Serine and Threonine Methyl Esters: Conformational Analysis and Relative Stabilities

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The conformational equilibrium of some amino acids and their derivatives have been recently investigated [1-3]. It was found that ubiquitous steric and hyperconjugative interactions, and not H-bonding, are responsible for conformational preferences of these compounds.

The side chain is of the special importance for the conformational equilibrium of amino acids. Serine and threonine exhibit complex side chains due the presence of polar functional group –OH that dramatically increases the number of low-energy conformers. Indeed, the presence of the methyl group in the substitution of the one hydrogen atom present in serine, may increase the contribution of the steric effect on threonine and thus, these systems can be used as probe for investigate intramolecular interactions in biomolecules. However, it is well-known that amino acids in the gaseous phase adopt the nonionic form far from in situ conditions of the condensed medium in which biological reactions take place. Moreover, in aqueous solution and in crystals, these compounds present zwitterionic structure, i.e, a bipolar form of the type (H$_3$N$^+$-CHRCOO$^-$), which does not occur in the polypeptide chain. In this work, we propose the conformational analysis of serine (Ser-OMe) and threonine (Thr-OMe) methyl esters, that do not show zwitterionic forms in solution, by $^1$H NMR and theoretical calculation. The minima of energy of these systems were obtained by three-dimensional potencial energy surfaces built at the B3LYP/cc-pVDZ theoretical level by scanning both the $\chi_1$ [N-C-C-O(H)] and $\chi_2$ [C-C-O-H] dihedral angles while the other angles were previously optimized for the alanine methyl ester [3]. There were obtained 27 and 41 conformers for Ser-OMe and Thr-OMe, respectively. Subsequently, each conformer was optimized (B3LYP/aug-cc-pVDZ) including solvent effects (acetonitrile, pyridine, methanol and DMSO) through the CPCM solvation model. Then, $^3J_{HH}$ spin-spin coupling constant calculations were carried out at the B3LYP method and EPR-III(for C and H) and aug-cc-pVDZ (for O and N) basis sets. The calculated values are in agreement with the experimental data and show that $^3J_{HH}$ obtained in different solvents do not show changes with their polarity indicating that there are no changes in the conformer populations in the equilibrium relative to the side chain. It was found that the presence of methyl group have marked importance on the conformational preference of relatively stable conformers. In addition, in order to understand the effects that rule the conformational equilibrium of these systems, NBO (Natural Bond Orbital) and QTAIM (Quantum theory Atoms In Molecules) were employed. The
results show that steric and hyperconjugative effects together with H-bonding are the interactions responsible for conformational preferences of Ser-OMe and Thr-OMe.

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