Hydrogen Bonding

Influence of Fluorination on the Conformational Properties and Hydrogen-Bond Acidity of Benzyl Alcohol Derivatives

Elena Bogdan,[a] Guillaume Compain,[b] Lewis Mtashobya,[b] Jean-Yves Le Questel,[a] François Besseau,[a] Nicolas Galland,[a] Bruno Linclau,[b] and Jérôme Gratont

Abstract: The effect of fluorination on the conformational and hydrogen-bond (HB)-donating properties of a series of benzyl alcohols has been investigated experimentally by IR spectroscopy and theoretically with quantum chemical methods (ab initio (MP2) and DFT (MPWB1K)). It was found that o-fluorination generally resulted in an increase in the HB acidity of the hydroxyl group, whereas a decrease was observed upon o,o’-difluorination. Computational analysis showed that the conformational landscapes of the title compounds are strongly influenced by the presence of o-fluorine atoms. Intramolecular interaction descriptors based on AIM, NCI and NBO analyses reveal that, in addition to an intramolecular OH···F interaction, secondary CH···F and/or CH···O interactions also occur, contributing to the stabilisation of the various conformations, and influencing the overall HB properties of the alcohol group. The benzyl alcohol HB-donating capacity trends are properly described by an electrostatic potential based descriptor calculated at the MPWB1K/6-31+G(d,p) level of theory, provided solvation effects are taken into account for these flexible HB donors.

Introduction

The fluorination of organic compounds to modify their properties has a major impact in many chemistry-related fields such as medicinal chemistry,[1] agrochemistry,[2] materials science[3] and crystal engineering.[4] The high fluorine electronegativity, with the resulting highly polarised C···F bond and nonpolarisable fluorine lone pairs, is at the origin of a multitude of effects resulting from the introduction of one or more fluorine atoms.[5] Fundamental studies aimed at improving our understanding of the effects of fluorination in organic compounds are still ongoing. Significant and sometimes unexpected consequences of fluorination on the physical and chemical properties of adjacent functional groups[6] or regarding C···F mediated inter- and intramolecular interactions, continue to be described.[7] Organofluorine chemists are especially captivated by the ability of fluorine to behave as a hydrogen-bond (HB) acceptor,[8] and it is now accepted, through key contributions from Vulpetti and Dalvit,[9] as well as Laurence and co-workers,[10] that organofluorine can act as a weak HB acceptor. Furthermore, seminal works by Vasella, Bernet and Gouverneur have highlighted OH···F intramolecular hydrogen bonds (IMHBs) by using NMR techniques.[10]

Recently, we have experimentally determined HB-donating capacities (or HB acidities) of fluoroalcohols through the adaptation of an established[11] procedure by using FTIR spectroscopy.[12] The insights revealed in this study, for example the influence of OH···F IMHB interactions on alcohol hydrogen-bond properties, pointed out the need for comprehensive investigations on a wide range of fluorinated compounds to probe the effects of fluorine on HB interactions in diverse chemical environments, and to optimise HB property prediction tools.

Herein we report on the influence of ortho-fluorination on the hydrogen-bond-donating capacity of benzyl alcohols through a combined experimental and theoretical approach. The experimental HB acidities (pK\text{\textsubscript{A}}) are presented and rationalised by quantum chemistry calculations, including detailed conformational analysis, to allow insights to be gained on the influence of the fluorine atom(s) on the conformational features of substituted benzyl alcohols. Atoms In Molecules (AIM),[13] Noncovalent Interaction (NCI)[14] and Natural Bond Orbital (NBO)[14] analyses have been performed to provide an accurate description of the different IMHB interactions occurring in the various compounds. In the final part of this work, we show the feasibility of accurately predicting the HB acidity values of the substrates involved by using an electrostatic-based descriptor ($\mu$) computed for the various molecules.
Benzyl alcohols are common building blocks of drugs (e.g., antimuscarinic drugs (fesoterodine), neuroprotective agents, anticonvulsant agents (gastrodin)), and their conformational preferences are still a matter of debate.[16]

An interesting effect of fluorine substitution has been reported for ring-hydroxylated biogenic amines such as norepinephrine (Figure 1). Depending on the position of the fluorine, the analogues were shown to have markedly different agonist properties.[17] Intramolecular hydrogen-bonding effects and/or dipole-dipole repulsions between the COH and CF moieties have been considered as factors that could result in conformational preferences that are favourable for binding to α- or β-adrenergic receptors.[17–18] A more recent explanation involves preferential orientation of the C–F bond of both 2F-NE and 6F-NE to an asparagine residue, resulting in a different presentation of the aromatic alcohol groups.[19]

![Figure 1. Fluorinated norepinephrine analogues with different agonist activities.](image)

**Results and Discussion**

**Synthesis**

The synthesis of substrates 1b, 2b, 6b and 6c (Figure 2) is detailed in the Supporting Information. All other compounds were purchased. Compounds 4c, 5c, 9a and 9b were only investigated computationally.

**Conformational IR Analysis of the Hydroxyl Stretching Region**

The experimental data set investigated in this study is composed of eight reference benzyl alcohols 1a–8a, eight mono-fluorinated 2-fluorobenzyl alcohols 1b–8b and five difluorinated 2,6-difluorobenzyl alcohol derivatives 1c–3c, 6c and 7c. The νOH bands of the title compounds at 25°C in dilute CCl4 solutions are shown in Figure 3.

For most of the nonfluorinated benzyl alcohols, the νOH region is rather complex, with two bands separated by ca. 20 cm⁻¹, which is indicative of different conformations. A deconvolution of the absorption spectra in this region has therefore been carried out; the resulting νOH stretching frequencies are reported in Table 1. For series a, without any ortho substituent, the low-frequency band νOH(I) peaked at 3616 cm⁻¹ irrespective of the nature of the meta substituent. The position of the νOH(II) absorption band is measured at a slightly higher frequency, 3629 cm⁻¹ for 1a and 2a, and 3635 cm⁻¹ for 3a–6a (Figure 3A, Table 1). However, their relative intensity is dependent on the substitution: whereas νOH(II) is shown to be the main band, the contribution of νOH(I)

![Figure 2. Chemical structures of the benzyl alcohol derivatives under study.](image)

![Figure 3. IR spectra in the νOH stretching region of A) benzyl alcohols, B) 2-fluorobenzyl alcohol and C) 2,6-difluorobenzyl alcohols.](image)
With the nitro-derivative 6a, the band at 3635 cm$^{-1}$ shows the largest contribution. Only one conformer absorbing at low frequency (3617 cm$^{-1}$) is observed in the presence of a methyl group in the $\alpha$-position (7a), whereas when the methyl group is in the $\alpha$-position (8a) (not shown), the band profile is similar to that of 1a.

Within series b (Figure 3B), the $\nu_{OH}$ bands are slightly blue-shifted by ca. 3–10 cm$^{-1}$, and are less resolved. The $\nu_{OH}$ contribution appears to be higher than in series a.

