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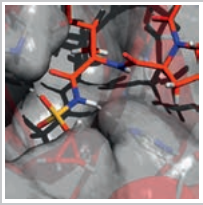

International Year of the Periodic Table 2019: Elements Important for Life Sciences

Division of Medicinal Chemistry and Chemical Biology
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Organic Fluorine: The Mighty Mite

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Covalently bound fluorine is often considered similar in size as hydrogen, and the C–F unit as 'bioisosteric' to C–H. True or not?

Comparing the C–F and C–H bond lengths as well as the atomic van der Waals radii of fluorine and hydrogen, it is obvious that a C–F unit extends substantially further out than a corresponding C–H unit (Fig. 1). The volume change by H/F replacement is close to one third of the volume increase due to the introduction of a methyl group;[2] and three H/F replacements, such as in going from a CH_3 to a CF_3 group, result approximately in a volume increase corresponding to an additional methyl group. Accordingly, a CF_3 group occupies approximately the volume equivalent of two methyl groups or has the size, but not the shape, of an ethyl group.[3] Nevertheless, covalently bound fluorine is indeed the smallest substituent replacing hydrogen or its isotopes in organic substrates. The concept of 'isosterism' has undergone many redefinitions over 100 years of its original introduction by Langmuir.[4] It is currently being used in medicinal chemistry in a most relaxed manner for almost any type of designed structural analogy.[5] The prefix 'bio' is not very helpful either as this property, by definition, depends on the biological context. This reduces the utility of the term 'bioisosteric' in most cases to glamor in publication titles.

Fluorine is the most electronegative substituent. In spite of its minute size, its incorporation into an organic compound can cause dramatic changes on the compound's chemical, physical, and biological properties. Many experimental data on diverse compound properties accumulated towards the end of the last century prompting first comparative overviews by Smart in the mid-nineties.[6] Further excellent reviews,[7] special journal issues,[8] and books[9] followed during the two subsequent decades. They document the enormous momentum that organofluorine chemistry has taken since the end of the last century, giving evidence of an impressive expansion of synthetic methods and ever-growing structural diversity of fluorine-containing building blocks. They attest a steadily increasing amount of property data providing the foundation of continuous attempts to rationalize fluorine-induced compound property changes with concomitant development of powerful molecular design concepts. Much data is now obtained by computational methods.[10] Whereas this is legitimate for limited analogue series with suitable calibration, there is nothing that should replace experimental data. Every effort must be taken to fill still existing gaps in our knowledge regarding properties of F-containing compounds.[11]

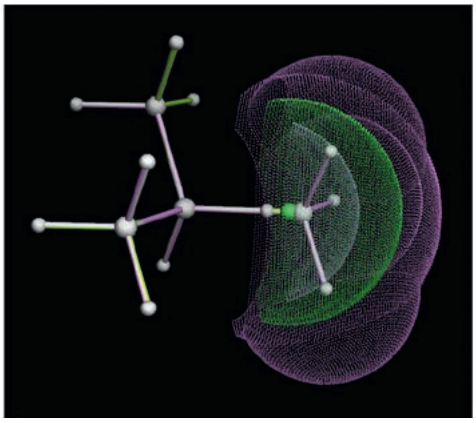

Fig. 1. Superposition of models of propane, 2-fluoropropane, and isobutane with computed van der Waals surfaces around H–C(2), F–C(2), and CH_3–C(2) as dotted surfaces in white, green, and pink, respectively. With bond lengths of aliphatic C–H and C–F bonds of b_{CH} ~1.09 Å and b_{CF} ~1.39 Å, respectively, and van der Waals radii of hydrogen and fluorine of ρ_H ~1.2 Å and ρ_F ~1.47 Å, respectively, the C–F unit extends further out than a C–H unit by $\Delta b_{CH/CF} + \Delta\rho_{H/F}$ ~0.57 Å, and occupies more volume by $\Delta V^{vdw}_{H/F}$ ~5 Å^3. This quantity may be compared to the van der Waals volume change upon replacement of the hydrogen atom by a methyl group with a difference volume of $\Delta V^{vdw}_{H/CH3}$ ~17 Å^3. Modeling and calculations done by the modeling suite MOLOC.[1]

The large electronegativity difference between carbon and fluorine confers a strong polarization to the C–F bond with a concomitant high bond energy, which is higher than that of any other C–X single bond. This provided the early motivation for H/F substitution as a means to block or reduce oxidative C–H metabolism.[12] The polarization is not confined locally, but extends inductively to rather remote sites, with approximately exponential attenuation as a function of topological distance. This is well evidenced by the substantial basicity reduction when fluorine is introduced close to an amine unit, and still significant basicity modulations by fluorine substituents in rather distant locations.[7a,13] The transmission of the inductive polarization effect is optimal through *trans*-aligned sigma bonds, whereas *gauche* arrangements along an inductive σ-path may reduce the transmission. This is particularly evident for cyclic amines, where H/F replacement at an equatorial position exerts a remarkably stronger effect than in the corresponding axial position.[14] However, there is also another important contribution, in particular for an axial fluorine substituent in β-position to a protonated amine. Thus, in protonated 3-fluoro-piperidine the bond dipole moment of an axial C–F unit adopts a (1,3)-parallel orientation to the axial $^+$N–H bond, which is polarized in the opposite direction. This results in a favorable (1,3)-antiparallel dipole–dipole interaction that stabilizes the protonated amine, thus reducing the basicity lowering effect by fluorine.[14] An analogous way is to consider favorable electrostatic interactions between the positive and negative partial charges at the nitrogen-bound proton and the axial

fluorine ligand, respectively.[7b] (1,3)-antiparallel dipole–dipole interactions between C–F and polar X–H (X = O, N, C) bonds[2,15] have emerged as a powerful concept in rationalizing diverse observations in organofluorine structural chemistry.

