

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

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The osmium-catalyzed asymmetric dihydroxylation of olefins constitutes one of the most successful examples of application of transition metal complexes to the practical synthesis of biologically important compounds.^{1,2} A lot of experimental studies have been devoted to the understanding of the mechanism of this reaction.^{3–10} In particular, there has been a lot of controversy on the precise mechanism of the key step where the stereoselectivity of the reaction is decided, namely the formation of the cyclic ether. Different pathways have been postulated, but all of them seem to be summarized in two major proposals: (i) a concerted [3 + 2] cycloaddition of two oxygens to the olefin bond^{3–5} 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.^{1,6,8}

Theoretical work has been also devoted to this topic. Early extended Hückel studies predicted a [3 + 2] mechanism,¹¹ while the [2 + 2] mechanism found support in the theoretical study of epoxydation 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 OsO₄(NH₃) + C₂H₄ has provided a substantial boost to the [3 + 2] proposal, with similar

results by us¹⁴ and two other groups^{15,16} 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 plot⁹ and a Michaelis–Menten kinetics.¹⁰ The nature of such an intermediate remains unknown, having been postulated from experiments to be either the [2 + 2] osmaoxoethane^{1,9} 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,^{18–20} 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 (DHQD)₂PYDZ–OsO₄ [(DHQD)₂PYDZ = bis(dihydroxyquinidine)–3,6-pyridazine] + CH₂=CHPh 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.^{4,10} 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 corresponding eigenvector 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**

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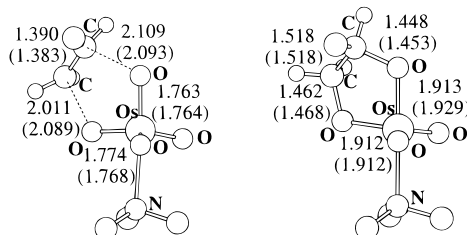


Figure 1. IMOMM(BECKE3LYP:MM3)-optimized geometries (Å) of the reaction center in transition state **3** and product **4**. Corresponding parameters of the BECKE3LYP optimizations of the model system with the same basis set are shown in parenthesis for comparison.

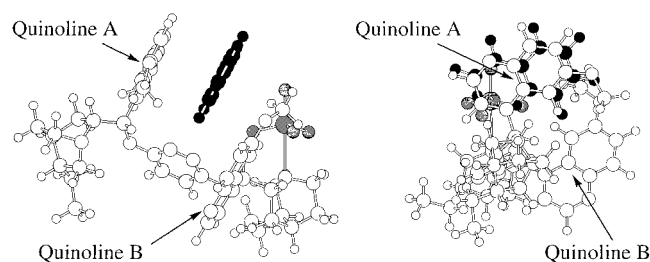


Figure 2. IMOMM(BECKE3LYP:MM3)-optimized structure of intermediate **2**. Atoms in the styrene substrate are depicted in black, and the OsO₄ subunit is depicted in gray. Two views are shown for clarity.

is not located because its transition vector would have its main components in the molecular mechanics part, and the current implementation of the method does not allow this type of calculation.

The relationship between the optimized geometries of transition state **3** and product **4** with those obtained by pure QM optimization of the model system is obvious from the geometrical data collected in Figure 1. Bond distances in the 5-membered ring are practically the same in both calculations for the product, with the larger difference being 0.016 Å. For the transition state there are slightly larger differences, with one of the C–O distances being shorter by 0.078 Å (2.011 vs 2.089 Å) in the IMOMM calculation than in the QM calculation. The transition state is therefore a little later and less symmetric in the IMOMM calculation. Energetics are also quite similar. The IMOMM(BECKE3LYP:MM3) energies of **2**, **3**, and **4** with respect to **1** are –9.7, –3.3, and –34.3 kcal/mol, respectively. The corresponding values for **3** and **4** in the calculation of the model system with the same basis set are 3.9 and –33.6 kcal/mol. The relative energy of the product is practically the same in both calculations (–34.3 vs –33.6 kcal/mol). The transition state appears below the reactants in the IMOMM calculation, but this is related to the appearance of intermediate **2** in the IMOMM calculation. The similarity of the IMOMM geometries for **1**, **3**, and **4** with those obtained on calculations on a model system,^{14–16} as well as that of the energy difference between **1** and **4**, was not granted a priori and has the significant implication that the late stages of this cycloaddition reaction can be faithfully reproduced by calculations on the model OsO₄(NH₃) + C₂H₄ system.

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 (Criegee–Corey–Noe, CCN model),⁵ an orientation that is conserved in transition state **3** and

product **4**. The validity of the CCN model is thus confirmed. The only nuance introduced by the present calculations is that the importance of the two sandwiching nearly parallel methoxyquinoline walls seems to be quite unbalanced. While there is an almost perfect overlap of the styrene substrate with one of the methoxyquinoline rings (labeled as quinoline A in the figure) the overlap with the other one is quite small, even if it increases as one goes toward the product.

The second remarkable aspect of the geometry of intermediate **2** is the large distance between the osmium catalytic center and the styrene substrate. The C(olefin)–O(Os) distances are 3.136, 3.202 Å, to be compared with values of 2.011, 2.109 Å in transition state **3** and 1.462, 1.488 Å in product **4**. The distance of the olefin carbons with respect to the osmium atom are even larger, 4.163, 4.114 Å. The methoxyquinoline ring A is not much closer to the substrate, with C(styrene)–C(quinoline A) distances between 3.5 and 3.7 Å, but it is in the optimal orientation for a π – π attractive interaction. In order to identify the main contribution to the binding of the substrate in intermediate **2**, we carry out additional calculations on the isolated (DHQD)₂PYDZ·OsO₄ and CH₂=CHPh fragments frozen at the geometry they have in **2**. These frozen fragments have an energy 2.7 kcal/mol above the optimized reactants **1** and, therefore, 12.4 kcal/mol above the intermediate. The decomposition of this difference in QM and MM contributions is very clarifying. The QM component, representing the direct interaction between the OsO₄ unit and the olefin, is only 0.8 kcal/mol, while the MM component, representing the interaction of the styrene substrate with the cinchona ligand, is 11.6 kcal/mol. Therefore, these results show that the stabilization of the intermediate **2** comes essentially from the π – π interaction between 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 on the studied system, (DHQD)₂PYDZ·OsO₄ + CH₂=CHPh, confirm previous proposals by Corey and Noe based on experimental results.⁵ 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 olefins⁹ may be attributed to attractive interactions between the alkyl groups and the π system of the NR₃ ligands, but the explanation of recent results²² 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,¹⁵ the existence of an intermediate in the particular system studied here is also required by its Michaelis–Menten kinetics.¹⁰ Although the full clarification of these mechanistic features will surely require

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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/DFT²³ and mm3(92).²⁴ The MO calculations are carried out on the OsO₄ + NH₃ system at the BECKE3LYP level.²⁵ The basis set is LANL2DZ for Os,²⁶ 6-31G(d) for O,²⁷ and 6-31G for N, C, and H.^{27a} Molecular mechanics calculations use the MM3(92) force field,²¹ and Van der Waals parameters for Os are taken from the UFF force field.²⁹ Torsional contributions involving dihedral angles with the metal atom in terminal position are set to zero.

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All geometrical parameters are optimized except the bond distances connecting the QM and MM parts: N–H (1.015 Å) and C–H (1.101 Å) in the ab initio calculation and N–C (1.448 Å) and C–C (1.434 Å) in the molecular mechanics calculation.

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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.

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