Models for Stereoselective Additions to Chiral Allylic Ethers: Osmium Tetroxide Bis-hydroxylations

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Abstract: Density functional calculations (Becke3LYP/6-31G(d)) on the (3 + 2) transition structures of osmium tetroxide mediated dihydroxylations of chiral allylic ethers show that the stereoselectivity is controlled by the "inside alkoxy effect" (Stork/Houk-Jäger model). In the special case of *Z*-disubstituted alkenes, 1,3-allylic strain (Kishi model) controls the stereoselectivity.

Introduction

Since the first development of the catalytic oxidation of olefins with osmium tetroxide,[1] the scope and utility of this reaction have been improved steadily. The discovery that the reaction is accelerated by the addition of ligands[2,3] led to the first enantioselective dihydroxylation.[4] The most recent developments in this area have involved catalytic asymmetric dihydroxylations pioneered by Sharpless and co-workers.[5] In a variety of natural products, 1,2-diols or derivatives are common structural elements. Since *E* or *Z* double bonds are easily prepared by connecting smaller fragments, the subsequent stereoselective introduction of hydroxyl groups by dihydroxylation provides a route to any desired diastereomer.

Before the asymmetric dihydroxylation—an example of reagent-controlled stereoselectivity—was developed, several groups investigated the substrate-controlling influence of neighboring stereogenic centers on the diastereoselectivity of the osmylation with osmium tetroxide. High stereoselectivity was observed with compounds bearing an allylic oxygen at a stereogenic center. The main product had 1,2-*anti* relationships between the original and the newly formed stereogenic center (Scheme 1). These results led to three proposed transition state models.

Kishi's empirical rule[6] invokes 1,3-allylic strain to rationalize the reactive conformation. The smallest group at the stereogenic center (usually hydrogen) is aligned parallel to the double bond, and the osmium tetroxide attacks on the opposite side from the C−O bond to avoid the electrostatic repulsion of negatively charged oxygens of the allylic center and osmium tetroxide (Figure 1). This rule is not readily reconciled with the experimental results of Evans because, as the size of the alkyl group (R) increases, the stereoselectivity increases instead of decreases.[7]

These results match better with the "inside alkoxy effect" model first proposed for dihydroxylations of γ-hydroxyenones

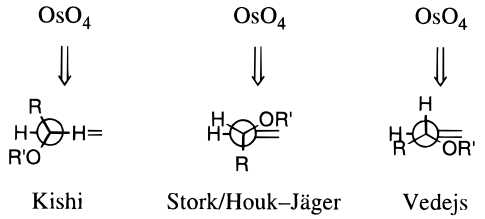
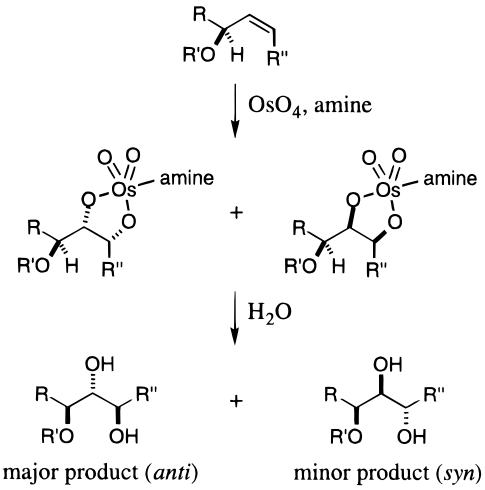


Figure 1. Proposed models for the attack of osmium tetroxide on chiral allylic ethers.

Scheme 1



by Stork[8] and for allylic ethers in general by Houk and Jäger.[9] The most favorable conformer in the preferred transition state should have the large alkyl group anti to the incoming oxidant, while the C−O bond takes up the inside position due to the inside alkoxy effect. This was proposed to be the best position for alkoxy groups for electronic reasons.[9]

A third model was proposed by Vedejs[10] in which the hydrogen atom is aligned parallel to the direction of the attack to minimize steric hindrance, while the bigger groups are on the opposite side of the double bond with the C−O bond directed toward the double bond as in the "inside alkoxy" model.

