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Short Communication

The Influence of Ortho-Fluorination on the Hydrogen-Bond of Benzyl Alcohols

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DESCRIPTION

The impact of fluorination on the conformational and Hydrogen-Bond (HB)-donating properties of a series of benzyl alcohols has been investigated through experimentation by IR spectrometry and theoretically with quantum chemical strategies (ab initio (MP2) and DFT (MPWB1K)). It was found that o-fluorination typically resulted in a rise within the hydrogen-bond acidity of the hydroxyl, whereas a decrease was determined upon o,o′-difluorination. The conformational landscapes of the title compounds are powerfully influenced by the presence of o-fluorine atoms. Intramolecular interaction descriptors supported by AIM, NCI and NBO analyses reveal that additionally to an intramolecular OH···F interaction, secondary CH···F and/or CH···O interactions occur, conducive to the stabilization of the varied conformations, and influencing the hydrogen-bond properties of the alcohol group. The benzyl alcohol HB-donating capability trends are properly represented by an electrostatic potential-based descriptor calculated at the MPWB1K/6-31+G (d,p) level of theory, provided solvation effects are taken under consideration for these versatile hydrogen-bond donors.

The fluorination of organic compounds to change their properties has a significant impact in several chemistry-related fields like medicinal chemistry, agrochemistry, materials science and crystal engineering [1-3]. The high fluorine electronegativity, with the resulting highly polarized CF bond and nonpolar sable fluorine lone pairs, is at the origin of a multitude of effects ensuing from the introduction of 1 or more fluorine atoms. Significant and generally unexpected consequences of fluorination on the physical and chemical properties of adjacent functional groups or regarding CF mediated inter-and intramolecular interactions. Organ fluorine chemists are particularly captivated by the ability of fluorine to behave as a Hydrogen-Bond (HB) acceptor. Furthermore, seminal works by Vasella, Bernet and Gouverneur have highlighted OH···F Intramolecular Hydrogen Bonds (IMHBs) by using NMR techniques. Recently, we've got experimentally determined HB-donating capacities (or HB acidities) of fluorohydrins through the adaptation of an established procedure by using FTIR spectrometry. The insights discovered during this study, for instance, the influence of OH···F IMHB interactions on alcohol hydrogen-bond properties, discovered the necessity for comprehensive investigations on a large range of fluorinated compounds to probe the consequences of fluorine on hydrogen-bond interactions in numerous chemical environments and to optimize HB property prediction tools.

Herein we tend to report on the influence of ortho-fluorination on the hydrogen-bond-donating capability of benzyl alcohols through a combined experimental and theoretical approach. The experimental HB acidities (pKAHY) are presented by quantum chemistry calculations, together with elaborated conformational analysis, to permit insights to be gained on the influence of the fluorine atom (s) on the conformational features of substituted benzyl alcohols. Atoms In Molecules (AIM), Noncovalent Interaction (NCI) and Natural Bond Orbital (NBO) analyses are performed to supply a correct description of numerous IMHB interactions occurring within the various compounds. Within the final part of this work, we tend to show the feasibility of accurately predicting the HB acidity values of the substrates concerned by using an electrostatic-based descriptor (Vα(r)) computed for the varied molecules [4]. Benzyl alcohols are common building blocks of medicine (e.g., antimuscarinic medication (fesoterodine), neuroprotective agents, and medication agents (gastrodin)).

An interesting effect of fluorine substitution has been reportable for ring-hydroxylated biogenic amines like norepinephrine. Depending on the position of the fluorine, the analogs were shown to own markedly completely different agonist properties. Intramolecular hydrogen-bonding effects and/or dipole-dipole repulsions between the COH and CF moieties are thought about as factors that would lead to conformational preferences that are favourable for binding to α- or β-adrenergic receptors. A more recent explanation involves the preferential orientation of the CF bond of each 2F-NE and 6F-NE to an amino acid residue, leading to a special presentation of the aromatic alcohol group. An increase in HB acidity is quasi-systematically measured upon monofluorination, because of the electron-withdrawing impact of fluorine [5]. This can be nicely illustrated by the rise of the electrostatic potential descriptor Vα(r) values; all the conformers contributing to the HB-donating capability increase, however, its population isn't necessarily enough to have a significant influence on the HB-donating capability.

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The tremendous loss of HB-donating capability upon difluorination, with the corresponding alcohol being a weaker HB donor than its nonfluorinated counterpart. The contribution of the perp structures would result in an increase in hydrogen-bond acidity compared with monofluorinated benzyl alcohols; however, this can be overcompensated by a large number of chemical change conformers. The lowering of the computed Vα(r) values for these chemical change conformers characterizes the hydrogen-bond acidity. The modulations of the hydrogen-bond acidity will so be simply rationalized by the Vα(r) descriptor, by considering its evolution on the conformational profile.

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