CONFORMATIONAL ANALYSIS OF NUCLEIC ACIDS. EXTENDED HUCKEL STUDY OF 5′ ADENOSINE MONOPHOSPHATE (5′ AMP)

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1. Introduction

Conformational analysis of a 5′-nucleotide requires the minimization of its energy with respect to three angular parameters denoted by θ_1, θ_2, X [1] (see fig. 1). Some quantum calculations have been made on the ribose-phosphate unit, assuming different conformations for the sugar [2–4]. Moreover, studies on the purine or pyrimidine base orientation with respect to the sugar, that is studies on rotation X, about the glycosidic bond, have been performed only, till now, for nucleosides [5–8].

The preferred conformations of a nucleotide are predicted for the first time, in the present work, by quantum calculations.

2. Calculations

These calculations were made using Extended Hückel Theory (EHT) [9]. Details about the program used to perform calculations along with the input data (the atomic parameters and the adjustable constant K occurring in the calculation of the off diagonal terms of the Hamiltonian matrix) may be found in [3]. As far as the nitrogen atoms are concerned, the atomic parameters, which did not appear in our first study, have been assigned the following values: Slater orbital exponent ζ = 1.950, diagonal elements of the Hamiltonian matrix H_{ii} (2s) = −26.00 eV. H_{ii} (2p) = −13.40 eV.

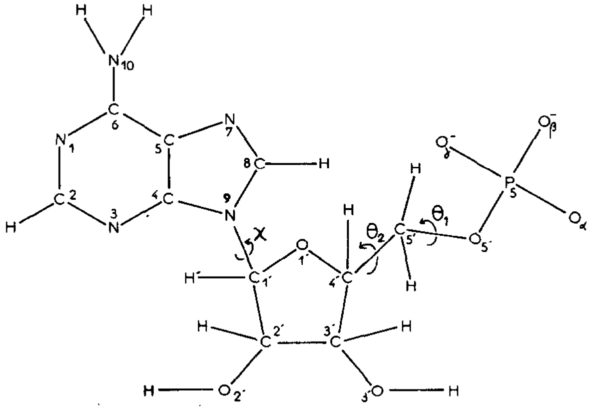

Fig. 1. 5′-AMP molecule. Notations and conventions chosen for the conformational angles are those of Lakshminarayanan and Sasisekharan [1]. Atomic coordinates are those given in [1] for the adenine-ribose (C3′-endo)-phosphate unit. With regard to the O_α, O_β, and O_γ atoms coordinates, which are not given in [1]. The following bond lengths and bond angles were used: P=O: 1.492 Å; P–O⁻: 1.509 Å; O=P–O⁻: 117°.20; O=P–OR: 106°.56; O⁻–P–OR: 108°.90.

Our work on 5′-AMP began with a study on rotations θ_1 and θ_2 about the C5′–O5′ and C4′–C5′ bonds. In this preliminary study the adenine base was not taken into account. Moreover, the OH group attached to C2′ was suppressed to save computer time. In fact, we think this suppression will make no major change in the predicted conformations. The terminal atoms C1′ and C2′ were assigned closed electronic shells. The drawing of energetic curves E (θ_1, θ_2 = ct) and E (θ_1 = ct, θ_2) brought into light the existence of three regions in which the energy E (θ_1, θ_2) takes the following minimal values: E (180°, 180°) = −34,390.85 kcal/mole, E (180°, 50°) =

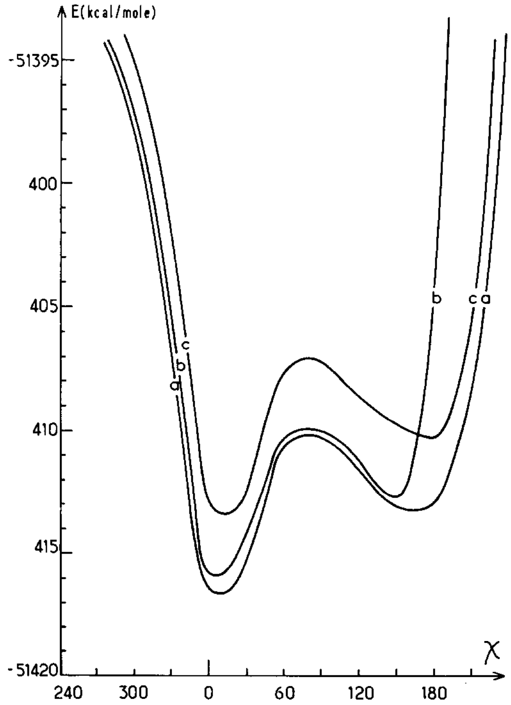

Fig. 2. The energy of 5'-AMP as a function of X.
a: $E(X)$ with $\theta_1 = 180^\circ$, $\theta_2 = 180^\circ$.
b: $E(X)$ with $\theta_1 = 180^\circ$, $\theta_2 = 50^\circ$.
c: $E(X)$ with $\theta_1 = 180^\circ$, $\theta_2 = 300^\circ$.
The figure clearly shows the existence of a main minimum for $X = 10^\circ$ and of a secondary one for $X \in (150^\circ, 180^\circ)$.

−34,390.57 kcal/mole, $E(180^\circ, 300^\circ) =$ −34,387.71 kcal/mole.

