The Polar Hydrophobicity of Fluorinated Compounds

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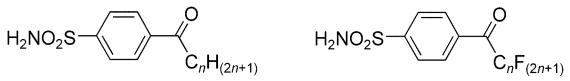
Brief Survey of Fluorine Substitution

Fluorine substitution is a powerful tool in bioorganic and medicinal chemistry.[1–4] The chemical inertness and relatively small size of fluorine[5,6] coupled with the short C–F bond length have made C–F substitution attractive for the replacement of a number of functional groups, including C–OH, C–H, and C=O. Fluorine incorporation into biologically active compounds can alter drug metabolism[7–12] or enzyme substrate recognition.[13–18] The hydrophobic nature of fluorinated compounds is also cited for improved transport across the blood–brain barrier.[19–22] Improved oral bioavailability is seen in some systems where fluorine substitution leads to improved hydrolytic stability.[21,23–26] Furthermore, replacement of sensitive or reactive groups with fluorinated substituents has led to mechanism-based inhibitors for a wide variety of diseases and to chemotherapeutic drugs.[19,27–31] Review articles appear regularly on these subjects; some recent examples are given in refs. [9, 27, 32–37].

Properties of Fluorinated Compounds

Fluorinated compounds, like hydrocarbons, have negative entropies of aqueous solvation (at room temperature) due to the tendency of water molecules to "order" around the hydrophobic portions of the solute,[38–42] although the exact nature of this "hydrophobic hydration" is a matter of considerable controversy.[43,44] Generally, the entropy of binding hydrophobic substrates to protein receptors is large and positive due to the liberation of water by desolvation of the solute. Several strategies have been developed to exploit the hydrophobic effect[37,40–42] for the design of enzyme inhibitors with increased free energies of binding. One germane approach from the group of Whitesides relied on the attachment of a hydrophobic group to the substrate at a point distant from the specifically recognized portion of the molecule.[45] In this work, the binding of the inhibitors (Scheme 1) to carbonic anhydrase was directly proportional to the total surface area of the hydrophobic group, irrespective of its (branched or fluorinated) nature, a result indicating that hydrophobic hydration of appended fluorocarbon and hydrocarbon segments enhances the free energy of binding by a similar mechanism. The greater affinities observed for fluoroalkylated compounds were attributed solely to the larger hydrophobic surface areas desolvated upon binding. It should be noted that this general enhancement of molecular recognition is expected to be larger if hydrophilic groups are replaced by fluorocarbon moieties or if the fluorocarbon segment is incorporated into the binding pocket.



Scheme 1. *Inhibitors of carbonic anhydrase featuring hydrocarbon and fluorocarbon tails of varying lengths.*

It is not controversial that fluorocarbon groups are hydrophobic.[6] However, whether the C–F bond can participate in *strong* polar interactions is a matter of some debate. The C–F bond is highly dipolar, as is evidenced by the large dipole moments (μ) of fluorinated hydrocarbons (Table 1). A second critical feature of the C–F bond is that it is relatively nonpolarizable, which accounts, in part, for the extremely low refractive indices of fluorocarbons. (C–F bonds also reduce overall molecular polarizabilities of organic molecules by increasing the hardness of the carbon framework, a fact that helps account for the general increase in lipophilicity (π),[46,47] of fluorinated aromatics.) Thus, the C–F bond is expected to act as a hard Lewis base.

Table 1. *Physical properties of the C–F bond.*[77]

Compound	Dipole moments [debye]	Compound	Refractive index	b.p. [°C]
CH_3F	1.85	perfluorohexane	1.2515	57.1
CH_2F_2	1.97	hexane	1.3751	69
fluorobenzene	1.70	hexafluorobenzene	1.3777	80.5
		benzene	1.5011	80.1

