Conformational analysis of cytidine with cobaloximes

J V Madhuri and S Satyanarayana*
Department of Chemistry, Osmania University, Hyderabad 500 007, India

Received 25 March 2003; accepted 3 November 2003

The structure of cytidine bound with alkyl cobaloximes was optimized using molecular mechanics. By means of CONFLEX, an extensive conformational search was undertaken using Bio Med Cache 5.02 software, which generated numerous conformations and finally arrived at the lowest energy conformer. The conformational search is crucial for discovering new drugs where the conformation of the pharmacaphore is important.

Keywords: binding, cobaloximes, conformational analysis, conformer, DNA

IPC Code: Int. Cl. 7 C 07 C 251/00, C 07 H 19/073 // A 61 K

Introduction

The conformational analysis searches as many minima as possible, including the global minimum, and computes the Boltzmann population. In doing so, a large number of high energy starting conformations is generated, which are then minimized. However, in the majority of inorganic and bioinorganic molecular modeling studies, very few conformational searches have been conducted due to following reasons: i) Coordination of a ligand to a metal constrains the ligand’s flexibility and subsequently the number of conformations available to the metal ligand system are reduced; and ii) Methods using internal coordinate frames (torsion angles) are complicated by the number of adjacent cyclic systems formed by metal-ligand complexation.

The outcome of Genome project has revolutionized the drug development by increasing the number of potential targets. Biological activity of the drug is dependent on the conformation of the pharmacaphore. Most of the anticancer, antimalarial and antiviral drugs act by interacting with DNA. They generally exhibit high chemical reactivity, which can cause a significant loss in the drug potency before it reaches the DNA because a high proportion of the drug may be lost by hydrolysis and interaction with other cellular macromolecules. Hence, conformational flexibility is an important factor for selecting the suitable substrate orientation to interact with DNA.

The molecules binding to electronically saturated systems show modified properties. Porphyrins exhibit the biological activity by facilitating intercalation, which depends on the overall electron richness and electronic distribution. Efficient drugs behave as good alkylating-agents, while most of the inactive drugs are being unable to alkylate the porphyrin ring. However, they may be varied by introduction of various substituents in the ring system, resulting in new strategies to study. Medical aspects of DNA-porphyrin interactions are well studied but there is a need to develop new methodologies.

Considerable interest has been shown in the design, synthesis and characterization of molecules that target RNA or DNA motifs; either to inhibit the binding or cognate proteins or enzymes to mediate strand scission. Inorganic complexes that cleave DNA and RNA in a sequence specific manner are of potential value in the treatment of cancer and viral diseases and for application in biotechnology. For the new conformations arising due to the binding, there is a possibility for the new sequence specific binding of DNA.

In the present work, attempt to bind cytidine to alkyl aquo cobaloxime (a= methyl, ethyl, propyl and butyl) and the respective conformational search is undertaken to get a conformation of low energy. The study provides a new methodology of modifying the conformation of a molecule suitable for binding with DNA in a sequence specific manner without much change in the properties.

*Author for correspondence:
Tel: 040-27090136; Mobile: 31049080
E-mail: ssnsirasani@yahoo.com
Materials and Methods

Bio Med Cache 5.02 software was used for the conformational search. Initially, alkyl\textsuperscript{a} aquo cobaloximes (a=methyl, ethyl, propyl and butyl) were constructed and the structures optimized using MM3 (molecular mechanics) parameterization. Such obtained alkyl cobaloximes were bound with the nucleoside cytidine and the resulting structure was also optimized. Now, each bound molecule was taken and CONFLEX was performed, which resulted in the generation of low energy conformations by sequentially searching an unlimited number of conformations (Figs 1-8).

Molecular mechanics calculations were carried out with software and they augmented it in three ways: i) Extending the force field to additional bond and atom types by including weak, coordinate and ionic bonds, and atoms with hybridizations higher than SP\textsuperscript{3}; ii) Recognizing conjugated and other aromatic systems; and iii) Systematically applying a set of empirical rules which estimated missing force field constants. The energy terms for bond stretch, bond angle, dihedral angle, improper torsion, van der Waals, electrostatic and hydrogen bonding interactions were included in each calculation. The total (steric) energy ($E_{\text{total}}$) of a molecule was considered to be the sum of steric and non-bonded interactions:

$$E_{\text{total}} = E_s + E_b + E_r + E_{\text{VDW}}.$$  

Figs 1-4—Conformational search graph for: 1, methyl cobaloxime bound with cytidine; 2, ethyl cobaloxime bound with cytidine; 3, propyl cobaloxime bound with cytidine; and 4, butyl cobaloxime bound with cytidine.
where $E_s$ is the bond stretching energy, $E_b$ is the angle bending energy, $E_t$ is the torsional energy and $E_{VDW}$ is the energy arising from van der Waals interactions of non-bonded pairs of atoms.