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

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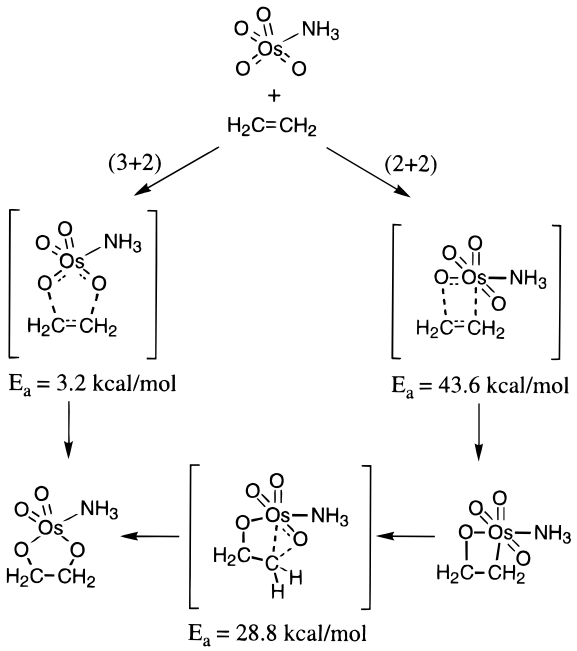
Scheme 2



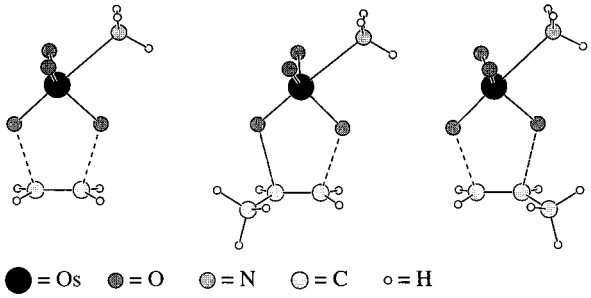
Criegee's concerted (3 + 2) cycloaddition pathway[2] for the reaction has been supported by the work of Corey[11] (Scheme 2), while Sharpless[12] had suggested that a stepwise mechanism involving formation of an osmaoxetane followed by ring expansion better explains the temperature dependence observed in the catalytic asymmetric dihydroxylation as well as the relative rates of reactions of different alkenes in the presence or absence of amine ligands.[13] On the theoretical side, recent DFT calculations have given strong support to the (3 + 2) pathway;[14] the activation barrier is only 3.2 kcal/mol compared to 43.6 kcal/mol for the (2 + 2) addition pathway. Also, the ring expansion step has an energy barrier of 28.8 kcal/mol.

The reasonable agreement of calculated kinetic isotope effects for the model reaction of propene with osmium tetroxide and ammonia as ligand with experimental results for several alkenes also supports the (3 + 2) mechanism.[15]

In this paper, we present a computational analysis of the osmium tetroxide bis-hydroxylation reaction with both achiral and chiral model alkenes. We have assumed the (3 + 2) mechanism for the calculations performed here. The results show that both the Stork/Houk-Jäger and the Kishi models can be relevant in specific cases, depending on the substituents on the alkene.

Computational Methods

All calculations were carried out using the program Gaussian 94.[16] The geometries were optimized at the density functional theory (DFT) level of theory with the Becke3LYP functional using a quasirelativistic effective core potential (ECP) for osmium with a (341/321/21) basis set for the "valence" electrons[17] in conjunction with a 6-31G(d) basis set for all other atoms.



1 ***ap*-2**: 0.0 kcal/mol ***eq*-2**: +0.3 kcal/mol

Figure 2. Calculated transition structures for the reaction of osmium tetroxide with ethene (**1**) and propene (**2**).

Results

A (3 + 2) transition structure (**1**) for the reaction of osmium tetroxide/ammonia with ethene was located (Figure 2);[14a] it is essentially identical with Frenking's structure.[14b] The ligand sphere of the osmium atom can be described as a distorted trigonal bipyramid with ammonia and the opposite oxygen in the apical positions and the remaining three oxygen atoms in the equatorial positions. The osmium atom is located 0.3 Å above the plane of the three equatorial oxygens toward the apical oxygen atom. Therefore, substituents at the alkene carbon atom close to the apical oxygen atom are called apical (ap), while those on the other alkene carbon atom are named equatorial (eq).

The introduction of one additional methyl group leads to two distinct transition structures (ap-**2**, eq-**2**) for the osmylation of propene (Figure 2). The nature of these transition structures leading to the desired starting material or products was confirmed by frequency calculations. Both gave one imaginary frequency with matching vectors for the movement of the carbon and oxygen atoms involved in the bond formation.[14a] Placing the methyl group next to the apical oxygen is preferred over placement next to an equatorial oxygen by 0.3 kcal/mol. The activation energies are 4.6 kcal/mol (ap-**2**) and 4.9 kcal/mol (eq-**2**). The C−O distances at the substituted centers are slightly longer than that in the parent system by 0.038 Å (ap-**2**) and 0.034 Å (eq-**2**). The introduction of the methyl group also leads to a distortion of the O··C═C··O dihedral angle by 6.2° (ap-**2**) and 6.8° (eq-**2**) with the methyl group bent away from the osmium atom. The atoms attached to the alkene are eclipsed with the *E*-substituents, forming a 165° dihedral angle. The C−H bonds of the methyl group are staggered with respect to the bonds to the neighboring carbon atom. This conformational preference is quite general in transition states[18] and alters the substituent locations relative from those in the alkene reactant.

