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Quantum-Mechanical Exploration of the Properties of the Sugar Rings

I. Electrostatic Molecular Potential, Hydration and Cation Binding Scheme of $C_{3'}$-Endo-*gg*-Ribose

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The *ab initio* SCF method is used for computing the main electronic properties of the ribose unit of the nucleic acids. The present study is devoted to the ribose in the $C_{3'}$-endo, *gg* conformation. The properties investigated include the distribution of the electronic charges, the electrostatic molecular potential around the four oxygens of the unit, the hydration and the Na^+ binding schemes studied in the supermolecule approximation. The possibilities of through-water binding of the cation to the sugar are also explored. The predictions of the computation in particular with regard to cation binding to the ribose ring are correlated with recent experimental results.

Key words: $C_{3'}$-endo ribose – Sugar rings, quantum mechanical exploration of ~

1. Introduction

Nucleic acids are made up of three main components: the purine and pyrimidine bases, the phosphate groups and the sugars. A considerable amount of work has been carried out by quantum-mechanical methods on the electronic and conformational properties of the first two components (see e.g. [1–4]), recent studies involving moreover such particularly interesting characteristics as the electrostatic molecular potentials [5–8] or the hydration [9, 10] and cation binding scheme [11, 12] associated with these units. On the other hand, very little has been done from that point of view for the third unit, the ribose or deoxyribose rings. The intention of this paper is to fill this gap with the double aim of enlarging our knowledge on the electronic properties of the sugars themselves and enabling a better understanding of their behaviour in the higher structural units of the nucleic acids, their nucleosides and nucleotides.

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2. Method

For this first study we have chosen ribose in the $C_{3'}$-endo conformation of the ring, with a gauche-gauche (*gg*) orientation of the extracyclic CH_2OH group about the $C_{4'}$–$C_{5'}$ bond (for the numbering of the atoms see Fig. 1, for details on definitions and notations see Ref. [4]), which is one of the preferred conformations observed for the sugar in nucleic acids and their constituents. As a matter of fact the precise geometrical input data are taken from the crystallographic results for the sugar in

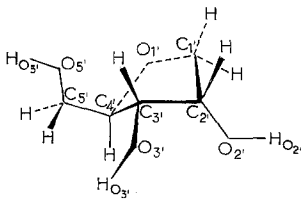

Fig. 1. Numbering of the atoms in the ribose unit

Green's *et al.* [13] study of uridine. They correspond in particular to $\Phi_{C_{4'}-C_{5'}} = 45°$, $\Phi_{C_{2'}-O_{2'}} = 106°.7$, $\Phi_{C_{5'}-O_{5'}}$ and $\Phi_{C_{3'}-O_{3'}}$ were fixed in some of the computations (*vide infra*) at their crystallographic value (142 and 156° respectively) or at 180° and 240° respectively, values typical for the corresponding torsion angles in 3′-nucleotides [4].

The computations have been carried out by the *ab initio* SCF LCAO procedure [14] using Clementi's (7*s*, 3*p*/3*s*) set of Gaussian functions contracted into a minimal set as in Ref. [15]. They were done with the program Gauss 70 [16].

Besides the primary image of the electronic structure as given by a standard Mulliken population analysis we have been interested in three major features of the ribose ring relevant to its possible behaviour in biological systems. These are: a) The electrostatic molecular potential associated in particular with the regions in space surrounding the different oxygens of the sugar; b) the hydration scheme of the sugar and c) its cation binding abilities. These two last properties have been investigated within the supermolecule approach as used in the similar study for the nucleic acid bases [9, 10] and the phosphodiester linkage [11, 12].

It is expected that this study will put into light some of the general characteristics of the electronic structure of the sugar rings encountered in the nucleic acids. It is, however, evident that these characteristics will depend to some extent on the conformational state assumed for these rings. The exploration of these variations is planned for future publications of this series.