With the 2,6-difluoro series c (Figure 3C), only one stretching $\nu_{C=O}$ band is observed and its half-width is significantly smaller than in compounds a and b. This feature might indicate that the conformational flexibility around the hydroxyl moiety is lost in these derivatives, which would reduce the number of existing conformers with respect to series a and b. Similarly, compound 8b, having two $\alpha$-substituents, exhibits a $\nu_{OH}$ stretching band with a small half-width (not shown), closer to the profile of compounds of series c than to the series b.

### Computational Analysis

**Introduction: Conformational Studies**

The conformational properties of benzyl alcohol, described either through experimental or theoretical studies, are still a matter of debate, whereas they seem to be more established for benzylic compounds, $\text{C}_7\text{H}_8\text{CH}_2\text{X}$. When X is an alkyl group or a halide, the $\text{C}-\text{C}-\text{C}-\text{X}$ dihedral angle was shown to be 90°, with the C–X bond in a plane orthogonal to the benzene ring.$^{[20]}$ This **perpendicular** conformation minimises steric repulsive effects between the $\text{-CH}_2\text{X}$ group and the phenyl ring. If the X group contains a triple bond (ethinyl or cyanide), the dihedral angle is near 0°, with the C–C bond lying in the plane of the phenyl ring.$^{[21]}$ The preference for this **planar** structure has been rationalised by the presence of a stabilising $\text{CH}^-\pi$ HB interaction between an aromatic CH bond and the triple bond $\pi$-electron cloud.

Although benzyl alcohol has been the subject of extensive experimental and theoretical studies,$^{[16a,22]}$ there remains a degree of uncertainty about the number of stable conformers and their relative stabilities. The hydroxymethyl side chain is flexible and it is generally accepted that several conformers simultaneously exist in the gas phase, a situation similar to benzylamine and its derivatives.$^{[23]}$ The main suggested conformers of benzyl alcohol derivatives, defined by the $\psi (\text{C}_{\text{ipso}}\text{C}_{\text{ipso}}\text{C}_0)$ and $\chi (\text{C}_{\text{ipso}}\text{C}_0\text{OH})$ dihedral angles, are the gauche_gauche ($g, g$, also sometimes referred to as gauche_gauche, cis), gauche_trans ($g, t$), planar (pl) and perpendicular (perp) conformers (Figure 4a,b and the Supporting Information for further details). In monofluorinated benzyl alcohols, the introduction of a methyl group at the C$_3$ carbon was found to have a significant influence on the preferred conformation compared with 2-fluoro benzyl alcohol, preferentially showing an OH···F IMHB,$^{[24]}$ to 2-fluoro-$\alpha$-methylbenzyl alcohol,$^{[25]}$

**Table 1. Experimental spectroscopic features, $\nu_{C=O}$, $\nu_{OH}$, and $\Delta\nu_{C=O}$ and $\Delta\nu_{OH}$ properties of benzyl alcohols under study.**

| Entry | $\nu_{C=O}$ | $\nu_{OH}$ | $\gamma_{OH}$ | $\Delta\nu_{C=O}$ | $\Delta\nu_{OH}$ |
|-------|-------------|-------------|---------------|-------------------|-----------------|
|       | [cm$^{-1}$] | [cm$^{-1}$] | [L mol$^{-1}$ cm$^{-1}$] | [kJ mol$^{-1}$] | [cm$^{-1}$] |
| 1a    | 3629        | 3616        | 73            | 1.03             | -5.9           | 193            |
| 1b    | 3639        | 3624        | 75            | 1.16             | -6.6           | 207            |
| 1c    | $^{\text{abi}}$ | 3627        | 117           | 0.94             | -5.4           | 222            |
| 2a    | 3629        | 3616        | 76            | 1.06             | -6.1           | 197            |
| 2b    | 3639        | 3623        | 74            | 1.21             | -6.9           | 208            |
| 3a    | 3635        | 3616        | 72            | 1.32             | -7.5           | 205            |
| 3b    | 3638        | 3623        | 66            | 1.48             | -8.4           | 224            |
| 4c    | $^{\text{abi}}$ | 3626        | 107           | 1.21             | -6.9           | 229            |
| 4a    | 3635        | 3616        | 70            | 1.46             | -8.3           | 231            |
| 4b    | 3638        | 3622        | 78            | 1.70             | -9.7           | 241            |
| 5a    | 3635        | 3616        | 70            | 1.48             | -8.4           | 213            |
| 5b    | 3638        | 3622        | 77            | 1.67             | -9.5           | 240            |
| 6a    | 3635        | 3616        | 73            | 1.79             | -10.2          | 245            |
| 6b    | 3636        | 3621        | 88            | 1.98             | -11.3          | 259            |
| 6c    | $^{\text{abi}}$ | 3626        | 123           | 1.69             | -9.6           | 276            |
| 7a    | $^{\text{abi}}$ | 3617        | 86            | 0.96             | -5.5           | 193            |
| 7b    | 3630        | 3619        | 80            | 1.05             | -6.0           | 201            |
| 7c    | $^{\text{abi}}$ | 3622        | 115           | 0.70             | -4.0           | 206            |
| 8a    | 3637        | 3619        | 73            | 0.99             | -5.7           | 197            |
| 8b    | $^{\text{abi}}$ | 3624        | 110           | 0.94             | -5.4           | 215            |

[a] Calculated from the $\nu_{C=O}$ value. [b] Not observed.

The X group contains a triple bond (ethinyl or cyanide), the dihedral angle is near 0°, with the C–C bond lying in the plane of the phenyl ring.$^{[21]}$ The preference for this **planar** structure has been rationalised by the presence of a stabilising $\text{CH}^-\pi$ HB interaction between an aromatic CH bond and the triple bond $\pi$-electron cloud.

Figure 4. Benzyl alcohol conformations: a) Description of the $\phi$ and $\chi$ dihedral angles of interest. b) Main conformations encountered in the benzyl alcohol structures in Newman representation along the C$_{ipso}$C$_{ipso}$C$_0$ bond. c) Definition of proximal, distal and chelated gauche conformations for substituted benzyl alcohols. See the Supporting Information for detailed aspects of the nomenclature used.
stabilised with an OH⋯π interaction. Theoretical calculations in the gas phase generally attribute the absolute minimum to the gauche_gauche conformation.\(^{[16a,b,d]}\) However, depending on the theoretical methods and experimental techniques selected, different geometries have been proposed for the first local minima\(^{[16a,22]}\) and the situation is even more challenging in the solution state. In a previous study based on IR spectroscopy in CCl\(_4\) and Cs\(_2\), solutions, the presence of gauche and planar conformations was suggested, but the perpendicular conformation could not be excluded.\(^{[22a]}\)

Hence, to support our experimental H\(_2\) measurements, a detailed conformational analysis of the benzyl alcohol derivatives was required. Following the recommendations of Basso,\(^{[26]}\) our analysis involved a polarisable continuum model (PCM) explicitly describing the hydrogen atoms to take into account the solvation effects on the conformational equilibrium of benzyl alcohol derivatives at the MP2/6-311+ + G(2d,p) level of theory, after optimisation at the IEFPCM-MPWB1K/6-31 + G(d,p) level. The results are given in Tables 2–4, wherein the theoretical frequencies of the \( \nu_{OH} \) stretching vibrations are also listed, and details of the computed relative free energies and conformer populations are provided in the Supporting Information (Table S1).

