Relationship Between the Conformation of the Cyclopeptides Isolated from the Fungus *Amanita Phalloides* (Vaill. Ex Fr.) Secr. and Its Toxicity

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Abstract: The electronic structures and conformational studies of the cyclopeptides, *O*-methyl-α-amanitin, phalloidin and antamanide, were obtained from molecular parameters on the basis of semiempiric and *ab initio* methods.

Introduction

During this century *Amanita phalloides* - the most toxic fungus known up to now - has been studied from different points of view. This basidiomycete biosynthesizes mono- and bicyclic peptides composed of rare amino acids. In order to determine the structure/activity relationships chemical modifications were carried out and the properties of these compounds were evaluated. These results were confirmed by studying the conformations of three selected compounds representative of the major groups of the macroconstituents of this fungus.

Experimental

Hyperchem package (HyperCube, version 5.2) was used for semiempirical studies, the molecular geometry being optimized by STO-631G. Net charges were calculated with HyperCube PM3 and the Polack-Ribiere algoritm. GAUSSIAN 98 was used for *ab initio* studies.

Results and Discussion

We were interested in obtaining information on the conformations that the cyclic peptides may adopt and about the potential energy maps in order to locate the regions related to the binding to protein molecules, such as F-actin and RNA-polymerase. *O*-methyl-α-amanitin, phalloidin and antamanide were selected. Minimal energy, polarizability, interaction regions, intra- and intermolecular hydrogen bonding, potential energy maps and charge density on each atom were calculated for the molecules mentioned above.

Thus, the ***O*-methyl-α-amanitin** contains a tryptathionine moiety with a sulphur atom as sulfoxide with *R*-configuration, which we have now demonstrated that is positioned ahead of a marked hydrophobic area. Upon opening the C-S bond, one of the cycles is lost, giving rise to an unstable structure with a concomitant conformational change. These results explain the loss of activity. The other face is surrounded by a cycle with highly hydroxylated side chains around, which are being stabilized by intramolecular hydrogen bonding. The dipolar moments of the hydroxyls contribute to the solubility in solvents of high dielectric constants. The side amino acid moieties are distributed all over the borders and practically all separated enough to form a globular picture, which is further stabilized by hydrogen bonding that misshape them by reaching the terminal portions and shifting them to the upper side of the molecule.

Phalloidin shows a similar conformation to that of the methyl derivative of α-amanitin with the heterocycle clearly exposed. In one of the faces, stereochemical changes as well as modifications of the total energy and the dipolar moment are recorded. The sulphur of the thioether and the tryptathionine adopt a unique conformation due to the occurrence of the (*n*) unpaired electrons, which affects the whole molecule. These facts result in an alteration in one of the side rings, which is therefore sloped towards the face containing the tryptathionine moiety. Hence, this molecule shows a different reactivity in comparison to the former.

Antamanide is a monocyclic compound, which contains ten amino acids and aromatic residues well exposed. It is remarkable the occurrence of two of them in the internal region, which due to be able to induce dipoles give rise to a selected molecule inclusion. The whole conformation is rather non-polar and of planar type without any folding. Certain cations may affect this conformation depending on the inclusion degree into the internal cavity.

Both semiempirical and *ab initio* methods have been compared, showing coincidence in the trends.

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References and Notes

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