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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · FEBRUARY 2011

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Influence of the Structure of Polyfluorinated Alcohols on Brønsted Acidity/Hydrogen-Bond Donor Ability and Consequences on the Promoter Effect

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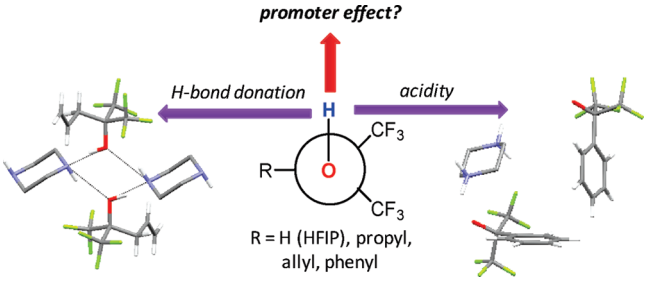
Received December 2, 2010



The influence of substituents on the properties of tri- and hexafluorinated alcohols derived from 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was examined. Measurements of specific solvent−solute interactions revealed that H-bond donation (HBD) of fluorinated alcohols is sensitive to the steric hindrance of the OH group, whereas their Brønsted acidity is dependent only on the number of fluorine atoms. For hexafluorinated alcohols (HFAs), their association with amines characterized by X-ray diffraction showed that the balance between HBD and acidity is influenced by their structure. Moreover, the ability of HFAs to donate H-bonds is exerted in synclinal (sc), synperiplanar (sp), and also antiperiplanar (ap) conformations along the C−O bond. Comparison of the effects of fluorinated alcohols as promoting solvents in three reactions is reported. The positive correlation between rate constants and H-bonding donation ability for sulfide oxidation and imino Diels−Alder reaction brings to light the role of this property, while acidity might have a minor influence. In the third reaction, epoxide opening by piperidine, none of these properties can clearly be put forward at this stage.

Introduction

The impact of fluorine atom on organic molecules is considerable, with dramatic consequences at physical and chemical levels.[1] This effect is particularly striking for the fluorinated alcohols trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP); these easily available chemicals exhibit unique features, far different from those of their hydrogenated counterparts ethanol and isopropanol (Figure 1a). Indeed, the presence of the strong electron-withdrawing trifluoromethyl group influences several key parameters: ionizing power, Brønsted acidity, and hydrogen-bond donation HBD (or H-bond acidity) are increased, whereas nucleophilicity and hydrogen-bond acceptance HBA (or H-bond basicity) are significantly depleted.[2,3] Because of such specificities, these fluorinated alcohols have met noteworthy applications in various domains. For example, in biochemistry TFE and HFIP are used to modify the conformation of proteins,[4] and they are also widely accepted as exceptional promotion media to perform organic reactions.[5,6] To explain this "booster

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Published on Web 01/18/2011 DOI: 10.1021/jo1023816

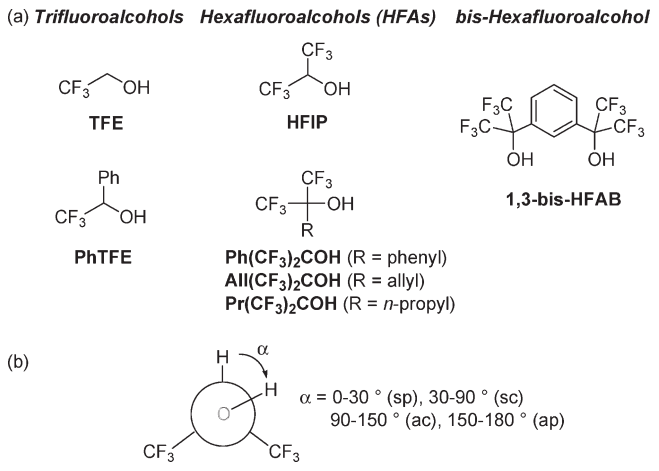

FIGURE 1. (a) Some primary, secondary, and tertiary polyfluorinated alcohols. (b) Conformations of HFIP.

effect",[7] fluorinated alcohols are often compared to Lewis acids, acting thus as electron acceptors, either through proton release or through hydrogen-bond donation. So, it is not unusual to see the terms Brønsted acidity and H-bond donor ability being indifferently evoked in the literature, inducing sometimes confusion between these two notions. Nevertheless, in the activation of hydrogen peroxide by fluorinated alcohols for oxidation reactions,[8−11] the role of HBD seemed to be prominent as supported by theoretical and experimental studies.[7,12] In particular, Berkessel deduced from crystal structures that the HBD was strongly connected to the conformation along the C−O bond and that synclinal (sc) and synperiplanar (sp) conformations were essential (Figure 1b). Moreover, it was suggested that aggregation of HFIP as dimers or trimers could also enhance this property.[7]

To a much lesser extent some tertiary hexafluorinated alcohols (HFAs) have also been shown to have a remarkable influence as additives on the course of reactions, even much better than that of HFIP (Figure 1).[13] Thus, Radinov reported that the presence of 2−10 mol % of $Ph(CF_3)_2COH$ or 1,3-bis-HFAB controlled the selectivity of a Pd-catalyzed isomerization of a diene mono-oxide.[14] The authors connected this effect to the relative Brønsted acidity of the HFA additives. More recently, Hedrick showed that a 1,3-bis-HFAB-type catalyst was able to catalytically assist the ring-opening polymerization of lactides through hydrogen bonding with the carbonyl group.[15]

In this context, we now report on the influence of the structure of tri- and hexafluorinated alcohols on their hydrogen-bonding properties through quantitative (spectroscopic measurements) and qualitative experiments (formation of adducts with amines) and the consequences on their behavior as reaction media.

