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VIP Hydrogen Bonding

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An Unexpected and Significantly Lower Hydrogen-Bond-Donating Capacity of Fluorohydrins Compared to Nonfluorinated Alcohols**

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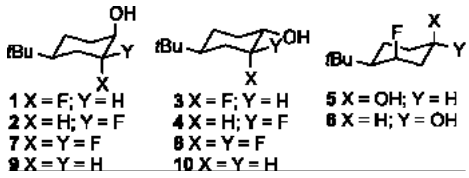
The success of fluorination in improving molecular properties over a wide range of applications (including pharmaceuticals,[1] agrochemicals,[2] materials,[3] and crystal engineering[4]) has been remarkable. Up to 20% of the pharmaceuticals prescribed or administered in the clinic, and a third of the leading 30 blockbuster drugs, contain at least one fluorine atom[1a] and 30–40% of currently marketed agrochemicals contain fluorine.[5]

In many cases, fluorine is introduced following a particular rationale.[6] Examples include enhancement of metabolic stability, functional-group (FG) reactivity or acid/base-property modification, and conformational stabilization. Importantly, these alterations cannot be considered individually as usually a number of properties are influenced simultaneously.[7] For example, fluorination of amines in order to decrease their pK_a value also leads to an increase in their lipophilicity and may induce significant conformational changes. Furthermore, this decrease in pK_a can be attenuated if intramolecular $NH^+\cdots F$ electrostatic interactions can occur.[8] Hence, a comprehensive understanding of the effects of fluorination is a prerequisite for successful planning and rationalization of fluorine introduction, and research that increases our knowledge in that respect is highly relevant.

The hydrogen bond (H-bond) is an important specific interaction between a molecule and its local environment.[9] Crucial functional roles include the binding of ligands to protein receptors and the promotion of enzyme catalysis. In the design of bioactive compounds, H-bonding impacts on a wide range of molecular properties such as potency, selectivity, permeability, and solubility.[10] Given the strong electrostatic contribution to the overall energy of an H-bond,[11] introduction of the small and highly electronegative fluorine atom is expected to significantly modify the H-bond properties of an adjacent FG. It is therefore surprising that despite H-bond acidity of alcohols has been previously studied,[12] a thorough investigation of the influence of fluorination on H-bond acidity appears limited to that of polyfluorinated solvents such as trifluoroethanol (TFE) and hexafluoroisopropyl alcohol (HFIP),[13] and to certain supramolecular receptor systems.[14] TFE and HFIP are very strong H-bond donors (and very poor acceptors), which has been exploited, when they were used as solvents, to influence the reactivity of certain reagents.[13a,15] The H-bond properties of TFE and HFIP are generally considered to originate from the strong inductive effect of fluorine, leading to statements in the literature such as "the ability of fluorine … as an inductive activator of a H-bond donor group"[16] and "fluorination always increases H-bond acidity".[17]

Herein, we show that this is incorrect as a general rule. Indeed, experimental determination of H-bond acidities of a range of fluorohydrins shows that fluorination can lead to an attenuation, in some cases very pronounced, of H-bond acidity. In order to exclude conformational complications (e.g., the fluorohydrin *gauche* effect),[18,19] this study was carried out using conformationally restricted model compounds **1**–**8** (Scheme 1), which adopt only chair conforma-



Scheme 1. Fluorohydrin model compounds and nonfluorinated reference alcohols.

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