3. Results and Discussion

3.1. Mulliken Population Analysis

Fig. 2a presents the distribution of electronic charges in the ribose unit in the conformation studied. One of the essential results of interest in relation with the

properties studied hereafter concerns the electronic charges of the four available oxygens. They all carry, of course, an excess of charge and range, from that point of view, in the order: $O_{3'} > O_{5'} > O_{2'} \gg O_{1'}$. The OH hydrogens are in the order of decreasing positive charge: $H_{O_{2'}} > H_{O_{5'}} \simeq H_{O_{3'}}$.

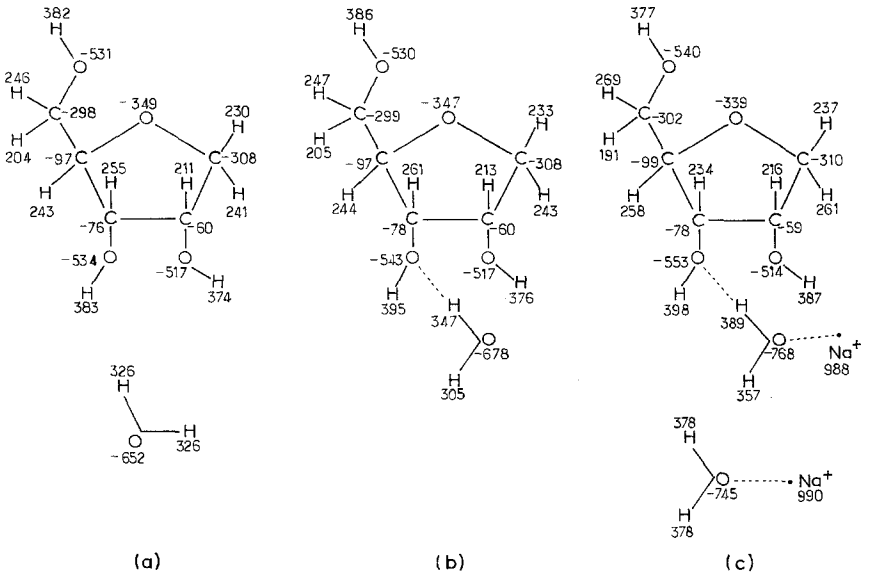

Fig. 2. Distribution of net atomic charges (10^{-3} e) in: (a) free ribose and free water; (b) a ribose-water adduct; (c) sodium-water and Na^+-water-ribose adducts

3.2. Molecular Electrostatic Potential

Fig. 3a presents the molecular electrostatic potential map in the vicinity of $O_{1'}$. It is constructed in the plane bisecting the $C_{1'}O_{1'}C_{4'}$ angle. Fig. 3b–3d presents the potential in the regions of space surrounding the remaining oxygen atoms of the ribose, 2′, 3′ and 5′. The maps are constructed in the planes bisecting the corresponding COH angle. They correspond to the torsion angle $\Phi_{C_{3'}-O_{3'}} = 240°$.

All the maps indicate an appreciable attraction of all the oxygens for a point positive charge. The minima on all the maps are somewhat smaller than that associated with a molecule of water (−69.6 kcal/mole). This signifies that the electrostatic components of the interaction energies for, say, protonation, will be smaller for the oxygens of ribose than for water. This however does not imply the same order of basicities [17, 18].

The order of the minima around the different oxygens of ribose are (in absolute value): $O_{3'} > O_{1'} > O_{5'} > O_{2'}$. They differ thus from the order of the electronic charges on these atoms, indicating the cumulative effects of the whole molecular periphery in the determination of the potential.