In the gas phase, polar fluorinated hydrocarbons such as fluoromethane ($\mu = 1.85$ debye) act as hydrogen-bond acceptors and form hydrogen bonds that are roughly half the strength of hydrogen bonds formed to water for the same proton donor.[48] Despite this observation, hydrogen bonding to C–F dipoles of fluorinated organic molecules is generally not observed in polar solvents such as alcohols, amines, or water.[49] The reason for this divergent behavior is clear; the C–F bond

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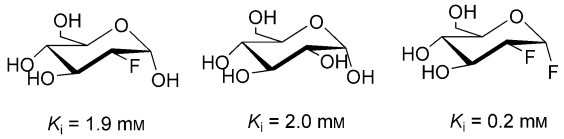
can interact with ionic or dipolar groups by electrostatic (dipole–dipole or point–dipole) interactions, but time-dependent (dipole-induced dipole, ion-induced dipole, and dispersion) interactions are not as favorable for the relatively nonpolarizable C–F bond as they are for solvent heteroatoms. In addition, any covalent (exchange) contribution to C–F hydrogen bonding is smaller because of the large difference in ionization potentials between fluorine and the competing heteroatom hydrogen-bond acceptors.[50] Nevertheless, the gas-phase data indicate that C–F dipolar interactions can be significant when competing heteroatoms are absent.

There is a growing body of evidence that C–F bonds can participate in strong dipolar interactions in the solid state or in preorganized macrocyclic systems. In 1983, Glusker et al. surveyed the Cambridge Database and systematically analyzed the crystal structures of compounds with C–F bonds; they found weak evidence for hydrogen bonding.[51,52] The empirical rules developed from these studies stated that "in structures with an excess of proton donors over acceptors,…we might expect C–F···H bonding to be observed in the crystal packing."[51]

Such C–F···H–C interactions have been proposed as a design principle for crystal engineering; Desiraju and co-workers, in particular have argued that these short range (2.5 Å) interactions are responsible for the solid-state ordering seen in the crystal structures of partially fluorinated aromatic compounds.[53,54]

In contrast to the relatively sparse data supporting hydrogen bonds to C–F moieties, an updated review of the crystallographic literature and recent work with macrocyclic fluorinated ligands conclusively demonstrate C–F···M ligation, where M is an alkali metal cation.[55–60] Dipolar C–F···M interactions in preorganized, polyfluorinated hosts are sufficiently strong to bind a variety of cations, even in polar solvents. Consideration of these data leads to two key conclusions: 1) the energies of electrostatic interactions of the C–F bond dipole with positive ions or dipoles can be substantial in appropriately organized systems, and 2) these same interactions are of minimal importance in polar heteroatom solvents. These two points are the basis of the polar hydrophobic effect.

In carbohydrate chemistry, replacement of single hydroxy groups with a fluorine atom has been advanced as a standard method to probe whether a binding site contains a hydrogen-bond-donating or -accepting residue at a specific position.[61–63] It is postulated that a hydrogen-bond donor in the receptor site leads to near normal binding, while a hydrogen-bond acceptor results in decreased free energies of binding (higher inhibition constant (K_i) values) for the fluorinated carbohydrate. Although the vast majority of work has been performed with selectively monofluorinated deoxyhexose analogues, hexose analogues incorporating multiple fluorine substitutions have been observed to bind more strongly than the normal substrates in some cases. Specific examples are the preferential binding of 2-deoxy-2,2-difluoro-D-glucose to yeast hexokinase[64] and the enhanced inhibition of glycogen phosphorylase by 2-deoxy-2-fluoro-α-D-glucosyl fluoride (Scheme 2).[62] In these examples, the corresponding monofluorinated derivatives had greater affinity for the respective enzymes than D-glucose and the difluorinated derivatives had even more.



