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A GENERALIZED, CIRCULAR DICHROISM RULE FOR NITROGEN HETEROCYCLES ATTACHED TO ALDITOL RESIDUES

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ABSTRACT

For alditol-1-yl derivatives of nitrogen heterocycles having C-1 of the alditol-1-yl group in the *R* configuration and having this group lying "below" the base, the sign of the Cotton effect will be negative if, for the most stable conformer, the bond to C-1 and the dipole-moment vector of the base point in the same direction, and positive if they they point in opposite directions. If the alditol-1-yl bond is essentially aligned with the dipole-moment vector of the nitrogen heterocycle, the sign of the Cotton effect is independent of the conformation. Consequently, if the dipole-moment vector of the nitrogen heterocycle and the alditol-1-yl group point in the same direction, the sign of the Cotton effect will be negative; it will be positive if the two oppose each other.

INTRODUCTION

The circular dichroism (c.d.) of pyrimidine and purine nucleosides has been extensively studied[1–4]. It has been shown that dipole–dipole coupling between the near-ultraviolet bands of the chromophore and the far-ultraviolet bands of the glycosyl group produces a coupled-oscillator contribution to the optical activity of the aromatic chromophore. Several rules have been proposed to correlate the sign of the Cotton effect of nucleosides with their conformation, and, more specifically, with the angle between the plane of the nitrogen-heterocyclic ring and the direction of the C-1′ → O bond[1,3,4]. El Khadem and co-workers[5] used similar parameters to develop an empirical rule that predicts the sign of the Cotton effect of glycosyl-pyrimidines and -purines linked to various positions of these bases.

DISCUSSION

The aim of the present work was to develop a generalized rule that would apply to nitrogen heterocycles linked to cyclic sugars or hydroxyalkyl chains. The present rule correlates the sign of the Cotton effect of the nitrogen heterocycle with the following variables: (*a*) the *R* or *S* configuration of the first chiral center attached to the nitrogen heterocycle; (*b*) the direction of the principal axis of polarizability of the alditol residue, defined by the direction of the C-1 → O vector relative to the electric dipole-moment vector of the nitrogen heterocycle in the more stable rotamer; and (*c*) the position of the alditol-1-yl group relative to the dipole-moment vector of the nitrogen heterocycle.

A study of the optical properties of known compounds led to the following generalizations; these may be used to predict the sign of the Cotton effect of as-yet-unknown nitrogen heterocycles linked to hydroxyalkyl chains or cyclic sugars. (1) For such nitrogen-heterocycle derivatives having C-1 of the alditol-1-yl group in the *R* configuration and having this group lying below the base (in the customary depiction), the sign of the Cotton effect will be negative if the C-1 → O bond and the dipole-moment vector of the base point in the same direction. The sign of the Cotton effect will be positive if these two vectors point in opposite directions. Conversely, if the alditol-1-yl group lies above the base, the sign of the Cotton effect will be positive when the C-1 → O bond and the dipole-moment vector are in the same direction, and negative if they are in opposite directions.(2) If the alditol-1-yl bond is essentially aligned with the dipole-moment vector of the nitrogen heterocycle, the sign of the Cotton effect is independent of rotation about this bond (conformation). If the dipole-moment vector of the nitrogen heterocycle and the alditol residue point in the same direction, the sign of the Cotton effect will be negative, and it will be positive if the two oppose each other.

The application of these rules to four types of alditol-1-yl derivatives of nitrogen heterocycles or nitrogen chromophores will now be discussed.

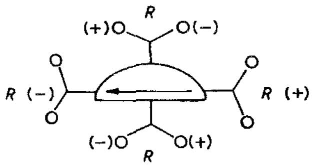
1. Nitrogen heterocycles having no plane of symmetry along the dipole-moment vector

Formula **1** depicts an idealized nitrogen heterocycle having the dipole-moment vector pointing towards the negative end of the *x* axis; it shows the predicted sign of Cotton effects for a hydroxyalkyl chain or a cyclic sugar attached to the nitrogen heterocycle at various angles relative to the dipole-moment vector.

