Fluorocarbons

International Edition: DOI: 10.1002/anie.201511055
German Edition: DOI: 10.1002/ange.201511055

Accurate Lipophilicity (log *P*) Measurements Inform on Subtle Stereoelectronic Effects in Fluorine Chemistry

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fluorine · fluorocarbons · lipophilicity · NMR spectroscopy

In issue 2/2016 of *Angewandte Chemie*, Linclau and co-workers[1] disclose a new and straightforward ^{19}F-NMR method for determining the lipophilicity of fluorine-containing compounds by quantifying their partition between immiscible phases (exemplified with *n*-octanol/water, the accepted standard for bioactive molecules). Fluorine is found in around 20% of current pharmaceuticals[2] and 30% of agrochemical candidates,[3] together constituting a highly relevant subclass of bioactive organic compounds. Lipophilicity is commonly estimated from the partition coefficient, usually expressed as log *P*, or the pH-dependent distribution coefficient (log D_{pH}, typically measured at pH 7.4), relevant to molecules with ionizable centers. These primary measurements are universally used to explore the structure–property relationships of bioactive molecules, giving insight into their solubility and interaction with physiologically relevant macromolecules and environments. These values, determined in *n*-octanol/water, have been widely measured and can often be predicted to a reasonable degree of precision using computational methods, based on molecular fragment input data pioneered by Hansch et al.[4] The *n*-octanol/water partitioning method has some limitations (most notably with poorly soluble compounds), which is why contemporary methods, such as relating lipophilicity to reversed-phase HPLC retention, are increasingly being employed.[5] HPLC, like commonly employed higher-throughput *n*-octanol/water set-ups, generally requires the compound to have a chromophore for UV detection. The impact of lipophilicity on the behavior of bioactive molecules is profound and much of the optimization process in drug development is focused on modulating log *P*; the many guidelines and rules which purport to describe "drug-likeness" invariably have log *P* and/or log $D_{pH7.4}$ as a cornerstone—and most oral drugs lie in the relatively narrow log *P* range of 1 to 4.[6] The subtle and sometimes profound effects of fluorine on the interactions and conformation of such molecules are becoming increasingly well understood,[2b] yet the physical implications, particularly with respect to lipophilicity, are not well researched.

The new method[1] is simply applied as it measures the distribution between *n*-octanol and water relative to an internal (fluorinated) reference such as 2-fluorophenol. After shaking the mixture of the solute and reference to distribute them between the phases in a separating funnel (equal volumes are not required), an aliquot of each of the settled phases is analyzed by ^{19}F{^{1}H}-NMR. The ^{19}F{^{1}H}-NMR integration ratio of solute to reference (of known log *P*) in each phase is cross-correlated allowing the log *P* of the solute to be determined. The correlation of a ratio of ratios cancels out any errors associated with measuring volumes and masses and generates results of high reproducibility and accuracy (log *P* ± 0.01) including in the very hydrophilic region, where chromatographic retention is not achieved. The method relies on accurate integrations so factors such as decoupling fluorine from hydrogen, optimizing relaxation times, narrowing sweep width, etc. have to be considered. The method should extend to all organofluorine compounds (also enabling subtleties in pK_a effects for ionizable compounds to be explored as log *D*) but is particularly exemplified for fluorinated alcohols and deoxyfluoro carbohydrates. What emerges is a set of data on polarity, which can be used to explore the more subtle influences of fluorine substitutions.

The dogma had been that a change of a fluorine for a hydrogen substituent on a carbon atom results in a lipophilicity increase, but Müller et al.[7] in particular have highlighted flaws in such a generalization. Increased hydrophobicity may hold for many fluoroarenes where F has replaced H, but it is less consistent for aliphatic compounds. Such a replacement (H→F) often increases polarity and even the introduction of a CF_3 group can lower log *P*, where the impact of a polarity change dominates lipophilicity. These observations have significantly developed our understanding of selective fluorination and reinforcement emerges from the data presented in the current Linclau et al. paper.[1] Invariably, monofluoro alcohols are shown to be around half to a full log *P* unit more hydrophilic than their parent alcohols. For example, 5-fluoropentanol (**3**; log *P* = +0.52), 4,4-difluoropentanol (**4**; log *P* = +0.77) and even 5,5,5-trifluoropentanol (**2**; log *P* = +1.22) are all more hydrophilic than pentanol (**1**; log *P* = +1.51). Intriguingly, tetrafluoropentanol **5** (log *P* = +0.97) with a terminal difluoromethyl group was

