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Calculations on the Reaction of Ruthenium Tetraoxide with Olefins Using Density Functional Theory (DFT). Implications for the Possibility of Intermediates in the Osmium-Catalyzed Asymmetric Dihydroxylation (AD)

Per-Ola Norrby,[1] Hartmuth C. Kolb, and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037

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Density functional theory (DFT) calculations were performed on several Ru(VI) and Ru(VIII) complexes to investigate the mechanism of the dihydroxylation of olefins catalyzed by OsO_4 and RuO_4. Experimental and calculated data agree well in the case of known compounds. Some metallaoxetanes have been shown to be energetically accessible, and they are, therefore, feasible as intermediates in the reaction. These calculations form a basis for the rationalization of the high enantioselectivity in the asymmetric dihydroxylation reaction.

Recent ligand and process improvements have turned the osmium-catalyzed asymmetric dihydroxylation (AD) into one of the most general enantioselective processes known.[2] However, the mechanism of this reaction is still uncertain, despite substantial efforts.[3] We have recently shown[4] that the reaction mechanism has to involve at least *two sets* of diastereomeric transition states. In line with an earlier proposal that the reaction may proceed through a metallaoxetane intermediate (Scheme 1),[5] we now report density functional theory (DFT) calculations showing that such an intermediate is plausible.

Calculations on osmium are presently beyond our computational capabilities, and we have, therefore, performed all calculations on ruthenium complexes.[6] Ruthenium tetraoxide is known to stereospecifically *cis*-dihydroxylate olefins at low temperature,[7] and when the standard AD chiral ligands are present, the same enantiofacial selectivity as with osmium tetraoxide is observed.[7b] Calculated structures of ruthenium complexes also closely match the known structures for the corresponding osmium complexes (*vide infra*).

Background

The classical mechanism for the dihydroxylation process involves a concerted [3 + 2] cycloaddition.[8] In the absence of ligand, the end product is a dimer of **5**, while an alternative, much faster pathway is open for the reaction in the presence of a cinchona alkaloid, leading to the formation of a complex of type **6**, with only one coordinated ligand.[9] However, in the presence of certain ligands, such as ammonia[10] or pyridine,[11] an alternative pathway, yielding as end product osmate esters with two coordinated ligands and leading to second-order behavior in ligand, seems to be operative. Since ligand addition to OsO_4 is fast and reversible,[12] the resulting overall reaction is first order in olefin and OsO_4 but shows saturation kinetics in the presence of *cinchona* alkaloid ligands.[9] In this paper, we are mainly concerned with the mechanism of the AD reaction, and we will, therefore, only consider mechanisms involving one molecule of each reactant.

Both the [3 + 2] and [2 + 2] mechanisms are consistent with all kinetic observations for the AD reaction, and they are, therefore, kinetically indistinguishable[9c] (Scheme 1). The [2 + 2] mechanism involves the formation of an intermediate oxetane (**3** and/or **4**), which then rearranges to the observed primary product, a cyclic osmate ester (**5** and **6**).

We have recently shown that at least two distinct transition states, each having two diastereomeric forms, are necessary to explain the temperature dependence of the observed enantioselectivity in the AD reaction.[4] This

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[1] Current address: Department of Organic Chemistry, The Royal Institute of Technology, S-100 44 Stockholm, Sweden.

[2] (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992,** *57,* 2768 and references cited therein. (b) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993,** *58,* 3785.

[3] (a) Henbest, H. B.; Jackson, W. R.; Robb, B. C. G. *J. Chem. Soc. B* **1966,** 803–807. (b) Jørgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986,** *108,* 1867–1876. (c) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989,** *111,* 737–739. (d) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989,** *111,* 1123–1125. (e) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993,** *115,* 3828–3829.

[4] Gōbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993,** *32,* 1329.

[5] (a) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977,** *99,* 3120. (b) Jørgensen, K. A.; Schiøtt, B. *Chem. Rev.* **1990,** *90,* 1483–1506. [2 + 2] cycloaddition reactions to form metallacyclobutane complexes can be very fast and reversible; for a review, see: (c) Feldman, J.; Schrock, R. R. *Prog. Inorg. Chem.* **1991,** *39,* 1. Recently, a chromaoxetane was synthesized and characterized; see: (d) Sundermeyer, J.; Weber, K.; Pritzkow, H. *Angew. Chem., Int. Ed. Engl.* **1993,** *32,* 731.