The idealized, nitrogen heterocycle does not possess a plane of symmetry in the direction of the dipole-moment vector, and must be properly oriented along the *x* axis in order to define its upper and lower parts before the Cotton effect of hydroxyalkyl chains or cyclic sugars attached to one of the two parts of the ring can be predicted. This is not, however, necessary if the bond linking the nitrogen heterocycle to the carbohydrate residue is aligned with the dipole-moment vector. Thus, in heterocycle **2**, where the bond linking the heterocycle to an *R* chiral center points in a direction opposite to that of the dipole-moment vector, the sign of the Cotton effect will be positive; and, conversely, it will be negative if both these two vectors are aligned and point in the same direction.

This seems to be a general rule applicable to compounds having hydroxyalkyl groups attached to nitrogen heterocycles or chromophores by bonds aligned with the dipole moment of the heterocyclic ring or chromophore. Such molecules can exist in a multitude of enantiomeric pairs of conformers which cancel each other's effect on the circular dichroism. The conformation of the first chiral center next to the nitrogen heterocycle will, therefore, have no effect on the sign of the Cotton effect, and the latter will be solely determined by the configuration of this first chiral center.

If the sugar ring or hydroxyalkyl chain on the nitrogen heterocycle is perpendicular to the dipole-moment vector of the heterocycle, or has a component in the direction of the *y* axis, as in heterocycle **3**, it will be necessary, in order to predict the sign of the Cotton effect of the stable conformer, first to establish the position of the carbohydrate residue relative to the dipole-moment vector, and to define whether it is attached to the lower or the upper part of the heterocyclic ring. This is because exchange of the position of the sugar in the semicircles depicted will result in an inversion of the sign of the Cotton effect. The means of determining the exact orientation of the nitrogen heterocycle around the *x* axis presents the main difficulty in the present rule. In general, the negative substituent or heteroatom in the ring is located in the upper half of the ring and the hydroxyalkyl chain in the lower. Assuming that the stable conformation for the hydroxyalkyl chain is that in which the oxygen atom of the hydroxyl group of the chiral center attached to the heterocycle will tend to move away from the negative end of the dipole, the sign of the Cotton effect will be determined by the configuration of the first chiral center attached to the ring. If the configuration is *R*, the Cotton effect is positive; it is negative when the configuration is *S*, as exemplified by the (*R*)-oxadiazole **4** and the (*S*)-triazole **5**.



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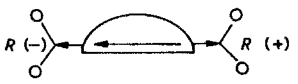

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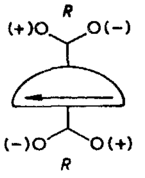

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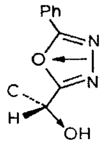

R (+)

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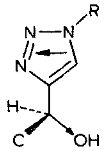

S (−)

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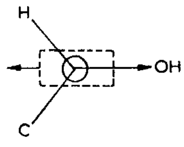

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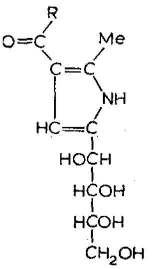
This rule may also be illustrated by the "Newman" projection **6**, in which a heterocyclic ring lies behind and perpendicular to the plane of the paper, and the first chiral center attached to it protrudes towards the observer. If, as expected, the stable conformer will tend to have the hydroxyl group away from the negative end of the dipole-moment vector, the compound will follow the generalized rotation rule[6] which states that the rotation of a hydroxyalkyl-substituted, nitrogen heterocycle is determined by the configuration of the first chiral center. When this has the *R* configuration, the rotation is (+), and when the configuration is *S*, the rotation is (−).

If the stable conformer of all of these compounds does tend to have the hydroxyl group (which is the most negative part of the first chiral center) away from the negative end of the dipole moment of the ring, the *R* form of these compounds will be dextrorotatory, or have a positive Cotton effect, and the *S* form will be levorotatory and have a negative Cotton effect.

A review of the literature reveals several examples of nitrogen heterocycles attached to hydroxyalkyl chains, or to glycosyl rings, that obey the foregoing, generalized rule for c.d. These include the (hydroxyalkyl)pyrroles[7] [such as the (hydroxyalkyl)-imidazoles[8] and thio-imidazoles[9] and the (hydroxyalkyl)oxadiazoles prepared by H. El Khadem and co-workers[10]] and the (hydroxyalkyl)-1,2,3-triazoles prepared by Horton and co-workers[11] (see formulas **7**–**12**).



