

A MOLECULAR ORBITAL INVESTIGATION
OF THE DIPOLE MOMENTS OF THE SYN AND ANTI CONFORMERS
OF PURINE AND PYRIMIDINE NUCLEOSIDES.

H. Berthod and B. Pullman,

Institut de Biologie Physico-Chimique, 13, rue P. et M. Curie, Paris 5è, France.

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Summary. Molecular orbital calculations predict that the nucleosides of adenine, cytosine, uracil, purine and xanthine should in general have a higher dipole moment in the anti than in the syn form. The reverse should be true for the nucleosides of guanine and hypoxanthine. The result depends primarily on the direction of the dipole moment in the free bases.

The conformational energies of purine and pyrimidine nucleosides have been extensively investigated recently by a number of theoretical methods, both "empirical" (1)-(5) and quantum-mechanical (6)-(8). In agreement with experimental evidence, coming mainly from X-ray crystallography, they point to the predominance of the anti forms, although they account satisfactorily for the cases in which the compounds exist in the syn form or in which both conformers are observed in the assymmetric unit⁽⁶⁾.

It appears, however, that a changement in conformation may accompany the transition from the crystal to solution (e.g. 4-thiouridine⁽⁹⁾⁽¹⁰⁾ is syn in the solid state and anti in solution) or that a mixture of conformers may coexist in solution⁽¹¹⁾⁻⁽¹³⁾. This is not surprising a priori, given the relatively low barriers computed for some types of nucleosides. The situation raises the problem of the environmental stabilizing factors and of the identification of the conformers present in solution. The application of the optical methods generally used for this sake, NMR, ORD, CD, NOE, etc.. involves frequently numerous difficulties (e.g. (14)-(19)).

Recent success obtained in the joint utilization of computed and observed dipole moments for the identification of purine and pyrimidine tautomers⁽²⁰⁾⁻⁽²⁵⁾ suggests a similar approach towards nucleosides. Provided that the dipole moments computed for the syn and anti conformers are sufficiently different and that the

solubility problem may be overcome, the comparison of the computed and measured dipole moments should help to identify the conformers present and to elucidate their preferential stabilization in different solvents.

In this Note we describe the results of the theoretical computation of the dipole moments associated with the syn and anti conformers of the principal purine and pyrimidine nucleosides. The method utilized is the quantum mechanical PCILO (Perturbative Configuration Interaction using Localized Orbitals) method, which we have used for the calculations of the conformational energy maps of these nucleosides⁽⁶⁾⁽⁷⁾. For each pair of conformers of each type of nucleoside, the distribution of the electronic charges and the dipole moment are calculated for the values of the glycosidic torsion angle, χ_{CN} , indicated as the most stable one by the calculations of ref. (6)(7). The geometries utilized are those of the representative compounds of ref. (6) (7). The results (Table I) although applying strictly only to the examples studied may nevertheless certainly be considered as indicating broadly the general aspect of the phenomenon.

They show that the dipole moments should be greater in the anti than in

TABLE I.

Computed dipole moments (Debye units).

Nucleoside	Sugar		χ_{CN}		Dipole moment	
	Pucker	Orientation about C(4')-C(5')	anti	syn	anti	syn
Uridine	C(3')-endo	gg	20°	220°	7.0	3.4
Deoxyuridine	C(2')-endo	gt	60°	240	4.8	4.8
Cytidine	C(3')-endo	gg	10°	200	8.8	6.7
Deoxycytidine	C(2')-endo	gg	60°	240	10.0	4.1
Adenosine	C(3')-endo	gg	20°	240 280	5.6	1.9 2.8
Adenosine	C(2')-endo	gg	70°	260	8.2	4.4
Guanosine	C(3')-endo	gg	30°	280	4.6	10.0
Deoxyguanosine	C(2')-endo	gg	60°	230	5.9	6.3