With the assumption that the preference of 0.3 kcal/mol of the apical over the equatorial position for the methyl group is similar for larger groups, further calculations were only

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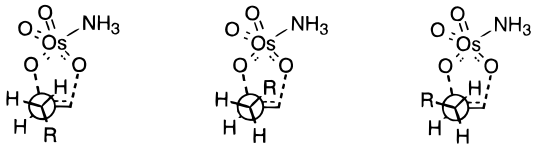
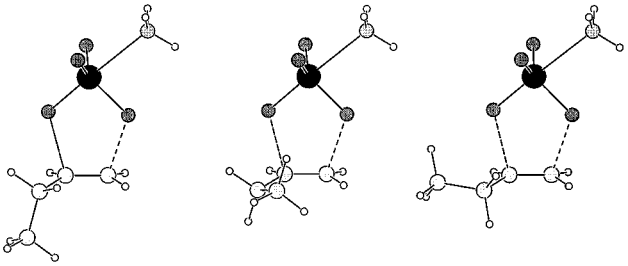


A: anti **B**: inside **C**: outside

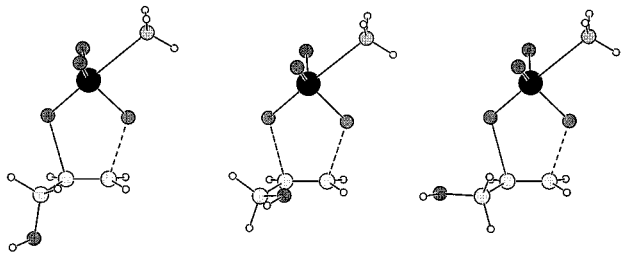
3: R = CH_3 **4**: R = OH

Figure 3. Positions of substituents in the allylic positions in bis-hydroxylation transition structures.



3A: 0.0 (265.9) **3B**: +0.5 (24.3) **3C**: +0.8 (172.4)

Figure 4. Transition structures for the osmylation of 1-butene with relative energies (kcal/mol) and dihedral angles C—C—C═C.



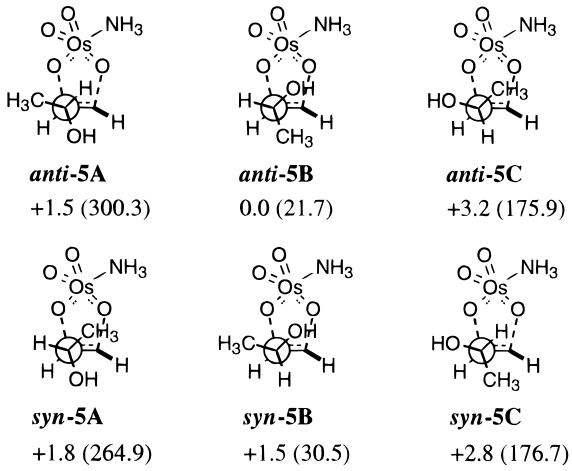
4A: +0.9 (270.2) **4B**: 0.0 (20.1) **4C**: +2.4 (178.1)

Figure 5. Transition structures for the osmylation of allylic alcohol with relative energies (kcal/mol) and dihedral angles O—C—C═C.

conducted for substituents in the apical position. However, both transition states will contribute to the reaction stereochemistry.

Three conformers were located for the 1-butene transition state. C-4 can take up the *anti* (**3A**), the inside (**3B**), or the outside position (**3C**) with respect to the attacking oxygen (Figure 3). The relative energies of **3B** and **3C** compared to **3A** are 0.5 and 0.8 kcal/mol, respectively (Figure 4). This can be explained simply by the increasing steric interaction of the methyl group with the osmium tetroxide in the transition state.

The transition state conformations are quite different for allyl alcohol. The *anti* (**4A**) and the outside positions (**4C**) are disfavored over the inside position (**4B**)[19] by 0.9 and 2.4 kcal/mol, respectively (Figure 5). Here, the electrostatic interactions are much stronger and cause the "inside alkoxy effect." The outside position (**4C**) is the least stable because of the repulsion of the two electronegative and electron-dense oxygen atoms. The sum of the Mulliken charges at the propene in **4A** is +0.26 whereas that in **4B** is +0.28. This increase of electron density at the propene in **4A** reflects the destabilization of **4A** due to the decrease of electron donation to the osmium tetroxide because of σ/π interactions between the C—O σ^* orbital and the C═C π bond orbital.



