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Conformational Study of 9-Dehydro-9-Trifluoromethyl Cinchona Alkaloids via ^{19}F NMR Spectroscopy: Emergence of Trifluoromethyl Moiety as a Conformational Stabilizer and a Probe

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Supporting Information

ABSTRACT: The trifluoromethyl substituent has been incorporated into quinidine as a conformational stabilizer and a probe to provide straightforward insight into the conformational behavior of cinchona alkaloids. By significantly decreasing the rotation rate of the quinoline−carbinol bond, the relatively bulky CF_3 group enables the NMR signals of the syn and anti conformers to be differentiated at room temperature. In addition to the stabilizing effect, the introduction of the fluorinated moiety also facilitates the application of ^{19}F NMR spectroscopy, thereby allowing conformational studies under various conditions without the use of deuterated solvents.

Cinchona alkaloids and their derivatives are widely applicable in asymmetric synthesis as efficient catalysts.[1] The conformations of cinchona alkaloids have been found to play a crucial role in their catalytic activities through the formation of energetically favorable diastereomeric complexes with substrates as transition-state structures.[2−5] A wealth of conformational information on cinchona alkaloids has been obtained by Dijkstra, Wynberg,[6,7] and Sharpless[7] by means of NMR spectroscopy and molecular modeling and such studies have identified four species as the energetically preferred conformations (Scheme 1). Additionally, extensive investigations recently performed by Baiker[8] and Zeara[9] revealed the environmental dependence of the conformational behavior of cinchona alkaloids. In fact, the interconversion between the open and closed conformations has been thoroughly investigated by conventional NMR techniques, particularly vicinal coupling constant analysis and dynamic NMR spectroscopy. In contrast, processes involving exchange between the syn and anti conformations have exclusively been studied by nuclear Overhauser enhancement (NOE) spectroscopy, which, however, may lead to considerable uncertainty in the determination of the populations of these two conformations.[10] In particular, Sugiura and co-workers[11] utilized cross-relaxations and correlation times for molecular reorientation to obtain a relatively accurate conformational analysis of quinidine. Although sporadically used, this relaxation method remains incapable of providing the detailed conformational profile along τ_2. Hence, an efficient and reliable method for the accurate determination of the populations of the syn and anti conformations is still ardently sought.

Apparently, the present difficulty in the investigation of the τ_2 rotation is primarily due to the rapid interchange between the syn and anti conformations at room temperature, which results in the complete coalescence of the corresponding NMR signals. Although spectral decoalescence can in theory be achieved by lowering the temperature, the extremely low temperatures required in these experiments (∼183 K) are not applicable under many scenarios.[8a] Alternatively, we envisioned that τ_2 could be considerably restricted if H_8 were to be substituted by an appropriate alkyl group possessing sufficient steric demand. In this case, direct observation of the spectra of individual conformers arising from the τ_2 rotation could be achieved at relatively high temperatures.

Among various alkyl groups, the trifluoromethyl group was ultimately chosen to function as a conformational stabilizer and a probe. Simply, this twofold advantage of the CF_3 moiety relies on the bulkiness of the CF_3 moiety[13] and the applicability of highly sensitive ^{19}F NMR spectroscopy.[14] Sterically, a trifluoromethyl group is significantly larger than a methyl group and indeed is isosteric with an isopropyl or *sec*-butyl group, depending on the choice of steric scale (Figure 1).[15] In fact, Casarini et al.[12] demonstrated that the rotational barrier around the sp^2-sp^3 Ar−COH bond in α,α-dialkylnaphthylcarbinols is elevated to 14.9 kcal/mol when two isopropyl groups are present in the molecules. The interconversion barriers around both τ_1 and τ_2 were therefore anticipated to be considerably increased because of the substitution of H_8 with the CF_3 group, allowing the conformers to possess sufficient lifetimes on the NMR time scale. In contrast, the three-dimensional structures of the minimum-energy conformations and their population distribution presumably would resemble those of the parent molecules.