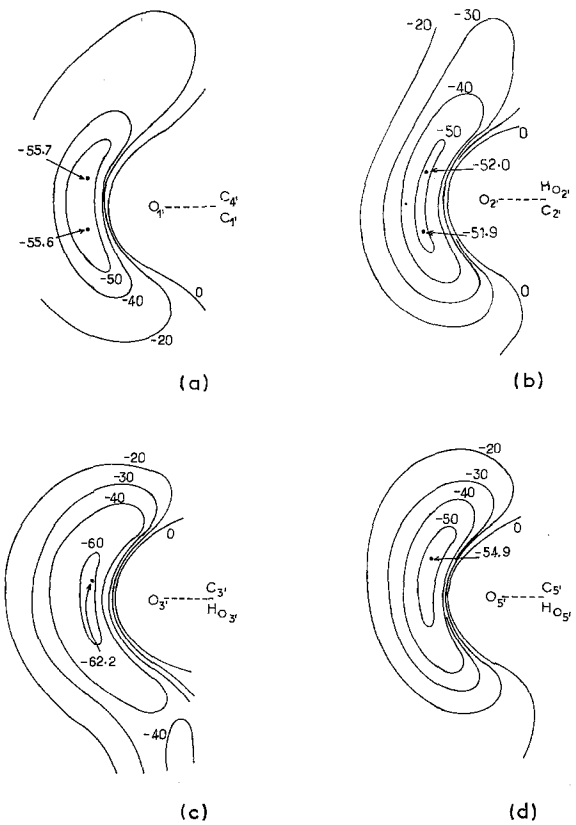

Fig. 3. Molecular electrostatic potential around the oxygens of ribose ($\Phi_{C_{3'}-O_{3'}}=240°$)
(a) in the plane bisecting the $C_{1'}O_{1'}C_{4'}$ angle.
(b) in the plane bisecting the $C_{2'}O_{2'}H_{O_{2'}}$ angle.
(c) in the plane bisecting the $C_{3'}O_{3'}H_{O_{3'}}$ angle.
(d) in the plane bisecting the $C_{5'}O_{5'}H_{O_{5'}}$ angle.
In each case the atom which is situated *in front* of the plane is the one written *above* the dotted line, e.g. $C_{4'}$ in (a)

It must be underlined that the order of the minima as indicated above is characteristic of the free ribose. It need not be conserved, of course, in more complex structures involving these units. In fact, a recent investigation, from that point of view, of uridine, the nucleoside of uracil, has shown [19] that in this composite structure, the differential screening of the potential by the overall construction results in their following modified order: $O_{3'} > O_{2'} > O_{1'} > O_{5'}$.

Because of the importance of the potentials around $O_{3'}$ and $O_{2'}$ in the nucleoside we have also evaluated the potential around these oxygens, corresponding to the conformation with $\Phi_{C_{3'}-O_{3'}}=156°$. These are reproduced in Figs. 4a and 4b. It is seen that the minima of the potentials are increased (in absolute values) in this conformation with respect to those of Fig. 3. The potential around $O_{3'}$ remains the stronger one.

3.3. The Hydration Scheme

The hydration scheme has been investigated by the supermolecule approach [20] using one water molecule for the determination of the main features of the hypersurface of interaction and, in particular, for the determination of the preferred

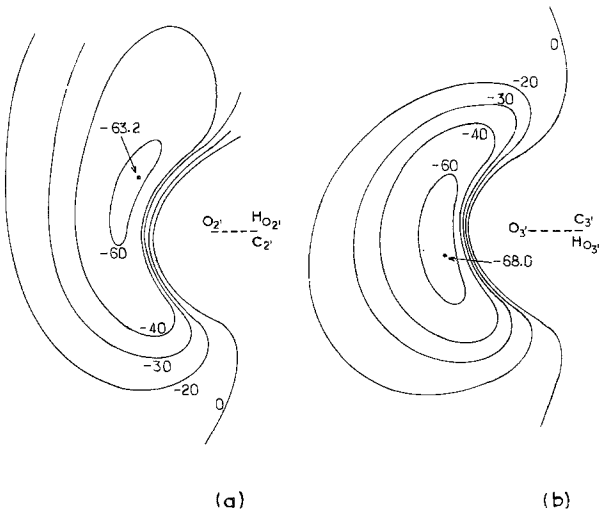

Fig. 4. Molecular electrostatic potential around the oxygens $O_{3'}$ and $O_{2'}$ of ribose ($\Phi_{C_{3'}-O_{3'}} = 156°$)
(a) in the plane bisecting the $C_{2'}O_{2'}H_{O_{2'}}$ angle
(b) in the plane bisecting the $C_{3'}O_{3'}H_{O_{3'}}$ angle
same convention as in Fig. 3

sites of binding of water to the ribose. In this study the torsion angle $\Phi_{C_{3'}-O_{3'}}$ was fixed at 240° and $\Phi_{C_{5'}-O_{5'}}$ at 180°.