### Table 2. Calculated populations \( p_i \) of the conformers of nonfluorinated benzyl alcohol derivatives (1a–9a) in CCl\(_4\) medium at the IEFPCM-MP2/6-311+ + G(2d,p) level of theory. Optimised dihedral angles \( \phi \) (C\(_{ortho}\),C\(_{meta}\),C\(_{ortho}\)) and \( \gamma \) (C\(_{ortho}\),C\(_{ortho}\)) characterising the hydroxyl moiety orientation and calculated \( \nu_{OH} \) stretching frequencies (IEFPCM-MPWB1K/6-31 + G(d,p)).\(^{[26]}\)

| Compound | Conformer | \( p_i [\%] \) | \( \psi [\%] \) | \( \chi [\%] \) | \( \nu_{OH} [\text{cm}^{-1}] \) |
|----------|-----------|----------------|----------------|----------------|------------------|
| 1a | \( g-g \) | 82 | 33 | 60 | 3616 |
| | \( pl \) | 18 | 0 | 180 | 3646 |
| 2a | \( g-g \) | 61 | 26/36 | 59/61 | 3616 |
| | \( p-g \) | 21 | 10/15 | 173/174 | 3645 |
| | \( pl \) | 18 | 0 | 180 | 3645 |
| 3a | \( g-g \) | 57 | 28/29 | 63/64 | 3618 |
| | \( pl \) | 43 | 0/5 | 177/180 | 3646 |
| 4a | \( g-g \) | 82 | 26/31 | 64/66 | 3618 |
| | \( pl \) | 18 | 0/8 | 175/180 | 3645 |
| 5a | \( g-g \) | 74 | 21 | 65/67 | 3618 |
| | \( pl \) | 26 | 0/2 | 179/180 | 3645 |
| 6a | \( g-g \) | 68 | 23/30 | 68/69 | 3619 |
| | \( pl \) | 32 | 0 | 180 | 3645 |
| 7a | \( g-g \) | 92 | 36/39 | 57/61 | 3609 |
| | \( pl \) | 8 | 19 | 174 | 3630 |
| 8a | \( g-g \) | 78 | 10/69 | 55/66 | 3619 |
| | \( pl \) | 14 | 0 | 180 | 3646 |
| 9a | \( g-g \) | 8 | 66 | 174 | 3626 |
| | \( g-g \) | 89 | 61/87 | 47/58 | 3615 |
| | \( pl \) | 8 | 80 | 173 | 3618 |
| | \( perp \) | 3 | 22/63 | 174/176 | 3640/3623 |

[a] See Figure 4 for conformation definitions. When relevant, proximal/distal, anti/syn and E/Z conformations are grouped together. The detailed computed relative free energies and conformer populations are provided in the Supporting Information (Table S1). [b] Scaled by 3616/3972 = 0.91, the ratio between the calculated and the experimental \( \nu_{OH} \) value for benzylalcohol \( g-g \) conformer.

### The Various Substituted Benzyl Alcohol Conformations

It should be noted that additional gauche and planar conformations can be distinguished when substitution in the ortho and/or meta position of the phenyl ring occurs. The proximal and distal conformers are therefore defined (Figure 4(c)) when the hydroxyl group is oriented towards or at the opposite side of the substituent (with the ortho substitution prevailing over meta substitution, and with \( \alpha \)-fluorine prevailing over \( \alpha \)-alkyl groups). With \( \alpha,\beta \)-difluorination, distal/proximal refers to the position of the meta substituent. We also distinguish a \( g\_chel \)
Table 4. Calculated populations \( p_i \) of the conformers of difluorinated benzyl alcohol derivatives (1–c, 7–a) in CCL medium at the IEFPCM-MP2/6-311+G(2d,p) level of theory. Optimised dihedral angles \( \phi \) (\( \text{C}_{\text{OMe}}-\text{C}_{\text{O}}-\text{C}_{\text{H}} \) and \( \text{C}_{\text{OMe}}-\text{C}_{\text{OH}} \) characterising the hydroxyl moiety orientation and \( \nu_{\text{OH}} \), stretching frequencies (IEFPCM-MPW1 K/6-31+G(d,p)).

| Compound | Conformer | \( p_i \) [%] | \( \phi \) [°] | \( \chi \) [°] | \( \nu_{\text{OH}} \) [cm\(^{-1}\)] |
|----------|-----------|--------------|-------------|-------------|------------------|
| 1c       | \( g_{\text{chel}} \) | 70           | 60          | 67          | 3618             |
|          | \( \text{perp}_t \)     | 39           | 89/91       | 179/180     | 3624             |
| 2c       | \( g_{\text{chel}} \) | 60           | 93/94       | 178/179     | 3624             |
|          | \( \text{perp}_t \)     | 35           | 59/63       | 67/69       | 3628/3635        |
| 3c       | \( g_{\text{chel}} \) | 62           | 59/63       | 67/69       | 3626/3636        |
|          | \( \text{perp}_t \)     | 33           | 93/94       | 178/179     | 3624             |
| 4c       | \( g_{\text{chel}} \) | 70           | 60/63       | 70/72       | 3618/3633        |
|          | \( \text{perp}_t \)     | 25           | 59/62       | 68/70       | 3628/3637        |
| 5c       | \( g_{\text{chel}} \) | 64           | 47/59       | 87/91       | 3624             |
|          | \( \text{perp}_t \)     | 48           | 93/94       | 178/179     | 3624             |
| 6c       | \( g_{\text{chel}} \) | 67           | 60/63       | 70/72       | 3618/3633        |
|          | \( \text{perp}_t \)     | 31           | 59/62       | 68/70       | 3628/3637        |
| 7c       | \( g_{\text{chel}} \) | 72           | 59/63       | 68/70       | 3624             |
|          | \( \text{perp}_t \)     | 48           | 93/94       | 178/179     | 3624             |

[a] When relevant, proximal/distal, anti/syn and E/Z conformations are grouped together. The detailed computed relative free energies and conformer populations are provided in SI (Table S1). (b) Scaled by 3616/3972 = 0.91, the ratio between the calculated and the experimental \( \nu_{\text{OH}} \) value for benzylalcohol \( g_{\text{chel}} \) conformer.

Table 4 shows the calculated populations of different conformers for the difluorinated benzyl alcohol derivatives. The table provides the optimized dihedral angles and the calculated stretching frequencies of the hydroxyl group. The conformers are categorized by their relative populations, with the most populated being \( g_{\text{chel}} \) at 70% and the least populated being \( \text{perp}_t \) at 35%. This indicates that the \( g_{\text{chel}} \) conformation is the most stable in this medium, followed by \( \text{perp}_t \) and \( g_{\text{chel}} \) conformations.

