Article VII

"Theory Does Not Support an Osmoxetane Intermediate in the Osmium-Catalyzed Dihydroxylation of Olefins"

Stefan Dapprich, Gregori Ujaque, Feliu Maseras, Agustí Lledós, Djamaladdin G. Musaev, Keiji Morokuma

Theory Does Not Support an Osmoxetane Intermediate in the Osmium-Catalyzed Dihydroxylation of Olefins

Stefan Dapprich,1 Gregori Ujaque,2 Felicí Maseras,1,4 Agustí Lledó,4 Djamaladdin G. Musaev,4,1 and Keiji Morokuma*3

Chemistry and Science Computation
Emory University, Atlanta, Georgia 30322
Unidad de Química Física, Departamento de Química
Universitat Autònoma de Barcelona
08193 Bellaterra, Barcelona, Spain
Laboratoire de Structure et Dynamique des Systèmes Moléculaires et Solides
U.M.R. 5636, Université de Montpellier II
34095 Montpellier Cedex 5, France

Received July 29, 1996

The osmium-catalyzed asymmetric dihydroxylation of olefins (Scheme 1) is a highly efficient and experimentally well-studied example of the application of transition metal complexes for practical syntheses of biologically important compounds.1 Its outstanding selectivity and broad scope is unique for an organic reaction. However, despite the large number of experimental studies a conclusive determination of the reaction mechanism has not yet been achieved.1–4 On the contrary, a certain controversy on the subject can be found in recent chemical literatures.5–7 At this point, two major pathways for the formation of the cyclic ether intermediate are supported by different experimental data provided by different research groups.

One pathway postulates an initial [2 + 2] cycloaddition leading to an osmoxoetane intermediate, followed by a rearrangement to a five-membered ring, the osmium(VI) glycolate product.8,9 Kinetic studies have shown this nonlinear temperature—enantioselectivity relationship, strongly supporting the presence of an intermediate on the reaction pathway and at least two selectivity-determining steps.7 The other suggested pathway is a concerted [2 + 3] cycloaddition, leading directly to the formation of the primary product.4–10 In cases where monodentate chiral bases were used, a rapid, reversible formation of an osmium—Os(VIII) π—d complex prior to the [2 + 3] cycloaddition step should appear.5 This enzyme—substrate-like complexation has been shown to follow Michaelis—Menten kinetics.5 However, none of the mechanisms have been proven directly; though a number of indirect evidences is accumulated in favor of each of them.

Theoretical calculations have not yet been able to solve this controversy.11–14 An ab initio study based on Hartree—Fock (HF) geometry optimizations could not locate the transition states (TS) because of the large effect of correlation energy.12 Molecular mechanics have been able to explain experimental stereoselectivity in a satisfactory way.13 Remarkably, the same qualitative results have been obtained through the assumption of each of the two possible mechanisms mentioned above.13,14

In this paper, we present the theoretically determined structures and energetics for the transition states and products for the [2 + 2] and [2 + 3] cycloaddition steps without base and with one and two NH3 ligands as model bases. Figure 1 shows the calculated geometries and energies without base, and Figure 2 shows those with one and two NH3 ligands. Experimental structures for some related cyclic ether intermediates are in very good agreement with our theoretical values. For example, the experimental Os—N distance (2.243 Å) in complex 9 with pyridine as a coligand, the X-ray determined bond lengths are 1.72 Å for Os=O (1.78 Å calc.), 1.95 Å for Os—O (1.957 Å calc.), and 2.21–2.24 Å for Os—N (2.234 Å calc.).15 Without base, the formation of a four-membered ring 2 via [2 + 2] cycloaddition is calculated to be endothermic by 17.1 kcal/mol. The [2 + 3] cycloaddition leading to structure 4 is an exothermic process (−15.8 kcal/mol). The QCISD(T)/HF results by Veldkamp and Frenking16 (−13.6 kcal/mol for the reaction OsO2 + C2H4 —→ 2 and −16.7 kcal/mol for OsO2 + C3H4 —→ 4) are qualitatively in agreement with the present accurate energies at the CCSD(T) level. On the basis of the energetics of the reaction, these authors concluded that the [2 + 2] addition intermediate was at least energetically accessible on the potential energy surface. The optimized transition states 1 and 3 for the reaction pathways leading from the reactants to the intermediates 2 and 4 are also shown in Figure 1. Arrows indicate the eigenvectors of the imaginary frequency, showing the approach of each olefinic carbon center to its respective oxygen or osmium atom.

The activation barrier of 43.3 kcal/mol for the [2 + 2] pathway is very high. This result makes a [2 + 2] cyclization as an initial step of the osmium-catalyzed dihydroxylation highly unfavorable. In contrast, the activation barrier for the [2 + 3] addition is only 1.9 kcal/mol, which is even much lower than the energy of the [2 + 2] intermediate 2 (17.1 kcal/mol). The TS is very reactant-like with a carbon—oxygen distance of 2.365 Å. The carbon—carbon bond (1.374 Å) is slightly elongated in comparison with free ethene (1.348 Å). Our calculations strongly suggest that the osmium-catalyzed dihydroxylation involving a [2 + 2] cycloaddition step is practically impossible under base-free conditions. It was discovered very recently that similar results are obtained by Frenking and co-workers.18

Is this conclusion valid if bases are included? Figure 2 shows, in comparison with Figure 1, that the energetical changes of

1 Emory University.
2 Universitat Autònoma de Barcelona.
3 Université de Montpellier II.
17 Pidun, U; Boehme, C.; Frenking, G. Angew. Chem. 1996 In press.
activation barrier of 50.4 kcal/mol is even higher than under base-free conditions. The formation of the osmium(VI) glycolate ester 8 is more exothermic (−23.5 kcal/mol) than without NH$_3$ (−15.8 kcal/mol). In conjunction with a very low TS, which is only 1.4 kcal/mol higher than the reactants, these facts are compatible with the observation that the reaction is accelerated in the presence of bases.

