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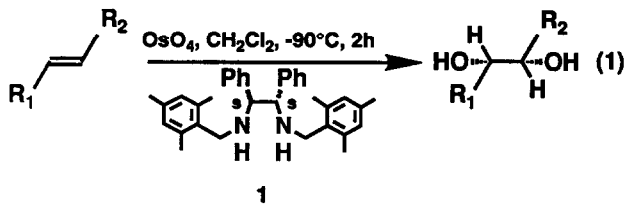
# THE ORIGIN OF ENANTIOSELECTIVITY IN THE DIHYDROXYLATION OF OLEFINS BY OSMIUM TETROXIDE AND CINCHONA ALKALOID DERIVATIVES

E. J. Corey and Gerald I. Lotto

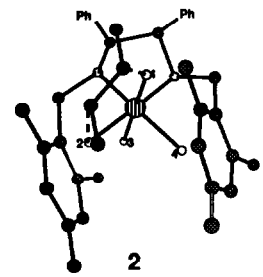
Department of Chemistry, Harvard University, Cambridge, MA 02138

*Summary:* A logical and simple mechanistic explanation is proposed for the enantioselectivity which has been demonstrated for the catalytic dihydroxylation of certain olefins by osmium tetroxide under the influence of derivatives of quinine and quinidine.

A recent report from this laboratory has described a new system for the highly enantioselective dihydroxylation of *E*-disubstituted and monosubstituted olefins, for example *E*-3-hexene with 50:1 enantioselectivity, according to equation (1).[1] Both chiral controller/catalytic ligand **1** and osmium tetroxide




**1**




**2**

can be recovered from the reaction mixture by a simple and efficient process. In addition we have presented the first clear mechanistic model for understanding the 1,2-diamine-catalyzed enantioselective dihydroxylation of olefins by $OsO_4$.[1] The strong catalysis by **1** implies that the reactive species is a 1:1 $C_2$ symmetric octahedral complex with $OsO_4$, as summarized in **2**. In this complex the two equivalent equatorial oxygens $O_2$ and $O_4$ are electron rich (and nucleophilic) relative to the axial oxygens $O_1$ and $O_3$.[1] In consequence attack by $O_2$ and $O_4$ on an olefin is disfavored relative to cycloaddition involving $O_1$ and $O_4$ or $O_1$ and $O_2$. The *(S,S)* ligand **1** sterically obstructs $O_1/O_4$ cycloaddition relative to $O_1/O_2$ cycloaddition and, further, greatly favors attack by $O_1/O_2$ on one face of an *E*-disubstituted olefin vs. the other[1] as shown in **2** for *E*-2-butene. Because the reactive complex of **1** with $OsO_4$ is $C_2$ symmetric, there is equivalence of the $O_1/O_2$ and $O_3/O_4$ modes of reaction and also the $O_1/O_4$ and $O_3/O_2$ modes of reaction. This model of the transition state assembly also provides a satisfactory explanation of the highly selective dihydroxylation reactions reported by Tomioka[2] and Hirama[3] for $OsO_4$ and other $C_2$ symmetric chiral 1,2-diamines.

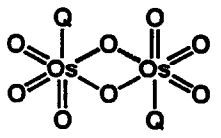
Because of the development of the mechanistic model described above, we were led to consider whether it could be applied to understanding Sharpless' enantioselective application of cinchona alkaloids such as quinine and quinidine derivatives in a catalytic system for dihydroxylation of olefins by $OsO_4$-*N*-methylmorpholine *N*-oxide.[4] Although considerably lower enantioselectivities are observed for quinine/quinidine derivative(QQD)-promoted as compared with diamine **1**-promoted dihydroxylation of olefins, the use of sub-stoichiometric amounts of $OsO_4$ is a positive feature of the former method. Unfortunately, the mechanistic basis for enantioselectivity in the QQD-promoted reactions has previously

been shrouded in mystery, despite an extensive X-ray structural study of various $OsO_4$-cinchona alkaloid complexes.[4d,5] In this note we extend our model of the 1,2-diamine-catalyzed dioxyosmylation reaction of olefins to encompass the QQD-promoted reactions with the help of logical chemical arguments and computer-assisted modelling.

