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Hindered Rotations

On the Nature of C–H···F–C Interactions in Hindered CF_3–C(sp^3) Bond Rotations**

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Hindered rotations about single bonds[1] 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 F_3C–C(sp^3) single-bond rotations have only been sporadically documented.[6–8] As they are generated by strong noncovalent interactions between the CF_3 group and its surrounding atoms (X), hindered CF_3 rotations offer an 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 CF_3–C(sp^3) rotations in *O*-alkyl-9-dehydro-9-trifluoromethyl-9-epiquinidine 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-epiquinidine (**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 be unusually restricted 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 hydroxy group in **1**, demonstrates an exceptionally broad signal in ^{19}F NMR spectrum at 298 K (Table 1, Entry 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 $^{2}J_{\text{F-F}}$ coupling constants of approximately 115 Hz and reveals the freezing of the rotation about the CF_3–C9 bond on the NMR time scale. Furthermore, hindered CF_3 rotations were also observed when a number of alkyl groups (R) possessing various steric demands were incorporated into **1** (**2b**–**2e**), (Table 1, Entries 2–5). The ^{19}F NMR spectra of **2c**–**2e** display partially decoalesced resonances even at 298 K, showing high-barrier-restricted rotations about the CF_3–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 CF_3 rotations, exhaustive experimental and computational studies were performed. Based on nuclear Overhauser enhancement spectroscopic studies (NOESY), **2a** was found to preferentially adopt a *syn*-closed conformation (Figure 1A; see the Supporting Information). In addition, through-space couplings were observed between the CF_3 and the OCH_3 group ($^{5}J_{\text{F-C}H_3} = 1.9$ Hz; $^{4}J_{\text{F-}CH_3} = 1.6$ Hz), indicating an interaction between these two functional groups.[12] A close contact between the CF_3 group and the C3'–H1 substructure was also evident by the corresponding scalar couplings ($^{5}J_{\text{F-H1}} = 1.6$ Hz; $^{4}J_{\text{F-C3'}} = 3.9$ Hz), further validating the *syn*-closed structure.

Our DFT calculations indicate the *syn*-closed conformation of **2a** to be 1.9 kcal mol^{-1} lower in energy than the *anti*-closed conformation in chloroform,[13] corresponding to a

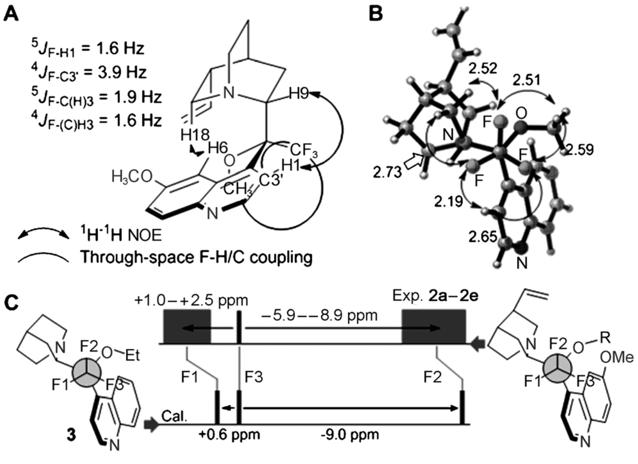

Figure 1. A) Conformational analysis of **2a** based on NMR spectroscopic studies; B) optimized conformation of **2a** at the B3LYP/6-31+G(d,p) level in the gas phase (the OCH_3 group on the quinoline ring is omitted for clarity); C) calculated ^{19}F NMR chemical shifts of **3** and experimental ^{19}F NMR chemical shifts of **2**.