For the reaction path with two NH$_3$ ligands coordinated on osmium the formation of the [2 + 3] intermediate 9 is energetically favored by 38.3 kcal/mol. In this case, there is no energy barrier between the reactants and the product, and the reaction is simply downhill. With two NH$_3$ ligands, the four-membered intermediate would require a seven-coordinated metal atom, and a [2 + 2] mechanism is not possible.

Our calculations have clearly shown that the reaction mechanism of the osmium-catalyzed dihydroxylation of olefins cannot involve a [2 + 2] intermediate, whether it is base-free or base-assisted. Even when the Gibbs free energies are used, the conclusion is unchanged. At the present time, we do not have an alternative explanation of the observed nonlinear Eyring relationship, which is attributed to a stepwise process. An explanation might involve either interactions between the olefin and large bases used in experiment or important influences of solvent molecules. Work along this line is in progress. The mechanism of the osmylation reaction still remains as a challenge for both experiment and theory.
Article VIII

"Theoretical Characterization of an Intermediate for the [3+2] Cycloaddition Mechanism in the Bis(dihydroxyquinidine)-3,6-Pyridazine-Osmium Tetroxide-Catalyzed Dihydroxylation of Styrene"

Gregori Ujaque, Feliu Maseras, Agustí Lledós

Chapter 4. Results

Theoretical Characterization of an Intermediate for the [3 + 2] Cycloaddition Mechanism in the Bis(dihydroxyquinidine)-3,6-Pyridazine-Osmium Tetroxide-Catalyzed Dihydroxylation of Styrene

Gregori Ujaje, F. Feltu Maseras, and Agusti Lledós

Received July 23, 1997

The recent application of non-local DFT methods to the location of transition states, with however not possible because of the need for electron definitve clarification of the reaction mechanism was necessary. In particular, there has been a lot of controversy on the precise mechanism of the key step in the theoretical study of epoxylation processes. Diffrent pathways have been postulated, but all of them seem to summarize in two major proposals: (i) a concerted [3 + 2] cycloaddition of two oxygens to the olefin bond and (ii) a stepwise mechanism starting with a [2 + 2] addition of the olefin to an Os–O bond and going through an osmaoxoethane intermediate.1,8

Theoretical work has been also devoted to this topic. Early extended Hückel studies predicted a [3 + 2] mechanism for the [3 + 2] mechanism found support in the theoretical study of epoxyation processes.12 The definitive clarification of the reaction mechanism was however not possible because of the need for electron correlation in the location of transition states, with results based in RHF-optimized geometries being inconclusive.13 The recent application of non-local DFT methods to the model system OsO2(NH2) + CH2Ph has provided a substantial boost to the [3 + 2] proposal, with similar results by us14 and two other groups1,16 indicating a difference in energy barriers as large as 53.8 kcal/mol between the two mechanisms. These theoretical studies have however failed to locate any intermediate in the reaction, an intermediate that is required by the experimental evidence emerging from the independent experiments indicating the existence of an inversion point in the Eyring plot18 and a Michaelis-Menten kinetics.19 The nature of such an intermediate remains unknown, having been postulated from experiments to be either the [2 + 2] osmaoxoethane1,9 or a weak olefin–Os(VIII) π–d complex.5,10

This paper presents the application of the hybrid method IMOMM17 to this problem. This method, mixing quantum mechanics (QM) and molecular mechanics (MM) descriptions for different parts of the same system, has already been proved successful in a number of examples,16–20 including a case with complexes related to the process under study.20 The use of an MM description for part of the system is the only option allowing the introduction in the calculation of the large NR3 ligand, which is indeed the key factor deciding the stereoselectivity of the reaction. Pure MM studies previously carried out on these systems21 had the serious limitation of relying on MM parameters for osmium, not necessarily well fitted to this reaction.

IMOMM(becke3lyp:mm3) calculations are carried out on the [DHOQD]2PYDZ-OsO4, [DHOQD]2PYDZ = bis(dihydroxyquinidine)-3,6-pyridazine + CH2Ph system. This system is chosen because, despite its relative simplicity, it provides a high experimental enantioselectivity for the R product and because there are a lot of experimental data available as a result of the extensive work by Corey, Noe, and their coworkers.20 These available data are used to choose the conformation of the reactant, as well as the disposition of the phenyl substituent in the attacking styrene.

Full geometry optimizations succeed in locating four different stationary points: the separated reactants (1), the intermediate (2), the transition state (3), and the osmium(VI) glycolate product (4). The transition state 3 has a negative eigenvalue of −0.070 au in the approximate Hessian, with the in-plane Os–O eigenvalue having large components in the O–C distances. The connection of 2 and 4 through 3 is further proved by downhill geometry optimizations with small step size from 3. The possible transition state connecting 1 and 2

145


Corresponding parameters of the BECKE3LYP optimizations of the model system with the same basis set are shown in parenthesis for comparison.