Results and Discussion

It is already known from the literature that the introduction of aromatic or aliphatic substituents on fluorinated alcohols has a weak influence on their acidity. For example,

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TABLE 1. Empirical Solvent Parameters of Fluorinated Alcohols[a]

compound	β[b]	$E_T(30)$ [E_N^T]	AN
EtOH	0.81	51.8 [0.65]	37.1
TFE	0.22	59.8 [0.90]	51.1
$Ph(CF_3)CHOH$	0.28	55.0 [0.75]	46.7
HFIP	~0 (−0.12)	66.0 [1.07]	59.3
$Ph(CF_3)_2COH$	~0 (−0.08)	49.5 [0.58]	41.8
$All(CF_3)_2COH$	0.03	52.6 [0.68]	44.1
$Pr(CF_3)_2COH$	~0 (−0.02)	51.4 [0.64]	42.3

[a] β = Kamlet−Taft HBA scale; $E_T(30)$ = Reichardt HBD scale, [E_N^T = normalized Reichardt scale with Me_4Si = 0 and H_2O = 1.0, see ref 2a]; AN = Gutmann's acceptor number. [b] For hexafluorinated alcohols where $\beta < 0$, β values were assimilated to 0. Measured values are indicated in parentheses.

with a phenyl group the pK_a slightly decreases, as exemplified by $pK_a(TFE)_{H_2O}$ = 12.4 versus $pK_a(Ph(CF_3)CHOH)_{H_2O}$ = 11.9,[16,17] and $pK_a(HFIP)_{H_2O}$ = 9.3 versus $pK_a(Ph(CF_3)_2COH)_{H_2O}$ = 8.8.[16,18] In contrast the presence of an alkyl chain renders the compound slightly less acidic: $pK_a(CH_3(CF_3)_2COH)_{H_2O}$ = 9.6.[16] Globally, the pK_a of such substituted fluorinated alcohols differs from those of TFE and HFIP by only ±0.5 unit. Their Brønsted acidity thus mostly depends on the number of CF_3 groups rather than on the degree of substitution. However, the structure could influence some other features, and our investigations were oriented toward various fluorinated alcohols for which pK_a values have been determined in a methanol/water mixture: TFE (11.8), $Ph(CF_3)CHOH$ (11.7), HFIP (9.5), $Ph(CF_3)_2COH$ (9.3), $All(CF_3)_2COH$ (9.6), and $Pr(CF_3)_2COH$ (10.1), confirming thus the influence of fluoroalkyl chains on acidity.[19]

Some specific solvent parameters have been measured for these compounds and compared to ethanol: β parameter to measure the hydrogen-bond acceptance of the oxygen lone pairs, and $E_T(30)$[2a,21] and AN (acceptor number)[22] parameters for which the H-bond donation of the OH group is the main contributor.

Investigations on solute−solvent interactions have been performed at the molecular level. In this approach the solvent effect on the molecular property of a probe is measured.[23] In the following, three spectroscopic properties, giving rise to three solvent parameters (β, $E_T(30)$, and AN), have been evaluated (Table 1). The corresponding molecular probes **1**−**4** are shown in Figure 2.

Hydrogen-Bond Acceptance (HBA): β Parameter. This parameter is defined from the enhanced solvatochromic shift of the longest wavelength $\pi \rightarrow \pi^*$ transition of 4-nitrophenol

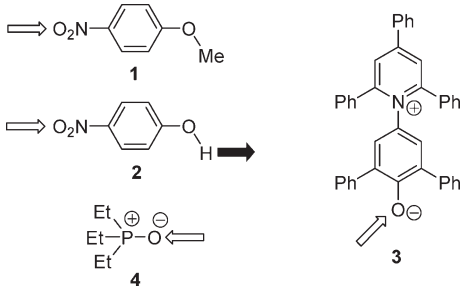

FIGURE 2. Molecular probes **1**−**4** used for the determination of β (**1**, **2**), $E_T(30)$ (**3**), and AN (**4**) scales: (open arrow) H-bond acceptor sites; (black arrow) H-bond donor site.

2 compared to 4-nitroanisole **1**.[3,20] For non-H-bond donor solvents, this enhanced shift measures unambiguously the H-bond acceptance ability of the solvent. However, for strong H-bond donor solvents the solvatochromic comparison fails, because the nitro group of 4-nitroanisole is a better H-bond acceptor than the nitro group of 4-nitrophenol, and negative values of β are obtained.[24] Hence, the negative values of most hexafluorinated alcohols are assimilated to zero. The observed order EtOH ≫ $Ph(CF_3)CHOH \approx TFE \gg$ HFAs illustrates the impact of the number of fluorine atoms that lowers significantly the HBA of the oxygen lone pairs.

Hydrogen-Bond Donation (HBD): $E_T(30)$ and AN Parameters. $E_T(30)$ is defined from the solvatochromic shift of the charge transfer transition of the 30th Reichardt's betaine (**3**),[2d,21] and AN from the NMR chemical shift δ of the ^{31}P atom of triethylphosphine oxide **4** (Figure 2).[22] To the first approximation $E_T(30)$ measures the bulk polarity of the solvent since polar solvents stabilize the zwitterionic ground state of the dye. However, some additional solvent-probe specific interactions can contaminate the overall polarity measurement.[25] For H-bond donor solvents such as alcohols, both parameters actually register their ability to donate hydrogen bonds, since the oxygen atoms of **3** and of Et_3PO are strong H-bond acceptors (Figure 2). Fluorinated alcohols are rather strong H-bond donors, and it can be considered that their $E_T(30)$ and AN values vary mainly according to the influence of their HBD. Indeed, there exists a good correlation, $E_T(30) = 0.614 \times AN + 29.28$ (R^2 = 0.986), for 8 alcohols as H-bond donors (*n*-BuOH, *i*-PrOH, *n*-PrOH, EtOH, MeOH, TFE, HFIP, and H_2O) for which both parameters have been measured (Figure 3). This correlation shows that, for OH donors, a common single property explains the variance of $E_T(30)$ and AN values. The presence of a strongly basic oxygen atom in the structure of the probes **3** and **4** clearly indicates that this property is the HBD. However, whereas HFIP obeys the above correlation, $Ph(CF_3)CHOH$, $Ph(CF_3)_2COH$, $All(CF_3)_2COH$, and $Pr(CF_3)_2COH$ deviate significantly below the correlation line, and tertiary HFAs exhibit the greatest deviations (Figure 3).[26]