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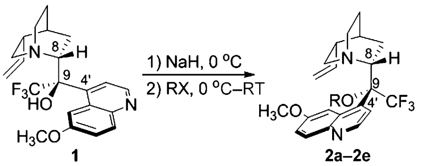
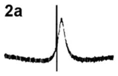
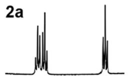
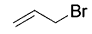
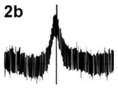
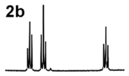
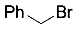
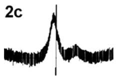
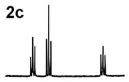
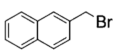
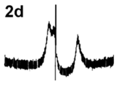
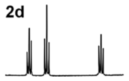
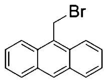
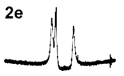
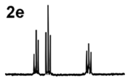
Table 1: Synthesis of *O*-alkyl 9-dehydro-9-trifluoromethyl-9-epiquinidine compounds, their ^{19}F NMR spectra and activation parameters derived from Eyring plots.



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

[a] Yields of isolated products. [b] Performed in CDCl$_3$. [c] Rotations frozen on the NMR time scale. [d] DNMR experiments were performed in CDCl$_3$.

population distribution of 94:6 (*syn*-closed/*anti*-closed), consistent with the population ratio observed in the ^{19}F NMR spectrum (ca. 95:5).[14] The accuracy of the B3LYP method is expected to be approximately ±2 kcal mol^{-1} 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 CF_3 rotations in the *syn*-closed-**2a** and the *anti*-closed-**2a** conformers with implicit consideration of solvation. The CF_3 rotational barriers in the *syn*-closed and the *anti*-closed conformations were calculated to be 12.1 and 6.8 kcal mol^{-1}, respectively. These two conformations likely correspond to the broad and the sharp peaks observed in the ^{19}F NMR spectrum (see the Supporting Information).

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 the majority of the surrounding protons were within the sum of the 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,i]

To make a quantitative assessment of the CF_3–C(sp^3) rotational barriers in **2a**–**2e**, dynamic NMR (DNMR) experiments were performed (see the Supporting Information). Utilizing Eyring plots, activation enthalpies and entropies of the rotations of **2a**–**2e** were determined to show first order relationships. The enthalpy barriers ($\Delta H^{\ddagger}$) to the CF_3 rotations were found to increase as the substituent was altered from a methyl group to an allyl group (ca. 9.0 versus ca. 10.1 kcal mol^{-1}). 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 CH_3 group in **2a** can undergo a correlated rotation with the CF_3 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, CF_3···R–O interactions in **2b**–**2e** only occur between the CF_3 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 CF_3 groups in **2b**–**2e**, neither in the TS nor in the ground state. Noticeably, $\Delta S^{\ddagger}$ was found to increase from **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 CH_3 group

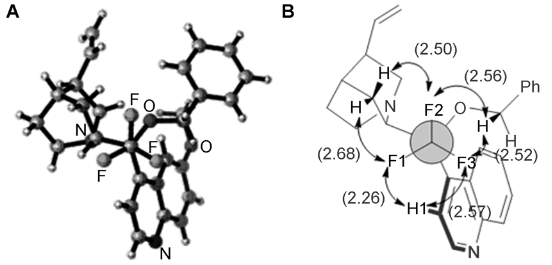


Figure 2. A) X-ray crystal structure of **2c**; B) short proton–fluorine contacts as indicated by the crystal structure of **2c** (as the average values measured in both molecules in the unit cell).

has a largely unhindered rotation, contrary to the bulkier R groups of **2b**–**2d**. The entropic effect of hindering the CH_3 rotation in the TS will thus be relatively large in **2a**. Such hindered CH_3 rotation is also indicated in our DFT calculations on **2a**, which show a contraction of the C–F_3···H_3CO distance by 0.31 Å (12 %) in the TS.

Having a wealth of 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 CF_3 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 versus $\delta = 7.33$ ppm 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 $^5J_{\text{F-H1}}$ constants in **2a**–**2e** are essentially identical (1.6–1.7 Hz), which indicates very similar C–F···H1-C3’ 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.

