STACKED AND EXTENDED CONFORMATIONS OF SINGLE STRANDED POLYNUCLEOTIDE CHAIN FAVOURED BY VAN DER WAALS FORCES

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Recently, Arnott and Hukins [1] pointed out, that experimental values of conformational angles for mono- and polynucleotides are confined in the same narrow range. This fact supports the assertion that van der Waals interactions play an essential part in the selection of the most stable conformations for those biopolymers. The same situation was shown to prevail in the case of polypeptides [2]. We think therefore that the computation of the conformations of minimum energy on the basis of van der Waals interactions alone might give a valuable first approximation to the folding of a polynucleotide chain.

In this paper, we make such a calculation for an adenylic dinucleotide. Two conformations of minimal van der Waals energy, allowing some stacking of the bases, are found. The first one corresponds closely to the conformation occurring in double stranded helicoidal structures. The other one, which is nearly a fully extended conformation, may be representative of the mean structure adopted by single stranded polynucleotide.

Van der Waals energy $\nu(r) = A\ \exp(-Br)-C/r^6$ takes into account two effects. Steric repulsion between atoms at very short distances ($A\ \exp\ (-Br)$) and attractive London dispersion forces at intermediate range ($-C/r^6$).

In aqueous solution, the net result of the so called "hydrophobic forces" is to reinforce the natural tendency of aliphatic and aromatic groups to come in close contact in order to minimize the London dispersion energy. For these groups, the attractive part of the van der Waals energy acts thus in the same direction as hydrophobic forces.

The chemical structure of polynucleotides is such that it appears advisable, in a computational approach, to consider succesively two types of conformational unit [3].

The first one, the "mononucleotide unit" (fig. 1), extends from one phosphorus atom P_i to the next one P_{i+1} on the chain. The conformation of such a unit is determined by four internal rotational angles Θ_1, Θ_2, Θ_3, χ. (The sugar being considered as a rigid moiety in the C3′ endo conformation. The hydrogen atom on the oxygen O2′ is not taken into account; its effect on van der Waals energy would be negligeable in most cases.) In the following, we will denote this segment of the polynucleotide chain by the symbol "P_i–P_{i+1} unit".

The second conformational unit, the "dinucleotide unit" (fig. 2), extends from P_i to P_{i+2} and is centered on P_{i+1}. The conformation of this segment, denoted in short P_i–P_{i+2} unit, is determined by the knowledge of the conformation of the P_i–P_{i+1} and P_{i+1}–P_{i+2} units and the values of the rotational angles ϕ and ψ at the level of the P_{i+1} atom.

The partition of the polynucleotide chain into P_i–P_{i+1} and P_i–P_{i+2} units can be legitimated by the following facts.

At the level of the P_i–P_{i+1} unit, it is mostly the first term of the van der Waals energy (steric repulsion) which plays a prominent role in determining the allowed structures. On the other hand, one can foresee that the most probable conformations of a P_i–P_{i+2} unit will be those realizing the best stacking between two successive P_i–P_{i+1}, P_{i+1}–P_{i+2} units; in other words those minimizing the second term of van der Waals energy (London dispersion energy).

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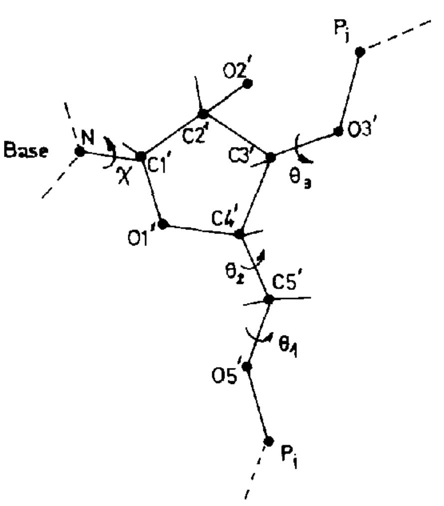

Fig. 1. The mononucleotide P_i–P_{i+1} unit. Bond lengths and valence angles were taken from [3] for the sugar-phosphate moiety and from [5] for the base. The zero angle of rotation is the cis conformation for successive chain bonds (For χ, the zero angle refers to the O1′–C1′ and NC(H) bonds). The rotation are taken to be positive when, looking along the bond, the near end rotates anticlockwise relative to the fixed far end.