The very large rate acceleration of the $OsO_4$ dioxyosmylation of olefins caused by diamines such as **1** is a reflection of the greatly intensified reactivity of hexacoordinate octahedral Os(VIII) as compared to tetrahedral $OsO_4$[1,6,7] and is associated in part with favorable energetics for preserved octahedral geometry through the sequence, reactant → transition state → product. The geometry of known complexes of $OsO_4$ with quinuclidine[8] and cinchona alkaloids,[4d] which is that of a trigonal bipyramid distorted toward a tetrahedral $OsO_4$ subunit, is probably less favorable for [3 + 2] cycloaddition to an olefin than with octahedral $OsO_4$ complexes.[7] Indeed, the experimental observation of enantioselectivity in reactions of QQD ligands with $OsO_4$ and olefins seems totally inconsistent with a direct reaction of olefin with a 1 : 1 alkaloid-$OsO_4$ adduct containing pentacoordinate osmium.[5] Any structure for the complex having that geometry or undistorted trigonal bipyramid geometry lacks the sort of steric bias which would lead to face selectivity in reaction with an olefin. On the other hand, dimerization of two such pentacoordinate species by [2 + 2] cycloaddition of metal oxo linkages can lead to an octahedral binuclear structure **3** with very favorable three dimensional properties for enantioselective transition state formation, including possible $C_2$ symmetry and strong electronic and steric differentiation between the three oxo oxygens on each osmium. Such dimerization reactions of similar dioxo metal compounds are well known. For example, $MoO_2Cl_2$ exists as a mixture of monomer and oxygen-bridged dimer in the gas phase[9] and as octahedral complexes of type $MoO_2Cl_2 \cdot 2S$ in donor solvents such as dimethylformamide.[10] Further, dimeric oxygen bridged structure **4** has been observed in the solid phase.[11] Only a small fraction of the QQD-$OsO_4$ complex need be as dimer if, as we suspect, the dimer is much more reactive towards olefins than the monomer.

On the basis of the analysis previously described,[1] and summarized above, the equatorial oxygens in **3** should be nucleophilic relative to the axial oxygens (*trans* to Q),[12] leading to a transition state in which the olefinic carbons attach to one of the equatorial oxygens and the axial oxygen on the same osmium. With that restriction, enantioselective control by the chiral group Q requires only a higher degree of steric screening by Q of the approach by olefin to one of the equatorial oxygens relative to the other. This simple and logical possibility for enantiocontrol was examined in detail by molecular modelling for the catalytic ligand **5** (dihydroquinidine *p*-chlorobenzoate) by the following procedure.

The ligand **5** was affixed to osmium as in **3**, Q=**5**, with 2.23 Å separation between N and Os (from X-ray[11]). (The isomeric structure in which both Q's are *cis* to one another is very unfavorable sterically.) The groups Q were rotated about the N-Os bond to minimize repulsion with the nearby *cis* oxo group, generating two $C_2$-symmetric forms of **3**, Q=**5**. In one of these ($C_2$ open) the piperidine ring face C-1,2,3,4,5,6 is proximate to the *cis* oxo group and in the other ($C_2$ closed) the piperidine face C-1,2,3,4,7,8 occupies this location. The conformer in which the piperidine face C-1,4,5,6,7,8 is closest to the *cis* axial oxo group is very unstable sterically. A minimum energy trial structure with regard to ligand **5** geometry was then derived for $C_2$ open and $C_2$ closed forms of **3**, Q=**5**. Based on these starting conformations, structural minima for the cinchona alkaloid monomer were calculated using both CHARMm and locally modified MM2 programs.[13] Grid search techniques and energy embedding were used to generate new starting structures which were also minimized. Two of the resulting minima were found to differ by approximately 0.3 kcal. and to resemble the starting conformations closely. These were the only minima which could be used to construct $C_2$ dimeric complexes with $OsO_4$. Using the 2.23 Å osmium-nitrogen bond lengths, pairs of cinchona ligands were positioned for bonding to the bridged osmium complex. Grid search techniques were employed to compare the energies of rotomers with respect to the osmium-nitrogen axes, and a new set of conformers was generated for both $C_2$ open and $C_2$ closed geometries. The final structures were subjected to further minimization. The resulting minimum energy conformers are shown for the $C_2$ open form of **3**, Q=**5**, (stereopair **6** and ball/stick formula **6a**) and the $C_2$ closed form of **3**, Q=**5**, (stereopair **7**).