We attribute these deviations to a steric effect of the phenyl, allyl, and propyl substituents on the hydrogen bonding of these alcohols to the betaine **3**, as confirmed by the

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(26) It can also be noted that a very good correlation among fluorinated alcohols is observed in Figure 3 (R^2 = 0.989). However, no rationale could be found to explain this observation.

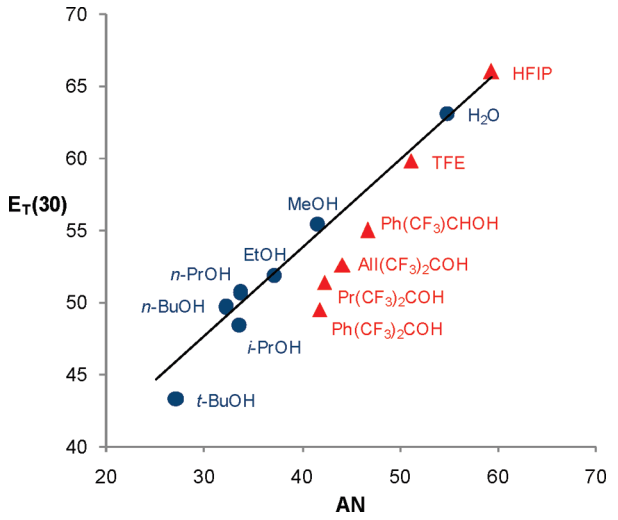

FIGURE 3. Plot of $E_T(30)$ versus AN, showing the deviations of alcohols with hindered OH groups (▲, fluorinated alcohols; ●, others). The full line corresponds to the relation $E_T(30) = 0.614 \times AN + 29.28$.

deviation also observed for *t*-BuOH. Indeed, the oxygen of betaine **3** is flanked by two bulky phenyl groups in the *ortho* positions (see Figure 2). In contrast, the phosphoryl oxygen of Et_3PO is unhindered and is consequently less sensitive to steric effects in the fluorinated alcohols. Thus, from AN measurements reported in Table 1, it emerged that HFIP acts as the strongest H-bond donor (AN = 59.3), followed by TFE (51.1). Whereas it is not surprising to see that HFIP is the best hydrogen-bond donor, it appears that TFE is a better donor than $Ph(CF_3)CHOH$ and even better than tertiary hexafluorinated alcohols. These latter ones have a H-bond donor ability standing between those of TFE and EtOH.

From these studies on ethanol and fluorinated alcohols, it is clear that acidity and H-bond acceptance are connected to the number of fluorine atoms, while the bulkiness of fluorinated alcohols seems to play a prominent role in their HBD.

Hydrogen-Bonding versus Acidity: Influence of the Structure and Conformation. In addition to spectroscopic analyses, the H-bond donor ability can also be measured qualitatively through the formation of complexes with Lewis bases. This has been well exemplified between fluorinated alcohols and ethers: for example, the THF−HFIP adduct has a bp =100 °C, far above the boiling point of each component.[7,27] Recently, we reported that amines could also be excellent partners since piperidine afforded a solid adduct with HFIP through H-bonding.[28] X-ray diffraction showed that the structure was composed of 2 molecules of piperidine for 4 molecules of HFIP in a hexagonal arrangement. A surprising result thus emerged: HFIP actually acted as a very poor H-bond donor (d(OH···N) = 2.30 Å and ∠(OHN) = 95°) but behaved as a very good H-bond acceptor with N−H (d(NH···O) = 1.71 Å and ∠(OHN) = 164°).[28] It is also worth noting that, in this structure, HFIP adopted an anticlinal conformation (ac; torsion angle =104°). It thus confirms previous reports from Berkessel in which it was assumed that H-bond donation was favored only under sc or sp conformation, since "the donor orbital energy (σ^*_{OH}) decreased and the dipole moment (μ) increased drastically from ap to sp conformation".[7]

This HFIP-piperidine structure is clearly contradictory to H-bond measurements (AN and β), where HFIP appeared to be an excellent H-bond donor with almost no inclination for acceptance. However, it is important to distinguish properties that are determined in liquid or solid state. In the latter case, crystal packing effect might play an important role, and comparison of these two types of measurement must be interpreted with caution.

The ability of tertiary HFAs to donate hydrogen bonds has also been shown to be significant. Indeed, their association with sp^2 oxygens has been brought to light and exploited in the design of chemical vapor sensors for the detection of phosphonate nerve agents.[29] Recently, we disclosed the preparation of gold nanoparticles coated with a tertiary HFA terminated by a thiol group (HFA-AuNPs), which were able to make supramolecular associations with amines.[30] In this context, we reasoned that associating various fluorinated alcohols with amines to obtain crystalline adducts, characterizable by crystallography, would bring additional structural elements to the H-bond scales described above. Thus, tertiary hexafluorinated alcohols were first mixed with piperidine, but no solid adducts were obtained with this partner. However, with piperazine,[31] crystalline structures were afforded from the hexafluorinated alcohols HFIP, $Ph(CF_3)_2COH$, and $All(CF_3)_2COH$ (Figure 4a−c and Table 2).[32] For all these HFA-amine adducts reported here, the corresponding X-ray structures were obtained with a residual factor *R*-factor < 0.08, allowing unambiguous location of hydrogen atoms (i.e., to distinguish between a H-bond adduct and a salt).

