

On the Nature of C–H...F–C Interactions in Hindered CF₃–C(sp³) 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 F₃C–C(sp³) single-bond rotations have only been sporadically documented.^[6–8] As they are generated by strong noncovalent interactions between the CF₃ group and its surrounding atoms (X), hindered CF₃ 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 CF₃–C(sp³) 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 ¹⁹F 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 ²J_{F–F} coupling constants of approximately 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**), (Table 1, Entries 2–5). 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 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 CF₃ and the OCH₃ group (³J_{F–CH₃} = 1.9 Hz; ⁴J_{F–CH₃} = 1.6 Hz), indicating an interaction between these two functional groups.^[12] A close contact between the CF₃ group and the C3'–H1 substructure was also evident by the corresponding scalar couplings (⁵J_{F–H1} = 1.6 Hz; ⁴J_{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

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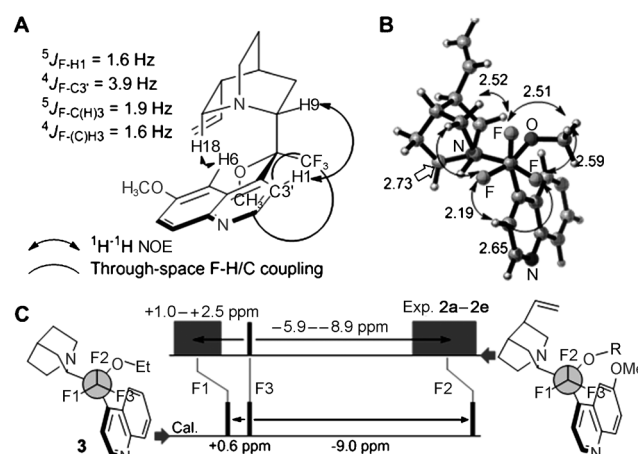
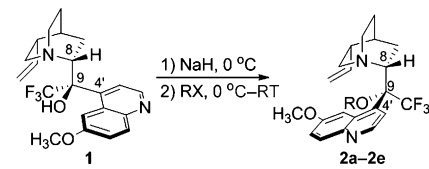
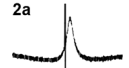
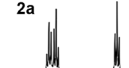
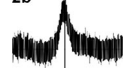
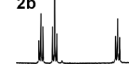
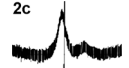
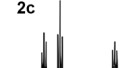
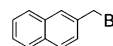
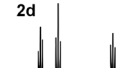
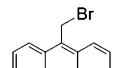
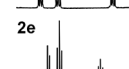


Figure 1. A) Conformational analysis of **2a** based on NMR spectroscopic studies; B) optimized conformation of **2a** at the B3LYP/6-31+G(d,p) level in the gas phase (the OCH₃ group on the quinoline ring is omitted for clarity); C) calculated ¹⁹F NMR chemical shifts of **3** and experimental ¹⁹F NMR chemical shifts of **2**.

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			9.0 ± 0.2	-9.7 ± 0.6
2		2b	69			10.1 ± 0.2	-6.2 ± 0.8
3	$\text{Ph-CH}_2\text{Br}$	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] 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 1B). The computed individual chemical shifts of the fluorine nuclei in **3** are in good agreement with the NMR spectroscopic study (Figure 1C). 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 2A). 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 2B).^[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(sp³) 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

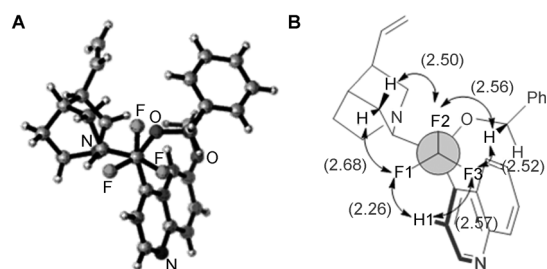


Figure 2. A) X-ray crystal structure of **2c**; B) short proton–fluorine contacts as indicated by the crystal structure of **2c** (as the average values measured in both molecules in the unit cell).