Conformational Analysis of Substituted Benzyl Alcohols

Within the series of nonfluorinated compounds 1a–9a (Table 2), two or three of the various conformations evoked above are found, depending on the studied structure. In all cases, the \( g_{\text{chel}} \) is systematically calculated to be the most populated conformation, though it is the absolute energetic minimum only for 1a, 4a, 6a, 7a and 9a. The other compounds (2a, 3a, 5a and 8a) show a planar geometry as the most stable conformation. Our calculations confirm therefore that the \( g_{\text{chel}} \) conformation is by far the most (in many cases even the only) populated of the possible gauche conformations. A perpendicular conformation is seen for 9a only.

The computed frequencies of the \( \nu_{\text{OH}} \) stretching vibrations show that all the \( g_{\text{chel}} \) conformers absorb at a lower frequency than the \( \text{pl}, \text{g}_t \) and \( \text{perp} \) forms. Therefore, the observed lower frequency absorption band was attributed to the \( g_{\text{chel}} \) conformer, with the higher frequency band containing the possible contribution of the other conformers. This analysis is in line with a previous attribution by Visser.[22a] No further discrimination can be achieved between the other conformers because of the close values of their IR absorptions. Note that a scale factor has been applied to all computed \( \nu_{\text{OH}} \) values to compare easily the experimental and the calculated \( \nu_{\text{OH}} \) values for the benzyl alcohol \( g_{\text{chel}} \) conformer.

Within the series of \( \alpha \)-monofluorinated compounds 1b–6b (Table 3 and Table S1 in the Supporting Information), the most abundant conformation is gauche, despite the planar structure is slightly more stable than the most stable gauche conformer, generally by approximately 1 kJ mol\(^{-1}\). This contrasts with a previous study dealing with 2-fluorobenzyl alcohol 1b, for which the planar conformation was not identified as a major conformer by MW spectroscopy and MP2 calculations.[24b] For the \( \alpha \)-monofluorinated secondary benzyl alcohol 7b, the planar conformation does not feature in the low-energy conformational landscape. In its main low-energy structures, the CHOH–CH\(_2\) bond is perpendicular to the plane of the phenyl ring, similar to the major ethyl benzene conformation and as found previously in the gas phase by MW spectroscopy.[23] In addition, approximately 10% of the conformers have both the methyl and the hydroxyl groups in the gauche position. It is interesting to note that, apart from the chelated conformer, there is little preference for fluorene position: the proximal and distal populations are not significantly different. For the \( \alpha \)-fluoro-\( \alpha \)-alkyl substrates 8b and 9b, the calculations predict only proximal gauche conformations. Presumably, steric hindrance is also a significant factor for 8b–9b. In all cases, the gauche conformations overwhelmingly display a \( \chi \)-angle of approximately 60° (i.e., \( g_{\text{chel}} \)), whereas \( \text{pl} \) and \( \text{perp} \) conformations display a \( \chi \)-dihedral angle of 180°.

Notably, all the planar conformations have a distal orientation, with a \( \chi \)-angle of approximately 180°. Proximal planar conformations, with \( \chi = 180^\circ \), are not stabilised, presumably because of a repulsive interaction between the O and F atoms. From an IMHB perspective, one would expect to observe proximal planar conformations, with \( \chi = 0^\circ \). However, a geometrical relaxation systematically leads to a gauche conformation (\( g_{\text{chel}} \)) for which a short H–F distance can be measured. Within series b, this distance varies from 2.166 to 2.317 Å; that is, 10 to 16% shorter than the sum of fluoride and hydrogen van der Waals radii.[23] The contributions of this conformation to the whole population vary from 4% in 4b (with the \( \text{m}-\text{trifluoromethoxy} \) substituent) to almost 30% in 7b (\( \text{m}-\text{ethylbenzylalcohol} \)). In compound 8b (\( \alpha \)-methyl group), the chelated form represents only 10% of the population. Conversely, in 9b (\( \text{tert-butyl} \) substituent), \( g_{\text{chel}} \) (83%) is significantly favoured in comparison with the other conformations, probably because of the steric hindrance induced by this bulky substituent.

The computed frequencies of the \( \nu_{\text{OH}} \) stretching band are similar to those of series a. Indeed, the \( \text{pl} \) conformations are predicted to absorb at approximately 3640 cm\(^{-1}\) and the \( g_{\text{chel}} \) forms at approximately 3620 cm\(^{-1}\). In addition, the \( \nu_{\text{OH}} \) stretching vibration of the \( g_{\text{chel}} \) conformers absorbs at 3630 cm\(^{-1}\).
This can explain the shape of the experimental $\nu_{\text{OH}}$ bands, which display broad envelopes with no clear maxima, as opposed to three distinguishable bands.

The conformational features of series $\mathbf{c}$, with two ortho-fluorine atoms, eventually appear to be the simplest (Table 4). Consistent with the existence of only distal planar conformations for which there is a fluorine atom in the $o$-position, with $o,o'$-difluorination, no planar conformations are observed at all. The electronic repulsion between the lone pairs of the oxygen and fluorine atoms is expected to repel the hydroxyl group out of the aromatic plane. Hence, only gauche and perpendicular conformations are found, the energetically favoured one depending on the chemical nature of the substituent. In this series, the proportion of the OH–F $g^*_\text{chel}$ forms is much more important than in the $\mathbf{b}$ series (e.g., from 25% in $\mathbf{5c}$ to 70% in $\mathbf{1c}$). It is also interesting to compare the relative population of the proximal and distal chelated conformations. Indeed, from $\mathbf{2c}$ to $\mathbf{6c}$, the $g^*_\text{chel}$ conformers are slightly, but systematically, preferred over the $g^*_t\text{chel}$ conformers, indicating a difference in IMHB accepting capacity of the two ortho-fluorine atoms. Finally, it is noteworthy that, in most cases in the $\mathbf{c}$ series, the gauche conformations are systematically chelated, but $\mathbf{7c}$ also shows $g,g^*$ and $g,t$ conformers.

The $\nu_{\text{OH}}$ stretching vibrations for the various conformations of a given compound in series $\mathbf{c}$ are computed at closer wave-numbers than in series $\mathbf{a}$ and $\mathbf{b}$ (from 3612 to 3637 cm$^{-1}$ instead of 3606 to 3648 cm$^{-1}$). This suggests that these conformations absorb at approximately the same frequencies in the 2,6-difluorination derivatives, in agreement with the narrow bands observed experimentally, contrasting with the broad bands obtained for nonfluorinated and monofluorinated compounds.

**AIM and NCI Analysis**

The presence of intramolecular interactions, including a possible OH–F IMHB interaction, was investigated by AIM analysis. However, in some cases that have been described previously, the AIM theory has been shown to fail in identifying any bond-critical point (BCP) for an IMHB, whereas other theoretical and experimental features were consistent with the occurrence of such an interaction.$^{28}$ We have therefore complemented the AIM calculations by conducting an NCI analysis.