[6] Recently, complex **4a** (M = Os) was calculated using an ECP basis set for Os. The bond lengths are very similar to those in **4a** (M = Ru). We thank Dr. Thomas Raeuchle of Cray Research, Inc., for performing this calculation, prior to release of the basis set.

[7] (a) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976,** *98,* 1986. (b) Xu, D.; Sharpless, K. B. Unpublished results.

[8] (a) Böseken, J. *Recl. Trav. Chim. Pays-Bas* **1922,** *41,* 199. (b) Criegee, R. *Justus Liebigs Ann. Chem.* **1936,** *75,* 522. (c) Criegee, R. *Angew. Chem.* **1937,** *50,* 153. (d) Criegee, R. *Angew. Chem.* **1938,** *519,* 51. (e) Criegee, R.; Marchland, B.; Wannowias, H. *Justus Liebigs Ann. Chem.* **1942,** *550,* 99.

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[10] Burton, K. *Biochem. J.* **1967,** *104,* 686–694.

[11] (a) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Bioinorg. Chem.* **1971,** *1,* 35–55. (b) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Inorg. Chem.* **1972,** *11,* 2621–2626. (c) Clark, R. L.; Behrman, E. J. *Inorg. Chem.* **1972,** *14,* 1425–1426.

[12] The ligand exchange on OsO_4 is fast on the NMR time scale at 20 °C, as revealed by ligand competition experiments.

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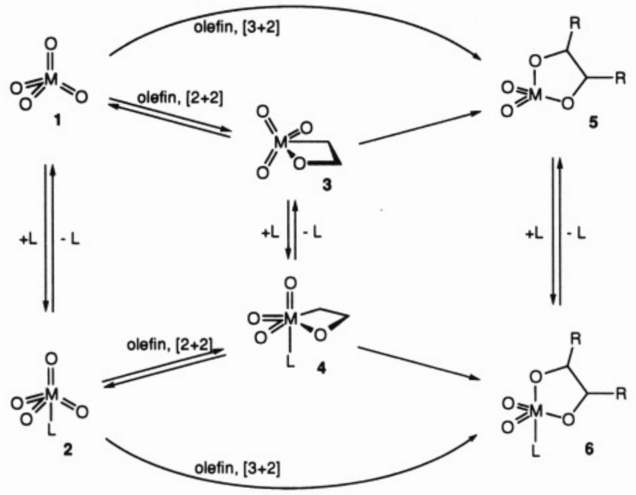
Scheme 1. Possible Pathways for the Dihydroxylation Reaction[a]



[a] In the calculations, M = Ru and L = NH_3. In the AD reaction, M = Os and L is a *Cinchona* alkaloid derivative.

Table 1. Experimental[14] and Calculated Vibrational Spectra of RuO_4[a]

	$\nu_1(A_1)$	$\nu_2(E)$	$\nu_3(T_2)$	$\nu_4(T_2)$
exptl	882	323	914	334
calcd[b]	871	305	906	322

[a] Frequencies are in cm^{-1}. [b] The RuO_4 structure has been calculated without symmetry constraints. This and the numerical calculations in DGauss cause the degeneracy to be lost to a small extent. Only the mean of each group is given here. The largest deviation within a group is ±2 cm^{-1}.

is compatible with a path proceeding through an intermediate complex composed of all three reactants, but not with a single concerted step.

Results and Discussion

As far as we are aware, the only Ru(VIII) species that has been structurally characterized is the tetraoxide **1**.[13] In the osmium series, compounds of type **1**, **2**, and **6** have been isolated and studied. In the two tetraoxides, the observed bond lengths are very similar (both ~1.71 Å).[13] The Ru═O bond length is calculated to be 1.74 Å, which is fairly close to the observed value. The vibrational spectrum has been calculated and compared to the experimental spectrum (Table 1). The results show a surprisingly good correspondence, the largest error being 18 cm^{-1}, despite the fact that our calculations do not take into account the anharmonicity of real vibrations.

The calculated structures for compounds **2** and **6** (M = Ru) can only be compared to similar osmium compounds, due to lack of structural data for ruthenium compounds. However, the close correspondence between the bond lengths in the respective tetraoxides lends credibility to such a comparison.[6] The calculated structures **2a** and **6a** (M = Ru) are shown in Figure 1, together with the relevant parts of two X-ray structures **2b** and **6b** of similar osmium compounds. In both structures **2b** and **6b** the ligand is a dihydroquinidine derivative.