**Results and Discussion**

The bis(dimethyl glyoximato) Co(III) systems are generically known as cobaloximes. Dimethyl glyoximato (DMG) is not a corrin ring but successfully mimics the chemistry of Vit B$_{12}$. The study of cobaloximes with various alkyl groups has a direct relevance in the metabolic reactions of Vit B$_{12}$. Alkyl cobaloximes are ideal for structural comparisons and provide an insight about the factors influencing any of the properties as the axial ligands are varied. For the steric *cis* and electronic *trans* influences, changes may be noticed in the bond length between the atoms, in which one of them is Co(III). These *cis* and *trans* influences play a pivotal role in interaction with DNA and hence, different conformers were obtained. The system was electronically saturated and rings that were present found to be rigid. Thus, the resulting conformers were generated due to the binding of cytidine to alkyl cobaloximes.

The number of conformers formed for methyl, ethyl, propyl and butyl cobaloximes were four, two, two and four, respectively (Figs 1-4) as indicated in the contrast-coloured line of the graph and the ball
indicates the first conformer. Also, on the X-axis of the graph, there is a sequence of conformers indicating their number. In Fig. 4, the sequence is 1.00 to 2.00 step only as the other two conformers are easily inter-convertible. The active conformation at a receptor might not always be the minimum energy structure; hence, it was important to examine all potentially accessible conformations. Further, every conformer should also be tested for its biological activity and binding with DNA. The ball seen in the figures is the conformer and the graph shows the position of the conformer with rise in the potential energy.

The bond lengths are comparable and there has not been much change in the cobaloximes bound with cytidine (Table 1). Being an electronically saturated system, the bound cytidine would be responsible for the properties exhibited by the molecule. Nucleic acids and proteins recognize each other by very specific and selective interactions through amino acid chains and nucleic acid constituents. This method might be adopted to obtain a suitable conformation of a molecule without changing its properties. The low energy conformers for cytidine bound with alkylcobaloximes are shown in Figs 5-8.

To target the DNA specifically without any loss in the biological activity of the molecule, it may be bound to an electronically saturated system without much change in the properties. In the conformational search, the low energy conformer always carries an importance and hence, goal of any optimization is to search, the low energy conformer always carries an much change in the properties. In the conformational

| Table 1—Bond lengths of the conformations of alkylcobaloximes bound with cytidine |
|------------------------------------------|----------------|---------------|---------------|---------------|
| Methyl cobaloxime | Ethyl cobaloxime | Propyl cobaloxime | Butyl cobaloxime |
| Co-N1* | 1.934 | 1.934 | 1.953 | 1.954 |
| Co-N2* | 1.929 | 1.930 | 1.943 | 1.942 |
| Co-N3* | 1.935 | 1.937 | 1.950 | 1.953 |
| Co-N4* | 1.926 | 1.926 | 1.943 | 1.941 |
| Co-C** | 1.948 | 1.962 | 1.960 | 1.962 |
| Co-N5 | 1.977 | 1.980 | 1.980 | 1.984 |
| C-N1* | 1.266 | 1.266 | 1.264 | 1.265 |
| C-N2* | 1.263 | 1.264 | 1.262 | 1.261 |
| C-N3* | 1.267 | 1.267 | 1.264 | 1.264 |
| C-N4* | 1.263 | 1.263 | 1.262 | 1.261 |

* Cobalt in bonding with N of DMG modeling the corrin ring
** Cobalt linked with the carbon of the alkyl group
# Cobalt linked with the nitrogen of chytidine
$ Carbon in the methyl group linked with N of DMG modeling the corrin ring

discovery. Transcriptional therapy, which targets the sequence specific binding proteins, is a possible approach for the cancer therapy and demands novel methodologies, where new macromolecules with specified conformations are in need.

References