This proposal is validated by the fact that the steric interactions between the quinuclidine and quinoline moieties are still predominant because of their considerably larger steric encumbrance in comparison with the CF_3 group. Moreover, with the hydroxyl and amino functionalities intact, the strong inter- and intramolecular interactions involving hydrogen bonding would also be expected to remain relatively unperturbed, thereby conserving the related conformational dependence upon environmental variations. In addition to the conformation-stabilizing effect, the presence of the CF_3 moiety also would make ^{19}F NMR

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spectroscopy applicable for the detection of the subtle conformational changes of the molecule.

To explore the aforementioned proposal, we initially converted quinine into the corresponding ketone through the oxidation reaction described by Woodward.[16] After it was crystallized from Et_2O and further identified as quinidinone by X-ray crystallographic studies, the ketone was treated with 2.5 equiv of trifluoromethyltrimethylsilane ($TMSCF_3$, the Ruppert–Prakash reagent) in the presence of a catalytic amount of tetrabutylammonium difluorotriphenylsilicate (TBAT) to obtain the desired trifluoromethylated compound (eq 1 in Scheme 2A).[17] The reaction afforded an inseparable mixture of two isomers (**1a** and **1b**) in an 83:17 ratio, as determined by ^1H and ^{19}F NMR spectroscopy in $CDCl_3$ (Scheme 2B, top). Further experiments employing a mixture of quinidinone and quininone resulted in four isomers (**1a**, **1b**, **1′a**, and **1′b**), unequivocally suggesting that **1a** and **1b** were not generated via epimerization of C_8 in quinidinone (Scheme 2B, bottom).[18] Moreover, instead of an 83:17 ratio, **1a** and **1b** were observed to have equal intensities in DMSO-d_6 as measured via both ^1H and ^{19}F NMR spectroscopy. In fact, the ratios of **1a** and **1b** turned out to decrease as the proportion of DMSO-d_6 in $CDCl_3$ was increased, eventually reaching 50:50 after the addition of 100 molar equiv of DMSO-d_6 (Scheme 2C,D). These remarkable interconversion phenomena evidently confirmed that the generation of **1a** and **1b** de facto originates from conformational isomerism instead of stereoisomerism. Thermodynamically, the relative populations of **1a** and **1b** (83:17) in $CDCl_3$ show that **1a** is energetically preferred by 1 kcal/mol, while in DMSO-d_6, the population equivalence suggests a negligible energy difference between the two isomers. As established by X-ray crystallographic analysis, **1** was revealed as a 9-trifluoromethylated epimer of quinidine (Scheme 2A).

Exhaustive conformational analyses of **1** were conducted using various NMR techniques [see the Supporting Information (SI)]. As depicted in Scheme 3, the observed conformation of **1a** can be rationalized as a weighted average of two conformers (**1a**$_1$ and **1a**$_2$) generated by a partially unrestricted rotation around τ_2. On the other hand, the overall restriction of τ_2 in $CDCl_3$ results in the formation of two NMR-distinguishable species presenting as kinetically persistent atropisomers, **1a**$_1$/**1a**$_2$ and **1b**$_1$, which have

Scheme 1. The Four Energetically Preferred Conformations of Cinchona Alkaloids and Their Interconversions