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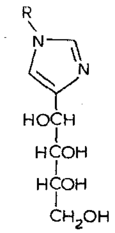

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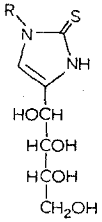

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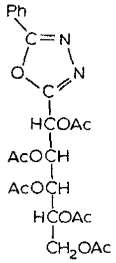

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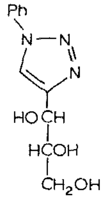

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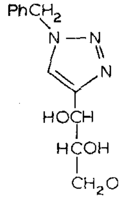

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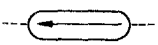
2. Nitrogen heterocycles having a plane of symmetry along the dipole-moment vector

Another class of heterocycles of interest is composed of hydroxyalkyl derivatives of heterocycles having a plane of symmetry along the dipole-moment axis. The upper half of these heterocycles is the mirror image of the lower half, shown in **13**. As with the nitrogen heterocycles discussed in the previous section, if the bond linking the hydroxyalkyl chain to the heterocycle is aligned with the dipole-moment vector, the sign of the Cotton effect will depend only on the configuration of the first chiral center. It will be positive for the *R* compound, irrespective of conformation, if the bond linking the heterocycle to the sugar residue points in the direction opposite to that of the dipole-moment vector, and, if *vice versa* (**14**, **15**), it will be negative for the *S* compound.



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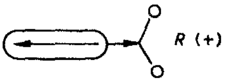

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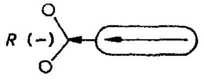

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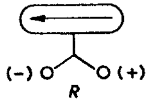
If the bond linking the nitrogen heterocycle to the carbohydrate residue is perpendicular to the dipole-moment vector, or has a component in that direction, the relationship discussed for the group of heterocycles lacking a plane of symmetry along the x axis will hold true, the only difference being that the upper and lower halves of the molecule are mirror images, and the molecule does not require any orientation by rotation around the x axis. By convention, the hydroxyalkyl group or the glycosyl ring will lie below the ring of the nitrogen heterocycle, as in **16**.



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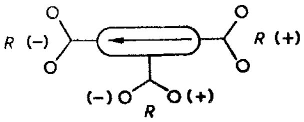
In most compounds, the stable conformer will tend to have the hydroxyl group away from the negative end of the dipole-moment vector. For an *R* configuration with this hydroxyl group pointing away from the dipole-moment vector of the ring, the Cotton effect will be positive, and it will be negative if the hydroxyl group points towards it; this could explain why the generalized rotation rule of El Khadem and El Shafei[6] holds true for this group of compounds.

The predicted sign of the Cotton effect of hydroxyalkyl groups that have the *R* configuration and are attached to the various positions of a heterocycle of this type is shown in **17**.



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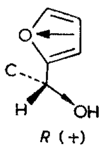
A review of the literature reveals several examples of nitrogen heterocycles attached to hydroxyalkyl chains, or to glycosyl rings, which possess a plane of symmetry along their dipole-moment vectors. These include the (hydroxyalkyl)furans described by Horton and Tsuchiya[12] and the 2-aryl-4-(hydroxyalkyl)-1,2,3-triazoles[13] depicted in formulas **18** and **19**.



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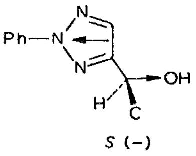

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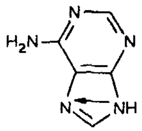
All of the previous compounds will obey rules *1* and *2*. Assuming that the stable conformation for the hydroxyalkyl chain is that in which the oxygen atom of the hydroxyl group of the chiral center attached to the heterocycle will tend to move away from the negative end of the dipole, the sign of the Cotton effect will be determined by the configuration of the first chiral center attached to the ring. If the configuration is *R*, the Cotton effect is positive; it is negative when the configuration is *S*. Here, and throughout this work, it is assumed that the priority of the groups attached to the first chiral center are OH > nitrogen-heterocyclic ring > the hydroxyalkyl chain > H.

3. *Fused-ring systems*

The application of the present rule to fused-ring systems presents certain problems. One approach, applied to purines by El Khadem and co-workers[5] was to treat the fused-ring system as one entity, and then establish the dipole moment of the whole system. The fused ring was now aligned along the x axis in such a way that the known nucleosides, in their favored conformation, gave the expected sign of the Cotton effect.

