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Molecular orbital computations on lipids: an ab initio exploratory study on the conformations of glycerol and its fluorine congeners

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Abstract

In order to characterize the set of topologically probable glycerol-3-phosphate backbone conformers, ab initio calculations were performed on glycerol as a preliminary study. Ab initio calculations were also completed for selected congeners of glycerol, such as 1,2-difluoro-3-hydroxylpropane and 1,2,3-trifluoropropane, in order to model the effects of changing electron densities on the glycerol-3-phosphate backbone geometry. The results show that conformations having intramolecular hydrogen bonds have a lower relative energy. The O–H stretching frequencies computed in different glycerol conformations were largely dependent on ϕ_i and ψ_i backbone dihedrals.

Keywords: Ab initio; Intramolecular hydrogen bonding; Glycerol; Glycerol models

1. Preamble

Glycerol is found as an intermediate [1,2] in many biological pathways and is purported to be a growth regulator for some plants [3]. The glycerol moiety also acts as the structural backbone of lipids [4]. Due to its viscous properties, glycerol may act as an ideal solvent to stabilize reactants [5] as well as to regulate the rate of selected reactions [6]. Some labeled glycerol substances have also been used as tracer materials for in vivo studies of metabolism [7].

Glycerol has many rotamers and although it is symmetrical, intramolecular hydrogen bonding between the hydroxyl (OH) groups can significantly alter the stability of each rotamer. Furthermore, the OH groups can form many hydrogen bonds with polar molecules and may be esterified or oxidized into other congeners such as glycerylaldehyde and phosphates [8]. For example, glycerol-3-phosphate, which is the backbone of phospholipids, is a product of glycerol phosphorylated by ATP at a terminal OH [9]. This reaction is catalyzed specifically by glycerol kinase [10–12]. The different rotamers of glycerol may interact with specific enzymes, resulting in specific products. The conformation flexibility of the glycerol backbone is believed to be an important factor in the proper orientation and position of the fatty acid chain attached to the phospholipid molecule, which interacts with and regulates transmembrane proteins such as the G-protein [13].

2. Introduction

Many investigations have been conducted on glycerol, whereby X-ray crystallography has often been used to characterize conformation-specific glycerol-enzyme binding properties [14]. Experiments, in which glycerol analogues with inhibitory effects were produced, have also yielded results suggesting that structural specificity plays an important role in interactions between glycerol and selected enzymes [15]. From these studies, there have been attempts to find specific types of enzyme-binding conformations in glycerol, as well as chemical interactions stabilizing these structures. Such experiments include computational simulations, modeling of glycerol as a solvent, and interactions

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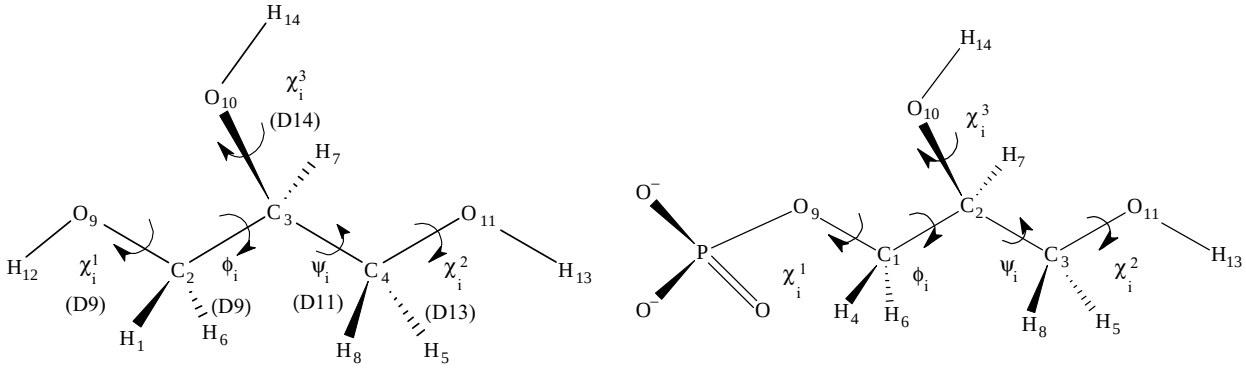


