

Intramolecular hydrogen bonding and conformational preferences on 2-fluoro-phenylaminocyclohexanol.

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Abstract

The aim of this study is to evaluate the influence and strength of possible intramolecular hydrogen bonding (IntraHB) involving N-H--O, O-H--N, O-H--F and N-H--F molecular moieties as a driving force on the conformational preferences of 2-fluoro-phenylaminocyclohexanol. To achieve our purpose we synthesized the compound and performed its characterization using Nuclear Magnetic Resonance Spectroscopy (NMR). Quantum mechanical calculations were carried out to evaluate the effect of IntraHB on the conformational stability. Experimental and theoretical results showed that N-H--F and O-H--N IntraHB have a greater influence on the conformational preferably adopted by the molecule.

Key words:

Fluorinated amino-alcohols, conformational analysis, intramolecular hydrogen bonding.

Introduction

Fluorinated amino-alcohols are important precursors in organic chemistry, mainly applied in the pharmaceutical industry, due to the possibility to present intramolecular hydrogen bonding (IntraHB).¹ Moreover, these interactions show a biological relevance improving the cell permeability.²

IntraHB interactions are well established in literature, however there are only a few studies about these interactions involving fluorinated amino-alcohols. To improve our knowledge in this subject, the present work aimed to evaluate the effect and strength of IntraHB in the conformational preferences of 2-fluoro-phenylaminocyclohexanol (Fig. 1).

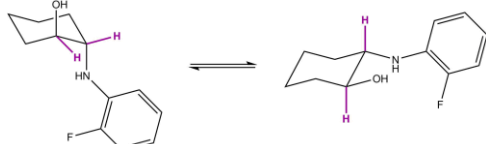


Figure 1. Equilibrium of the studied compound.

Results and Discussion

The compound was obtained through the reaction between 2-fluoroaniline and cyclohexene oxide using MgO as a catalyst.³ The structure of the product was confirmed by ¹H, ¹³C and ¹⁹F NMR spectra recorded on Bruker 500 MHz and 600 MHz spectrometers.

A conformational search was performed in the Spartan16 software, and then the minima of energy were optimized using M06-2X/aug-cc-pVDZ level of theory available in the Gaussian09 package.

Experimental ³J_{HH} values between the highlighted hydrogens in Fig. 1 showed that each hydrogen has two large couplings constants (~10 Hz) and a smaller one (~4Hz), according to Karplus equation⁴. The magnitude of these couplings indicates that the substituents on the cyclohexane ring adopted the *diequatorial* position.

Natural Bond Orbital (NBO) and Non-Covalent Interactions (NCI) results displayed two IntraHB: O-H...N and N-H...F for the unique stable conformer observed for this molecule. According to NBO analysis, these interactions correspond to 2.3 kcal mol⁻¹ and 0.9 kcal mol⁻¹, respectively (Fig. 2 a and b). Attractive NCI surfaces were observed (Fig. 2 c) between the atoms involved in the IntraHB's.

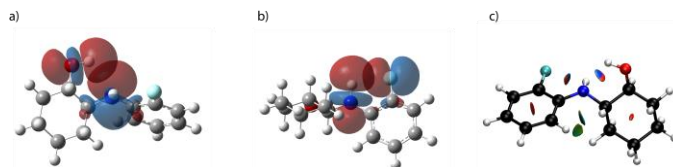


Figure 2. NBO interactions: a) LP(N) → σ*_{O-H} b) LP₂(F) → σ*_{N-H} and c) NCI surfaces.

The IntraHB N-H--F could be experimentally corroborated by the observed NOE between hydrogen and fluorine nuclei in the HOESY ¹H-¹⁹F experiment (Fig. 3). The observed NOE indicates that fluorine and hydrogen nuclei are spatially close supporting the through hydrogen bonding ¹hJ_{FH} transmission observed experimentally.

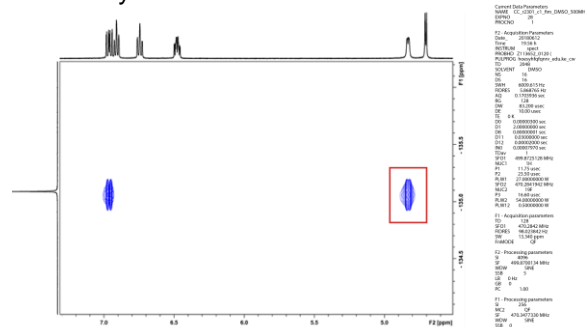


Figure 3. HOESY ¹H-¹⁹F contour map of 2-fluoro-phenylaminocyclohexanol in DMSO-*d*₆. The NOE between H (NH) and F is highlighted.

Conclusions

In this work, it was observed that 2-fluoro-phenylaminocyclohexanol shows two IntraHB, with energy around 3 kcal mol⁻¹, suggesting that these interactions play a fundamental role in the stabilization of the *diequatorial* conformer.

Acknowledgement

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