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On the Nature of C-H...F-C Interactions in Hindered CF₃-C(sp³) Bond Rotations

Prof. Dr. G. K. Surya Prakash*, Fang Wang, Dr. Martin Rahm, Dr. Jingguo Shen, Dr. Chuanfa Ni, Prof. Dr. Ralph Haiges, and Prof. Dr. George A. Olah*

Loker Hydrocarbon Research Institute and Department of Chemistry University of Southern California University Park, Los Angeles, CA-90089-1661 (USA)

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Hindered rotations about single bonds¹ are of immense scientific significance due to their applications in the investigation of intramolecular interactions,² in asymmetric synthesis and catalysis,³ as well as in many other fields.⁴ Although slow rotations of many bulky tetrahedral moieties are frequently reported,⁵ restricted F₃C-C(sp³) single bond rotations have only been sporadically documented.^{6,7,8} As they are generated via strong non-covalent interactions between the CF₃ group and its surrounding atoms (X), hindered CF₃ rotations offer ideal opportunity for investigating various C-F...X interactions. In particular, C-F...H-N/O hydrogen bondings have received much attention in the fields of physical organic and biological chemistry, whereas prevalence and energetic importance of C-F...H-C interactions are frequently debated.⁹ To address these problems, we have investigated CF₃-C(sp³) rotations in *O*-alkyl-9-dehydro-9-trifluoromethyl-9-*epi*quinidine scaffolds. Extremely short C-F...H-C distances have been observed both in solution and in the solid state, providing insights into the nature of C-H...F-C interactions.

9-Dehydro-9-trifluoromethyl-9-*epi*quinidine (**1**) was recently synthesized in our laboratory to enable the conformational study of cinchona alkaloids in various solvents.¹⁰ The C₉-C₄ bond was found to possess unusual restriction leading to slow exchange between the *syn*- and the *anti*-conformers, which clearly indicates a considerable steric encumbrance around the C₉ atom. Interestingly, ether **2a**, prepared through the methylation of the hydroxyl group in **1**, demonstrates an exceptionally broad signal in ¹⁹F NMR spectrum at 298 K (Entry 1, Table 1). Upon lowering the temperature, the signal broadens further and then appears as three individual sharp pseudo triplets, indicating a gradual decrease in rotational rates. At 223 K, a clear first order AEM-type spin system exhibits ²J_{F-F} coupling constants of ca. 115 Hz and reveals the freezing of the rotation about the CF₃-C₉ bond on the NMR time scale. Furthermore, hindered CF₃ rotations were also observed when a number of alkyl groups (R) possessing various steric demands were incorporated into **1** (**2b–2e**), (Entries 2–5, Table 1). The ¹⁹F NMR spectra of **2c–2e** display partially decoalesced resonances even at 298 K, showing high barrier restricted rotations about the CF₃-C₉ bonds.

It has been shown that cinchona alkaloid derivatives can adopt various conformations under different conditions.¹¹ To identify the conformations responsible for the restricted CF₃ rotations, exhaustive experimental and computational studies were performed. Based on

*Fax: (+1) 213-740-6679 gprakash@usc.edu, olah@usc.edu.

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nuclear Overhauser enhancement spectroscopic studies (NOESY), **2a** was found to preferentially adopt a *syn*-closed conformation (Figure 1-A), (See SI). In addition, through-space couplings were observed between the CF₃ group and the OCH₃ group ($^5J_{F-C(H_3)} = 1.9$ Hz; $^4J_{F-C(H_3)} = 1.6$ Hz), indicating an interaction between these two functionalities.¹² A close contact between the CF₃ group and the C₃-H₁ substructure was also evident by the corresponding scalar couplings ($^5J_{F-H_1} = 1.6$ Hz; $^4J_{F-C_3} = 3.9$ Hz), further validating the *syn*-closed structure.

Our DFT calculations indicate the *syn*-closed conformation of **2a** to be 1.9 kcal/mol lower in energy than the *anti*-closed conformation in chloroform,¹³ corresponding to a population distribution of 94:6 (*syn*-closed:*anti*-closed), consistent with the population ratio observed in the ¹⁹F NMR spectrum (ca. 95:5).¹⁴ The accuracy of the B3LYP method is expected to be ca. ±2 kcal/mol in this case. Therefore, the observed good agreement with the experiment is in part fortuitous. Several short H/C-F contacts in the *syn*-closed conformation are responsible for the observed through-space H-F and C-F couplings (Figure 1-B). The computed individual chemical shifts of the fluorine nuclei in **3** are in good agreement with the NMR spectroscopic study (Figure 1-C). We also performed a potential energy surface (PES) scan for the CF₃ rotations in the *syn*-closed-**2a** and the *anti*-closed-**2a** conformers with implicit consideration of solvent CHCl₃-solvation. The CF₃ rotational barriers in the *syn*-closed and the *anti*-closed conformations were calculated to be 12.1 kcal/mol and 6.8 kcal/mol, respectively. These two conformations likely correspond to the broad and the sharp peaks observed in the ¹⁹F NMR spectrum (See SI).