Another important conformational effect is exerted by two vicinal C–F units. The prototypic case is 1,2-difluoroethane which adopts a *gauche* conformation in the gas-phase, solution, and the solid state. It can be rationalized by stabilizing σ_{CH}–σ^*_{CF} hyperconjugative interactions which are optimal in a *trans* arrangement of the vicinal C–H and C–F bonds. It is a special case of the general observation of a pronounced stabilizing contribution to a *gauche* conformation for the -CHX-CHY- subunit with X and Y electronegative groups, and is particularly pronounced if either X or Y is fluorine.[16]

The strong polarization of the immediate neighborhood of a CF or CF_2 unit has further important consequences. A CF_2 unit renders a carbonyl group next to it highly electrophilic and thus enables hydrate formation. The geminal diol may serve as a mimic of the tetrahedral intermediate in amide hydrolysis. This concept has been used successfully in the design of aspartyl protease inhibitors.[17] C–H bonds geminal to C–F or CF_2 units are also markedly polarized with an increased partial positive charge on the proton. The latter can then engage in favorable electrostatic or dipolar interactions both intra- or inter-molecularly, contributing to conformational stabilization as well as enhanced binding in protein-inhibitor complexes or crystal packing. Such interactions often complement opposite electrostatic or dipolar interactions between C–F and aliphatic H–C units.[18b] Single C–F, CF_2, or CF_3 units of ligands bound to proteins are often found embedded in lipophilic pockets lined with many C–H units. Although individual C–F···H–C interactions are typically rather weak, the combined effect of many such interactions can result in notable contributions to the stabilization of ligand–protein complexes.[2,18] Such lipophilic interactions have been identified prototypically in the crystal packing of fluoromethoxy- and difluoromethoxyarene compounds as well as corresponding fluoromethyl- and difluoromethylarene analogs.[18b] Such interactions are sometimes also referred to as hydrogen bonding, suggesting significant covalent character in these interactions. However, it should be emphasized that fluorine, due to its very low atom polarizability, is a very poor hydrogen bond acceptor.[19] Only in cases where geometrical criteria are quite indicative, should one expect significant covalent character to be present in such interactions.[18]

The polar C–F bond may also engage in orthogonal dipolar interactions with carbonyl groups or other polar units.[20] Such non-covalent interactions may contribute small but significant stabilization to a protein–ligand complex. A particularly frequent interaction of this type is between a C–F bond and a π-exposed peptide unit in a lipophilic pocket. This constitutes a promising inhibitor design concept. A particularly educative example is provided by the X-ray crystal structure (Protein Data Bank [PDB] code: 1D1F) of the complex between an HIV aspartyl protease and a peptidomimetic inhibitor with a central α,α-difluoroketone hydrate motif.[17b] In this complex, the two geminal hydroxyl groups are tightly hydrogen bonded to one of the aspartyl groups at the catalytic site, and each hydroxy group interacts in an orthogonal dipolar manner, inter- and intra-molecularly, with π-exposed amide units of, respectively, the protease and peptidic inhibitor.[20b] In a fully analogous fashion, the two geminal α,α-fluoro substituents interact by orthogonal dipolar interactions, inter- and intramolecularly, with corresponding amide units of, respectively, the protease and peptidic inhibitor on the opposite side. This case not only illustrates orthogonal dipolar interactions by polar C–F and C–O units, but also confirms the analogy between C–F and C–O bonds as proposed by DiMagno and coworkers.[21]

The notion of a dominant C–F bond dipole moment has led to a simple but powerful rule-of-thumb to rationalize changes of lipophilicity due to the introduction of one or more fluorine substituents into aliphatic units of a given compound.[2,11] It is based on a vector superposition of just the polar C–F bond moments and an account of the total volume increase due to all involved H/F replacements. The combined effects of polarity- and volume-based lipophilicity modulations provide reasonable estimates of expected over-all lipophilicity changes due to the incorporation of specific fluorination patterns. The simple method has been expanded to partially fluorinated alkoxy and alkylamine moieties, taking into account appropriate bond polarity vectors for the somewhat less polar C–O and C–N bonds.[11] A remarkable outcome is the prediction of conformational equilibria for certain partially fluorinated alkoxy derivatives with distinctly different lipophilicities for the individual conformations due to enhancement or compensation of C–F and C–O bond polarities. Those fluoroalkoxy groups with relatively narrow energy gaps between conformations of different lipophilicity can be regarded as 'lipophilicity chameleons' that can switch from polar to non-polar conformations in response to changing chemical environments.[22] This unique property makes them promising candidates for lead optimization in medicinal chemistry. An outstanding case is the difluoromethoxy group which has already been found to have great potential in medicinal chemistry.[23]

Whereas lipophilicity is a cardinal compound property in drug discovery, many other properties are equally relevant in pharmacology.[24] They correlate to some extent with lipophilicity, such as solubility, membrane permeation, or metabolic liability. However, there are no simple relationships in general. The influence of fluorine incorporation on such and other pharmacologically relevant parameters are still difficult to predict, although certain patterns have become evident.[7–9]

This account provides a short outline of the diverse and sometimes dramatic impacts that one or more fluorine substituents can have on pharmacologically relevant compound properties. Many 'fluorine effects' are now well understood and have become part of molecular design strategies that are well established in modern Drug Discovery. Others still meet with surprise. With novel enabling synthetic methods, new discoveries at both molecular and material levels, more explorations and improved understanding, and an ever-expanding diversity of accessible fluorine-containing structural motifs and synthetic building blocks, organofluorine chemistry continues moving full steam ahead.

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