Figure 1. IMOMM(BECKE3LYP:MM3)-optimized geometries (Å) of the reaction center in transition state 3 and product 4. The geometry of intermediate 2 (Figure 2) presents several interesting features. In first place, the cinchona ligand takes the U-shape conformation predicted by Corey and Noe based on experimental results. The formation of the intermediate 2 seems to be associated to an attractive π–π interaction between the aromatic ring of the substrate and one of the methoxyquinoline rings of the cinchona ligand and the phenyl substituent of the substrate.

The results presented in this paper provide the first theoretical characterization of an intermediate for the [3 + 2] cycloaddition of a substituted olefin to a OsO₄(NR₃) catalyst. The results of the studied system, (DHQD)²-PYDZ-OsO₄ + CH₂=CHPh, complement proposals by Corey and Noe based on experimental results.

The formation of the intermediate 2 seems to be associated to an attractive π–π interaction between the aromatic ring of the substrate and one of the methoxyquinoline rings of the ligand, rather than with a π–d interaction of the olefin with the metal center. It has to be admitted, however, that although this type of attractive π–π interaction explains a number of the experimental observations, it does not account for all of them. The observation of an inversion point in the Eyring plot of systems with alkyl-substituted olefins may be attributed to attractive interactions between the alkyl groups and the π system of the NR₃ ligands, but the explanation of recent results indicating the existence of inversion points in systems with base-free OsO₄ is more troublesome. In any case, it is worth mentioning that regardless of the significance of the presence of inversion points on these Eyring plots, which has been called into question, the existence of an intermediate in the particular system studied here is also required by its Michaelis–Menten kinetics. Although the full clarification of these mechanistic features will surely require...
additional experimental studies, we feel that the application of the IMOMM method presented in this paper opens a promising way for the theoretical method to contribute to the understanding of this important process.

**Computational Details**

IMOMM calculations are performed with a program built from modified versions of the standard programs Gaussian 92/DFT and mm3(92). The MO calculations are carried out on the OsO$_4$ + NH$_3$ system at the BECKE3LYP level. The basis set is LANL2DZ for Os, 6-31G(d) for O, and 6-31G for N, C, and H. Molecular mechanics calculations use the MM3(92) force field and Van der Waals parameters for Os are taken from the UFF force field. Torsional contributions involving dihedral angles with the metal atom in terminal position are set to zero.

(23) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. B.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian 92/DFT, Gaussian Inc, Pittsburgh PA, 1993.

(24) Allinger, N. L. mm3(92); QCPE: Bloomington IN, 1992.


Notes

All geometrical parameters are optimized except for the bond distances connecting the QM and MM parts: N–H (1.015 Å) and C–H (1.011 Å) in the ab initio calculation and N–C (1.448 Å) and C–C (1.434 Å) in the molecular mechanics calculation.

**Acknowledgment.** We thank Prof. K. Morokuma (Emory) for helpful advice. F.M. thanks the CNRS for a position of Research Associate. G.U. and A.L. acknowledge financial support from the DGES through project No. PB95-0639-C02-01.

**Supporting Information Available:** Optimized geometrical structures in Cartesian coordinates for all stationary points, both at the pure QM level for the model system, and at the IMOMM level for the real system (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

J0971345B
Article IX

"Theoretical Study on the Origin of Enantioselectivity in the Bis(dihydroquinidine)-3,6-Pyridazine·Osmium Tetroxide-Catalyzed Dihydroxylation of Styrene"

Gregori Ujaque, Feliu Maseras, Agustí Lledós

*J. Am. Chem. Soc.*, Accepted.
Chapter 4. Results

Theoretical Study on the Origin of Enantioselectivity in the Bis(dihydroquinidine)-3,6-pyridazine-Osmium Tetroxide-Catalyzed Dihydroxylation of Styrene

Gregori Ujare, Felip Maseras,* and Agustí Lledós

Contribution from the Unitat de Química Física, Edifici C.n, Universitat Autònoma de Barcelona,
08193 Bellaterra, Catalonia, Spain

Received May 11, 1998

Abstract: The origin of enantioselectivity in the dihydroxylation of H2C=CH(Ph) catalyzed by (DHQD)2PYDZ-OsO4 (DHQD)2PYDZ = bis(dihydroquinidine)-3,6-pyridazine) is analyzed theoretically by means of hybrid QM/MM calculations with the IMOMM(Becke3LYP:MM3) method. Twelve different possible reaction paths are defined from the three possible regions of entry of the substrate and its four possible orientations and characterized through their respective transition states. The transition state with the lowest energy leads to the R product, in agreement with experimental results. The decomposition of the interaction energy between catalyst and substrate shows how the selectivity is essentially governed by stacking interactions between aromatic rings, with a leading role for the face-to-face interaction between the substrate and one of the quinoline rings of the catalyst.

Introduction

The osmium-catalyzed dihydroxylation of olefins is a powerful method for the enantioselective introduction of chiral centers in organic substrates.1,2 The key step of the reaction, where the chirality of the diol product is decided, is the formation of a cyclic oxaime ether intermediate. The detailed mechanism of formation of this intermediate has been obscure for a long time,3-6 and only recently is a consensus emerging in favor of the so called [3 + 2] model, where the reaction takes place through a concerted cycloaddition of two oxygens to the olefin bond. Theoretical ab initio studies on the OsO4(NH3)2 + H2C=CH2 model system have been determinant in the creation of this consensus, because they predict a difference of ca. 200 kJ mol-1 between the [3 + 2] mechanism and the alternative [2 + 2] mechanism.7-10 Other recent support for the [3 + 2] mechanism has come from a critical analysis of available experimental data,11 and from new measurements of kinetic isotope effects.12-13