The difference in population between chelated and nonchelated gauche conformers for series $\mathbf{b}$ and $\mathbf{c}$ invited analysis. It was found that, for the relevant $g^*_\text{chel}$ conformations of these compounds, AIM and NCI analyses do confirm the occurrence of an intramolecular OH–F hydrogen bond. The electron density at the BCP, $\rho_{\text{BCP}}$, ranging from 0.010 to 0.015 e/bohr$^{-3}$, and the positive value of the Laplacian, $\nabla^2 \rho_{\text{BCP}}$, are consistent with an IMHB between the fluorne and the hydroxyl moieties for $g^*_\text{chel}$ conformations of the 2-fluorobenzyl alcohols (Table S2). For the 2,6-difluorinated benzyl alcohols, no significant difference between $\rho_{\text{BCP}}$ and $\nabla^2 \rho_{\text{BCP}}$ is found with respect to series $\mathbf{b}$, suggesting that the OH–F interaction strength is similar for the 2-fluoro- and 2,6-difluorobenzyl derivatives. Nevertheless, comparing the proximal and distal conformers, $\rho_{\text{BCP}}$ is generally found to be slightly higher when the IMHB involves the 6-fluoro (distal) rather than the 2-fluoro (proximal) atom. This suggests a slightly stronger interaction with the 6-fluorine atom. Moreover, the NCI analysis also shows, for the 2,6-difluorinated derivatives, that an additional C$_6$H–F attractive contribution occurs, as illustrated in Figure 5 with the example of the $\mathbf{1c}$ $g_{\text{chel}}$ conformer. This extra stabilising interaction is clearly not possible for the chelated monofluorinated benzyl alcohols. In addition, with two fluorine atoms in the ortho position in series $\mathbf{c}$, the $g,g$ conformations appear as $g_{\text{chel}}$ conformations, to optimise the attractive OH–F and C$_6$–F interactions and minimise the repulsive O–F interactions. This may explain the significant difference in population of the $g^*_\text{chel}$ structure between series $\mathbf{b}$ and $\mathbf{c}$.

**Figure 5.** NCI isosurface plots of $g^*_\text{chel}$ benzyl alcohol conformations of $\mathbf{1b,c}$ drawn with a reduced density gradient (RDG) value of 0.6 and the blue (attractive) green (van der Waals) red (repulsive) values ranging from $-0.02$ to 0.01 a.u. An attractive OH–F contribution is observed in $\mathbf{1b}$, and a weak additional C$_6$H–F interaction is found in $\mathbf{1c}$.

An estimation of the HB energy ($E_{\text{HB}}$), based on the potential energy density $V_\text{r}$ at the BCP, has been proposed previously$^{29}$ and was found to be 12 kJ mol$^{-1}$ in the case of CH–O IMHBs.$^{30}$ In the compounds under study, it appears that the energies of the IMHBs occurring between the fluoride and the hydroxyl groups are slightly larger, ranging from 12 to 19 kJ mol$^{-1}$ (Table S2). An examination of the computed $E_{\text{HB}}$ values for the various derivatives does not reveal any general trend indicating that a significant increase of HB energy occurs from monofluorinated (series $\mathbf{b}$) to difluorinated (series $\mathbf{c}$) benzyl alcohols. Nevertheless, comparing the proximal and distal conformers in series $\mathbf{c}$, the HB energy values are generally found to be slightly higher when the IMHB involves the 6-fluoro (proximal) rather than the 2-fluoro (proximal) atom. This suggests a slightly stronger interaction with the 6-fluorine atom.

In fact, many additional intramolecular interactions are revealed by the NCI analysis occurring besides or instead of the OH–F interaction, which may provide insight into how the different conformations are stabilised (Figure 6). For example, in the planar conformation of $\mathbf{1a}$ and $\mathbf{1b}$ (Figure 6(a)), an attractive C$_6$H–O–H interaction is found (Table S2), with a concomitant C–F repulsive contribution for $\mathbf{1b}$. For a hypothetical $p^F$ conformation, the NCI analysis reveals a rather large F–OH repulsion, which may explain why there is no $p^F$ conformation in series $\mathbf{b}$, and no planar conformation in series $\mathbf{c}$. For the gauche conformers (Figure 6(b)), an attractive C$_6$H–O–H interaction similarly stabilises the $g,g$ conformation. In addition, for $\mathbf{1b}$, the ortho-fluorination now provides a weak attractive van
der Waals C=H–F interaction (for the distal gauche). Conversely, the 1b $g'$ structure is destabilised by an O–F repulsion. Weak van der Waals C=H–F interactions also occur in the perpendicular forms of 1b and 1c (Figure 6(c)). These extra intramolecular interactions can also provide an explanation as to why the $g'$ conformers rarely occur in the various compounds. It is actually often found that starting from such a conformer, relaxation to a planar conformation to accommodate a stabilising CH–O interaction, or to a perpendicular conformation to minimise the O–F repulsion and favour van der Waals C=H–F interactions, occurs.

In most, if not all cases, there are a multitude of attractive and repulsive effects operating and it is difficult to explain population differences between rotamers based on simple comparisons of interactions.

NBO Calculations

A further analysis of the conformational preferences of benzyl alcohol derivatives was carried out through NBO calculations. Only the benzyl, m-fluorobenzyl and m-nitrobenzyl alcohol series with zero, one, and two ortho-fluorines (1a–c, 3a–c, 6a–c) were considered, each having zero, an intermediate, and a large m-substituent effect, respectively. The main $D_2^s$ interaction energies are gathered in Table S3 in the Supporting Information.

Considering the conformations exhibiting an OH–F IMHB, the interaction energies between the $n_1$ fluorine lone pairs and the $\alpha^*_C$ antibonding orbital are rather small (ca. 4 kJ mol$^{-1}$), and do not fundamentally differ from the monofluoro to the difluorobenzyl alcohols. A slight increase of the interaction energies is observed when the chelation occurs with the 6-fluoro substituent rather than with the 2-fluoro substituent. These trends are in reasonable agreement with the electron densities $\rho_{nb}$ and $E_{nb}$ calculated at the BCP, and further clarify why the chelated structures are not dominant in monofluorinated benzyl alcohols.

For the planar and perpendicular conformations, the $n_2\rightarrow\alpha^*_C$ interactions are rather weak, with $E_{nb}$ of 6–8 kJ mol$^{-1}$. In return, hyperconjugation occurs between the $a_{OH}$ and $\alpha_C$ orbitals (ca. 13 kJ mol$^{-1}$ for $a_{OH}\rightarrow\alpha^*_C$ and 8 kJ mol$^{-1}$ for $\alpha_C\rightarrow\alpha^*_p$). In addition, the weak $n_2\rightarrow\pi^*_C$ interaction stabilises the planar forms of series a and b slightly (ca. 3 kJ mol$^{-1}$), and an energetically equivalent $n_2\rightarrow\pi^*_O$ interaction also occurs in series b. Clearly, the aromatic system is also available to provide a stabilising interaction with the hydroxyl moiety. The charge transfer from the $\pi$ bonding orbitals to the $\pi_C\rightarrow\pi^*_O$ antibonding orbital shows the highest contributions (up to 30 kJ mol$^{-1}$), smaller $\alpha_{C-O}\rightarrow\pi^*_C$, $\alpha_{C-O}\rightarrow\pi^*_C$, and $\alpha_{C-C}\rightarrow\pi^*_C$ contributions being systematically found irrespective of the considered conformation.

