Pergamon

Tetrahedron Letters, Vol. 35, No. 18, pp. 2861-2864, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0451-3

X-Ray Crystallographic Studies Provide Additional Evidence That An Enzyme-Like Binding Pocket Is Crucial to The Enantioselective Dihydroxylation of Olefins by OsO_4–Bis-cinchona Alkaloid Complexes

E. J. Corey,* Mark C. Noe and Sepehr Sarshar

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Summary: *X-Ray crystallographic analysis on single crystals and ^1H NMR studies in solution of various bis-cinchona alkaloid derivatives reveal a general preference for a conformation which possesses a U-shaped binding pocket with favorable dimensions for the inclusion of olefinic substrates and the acceleration of face selective dihydroxylation by a proximate pentacoordinate OsO_4.*

Remarkable progress has been made in the asymmetric dihydroxylation of olefins by osmium tetraoxide and chiral amine ligands.[1] The cinchona alkaloid based system evolved by Sharpless is especially practical due to the high catalytic turnover, magnitude of the observed enantioselectivity and the wide range of substrates which may be selectively oxidized.[2] We have recently presented strong evidence[3] that the high enantioselectivity of the dihydroxylation reaction with bis-cinchona ligands such as **1**[4] is due to the following factors: (1) a preference for the conformation **2** for the OsO_4 complex of **1** (but not for free **1**), (2) the ability of **2** to bind olefinic substrates such as styrene in a pocket composed of the two methoxyquinoline units and the pyridazine connector, as shown, (3) the proximity of one axial oxygen and one equatorial oxygen of the complexed OsO_4 unit to the olefinic carbons, as shown in **2**, and (4) a minimum motion pathway for the [3+2] cycloaddition which produces the pentacoordinate osmate ester in the energetically most favorable geometry.[5] This model explains readily both the acceleration of rate produced by **1** and the absolute olefin face selectivity. A crucial part of the evidence favoring this interpretation derives from the study of the bridged ligand **3** which is conformationally restricted and which behaves almost identically with **1** in terms of rate acceleration and enantioselectivity in the dihydroxylation of a variety of olefins. We now show that bis-methiodide derivatives of **1** and **3** adopt similar, U-shaped geometries in the solid state as determined by X-ray crystallography and in solution as determined by ^1H NMR analysis.

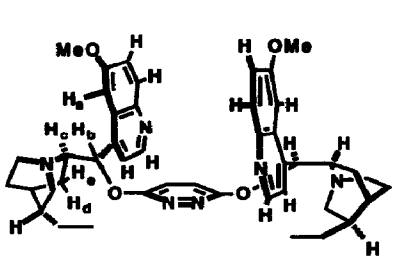
The bis-methiodide of **1** was prepared by reaction of **1** with 2 equivalents of CH_3I at 23° C in ethanolic solution. The X-ray crystal structure **4** (and the space-filling equivalent **4'**) was obtained by analysis of a crystal obtained directly from this mixture and mounted in a sealed capillary containing mother liquor.[6] As indicated by the crystal structure, the two methoxyquinoline rings extend in parallel planes with a 7.2 Å separation between them. The pyridazine ring is oriented so as to allow conjugation of the ring with the two alkoxy substituents. It should be noted that this orientation of the aromatic linker group allows enough room for an olefin such as styrene to fit well into the binding pocket established by the methoxyquinoline rings and that the tilt of the pyridazine group may be adjusted during the reaction so as to maximize binding interactions and minimize steric repulsions.

In the X-ray structure for **4/4'** the N2–C13–C12–O2 dihedral angle is *ca.* 65°. A slightly larger value for this dihedral angle for solutions of **4** is indicated by the 2.4 Hz H_bH_c NMR coupling constant observed for both the bis CH_3I salts and OsO_4 complexes of **1**. Additionally, H_d and H_e exhibit unusual shielding and deshielding effects of the methoxyquinoline rings of **4** and the bis-OsO_4 complex of **1** (for **4**: δ H_d = 2.73 ppm, δ H_e = 1.45 ppm; for the OsO_4 complex of **1**: δ H_d = 2.06 ppm, δ H_e = 0.94 ppm).[7,8] This observation is consistent with the conformation depicted in **1**, as H_d resides in the deshielding cone of the methoxyquinoline ring, while H_e points directly into its shielding cone. These results indicate that the population of the conformation corresponding to **4** (or **4'**) for osmium complexes of **1** in solution is significant. It is important to note, however, that *the free ligand **1** in solution must exist as a mixture of conformers* in addition to the conformer **1** which is drawn, because JH_bH_c has a value of 6.3 Hz (in $CDCl_3$).