Despite its undisputable relevance, the preference for the [3 + 2] model does not provide in itself an explanation to the stereoselectivity of the reaction. One can indeed have both enantiomers via the [3 + 2] mechanism. Studies published so far on the origin of stereoselectivity are mostly of a qualitative nature. The analysis by Corey and Noe11 mentioned above is based essentially on the geometrical features of the catalysts and the space available for placement of the substrate. Houk and co-workers12 and Sharpless and co-workers13 have published pure molecular mechanics studies on the problem that compute the correct stereoselectivity. Their predictive power is however questionable because of a certain arbitrariness in the geometry of the reaction center, which is frozen in one case,13 and computed with force field parameters based on the validity of the [2 + 2] model in the other case.14 Another recent pure DFT study15 on the OsO4(NH3)2 + H2C=CH(CHOH) reaction draws its interest from the comparison with purely organic systems, but touches only marginally the topic of enantioselectivity, which is governed in experimental systems by the nature of the bulky cinchona alkaloid attached to the metal.

The goal of the present paper is to provide a quantitative theoretical characterization of the origin of enantioselectivity in the osmium-catalyzed dihydroxylation of olefins. To accomplish it, we have carried out IMOMM calculations on the (DHQD)2PYDZ-OsO4 (1) + H2C=CH(Ph) (2) system. IMOMM is a hybrid method mixing quantum mechanics and molecular mechanics descriptions for different parts of the system,16 the performance of which has been already tested in a satisfactory way for a number of transition metal systems.17-20 In particular, we have already applied it to the study of two

10.1021/ja9816335 CCC: $18.00 © xxxx American Chemical Society
Published on Web 00/00/0000 PAGE EST: 6.5
based on a heterocyclic spacer, in this case pyridazine. The substrate, styrene, has been proved experimentally to show high selectivity with this catalyst, giving in particular an enantiomeric excess of 96 for the R isomer. In a previous work, we studied the reaction of formation of one of the possible osmate products from the reactants, and characterized an intermediate and a transition state along the reaction path. In the present paper, the study is extended to all the possible osmate products, the barrier for each path being characterized by the energy of its transition state. The energies of the more relevant transition states are then decomposed and compared term by term to quantify the different factors defining the selectivity. Different from previous studies, this work is carried out through a first principles method such as IMOMM, with full optimization of each of the transition states.

The paper is organized in different sections. After this introduction and the computational details, the sections are concerned with the definition of the possible paths, the determination of the region of entry of the olefin, and the elucidation of the preferred orientation of the olefin within this region. The final sections contain an overall view of the mechanism of selectivity and the conclusions.

**Computational Details**

IMOMM calculations were performed with a program built from modified versions of the standard programs Gaussian 92/DFT for the quantum mechanics part and MM3(92) for the molecular mechanics part. The molecular orbitals calculations were carried out on the QM part. The molecular mechanics part was performed with a program built from the modified versions of the standard programs Gaussian 92/DFT and MM3(92) on both the isolated and complexed ligand.

**Results**

The computational algorithms applied are efficient in the search of single local minima, but they are not capable of carrying out a conformational search, i.e., the search for the most stable of all possible local minima. Because this limitation could be critical in a system with so many atoms, special care was taken in the choice of the conformation of the cinchona ligand. Our starting geometry for the ligand was taken from previous experimental (X-ray and NMR) and theoretical studies (MM) on both the isolated and complexed ligand. Furthermore, in a selected case, to be mentioned, an additional conformational search was also tested.


(23) Allinger, N. L. mol2(92); QCPE: Bloomingtom, IN, 1992.


Chapter 4. Results

29 A second question is whether the R enantiomer, and when it is n or IV the S product is formed.

The joint consideration of the three regions of the four hydrogens of ethylene, giving rise to four different "regions" A, B, and C, following the same nomenclature used for the placement of the phenyl substituent of the styrene substrate, allows the classification of the different paths into a total of twelve different pathways. The overall consideration of the osmate ester, one must take into account all the different transition states associated with the formation of the o xoammonium intermediate in the reaction path.

Twelve Possible Pathways

To investigate the transition state associated with the formation of the o xoammonium ester, one must take into account all the different pathways in which the olefin 2 can approach catalyst 1. These different pathways are classified according to the criteria depicted in Figure 1. Figure 1a shows the possible regions of approach of the olefin to the catalyst from a top view along the O—Os—N axis. Catalyst 1 has a trigonal bipyramidal coordination around the metal, with the O(Os) and C(N) substituents taking a staggered orientation with respect to the Os—N bond. The alkene forms bonds with the axial and with one of the three equatorial oxygen atoms. Since the three equatorial oxygen atoms are not equivalent, the approach of each of them defines therefore a distinct family of reaction paths, which we have labeled as "regions" A, B, and C, following the same nomenclature proposed by Sharpless and co-workers. A second question is whether the R enantiomer, and when it is n or IV the S product is formed. The joint consideration of the three regions of approach and the four possible positions of the phenyl ring per region yield a total of twelve different pathways. The overall selectivity of the reaction depends on the orientation of the substrate. When the orientation is I or III, the final diol product is the R enantiomer, and when it is II or IV the S product is obtained.

Each of these twelve possible paths were theoretically characterized through the location of the corresponding transition state, their energies being collected in Table 1. The energies are relative to that of the lowest transition state, B-I, to emphasize the comparison between different paths. The values generally should be ca. 25 kJ-mol⁻¹ above those of the corresponding intermediates. It is noteworthy that each of the twelve calculations converged to a different saddle point in the potential energy hypersurface, with a negative eigenvalue in the approximate Hessian, and with the corresponding eigenvector having large components in the O—C distances. There are therefore twelve different geometries to be analyzed, each with its corresponding energy. The reaction is in any case going to proceed mostly through the lowest energy saddle point, which will be the true transition state of the reaction.

