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Effect of Protonation on the Conformation of Cinchonidine

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Cinchona alkaloids, compounds found naturally in the bark of the Cinchona tree, have found a number of applications as pharmaceuticals for the treatment of malaria[1] and cardiac arrhythmias,[2] as additives for soft drinks,[3] as starting materials for organic synthesis,[4] as chiral resolving agents in fractional crystallization[5] and chromatographic[6] techniques, and as agents for promoting enantioselective transformations in both homogeneous[7] and heterogeneous[8] catalysis. These cinchona, represented here by cinchonidine (Figure 1), are characterized by an aromatic quinoline ring connected to a quinuclidine tertiary amine through a chiral alcoholic carbon. Most of the desirable properties of the cinchona have been traced back to the environment around the chiral linker and appear to involve the participation of the nitrogen in the aliphatic amine.[9,10] In fact, it has been shown that protonation of that amine severely influences the chemistry of the cinchona,[11,12] presumably by inducing a change in molecular conformation.[13−15] Here we provide direct evidence for such a connection between the protonation of the amine and a change in conformational preference in the cinchona through a combination of nuclear magnetic resonance[16] and ab initio computational methods.[17] Significantly, we find that the free rotations around the central C−C bonds are severely impaired by protonation, and that the conjugate base anion plays an active role in stabilizing the resulting structures.

Figure 2 shows expanded regions of the NOESY spectra for free and HCl-protonated cinchonidine in deuterated methanol solutions (full spectra in Supporting Information). Cross-peaks are seen in the spectrum for the free cinchonidine, indicating close contacts between the H_1 and H_5 atoms of the quinoline aromatic ring and the H_8 and H_9 atoms of the linker chiral centers as well as the H_{11}, H_{14}, and H_{16} axial atoms of the quinuclidine ring. This indicates nearly free molecular rotation around both $C_{4'}-C_9$ and C_9-C_8 bonds or, as previously reported in other solvents, fast interconversion among a number of stable conformations.[18−20] Notice, however, the absence of signal for the interaction between H_5 and H_{11}, which points to some limitations to this free rotation.

The NOESY spectrum of the protonated cinchonidine, on the other hand, displays a significantly lower number of cross-peaks, indicating close interactions only between the H_5-H_8, H_5-H_9, and H_1-H_{14} pairs of atoms. These data can be easily interpreted as corresponding to conformations where the C_9-C_8 bond is approximately at a right angle from the quinoline ring, the OH group pointing toward the H_1 side of that ring, and the $C_{4'}-C_9$ and C_8-N bonds roughly aligned. Such a structure is analogous to the so-called Open(3) arrangement identified in similar systems by X-ray crystallography[13] and quantum mechanical calculations.[15,19]

Pointedly, the protonation of cinchonidine appears to hinder rotation around the $C_{4'}-C_9$ and C_9-C_8 bonds and to favor only a narrow range of the conformational space of the molecule. Previous studies on the behavior of cinchonidine in the presence of acetic,[21]

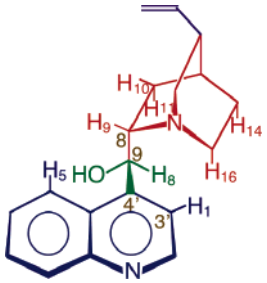

Figure 1. Cinchonidine.

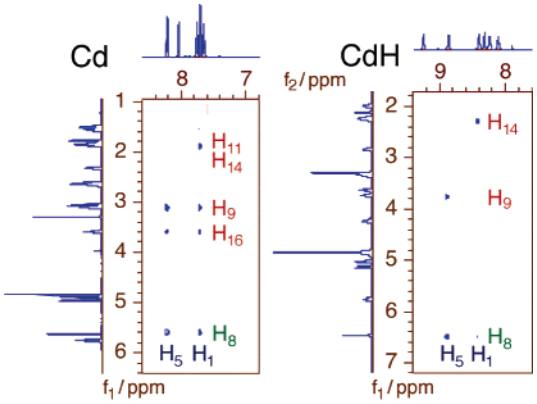

Figure 2. Details of ^{1}H NOESY 2D NMR spectra from ∼10 mM solutions of free base (Cd, Aldrich 96% purity) and HCl-protonated (CdH, prepared by titration with HCl) cinchonidine in deuterated methanol (Aldrich, NMR grade). The disappearance of many of the quinoline (f_2) − quinuclidine (f_1) cross-peaks (shown as positive relative to a negative diagonal) seen in the CdH case indicates locking of the molecule around an open conformation upon protonation. Signal assignments were made by COSY and NOESY experiments (see Supporting Information) on a Varian Inova 500 MHz spectrometer. Similar results were obtained with other solvents, including CD_3CN, DMSO, D_2O, and THF.

mandelic,[22] and tiglic[23] acids indicating similar rotational restrictions were explained by the formation of Coulombic complexes between CdH and the carboxylate group of the corresponding conjugate base via a hydrogen-bonded bridge from the protonated quinuclidine nitrogen to the acidic hydroxo group. However, in those cases, the argument was made that the driving force for such an interaction is the particular fit of the carboxylate ions in the bridging position of the Open(3) conformation of cinchonidine, perhaps because of its bidentate coordination.[21] With other acids and with different cinchona isomers, direct hydrogen bonding between the amine and hydroxyl groups, without the intervention of the counterion, has been invoked to justify similar restrictions in molecular rotations.[24] Competition between direct inter- and intramolecular hydrogen bonding has also been used to justify the varying biological activity of different cinchona.[11,14,15]