As a second step, the value of X was varied while successively keeping the phosphate group in three positions corresponding to $(\theta_1 = 180^\circ, \theta_2 = 180^\circ)$, $(\theta_1 = 180^\circ, \theta_2 = 50^\circ)$, $(\theta_1 = 180^\circ, \theta_2 = 300^\circ)$. Again, the OH group substituted on C2′ and C3′ were out off for the reasons indicated above.

3. Results and discussion

Results are given in fig. 2. Clearly, the ANTI conformation ($X = 10^\circ$) is preferred, while another minimum is observed in the SYN region ($X \in (150^\circ, 180^\circ)$). To make the minimum position more precise, we used a mathematical method of minimization of functions with respect to several variables. This search was made from the two main energy minima corresponding to the conformations $(\theta_1 = 180^\circ, \theta_2 = 180^\circ, X = 10^\circ)$ and $(\theta_1 = 180^\circ, \theta_2 = 50^\circ, X = 10^\circ)$. The results (with a 10° uncertainty) are nearly the same as those obtained from energetic curves where only one parameter was varied. We found the following energies: $E(\theta_1 = 180^\circ, \theta_2 = 50^\circ, X = 10^\circ) =$ −51,415.95 kcal/mole and $E(\theta_1 = 180^\circ, \theta_2 = 190^\circ, X = 10^\circ) =$ −51,416.78 kcal/mole, corresponding to two conformations that we have, respectively, denoted by α and β.

The comparison of our results with available data can be only indicative because these ones do not deal

Table 1

		θ_1	θ_2	X
Hard-sphere model [1]		Around 180°	60°, 180°, 300°	0°–60° 210°–230°
Potential energy calculations [10]		180°, 80°	60°, 180°, 300°	20° and 210°
Quantum	Govil and Saran (EHT) [2]	180°	60°, 180°, 300°	
Calculations	Berthod and Pullman (PCILO) [8]			In the range (−20°, 60°); 280°
	Jordan and Pullman (EHT) [5]			18° and 258°
Our results		180°, 90° and 270°	50°, 190°, 300°	10° and 180°

Table 2

Observed structure		177°.2	40°	25°.7
Our calculations	α Conformation	180°	50°	10°
	β Conformation	180°	190°	10°

with the simultaneous variation of the three angles θ_1, θ_2, and X. We compare in table 1 the results of our calculations on 5′-AMP with those obtained by hard sphere, potential energy and quantum calculations on D-ribose (C3′-endo) phosphate or on adenosine. Our results are in good agreement with the others. We can however notice a displacement of the secondary minimum towards the region X = 180°. This is probably due to the steric effect introduced by the oxygen atoms of the phosphate group. The crystalline structure of 5′-AMP, determined by Krant and Jensen [11] by X-ray diffraction is in good agreement with our α conformation (see table 2).

The existence of the β conformation leads to some hypotheses. A first one may be laid down by taking into consideration the fact that we are working without natural support for the molecule. We made our calculations without taking into account the interaction of 5′-AMP with its environment and we therefore neglected the effect of the natural solvent (electrolyte). In this case, we may think that neglecting these fundamental interactions could contribute to overstabilize the β conformation. In the light of experimental results obtained till now, this conformation cannot be kept although it seems to be allowed. A second hypothesis is to consider the β conformation as possible. This one finds its support in the recent crystallographic works made on a nucleoside: 6-methyluridine by Suck et al. [12]. In fact these authors experimentally found that this nucleoside occurs in the SYN conformation, with two possible shapes in the same monocrystal. These two shapes correspond to two conformations named A: (θ_2 = 62°.5) and B (θ_2 = 179°.8). So it is not prohibited to think that 5′-AMP could also present two shapes. The possible existence, predicted by EHT calculations, of two conformations for the same molecule is only hypothetical because, till now, studies on the crystalline structure of 5′-AMP did not reveal it. However the question is now open and only other experimental results would help to answer.

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References

[1] A.V. Lakshminarayanan and V. Sasisekharan, Biochim. Biophys. Acta 204 (1970) 49.
[2] G. Govil and A. Saran J. Theor. Biol. 30 (1971) 621.
[3] D. Vasilescu, F. Camous and J.N. Lespinasse, FEBS Letters 21 (1972) 179.
[4] B. Pullman, D. Perahia and A. Saran, Biochim. Biophys. Acta 269 (1972) 1.
[5] F. Jordan and B. Pullman, Theoret. Chim. Acta 9 (1968) 242.
[6] Sungzong Kang, J. Mol. Biol. 58 (1971) 297.
[7] J.L. Coubeils, B. Pullman and PH. Courrier, Biochem. Biophys. Res. Commun. 44 (1971) 1131.
[8] H. Berthod and B. Pullman, Biochim. Biophys. Acta 232 (1971) 595; 246 (1971) 359.
[9] R. Hoffmann, J. Chem. Phys. 39 (1963) 1397.
[10] A.V. Lakshminarayanan and V. Sasisekharan, Biopolymers 8 (1969) 475; 8 (1969) 489.
[11] J. Krant and L.H. Jensen, Acta Cryst. 16 (1963) 79.
[12] D. Suck, W. Saenger and H. Vorbrüggen, Nature 235 (1972) 333.