Scheme 2. *Inhibitors of glycogen phosphorylase showing the enhanced binding of the difluorinated derivative. See ref. [62].*

These results are difficult to rationalize by specific hydrogen-bonding arguments, but are readily explained by invoking polar hydrophobicity. According to this hypothesis, binding of fluorinated carbohydrates probes the static dipole–dipole and charge–dipole interactions within the receptor site *and* the nature of the compound's aqueous solvation. Since the multiply fluorinated compounds are more hydrophobic than the corresponding carbohydrates, the enhanced protein-binding affinity is not surprising. Furthermore, these results indicate that the polar hydrophobic effect is cooperative; thus, extensive fluorine substitution for polar hydrophilic groups may increase the free energy of binding because the hydrophobic fluorocarbon surface is desolvated upon transfer to the receptor, thereby liberating water molecules to the bulk solvent. Concomitantly, enthalpically favorable dipolar interactions of the C–F bonds with cationic or dipolar residues in the receptor site can be retained. These considerations lead to a general strategy for enhancing molecular recognition: increasing the fluorocarbon content of a substrate molecule (by judicious C–F substitution for hydrophilic groups) without significantly perturbing the molecular shape should enhance specific binding in preorganized sites that are able to stabilize the negative ends of the C–F dipoles. Ideal sites would feature a combination of hydrophobic, positively charged, dipolar, or hydrogen-bond-donating residues.

Heavily Fluorinated Carbohydrate Analogues

Inspection of Table 2 indicates that the aggregate size of the C–F bond is actually substantially larger than C–H and smaller than C–OH, while an excellent match is found for C=O. Figure 1 displays a comparison between the relative sizes of the hydroxymethylene and *gem*-difluoro groups. Although the

Table 2. *Steric consequences of fluorine substitution. For the CHOH group, the measured distance is to the center of the cone swept out by the hydroxy proton.*

Bond	Length [Å]	van der Waals radius [Å]	Total size [Å]
C–H	1.09	1.20	2.29
C=O	1.23	1.50	2.73
C–O–	1.43	1.52	2.95
C–F	1.35	1.47	2.82
O–H	0.96	1.20	2.16

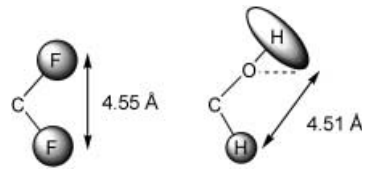


Figure 1. *A comparison of the relative sizes of the hydroxymethylene and* gem*-difluoro groups.*