If we compare first the structures **2a** and **2b**, it can be seen that the correspondence is quite good. The M═O bonds are calculated to be 1.75 Å, which is slightly longer than the observed values (1.68–1.73 Å). The M—L bond is also slightly too long in **2a** (2.52 Å vs 2.48 Å in **2b**). The calculations suggest that this bond is very weak, since there is very little energy difference between calculated structures with different fixed Ru—N bond lengths. This corresponds well with the fact that observed values of the lengths of this type of bond show large variations in different crystal structures,[15,16] and the bond can be as short as 2.31 Å in the case of pyridine as ligand. The axial–equatorial O═M═O angle is calculated to be 103°; the observed values are 101–102°. The gas-phase binding enthalpy between tetraoxide and amine is calculated to be 31 kJ/mol (Chart 1). The observed binding constants for osmium tetraoxide range from less than 1 M^{-1} for 2-substituted quinuclidines in *tert*-butyl alcohol to ~10^5 M^{-1} for quinuclidine in toluene.[9c] It is hard to draw conclusions from a comparison of RuO_4 gas-phase binding with OsO_4 complexation in solution, but the results seem reasonable.

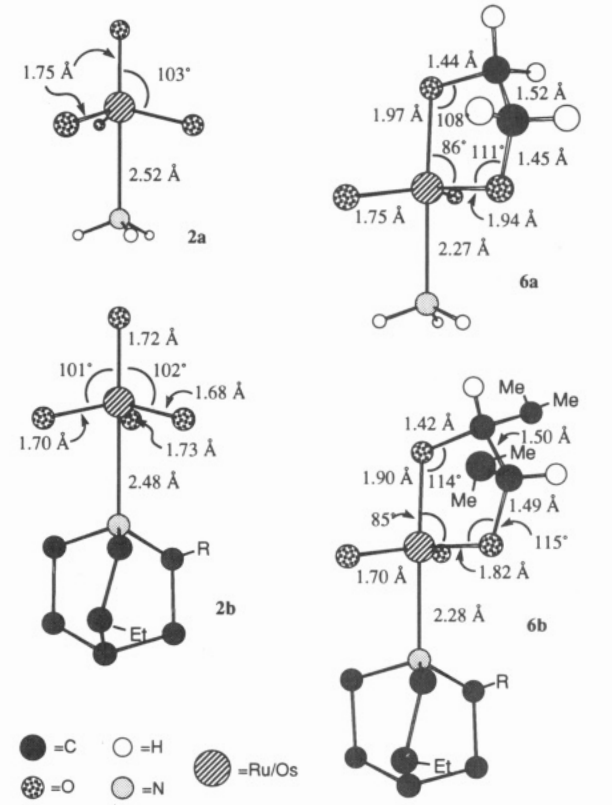


Figure 1. Calculated structures of complexes **2** and **6** (M = Ru, top), together with X-ray structures of similar osmium complexes (bottom).[15]

In the X-ray structure **6b**, the two different M═O double bonds have different lengths, 1.70 and 1.75 Å. The corresponding calculated bond lengths in **6a** are both 1.75 Å. The M—O single bonds differ in both the calculated and experimental structures. The distance from the metal to the axial oxygen, which is trans to the amine ligand, is

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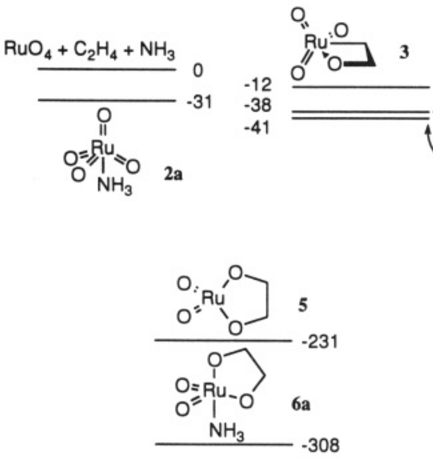
[13] Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; Wiley: New York, 1988; pp 177–178.

[14] Müller, A.; Diemann, E. In *MTP International Review of Science, Inorganic Chemistry, Series 2*; Sharp, D. W. A., Ed.; Butterworths: London, 1974; Vol. 5, pp 71–110.