***anti*-5A** +1.5 (300.3) ***anti*-5B** 0.0 (21.7) ***anti*-5C** +3.2 (175.9)

***syn*-5A** +1.8 (264.9) ***syn*-5B** +1.5 (30.5) ***syn*-5C** +2.8 (176.7)

Figure 6. Transition structures for the osmylation of 3-buten-2-ol with relative energies (kcal/mol) and dihedral angles O—C—C═C.

Figure 6 summarizes the energies of various transition states for the reaction of 3-buten-2-ol, containing an allylic stereogenic center with hydrogen, methyl, and hydroxyl substituents. Since the inside position for the hydroxyl group and the *anti* position for the methyl group are most stable in the parent systems, the combination of these positions in 3-buten-2-ol (*anti*-**5B**) leads to the lowest energy of all transition state conformers of the two diastereomorphic reaction pathways in the diosmylation of 3-buten-2-ol. *anti*-**5B** gives the *anti* diastereomer as the product (Figure 6). The *syn* transition state *syn*-**5B** is the lowest in energy of all of the *syn* transition states; it is 1.5 kcal/mol less stable than *anti*-**5B**. As expected from the previous results, *syn*-**5B** has the hydroxyl group inside and the methyl group outside. According to these results, the diastereoselectivity in the dihydroxylation of monosubstituted alkenes with the stereogenic center in the allylic position is controlled by the "inside alkoxy effect".

As noted by Kishi, a *Z*-substituent on the alkene should introduce steric hindrance to an inside substituent.[6] To determine whether such effects alter the "inside alkoxy effect", additional computations were undertaken. The *Z*-substituted compound, 4-penten-2-ol was used as a model. The stereogenic center was as in the other cases placed in the apical position. The most stable transition structure (*anti*-**6A**) leading to the *anti* product has the hydroxyl group in the *anti* position and the methyl group in the outside position (Figure 7), as proposed by Kishi. The destabilization when the hydroxyl group is in the outside position (**4C**) compared to the *anti* position (**4A**) is much bigger than for the methyl group in **3C** and **3A**. This destabilization for **4C** disfavors also *syn*-**6C** over *syn*-**6B** by 1.0 kcal/mol. The latter is the most stable transition structure producing the *syn*-osmate. It is 1.5 kcal/mol higher in energy than *anti*-**6A**. Therefore, 1,3-allylic strain controls the conformation of the major diastereomeric transition structure of *Z*-alkenes. The Kishi model is also valid in cyclic alkenes where the stereogenic center is fixed in a position resembling that dictated by the 1,3-allylic strain.

Conclusion

Substituents in allylic positions of alkenes take eclipsed positions with respect to the attacking oxygen and the two atoms

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(19) The dihedral angle *d*(HOCC) was fixed at 180° to prevent a hydrogen bond to the oxygen atom of the osmium tetroxide. Allowing the hydrogen bond lowers the energy of the transition structure by 3.0 kcal/mol.

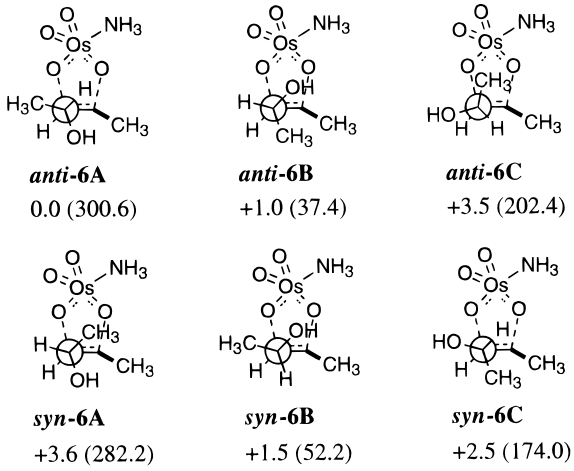

Figure 7. Transition structures for the osmylation of (*Z*)-3-penten-2-ol with relative energies (kcal/mol) and dihedral angles O—C—C═C.

bound to the closer alkene carbon atom. Alkyl substituents prefer to be *anti* to the attacking oxygen to avoid steric interactions, while electron-rich oxy substituents are found in the inside position where electrostatic repulsions and the disfavorable σ/π interaction with the double bond are minimized. Therefore, the diastereoselectivity in the dihydroxylation of chiral allylic ethers giving *anti* products is explained by the "inside alkoxy effect" where both requirements for substituent positions are fulfilled. With *Z*-disubstituted alkenes 1,3-allylic strain predominates in the transition structure leading to the main *anti* product.

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