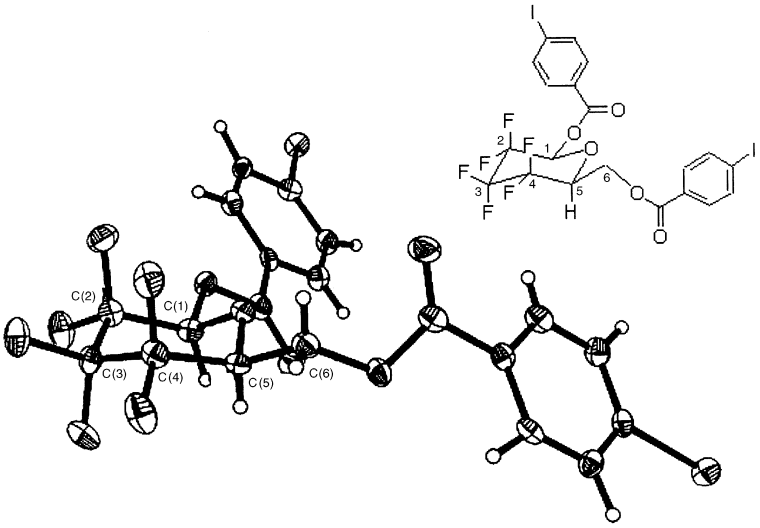


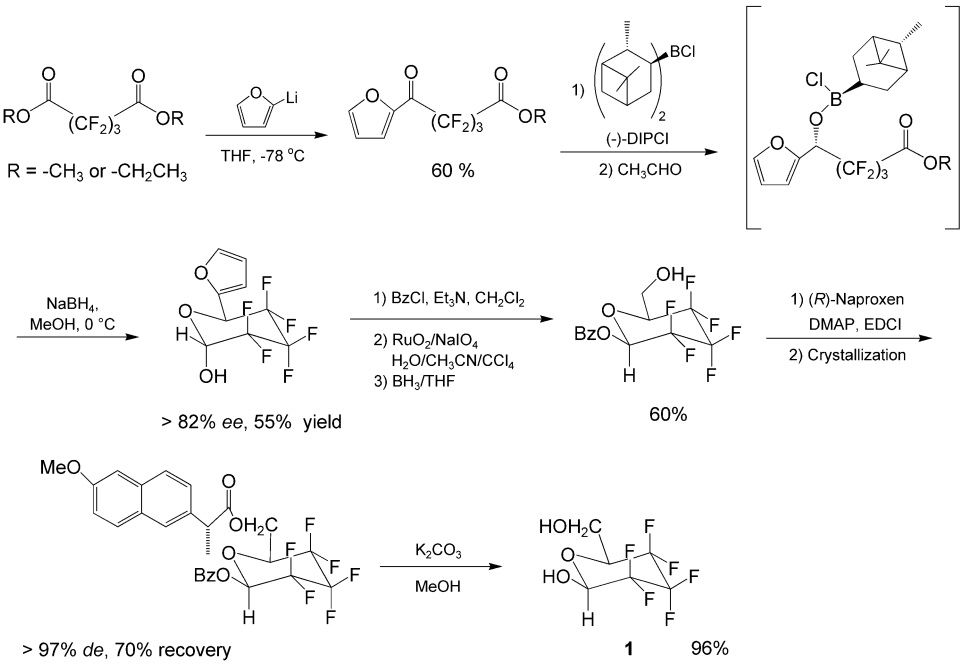
Figure 2. *X-ray crystal structure of* ***2*** *showing the absolute stereochemistry of the* S *center.*

angular orientation is slightly different, the spatial extent of the two groups is very similar. On purely steric grounds, the *gem*-difluoro group should be superior to CFH as a substitution for CHOH.

Initial studies designed to test the polar hydrophobicity concept focused on heavily fluorinated carbohydrate analogues, such as 1-hydroxy-5-hydroxymethyl-2,2,3,3,4,4-hexafluorooxane, **1** (see Scheme 3). These analogues retain the overall shape and pseudoquadrupolar charge distribution of the natural compounds but should have diminished polarizability due to the increased fluorocarbon content.

In addition to changing solvation and polarizability characteristics, the 2,2-*gem*-difluoro group has profound electronic impact on the reactivity of **1**. Strong electron-withdrawing groups (like perfluorocarbons) destabilize the sp^2-hybridized carbonyl form of aldehydes, thus the mutarotation rate decreases dramatically and the cyclic acetals are more strongly preferred for these analogues than for typical sugars. Anomeric activation of **1** via an oxocarbenium ion is also quite difficult, as the electron-withdrawing perfluoroalkyl group destabilizes an adjacent carbocation center.[65]

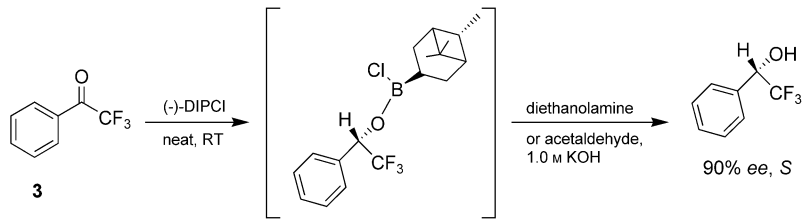
The synthesis of **1** (shown for the *S* enantiomer) depicted in Scheme 3 is straightforward and either enantiomer is obtainable in good yield after resolution of the enantiomerically enriched products. This synthetic methodology has proven to be quite general and permits preparation of the 2,3-dideoxy-2,2,3,3-tetrafluoropentofuranose derivatives as well.