HFIP-Piperazine. (Figure 4a) An excess of HFIP was added to piperazine, and after slow evaporation, white crystals were afforded (mp = 79 °C). The cohesion is due to an H-bond network between 2 HFIP and 2 nonequivalent piperazines, where the four of them behave as acceptor and donor. However, conversely to the previously described adduct with piperidine, HFIP acted here as a better H-bond donor than acceptor as shown by H(11O)···N(1) (d = 1.58 Å and ∠(OHN) = 173°) compared to N(1)−H(1A)···O(11) (d = 2.21 Å and ∠(OHN) = 157°). Moreover, it can be noted that some non-negligible interactions occurred between F and hydrogen from NH as for N(4)−H(4A)···F(12) (d = 2.47 Å and ∠(FHN) = 140°). Moreover, in accordance with the HBD/conformation relation assumed by Berkessel, HFIP adopted in this structure a sp conformation (∠H(11O)−O(11)−C(11)−H(11A) = 8°). While there is no clear evidence to explain this difference between HFIP-piperidine and HFIP-piperazine, it can be assumed that it could result from different crystal packing forces in these two cases.

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(31) Piperazine is a white solid with mp = 109−112 °C, bp = 145−146 °C; $pK_a1(piperazine)_{H_2O}$ = 9.73 and $pK_a2(piperazine)_{H_2O}$ = 5.35: Khalili, F.; Henni, A.; East, A. L. L. *J. Chem. Eng. Data* **2009**, *54*, 2914–2917.

(32) No solid adducts were obtained from TFE and $Ph(CF_3)CHOH$ with piperazine or any other amine assessed.

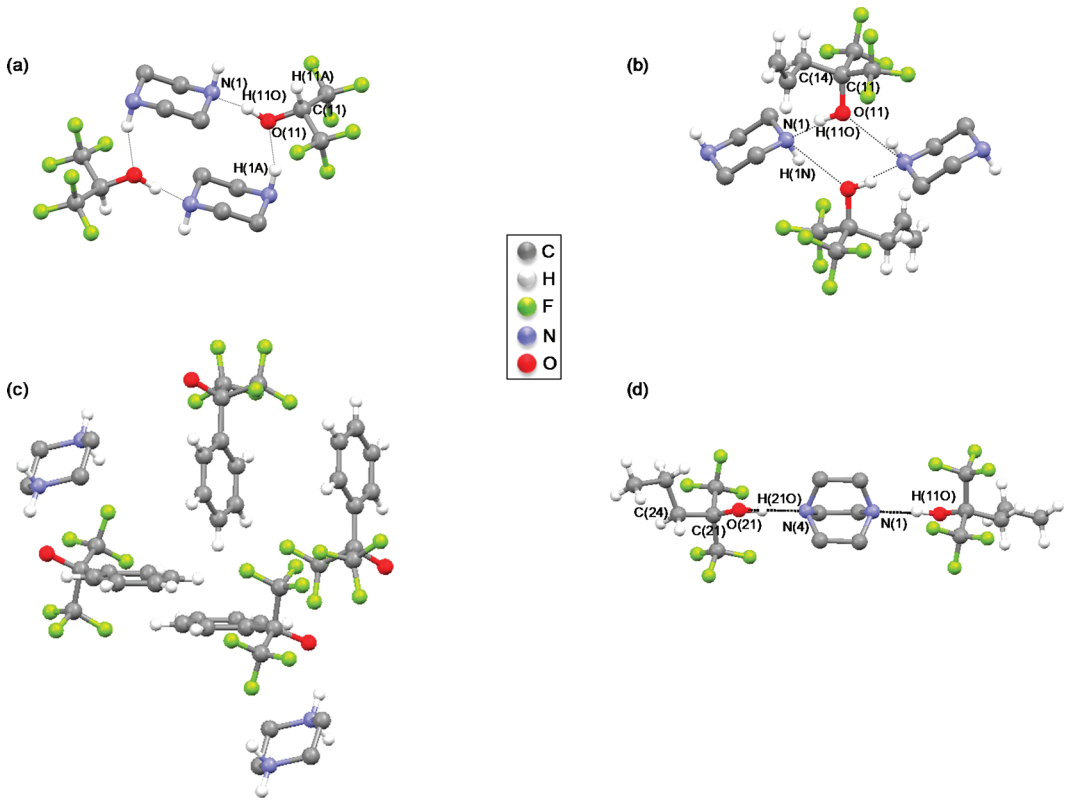

FIGURE 4. Single crystal X-ray structures of fluoroalcohol-amine adducts: (a) HFIP-piperazine, (b) All$(CF_3)_2$COH-piperazine, (c) Ph$(CF_3)_2$COH-piperazine, and (d) Pr$(CF_3)_2$COH-DABCO (DABCO = diazabicyclo[2.2.2]octane). Hydrogen atoms (C−H) in amines have been omitted for clarity.

TABLE 2. Characteristics of Hexafluoroalcohol-Amine Adducts

		OH···N		NH···O		
HFA-amine adduct	mp [°C]	*d* [Å]	∠ [deg]	*d* [Å]	∠ [deg]	torsion angle [deg] /conformation
HFIP-piperidine[a]	95	2.30	95	1.71	164	104/ac
HFIP-piperazine	79	1.58	173	2.21	157	8/sp
All$(CF_3)_2$COH-piperazine	62	1.66	169	2.20	150	42/sc
Ph$(CF_3)_2$COH-piperazine	78					
Pr$(CF_3)_2$COH-DABCO	79	1.74	165			173/ap

[a]Taken from ref 28.

