On the Structure of Osmium Tetraoxide–Cinchona Alkaloid Complexes

Summary: The solid-state and solution structures of cinchona alkaloid derivatives and their osmium tetraoxide complexes were determined by X-ray and NMR methods, with the aim of gathering information relevant to the mechanism of the osmium-catalyzed asymmetric dihydroxylation process.

Sir: A practical route to homochiral diols is provided by the stoichiometric[1] and, more recently, the catalytic[2] asymmetric dihydroxylation of olefins by osmium tetraoxide, employing cinchona alkaloids as chiral ligands.[3] The identification and characterization of the coordination complexes involved is crucial to elucidating the mechanisms of these processes. We have previously provided kinetic evidence for a 1:1 alkaloid–OsO_4 complex as the asymmetry-inducing oxidant in both the stoichiometric and catalytic dihydroxylation reactions.[4] We report here the solid-state and solution structures of several such complexes, as well as solution conformations of some free alkaloid derivatives.

Addition of 1 equiv of (dimethylcarbamoyl)dihydroquinidine (1) to osmium tetraoxide in toluene produced a deep orange solution, which deposited orange-red crystals of the 1:1 complex upon slow cooling to −20 °C. Single-crystal X-ray analysis revealed the structure shown in Figure 1.[5] Several interesting features emerge: (1) the quinuclidine nitrogen is coordinated to osmium via a long bond of 2.49 Å;[6] (2) viewed along the Os–N bond, each equatorial oxo oxygen lies between the quinuclidine methylenes in a staggered conformation; (3) the quinuclidine ring has a substantial twist most probably resulting from the minimization of the steric interactions between the ethyl group and the C-9 substituent (for the numbering scheme, see Figure 2a); (4) the quinoline ring and the dimethylcarbamoyl substituent are remote from the osmium tetraoxide moiety, and interactions with the osmium center involving either the carbamoyl or the aromatic methoxy group are not apparent; and (5) the dihedral angle between H-8 and H-9 is about 65° with the quinuclidine nitrogen anticlinal to the quinoline ring, hence the alkaloid is in an "open" conformation.

In order to establish the conformational preferences of the cinchona alkaloid derivatives[7] and their osmium tetraoxide complexes in solution, a detailed NMR study was undertaken. The conformations of the uncomplexed alkaloids[8] were first investigated. A prerequisite for the conformational analysis was an unambiguous assignment of each proton signal. This was achieved through the use of homonuclear decoupling and COSY experiments.

Several studies of conformational aspects of the cinchona alkaloids[9] have pointed out that the C-9–C-4′ and the C-9–C-8 bonds linking the rigid quinoline and quinuclidine ring systems display a certain degree of rotational freedom. The overall conformations of the alkaloids are determined by the torsional angles of these two bonds. The torsional angle of the C-9–C-8 bond can be estimated from the coupling constant between H-8 and H-9 by using the Karplus equation.[10] The $^3J_{H8H9}$ coupling constants obtained for 1 and (*p*-chlorobenzoyl)dihydroquinidine (2) are 7.8 and 7.5 Hz, respectively, and 6.1 Hz for (*p*-chlorobenzoyl)dihydroquinine (3). Using the Karplus equation, we estimate the H-8–C-9–C-8–H-9 dihedral angle to be ~160° for the quinidines 1 and 2 and ~150° for the quinine analogue 3. This angle can only be accommodated by a synclinal conformation in which the quinuclidine nitrogen lone pair points over the quinoline ring. This "closed" conformation, depicted in Figure 2a, has not been observed previously for the cinchona alkaloids. However, care has to be exercised in applying the Karplus equation to such highly perturbed systems. Therefore, NOE experiments were undertaken to substantiate this conformational assignment.

Upon irradiation of H-8, large NOE's were recorded for H-5 and H-18, suggesting that these atoms are located in close spatial proximity. Irradiation of H-9 resulted in strong NOE's at H-1 and H-11 together with smaller enhancements at H-16 and H-8. These observations not only confirm the nearly anti arrangement of the H-8–H-9 atoms, but also establish the C-3′–C-4′–C-9–C-8 dihedral angle to be close to −90°, as depicted in Figure 2a.