[15] **2b**, R = (*N*,*N*-dimethylcarbamyl)(6-methoxy-4-quinolyl)methyl: Svendsen, J. S.; Marko, I.; Jacobsen, E. N.; Rao, C. P.; Bott, S.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2263. **6b**, R = ((4-chlorobenzoyl)oxy)(6-methoxy-4-quinolyl)methyl: Pearlstein, R. M.; Blackburn, B. K.; Davis, W. M.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 639.

[16] (a) The N–Os distance is 2.32 Å for the 4-(pyrrolidino)pyridine–OsO_4 complex: McGrath, D. V.; Sharpless, K. B. Unpublished results. (b) d(N—Os) = 2.37 Å for the quinuclidine–OsO_4 complex: Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413. (c) d(N—Os) = 2.41 Å for the 4-cyanoquinuclidine–OsO_4 complex: Kolb, H. C.; Sharpless, K. B., unpublished results.

Chart 1. Calculated Relative Enthalpies (kJ/mol) for All Species in Scheme 1



longer than the distance from metal to the equatorial oxygen in both cases. The calculated bond lengths are 1.97 and 1.94 Å, and the observed values are 1.90 and 1.82 Å, respectively. In the metal(VI) glycolate complexes **6** the M—N bond is both shorter and stronger than the M—N bond in the metal(VIII) tetraoxide complex **2**. The calculated bond length is 2.27 Å; the observed length is 2.28 Å. The calculated binding enthalpy is as high as 77 kJ/mol (Chart 1), which agrees well with the comparatively short M—N bond.

Calculated relative enthalpies for all species in Scheme 1 are shown in Chart 1. Three possible metallaoxetane structures have been found, one without[17] and two with ligand. The structures of these are shown in Figure 2.

Structure **3** can be viewed as a severely distorted trigonal bipyramid, with one axial and two equatorial oxo groups. The angle between the two axial substituents (the ring oxy and one oxo) is 144°. The axial oxo and all four atoms in the ring lie in one plane. The angles between the three oxos (105–117°) suggest that the structure may also be seen as distorted tetrahedral, with the oxetane ring occupying one vertex. The angle between the two equatorial oxos is 117° in **3a**, whereas observed angles between multiply bonded cis oxygens in d^0 transition-metal complexes usually lie in the range 102–112°.[18] However, the calculated enthalpy of **3** is lower than that of the starting materials. Although ΔS is expected to be negative when a strained ring compound is formed in a bimolecular reaction, **3** is still energetically accessible. In order for complex **3** to be part of the reaction pathway, the formation from tetraoxide and olefin must be fast and reversible. A very recent investigation of the reaction of olefins with d^0 vanadium complexes has indeed shown that the double bond between a heteroatom and a d^0 metal can add to an olefin in a fast, reversible reaction.[19a] Thus, the ring methylenes of 2-azavanadacyclobutane **7a** have been shown to undergo rapid interconversion on the NMR time scale even at −90 °C (Scheme 2). A similar but somewhat slower process has been observed for 2-azazirconacyclobutane **7b**.[19b] In a kinetic study of the related 2-azatitanacyclobutane, the free energy of activation for the interconversion has been determined to be 8.9 kcal/mol (37.2 kJ/mol) at 25 °C.[19c]

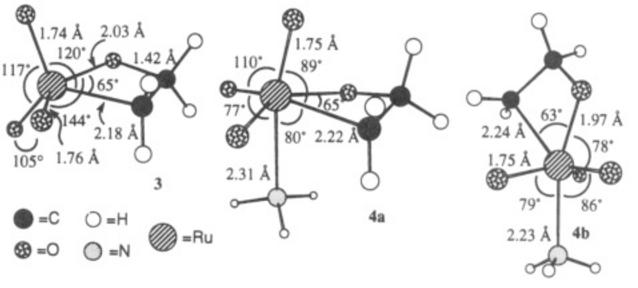
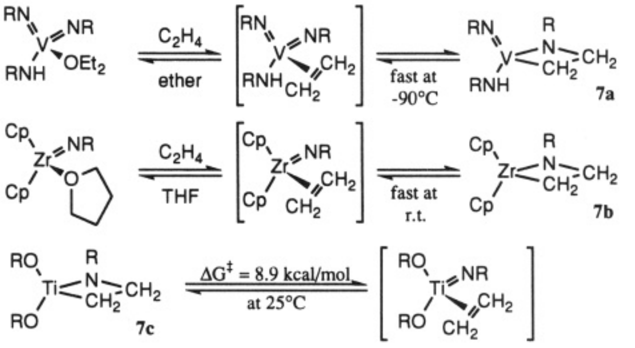


Figure 2. Calculated optimum metallaoxetanes,[6] with and without ligand.