Scheme 3. *Synthesis of the heavily fluorinated hexose analogue (S)-***1***. THF = tetrahydrofuran, (−)-DIPCl =* B*-chlorodiisopinoxampheylborane, Bz = benzyl, DMAP = 4-dimethylaminopyridine, EDCI = 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride.*

Enantiomeric excess was determined by analytical chiral HPLC (Chiracel OD, 95% hexane, 5% isopropanol) of 1,6-dibenzoate derivatives. The absolute stereochemistry set in the initial DIPCl reduction was determined by anomalous dispersion in the X-ray crystal-structure determination of the diiodinated derivative shown in Figure 2. The observed stereoselectivity is consistent with previous reports by Ramachandran et al. describing the DIPCl reduction of fluorinated ketones (Scheme 4);[66] the reduction by (−)-DIPCl yielded the *S*-enriched carbohydrate analogue (Scheme 3).

Racemic compound **1** is a somewhat volatile (sublimed at 57 °C, 0.02 mm Hg), sweet-smelling crystalline material. Structural ^{1}H and ^{19}F NMR spectroscopy studies were performed on several of the intermediates in the synthetic pathway, thereby al-



Scheme 4. *Use of (−)-DIPCl in the synthesis of S alcohols from perfluoroalkyl aryl ketones.*[66]

lowing all fluorine and proton resonances for the α and β anomers of **1** to be assigned**.** These assignments were used to distinguish between the two diastereomeric forms of the analogue in two-dimensional EXSY experiments probing transport across the membrane of red blood cells (RBCs).

Glucose Transporter Studies

Transport studies of 1-, 2-, 3-, 4-, and 6-monodeoxyfluoro-D-glucose across the RBC membrane have been performed to probe the binding requirement for transmembrane transport and anomeric preferences for mediated transport through the RBC membrane have been noted.[67–70] 2-Deoxy-2-fluoro-D-glucose (2-DFG) and 3-deoxy-3-fluoro-D-glucose (3-DFG) cross the erythrocyte membrane at rates very similar to that of glucose, while permeabilities for the 4- and 6-substituted derivatives (4-DFG and 6-DFG) are roughly halved.[68] The α anomer of each monofluorinated monodeoxyglucose isomer is transported more rapidly than the β anomer. While fluorine substitution at individual positions on glucose has a relatively small effect on the transport rates, alteration of the configuration of a single hydroxy group on the ring has a profound effect; for example, galactose is transported over tenfold more slowly than glucose.[71] The transport data from nonphysiological substrates indicate that the active site is sterically fairly discriminating and that the hydroxy moieties at positions 2–4 are probably interacting with positively charged, hydrogen-bond-donating, or hydrophobic groups. Thus, this system serves as an ideal receptor to test the polar hydrophobic hypothesis with **1**.