For the gauche conformations, the $n_2\rightarrow\alpha^*_C$ interaction is significant, with $E_{nb}$ of 30 to 40 kJ mol$^{-1}$ in comparison with the planar and perpendicular conformations. This may explain the significant preference of the $g$ $g'$ configuration over the corresponding $g'$ conformation (see above). In addition, the $\pi_C\rightarrow\pi^*_C$ interactions are also significant, but, interestingly, only for the fluorinated derivatives ($E_{nb}$ of 20 to 30 kJ mol$^{-1}$ for series b, c, but <10 kJ mol$^{-1}$ for series a). In summary, numerous hyperconjugative interactions occur in the different conformers of fluorinated benzyl alcohols. If an OH–F IMHB indeed appears in some of the gauche conformers, it is clearly not a driving force for the conformational preference, with the $n_2\rightarrow\alpha^*_C$ interactions being at least of the same order of magnitude.

Main Conformational Features

To sum up this section, it is shown that the conformational preferences adopted by benzyl alcohols are significantly influenced by the presence of fluorine atom(s) in the ortho position. Without any fluorine, g $g'$ and pl conformers represent 80 to 100% of the relative populations in series a, with an attractive C=H–O interaction stabilising these conformations. An OH–F IMHB conformer, from 4 to 83%, appears in series b with the presence of one fluorine atom, decreasing the relative population of the $g$ $g'$ conformers, the pl population being almost unchanged. The g $g'$ and perp structures represent 100% of the population in most difluorinated benzyl alcohols. The stabilisation of the perp conformers is due to attractive C=H–F contacts occurring with both ortho-fluorine atoms, whereas an OH–F IMHB with one fluorine atom and a C=H–F interaction with the second fluorine concomitantly stabilise the g $g'$ structures. The second case is almost systematically preferred over the first.

Figure 6. NCI isosurface plots of benzyl alcohols 1a–c drawn with a reduced density gradient (RDG) value of 0.6 and the blue-green-red values ranging from –0.02 to 0.01 a.u. The pl and some $g$, $g'$ conformations show an attractive CH–O contribution, whereas a weak CH–F interaction is found in the perp and other $g$, $g'$ conformers.
HB Acidity of Benzyl Alcohols

Experimental HB Acidity Measurements

The HB-donating capacity of the alcohols was determined by using an IR method through complexation with a standard HB acceptor, N-methyl-2-pyrrolidinone (NMP) in CCl₄ at 25 °C (Scheme 1).[31] The decrease in intensity of the νₓOH band with increasing amount of NMP was measured, as well as the actual frequency shifts, ΔνₓOH, resulting from complexation with NMP in relation to the corresponding free νₓOH band. The former allows determination of the equilibrium constant of the reaction, expressed as the thermodynamic HB acidity value Kᴬᴴᵞ, and the latter is an indication of the relative strength of the hydrogen bond that is formed. Considering homogeneous families of compounds that do not exhibit additional specific effects (such as steric effects or IMHB), these two experimental parameters are generally well correlated, with ΔνₓOH then corresponding to a spectroscopic HB scale.[31]

The frequency shifts, ΔνₓOH, the measured pKᴬᴴльц, and the corresponding free energies of complexation, ΔGᴬᴴльц, are gathered in Table 1. An energetic range of approximately 7 kJ mol⁻¹ (1.3 pK units) is covered by the current data set.

Measurement of the Equilibrium Constants (Kᴬᴴльц)

The increase of the HB acidity, pKᴬᴴльц for the nonfluorinated benzyl alcohols (1a–6a) follows the increase in the electron-withdrawing substituent effects of R (H < MeO < F < CF₃ < OCF₃ < NO₂) in the meta position, αᵣᵣ.[32] Therefore, from the unsubstituted benzyl alcohol (1.03) to 3-nitrobenzyl alcohol (1.79), the HB acidity increase represents 4.3 kJ mol⁻¹. With the addition of one methyl group in the ortho- (8a) or in the α-position (7a), a slight decrease in pKᴬᴴльц is measured (0.2 or 0.4 kJ mol⁻¹, respectively).

Similar trends are observed (Figure 7) in the ortho-mono-fluorinated and ortho'-difluorinated series b and c, with respective energetic ranges of 5.3 and 4.2 kJ mol⁻¹. More interestingly, irrespective of the nature of the meta-substituent in series b, an increase of HB acidity values (between 0.13 and 0.24 pK units, from 0.5 to 1.4 kJ mol⁻¹) is measured upon monofluorination with respect to the nonfluorinated counterpart in series a. The fluorine atom plays its role of electron- withdrawing substituent, decreasing the electron density around the hydroxyl moiety. With a pKᴬᴴльц value of 1.98, 2-fluoro-5-nitrobenzyl alcohol (6b) is the strongest HB donor in the current experimental data set.

Conversely, further fluorination at the second ortho-position does not lead to a further increase of HB acidity (series c), highlighting a different behaviour. Indeed, a significant decrease is measured of 0.22 to 0.35 pK units in comparison with series b, rendering the pKᴬᴴльц values even weaker than for the nonfluorinated benzyl alcohols.

Scheme 1. Experimental determination of the HB-donating capacity of the benzyl alcohol derivatives.

Figure 7. Repartition of the pKᴬᴴльц acidity of substituted benzyl alcohols upon ortho-mono- and difluorination.

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The conformational analysis has shown that the OH–F IMHBS are not stronger in the difluorinated than in the monofluorinated derivatives, but rather that the chelated forms allow an optimal accommodation of the attractive OH–F and C,H–F and the repulsive O–F interactions, increasing their relative populations (compare the populations of g\textsuperscript{d, chel} conformers in b and c derivatives in Tables 3 and 4). This suggests that the decrease of HB acidity in series c could originate in the higher propensity of difluorinated derivatives to be intra-molecularly chelated. A rational tuning of HB acidity can therefore be realised in such benzyl alcohols by choosing monofluorination rather than difluorination, or vice versa.

A similar evolution is observed for the α-methylbenzyl alcohols, for which an expected HB acidity increase is measured (+0.09) upon monofluorination, whereas the presence of a second fluorine atom has a dramatic weakening effect (−0.35).

Interestingly, a decrease of HB acidity is observed upon fluorination in the case of compounds 8, rather than an increase, as found for the monofluorinated benzyl alcohols. The OH–F IMHB contributes to the HB acidity decrease, but not in a higher proportion than in the other monofluorinated benzyl alcohols because the relative population of the chelated forms are of the same order of magnitude (see below).