Earlier results indicated that the rigid catalyst **3** is an excellent model for this conformation of **1** in the asymmetric dihydroxylation reaction.[3] Thus solution and solid state structures of derivatives of **3** were obtained and compared with those of **1**. Crystals of the bis-CH_3I quaternary ammonium salt were grown directly from the reaction of **3** with 2 equivalents of CH_3I in 2-butanone. X-ray quality crystals were obtained after seeding from a similar reaction over a 72 h period.[9] The crystal structure **5** (or **5'**) displays structural features similar to those of **4**, most notably with regard to the orientation of the two methoxyquinoline rings and the aromatic spacer group. As in **4** and bis-OsO_4 complexes of **1**, a 0 - 2 Hz H_bH_c coupling constant was observed both for **5**, free ligand **3** and its OsO_4 complex. The *ca.* 65° dihedral angle about N2–C12–C11–O2 indicated in the crystal structure **5/5'** corresponds to that observed for **4/4'**. Similarly, shielding and deshielding effects of the methoxyquinoline ring are noted for H_d (2.22 ppm) and H_e (1.00 ppm) for free ligand **3**, its bis CH_3I salt (δ H_d = 2.8 ppm, δ H_e = 1.5 ppm) and its OsO_4 complex (δ H_d = 2.20 ppm, δ H_e = 0.98 ppm). Free ligand **3** and its OsO_4 complex show strong NOE effects between H_b and H_a (14.5 %) and H_c and H_a (4.3 %), indicating the same orientation of the methoxyquinoline ring as observed in the X-ray crystal structure **5**.[7,8] *Thus, ligand **3** is constrained to exist in the favorable binding conformation which is shown by virtue of the geometry imposed by the adipyl bridge.*

The X-ray and NMR data indicate that quinuclidine complexed forms of pyridazine-linked bis-cinchona alkaloids adopt a conformation suitable for binding a hydrophobic olefinic substituent in a U-shaped binding cleft established by the two methoxyquinoline rings and the pyridazine connector. These results add to the already compelling case that ligand **3** is a structurally rigid model for the active conformation of ligand **1** and analogs in the asymmetric dihydroxylation reaction. The tilt of the aromatic linker group is not precisely defined by these studies, and it is likely that its orientation is adjustable to accommodate various substituents of the olefinic substrate.

Of all the enantioselective catalysts studied to date the bis-cinchona alkaloid derivatives such as **1** and **3** are the closest to enzymes in terms of general function. These catalysts have specific binding sites for OsO_4 and the olefin, the latter being a pocket which involves non-covalent, shape/size selective interactions, and they accelerate and control the stereochemistry of the reaction by means of a favorable 3-dimensional arrangement in the transition state.[10]



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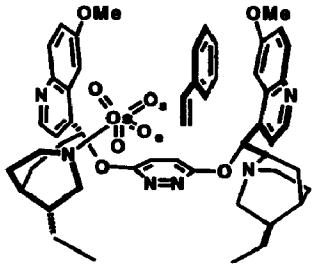

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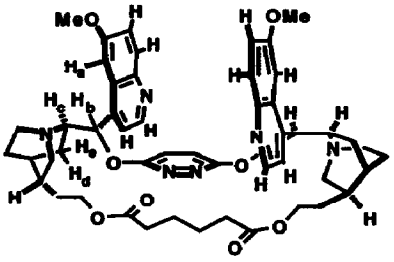

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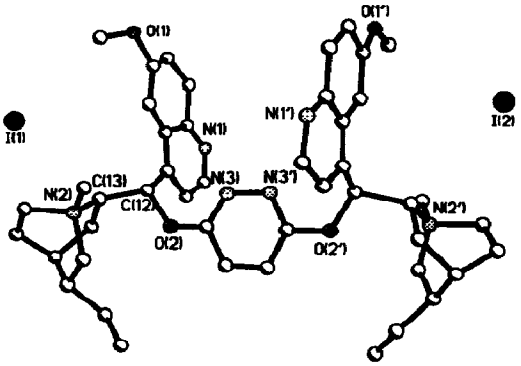