All$(CF_3)_2$COH-Piperazine. (Figure 4b) In the same way, mixing All$(CF_3)_2$COH and piperazine afforded a solid, albeit with a melting point lower than the previous one (mp = 62 °C). In this case, the H-bond arrangement is tetragonal with two All$(CF_3)_2$COH molecules for two piperazines (equivalent), each one being H-bond acceptor and donor. As for the HFIP-piperazine complex, the HBD is clearly dominating: O(11)−H(11O)···N(1) (d = 1.66 Å and ∠(OHN) = 169°) versus N(1)−H(1N)···O(11) (d = 2.20 Å and ∠(NHO) = 157°). It is observed that these distance and angle values are close to those measured for HFIP with the same amine and that the torsion angle was also low (∠H(11O)−O(11)−C(11)−C(14) = 42°; sc conformation).

Ph$(CF_3)_2$COH-Piperazine. (Figure 4c) A solid was also obtained, with mp = 78 °C. Crystal structure revealed that the ratio Ph$(CF_3)_2$COH/piperazine was 4:2. Actually, this solid was not formed of hydrogen bonds but was an alcoholate/ammonium salt, where each nitrogen atom of piperazine was protonated. Concerning other interactions, the possibility of F···HN bonds can reasonably be considered since some F···H distances of 2.36 Å are observed (however, the F−H−N angle varies from 116° to 162°). It can be noted that in head-to-tail arrangement of Ph$(CF_3)_2$COH by pairs aromatic rings appear to be parallel (albeit with a too long distance to assume a π-stacking interaction), each pair being orthogonal to the other.

Compared to HFIP and All$(CF_3)_2$COH, this result is surprising and could be *a priori* the consequence of the slightly highest acidity of Ph$(CF_3)_2$COH ($pK_{a\,H_2O}$ = 8.8 for Ph$(CF_3)_2$COH versus 9.3 for HFIP), but this does not appear to be completely satisfactory. Actually, this phenomenon could be related to a competition between acidity and HBD ability where steric factors would play an important role: in the presence of a molecule being both a Brönsted and a Lewis base, a polyfluorinated alcohol can behave either as a proton or as an H-bond donor. As noticed from Figure 3, Ph$(CF_3)_2$COH exhibits the greatest deviation to the linear relation between $E_T(30)$/AN, showing thus that its tendency

to donate H-bond is strongly connected to the size and nature of the acceptor partner. Therefore, it is likely that the competition between proton and H-bond donation is driven by steric factors, and in the case of $Ph(CF_3)_2COH$ its association with piperazine is "easier" through the formation of an alcoholate/ammonium salt than through H-bond association.[33]

$Pr(CF_3)_2COH$-DABCO. (Figure 4d) We finally assessed tertiary alcohols with a tertiary amine to know whether the HBD from amines plays a significant role in the global cohesion structure. For this purpose, DABCO (diazabicyclo [2.2.2]octane) was used as H-bond acceptor partner: unfortunately no crystal structures could be obtained with any of the three HFAs assessed above. However, from $Pr(CF_3)_2$-COH as fluoroalcohol, ordered crystals were isolated and characterized (mp = 79 °C). In this case, each nitrogen atom of the diamine formed a hydrogen bond with a fluoroalcohol molecule (d N(1)···H(11O) = 1.74 Å, ∠(OHN) = 165°, and d N(4)···H(21O) = 1.73 Å, ∠(OHN) = 166°). Surprisingly, in this structure, the fluoroalcohol adopted an antiperiplanar (ap) conformation (∠ H(21O)−O(21)−C(21)−C(24) = 173°). It is worth noting that in HFIP- and $All(CF_3)_2$-COH-piperazine adducts (sp and sc conformations, respectively) the OH groups behave as strong H-bond donor along with a weaker H-bond acceptance. These two contributions might be cooperative and responsible for the low angle value conformation of the fluorinated alcohols. Conversely, for $Pr(CF_3)_2COH$-DABCO only the HBD of the hydroxyl is involved, resulting in an "increase of its size" and forcing thus the fluorinated alcohol to adopt a conformation with a minimal steric hindrance between the substituents.

These crystal structure studies show that the tertiarization of HFAs does not prevent them from acting as H-bond donors, as exemplified by the formation of adducts between $All(CF_3)_2COH$ and $Pr(CF_3)_2COH$ with secondary and tertiary amines. However, for all HFAs there is a competition between proton and H-bond donation where HBD appears to be prominent for less sterically hindered alcohols (HFIP, $All(CF_3)_2COH$, and $Pr(CF_3)_2COH$); conversely, Brønsted acidity seems to override H-bond donation for the bulky $Ph(CF_3)_2COH$. In the case of association through hydrogen bonding, despite the very weak HBA of hexafluorinated alcohols measured in solution, HFAs can act as H-bond acceptors in the solid state. Torsion angle comparisons confirm that HFAs exhibit a stronger HBD under sp and sc conformation than under ac conformation. However, these two first conformations appear to be favored when the hydroxyl group combines strong HBD to a weaker HBA. When the OH is the only H-bond donor ($Pr(CF_3)_2COH$-DABCO adduct), the alcohols adopt the less sterically demanding ap conformation.