The preference for the *syn*-closed conformation was also confirmed by the X-ray crystal structure of **2c** (Figure 2-A). The interatomic distances between F atoms and majority of the surrounding protons were within the sum of van der Waals radii (ca. 2.5 Å) (Figure 2-B).^{9d} In particular, a short C-H...F-C distance of 2.26 Å was found between F₁ and H₁ (corresponding to the computed distance of 2.19 Å in **2a**), which is among the shortest C-H...F-C contacts ever reported in the solid state.^{9f,9i}

To make a quantitative assessment of the rotational barriers in **2a–2e**, dynamic NMR (DNMR) experiments were performed (See SI). Utilizing Eyring plots, activation enthalpies and entropies of the rotations of **2a–2e** were determined to show first order relationships. The enthalpy barriers ($\Delta H^\ddagger$) of the CF₃ rotations were found to increase as the substituent was altered from a methyl group to an allyl group (ca. 9.0 kcal/mol versus ca. 10.1 kcal/mol). However, no significant impact on the activation enthalpies was found by further increasing the bulkiness of the substituents (R) (**2a**<**2b**≈**2c**≈**2d**≈**2e**, Table 1). Compared with other substituents possessing lower symmetries, the CH₃ group in **2a** can undergo a correlated rotation with the CF₃ rotation, thereby releasing more steric strain ($\Delta H^\ddagger$) in the transition state (TS) than other substituents. On the other hand, as shown by conformational studies, CF₃...R-O interactions in **2b–2e** only occur between the CF₃ group and the intervening methylene group in R. Therefore, the increase in the bulkiness of R does not significantly increase the steric strain around the CF₃ groups in **2b–2e**, neither in the TS nor in the ground state. Noticeably, $\Delta S^\ddagger$ was found to increase in **2b** to **2e**, following their increase in size. **2a** stands out with a small R group but a large $\Delta S^\ddagger$ value, the latter comparable to those of **2b–2d**. This might be attributed to the ground state of **2a**, in which the CH₃ group has a largely unhindered rotation, contrary to the bulkier R groups of **2b–2d**. The entropic effect of hindering the CH₃ rotation in the TS will thus be relatively large in **2a**. Such hindered CH₃ rotation is also indicated in our DFT calculations, which show a contraction of the C-F₃...H₃CO distance by 0.31 Å (12%) in **2a**.

Having a wealth of valuable geometric and spectroscopic information in hand, we were able to explore the nature of the C-F₁...H₁-C₃ interactions and their effects on the hindered CF₃

rotations. First of all, in addition to the short C-F₁⋯H₁-C₃' distance in **2c**, the C₃-H₁⋯F angle is 130.1°, which fulfills the directionality requirement for hydrogen bonding (>110°).^{15,16} Noticeable proton deshieldings for H₁ ($\delta > 7.42$ ppm versus $\delta = 7.33$ in **1**) were also observed in **2**, which could be indicative for the occurrence of C-F⋯H₁-C₃' hydrogen bonding (Figure 3).^{15,17} It is worth noting that ⁵J_{F-H1} constants in **2a–2e** are essentially identical (1.6–1.7 Hz), which indicates very similar C-F⋯H₁-C_{1 3}' distances.^{12a} Thus, lower field chemical shifts observed in **2c–2e**, compared with those of **2a** and **2b**, are probably due to increased ring current induced deshieldings from different aromatic substructures, instead of stronger hydrogen bonding interactions or shorter H⋯F distances.