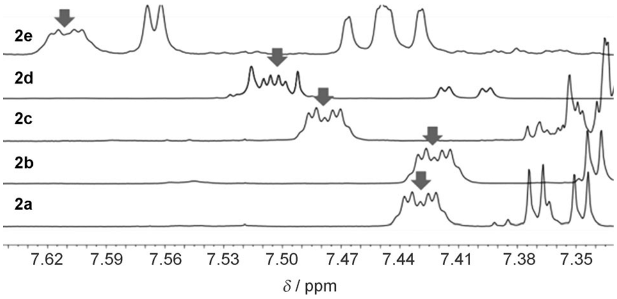
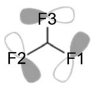
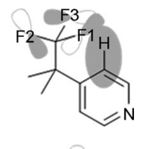
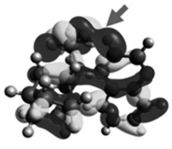
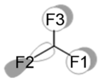
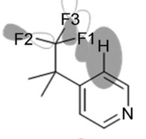
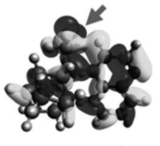
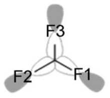
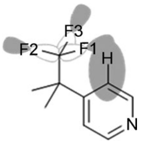
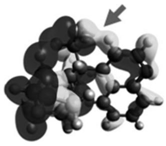
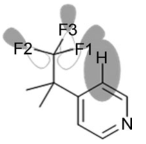
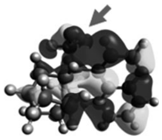


Figure 3. ^{1}H NMR chemical shifts of H1 in **2a**–**2e** in $CDCl_3$. The chemical shift of H1 in **2d** was estimated through HSQC spectroscopy.

In addition, several canonical molecular orbitals were found to occupy the space between the CF_3 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 indices[18] were calculated from natural atomic orbitals (NAOs).[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 a bond index of 0.0296 and a bond energy of 4.6 kcal mol^{-1})[19] and the C–H···F–C hydrogen bonding in the CH_2F_2 dimer (with bond indices of 0.0007–0.0018 and an average hydrogen bonding energy of 0.6 kcal mol^{-1}).[9h] The remaining six C–F···H–C interactions were calculated to be only 13–31 % of this value. Additionally, NBO second-order perturbation analysis[20] was used to estimate the interaction energies of the fluorine lone pairs with the C3′–H1 antibonding 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 $n_F \rightarrow \sigma^*_{\text{H1-C3'}}$ interaction energies were found to be only 0.6 and 1.3 kcal mol^{-1}, further suggesting a rather limited contribution of the C–F1···H1–C3’ hydrogen bonding interaction to the overall rotational barrier.

Table 2: Canonical MOs showing C3′–H1···F1–C interactions in **3**.

MO number	Cartoon representations of contributing atomic orbitals	Cartoon representations of H–F interactions	Computed MOs
MO-69			
MO-63			
MO-59			
MO-44			

Investigation of the TS structure has revealed the importance of the steric strain to the hindered rotation. The CF_3 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 CF_3 rotation. Despite a shorter distance, which is typically taken as an indication of a stronger hydrogen bonding interaction, the single $n_F \rightarrow \sigma^*_{\text{H1-C3'}}$ interaction energy is reduced to 0.5 kcal mol^{-1}. This again hints to a limited importance of the C–F1···H_1–C3’ hydrogen 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^+R_3 hydrogen bonding interactions, which are strengthened by stronger acidities of H–N^+R_3 type motives.[9]

In conclusion, we have investigated hindered CF_3 rotations in cinchona alkaloid-based scaffolds. DNMR studies have shown barriers to rotations in the range of 11.9 to 13.5 kcal mol^{-1}. The increase in barriers to CF_3 rotations in **2b**–**2e** is governed by increases in entropic penalty. Quantum mechanical and experimental studies have shown that the noncovalent C3′–H1···F–C interactions possess some hydrogen bonding-like character. Nonetheless, their contributions to the restricted CF_3 rotations are rather limited. Instead, the steric interactions between the C3′−H1 moiety and the CF_3 group plays a pivotal role in the hindered rotations in the present systems.

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Keywords: cinchona alkaloids · conformational isomerism · fluorine · hydrogen bonding · steric hindrance

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