Assessment of Fluorinated Alcohols As Promoting Solvents. When fluorinated alcohols are used as reaction media, acidity and H-bond donation are often claimed to be major factors responsible for the promotion of the transformation. By exploiting the scales of HBD and Brønsted acidities obtained from the various fluorinated alcohols studied above, we reasoned that we could assign the respective role of these two parameters in the "booster effect" for some reactions. Since H-bond donation decreases when temperature rises, its influence can be properly evaluated only in reactions performed at moderate temperatures.[6a] Secondary and tertiary fluorinated alcohols were thus assessed in three typical test reactions in which HFIP and/or TFE have been previously shown to have a remarkable effect at room temperature, without any supplementary additive: (1) the oxidation of thioanisole into methyl phenyl sulfoxide,[8a,b] (2) the opening of 1,2-epoxy-3-phenoxypropane with piperidine,[34] and (3) the imino Diels−Alder reaction (or Povarov reaction) between benzalaniline and butyl vinyl ether.[35,36] To measure kinetics and to obtain rate constants, these reactions usually performed at room temperature have been performed at 0 °C. Results are reported in Table 3.

As already reported, ethanol was ineffective as solvent for sulfide oxidation and imino Diels−Alder reaction. Concerning fluorinated alcohols, their behavior was extremely different according to the reaction studied. In the sulfide oxidation, all of the fluorinated solvents were able to promote the selective oxidation of sulfide into sulfoxide, albeit with a huge difference in the rate of conversion between HFIP and the others. While trifluorinated and tertiary hexafluorinated alcohols fell into the same range ($1.7 < k < 2.3$ $L \cdot mol^{-1} \cdot h^{-1}$), the reaction was extremely fast in HFIP ($k = 676$ $L \cdot mol^{-1} \cdot h^{-1}$). For the opening of the epoxide with piperidine, tertiary HFAs hardly behave better than ethanol (7.5×10^{-2} and 8.7×10^{-2} $L \cdot mol^{-1} \cdot h^{-1}$ for $All(CF_3)_2$-COH and $Ph(CF_3)_2COH$ versus 5.9×10^{-2} $L \cdot mol^{-1} \cdot h^{-1}$ for EtOH), and trifluorinated alcohols were the best promoters, the reaction being two times faster in $Ph(CF_3)CHOH$ than in TFE (56.7×10^{-2} versus 27.6×10^{-2} $L \cdot mol^{-1} \cdot h^{-1}$, respectively). The most striking result was the total absence of any conversion in HFIP as solvent. As a matter of fact, as soon as piperidine was dissolved in HFIP, a white precipitate was irreversibly formed for which analyses (^1H NMR, mp) matched those of the HFIP-piperidine adduct.[28] Concerning the imino Diels−Alder reaction, only TFE and HFIP promoted the reaction to yield the tetrahydroquinoline, and the reaction was incredibly faster in the hexafluorinated alcohol ($> 31 \times 10^3$ times). In all other media, the substrate remained unchanged.

To estimate the role that H-bond donation and acidity of the solvents could play in the promotion of these three reactions, their rate constants k have been plotted according to the AN and pK_a values of the alcohols, and the corresponding correlation coefficients R^2 were measured (Table 4).

On a mechanistic standpoint, sulfoxidation is an electrophilic process where free protons as well H-bond donation could activate H_2O_2. In the first case, if there is a negative correlation between k and pK_a, the low value of $R^2 = 0.217$ rules out the possibility of a major role of acidity in the promotion of this transformation. In contrast, the positive correlation and the significant value of R^2 (0.637) for k/AN are more satisfactory and are in favor of an action of the H-bond donation, as already assumed in previous investigations

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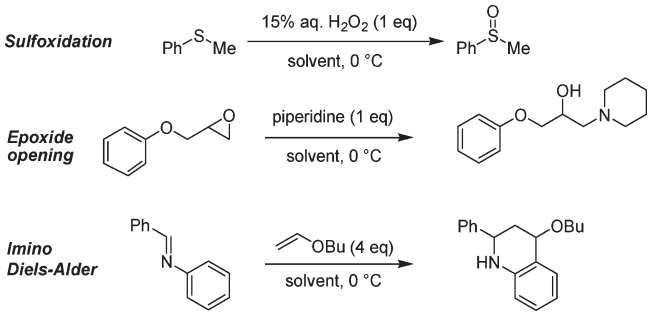
TABLE 3. Fluorinated Alcohols As Reaction Media in Sulfoxidation, Epoxide Opening, and Imino Diels−Alder Reactions[a]



	rate constant k ($L \cdot mol^{-1} \cdot h^{-1}$)		
solvent	sulfide oxidation[b]	epoxide opening[c]	imino Diels−Alder reaction[d]
EtOH	0	5.9×10^{-2}	0
TFE	2.1	27.6×10^{-2}	0.05
$Ph(CF_3)CHOH$	2.3	56.7×10^{-2}	0
HFIP	676	0	1574
$Ph(CF_3)_2COH$	1.9	8.7×10^{-2}	0
$All(CF_3)_2COH$	1.7	7.5×10^{-2}	0

[a]Based on refs 8, 34, and 36. In all cases, no side product was detected. [b]Reaction monitored by GC with 4-nitrotoluene as internal standard. [c]Reactions monitored by ^{1}H NMR with *tert*-butylbenzene as internal standard. [d]Reactions monitored by ^{1}H NMR with dichloromethane as internal standard.

TABLE 4. Relation between Rate Constants k of Various Reactions and AN and pK_a of Alcohols[a]

	correlation coefficient R^2	
reaction	AN	pK_a
sulfide oxidation	0.637	0.217
epoxide opening	3×10^{-5}	0.017
imino Diels−Alder reaction	0.635	0.215

[a]See Supporting Information for details.

for the oxidation of olefins with the same oxidant.[12] However, the solvent effect cannot be attributed to the sole HBD ability, since the difference between AN values cannot explain the close k values for trifluorinated alcohols and tertiary HFAs and even less the incredible effect of HFIP with regard to the other alcohols (the rate constant of HFIP is more than 300 times higher than for any other fluorinated alcohol, whereas the AN value is only 0.4 times superior compared with that of the weakest). The absence of reaction in ethanol is also surprising since its AN value is only 11% below that of $Ph(CF_3)_2COH$ (37.1 versus 41.8). However, in this case the strong H-bond acceptance of EtOH could have a negative influence by counterbalancing the HBD for H_2O_2 activation.