The nature of the lower energy paths and the factors defining their preference are going to be discussed in detail in the next sections, but a first general discussion on Table 1 can already be made here. The decomposition of the energy in quantum mechanics (QM) and molecular mechanics (MM) parts shows that the differences are mostly in the MM part (differences of up to 35.2 kJ-mol⁻¹) with differences in the QM part being much smaller (a maximum difference of 6.9 kJ-mol⁻¹). This is an important point, because it proves that the enantioselectivity is governed by the steric interactions between the catalyst and the olefin.

Table 1. Relative IMOMM(Becke3LYP-MM3) Energies (kJ-mol⁻¹) of the Transition States Associated to Each of the 12 Possible Reaction Paths:

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>QM</td>
<td>MM</td>
<td>total</td>
</tr>
<tr>
<td></td>
<td>-3.0</td>
<td>0.00</td>
<td>-2.2</td>
</tr>
<tr>
<td>II</td>
<td>QM</td>
<td>MM</td>
<td>total</td>
</tr>
<tr>
<td></td>
<td>-1.7</td>
<td>-0.4</td>
<td>1.2</td>
</tr>
<tr>
<td>III</td>
<td>QM</td>
<td>MM</td>
<td>total</td>
</tr>
<tr>
<td></td>
<td>-2.4</td>
<td>2.7</td>
<td>3.9</td>
</tr>
<tr>
<td>IV</td>
<td>QM</td>
<td>MM</td>
<td>total</td>
</tr>
<tr>
<td></td>
<td>-1.7</td>
<td>0.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* All energies are relative to that of the lowest transition state (B-I). Reaction paths are labeled following Figure 1.

The fact that the differences between the several transition states are mostly in the MM part may put into question the real need of the IMOMM method for this problem. The application of the simpler MO-then-MM approach has however serious problems related to the nature of the more stable arrangement of hydrogen substituents resulting from MO calculation, and test calculations of this type yielded unsatisfactory results.

Region of Entry of the Substrate: A, B, or C?

The discussion on which are the lower energy paths is divided in two parts. In this section, the region of entry of the olefin is defined. It can be seen in Table 1 that the three lower energy saddle points correspond to region B: B-I, B-III, and B-IV, with relative energies of 0.0, 0.4, and 11.1 kJ-mol⁻¹, respectively. Although the other saddle point corresponding to this region, B-II, is somehow higher in energy at 22.6 kJ-mol⁻¹, there is no doubt that this is the preferred region of entry for the olefin. The lowest energy saddle points for regions A and C are at ca. 20 kJ-mol⁻¹ above that for region B. This computed preference for region B is in full agreement with the suggestions emerging from kinetic observations by Sharpless and co-workers. In a thorough study on the (DHQD)₂PHAL-OsO₄/((DHQD)₂PHAL = bis(dihydroquinidine)phthalazine) catalyst, they found that the nature of substituents at C₂ and, especially, O₂ (Figure 1a), affects substantially the rate of the reaction. These substituents are likely to affect mostly the B region.

The fact that region B is preferred over region A has a direct consequence on the nature of the steric interactions between catalyst and substrate. It is clear from Figure 1a that region A has the least steric crowding. Therefore the magnitude of steric interactions must be smaller in region A than in region B. The fact that the energy of the saddle points is lower in region B can only mean that the steric interactions are of an attractive nature. This is in fact also fully consistent with the existence of an intermediate in the reaction path. B is therefore the preferred region for the reaction, and the discussion on enantioselectivity in the next section will be carried out only within this region. It is, however, worth noticing that enantioselectivity happens precisely in the way it happens...
because the reaction goes through region B. If the reaction went through the less sterically hindered region A, there would be almost 50% of R and S products, coming from the very close relative energies of the saddle points corresponding to isomers A-I (20.2 kJ·mol⁻¹) and A-IV (19.6 kJ·mol⁻¹). If the reaction were to go through path C the main product would actually be the S isomer (either through path C-IV, 20.4 kJ·mol⁻¹, or C-II, 20.7 kJ·mol⁻¹), with a minor nonneglectable quantity of the R product (through path C-I, 27.3 kJ·mol⁻¹). Therefore, the overall R selectivity of the reaction is intimately related to the fact that it goes through region B.

**Orientation of Substrate within Region B: I, II, III, or IV?**

After showing that the reaction goes through region B, the analysis shifts to which is the preferred orientation of the substrate within this region. This is the point where selectivity is decided, since isomers I and III lead to the R product, and isomers II and IV lead to the S product. The results, collected in Table 1, are conclusive, the R isomer will be formed, because the two lowest energy saddle points (with an energy difference of only 0.4 kJ·mol⁻¹ between them) are B-I and B-III.

Experimental results on this system show that the product is the R enantiomer, being therefore in good agreement with these calculations. The agreement reaches even the value of the enantiomeric excess. Its computational estimation relies on some hypothesis, namely that the ratio of the products follows that of a Maxwell–Boltzmann distribution based on the internal energies of the transition states at 0 K. Accepting this hypothesis, one obtains a ratio of reaction paths of 53.5% through path B-I, 45.9% through path B-III, and 0.6% through path B-IV. Since both B-I and B-III give the R isomer, this would mean a proportion of 99.4% of R product, in good agreement with the reported experimental enantiomeric excess of 96.1%. This is indeed a quite remarkable success for the first-principles IMOMM method.

