



Solution conformations for the flexible 1-chloro-1,1-difluoro-2-pentanol unveiled using multinuclear magnetic resonance



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ABSTRACT

The preferred conformations of a small polyfunctional molecule containing fluorine, chlorine and hydroxyl groups, the 1-chloro-1,1-difluoro-2-pentanol (**CDP**), were completely elucidated using ¹H, ¹³C and ¹⁹F NMR in three different solvents. While the Cl-C-C-O dihedral angle was asserted using coupling constant data for the diastereotopic fluorines, the Et-C-C-O torsional angle was analyzed by means of ¹H NMR spectra with selective irradiation of the diastereotopic hydrogens and fluorines. In addition, unusual couplings of the hydroxyl hydrogen with a diastereotopic hydrogen and fluorines provided information on the O-H orientation. The behavior of ¹J_{C,F} when the solvents varied agrees with a weak F...HO intramolecular hydrogen bond. These findings were corroborated, and the governing interactions rationalized with the aid of high level CCSD(T) theoretical calculations. Noteworthy, hyperconjugation involving the electron-acceptor σ*_{C-Cl} orbital drives the conformational equilibrium rather than the fluorine *gauche* effect.

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1. Introduction

The well-known Karplus¹ curve describing the angular dependence of the ³J_{H,H} coupling constant can be readily applied to determine the conformational preferences of substituted six-membered rings,² since only two conformers (axial and equatorial) are expected from the chair inversion and a ³J_{H,H} between antiperiplanar hydrogens is much larger than for *gauche* hydrogens. On the other hand, the conformation analysis using NMR data for acyclic systems is more challenging.

In addition, discussion on the conformer stabilities of small organic compounds are mostly focused on a few set of intramolecular interactions, due to the simplicity of the systems usually studied and the status of the knowledge on emerging interactions claimed as ruling forces of conformational equilibria. For instance, the main conformations of the textbook molecules ethane and butane used to be explained in terms of steric hindrance,³ but in the 2000's hyperconjugation was found to contribute at least partially for their rotational barriers.^{4–7} This finding was conclusive to explain the *gauche* effect in 1,2-difluoroethane and in other small

organofluorine compounds,^{8,9} i.e. the electrostatic repulsion between the fluorines should favor the anti-conformer, but this is overridden by stabilizing σ_{C-H} → σ*_{C-F} hyperconjugation and the *gauche* conformer is of lower energy. On the other hand, steric effects overweigh such an hyperconjugative interaction in the other 1,2-dihaloethanes.¹⁰

Intramolecular hydrogen bonding is another source of conformer stabilization, but it is usually explored separately from other interactions.^{11–13} 1-Chloro-1,1-difluoro-2-pentanol (**CDP**) is an acyclic organic compound containing bulky (chlorine and alkyl chain), electronegative (fluorine and oxygen), and hydrogen bond donor (a hydroxyl group) substituents capable of performing a variety of concomitant intramolecular interactions that can either stabilize or destabilize the three-dimensional molecular structure. Confrontation of so many interactions (steric, electrostatic and hyperconjugative interactions) as dictating factors of the conformational equilibrium within a single molecule is not a simple task. Most next generation inhalational anesthetics gather some of these structural features. Therefore, the design of performance molecules can benefit from the rationalization of the dominant interactions that rule the conformational preference of this small flexible compound. This is most usually demonstrated theoretically, but we now provide an NMR-based strategy both to determine and understand the conformational equilibrium of the model compound

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CDP in solution (Fig. 1).