In the opening of epoxide with piperidine, absolutely no correlation was found. For AN, the slope was close to 0 ($R^2 = 3 \times 10^{-5}$), and when considering pK_a, the correlation was even positive ($R^2 = 0.017$). Thus for this reaction, it is clear that neither the acidity nor the H-bond donation can be evoked to justify the booster effect occurring in TFE and $Ph(CF_3)CHOH$ (respectively, 4.6 and 9.6 times faster than in ethanol). This surprising absence of correlation is in opposition to the common claim: for these reactants where a too strong HBD deactivates the nucleophile, the effect of trifluorinated alcohols certainly also stems from other properties.

In the case of the imino Diels−Alder reaction, the difference of reactivity is striking since it occurs only in HFIP and TFE with an outstanding rate in the hexafluorinated solvent. However, if the positive correlation for k/AN with $R^2 = 0.635$ is in favor of an implication of the role of H-bond in the promotion of the reaction, it is insufficient to understand why the reaction takes place only in these two solvents, and we cannot provide any rationale for that at this stage.

From the evaluation of three reactions in polyfluorinated solvents, the following conclusions can be drawn: the promoter effect of fluorinated alcohols does not stem from Brønsted acidity, since for k/pK_a the correlation coefficients R^2 were all below 0.217. In contrast, the H-bond donation ability of fluorinated alcohol seems to play a role in the oxidation of thioanisole into methyl phenyl sulfoxide and in the imino Diels−Alder between benzalaniline and butyl vinyl ether ($R^2 > 0.635$). It can be suggested that fluorinated alcohols form a complex in the transition state that is prevented by steric effect of tertiary HFAs. However, in both these reactions HFIP exhibited an outstanding effect, being far more potent than any other fluorinated alcohol; this effect cannot be imputed to the sole HBD ability, and some other factors are certainly involved. Finally, in the opening of epoxide by piperidine, $Ph(CF_3)CHOH$ and TFE were the most effective media, whereas HFIP completely inhibited the reaction by forming an H-bond adduct with piperidine in an irreversible fashion. No correlation could be found with the acceptor number, and the solvent parameters promoting this transformation remain unclear at this stage.

Conclusion

The results obtained in this study can be summarized as follows:

(i) Measurement in the liquid state revealed that Brønsted acidity of polyfluorinated alcohols is only connected to the number of CF_3 groups and is not affected by the structure and topology. Conversely, H-bond donor ability is very sensitive to steric hindrance, and this property decreases for tertiary fluorinated alcohols (HFAs).

(ii) However, tertiary HFAs are able to form adducts with secondary and tertiary amines, and crystal structures have been examined. The competition between acidity and HBD appeared to be driven by steric factors, where the bulky $Ph(CF_3)_2COH$ seemed to exhibit acid properties, while other HFAs behave as H-bond donors.

(iii) In the H-bond adducts with secondary amines, crystal structures showed that, in the solid state, HFAs behave both as H-bond donors and acceptors with different conformations according to the strength of the H-bonds.

(iv) For three typical test reactions in which fluorinated alcohols exerted a booster effect (sulfide oxidation with hydrogen peroxide, oxirane opening with piperidine, and imino Diels−Alder), correlation between rate constants and HBD or pK_a showed that acidity cannot be reasonably involved. For sulfoxidation and imino Diels−Alder, HFIP was by far the best solvent. Although H-bond donation ability seems to have a beneficial effect, the reaction promotion cannot be imputed to this parameter only. Conversely, in the opening of epoxide with piperidine, trifluorinated alcohols gave the best results, and further studies with other nucleophiles will be performed to unveil the factors involved.

Experimental Section

1,1,1-Trifluoro-2-(trifluoromethyl)pent-4-en-2-ol ($Pr(CF_3)_2COH$)[37]. A round-bottom flask was charged with $All(CF_3)_2COH$ (10 g, 48 mmol) and Pd/C (1 g). A hydrogen balloon (1 atm) was added, and the reaction mixture was left under stirring at room temperature. After 18 h, the mixture was filtered and the product was distilled (bp = 97 °C, lit. bp = 98 °C[37]) to afford $Pr(CF_3)_2COH$ as a colorless liquid (9.1 g, 90% yield). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.02 (t, J = 7.1, 3H), 1.60 (sext, J = 7.1, 2H), 1.95 (t, J = 7.1, 2H), 3.09 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 15.4, 32.6, 76.5 (hept, J = 28.5), 123.3 (q, J = 287.6). ^{19}F NMR ($CDCl_3$, 188 MHz), δ: −77.6. APCI m/z (relative intensity): 209 $[M - H]^-$ (100%), 419 $[2M - H]^-$ (60%).

General Procedure for the Preparation of the Fluorinated Alcohol-Amine Adducts. A round-bottom flask was charged with the amine (5 mmol) and the fluorinated alcohol (25 mmol) was added. The mixture was left at room temperature for 2 days, and the crystals formed were filtered and crystallized.

HFIP-Piperazine Adduct. White crystals; crystallized from toluene; mp = 79 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.87 (s, 8H), 4.27 (s, 3H), 4.32 sept, J = 6.3, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 45.5, 69.3 (sept, J = 32.9), 122.0 (q, J = 281.0). ^{19}F NMR ($CDCl_3$, 188 MHz): δ −76.1 (d, J = 6.3). Anal. Calcd for $C_{10}H_{14}F_{12}N_2O_2$: C, 28.45; H, 3.34; N, 6.63. Found: C, 28.34; H, 2.98; N, 6.74.