Another approach to fused-ring systems is to consider only the ring to which the carbohydrate residue is fused, and to disregard the other ring. Its dipole moment could be determined and the sign of the Cotton effect predicted. For a glycosylpurine linked at N-7, C-8, or N-9, only the dipole moment of the imidazole ring, the *R* or *S* configuration of the first chiral center, and its orientation relative to the dipole moment of the base in the most stable conformer would be considered. One difficulty that may arise is the problem of accurately establishing the direction of the dipole-moment vector of one of the rings in a fused-ring system, as, experimentally, the dipole-moment measurements are made on the whole molecule. However, this can be calculated, and, usually, the dipole moments are shifted only slightly from the dipole-moment vectors of the monocyclic system. Formulas **20** and **21** are approximate representations of the dipole-moment vector of the imidazole ring of a purine and the pyridazine ring of a cinnoline, so oriented as to predict the Cotton effect by use of rules *1* and *2*.



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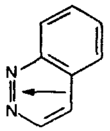

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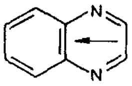

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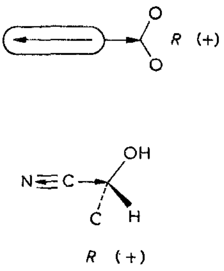
Attempted application to the quinoxaline system **22** may present a problem, as the diazine ring is symmetrical and has no dipole moment. However, it may be argued that a saccharide residue linked to C-3 of a quinoxaline ring will be located at the positive end of a dipole-moment vector pointing in the direction of the benzene ring, and that the C′-1 → O bond of the stable conformer will tend to move away from the negative end of the dipole moment in its vicinity.

4. *Acyclic chromophores*

A closer look at acyclic compounds that have the dipole-moment vector of their chromophore aligned with the bond linking the chromophore to the hydroxyalkyl chain or glycosyl ring reveals that these compounds have no favored conformation for the first chiral center relative to the chromophore. They should, therefore, follow the rule that governs the sign of the Cotton effect of heterocycles having their dipole-moment vector aligned with the bond linking the heterocyclic ring to the first chiral center.

Thus, for example, hydroxyalkyl nitriles have the bond linking the first chiral center to the *sp*-hybridized orbital of the nitrile group in direct alignment. Accordingly, it would not be expected that any C-1 rotamer would be favored and would preponderate. The sign of the Cotton effect will, therefore, depend mainly on the configuration of the first chiral center. It would be expected that, when the direction of the vector going from the chromophore towards the first chiral center is opposite to that of the dipole-moment vector of the chromophore, the rotation would be positive for an *R* chiral center; this would explain why the rotation of nitriles depends on the first chiral center attached to the CN group, and is positive when the first chiral center[14] has the D configuration **23**.



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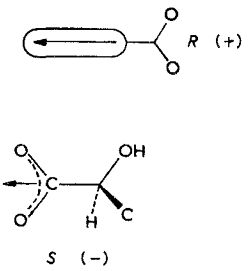

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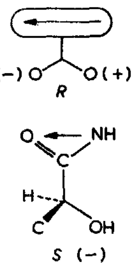
Other examples of acyclic compounds having the bond linking the chromophore to the first chiral center aligned with the dipole-moment vector of the chromophore are the alkali-metal salts of aldonic acids. These compounds exist in the ionic, carboxylate form, and their dipole moment is aligned with the bond linking the carboxylate group to the first chiral center. Unlike the carboxylic acids, whose rotations are not predictable by the present rules, the rotations of the alkali-metal salts of sugar acids depend solely on the configuration of the first chiral center. As the direction of the bond going from the carboxylate group to the first chiral bond opposes the dipole-moment vector of the carboxylate group, the rotation should be positive for *R* compounds, and negative for *S* compounds (**24**). A rotation rule first described over 60 years ago foreshadowed this conclusion.[15]

Interestingly, certain acyclic compounds having the dipole moment of their chromophore perpendicular to the bond linking their first chiral center to the chromo-



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phore seem to obey the rules applicable to heterocyclic rings. Thus, for example, the rotation of sugar acid amides and hydrazides depends solely on the configuration of the first chiral center, being[16] positive for *R* compounds and negative for *S* (**25**).

It should be noted that this rotation rule is not applicable to all acyclic compounds, because of hydrogen bonding. Thus, hydroxyalkyl carboxylic acids do not obey the rule, probably because they exist as equilibum mixtures with the various lactones possible.

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