Gradual addition of osmium tetraoxide to the alkaloid solutions induced dramatic changes in the ^1H NMR spectra.[11] The most noticeable changes are found in the chemical shift values, as well as in the reduction of the $^3J_{H8H9}$ coupling constant. The decrease in $^3J_{H8H9}$ suggests a reduction of the C-9–C-8 torsional angle upon complexation, causing H-8 and H-9 to approach a staggered conformation, requiring the quinuclidine nitrogen to move away from the quinoline ring. This rotation around the C-9–C-8 bond results in an "open" conformation as depicted in Figure 2b.

The coordination-induced shift of the alkaloid from a "closed" to an "open" conformation is further supported

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(2) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

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(5) Crystal data: orthorhombic crystals, $P2_12_12_1$ (19), with a = 10.233 (2) Å, b = 10.638 (4) Å, c = 27.812 (9) Å, V = 3028 (3) Å^3, Z = 4, D_{calcd} = 1.63 g cm^{-3}. Structure solution and refinement based on 1980 reflections with $F_0 \geq 2.5\sigma(F_0)$ (Mo Kα, λ = 0.71069 Å) converged at a discrepancy factor of R = 0.052, R_W = 0.060.

(6) A slightly shorter Os–N bond of 2.39 Å was observed by Griffith in the case of the OsO_4–quinuclidine complex: (a) Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413. (b) Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 941.

(7) A complementary study has been carried out by the Kellog–Wynberg group at the University of Groningen on the parent quinine and quinidine for which they observe, as we did in the case of dihydroquinine/dihydroquinidine, an open conformation: Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H., submitted for publication.

(8) The conformation of the cinchona alkaloids appears to be highly sensitive to the nature of the substituent present on C-9. A study of the conformations of the cinchona alkaloid derivatives resulting from structural variations, especially in the C-9 substituent, using NMR techniques and MM2 calculations will be reported elsewhere: Dijkstra, G. D. H.; Kellogg, R. M.; Markó, I.; Sharpless, K. B.; Svendsen, J. S.; Wynberg, H., manuscript in preparation.

(9) (a) Prelog, V.; Wilhelm, H. *Helv. Chim. Acta* **1954**, *37*, 1634. (b) Meurling, L. *Chem. Scr.* **1975**, *7*, 90. (c) Hiemstra, H. Ph.D. Thesis, University of Groningen, 1980.

(10) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

(11) Because of the modest equilibrium constant (~30) for the formation of the OsO_4–alkaloid complex, one has to ensure that complete complexation has taken place (by gradual addition of OsO_4 until the NMR spectrum remains constant) before analyzing the NMR spectra. It is crucial to understand that the equilibrium between free and bound alkaloid is extremely rapid on the NMR time scale, and therefore the spectrum obtained represents the average spectrum of both species. Attempts to freeze the equilibrium and observe separate signals for both species have been unsuccessful. Even at −80 °C only one set of signals was obtained.

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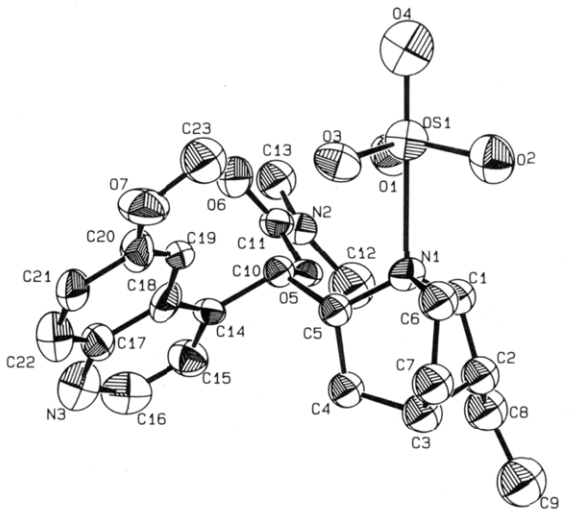

Figure 1. ORTEP view of the osmium tetraoxide complex of (dimethylcarbamoyl)dihydroquinidine (1).