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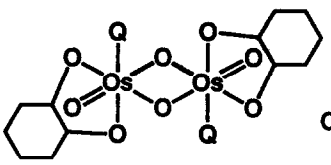

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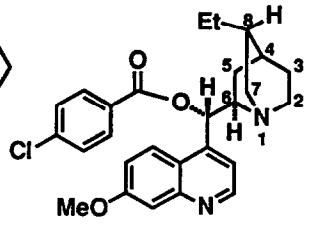


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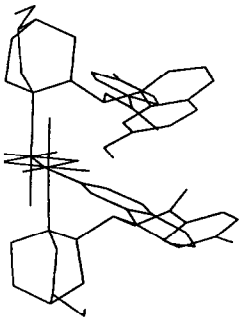
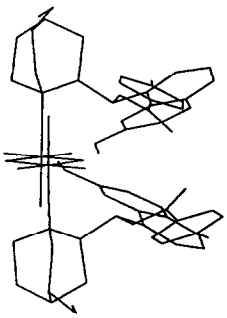
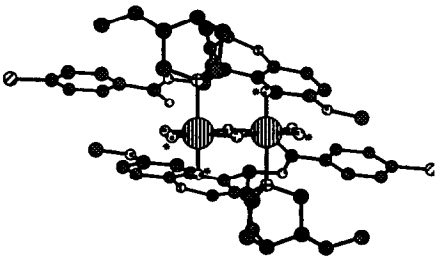
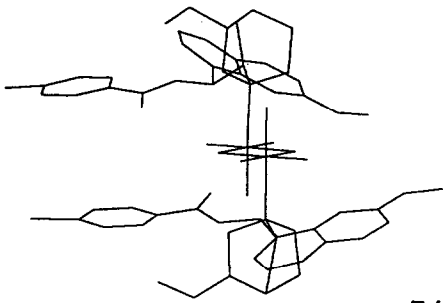


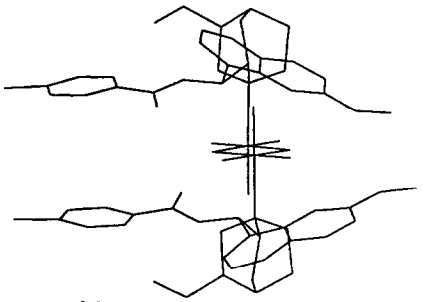


6 (stereopair)

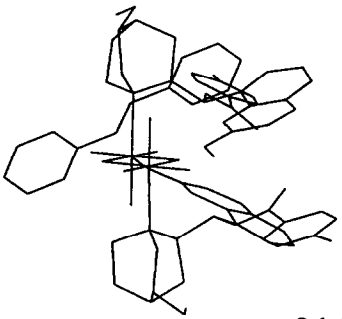


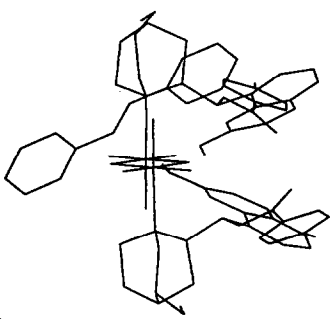
6a (reaction at O$^{\bullet}$)





7 (stereopair)





8 (stereopair)

Whereas the $C_2$ closed structure **7** does not allow access of an olefin to an axial-equatorial pair of oxygens on osmium, $C_2$ open structure **6** does. Further, the $C_2$ open structure **6** definitely favors attack by an *E*-disubstituted olefin such as *trans* stilbene at one of the equatorial oxygens over the other and with a clear preference for the pro-*R* face of the olefin. The favored transition state assembly is shown in stereopair **8**. This stereochemical outcome is in accord with the experimental data for $OsO_4$-ligand **5**-mediated dihydroxylation of a variety of olefinic substrates.[4] Replacement of **5** by dihydroquinine *p*-chlorobenzoate leads to a dimeric structure **3** for which a $C_2$ open structure analogous to **6** can be derived and which is predicted to attack the pro-*S* face of *E*-1,2-disubstituted olefins selectively, as observed.[4]

The π-stacking in the $C_2$ open structure **6** which involves favorable van der Waals contact distances clearly favors this conformer and provides an explanation for the experimental finding that this ester is superior to some 20 others which were screened.[4c]

We believe that the mechanistic explanation advanced above provides a logical interpretation of previous results and leads to predictions which are subject to experimental test.[14]

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5. As mentioned by Sharpless et al.,[4d] "the chiral centers in the cinchona alkaloid ligand are quite remote from the oxo ligands (of the 1 : 1 $OsO_4$ alkaloid complex), 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 of addition of osmium tetraoxide to olefins." More recently rate evidence has been presented that the ratio of QQD to Os along the reaction pathway is 1, and not 2; E N. Jacobsen, I. Markó, M. B. France, J. S. Svendsen, and K. B. Sharpless, *J. Am. Chem. Soc.*, **111**, 737 (1989).
6. Only a very small fraction of diamine **1** is coordinated to $OsO_4$ in non-polar solvents even at low temperatures.
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