In addition, several delocalized molecular orbitals can be envisioned between the CF₃ group and the surrounding hydrogen atoms (Table 2).¹³ This is particularly obvious for the C-F⋯H₁-C₃' interaction. To estimate the magnitude of the different interactions, Wiberg bond indices¹⁸ were calculated from natural atomic orbitals (NAO).¹³ The bond index for the strongest interaction (C-F₁⋯H₁-C₃') was found to be 0.0055. This suggests a relatively weak hydrogen bonding-like interaction as compared with the H⋯F hydrogen bonding in the HF dimer (with bond index of 0.0296 and bonding energy of 4.6 kcal/mol)¹⁹ and the C-H⋯F-C hydrogen bondings in the CH₂F₂ dimer (with bond indices of 0.0007–0.0018 and an average hydrogen bonding energy of 0.6 kcal/mol).^{9h} The remaining six C-F⋯H-C interactions were calculated to only 13–31% of this value. Additionally, NBO second-order perturbation analysis²⁰ was used to estimate the interaction energies of the fluorine lone pairs with the C₃-H₁ anti-bonding orbital. It is well established that such hyperconjugative interactions, which are a measure of charge transfer, are the major contributors to hydrogen bonding.^{20a} The two relevant n_F→σ*_{H1-C3'} interaction energies were found to be only 0.6 and 1.3 kcal/mol, further suggesting a rather limited contribution of the C-F₁⋯H₁-C₃' hydrogen bonding interaction to the overall rotational barrier.

Investigation of the TS structure has revealed the importance of the steric strain to the hindered rotation. The CF₃ group was found to undergo noticeable geometric distortions in the TS, indicating an increased steric strain upon rotation.²¹ Also worth noting is the 0.05 Å (ca. 2%) contraction of the F₁⋯H₁ distance in the TS corresponding to CF₃ rotation. Despite a shorter distance, which is typically taken as an indication of a stronger H-bonding interaction, the single n_F→σ*_{H1-C3'} interaction energy is reduced to 0.5 kcal/mol. This again hints to a limited importance of the C-F₁⋯H₁-C₃' H-bonding interaction to the actual ground state geometry or the hindered rotation in this studied system. In other words, the extraordinary short F₁⋯H₁ distance in **2a** appears to be a consequence of steric crowding (buttressing), rather than any meaningful measurable of hydrogen *bonding* interaction. The weakness of these C-F₁⋯H₁-C₃' interactions is in sharp contrast to C-F⋯H-N⁺R₃ H-bonding, which are strengthened by stronger acidities of H-N⁺R₃ type motives.⁹

In conclusion, we have investigated hindered CF₃ rotations in cinchona alkaloid-based scaffolds. DNMR studies have shown the barriers to rotations in the range of 11.9 to 13.5 kcal/mol. The increase in the hindrance of the CF₃ rotations in **2b–2e** is driven by the difference in their entropic changes. Quantum mechanical and experimental studies have shown that the non-covalent C₃-H₁⋯F-C interactions possess some hydrogen bonding-like character. Nonetheless, their contributions to the restricted CF₃ rotations are rather limited. Instead, the steric interactions between the C₃-H₁ moiety and the CF₃ group plays a pivotal role in the hindered rotations in the present systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

A. Conformational analysis of **2a** based on NMR spectroscopic studies; B. Optimized conformation of **2a** at the B3LYP/6-31+G(d,p) level in the gas phase (the OMe group on the quinoline ring is omitted for clarity.); C. Calculated ${}^{19}\text{F}$ NMR chemical shifts of **3** and experimental ${}^{19}\text{F}$ NMR chemical shifts of **2**.

Figure 2.

A. X-ray crystal structure of **2c**; B. Short proton-fluorine contacts as indicated by the crystal structure of **2c** (as the average values measured in both molecules in the unit cell).

Figure 3.

^1H NMR chemical shifts of H_1 in **2a–2e** in CDCl_3 . The chemical shift of H_1 in **2d** was estimated through HSQC spectroscopy.

Table 1

Synthesis of *O*-alkyl-9-dehydro-9-trifluoromethyl-9-*epi*quinidine compounds, their ^{19}F NMR spectra and activation parameters derived from Eyring plots.

Entry	RX	Product	Yield(%) ^a	^{19}F NMR(298K) ^b	^{19}F NMR(223K) ^{b,c}	$\Delta H^\ddagger$ (kcal/mol) ^d	$\Delta S^\ddagger$ (cal/mol·K) ^d
1	CH_3I	2a	81			9.0±0.2	-9.7±0.6
2		2b	69			10.1±0.2	-6.2±0.8
3		2c	82			10.2±0.2	-7.5±0.7
4		2d	65			10.4±0.3	-7.0±1.1
5		2e	74			10.3±0.5	-10.7±1.7

^a Isolated yields;

^b performed in CDCl_3 ;

^c rotations frozen on the NMR time scale;

^d the DMMR experiments were performed in CDCl_3 .

Table 2Canonical MOs showing $C_3-H_1 \cdots F_1-C$ interactions in **3**.

MO Number	Cartoon representations of contributing atomic orbitals	Cartoon representations of H-F interactions	Computed MO's
MO-69			
MO-63			
MO-59			
MO-44			