2. Results and discussion

The Cl-C-C-O dihedral angle (ϕ_1) was first analyzed through ^{19}F NMR, whose signal assignment for the prochiral fluorines was supported by chemical shift calculations (Table 1). The experimental $^3J_{\text{H,F}}$ values in a non-polar solution (C_6D_{12}) are similar in magnitude (Table 1), thus arising two possibilities: 1) the fluorines have the same dihedral relationship with H-2, leading to a predominance of conformer **1**; 2) conformers **2** and **3** are similarly populated and are anticipated to have alternate small and large values for $^3J_{\text{H,F,pro-R}}$ and $^3J_{\text{H,F,pro-S}}$, in such a way that the average $^3J_{\text{H,F}}$ is of intermediate magnitude; in this case, the amount of **1** should not affect the $^3J_{\text{H,F}}$ values. Fortunately, the solvent effect on the actual $^3J_{\text{H,F}}$ values is instructive (Table 1), since one coupling constant increases with the solvent polarity (from 7.5 to 8.0 Hz), while the other decreases (from 7.6 to 6.7 Hz) on going from cyclohexane to acetonitrile solution. This is consistent with a shift from **2** to **3** and, therefore, the coupling constant that increases with the solvent polarity is likely to correspond to $^3J_{\text{H,F,pro-R}}$. Moreover, conformer **3** is anticipated to be the most polar conformer (more stabilized in polar solution), due to the mutual orientation of the local dipoles originated from the C-F and C-O bonds, as confirmed by calculations hereinafter. Since the $^3J_{\text{H,F}}$ dependence with the solvent is small (0.50–0.97 Hz from C_6D_{12} to CD_3CN), it follows that **1** should be importantly populated (especially in nonpolar solution), because the calculated difference in both $^3J_{\text{H,F}}$ between **1b** and **3b** is smaller than between **2b** and **3b** (Table 2). Therefore, an additional conformational shift from **1** to **3** is expected by increasing the solvent polarity. Interestingly, $^3J_{\text{H,F,pro-S}}$ decreases more with the solvent polarity than the $^3J_{\text{H,F,pro-R}}$ increases, indicating that specific solute-solvent interactions affect more a coupling constant than another. Overall, both possibilities mentioned above take place in the conformational equilibrium of CDP, i.e. conformer **1** should be importantly populated in a non-polar medium, while **3** increases in population with the solvent polarity.

Second, the Et-C-C-O dihedral angle (ϕ_2) was checked. The signals for the carbinolic and diastereotopic hydrogens *pro-S* and *pro-R* are very complex and strongly superposed, in such a way that

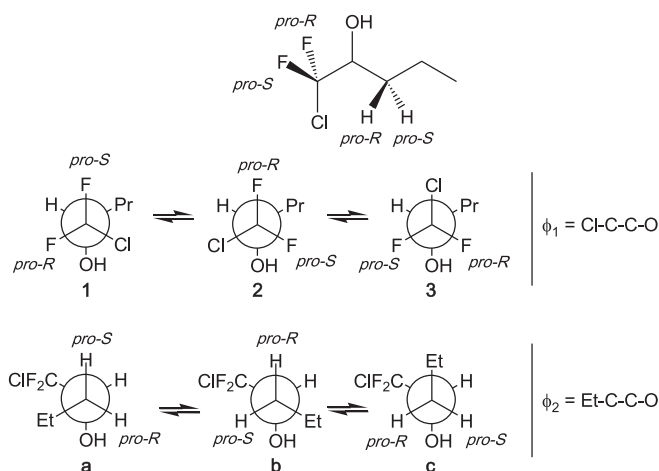


Fig. 1. Chemical structure of 1-chloro-1,1-difluoro-2-pentanol (CDP). The Newman projections (with the chiral center depicted arbitrarily) are shown in order to visualize the torsional angles ϕ_1 and ϕ_2 , as well as the relative orientations of the alkyl chain, chlorine, diastereotopic hydrogens and fluorines. The rotation around the C-O bond yields conformers further named with an apostrophe (').

Table 1

Dependence of experimental ^{19}F chemical shifts (ppm, relative to CFCl_3 , at 470.35 MHz) and $^3J_{\text{H,F}}$ coupling constants (Hz) with the solvent (10 mg mL^{-1}) for CDP:^a

Solvent	$\delta_{\text{F,pro-R}}$	$\delta_{\text{F,pro-S}}$	$^3J_{\text{H,F,pro-R}}$	$^3J_{\text{H,F,pro-S}}$
C_6D_{12}	−64.1	−66.3	7.50	7.65
CDCl_3	−63.5	−65.6	7.65	7.34
CD_3CN	−63.8	−65.3	8.00	6.68

