be negative if the *x* components are in opposite directions.

The inversion of the sign above and below the *x* axis in rules 1 and 2 is to be expected, as a rotation of 180° of the base inverts the sense of the ring in the *x,y* plane, and changes $\vec{e_B}$ to $-\vec{e_B}$, owing to the contributions of the transitional, bond-order term[1] to $\vec{e_B}$ as follows:

$$\vec{e_B} \times \vec{e_S} \cdot \overrightarrow{R_{BS}} = -\left[-\vec{e_B} \times \overrightarrow{e_{SR}} \cdot \overrightarrow{R_{BSR}}\right]$$

where $\overrightarrow{e_{SR}}$ and $\overrightarrow{R_{BSR}}$ are the $\vec{e_S}$ and $\overrightarrow{R_{BS}}$ vectors, respectively, rotated about the x axis by 180°. It may also be shown that a rotation of 180° around the y and x axes will not cause an inversion of the sign of the Cotton effect.

3. If $\overrightarrow{R_{BS}}$ is essentially aligned with $\vec{e_B}$, the glycosylic bond being aligned with the dipole-moment vector, as in 5-glycosylcytosines, the sign of the Cotton effect is independent of rotation about the glycosylic bond. This is to be expected, as, under these circumstances, rotation of the base with respect to the glycosyl group does not change the angle between $\vec{e_B}$ and $\vec{e_S}$. In such cases, if the $\overrightarrow{R_{BS}}$ vector is in the same direction as the $\vec{e_B}$ vector, the sign of the Cotton effect is negative; it is positive if the two vectors oppose each other.

For glycosyl groups having the *S* configuration of C-1′, the sign of the Cotton effect is the reverse of that described for the *R* configuration.

The foregoing rule may be applied to predict the sign of the Cotton effect of nucleoside analogs if three requirements are met. (*1*) The base itself is not modified in any way which would significantly change its dipole moment. Accordingly, 6-azacytidine, 3,5-anhydroadenosine, and 8-bromoadenosine are excluded. (*2*) The sugar is not significantly modified by derivatization. Thus, for example 4′-thiouridine and *p*-toluenesulfonic esters of nucleosides are excluded. (*3*) The base is not strained by ring formation. Thus, 2,2′- and 2,5′-anhydrouridine are excluded. Requirements *1* and *2* are necessary, as the relative orientation of the dipole moment of the base and the axis of polarizability of the glycosyl group is paramount in determining the sign of the Cotton effect. Requirement *3* is necessary because, as pointed out by Miles *et al.*[4], the strained conformation markedly alters the electronic spectra of anhydronucleosides and, hence, their Cotton effects.

The rule allows the replacement of a cyclic glycosyl group by a hydroxyalkyl chain having the same configuration at C-1′, because the latter also exists in favored conformations[12,13] and the sign of the rotation is governed[14] by the configuration of C-1′ and by the orientation with respect to the heterocyclic ring.

It should be noted that the transition between a positive and a negative sign of the Cotton effect for a given glycosyl-pyrimidine or -purine has not yet been accurately determined. In Fig. 1, it is roughly represented at an angle of 90° to the plane of the paper. As the conformation of more nucleosides is determined accurately, the exact angle will become better defined. It will also be possible to test whether the foregoing rules are applicable to other heterocyclic residues linked to glycosyl groups for which the dipole moments are known.

REFERENCES

1 D. W. Miles, L. B. Townsend, M. J. Robins, R. K. Robins, W. H. Inskeep, and H. Eyring, *J. Am. Chem. Soc.*, 93 (1971) 1600–1608.
2 J. S. Ingwall, *J. Am. Chem. Soc.*, **94 (1972)** 5487–5495.

3 T. L. V. Ulbricht, in W. W. Zorbach and R. S. Tipson (Eds.), *Synthetic Procedures in Nucleic Acid Chemistry,* Vol. 2, Wiley–Interscience, New York, 1973, pp. 177–213.
4 D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Am. Chem. Soc.*, 91 (1969) 831–838.
5 H. DeVoe and I. Tinoco, Jr., *J. Mol. Biol.*, 4 (1962) 500–517.
6 T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, 6 (1967) 843–850.
7 T. Nishimura, B. Shimizu, and I. Iwai, *Biochim. Biophys. Acta*, 157 (1968) 221–232.
8 D. W. Miles, W. H. Inskeep, M. W. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *J. Am. Chem. Soc.*, 92 (1970) 3872–3881.
9 S. David and A. Lubineau, *Carbohydr. Res.*, 29 (1973) 15–24.
10 D. W. Miles, S. J. Hahn, R. K. Robins, M. J. Robins, and H. Eyring, *J. Phys. Chem.*, 72 (1968) 1483–1491.
11 H. S. El Khadem, T. D. Audichya, D. L. Swartz, and J. Kloss, *Abstr. Pap. Am. Chem. Soc. Meet.*, 169 (1975) CARB-6.
12 H. S. El Khadem, D. Horton, and T. F. Page, *J. Org. Chem.*, 33 (1968) 734–740.
13 H. El Khadem, D. Horton, and J. D. Wander, *J. Org. Chem.*, 37 (1972) 1630–1635.
14 H. El Khadem and Z. M. El Shafei, *Tetrahedron Lett.*, (1963) 1887–1889.