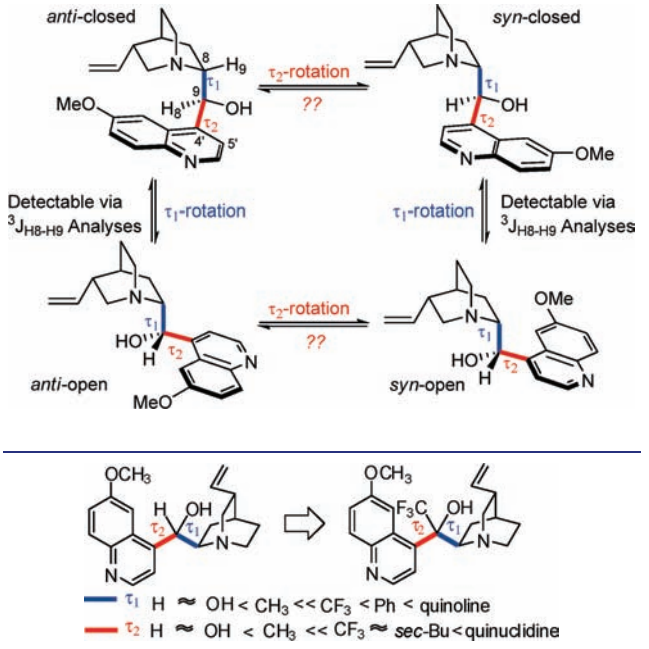
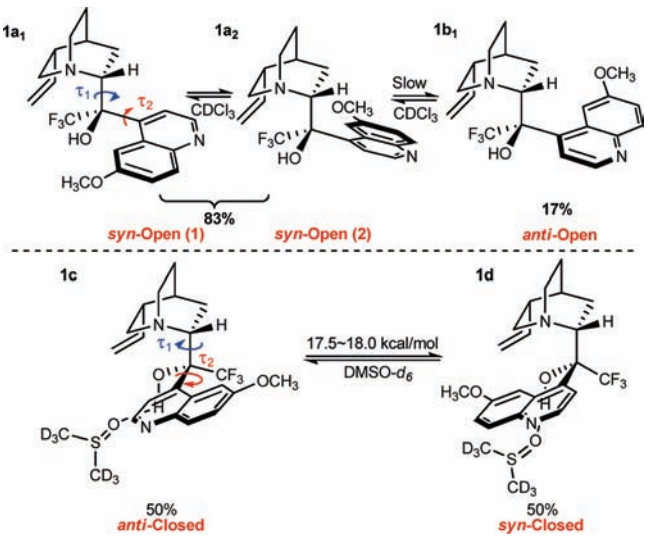
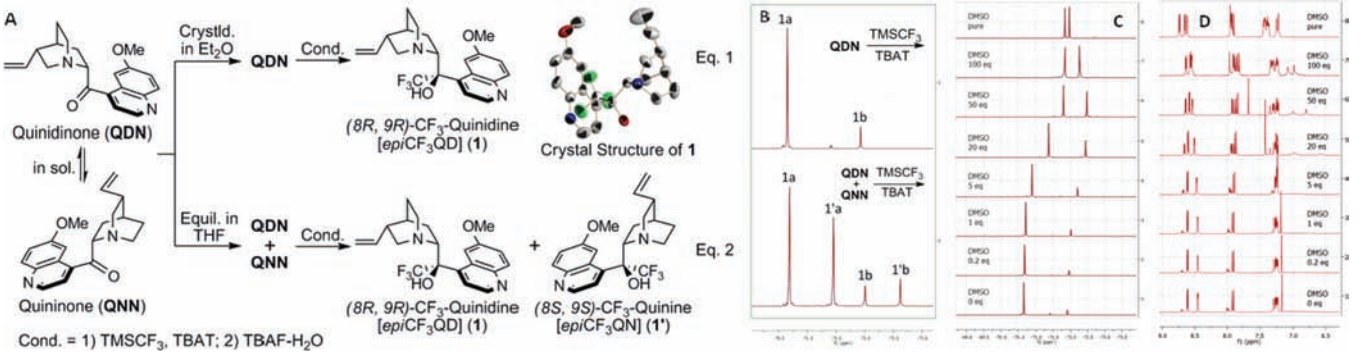


Figure 1. Substitution of H_8 with the trifluoromethyl moiety.