$All(CF_3)_2COH$-Piperazine Adduct. White crystals; crystallized from light petroleum ether; mp = 62 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.66 (d, J = 7.7, 4H), 2.82 (s, 8H), 4.3 (s, 4H), 5.21 (m, 2H), 5.28 (m, 2H), 5.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.4, 45.9, 75.6 (sept, J = 28.5), 120.8, 123.4 (q, J = 287.6), 129.1. ^{19}F NMR ($CDCl_3$, 188 MHz): δ −76.6 (s). Anal. Calcd for $C_{16}H_{22}F_{12}N_2O_2$: C, 38.26; H, 4.41; N, 5.58. Found: C, 38.11; H, 4.19; N, 5.63.

$Ph(CF_3)_2COH$-Piperazine Adduct. White crystals; crystallized from toluene; mp = 78 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.85 (s, 8H), 4.95 (s, 4H), 7.45 (m, 6H), 7.75 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 45.5, 77.2 (sept, J = 28.5), 123.2 (q, J = 287.6), 126.8, 128.3, 129.8, 131.3. ^{19}F NMR ($CDCl_3$, 188 MHz): δ −75.4 (s). Anal. Calcd for $C_{22}H_{22}F_{12}N_2O_2$: C, 46.00; H, 3.86; N, 4.88. Found: C, 45.96; H, 3.72; N, 4.87.

$Pr(CF_3)_2COH$-DABCO Adduct. White crystals; crystallized from light petroleum ether; mp = 79 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95 (t, J = 7.5, 3H), 1.55 (m, 2H), 1.80 (m, 2H), 2.75 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 15.5, 46.0, 77.0 (sept, J = 28.5), 123.7 (q, J = 287.9). ^{19}F NMR ($CDCl_3$, 188 MHz): δ −76.8 (s). Anal. Calcd for $C_{18}H_{28}F_{12}N_2O_2$: C, 40.61; H, 5.30; N, 5.26. Found: C, 40.71; H, 5.49; N, 5.26.

Methyl Phenyl Sulfoxide[38]. A 5 mL round-bottom flask was charged with thioanisole (124 mg, 1 mmol), 4-nitrotoluene (internal standard, 0.1 mmol, 14 mg), and the solvent (2 mL) and then cooled to 0 °C. Hydrogen peroxide (15% aq soln; 226 mg, 1 mmol), previously cooled at 0 °C, was then added. The reaction mixture was left under stirring at 0 °C. Aliquots (1 μL) were takenz at regular intervals and immediately analyzed by GC. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.72 (s, 3H), 7.52 (m, 3H), 7.65 (m, 2H).

1-Phenoxy-3-(piperidin-1-yl)propan-2-ol[39]. A solution of 1, 2-epoxy-3-phenoxypropane (150 mg, 1 mmol) and *tert*-butylbenzene (internal standard, 0.1 mmol, 13 mg) in the solvent (0.5 mL) was cooled at 0 °C and then added to the amine (1 mmol) charged in a 5 mL round-bottom flask. The reaction mixture was left under stirring at 0 °C. Aliquots (10 μL) were taken at regular intervals, dissolved in $CDCl_3$ (0.6 mL), and analyzed by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45−1.75 (m, 6H), 2.35−2.70 (m, 6H), 3.2 (br s, 1H), 3.9−4.2 (m, 3H), 6.9 (m, 3H), 7.3 (m, 2H).

***cis*-4-Butoxy-1,2,3,4-tetrahydro-2-phenylquinoline[40].** A 5 mL round-bottom flask was charged with benzalaniline (118 mg, 1 mmol) and dichloromethane (internal standard, 0.15 mmol, 13 mg) in the solvent (1 mL) and cooled to 0 °C. A solution of butyl vinyl ether (400 mg, 4 mmol) in the same solvent (1 mL) was then added. The reaction mixture was left under stirring at 0 °C. Aliquots (10 μL) were taken at regular intervals, dissolved in $CDCl_3$ (0.6 mL), and analyzed by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.00 (t, J = 7.2, 3H), 1.45−1.57 (m, 2H), 1.62−1.72 (m, 2H), 2.04−2.13 (m, 1H), 2.44−2.51 (m, 1H), 3.52−3.75 (m, 2H), 3.98 (br s, 1H), 4.58 (dd, J = 11.7, J = 2.5, 1H), 4.86 (dd, J = 10.6, J = 5.7, 1H), 6.57 (dd, J = 8.1, J = 1.0, 1H), 6.80 (td, J = 7.5, J = 1.0, 1H), 7.11 (td, J = 7.5, J = 1.0, 1H), 7.34−7.53 (m, 6H).

Acknowledgment. The European Union within the EST network BIOMEDCHEM (MEST-CT-2005-020580) is gratefully acknowledged for the Ph.D. grant of D.V. and financial support. The Region Ile-de-France and the GIS-Fluor are also thanked for support. Central Glass is acknowledged for the kind gift of HFIP, $All(CF_3)_2COH$. and $Ph(CF_3)_2COH$. M. Luçon (Univ. Nantes), Drs. C. Gueutin and J. Rodrigo de Losada (Univ. Paris Sud) are thanked for their kind help.

Supporting Information Available: Full experimental details for the measurements of pK_a, β, $E_T(30)$, AN parameters of alcohols, rate constants, correlations, ^{1}H and ^{13}C NMR spectra and crystallographic information files for the fluorinated alcohols-amine adducts (CIF files and crystal structure data). This material is available free of charge via the Internet at http://pubs.acs.org.

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