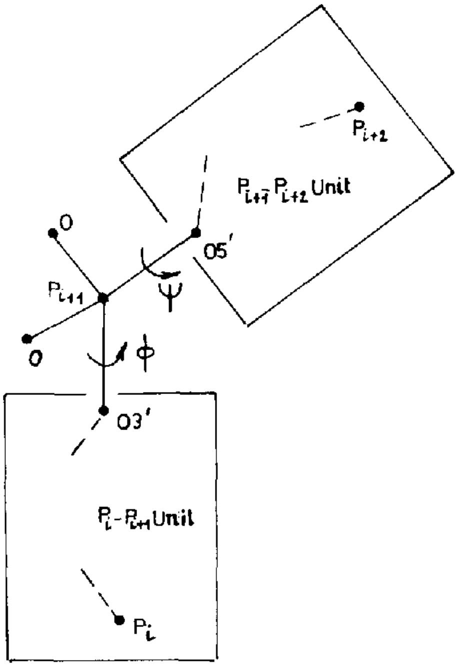

Fig. 2. The dinucleotide P_i–P_{i+2} unit. Bond lengths and valence angles for the phosphate group were taken from [7]. The zero angles and sense of rotation of ϕ and ψ are defined in the same way as those for Θ_1, Θ_2, Θ_3 and χ (fig. 1). They also agree with the new conventions for the description of polypeptide conformations [8].

Let us call, L, M, N, P, R,... the conformations of van der Waals minimum energy for a P_i–P_{i+1} unit and x the entire range of values for a pair of rotational angles ϕ and ψ.

In the present paper, we want to point out the interesting features presented by some members of the family XXY of possible conformations for an adenylic P_i–P_{i+2} unit (X and Y being L, M, N,...).

The first step of the analysis is the computation, as a function of Θ_1, Θ_2, Θ_3 and χ, of the van der Waals energy inside a P_i–P_{i+1} unit. We found 18 conformations of van der Waals minimum energy lower than zero kcal. Next we observed that the presence of a phosphate group, rather than a lone P atom, at the end of a P_i–P_{i+1} unit destabilizes substantially ($\sim$ 5 kcal) several of these conformations. The geometric parameters and the van der Waals energy of the conformations which are not destabilized in this way are reported in table 1. The six lowest energy states correspond in fact to the six allowed regions deduced from a similar analysis by Sasisekharen et al. [3], using a hard sphere approximation.

The second step of the calculation is to evaluate the van der Waals energy of a P_i–P_{i+2} unit. That is, in the approximation outlined above, to calculate the energy map, as a function of ϕ and ψ, for two successive P_i–P_{i+1}, and P_{i+1}–P_{i+2} units each in a conformation of minimum energy.

In a preliminary study, we do such a calculation for the three most probable states L, M and N (table 1) which happen to be the most frequently observed in mononucleotide crystals [4]. We calculated the ϕ, ψ energy map for the nine possibilities XXY (X and Y being L, M or N). We observed that the nine resulting maps may be classified into three groups. Each group contains three maps of very similar pattern which is characteristic of the Y state assumed by the P_{i+1}–P_{i+2} unit. This is due to the fact that the L, M and N states correspond to the same value of $\Theta_3 = -150°$

In the following, we discuss only the properties of the LXL, MXM and NXN maps since they are representative of the features of each group.

Table 1
Conformations of van der Waals minimum energy for a P_i–P_{i+1} unit (fig. 1).

Conformational states	Θ_1	Θ_2	Θ_3	χ	v.d.W. energy (kcal/mole)	Remarks
L	180	60	−150	0	−2.7	Base in
M	180	180	−150	0	−2.8	conformation
N	180	−60	−150	0	−2.9	*anti*
P	180	60	−150	100	−1.7	
R	180	180	−150	100	−1.6	
S	180	−60	−150	100	−1.7	
T	180	40	−150	180	−1.8	Base in
V	180	160	−150	200	−2.3	conformation
W	180	−80	−150	200	−2.4	*syn*

Van der Waals energy is calculated, for increments of 20° on each angles (10° for Θ_3), as the sum of pairwise interactions between non bonded atoms. Potential functions, previously defined [9], were used.

Several regions of minimum energy arise on each of these maps. Fig. 3 shows the energy map for LXL. The minima are labelled with small vowels a, e, i, ..., a*, e*... by analogy with the "stereoalphabet" proposed to described polypeptide conformations [5]. Table 2 reports the geometric parameters and van der Waals energy of the deepest minima occurring on the LXL, MXM and NXN maps.

It is interesting to note that two minima (LaL, MeM) correspond to conformations allowing some stacking of the bases. The first one (LaL) has geometric parameters in close agreement with those determined by X-ray diffraction analysis for several double stranded DNA and RNA in a Watson–Crick like helicoïdal structure (table 3). The other one (MeM) corresponds nearly to a conformation whose repetition along the chain gives rise to an extended structure. In this conformation, the bases lay parellel to each other; they are arranged on one side of the sugar phosphate chain in a linear lattice. This extended structure, in some ways similar to the β extended conformation of the polypeptide chain, may be representative of the mean structure adopted by flexible single stranded polynucleotide chain.

Another interesting feature of the results presented in table 2 is that the extended conformation MeM and also the other minima, LeL, La*L, NeN, correspond to values of rotational angles which might allow a subsequent stabilization by an hydrogen bond between the oxygen in position 2′ and one of the oxygen atom belonging to the phosphate group. It thus appears quite possible that those conformations could have, in some circumstances, a very low conformational energy. Such intra hydro-

Table 2
Conformations of van der Waals minimum energy for a P_i–P_{i+2} unit (fig. 2). The energy maps are calculated allowing variations on the angles ϕ, ψ of 20°.