Scheme 3. Interconversion of Different Conformations of 1 in (top) $CDCl_3$ and (bottom) DMSO-d_6



Scheme 2. (A) Stereoselective Synthesis of Trifluoromethylated Quinidine; (B) ^{19}F NMR Spectra of the Trifluoromethylated Products under Different Reaction Conditions; (C) ^{19}F NMR Spectra of 1 in Mixed Solvents of DMSO-d_6 and $CDCl_3$; (D) ^1H NMR Spectra (Aromatic Region) of 1 in Mixed Solvents of DMSO-d_6 and $CDCl_3$



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been identified as the syn-open and anti-open conformations, respectively. Similarly, two conformers with equal population were detected in DMSO-d_6 via ^{19}F NMR spectroscopy. Detailed 2D NMR studies suggested that **1c** and **1d** preferentially adopt the anti-closed and syn-closed conformations, respectively. Intriguingly, atmospheric pressure ionization (API) mass spectrometry revealed a 1:1 complex between **1** and DMSO-d_6, which presumably was formed through hydrogen-bonding interactions.[19]

To further elucidate the relationship of the two isomers, dynamic NMR (DNMR) studies of **1** in CD_2Cl_2 at low temperatures and in $CDCl_3$ at high temperatures were carried out to provide valuable conformational information (see the SI for details). Notably, although only line broadening occurred in the ^{19}F NMR spectra with the rise in temperature, complete coalescence of the signals for the aromatic protons of **1** was observed in the ^{1}H NMR spectra in $CDCl_3$ at 333 K because of the considerably smaller chemical shift differences of the two conformers in the latter. Similar to the observation described by Baiker et al.,[8a] this result apparently implies a rather restricted rotation around τ_2, confirming the previously proposed conformational stabilizing effect of the trifluoromethyl group. Likewise, as demonstrated by the ^{19}F NMR spectra in DMSO-d_6, the two signals of **1** were found to coalesce at 327 K with a frequency difference of 5.7 Hz. In accordance with the original and modified Eyring equations,[20] the rotational barriers around τ_2 were estimated to be 18.0 and 17.5 kcal/mol at 327 K by the respective methods (see the SI). Aside from these experimental studies, preliminary theoretical calculations also revealed the conformational profile of **1** in the gas phase according to a potential energy surface (PES) obtained as a function of the two critical torsion angles $CF_3-C_9-C_8-H_9$ and $O-C_9-C_{4'}-C_{5'}$. As indicated by the PES, the rotational barriers around τ_1 are 4−5 kcal/mol, suggesting that the C_8-C_9 bond undergoes a rather rapid rotation on the NMR time scale. In contrast, the barriers for interconversion between the syn and anti conformations were found to be considerably higher (>11 kcal/mol), which is consistent with the observation of the partially restricted τ_2 rotation (see the SI).

With **1** on hand, we were able to study the interconversion between the anti and syn conformations in various solvents via ^{19}F NMR spectroscopy. Importantly, in comparison with conformational studies using conventional NMR techniques, the present method has exhibited remarkably improved efficacy and accuracy in the measurement of the populations P_{syn} and P_{anti} because of the utilization of 1D NMR spectroscopy at room temperature. Thanks to the availability of ^{19}F NMR spectroscopy, both deuterated and nondeuterated solvents could be used in the conformational studies. Moreover, the identification of the syn and anti conformations could also be feasibly achieved by comparing the ^{19}F NMR spectra of a series of solutions of **1** with different $CHCl_3$ concentrations. Accordingly, we were able to investigate the conformational behavior of **1** in 47 different solvents, with dielectric constants spanning a range of ~80 units, within a single day! (See the SI for the data.)