Since this is the point where the enantioselectivity is decided, the properties of these saddle points are analyzed in some detail. The optimized structures of the three lower energy isomers, B-I, B-III, and B-IV, are presented in Figures 2, 3, and 4, respectively. Before entering in the discussion of each of the geometries it is worth mentioning that we confirmed that B-III was in its lowest energy conformation through an additional calculation. This geometry was specially doubtful because a similar geometry had been proposed from molecular mechanics calculations on the [2 + 2] reaction mechanism but with a slightly different conformation. We performed a full search of the saddle point starting from the alternative conformation of the cinchona group and reached a saddle point that was 9.3 kJ·mol⁻¹ above the structure for B-III presented above. This alternative structure is presented in Figure 5, and the difference from the most stable structure (Figure 3) is in the arrangement of the quinoline group labeled as "quinoline A", in particular a rotation of ca. 180° of the dihedral angle around the C–C bond connecting the quinoline to the rest of the catalyst. This alternative conformation will not be discussed any further because of its higher energy.

From Table 1 it is clear that most of the energy difference between the different saddle points is in the MM part, with the QM part being quite similar. Additional calculations were carried out to analyze the different contributions to the MM energy. In the first place, the interaction energy between substrate and catalyst is separated into binding and distortion contributions. To do this, the process of formation of each saddle point from the separate reactants is divided into two imaginary steps: (i) the first step where the catalyst and the substrate at infinite distance are distorted to the geometry they have in the saddle point (distortion energy) (ii) and the second step where they are put together to yield the saddle point structure (binding energy). The results of this analysis are collected in Table 2.
Enantioselectivity in the Dihydroxylation of Styrene

Figure 4. Two different views of the IMOMM(Becke3LYP:MM3) optimized transition state B-IV. The styrene substrate and the OsO₄ unit are highlighted in black.

Figure 5. Two different views of the IMOMM(Becke3LYP:MM3) optimized structure of the alternative higher energy conformer of transition state B-IV. The styrene substrate and the OsO₄ unit are highlighted in black.

Table 2. Decomposition of the Interaction Energy (E) in Binding Energy (E_b) and Distortion Energy (E_d) for Each of the IMOMM(Becke3LYP:MM3) Saddle Points Associated to Reaction Paths through Region B*

<table>
<thead>
<tr>
<th></th>
<th>E_b</th>
<th>E_d</th>
<th>E_t</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>19.6</td>
<td>-33.5</td>
<td>-13.8</td>
</tr>
<tr>
<td>MM</td>
<td>-13.8</td>
<td>64.3</td>
<td>-78.2</td>
</tr>
<tr>
<td>total</td>
<td>-10.5</td>
<td>24.9</td>
<td>-35.4</td>
</tr>
<tr>
<td>II</td>
<td>8.7</td>
<td>75.7</td>
<td>-67.3</td>
</tr>
<tr>
<td>MM</td>
<td>17.0</td>
<td>48.8</td>
<td>-31.8</td>
</tr>
<tr>
<td>total</td>
<td>-13.4</td>
<td>54.3</td>
<td>-67.7</td>
</tr>
<tr>
<td>III</td>
<td>18.1</td>
<td>47.1</td>
<td>-29.0</td>
</tr>
<tr>
<td>MM</td>
<td>-30.4</td>
<td>5.5</td>
<td>-35.9</td>
</tr>
<tr>
<td>total</td>
<td>-2.7</td>
<td>33.6</td>
<td>-56.3</td>
</tr>
</tbody>
</table>

*All energies are in kJ·mol⁻¹.

The analysis can be further refined to see which are the specific parts of the catalyst contributing to the binding energy. This can be done because the IMOMM partition in this particular system leaves most of the binding between catalyst and substrate in the MM part. The MM binding energies oscillate widely between -27.4 and -47.8, while the QM change is very small in comparison, with changes only between -29.0 and -31.9 kJ·mol⁻¹. Furthermore, the difference is in the so called van der Waals term. The dominance of this particular term can be surprising, but it must be said that it is very likely affected by the choice of the MM3 force field. Other force fields grant a lesser importance to van der Waals terms and give more weight to electrostatic contributions, for instance. If such other force fields had been applied the decomposition would likely be substantially different, and other terms should be more important in defining the difference. In any case, the total difference would have to be similar, as far as the different force fields are properly describing the same chemically reality. So this result is merely used in the sense that the more significant MM contributions correspond to what MM3 calls van der Waals interactions, without entering in the real chemical meaning of such terms.

Whatever the real chemical meaning of the MM3 van der Waals term, it has the very useful property for analysis of being defined by interactions between pairs of atoms. Using this fact, the interaction between the substrate atoms and those of the catalyst has been divided in different blocks for the four saddle points of region B, and the results are collected in Table 3. The different parts of the catalyst that have been considered are the two quinoline rings sandwiching the styrene substrate, labeled arbitrarily as quinoline A and quinoline B, the pyridazine spacer PYDZ, the OsO₄ unit, and the rest of the molecule. This classification is closely related to the analysis of the binding pocket that has been carried out previously by the groups of
interactions in this particular system.

The interactions between substrate and the two quinoline rings is well characterized in other chemical systems, and its consistency with the higher selectivity associated with the second face-to-face interaction with quinoline A. Quinoline A is the most important interaction for B-I, B-III, and B-IV is the face-to-face interaction with quinoline B and the face-to-edge interaction between styrene and pyridazine is face-to-edge. This type of interaction is well characterized in other chemical systems, and its existence is therefore not surprising here. It is moreover in agreement with the previously postulated importance of π-π interactions in this particular system.