Conformational states	ϕ	ψ	v.d.W. energy kcal/mole
LaL	−60	−60	−11.9
LeL	−60	180	−11.8
La*L	80	120	−11.4
MeM	−40	160	−12.5
NeN	−20	180	− 9.8

Table 3
Comparison between the calculated conformation of minimum van der Waals energy and the mean values of experimental results on double stranded helices.

Conformational state	Θ_1	Θ_2	Θ_3	χ	ϕ	ψ
LaL	−180	60	−150	0	−60	−60
Mean values for double stranded helices [1]	−172	51	−164	17	−70	−66

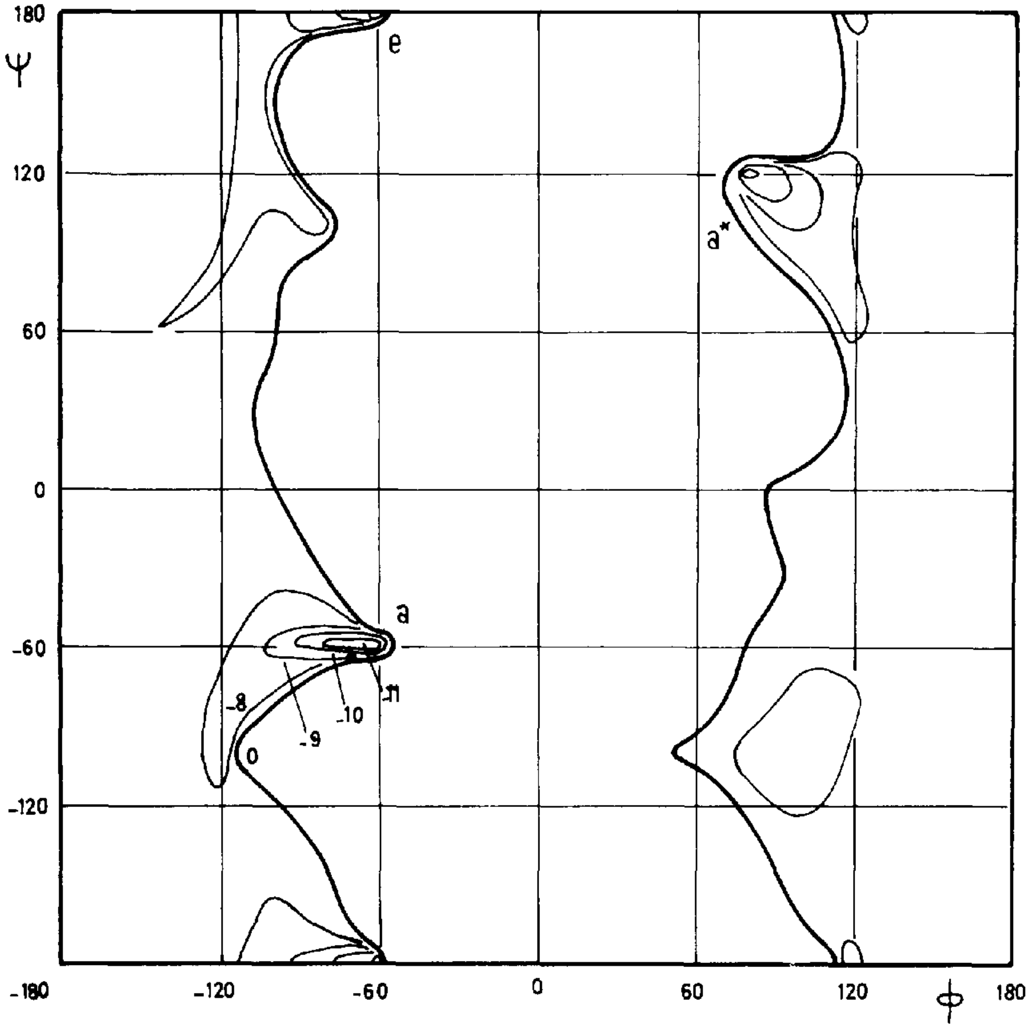

Fig. 3. Van der Waals energy map of a dinucleotide P_i–P_{i+2} unit. The mononucleotide P_i–P_{i+1} and P_{i+1}–P_{i+2} units are fixed in conformation L (table 1). Energy values on the contours are given in kcal/mole. Mean values for ϕ and ψ occurring in double stranded helices [1] are indicated by a dot.

gen bonded conformations might for example, play a role in the formation of some tRNA loops. Research, along those lines are in progress in our laboratory.

In conclusion, we think that it is noteworthy, that a single stranded helice, similar to one strand of a double stranded Watson–Crick like helix, can be generated from the repetition of one of the deepest minima (LaL) derived from the van der Waals analysis of a dinucleotide. On the other hand such an analysis reveals also other conformational potentialities of the polynucleotide chain which might be interesting for both physico chemical and biological purposes.

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