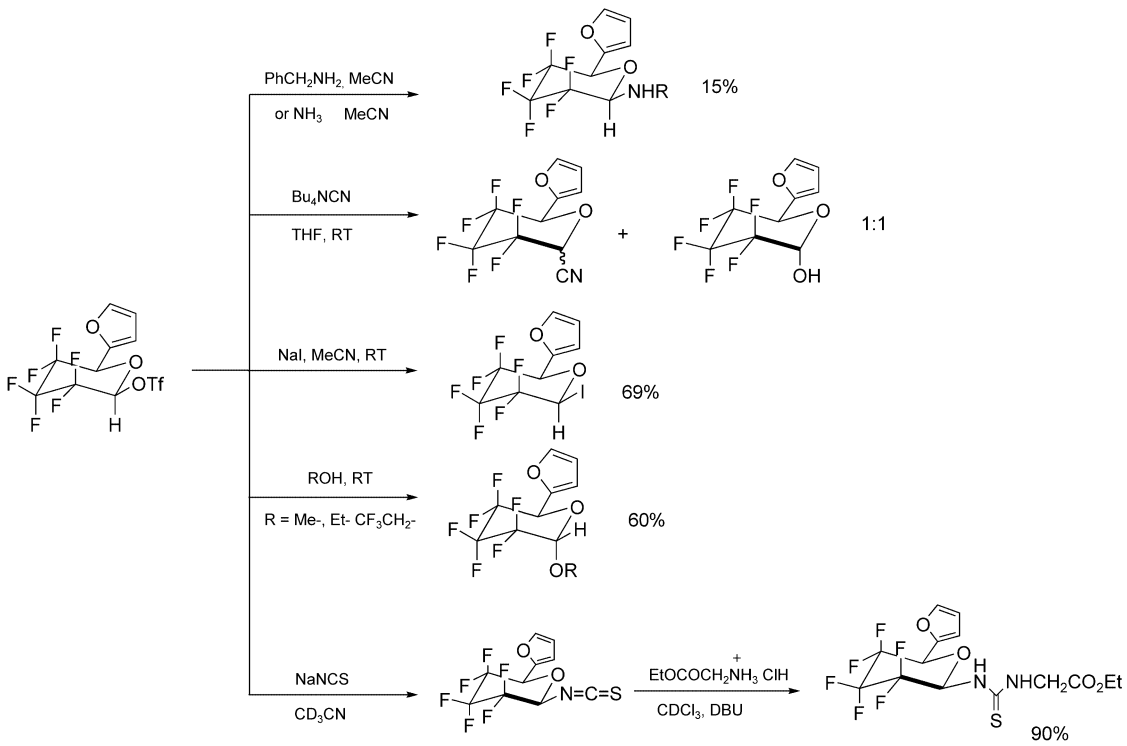
Two-dimensional EXSY experiments were employed to determine the absolute magnitudes of the transmembrane-transport rate constants for **1**.[69] Exchange rates (k_{exch}) for transmembrane transport were determined to be 54 s^{-1} for the α anomer and 15 s^{-1} for the β anomer. Individual efflux (k_{ef}) rate constants were extracted from the k_{exch} values after correcting for the differences in intra- and extracellular volumes, to give $k_{ef} = 22.2\ s^{-1}$ for the α anomer and $k_{ef} = 7.6\ s^{-1}$ for the β anomer.[72] A comparison of the permeability measured for **1** ($P_{ef\alpha} = 9.5 \times 10^{-4}\ cm\ s^{-1}$ and $P_{ef\beta} = 3.2 \times 10^{-4}\ cm\ s^{-1}$) with the values determined for 3-DFG ($P_{ef\alpha} = 0.58 \times 10^{-4}\ cm\ s^{-1}$ and $P_{ef\beta} = 0.44 \times 10^{-4}\ cm\ s^{-1}$) shows that the heavily fluorinated analogue crosses the RBC membrane at an approximately tenfold higher rate. Control experiments, including inhibition studies, verified that the increased permeability of **1** is consistent with mediated diffusion and enhanced affinity for the transport protein.

These data indicate that increasing the polar hydrophobicity of judiciously chosen substrates may be a useful strategy for improving biological molecular recognition. Given the large number of pharmaceutically relevant compounds that contain terminal hexopyranose moieties, and the recognized role that these hexopyranose moieties play in transport and delivery, there is ample opportunity to explore the effects of appending heavily fluorinated carbohydrate analogues in well-studied systems, provided that the requisite synthetic methodology is developed.

Derivatized Heavily Fluorinated Carbohydrate Analogues

Recent efforts in our laboratories have extended the synthetic chemistry to enable relatively facile anomeric activation and derivatization of carbohydrate analogues. It is amply documented that an electron-withdrawing perfluoroalkyl group exerts a potent destabilizing effect on an adjacent carbocation center.[65] Tidwell and co-workers[73] have shown that solvolysis reactions of 2-(trifluoromethyl)-2-propyl triflate occur at a roughly millionfold slower rate than isopropyl triflate. In this instance, only elimination products are obtained for the trifluoromethylated derivative. Atypical solvent effects indicate that a full cationic charge is never generated at the carbon center. Similarly, Olah and Pittman[74] have noted that 1,1,1-trifluoro-2-propanol does not ionize, even under super acid conditions (FSO_3H-SbF_5 SO_2); instead, the alcohol is quantitatively protonated. These considerations, together with the observation that longer perfluoroalkyl groups are more electron withdrawing than trifluoromethyl groups, dictate that a potent leaving group and/or strongly ionizing conditions are required to effect substitution of the anomeric position in heavily fluorinated carbohydrate analogues.[75] Indeed, this is the case; 1-tosyl, bromo, and iodo derivatives are inert to anomeric activation. Only the anomeric triflate, which is readily isolable by standard chromatographic methods, is easily displaced by a variety of nucleophiles (Scheme 5). Thus, incorporating these heavily fluorinated carbohydrate analogues into biological macromolecules can be accomplished with only minor modifications of existing synthetic techniques. It is hoped that these synthetic developments will enable the polar hydrophobic hypothesis to be surveyed more thoroughly by using heavily fluorinated carbohydrate analogues.

