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The gauche effect is governed by internal hydrogen bond in 2-amino-2-methyl-propanol

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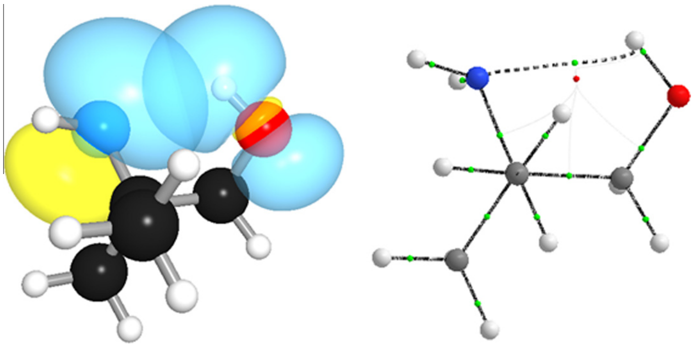
HIGHLIGHTS

- 2-Amino-2-methyl-propanol experiences the gauche effect.
- The gauche effect in 2-amino-2-methyl-propanol is due to internal hydrogen bond.
- The origin of hydrogen bond in 2-amino-2-methyl-propanol can be described by hyperconjugation.

GRAPHICAL ABSTRACT



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ABSTRACT

The conformational isomerism of 2-amino-2-methyl-propanol (AMP) was theoretically studied using *ab initio* and DFT methods, both in the gas phase and implicit solvents. A *gauche* structure among 13 possible conformers was highly prevalent in the vacuum, nonpolar (cyclohexane) and polar (acetonitrile) solution. Natural bond orbital analysis and the quantum theory of atoms in molecules indicate the appearance of intramolecular hydrogen bond, especially the OH…N interaction, which was found to govern the conformational isomerism and, therefore, the *gauche* effect in AMP for both the isolated molecule and in solution. Such an interaction has a strong hyperconjugative contribution, as well as the antiperiplanar interactions usually invoked to explain the *gauche* effect, namely the $\sigma_{CH} \rightarrow \sigma^*_{CN}$ and $\sigma_{CC} \rightarrow \sigma^*_{CO}$ interactions, which are stronger than the corresponding $\sigma_{CO} \rightarrow \sigma^*_{CN}$ and $\sigma_{CN} \rightarrow \sigma^*_{CO}$ interactions in the *anti* conformers. Intermolecular hydrogen bond takes place according to an explicit solvent (water) model. For the neat liquid, the *gauche* conformation is also preferred, according to infrared analysis of the C–O stretching mode, but intermolecular interactions should also be present.

Introduction

Aminoalcohols can experience different intramolecular interactions, with special emphasis on the hydrogen bond, in which nitrogen has been found to be better proton acceptor rather than oxygen in similar compounds [1,2]. Such an interaction can be responsible for the potential as vitrifying agent, *i.e.* the ability to avoid ice formation when the water containing the compounds is submitted to a temperature lower than the critical temperature. Thus, aminoalcohols have been evaluated as interesting compounds for long term cryopreservation of biological organs and tissues [3,4]. In addition, the aminoalcohol 4-hydroxypiperidine is one of the series of combretastatin derivatives, whose members family possess varying ability to cause vascular disruption in tumors. Its conformational stabilization originates from

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hyperconjugation of various intramolecular interactions, while a boat-like geometry with the hydroxyl group directed toward the endocyclic nitrogen was found to be stable [5]. This suggests the appearance of intramolecular hydrogen bond OH…N, despite not explicitly declared by the authors.

A main factor for the detailing study of aminoalcohols is their tendency to aggregate in normal experimental conditions, as well as their appreciable hygroscopicity; thus theoretical and vibrational methods appear as convenient approaches to study the main intramolecular interactions characterizing their conformations [6]. Nevertheless, the O–H and N–H stretching modes in aminoalcohols, such as 2-amino-2-methyl-propanol (AMP), overlap significantly, especially for the neat liquid (where the bands are highly broadened), difficulting the conformational analysis through the measure of individual band intensities. In addition, this compound does not have vicinal hydrogens, whose ^3J coupling constants could give insight about conformation due to its angular dependence. However, the use of appropriate theoretical levels of calculations can give reliable information about conformations and intramolecular interactions in this compound. Also, infrared studies of other vibrational modes for the neat liquid can explain the main conformations in AMP. For instance, the ν_{C-O} stretching mode in *trans*-2-halocyclohexanols gave insight about the hydrogen bond operating in the fluoro derivative relative to the other halogens [7].