Measurement of the Frequency Shifts (Δν\textsubscript{OH})

The highest values of the frequency shifts, upon complexation with NMP, are measured with the 2,6-difluoro derivatives, compared with 2-fluoro and finally nonfluorinated benzyl alcohols. This trend would suggest that the ability of the studied compounds to act as HB donor with an external HB acceptor should increase from series a to series c. However, as illustrated in Figure 8, the pK\textsubscript{\text{exp}}/Δν(OH) correlation breaks down for the difluorinated benzyl alcohols, with a systematic underutilization of the experimental HB acidity for the observed IR shift. This illustrates that pK\textsubscript{\text{exp}} and Δν\textsubscript{OH} measure two different character-istics: the former is the equilibrium with an external acceptor, the latter is the strength of the hydrogen bond formed. The difluorinated benzyl alcohols lead to the strongest HBs with the acceptor, but the equilibrium reaction with NMP is disturbed by IMHB with the fluorine atoms. Compound 8b, with its α-methyl substituent, is also a significant outlier, probably for steric reasons. In other words, these downward deviations from the pK\textsubscript{\text{exp}}/Δν(OH) correlation line, observed in a very homogeneous set of benzyl alcohols, are a clear indication of a significant amount of IMHB conformations for the corresponding compounds.

Interestingly, the dashed line in Figure 8 corresponds to the calibration line established for a series of (non-benzyl)c hydroxyl-containing compounds in which an upward deviation of the benzyl alcohol 6a remained unexplained.\textsuperscript{[31]} It is now rationalised because the benzyl alcohol family finally does not exactly fit to the hydroxyl series.

Theoretical HB Acidity Estimation

The electrostatic potential V\textsubscript{a}(r), as proposed by Kenny,\textsuperscript{[15]} has recently been shown to be an appropriate descriptor to estimate the HB acidity of hydroxyl compounds\textsuperscript{[31]} including fluorohydrins.\textsuperscript{[6c]} We have shown in fluorinated cyclohexanols that the ability of the hydroxyl group to behave as a HB donor is weakened when an IMHB occurs, and a concomitant decrease of the V\textsubscript{a}(r) value is observed. It remained to be seen whether the flexible fluorinated benzyl alcohol structures under study could be described accurately by this theoretical descriptor. The initial data set\textsuperscript{[6c, 31]} were considered in the gas phase at the MPWB1K/6-31+G(d,p) level of theory. The V\textsubscript{a}(r) value was determined for each conformation, and the predicted pK\textsubscript{\text{exp}} value was then the weighted sum.

Such a treatment leads to a poor correlation between the computed V\textsubscript{a}(r) descriptor and the experimental pK\textsubscript{\text{exp}} HB acidity. Indeed, predicted values and experimental data differ by −0.31 to 0.22, with a sum square of 0.472 and a standard deviation of 0.152 (not shown).

Therefore, a significant improvement of the theoretical methodology is clearly necessary to obtain useful predicted values. At first, such an improvement may be obtained by including solvation effects in the calculations. Indeed, for a given compound, the population of the different conformers can change significantly in CCl\textsubscript{4} hence impacting on the weighed V\textsubscript{a}(r) value, and ultimately the predicted pK\textsubscript{\text{exp}} values (Table 5). The statistics are actually only slightly improved by using either the IEFPCM or the SMD (data not shown) continuum models, with the sum squares decreasing to 0.325 and 0.403, and the standard deviations to 0.127 and 0.142, respectively. Notably, the relative population of the OH–F chelated conformers of the 2,6-difluorinated derivatives are systematically smaller at the MP2/6-311 + + G(2d,p) level with respect to the MPWB1K/6-31 + + G(d,p) level, whereas they are slightly higher for the 2-fluorinated derivatives. As a consequence, the MP2 weighed V\textsubscript{a}(r) values are larger than the MPWB1K values in series c, leading to higher predicted pK\textsubscript{\text{exp}} values. Conversely, the V\textsubscript{a}(r) values are lowered in series b at the MP2 level, and hence
the predicted $pK_{\text{BAV}}$ values are also lowered. A further improvement of the HB acidity prediction is therefore obtained at the IEFPCM-MP2/6-311G(2d,p)//MPWB1K/6-31+G(d,p) level, with a sum square value of 0.280 and a standard deviation of 0.112. Figure 9 illustrates the improvement of the correlation between the experimental HB acidity and the computed $V_{\text{sr}}(r)$ descriptor according to the selected level of theory. However, although a statistical improvement is found with MP2 values, the MPWB1K values are to some extent more chemically reliable. Indeed, if the observed decrease of H-bond acidity upon $\alpha$-,$\alpha'$-difluorination of the phenyl ring is rather equivalently estimated with both methods, the increase upon $\alpha$-monofluorination is much more properly described at the DFT level. On the contrary, the MP2 method quasi-systematically predicts a decrease of $pK_{\text{BAV}}$ which is clearly opposite to the experimental trend. For this reason, the use of IEFPCM-MPWB1K/6-311G(d,p) results for the H-bond acidity prediction of fluorobenzylalcohols is recommended.

Rationalisation of HB Acidity Evolution Trends

It is interesting to observe the evolution of the $V_{\text{sr}}(r)$ descriptor for the different conformations (Table S1). Comparing equivalent conformations, there is a clear trend for the $V_{\text{sr}}(r)$ values to be higher for the fluorinated compounds than for the non-fluorinated compounds. This is an expected effect of the fluorine electronegativity on its surroundings. The planar conformations (which are always distal in series b) generally have the largest $V_{\text{sr}}(r)$ values, owing to the emphasised CH–O stabilising interaction depleting the electron density around the oxygen atom and hence around the hydroxyl hydrogen. The fluorine electron-withdrawing effect also operates in the periplanar formers show an increased HB-donating ability. Furthermore, in this series, the absence of any pl conformations (showing high $V_{\text{sr}}(r)$ values) further exacerbates this decrease of HB-donating ability.

Table S5. Predicted $pK_{\text{BAV}}$ HB acidity of benzyl alcohols, calculated from the weighted $V_{\text{sr}}(r)$ values, estimated from either MPWB1K or MP2 populations. The difference with the experimental value is given.

| Entry | MPWB1K/6-311G(d,p) + G(2d,p) | MP2/6-311G(2d,p) + G(d,p) |
|-------|-----------------------------|---------------------------|
|       | $pK_{\text{BAV}}$ (calc) | $\Delta pK_{\text{BAV}}$ | $pK_{\text{BAV}}$ (calc) | $\Delta pK_{\text{BAV}}$ |
| 1a    | 1.04                        | 0.01                      | 1.01                      | -0.02                   |
| 1b    | 1.16                        | 0.00                      | 1.00                      | -0.16                   |
| 1c    | 0.70                        | -0.24                     | 0.78                      | -0.16                   |
| 2a    | 1.07                        | 0.01                      | 1.06                      | 0.00                    |
| 2b    | 1.14                        | -0.07                     | 1.00                      | -0.21                   |
| 2c    | 0.59                        | -0.27                     | 0.74                      | -0.12                   |
| 3a    | 1.45                        | 0.13                      | 1.44                      | 0.12                    |
| 3b    | 1.60                        | 0.12                      | 1.47                      | -0.01                   |
| 3c    | 1.05                        | -0.16                     | 1.15                      | -0.06                   |
| 4a    | 1.60                        | 0.14                      | 1.59                      | 0.13                    |
| 4b    | 1.69                        | -0.01                     | 1.55                      | -0.15                   |
| 4c    | 1.20                        |                          | 1.28                      |                        |
| 5a    | 1.61                        | 0.13                      | 1.60                      | 0.12                    |
| 5b    | 1.81                        | 0.14                      | 1.70                      | 0.03                    |
| 5c    | 1.38                        |                          | 1.47                      |                        |
| 6a    | 1.92                        | 0.13                      | 1.91                      | 0.12                    |
| 6b    | 2.07                        | 0.09                      | 1.96                      | -0.02                   |
| 6c    | 1.61                        | -0.08                     | 1.69                      | 0.00                    |
| 7a    | 0.83                        | -0.13                     | 0.82                      | -0.14                   |
| 7b    | 0.92                        | -0.13                     | 0.84                      | -0.21                   |
| 7c    | 0.67                        | -0.03                     | 0.72                      | 0.02                    |
| 8a    | 1.03                        | 0.04                      | 0.89                      | -0.10                   |
| 8b    | 0.84                        | -0.10                     | 0.85                      | -0.09                   |
| 9a    | 0.67                        |                          | 0.63                      |                        |
| 9b    | 0.39                        |                          | 0.41                      |                        |