the syn conformers for the nucleosides of Ura, Ade and Cyt (with the exception of C(2')-endo deoxyuridine, the only compound with a gt orientation about the C(4')-C(5') bond, for which the two forms have practically identical dipole moments), but that the situation should be reversed for the nucleosides of Gua. This general result can be easily accounted for by the consideration of the direction of the dipole moment in the bases and of the component of the moment of the ribose in the plane of the bases. Calculations by a number of quantum-mechanical methods (26)(27) lead to the schematic representation of the directions of the moments of the bases indicated in fig. 1 from which it can be seen that while the moments of Ura, Ade, and Cyt are located in the positive range of θ , between 44° and 102° , the moment of Gua points at $\theta = -31^\circ$. It is also found that the component of the dipole moment of the sugars in the plane of the bases corresponds, for the gg forms, to $+34^\circ < \theta < +160^\circ$ in the anti and to $-37^\circ < \theta < -171^\circ$ in the

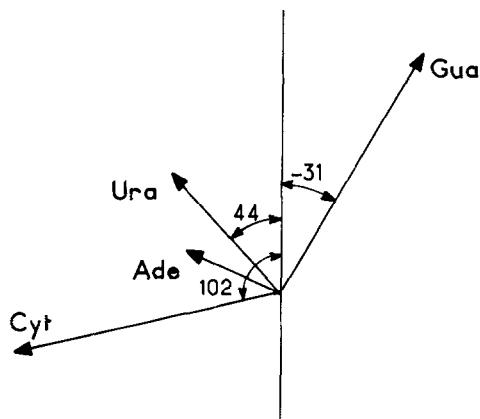


Figure 1. - The direction of the dipole moment in the bases, with respect to the $C_4 - C_5$ bond in purines and the $N_1 - C_4$ axis in pyrimidines. The angle, θ° , is positive for anticlockwise and negative for clockwise rotation.

syn conformers of the nucleosides. The combination of the two vectors leads thus to a higher dipole moment for the anti conformer in the nucleosides of Ura, Ade and Cyt and to a higher value of the moment for the syn conformer in the nucleosides of Gua. This is illustrated in fig. 2. Our result for C(3')-endo uridine is in agreement with a similar calculation by Kang⁽⁸⁾ using the INDO method. In the particular case of the C(2')-endo deoxyuridine, because of the gt orientation about the C(4')-C(5') bond, the component of the dipole moment of the sugar in the plane of the base shows up to have a very small value and its angle θ is -19° for the anti and $+2^\circ$ for the syn form. As a result, the influence of the sugar is altogether negligible and the moment of this nucleo-

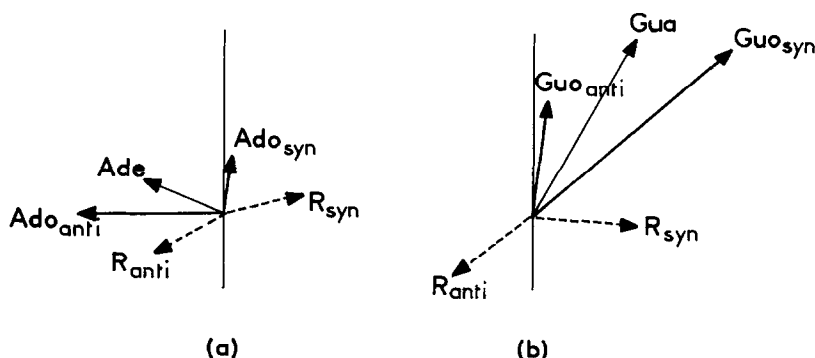


Figure 2. - The composition of the resultant moment in (a) adenosine and (b) guanosine. (R = component of the dipole moment of the ribose in the plane of the base).

side is practically identical to that of the free base and therefore independent of its conformation.

These considerations enable to predict that the nucleosides of purine ($\theta = 46^\circ$) and of xanthine ($\theta = 24^\circ$ for the N(9)H tautomer) should, in the gg forms of the endo-sugars, have higher dipole moments in their anti than in their syn conformations. On the contrary, hypoxanthine ($\theta = -16^\circ$ in the N(1)H - N(9)H tautomer) should have a higher dipole moment in its syn form.

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