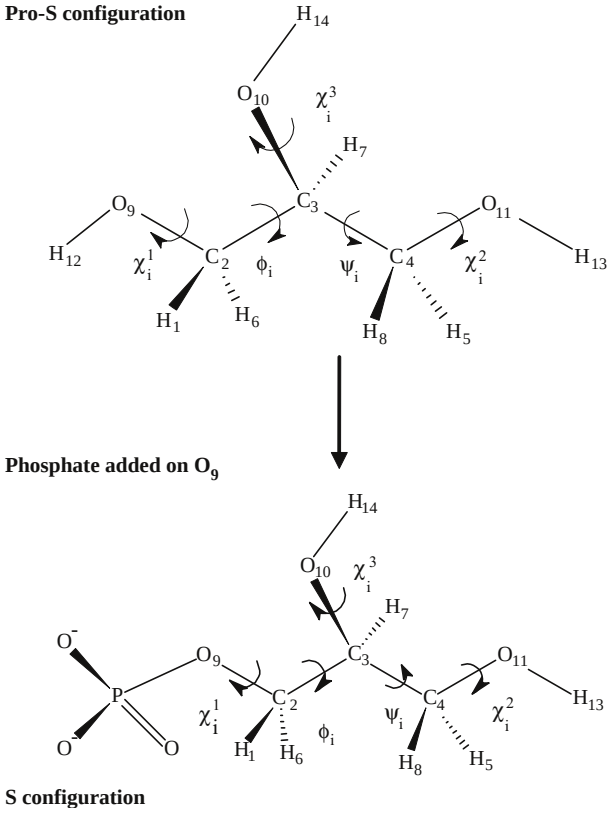
Fig. 1. Modular numbering of atoms used, following the definition standardized of the relative spatial orientation of all constituent atomic nuclei in the glycerol backbone. (pro-S) and an alternative method of numbering the glycerol which may facilitate in the building of modular units of lipids when modeling the lipid bilayer (pro-S also).

with ions in solution [16]. Conformational studies of glycerol have also been performed using neutron scattering experiments [17]. However, a systematic characterization of the conformational intricacies of the glycerol backbone is necessary to develop a more thorough understanding of how different structures can affect the nature of chemical reactions involving this molecule. Quantum mechanical ab initio molecular orbital computations provide a wealth of structural and electronic data on molecular systems. With the geometry optimizations of all possible backbone conformers, all stable conformations can be identified. These studies may also serve as a preliminary insight into molecular systems that are differently substituted or have different oxidation states. These might include glycerol-3-phosphate, glycerates and perhaps even the full molecular structure of a portion of the lipid bilayer and its interactions with transmembrane proteins.

3. Methods

A standardized definition of the relative spatial orientation of all constituent atomic nuclei was used to define the glycerol molecular structure (Fig. 1). In this figure, the picture on the right shows an alternative and modular numbering system that can be used to build larger lipid molecules for modeling lipid bilayers. This definition is similar to the IUPAC standard for peptides, where backbone dihedrals are defined by ϕ_i and ψ_i [18]. In peptides, the modules are covalently attached to each other in a linear fashion. However, modules attached to the glycerol backbone in phospholipids are not necessarily strung together in a linear manner. This methodology is further developed through the division of the glycerol backbone into parts that may potentially be extended using different substituents [19]. Multi Dimensional Conformational Analysis (MDCA) [20] is used to construct the topologically possible set of conformers. Each glycerol backbone dihedral (dihedral angle, defined as ϕ_i and ψ_i) has three MDCA predicted rotamers, specifically *gauche*$^+$ (g^+), *anti* (a), and *gauche*$^-$ (g^-). However, the three OH groups, defined as χ_i^1, χ_i^2, χ_i^3, are expected to have four topologically possible states due to the existence of lone pairs of electrons on each oxygen atom.

The possible conformations of the glycerol are the combinations of each topologically probable rotamer: three conformations per backbone dihedral (g^+, a, g^-), four conformations per sidechain (hydroxyl) dihedral (s, g^+, a, g^-); since there are two backbone dihedrals and three sidechain dihedrals in glycerol, the total number of possible conformations will be $3\times3\times4\times4\times4=576$.



Scheme 1.