Figure 9. Distribution of the experimental $pK_{\text{BAV}}$ HB acidity of benzyl alcohols (circle) towards the weighed $V_{\text{sr}}(r)$ electrostatic descriptor (top: IEF-PCM/MP2/6-311G(2d,p)//MPWB1K/6-31+G(d,p) level, bottom: IEF-PCM/MPWB1K/6-31+G(d,p) level). The calibration line between these two parameters was previously established with a series of alcohols and phenols (diamond) and of fluorohydrins (triangle).
Conclusions

A series of 25 benzyl alcohol derivatives has been investigated by FTIR measurements and quantum chemical calculations, revealing the following trends in terms of conformational preferences and HB-donating capacities.

The \( g,g \) conformers are found to be the most populated minima within the series of nonfluorinated compounds (series \( a \)), with significant amounts of \( pl \) conformers. An attractive \( C_{6a},H\cdots O \) interaction is found to stabilise these conformations. The occurrence of \( g,t \) and \( perp \) conformations are found to be more marginal.

With the introduction of one fluorine atom in the \( ortho \)-position (series \( b \)), additional \( g,g \) conformers appear, identified as \( g,\text{chel} \), showing an \( OH\cdots F \) IMHB interaction. Their occurrence ranges from 4 to 83% at the expense of the nonchelated \( g,g \) conformers. The population of the \( pl \) conformers remains almost the same as in series \( a \).

With a second \( ortho \)-fluorine (series \( c \)), the \( g,\text{chel} \) and \( perp \) conformations become almost the only populated forms, whereas they were clearly less abundant in series \( a \) and \( b \). It is shown that both structures benefit from one (\( g,\text{chel} \)) or two (\( perp \)) attractive \( C,H\cdots F \) contacts, in addition to the \( OH\cdots F \) IMHB for the \( g,\text{chel} \) conformers.

As a result, the \( OH\cdots F \) IMHB is not found to be the main driving force in guiding the conformational preferences of 2-fluorobenzyl alcohols. The population of such chelated conformers is significant for 2,6-difluorobenzyl alcohols with the help of a \( C,H\cdots F \) interaction, but in competition with \( perp \) conformers in which two \( C,H\cdots F \) interactions occur.

An increase of HB acidity is quasi-systematically measured upon monofluorination, because of the electron-withdrawing effect of fluorine. This is nicely illustrated by the increase of the electrostatic potential descriptor \( V_c(r) \) values; all the conformers contributing to the HB-donating capacity increase, except the \( g,\text{chel} \) conformer, but its population is not important enough to have a significant influence on the overall HB-donating capacity.

The tremendous loss of HB-donating capacity upon difluorination, with the corresponding alcohol being an even weaker HB donor than its nonfluorinated counterpart, is less expected. The contribution of the \( perp \) structures in series \( c \) would lead to a further increase in HB acidity compared with monofluorinated benzyl alcohols, but this is overcompensated by the large amount of chelated conformers. Indeed, a significant lowering of the computed \( V_c(r) \) values for these chelated conformers characterises the HB acidity decrease of series \( c \).

The modulations of the HB acidity can therefore be easily rationalised by the \( V_c(r) \) descriptor, by considering its evolution along the conformational profile. Hence, our study provides methodology to either increase or decrease the HB-donating capacity of benzylcyclic alcohols by judicious fluorination.

Experimental Section

Chemicals: Carbon tetrachloride solvent, of spectroscopic grade, was kept for several days over freshly activated 4 Å molecular sieves before use. Commercial N-methyl-2-pyrrolidinone (99.5 ± % purity) was also stored over molecular sieves in the dark to prevent its deterioration. All benzyl alcohols were dried over 4 Å molecular sieves for the liquid compounds and over P4O10 during their sublimation for the solid compounds.

FTIR spectrometry measurements: The handling of all chemicals and their CCl4 solutions and the filling of the cells for IR measurements were performed in the dry atmosphere of a glove box at RT. IR spectra were recorded in carbon tetrachloride solutions with a Fourier transform spectrometer (Bruker Vertex 70) at a resolution of 1 cm\(^{-1}\). An Infrasil quartz cell (1 cm path length and thermostatted at 25.0 ± 0.2 °C by Peltier effect regulation) was used for the studies of HB complexation. The HB acidity, \( pK_{\text{HB}} \) of the benzyl alcohols under study were measured as described recently.\(^{[10]}\) The molar absorption coefficients, \( e_{\text{ave}} \), required for the equilibrium constant measurements, were calculated for each compound at the frequency of the absorption maxima. It is consequently an apparent \( \varepsilon_{\text{ave}} \) value because the alcohol concentration is distributed over several conformers. This conformation equilibrium is re-established after HB complexation because the shape of this free \( \varepsilon_{\text{ave}} \) stretching band is constant, as shown in Figure 10. This apparent value can therefore be safely used to calculate the concentration of free alcohol, and, as a result, the HB equilibrium constant.

Computational Procedures

All DFT calculations were performed with the D.01 version of the Gaussian 09 program applying default procedures, integration

![Figure 10](image-url)
The Agence Nationale de la Recherche (ANR), through the ANR JCJC "ProOFE" grant (ANR-13-JS08-0007-01), and the Engineering and Physical Sciences Research Council (EPSRC), grant EP/ K016938/1, are gratefully acknowledged for their financial support. The current work was granted access to the HPC resources of [CCRT/CINES/IDRIS] under the allocation c2014085117 made by GENCI (Grand Equipement National de Calcul Intensif) and HPC resources from ArronaxPlus (grant ANR-11-EQPX-0004 funded by the ANR). We thank the CCIP (Centre de Calcul Intensif des Pays de la Loire) for grants of computer time. We are grateful for EPSRC Core Capability Funding (EP/K039466/1). L.M. thanks Mkwawa University College of Education for financial support.

**Keywords:** hydrogen-bond acidity • benzyl alcohol • conformation analysis • fluorine

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