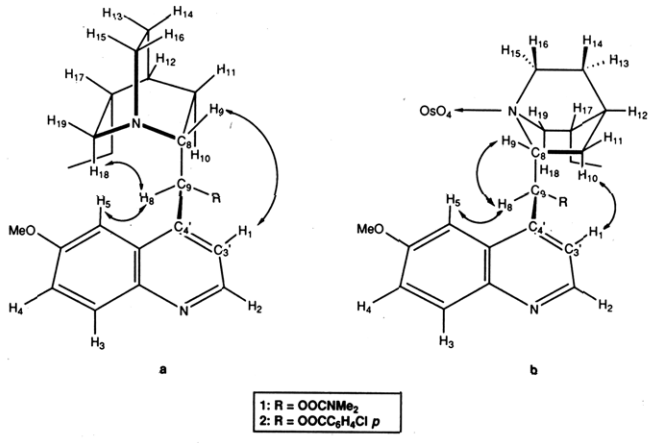

Figure 2. Atom numbering and important NOE's in the (a) closed and (b) open conformation of the cinchona alkaloids. Curved arrows indicate important NOE's.

by changes in the NOE connectivity pattern. Irradiation of H-8 in the complex yielded strong enhancements at H-5 and H-9, suggesting that these three nuclei are close to each other. A significant NOE was also observed between H-10 and H-1, which can only be accounted for by an "open" conformation. Additional substantiation of the conformational change was the disappearance of NOE's involving the pairs H-8, H-18 and H-9, H-1 upon complexation of the alkaloid to OsO_4.

Several important differences in the chemical shift values between free and complexed alkaloids, which could not be accounted for by direct shielding contributions from the heavy metal oxo species, can be explained by the change in the alkaloid conformation upon binding to osmium. In the transition from the "closed" to the "open" conformation, the quinuclidine ring rotates around the C-9–C-8 bond, changing the position of H-10 and H-11 relative to the quinoline ring. In the "open" conformation, H-11 is positioned in the shielding cone above the quinoline ring and experiences a strong upfield shift, whereas H-10, being in the same plane as the quinoline ring, suffers a downfield shift.

This NMR study reveals that the structure of the alkaloid–osmium tetraoxide complex in solution closely resembles the solid state structure in Figure 1. Since the 1:1 complex is known to oxidize a wide range of unfunctionalized olefins to their corresponding osmate esters with good to excellent levels of asymmetric induction, we hoped to be able to derive a coherent stereochemical model for the reaction from the data presented here. However, we find instead that the chiral centers in the alkaloid ligand are quite remote from the oxo ligands, and there is no clear indication of how chirality might be transmitted to the substrate. This is exacerbated by the fact that there is still very little known about the mechanism for the addition of osmium tetraoxide to olefins.[1a,12] One important piece of information obtained from the NMR studies may bear some relevance to the asymmetric dihydroxylation. The alkaloids which are effective ligands in the process all exist in a "closed" conformation in their uncomplexed state, whereas ineffective ligands (1, R = OH, OMe, $OSiMe_3$, H) all exist in an "open" conformation. The exact significance of this difference is not obvious, particularly since upon complexation to osmium tetraoxide all ligands adopt an "open" conformation. In any event, it is apparent that the steric and/or electronic factors governing the asymmetric osmylation reaction are extremely subtle and require considerably closer investigation. In this vein, solid state and solution studies of the corresponding osmate ester–alkaloid complexes are currently under way.

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Supplementary Material Available: Tables of atomic positions, bond lengths and angles, anisotropic temperature factors, and calculated hydrogen atom positions for 1–OsO_4 and chemical shift values for **1**, **2**, and **3** and of their osmium tetraoxide complexes. ^1H NMR spectra of **2** before and after addition of OsO_4 (27 pages). Ordering information is given on any current masthead page.

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Acid–Base Controlled Torquoselectivity: Theoretical Predictions of the Stereochemical Course of the Electrocyclic Reactions of Cyclobutene-3-carboxylic Acid and the Conjugate Base and Acid

Summary: Ab initio calculations using the 3-21G and 6-31G* basis sets were carried out on the electrocyclic reactions of cyclobutene-3-carboxylic acid and its protonated and deprotonated forms. The calculations predict that the stereochemistry of the cyclobutene-3-carboxylic acid ring opening can be reversed from outward to inward rotation by protonation of the acid.

Sir: Substituted cyclobutenes undergo thermally allowed conrotatory ring opening by inward or outward rotation

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