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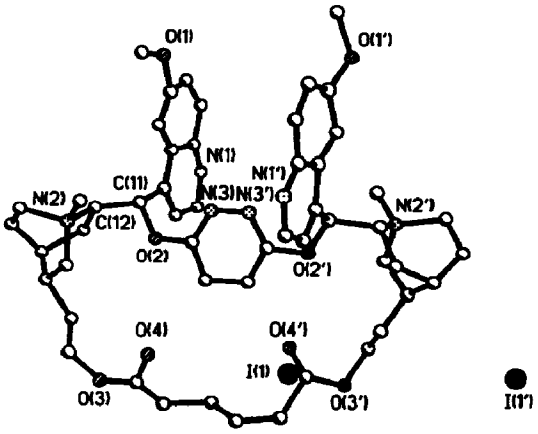

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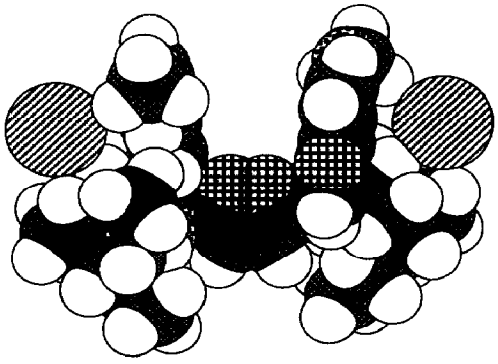
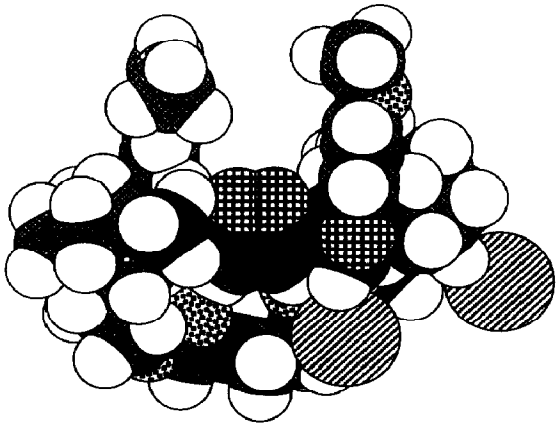


4'



5'

Carbon Oxygen Nitrogen N-CH_3

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6. The deep yellow crystals of **4** were found to contain four molecules of **4** and 16 molecules of ethanol in the unit cell: empirical formula $C_{54}H_{82}I_2N_6O_8$ (1197.1); crystal size 0.6 x 0.8 x 0.8 mm^3; space group $P2_12_12_1$; a = 9.855(1) Å, b = 11.995(1) Å, c = 50.691(7) Å; V = 5991.9(14) $Å^3$; d = 1.327 g/cm^3; (Mo Kα radiation, 23 °C); 6172 reflections collected, of which 3711 with $F_o > 4.0\,\sigma(F_o)$ were used in the solution of structure; R_w = 0.120; GOF 1.72. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

7. ^1H NMR studies were conducted using 0.03 M ligand in degassed $CDCl_3$ solution at 23 °C. ^1H NMR studies of bis quaternary ammonium salts were studied in CD_3OD solution at 23 °C. In the studies of OsO_4 complexes, changes in the ^1H NMR spectrum were monitored using varying amounts of OsO_4 (1 to 8 equiv), due to the modest K_{eq} for complexation of OsO_4 by the ligand.

8. For a discussion of proton assignments of analogous compounds and known effects of OsO_4 complexation on alkaloid ^1H NMR spectra, see: Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.

9. The deep orange crystals of **5** were found to contain four molecules of **5** and 8 molecules of 2-butanone in the unit cell: empirical formula $C_{60}H_{80}I_2N_6O_{10}$ (1299.1); crystal size 0.3 x 0.4 x 0.5 mm^3; space group $P2_12_12_1$; a = 8.322(2) Å, b = 25.092(5) Å, c = 29.586(6) Å; V = 6178(2) $Å^3$; d = 1.397 g/cm^3; (Mo Kα radiation, 23 °C); 5845 reflections collected, of which 2162 with $F_o > 4.0\,\sigma(F_o)$ were used in the solution of structure; R_w = 0.0981; GOF 1.71. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

10. This research was assisted financially by a grant and a graduate fellowship (to M.C.N.) from the National Science Foundation.

(*Received in USA* 12 *January* 1994; *revised* 23 *February* 1994; *accepted* 25 *February* 1994)