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

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 on **2a**, which show a contraction of the C–F₃...H₃CO 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 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 ($\delta > 7.42$ 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),

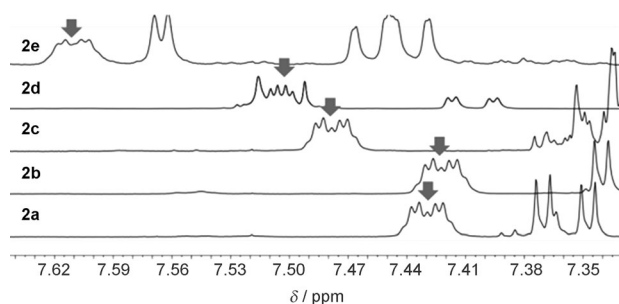


Figure 3. ¹H NMR chemical shifts of H1 in **2a–2e** in CDCl₃. The chemical shift of H1 in **2d** was estimated through HSQC spectroscopy.

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.

In addition, several canonical molecular orbitals were found to occupy the space 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 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 CH₂F₂ dimer (with bond indices of 0.0007–0.0018 and an average hydrogen bonding energy of 0.6 kcal mol^{–1}).^[9b] 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

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			

contributors to hydrogen bonding.^[20a] The two relevant $n_{\text{F}} \rightarrow \sigma^*_{\text{H1-C3'}}$ 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.

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 hydrogen bonding interaction, the single $n_{\text{F}} \rightarrow \sigma^*_{\text{H1-C3'}}$ interaction energy is reduced to 0.5 kcal mol^{–1}. This again hints to a limited importance of the C–F1...H1–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⁺R₃ hydrogen bonding interactions, 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 barriers to rotations in the range of 11.9 to 13.5 kcal mol^{–1}. The increase in barriers to CF₃ 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 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.