Scheme 2. Formation and Rapid Interconversion of 2-Azametallacyclobutanes by a Fast and reversible [2 + 2] Cycloaddition Mechanism[19]



The ligated metallaoxetane has been calculated in several possible conformations.[6] Only two low-energy, stable conformations have been found (Figure 2, **4a** and **4b**). Structure **4a** is a slightly distorted octahedron, with the three oxos sharing one "expanded" face (O═M═O angles are 105–112°), and the three other ligands sharing a "contracted" face (angles 65–82°). The distortions from octahedral geometry are large enough that the complex can also be viewed as a tetrahedron with three singly bonded ligands sharing one vertex. Isomer **4b** can be viewed as a trigonal bipyramid, with the four-membered ring occupying one vertex. The oxetane oxygen is eclipsed with one of the equatorial oxos. The distortions when **4b** is formed from **3** seem to parallel those when **2** is formed by addition of ligand to **1**.

The calculations indicate that both complexes **4a** and **4b** can be formed exothermically from either RuO_4–ligand complex (**2**) and ethylene or free oxetane (**3**) and ligand. Nevertheless, the free energy of these complexes is expected to be higher than the free energy of the starting materials due to an expected large negative ΔS. Calculation of entropies is presently beyond our computational abilities, but as a general rule of thumb the contribution from $T\Delta S$ in a bimolecular complexation reaction can be expected to be approximately −40 kJ/mol at 25 °C.[20] The fact that complex **4** has never been observed could be explained by its high resulting free energy and/or its fast

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[17] Additionally, an isomer of the unligated metallaoxetane **3**, having the two metal-bonded atoms of the oxetane switched, has also been calculated and found to be a saddle point (leading from one form of **3** to another where the three double-bonded oxygens have been rotated), albeit only ca. 4 k J/mol higher in energy than **3**.

[18] Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; Wiley: New York, 1988; p 157.

[19] (a) de With, J.; Horton, A. D.; Orpen, A. G. *Organometallics* **1993**, *12*, 1493–1496. (b) Walsh, P. J. Ph.D. Thesis, University of California at Berkeley, 1990. (c) Wolczanski, P. T. Private communication.

[20] Page, M. I. In *Enzyme Mechanics*; Page, M. I., Williams, A., Eds.; The Royal Society of Chemistry: Burlington House, London, 1987; p 6. The negative reaction entropy in a bimolecular reaction is estimated to be less than or equal to 150 J/(K mol), corresponding to a negative contribution to the free energy of less than 45 kJ/mol at 298 K. In the formation of a loose complex this value could be much lower. However, when a new ring is formed the entropy loss should be close to the maximum.

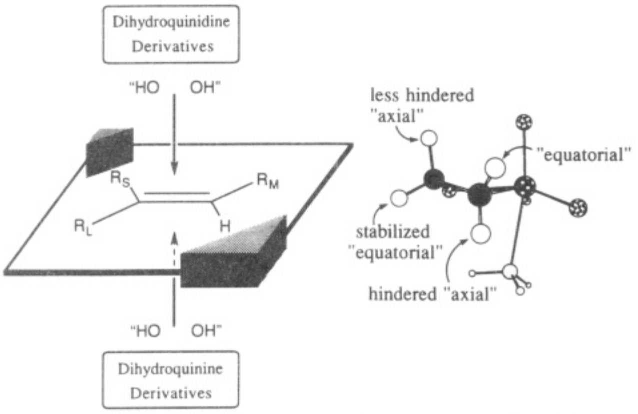

Figure 3. Comparison between the mnemonic device[2] and substituent positions in metallaoxetane ligand complex.

rearrangement to the glycolate product. The enthalpies are calculated to be similar in the reactions $\mathbf{3} + NH_3 \rightleftharpoons \mathbf{4}$ and $\mathbf{1} + NH_3 \rightleftharpoons \mathbf{2}$ (Chart 1); that is, binding of the ligand seems to be approximately equal over the range of Ru(VIII) species. On the other hand, the glycolate, being less coordinatively saturated, shows a stronger binding to the ligand. This effect can be observed in the osmium series, where complexes of type **6** have shorter Os—N bond lengths than complexes of type **2**. This is also in agreement with the fact that glycolate monomer **5** is very short lived.