The main results are summed up pictorially in Fig. 5. They point to the existence of a number of hydration sites, representing minima on the hypersurface of interaction, with interaction energies frequently greater than those corresponding to water-water interaction (6.1 kcal/mole in the same basis set, before angular optimization (see legend to Fig. 5). The three main hydration sites correspond to the positioning of the oxygen of a water molecule as a proton acceptor alongside the $O_{2'}$–H, $O_{5'}$–H and $O_{3'}$–H bonds in the decreasing order of binding energies. The four oxygen atoms of the ribose may also serve for hydration sites as proton acceptors but the energies involved are then smaller, and somewhat smaller than that associated with the formation of a water dimer. In the water dimer an improvement in the binding energy to -6.6 kcal/mole is obtained when the direction of the

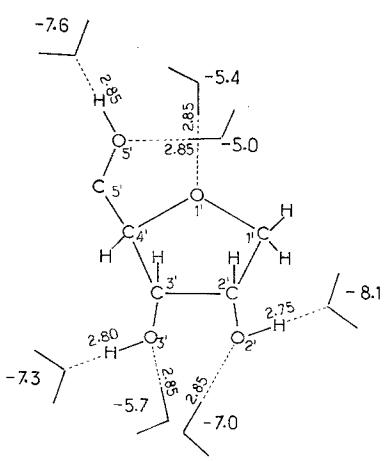

Fig. 5. The hydration scheme of ribose ($\Phi_{C_{3'}-O_{3'}} = 240°$). Preferred hydration sites (energies in kcal/mole). All values correspond to a linear H bond and to the OH proton-donor bond situated in the plane of the HOH or HOC proton-acceptor. An out-of-plane angular optimization performed for $O_{3'}$ proton acceptor yields $\Theta = 60°$ $\Delta E = -6.5$ instead of -5.7 kcal/mole. In the water dimer the angular optimization yields $\Theta = 50°$, $\Delta E = -6.6$, against -6.1 kcal/mole for $\Theta = 0$. The values of the present figure are to be compared to the $\Theta = 0$ value for the water dimer

hydrogen bond makes an angle of 50° with the HOH plane. We performed a corresponding angular optimization for water acting as proton donor to $O_{3'}$: the best binding energy −6.5 kcal/mole is reached for $\theta \simeq 60°$ (OH . . . $O_{3'}$ rotated towards the $O_{5'}$ group).

We have also explored the possibility of water binding in a bridge position simultaneously to $O_{2'}$ and $O_{3'}$: with $\Phi_{C_{3'}-O_{3'}} = 240°$ such a binding is improbable (2.6 kcal/mole). It becomes, however, an important hydration site when $\Phi_{C_{3'}-O_{3'}} = 156°$: the interaction energy equals then 8.1 kcal/mole.

Fig. 2 presents, as an illustration, the charge distribution in one of the water-ribose adducts. The perturbation with respect to the distribution in the isolated units (Fig. 2a) is in this case very small. There is an overall small transfer (0.026 e) of electrons from the ribose to the water molecule, a situation characteristic of water acting as proton-donor. When water acts as proton-acceptor with respect to the same $O_{3'}H$ group, the charge transfer is in the reverse direction.

3.4. Cation Binding Scheme

This has been explored with Na^+ but the results may probably be considered as qualitatively illustrative to a large extent of the situation occurring with other alkali ions, and to some extent of that corresponding to alkaline-earth cations.

Binding to individual oxygens was considered first, namely to $O_{1'}$, $O_{2'}$ and $O_{3'}$, simple examination of models showing that in the *gg* conformation adopted for the exocyclic CH_2OH group, steric factors, in particular interference with $H_{3'}$ will prevent cation binding to $O_{5'}$. Stable positions of binding have been found in the three cases in the plane $C_{ribose}O_{ribose}H$ at an equilibrium O . . . Na^+ distance of 2.1 Å, the energies of interaction ranging in the order $O_{3'}$ (−26.2 kcal/mole)> $O_{1'}$ (−26.0 kcal/mole)> $O_{2'}$ (−21.5 kcal/mole).