To investigate the role of the counterion in stabilizing the protonated cinchonidine structure, ^{1}H−^{19}F NMR experiments were

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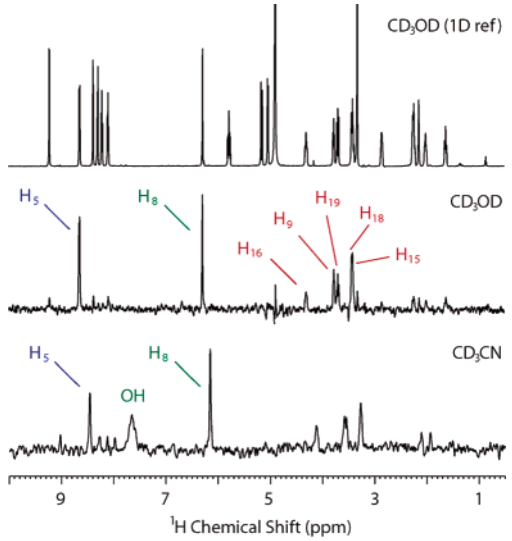

Figure 3. $^1H\{^{19}F\}$ NOE difference spectrum (τ_{mix} = 0.25 s) of the HF-protonated cinchonidine salt $CdH^+ \cdot F^-$ in acetonitrile (bottom) and methanol (middle). The F^- anion remains tightly associated with the $N-H^+$ moiety, giving rise to heteronuclear NOEs to the hydroxyl proton as well as H_5, H_8, and several protons on the quinuclidine ring. (Top) A 1D ^1H spectrum of $CdH^+ \cdot F^-$ in methanol is also shown for reference.

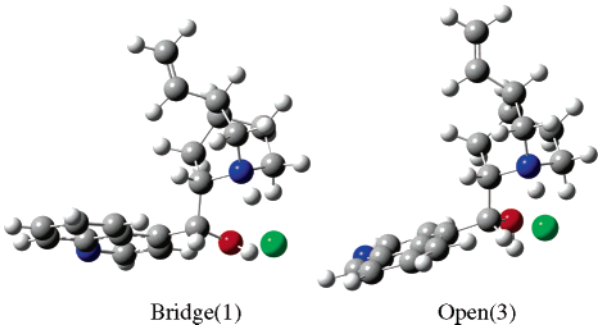

Figure 4. Minimum energy structures for protonated cinchonidine, calculated using Gaussian03 (DFT-B3LYP; 6-31G(d,p)). In the presence of either chlorine (shown) or fluorine (not shown) counterions, the two lowest-energy conformations have torsional constraints analogous to the acetate structure reported previously,[21] with the anion participating in either a hydrogen-bonding bridge (Bridge(1), left) or an ion pair conformation involving other non-acidic hydrogen atoms in the cinchona (Open(3), right).

performed on the HF-protonated cinchonidine salt ($CdH^+ \cdot F^-$) in both methanol and the aprotic solvent acetonitrile. Limited rotation was again observed in both cases, and close proximity between the fluorine anion and H_5, H_8, and the hydroxyl proton (in the acetonitrile solution) was identified by heteronuclear $^1H\{^{19}F\}$ NOE difference experiments (Figure 3).[25] This strongly suggests the participation of the counterion in stabilizing the conformations that result from protonation. The $^1H-^{19}F$ NMR are consistent with the conformation suggested by Figure 2 but also add the need for the formation of a bridge between the nitrogen atom in the quinuclidine ring and other hydrogens via the insertion of an HF (or an HCl) molecule.

Consistent with the NMR data, ab initio quantum mechanical calculations of the HF- and HCl-protonated cinchonidine yielded two similar minimum energy structures for each case, with approximately the same $C_{3'}-C_{4'}-C_9-C_8$ dihedral angle (~90°) and only a ~30° difference in the second $C_{4'}-C_9-C_8-N$ angle (Figure 4). In fact, the main difference between those two structures is in the position of the counterion: in one, the F^-/Cl^- is nested between the amino and hydroxo groups, while in the other, the interaction is with the non-acidic H_5 atom of the quinoline ring. The former is an additional low-energy minimum not present in the unprotonated Cd, while the latter structure corresponds most closely to the lowest energy Open(3) conformation of Cd, but with the conjugate base anion interacting with the electrostatically positive plane of the aromatic system. As the two conformations determined by our calculations have energies that differ by less than 1 kcal/mol, they are likely to be in fast exchange in solution; the structure implied by the NOESY data in Figure 2 is therefore taken to represent their average. Several other stable minima were found at higher energies (tabulated in the Supporting Information), but notably, those corresponding to the favorable Closed(1) and Closed(2) conformations in Cd ($C_{4'}-C_9-C_8-N$ angles of ~60−70°) were found to be extremely unfavorable in the salts, with energies greater than 9 kcal/mol above their respective ground states. The key conclusion is that the addition of the acid shifts the equilibrium to favor a small conformational subspace. The generality of this binding motif and the concomitant rotational restriction that it causes has important implications for understanding the reactivity of cinchona. In particular, it must now be realized that the conformational restriction in cinchona caused by simple diatomic acids may be more complicated than the simple N−H−O hydrogen-bonding mechanism previously proposed.

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Supporting Information Available: Expanded experimental details and full 2D NMR spectra; tabulation of stable minima found by ab initio calculations; complete ref 17. This material is available free of charge via the Internet at http://pubs.acs.org.

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