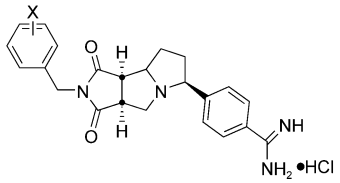
These embryonic results in the fluorinated carbohydrate area notwithstanding, there is much to be gained by embracing this concept and using it to interpret some of the more puzzling literature results. For example, in the elegant recent work by Banner, Müller, Diedrich, and co-workers, it was found that fluorine substitution on the aromatic ring of a family of



Scheme 5. *Utility of the 1-triflate group for anomeric functionalization of heavily fluorinated carbohydrate derivatives. Tf = triflate = trifluoromethanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.*

thrombin inhibitors (Table 3) led to enhanced binding for the 4-fluoro derivative but near normal binding for the 2- and 3-fluoro derivatives.[76]

Table 3. *Inhibition constant (K_i) data for fluorinated thrombin inhibitors.*



Inhibitor	X	K_i [μM]
(±)-**1**	–	0.31
(±)-**2**	2-F	0.50
(±)-**3**	3-F	0.36
(±)-**4**	4-F	0.057
(±)-**5**	2,6-F_2	0.61
(±)-**6**	3,5-F_2	0.59
(±)-**7**	1,2,3,4,5-F_5	0.27

Upon investigation of the protein crystal structures in which the various inhibitors were bound, the authors posited that a novel C–F···C=O dipolar interaction was responsible for the enhanced molecular recognition ($\Delta\Delta G = 1.0$ kcal mol^{-1}) of the 4-fluoro compound and that such interactions were lacking in the other derivatives. There are two intriguing aspects to these data; the first is that the "extra" binding energy of the 4-fluoro derivative seems exceptionally large given the literature precedents for C–F cation interactions, the second is that the 2- and 3-fluoro derivatives provide almost no change in the K_i value, although there are no obvious C–F stabilizing interactions in binding pocket, according to the structural analyses. These data are easily rationalized by invoking polar hydrophobicity. According to this argument, fluorine substitution on the aromatic ring reduces its polarizability, increases the hydrophobic surface area of the molecule, and provides an enhanced driving force for desolvation. One may estimate from lipophilicity data that this general driving force may be in the range of 0.2–0.5 kcal mol^{-1}. This additional driving force compensates for any unfavorable low-energy dipolar interactions in the active site of the 2- and 3-fluoro derivatives and is augmented by a favorable, but weak, C–F···C=O interaction for the 4-fluoro case. Consistent with the polar hydrophobic hypothesis, even a favorable dipolar interaction is sufficient to afford a sizeable increase in the binding constant.

Conclusion

In this review we have shown how the polar hydrophobic nature of fluorine-containing compounds can lead to increased affinity for natural receptors, despite the relatively weak dipolar interactions that characterize the hard C–F dipole. Although the polar hydrophobic concept was developed to help explain some of the puzzling protein-binding data characteristic of fluorinated carbohydrate analogues, we have attempted to show how this concept can be applied more broadly in medicinal chemistry.

Keywords: carbohydrates · enzyme inhibitors · fluorine · hydrogen bonds · hydrophobic interactions

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