^a The mean calculated $\delta_{\text{F,pro-R}}$ and $\delta_{\text{F,pro-S}}$ values for the three most stable conformers of CDP in the gas phase (**1b**, **2b** and **3b**) are −71.5 and −72.7 ppm, respectively, at the $\omega\text{B97X-D/6-311++G(d,p)}$ level.

the $^3J_{\text{H}_2,\text{H,pro-R/S}}$ coupling constants could not be readily assessed by simple inspection of the ^1H NMR spectrum. However, selective irradiation experiments were informative. In CDCl_3 , the carbinolic hydrogen at 3.94 ppm appears like a second-order split quintet, due to its large coupling with the fluorine atoms, with the hydroxyl hydrogen and with one of the neighboring diastereotopic hydrogens, by a similar magnitude, and there is also an additional small coupling (≈ 3 Hz) with the other diastereotopic hydrogen (Fig. 2). The small splitting disappears after irradiation at the 1.74 ppm. These results indicate that the two diastereotopic hydrogens (at 1.61 and 1.74 ppm) do not have similar angular orientation with the carbinolic hydrogen, thus discarding **a** as a possible driving conformation. In addition, a small $^4J_{\text{H(O),H}}$ of 0.65 Hz is suppressed after irradiation at 1.74 ppm. Consequently, the signal at 1.74 ppm is likely to correspond to $\text{H}_{\text{pro-R}}$ in conformation **b**, where there is only one *gauche* diastereotopic hydrogen relative to H-2 ($^3J_{\text{H-2,H,pro-R}} < ^3J_{\text{H-2,H,pro-S}}$), and it is capable of coupling in a “W” pathway with

Table 2

Calculated coupling constants (Hz) and dihedral angles (deg) for the most stable conformers of CDP, in gas phase, at the $\omega\text{B97X-D/6-311++G(d,p)}$ level.

Conformer	$^3J_{\text{H}_2,\text{F,pro-R}}$	$^3J_{\text{H}_2,\text{F,pro-S}}$	H-C-C-F _{pro-R}}	H-C-C-F _{pro-S}}
1b	6.0	3.0	62.5	−54.1
1c	3.3	4.9	68.9	−47.4
2b	−0.8	14.9	−57.1	−176.9
2b'	−1.9	15.1	−65.0	177.0
3b	14.6	1.0	−174.3	67.6
3b'	15.0	1.6	−179.9	62.0

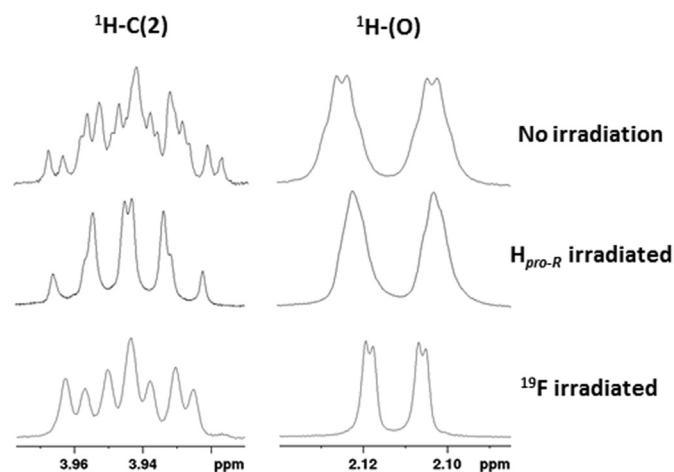


Fig. 2. ^1H NMR signals for the carbinolic and hydroxyl hydrogens of CDP (499.87 MHz, CDCl_3). A ddd for $^1\text{H-C(2)}$ and a dd for $^1\text{H-O}$ appear after ^{19}F decoupling, thus allowing for the identification of the H,H coupling constants (lower). A small coupling with $\text{H}_{\text{pro-R}}$ disappears from both $^1\text{H-C(2)}$ and $^1\text{H-O}$ signals after irradiation at 1.74 ppm (medium). The second order signal for $^1\text{H-C(2)}$ and the broad dq for $^1\text{H-O}$ without irradiation (upper).

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