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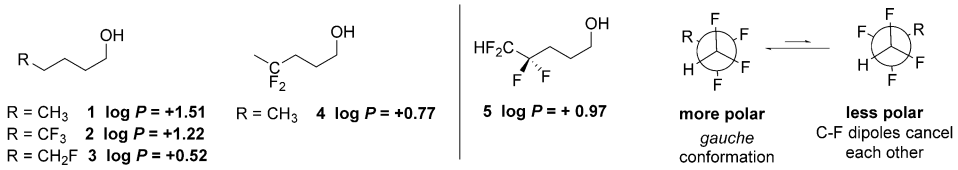

Figure 1. Polarity comparisons of selectively fluorinated pentanols.

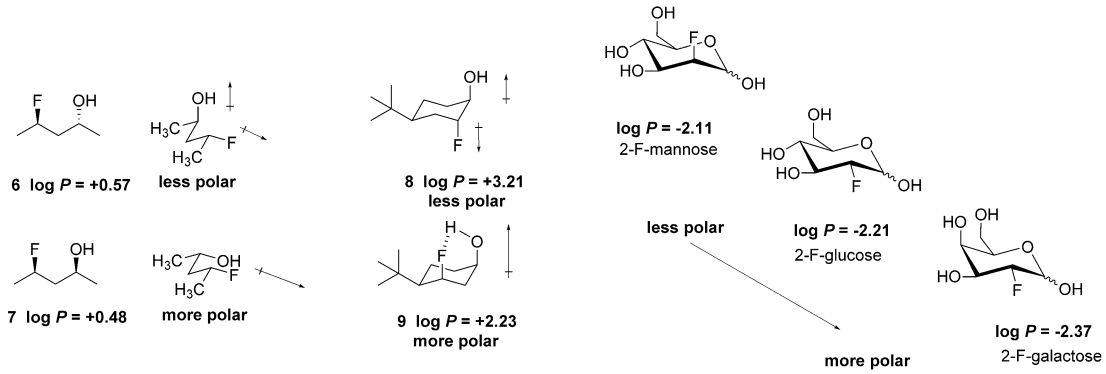

Figure 2. Polarity comparisons of regio- and stereoisomers of fluorinated alcohols and sugars.

found to be more hydrophilic than trifluoropentanol **2** ($\log P = +1.22$)! This outcome is rationalized by the dominant *gauche* conformation[8] in solution (H *anti*-periplanar to F rather than to R,), which results in a higher molecular dipole, and the terminal C–H bond will be significantly polarized (Figure 1).

The data also tease apart the influence of stereochemistry by comparing diastereomers. *Syn*-fluoropentanol **7** ($\log P = +0.48$) emerges to be more polar than *anti*-fluoropentanol **6** ($\log P = +0.57$) and it is proposed that the sum of dipoles of the two polar bonds (C–O and C–F) is greater in the solution conformation of **7**, making it more polar (Figure 2). Likewise, regioisomer **8** ($\log P = +3.21$) is more hydrophobic than regioisomer **9** ($\log P = +2.23$). Linclau et al.[9] have previously demonstrated that **8** is a better hydrogen-bonding donor than **9** because the hydrogen atom of the OH group in **9** is compromised as a donor as it is committed to a bridging O–H···F hydrogen bond, which cannot occur with **8**. It might reasonably follow that the better donor **8** will be more hydrophilic, but this is not the case. The 1,3-diaxial alignment of the polar C–O and C–F bonds in **9** generates a sufficiently high molecular dipole to overcome the weaker hydrogen-bonding-donor ability rendering **9** more polar.

There is an extensive literature on deoxyfluoro carbohydrates[10] in biophysical and enzymatic studies that explore the consequences of hydrogen bonding in carbohydrate biochemistry. The first accurate $\log P$ values of these very hydrophilic molecules ($\log P$ values below -2.0) are disclosed.[1] 2-F-Galactose ($\log P = -2.37$) is more polar than 2-F-glucose ($\log P = -2.21$), which is more polar than 2-F-mannose ($\log P = -2.11$). These observations are intriguing to rationalize and there is a lot to explore in the comparative polarity tables in the Supporting Information to this communication. This paper is a major step forward in evaluating $\log P$ values of polar fluorocarbons and provides a quantitative method to rationalize the more subtle stereoelectronic consequences of fluorine introduction.

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3858–3860
Angew. Chem. **2016**, *128*, 3922–3924

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Received: December 2, 2015
Published online: February 19, 2016