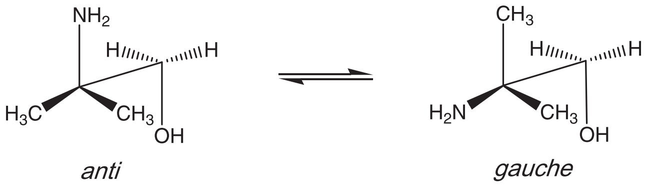

Fig. 1. Conformational isomerism in 2-amino-2-methyl-propanol (AMP).

AMP (Fig. 1) is an aminoalcohol structurally related to amino acids. The conformational study of amino acids and corresponding prototypes for the human organism is very useful, since their geometry is expected to impact the reactivity and biological activity. The conformational isomerism in a variety of amino acids has been reported to be due to steric and hyperconjugative effects rather than hydrogen bond [8–10]. Thus, AMP is reported in this work to evaluate the role of the hydrogen bond, as well as of hyperconjugation and Lewis-type interactions, on the conformational isomerism of this compound.

Experimental section

Theoretical calculations

The AMP was submitted to conformational distribution using Monte Carlo search at the HF/6-31g(d,p) level, using the Spartan program [11]. The fourteen structures found were fully optimized at the MP2/aug-cc-pVDZ and B3LYP/aug-cc-pVDZ levels, including frequency calculations to guarantee the absence of imaginary frequencies. One structure did not converge to a minimum, resulting in a total of thirteen conformers (Fig. 2), both in the gas phase and using implicit cyclohexane (nonpolar) and acetonitrile (polar) as solvents (through the polarizable continuum model, PCM [12]). Calculations with one water molecule as explicit solvent were also carried out at the above DFT level of theory. These calculations were performed using the Gaussian 09 program [13]. Hyperconjugative energies and interactions were obtained from natural bond orbital (NBO) analysis [14] using the B3LYP/aug-cc-pVDZ level, while hydrogen bonds were evaluated using the quantum theory of atoms in molecules (QTAIM) [15].

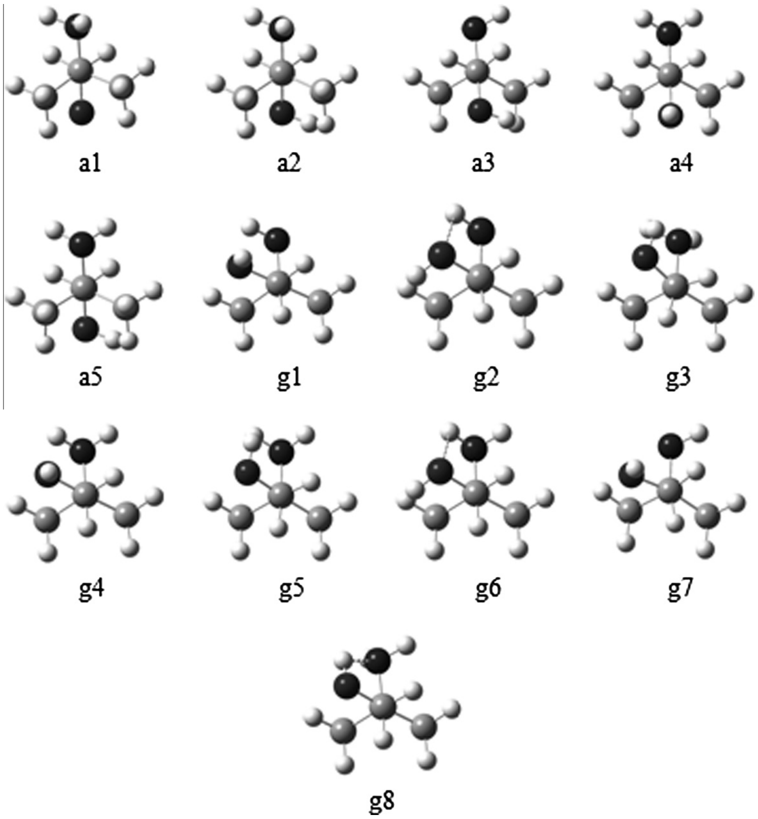

Fig. 2. Stable conformers for 2-amino-2-methyl-propanol (AMP).