THE SIGN OF THE B_{2u} COTTON EFFECT AND THE CONFORMATION OF PYRIMIDINE AND AZAPYRIMIDINE NUCLEOSIDES

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1. Introduction

Rogers and Ulbricht [1] have shown recently that whereas pyrimidine-β-D-nucleosides of biological importance (e.g. uridine) give positive B_{2u} Cotton effects in the optical rotatory dispersion, the corresponding 6-azapyrimidine nucleosides (6-azauridine) give negative Cotton effects. They have indicated that this situation could be explained by either of two possibilities : 1) the 6-azapyrimidine nucleosides tend to adopt a conformation somewhat different from that of the pyrimidine nucleosides with respect to the glycosidic torsion angle χ_{CN} [2] ; the change would imply a shift of this angle to somewhat greater values in the 6-azapyrimidines while still leaving it in the *anti* range, or 2) the direction of polarization of the B_{2u} transition ($\theta_{B_{2u}}$) is significantly different in the 6-aza derivatives than in the parent pyrimidines. Because of lack of experimental indications on the values of these quantities, the authors were unable to choose between the two possibilities although they seem to favour the first one.

In this note we would like to indicate that quantum-mechanical computations, which can be carried out for the values of both χ_{CN} and $\theta_{B_{2u}}$ can replace the missing experimental information and, in fact, solve the dilemma. Such calculations have already been carried out previously for the pyrimidines and shown to be in satisfactory agreement with available experimental data [3–5]. They are extended in this note to 6-azauracil and 6-azauridine. The comparison of the results with those for uracil and uridine enables a straightforward interpretation of the origin of the change in sign of the B_{2u} Cotton effect.

2. Methods

The computations on the direction of polarization of the B_{2u} transition in uracil and azauracil are carried out within the self consistent field molecular orbital method in the Parr-Pariser-Pople approximation with configurational interaction including all singly excited configurations. The procedure is described in detail in [5]. The evaluation of the glycosidic rotational angle in uridine and 6-azauridine is carried out by the PCILO method (Perturbative configuration interaction using localized orbitals) as described in details in [3]. The C(3′)-endo conformation is adopted for the sugar.

3. Results and discussion

Let us recall first the results for uracil and uridine. The computed value of $\theta_{B_{2u}}$ in uracil is $-9°$ with respect to the N_1-C_4 axis, negative values corresponding to a clockwise rotation of the polarisation vector (fig. 1). This is in good agreement with experimental data which indicate the value of 0° or 7° [6] or −19° or −23° [7]. The conformational energy map for rotation about the glycosidic bond in C(3′)-endo nucleoside of uracil is reproduced in fig. 2 [3]. The predictions of the theory, which point to a minimum at $\chi_{CN} \approx 5°$ (*anti* conformation) with the curve rising slowly towards positive values of χ_{CN} are again in good agreement with the experimental data : the

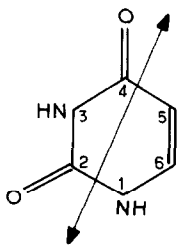

Fig. 1. Calculated direction of the polarization for the B_{2u} transition of uracil.

values in representative nucleosides extend between $5° < \chi_{CN} < 43°$ and are within 1 kcal/mole of the global minimum.

We may now turn over to the problem of the 6-aza derivatives. The computed direction of polarization of the B_{2u} transition in 6-azauracil is $-10°$, thus practically identical to that in uracil and this result rules out the possibility that the change in the Cotton effect could originate from the modification

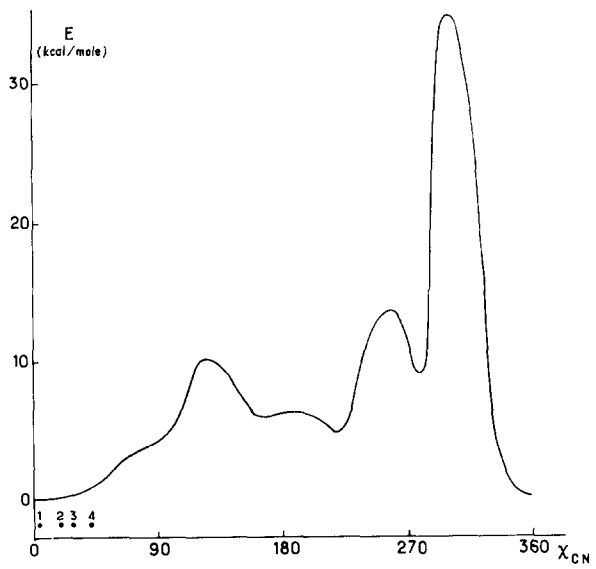

Fig. 2. Conformational energy map for rotation about the glycosidic bond in the nucleosides of uridine and thymidine. Experimental results (see [3]) : 1) Uridine in adenosine-2'-uridine-5'-phosphoric acid; 2) 5-bromouridine in complex with adenosine; 3) 5-methyluridine; 4) calcium thymidine 5'-phosphate.

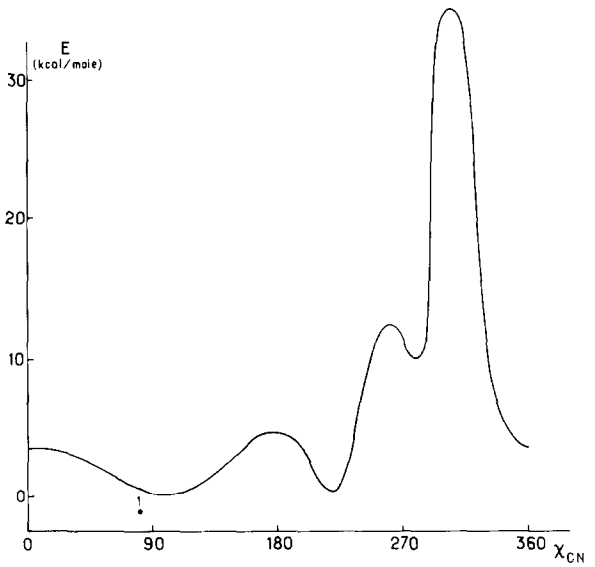

Fig. 3. Conformational energy map for rotation about the glycosidic bond in 6-azauridine. Experimental result : 1) 6-azauridine [8].

of $\theta_{B_{2u}}$. Moreover, the computed conformational energy map for the rotation about the glycosidic bond in 6-azauridine is presented in fig. 3. It indicates that the replacement of the C–H bond at position 6 by the N atom produces significant changes in the position of the energy curve between $0° < \chi_{CN} < 180°$. What is particularly striking is the shift of the global minimum to the vicinity of $\chi_{CN} = 90°$, thus in the direction predicted by Rogers and Ulbricht [1].

Altogether this evidence indicates therefore that the change in sign of the B_{2u} Cotton effect in 6-azauridine can be ascribed entirely to a variation of the torsion angle χ_{CN} with respect to its value in uridine. The reality of this displacement is, in fact, confirmed by the very recent result of an X-ray study of 6-azauridine [8] which provides the experimental value of $\chi_{CN} \approx 80°$. It may be anticipated without risk that the conclusion applies also to 6-azathymidine and 6-azacytosine. We have verified that the direction of polarization of the B_{2u} transition remains unchanged, within a few degrees, in these azapyrimidines with respect to the values in the pyrimidines. As to the evolution of the conformational energy map of χ_{CN}, it is sufficiently similar for cytidine and uridine [3] to warrant a similarity for the corresponding aza derivatives.

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