Besides binding to the individual oxygen atoms of the periphery, the possibility also exists, and was explored, of the cation binding simultaneously to $O_{2'}$ and $O_{3'}$, assuming a bridge position between the two. This is particularly feasible with $\Phi_{C_{3'}O_{3'}} = 156°$. The computations not only substantiate this possibility but indicate that it corresponds in fact to the strongest interaction, amounting to −35 kcal/mole. When not inhibited by other restraining or competing factors this mode of binding represents thus a privileged type of interaction between the sugar ring and Na^+ and possibly also other alkali and maybe alkaline-earth cations.

3.5. Ribose-Water-Cation System

Finally we have also explored some aspects of the interactions in the triple system: ribose-water-Na^+, which consists in fact of studying the possibilities of through-water binding of the cation to the ribose. The problem was examined in connection with the two main sites of direct cation binding: the bridge position between $O_{2'}$ and $O_{3'}$ and individual binding to $O_{3'}$.

The results indicate that the binding of Na^+ to the ribose through a water molecule attached in a bridge position to $O_{2'}$ and $O_{3'}$ ($\Phi_{C_{3'}-O_{3'}} = 156°$) corresponds to an appreciable binding energy: -41.1 kcal/mole. This energy measures the interaction of the cation with the *whole* ribose-water system. One may also consider the interaction of the ribose with the Na^+–H_2O entity. This is equal to -20.3 kcal/mole. These values are representative of the appreciable stabilization energies involved in the "through-water" binding of cations and biological substrates. This subject considered already by us in Ref. [21] will be discussed in more detail in a forthcoming publication.

A similar investigation for the "through-water" binding of Na^+ to $O_{3'}$ ($\Phi_{C_{3'}-O_{3'}} = 240°$) leads to similar results: the interaction energy of Na^+ with the ribose-water system is -34.9 kcal/mole, that of ribose with the Na^+–H_2O system is -12.5 kcal/mole.

Fig. 2c presents as an illustration, the charge distribution in the through-water adduct of Na^+ to $O_{3'}$. The modification of the distribution and the charge transfers between the linked units are altogether very small.

4. Conclusion

The present results provide the first theoretical information on such fundamental properties of the ribose ring as its electrostatic molecular potential, or its hydration and cation binding scheme, which are of potentially important significance for its behavior in biological systems. The results presented here are, of course, essentially appropriate for the conformation adopted for the ribose unit in this study and we intend to explore in future work the modifications that may be produced in these results with changes in the conformational state of the sugar. They are also fundamentally valid for the free ribose ring and it may be expected that they will be somewhat modified in the higher structural units of the nucleic acids, the nucleosides and nucleotides. This problem is under active investigation [19].

That some of the important results obtained here, in particular in relation to the hydration and cation binding scheme of the sugar, correspond nevertheless to intrinsically significant properties of that unit may be found in the results of recent crystallographic studies. Thus the significance of the bridge position between $O_{2'}$ and $O_{3'}$ for cation binding is evident from the crystallographic studies of hydrated monosodium inosine 5′-phosphate [22] or of barium uridine-5′-phosphate [23]. A similar type of chelation occurs in the crystal structure of the related hydrated calcium bromide complex of α-fucose [24]. In the absence of 2′-OH group, the significance of the $O_{3'}$ site for cation binding is illustrated by the crystal structure of deoxyguanosine 5′-phosphate [25]. Finally the possibility of "through-water" interaction of a cation with the $O_{3'}$ site of the ribose is illustrated in the crystallographic results of Bugg *et al.* [26] on the structure of barium adenosine 5′-monophosphate heptahydrate, and the possibility of "through-water" interaction with the $O_{2'}$ or $O_{3'}$ atoms is prominently visible in the interactions observed in the

crystal structure of sodium adenylyl-3′-5′-uridine hexahydrate (ApU) [27] and sodium guanylyl-3′,5′-cytidine nonahydrate (GpC) [28].

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