The analysis of the syn populations in several representative solvents showed that the anti conformations are generally stabilized in polar solvents such as ethanol, DMSO, and acetone (red squares in Figure 2). This outcome resembles the previous conclusion that the populations of the anti conformations [corresponding to the closed(1) and open(4) conformations in the previous studies] are increased with increasing solvent polarity.[8a] In particular, despite the unexpectedly high population

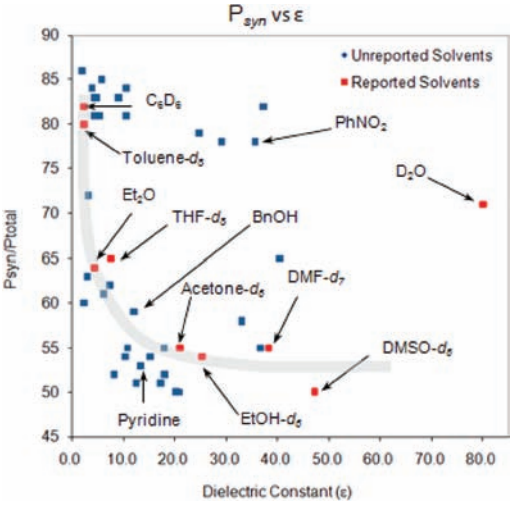

Figure 2. Relative populations of the syn conformations in various solvents.

of the syn conformers in D_2O, these data points are generally aligned in a curve similar to the one associated with $P_{Open(3)}$ of cinchonidine described by Baiker et al. (the gray curve in Figure 2), indicating the pivotal role of dipole−dipole interactions in the population distribution of different conformations. However, further attempts to correlate P_{syn} with the dielectric constants of the 47 different solvents resulted in a rather scattered plot (Figure 2), which can be attributed to the influence of other noncovalent interactions. Apparently, these specific interactions can include $\pi-\pi$ interactions, protonation of the quinuclidine and quinoline nitrogens, hydrogen-bonding interactions, and back-polarization of the solute caused by solvent polarization.

To further manifest the effects of specific intermolecular interactions on the conformational behavior of **1**, the relative populations of the syn conformers in a series of aromatic solvents were plotted versus the dielectric constants of the solvents. In fact, essentially identical syn populations (80−85%) were observed in simple aromatic hydrocarbons, aromatic halides, and aromatic ethers over a dielectric constant range of 10 units. In particular, despite the fact that nitrobenzene is known as a highly polar solvent (ε_r = 35.60), only a small decrease in the syn population (P_{syn} = 78%) was found, indicating that $\pi-\pi$ interactions can significantly stabilize the syn conformations and overwhelm the dipole−dipole interaction to a large extent. Intriguingly, the relative populations of the syn conformers in benzyl alcohol and pyridine were found to be dramatically decreased. Since the solvent polarity is not a crucial factor affecting the syn populations in the aromatic solvents, the current observation can be associated with the hydrogen-bonding interactions between **1** and the hydroxyl moiety in benzyl alcohol. Particularly, in comparison with other primary alcohols possessing similar dielectric constants, benzyl alcohol was capable of stabilizing the syn conformations more efficiently, further confirming the aforementioned stabilizing effect arising from the $\pi-\pi$ interactions.

In conclusion, we have developed a unique method for studying the conformational behavior of cinchona alkaloids by the introduction of the CF_3 moiety as a conformational stabilizer and a probe. As effectively stabilized by the restriction of τ_2, the corresponding atropisomers can possess sufficient lifetimes on the NMR time scale, thus allowing the feasible observation of the

conformers via 1D NMR spectroscopy at room temperature. Because of the feasible application of ^{19}F NMR spectroscopy, we were able to investigate the conformations of **1** in a large number of solvents and found that the conformations of cinchona alkaloids are also closely associated with many intermolecular interactions beyond the dipole−dipole mechanism. Importantly, in contrast to the well-known conformational tool of exploiting the electronic effects of the C−F bond to alter the population distributions of conformers,[21,22] the present strategy features increasing the interconversion barriers of critical rotations through the utilization of the steric encumbrance of the trifluoromethyl moiety. The catalytic utilities of **1** in asymmetric syntheses are currently under investigation.[23] Detailed discussions of the environmental dependence of the conformational behavior of **1** and the related computational studies will be published later.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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