As for their relative importance, it is clear from Table 3 that the most important interaction for B-I, B-III, and B-IV is the face-to-face interaction with quinoline A. Quinoline A is the one furthest away from the metal center, and its importance is consistent with the higher selectivity associated with the second generation catalysts. The dominance of the face-to-face interaction with quinoline A does not mean in any case that the face-to-face interaction with quinoline B and the face-to-edge interaction with the pyridazine is neglectable. This is still sufficient to allow for the enantioselectivity of first-generation catalysts, and can have a decisive importance in distinguishing between some paths.

Despite the fact that they have almost the same energy and lead to the same product, saddle points B-I and B-III have a series of differences. Saddle point B-I is the one that had been considered in previous analysis of the [3 + 2] mechanism, and indeed has the lowest energy. It has a good overlap between quinoline A and styrene (Figure 2), reflected in the largest distortion energy of 64.3 kJ·mol⁻¹. Saddle point B-III, a variant of which had been proposed as active in the [2 + 2] mechanism, has an energy only 0.4 kJ·mol⁻¹ higher. In this case, the interaction energy is less favorable (—67.7 kJ·mol⁻¹), but the distortion from the reactant structure is also significantly smaller (54.3 kJ·mol⁻¹). In what concerns the interaction with the different regions of the catalyst (Table 3), for both B-I and B-III the main interaction is the face-to-face interaction.

---

The labeling of the areas of the catalyst is indicated in Figures 2 to 4. Energies are indicated in kJ·mol⁻¹, with percentages with respect to total interaction in parentheses.

Corey and Sharpless Quinolines A and B define the parallel walls of the U-shaped binding pocket, with the pyridazine defining the bottom wall.

The results, collected in Table 3, allow a quantification of the relative importance of the different regions of the catalyst in the stereoselectivity of the reaction. The first result worth remarking on is how three of the considered fragments, quinoline A, quinoline B, and PYDZ, always account for more than 75% of the MM interaction between catalyst and substrate, showing the appropriateness of the analysis in terms of these fragments.

The interactions between substrate and the two quinoline rings are face-to-face stacking interactions and the interaction between styrene and pyridazine is face-to-edge. This type of interaction is well characterized in other chemical systems, and its existence is therefore not surprising here. It is moreover in agreement with the previously postulated importance of π-π interactions in this particular system.

As for their relative importance, it is clear from Table 3 that the most important interaction for B-I, B-III, and B-IV is the face-to-face interaction with quinoline A. Quinoline A is the one furthest away from the metal center, and its importance is consistent with the higher selectivity associated with the second generation catalysts. The dominance of the face-to-face interaction with quinoline A does not mean in any case that the face-to-face interaction with quinoline B and the face-to-edge interaction with the pyridazine is neglectable. This is still sufficient to allow for the enantioselectivity of first-generation catalysts, and can have a decisive importance in distinguishing between some paths.

Despite the fact that they have almost the same energy and lead to the same product, saddle points B-I and B-III have a series of differences. Saddle point B-I is the one that had been considered in previous analysis of the [3 + 2] mechanism, and indeed has the lowest energy. It has a good overlap between quinoline A and styrene (Figure 2), reflected in the largest distortion energy of 64.3 kJ·mol⁻¹ (Table 2). However, this is accomplished through a quite important distortion energy of 78.2 kJ·mol⁻¹ (Table 2). Moreover, this is accomplished through a quite important distortion energy of 64.3 kJ·mol⁻¹. Saddle point B-III, a variant of which had been proposed as active in the [2 + 2] mechanism, had an energy only 0.4 kJ·mol⁻¹ higher. In this case, the interaction energy is less favorable (—67.7 kJ·mol⁻¹), but the distortion from the reactant structure is also significantly smaller (54.3 kJ·mol⁻¹). In what concerns the interaction with the different regions of the catalyst (Table 3), for both B-I and B-III the main interaction is the face-to-face interaction.

---

Relationship to the Mechanism of Stereoselectivity with Other Substrates

Our calculations on the mechanism of the reaction of styrene with (DHQD)²PYDZ-OsO₄ reproduce properly the experimental stereoselectivity and provide a detailed explanation for its origin, but also have implications on the general mechanism of stereoselectivity for other substrates and catalysts. In this section we try to place these results into the context of known data and previous mechanistic proposals for these processes.

One point worth commenting on is that our results indicate that the reaction goes almost indistinctly through two different paths (B-I and B-III) leading to the same product. Remarkably, variations of both paths had already been proposed, but they have been used as supporting evidence for two opposing mechanistic proposals, the [3 + 2] and [2 + 2] mechanisms. Now that the reaction has been proved to take place through the [3 + 2] mechanism, it is not surprising to find that the reaction can go through the B-I path, which previously had been associated with this mechanism. But it was unexpected to find a competitive energy for path B-III, a variety of which had been used to support the now disproved [2 + 2] mechanism. The two paths that had presented as opposed, therefore happen to complement each other.