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- [1] W. J. Orville-Thomas in *Internal Rotations in Molecules* (Eds.: W. J. Orville-Thomas), Wiley, New York, **1974**.
- [2] a) M. Ōki, *Acc. Chem. Res.* **1990**, *23*, 351; b) I. K. Mati, S. L. Cockroft, *Chem. Soc. Rev.* **2010**, *39*, 4195.
- [3] a) Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155; b) J. M. Brunel, *Chem. Rev.* **2007**, *107*, PR1; c) J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem.* **2009**, *121*, 6516; *Angew. Chem. Int. Ed.* **2009**, *48*, 6398; d) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563.
- [4] a) T. R. Kelly, *Acc. Chem. Res.* **2001**, *34*, 514; b) G. S. Kottas, L. I. Clarke, D. Horinek, J. Michl, *Chem. Rev.* **2005**, *105*, 1281; c) E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem.* **2007**, *119*, 72; *Angew. Chem. Int. Ed.* **2007**, *46*, 72.
- [5] M. Ōki, *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH Publishers, Deerfield Beach, **1985**, chap. 6.
- [6] The barriers to rotations about F₃C–C(sp³) bonds are usually rather low: J. P. Lowe in *Progress in Physical Organic Chemistry* (Eds.: A. Streitwieser, Jr., R. W. Taft), Wiley, New York, **1968**, p. 36.
- [7] Kareev et al. have summarized hindered rotations of CF₃–C(sp³) bonds: I. E. Kareev, G. Santiso-Quinones, I. V. Kuvychko, I. N. Ioffe, I. V. Goldt, S. F. Lebedkin, K. Seppelt, S. H. Strauss, O. V. Boltalina, *J. Am. Chem. Soc.* **2005**, *127*, 11497.
- [8] Only a single report has demonstrated that the rotational barrier of CF₃–C(sp³) bonds can be higher than 25 kcal mol^{–1}: S. Toyota, Y. Watanabe, H. Yoshida, M. Ōki, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2751.
- [9] Selected examples and review articles on C–F...H–X: a) R. West, D. L. Powell, L. S. Whatley, M. K. T. Lee, P. von R. Schleyer, *J. Am. Chem. Soc.* **1962**, *84*, 3221; b) L. Shimoni, J. P. Glusker, C. W. Bock, *J. Phys. Chem.* **1995**, *99*, 1194; c) J. A. K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron* **1996**, *52*, 12613; d) J. D. Dunitz, R. Taylor, *Chem. Eur. J.* **1997**, *3*, 89; e) X. Wang, K. N. Houk, *Chem. Commun.* **1998**, 2631; f) V. R. Thalladi, H.-C. Weiss, D. Bläser, R. Boese, A. Nangia, G. R. Desiraju, *J. Am. Chem. Soc.* **1998**, *120*, 8702; g) T. J. Barbarich, C. D. Rithner, S. M. Miller, O. P. Anderson, S. H. Strauss, *J. Am. Chem. Soc.* **1999**, *121*, 4280; h) W. Caminati, S. Melandri, P. Moreschini, P. G. Favero, *Angew. Chem.* **1999**, *111*, 3105; *Angew. Chem. Int. Ed.* **1999**, *38*, 2924; i) J. Parsch, J. W. Engels, *J. Am. Chem. Soc.* **2002**, *124*, 5664; j) S. C. F. Kui, N. Zhu, M. C. W. Chan, *Angew. Chem.* **2003**, *115*, 1666; *Angew. Chem. Int. Ed.* **2003**, *42*, 1628; k) F. Hof, F. Diederich, *Chem. Commun.* **2004**, 484; l) S. A. Samsonov, M. Salwiczek, G. Anders, B. Kokschi, M. T. Pisabarro, *J. Phys. Chem. B* **2009**, *113*, 16400; m) M. Y. Anzahae, J. K. Watts, N. R. Alla, A. W. Nicholson, M. J. Damha, *J. Am. Chem. Soc.* **2011**, *133*, 728; n) M. T. Scerba, C. M. Leavitt, M. E. Diener, A. F. DeBlase, T. L. Guasco, M. A. Siegler, N. Bair, M. A. Johnson, T. Lectka, *J. Org. Chem.* **2011**, DOI: 10.1021/jo2015328.
- [10] G. K. S. Prakash, F. Wang, C. Ni, J. Shen, R. Haiges, A. K. Yudin, T. Mathew, G. A. Olah, *J. Am. Chem. Soc.* **2011**, *133*, 9992.
- [11] a) G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069; b) M. Aune, A. Gogoll, O. Matsson, *J. Org. Chem.* **1995**, *60*, 1356; c) T. Bürgi, A. Baiker, *J. Am. Chem. Soc.* **1998**, *120*, 12920; d) A. Urakawa, D. M. Meier, H. Rüegger, A. Baiker, *J. Phys. Chem. A* **2008**, *112*, 7250.
- [12] a) P. C. Myhre, J. W. Edmonds, J. D. Kruger, *J. Am. Chem. Soc.* **1966**, *88*, 2459; b) R. E. Wasylshen, M. Barfield, *J. Am. Chem. Soc.* **1975**, *97*, 4545; c) W. R. Dolbier, *Guide to Fluorine NMR for Organic Chemists*, Wiley, Hoboken, **2009**, chap. 1.
- [13] a) Computed using Gaussian03, Revision C.02, M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2004**; b) details of the computational studies are included in the Supporting Information.
- [14] In addition to the broad/decoalesced signal observed in each case, a sharp peak (with a relative population of ca. 5% according to the ¹⁹F NMR integrations) was also observed that shows temperature dependence in its lineshape.
- [15] T. Steiner, G. R. Desiraju, *Chem. Commun.* **1998**, 891.
- [16] G. R. Desiraju, *Angew. Chem.* **2011**, *123*, 52; *Angew. Chem. Int. Ed.* **2011**, *50*, 52.
- [17] G. C. Pimentel, A. L. McClellan, *The Hydrogen Bond*, Reinhold Publishing Corporation, New York, **1960**, p. 142.
- [18] K. B. Wiberg, *Tetrahedron* **1968**, *24*, 1083.
- [19] E. J. Bohac, M. D. Marshall, R. E. Miller, *J. Chem. Phys.* **1992**, *96*, 6681.
- [20] a) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899. Recent examples utilizing second-order perturbation analysis to estimate intramolecular hydrogen bond strengths: b) S. X. Tian, H.-B. Li, *J. Phys. Chem. A* **2007**, *111*, 4404; c) A. E. Shchavlev, A. N. Pankratov, V. Enchev, *J. Phys. Chem. A* **2007**, *111*, 7112; d) A. J. L. Jesus, M. T. S. Rosado, I. Reva, R. Fausto, M. E. S. Eusébio, J. S. Redinha, *J. Phys. Chem. A* **2008**, *112*, 4669; e) A. Lämmermann, I. Szátmari, F. Fülöp, E. Kleinpeter, *J. Phys. Chem. A* **2009**, *113*, 6197.
- [21] Several obvious distortions in the transition state include the increase in the F₃C–C9 bond distance (from 1.580 to 1.621 Å) and the increase in the F1–C–C9 angle (from 113.3 to 116.0°).