Quantum chemical calculation of the (S)-9-(2,3-dihydroxypropyl)adenine molecule^a

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ABSTRACT

Quantum chemical calculations of conformational maps of the molecule of a new virostatic agent (S)-9-(2,3-dihydroxypropyl)adenine were performed. The thermodynamically most advantageous conformation I corresponds, for the D-series, to the α -ribo configuration, while the following minima, which are close in energy (II,III), correspond to β -ribo and β -xylo configurations.

INTRODUCTION

Recently, a pronounced activity of (S)-9-(2,3-dihydroxypropyl)adenine, (S)-DHPA, against different forms of viruses was reported^{1,2}. It was suggested that (S)-DHPA forms a part of the adenosine molecule³ while in the 9-(2-hydroxyethyl-ethoxymethyl)guanine, acycloguanine, the upper part of the ribose molecule is joined to guanine⁴. Both compounds are announced^{2,4} as a new class of antiviral nucleoside analogues. Earlier studies have shown that the intact cyclic carbohydrate moiety is not necessary in order to mimic nucleoside binding to enzymes⁵ what initiated syntheses of nucleoside analogues bearing an acyclic side chain attached to the heterocyclic base^{4,5}.

Provided that acycloguanine and (S)-DHPA resemble guanosine and adenosine molecule at their virostatic activity, then the 5'-deoxy derivatives of adenosine should be active as well. However, the results with 5'-deoxyadenosine and 5'-chloro-5'-deoxyadenosine⁷ showing no virostatic activity speak against the structural resemblance of (S)-DHPA to adenosine at their biological action. We have therefore considered a similarity of (S)-DHPA molecule to another adenosine analogue. As it is

known, arabinosyladenine⁸ exhibits a remarkable virostatic activity and is one of the very few nucleoside analogues which is used as a virostatic agent in clinics^{9,10}. In the initial approach, the Dreiding model indicates that the molecule of (S)-DHPA cannot adopt the spatial arrangement of the arabinosyladenine molecule either. The biological results also suggest that both molecules differ in the mode of their biological action. While arabinosyladenine inhibits the virus-induced DNA polymerase⁹, the virostatic activity of (S)-DHPA seems to be dependent, *inter alia*, on the inhibition of SAH-hydrolase¹¹.

It was therefore interesting to know whether the (S)-DHPA molecule could express more structural similarity to the adenosine molecule than to that of arabinosyladenine or to another adenine nucleoside. Quantum chemical calculation of the (S)-DHPA molecule has been undertaken in order to find out the thermodynamically most advantageous conformation of the molecule.

RESULTS AND DISCUSSION

PCILO method was used for the quantum chemical calculations¹². The computed conformational maps involve rotations characterized by angles ψ_1 and ψ_2 assuming various values for the angle ψ_3 (see fig. 6). The computer program was modified in order to optimize values of bond polarities at each of the points on the conformational map. This modification of the PCILO program is, according to our knowledge¹³, necessary. Conformational maps were computed with a step size of 30°. The bond length and bond angle values were taken from refs.^{14,15}.

The two conformational maps which lie at lowest positions in the energy scale are depicted in figs 1 and 2. The total minimum was found at $\psi_1=60^\circ$, $\psi_2=300^\circ$, $\psi_3=90^\circ$ (cf. figs 1 and 3, conformation I, fig. 3). Conformational map computed for $\psi_3=180^\circ$ (fig. 2) lies 1.28 kJ mol⁻¹ higher in energy when compared with the map for which $\psi_3=90^\circ$ (fig. 1). The map exhibits three local minima for which the energy difference from the minimum on this map is not higher than 5 kJ mol⁻¹. The minima are located at $\psi_2=180^\circ$, $\psi_1=60^\circ$ (1.28 kJ mol⁻¹ from the total minimum, conformation II, fig. 4); $\psi_2=180^\circ$, $\psi_1=180^\circ$ (2.18 kJ

Fig.1: ψ_3 amounts to 90° ($\bullet$ - total minimum with respect to all conformational maps, conformation I).

Fig.2: ψ_3 amounts to 180° ($\bullet$ - total minimum with respect to this map, conformation II; X = local minimum, 0.9 kJ mol^{-1} , conformation III; + - local minimum, 3.9 kJ mol^{-1} , conformation IV).

(S)-DHPA

mol^{-1} , conformation III, fig. 5); $\psi_2 = 180^\circ$, $\psi_1 = 300^\circ$ (5.18 kJ mol^{-1} , conformation IV). The remaining conformational maps lie higher in energy. The energy difference between the total minimum and the lowest point on the maps computed for $\psi_3 = 150^\circ$ and 60° amounts to 3.37 kJ mol^{-1} and 4.02 kJ mol^{-1} , respectively. Conformations characterized by ψ_3 values of 0° and 60° exhibit large steric repulsions and the corresponding maps lie at substantially higher energies.

Fig. 3

The dihydroxypropyladenine molecule under study, which is of (S)-configuration on the asymmetric carbon atom, is theoretically able to adopt conformations corresponding to geometrical arrangement of both anomers of D-ribose, L-lyxose, D-xylose and L-arabinose. According to calculations of the relative content of

Fig. 4

the particular conformers on the basis of Boltzmann law the most preferred conformations will be those depicted in figs 3,4 and 5. The given conformations of (S)-DHPA are always related to a pair of pentoses (of series D and L), which are different in their configuration at the atom C_4 , what cannot occur with the molecule of the studied diol. Population of the particular conformers is decreasing in the series I, II and III. Population of other conformers is, for the isolated molecule, insignificant.

Fig. 5

Conformation I corresponds by the geometrical arrangement to gauche conformation of α -D-ribose or β -L-lyxose. Conformation II is related to β -D-ribose or α -L-lyxose and conformation III to β -D-xylose or α -L-arabinose. The mutual orientation of the C-O bonds of the diol is 60° for the conformers I-III and 180° for the conformation IV.

Fig. 6

The results obtained indicate that the conformation of the (S)-DHPA molecule does not correspond to the configuration of the 9-(β -D-arabinofuranosyl)adenine. From the calculation received, it is evident that several close minima exist which correspond to different conformation states (I,II, III) of the molecule; further that (S)-DHPA is able to transfer easily from one conformation to another and that none of the conformations is explicitly preferred.

By the influence of an interaction with the milieu a preferential of an energetically higher located conformation of the molecule may occur. Both configuration of α -D-ribose which corresponds to the most preferred calculated conformation of (S)-DHPA and the configuration of α -L-arabinose corresponding to the conformation III were not so far considered as nucleoside counterparts of the (S)-DHPA molecule. To our knowledge, the virostatic activity of α -D-adenosine^{16,17}, α -L-arabinofuranosyladenine¹⁸, and their 5'-deoxy derivatives was not described so far. An interpretation comes into consideration that the flexibility and thermodynamically acceptable transformation of the (S)-DHPA molecule into different conformations (I $\leftrightarrow$ II $\leftrightarrow$ III) may cause the high biological activity of the (S)-DHPA by its adaptability to the conformation of the active centre of the appropriate enzyme.

^aPart XXXII in the series Analogues of Nucleosides; Part XXXI Collect.Czech.Chem.Comm. (1980), in the press

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