A very attractive feature of complex **4a** as an intermediate is the enforced propinquity of the olefin and ligand moieties. This could account for the high observed enantioselectivity in the presence of chiral ligands. The expected major enantiomer in the AD reaction can be determined by a reference to a "mnemonic device" where the olefin is aligned in a groove in a way that minimizes interaction between large substituents and the two different crowded positions in the device. The dihydroxylation then takes place from one side selectively[2] (Figure 3). Both face selectivities are accessible by choice of one of a pair of easily available pseudoenantiomeric ligands. The predictions from this device have been successful over a wide range of substrates.

Under the assumption that the transition state is similar to the metallaoxetane **4a**, it is possible to identify the sectors in this mnemonic device with positions on the ring by taking its puckering into account.[21] Two sites are pseudoequatorial, with low crowding (the southwest and northeast corner of the device). The pseudoaxial position closest to osmium corresponds to the southeast corner of the device, where crowding is most severe. The ring model reveals some features of the reaction that were not obvious from the device. The group in the pseudoequatorial position furthest from the metal actually experiences a stabilizing van der Waals interaction with the ester/ether substituent present on C-9 of the AD ligands, as indicated by preliminary molecular mechanics calculations with a modified MM2* force field.[22] Thus, the isomer leading to the observed dominant enantiomer showed a van der Waals stabilization, whereas the intermediate leading to the minor enantiomer showed a global minimum without any stabilizing interactions. A corollary of these putative van der Waals stabilizations of the intermediate is that certain ligand–substrate combinations should experience increased reaction rates. Such accelerations, which are easily rationalized with an intermediate of type **4a** but not with **4b**, have been experimentally observed.[23]

Naturally, arguments concerning the facial selectivities in the AD reaction can only be based on the structure of the intermediate if it is similar to the transition state of the rate-determining step. The dihydroxylation, either with ruthenium or osmium tetraoxide, is strongly exothermic (cf. Chart 1), which makes the assumption of similarity valid under the Hammond postulate. A detailed knowledge of all relevant transition states would be preferable, but the very long calculation times required for a complete search of the plausible conformations at the necessary level of accuracy puts such an investigation beyond our current computational resources. Also, little is known about the reliability of the DFT method in transition-state calculations for organometallic complexes.

Conclusions

We have calculated some possible intermediates in the AD reaction. One of these can be used to explain the high enantioselectivity of the reaction, as well as the observed ligand acceleration. However, the intermediacy of the metallaoxetane is not proven by this. The good correspondence between the old empirical model (the mnemonic device) and one proposed intermediate is intriguing, but similar conclusions can be drawn also from a model based upon the [3 + 2] mechanism.[24] Additional support for the intermediacy of **4a**, using an MM2* parameter set based upon these calculations, will be presented in a separate paper.[22]

Computational Details

All DFT calculations have been performed on a Cray Y-MP computer using the UniChem DGauss 1.1.1 program.[25] The DZVP basis set supplied with the program has been used for all atoms. The Becke–Perdew nonlocal correction was applied self-consistently. No symmetry constraints were used. The DFT method for transition metals has recently been reviewed,[26] and some successful applications to the chemistry of metallacyclobutanes have recently appeared.[27] Molecular mechanics calculations have been performed using MacroModel 3.5[28] on an Iris Indigo, with a modified MM2* force field.[22]

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[21] It should be noted here that the unligated metallaoxetane has all four ring atoms in a plane; i.e., the substituents on the carbon atoms are eclipsed. Thus, the ligand seems to have an important influence in that it effects puckering of the four-membered ring.

[22] Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. Submitted for publication in *J. Am. Chem. Soc.*

[23] Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. Submitted for publication in *J. Am. Chem. Soc.*

[24] (a) Wu, Y. D.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1992**, *57*(5), 1362–1369. (b) Niwayama, S.; Houk, K. N. Private communication.

[25] DGauss 1.1.1, part of UniChem 1.1.1 from Cray Research, Inc. The current implementation does not include relativistic effects or f-type orbitals.

[26] Ziegler, T. *Chem. Rev.* **1991**, *91*, 651–667.

[27] (a) Folga, E.; Ziegler, T. *Organometallics* **1993**, *12*, 325–337. (b) Woo, T.; Folga, E.; Ziegler, T. *Organometallics* **1993**, *12*, 1289–1298.

[28] MacroModel V3.5X: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.