The relative energies for the four possible orientations of the styrene within region B (Table 1) suggest that, with this catalyst, a trans-disubstituted olefin should give higher stereoselectivity, and that a cis-disubstituted olefin should give a lower one. Both observations are in agreement with previous experimental reports. The dihydroxylation of cis-disubstituted olefins is in fact efficiently catalyzed only by osmium complexes containing...
Enantioselectivity in the Dihydroxylation of Styrene

Results reported in Table 3 concerning the effect of different areas of the catalyst are also in overall agreement with the empirical mnemonic device to predict stereoselectivity derived by Sharpless and co-workers from extensive experimental data. Extrapolation of the results obtained with the (DHQD)2PYDZ-OsO4 + H2C=CH(Ph) system likely produces certain explanations to a number of observed experimental features, but definite answers can only come from calculations on each specific system. In particular, further calculations could provide a precise characterization of the origin of the differences observed between six classes of olefin substrates, which are already somehow suggested in Table 1. Explanation of other experimental results would require new calculations. This is the case for the behavior of substrates with only saturated chains attached to the olefin, or larger substrates where the aromatic substituent is far away from the double bond. The performance of such calculations exceeds however the scope of the present paper, since although the method applied permits the study of systems which could not be treated before, the calculations still require a considerable amount of computational and human effort.

A final point concerning the relationship of the present theoretical results with experimental data is the fact that our calculations completely neglect solvation effects. This is obviously a limitation in the reproduction of the experiment, where a certain dependence of the enantiomeric excess on the nature of the solvent has in fact been reported. On the other hand, this situation has the advantage of allowing the computational experiment of carrying out the reaction without solvent. The results are conclusive in the sense that, for this particular substrate and catalyst, the calculation in the absence of solvent agrees well with the experimental observation for the dihydroxylation under conventional conditions.

Conclusions

The origin of enantioselectivity in the asymmetric dihydroxylation of styrene catalyzed by (DHQD)2PYDZ-OsO4 has been analyzed through theoretical calculations with the IMOMM method. The twelve different possible paths of approach have been examined and characterized through the energy of these transition states. The two lower energy paths are associated with the R isomer, and the lower path leading to the S isomer is 11.1 kJ-mol\(^{-1}\) higher in energy. This would lead to a 99.4% formation of the R product, in good agreement with the experimental observation of an enantiomeric excess of 96.

The analysis of the corresponding transition states leads to the identification of the factors governing the selectivity. The leading role is played by stacking interactions between aromatic rings of olefin and catalyst. These are the plane-to-plane interactions between the substrate and the two quinoline rings of the catalyst, as well as the plane-to-edge interaction between the substrate and the pyridazine ring. The larger contribution corresponds to the interaction with the quinoline ring of the second subunit of the "dimeric" catalyst, which has been labeled as quinoline A, accounting for ca. 50% of the total stabilization.

Acknowledgment. This paper is dedicated to Prof. Keiji Morokuma on the occasion of his 65th birthday. Financial support from the Spanish DGES through Project No. PB95-0639-C02-01 is acknowledged. FM thanks the French CNRS for financial support as a Research Associate.
References
References


(11). V. Fock, Physik, 61, 126 (1929).


List of Publications
Article I

“Computational Evidence of the Importance of Substituent Bulk on Agostic Interactions in Ir(H)₂(P'Bu₂Ph)₂”

Gregori Ujaque, Alan C. Cooper, Feliu Maseras, Odile Eisenstein and Kenneth G. Caulton


Article II

“Theoretical and Synthetic Studies on Dihaptoacyl and β-Agostic Acyl Complexes of Molybdenum”

Gregori Ujaque, Feliu Maseras, Agustí Lledós, Leopoldo Contreras, Antonio Pizzano, Dieter Rodewald, Luis Sánchez, Ernesto Carmona, Angeles Monge and Caridad Ruiz

*Organometallics*, submitted ................................................................. 81

Article III

“Different van der Waals Radii for Organic and Inorganic halogen atoms: a Significant Improvement in IMOMM Performance”

Gregori Ujaque, Feliu Maseras and Odile Eisentein

Article IV

"Breaking an Electronically Preferred Symmetry by Steric Effects in a Series of [Ir(biph)X(QR₃)₂] Compounds (X = Cl, Q = P or As)"

Gregori Ujaque, Feliu Maseras, Odile Eisenstein, Louise Liable-Sands, Arnold L. Rheingold, Wenbin Yao and Robert H. Crabree


Article V

"A Comparative Study of DFT and Traditional ab initio Methodologies on the OsO₄ Molecule"

Gregori Ujaque, Feliu Maseras and Agustí Lledós

*Int. J. Quant. Chem.*, submitted .................................................. 117

Article VI

"A Theoretical Evaluation of Steric and Electronic Effects on the Structure of [OsO₄(NR₃)] (NR₃ = Bulky Chiral Alkaloid Derivate)complexes"

Gregori Ujaque, Feliu Maseras and Agustí Lledós

Article VII

“Theory Does Not Support an Osmaoxetane Intermediate in the Osmium-Catalyzed Dihydroxylation of Olefins”

Stefan Dapprich, Gregori Ujaque, Feliu Maseras, Agustí Lledós, Djamaladdin G. Musaev and Keiji Morokuma

*J. Am. Chem. Soc.*, **118**, 11660-11661 ................................. 139

Article VIII

“Theoretical Characterization of an Intermediate for the [3+2] Cycloaddition Mechanism in the Bis(dihydroxyquinidine)-3,6-Pyridazine-Osmium Tetroxide-Catalyzed Dihydroxylation of Styrene”

Gregori Ujaque, Feliu Maseras and Agustí Lledós


Article IX

Theoretical Study on the Origin of Enantioselectivity in the Bis(dihydroquinidine)-3,6-Pyridazine-Osmium Tetroxide-Catalyzed Dihydroxylation of Styrene

Gregori Ujaque, Feliu Maseras and Agustí Lledós

*J. Am. Chem. Soc.*, accepted ........................................... 149