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Experimental and Theoretical Kinetic Isotope Effects for Asymmetric Dihydroxylation. Evidence Supporting a Rate-Limiting "(3 + 2)" Cycloaddition

Albert J. DelMonte,[1a] Jan Haller,[1b] K. N. Houk,*,[1b]
K. Barry Sharpless,*,[1c] Daniel A. Singleton,*,[1a]
Thomas Strassner,[1b] and Allen A. Thomas[1c]

*Department of Chemistry, Texas A&M University
College Station, Texas 77843
Department of Chemistry, The Scripps Research Institute
La Jolla, California 92037
Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90095-1569*

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The osmium tetroxide mediated dihydroxylation of alkenes is a basic organic reaction, and its catalytic asymmetric form has proven to be a powerful method for enantioselective synthesis.[2] Despite the broad utility of these reactions and extensive effort, a clear mechanistic picture has yet to emerge. Mechanistic hypotheses have generally focused on one of two basic themes: (1) a (3 atom + 2 atom) ("(3 + 2)") cycloaddition that directly forms the osmium glycolate primary product,[3] or (2) a stepwise ("(2 + 2)") mechanism involving formation of an osmaoxetane via an initial olefin complex followed by ligand-assisted ring expansion to form the osmium glycolate ligand complex.[4] Variations on these mechanisms differ as to whether
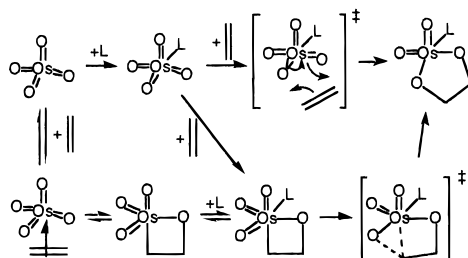
there is initial alkene complexation to the metal center, whether the catalyzing ligand is present during particular steps, and which of the steps is rate limiting. The difficulty of distinguishing these mechanisms was noted when the stepwise pathway was first proposed.[4] The intermediacy of an osmaoxetane was made attractive by analogy with the mechanism of oxidation of alkenes by chromyl chloride[4] and the well-established metallacyclobutanes of olefin metathesis. Support for a multi-step mechanism has come from studies of temperature effects on enantioselectivity[5] and an extended analysis of electronic effects in amine-accelerated osmylations.[6] The "(3 + 2)" process has less precedent but was shown to be plausible by Hoffmann.[7] Corey has recently argued that the (3 + 2) mechanism is more consistent with observed enantioselectivities,[8] though it is unclear why the (3 + 2) transition state and ring expansion of an osmaoxetane should have substantially different steric requirements. The (3 + 2) mechanism has recently received

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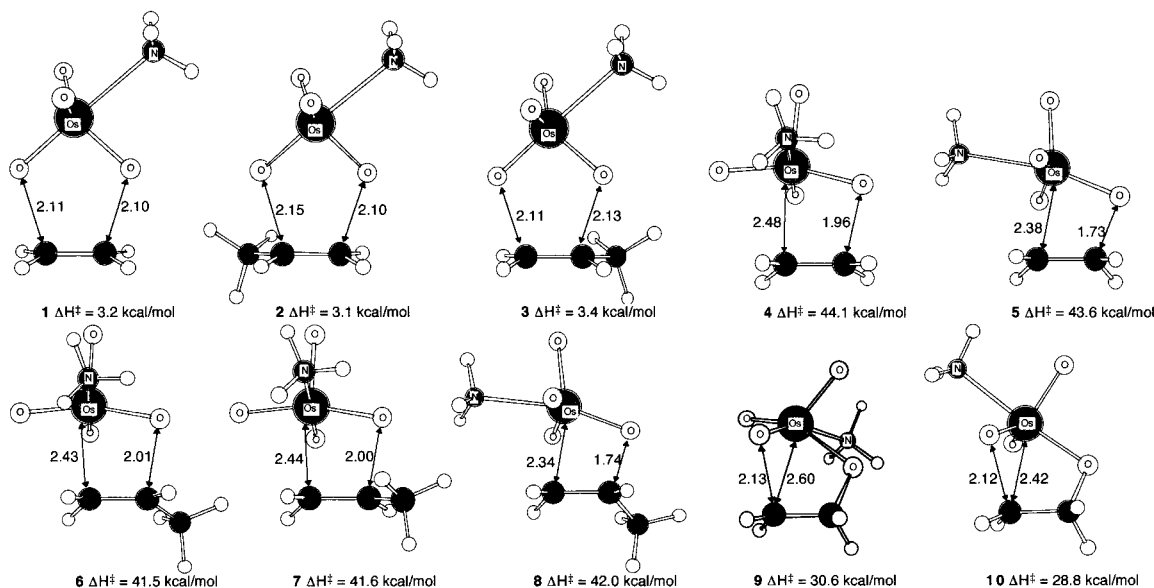(4) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.
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Table 1. Calculated and Experimental KIEs for Dihydroxylations (3 °C)

2, 3, 6–8: R = Me
9, 10: R = H
exp 1, 2: R = *t*-Bu

	H_{C2}	H_{cis}	H_{trans}	C_2	C_1
			Calculated[a]		
			(a) "(3 + 2)"		
2	0.907	0.913	0.921	1.025	1.025
3	0.909	0.912	0.921	1.025	1.024
			(b) Formation of an Osmaoxetane		
6	0.892	0.957	0.972	1.050	1.026
7	0.885	0.962	0.980	1.051	1.025
8	0.832	0.927	0.937	1.046	1.021
			(c) Ring-Expansion		
9	0.880	0.964	1.094	0.989	1.039
10	0.933	0.976	1.068	0.984	1.047
			Experiment[b]		
1	0.906(9)	0.919(5)	0.925(7)	1.027(1)	1.028(3)
2	0.908(4)	0.917(8)	0.926(14)	1.026(3)	1.025(3)

[a] See ref 17. [b] Experiments 1 and 2 are reactions carried to 90.5% and 85.6% completion, respectively. Standard deviations are shown in parentheses.

support from theoretical studies, based on the prediction of high activation barriers for formation and ring-expansion of osmaoxetanes.[9]

Recent studies have demonstrated that the comparison of a large set of high-precision experimental kinetic isotope effects (KIEs) with high-level transition structure/KIE calculations is an extremely powerful tool for defining the mechanism and transition state geometry of organic reactions.[10] Here we apply this methodology to asymmetric dihydroxylations. The results support a very symmetrical transition state and provide striking support for a rate-limiting (3 + 2) cycloaddition.

The ^{13}C and ^2H KIEs for asymmetric dihydroxylation of *tert*-butylethylene were determined combinatorially at natural abundance by recently reported methodology.[11] *tert*-Butylethylene was chosen to avoid the possibility of mixtures of regioisomeric (2 + 2)-pathway transition states contributing to the overall observed KIE, since transition states which put the bulky *tert*-butyl group on a carbon next to osmium should be disfavored. This problem complicates the interpretation of ^{13}C KIEs recently reported by Corey.[12] Reactions of *tert*-butylethylene on a 1.0-mol scale employed 1% (DHQD)$_2$-PYR, 0.2% K$_2$OsO$_2$(OH)$_4$, and 3.0 equiv each of K$_3$Fe(CN)$_6$ and K$_2$CO$_3$, and were carried out in a *t*-BuOH/water biphase at 3 °C. Reactions taken to 90.5% and 85.6% conversion were quenched by the addition

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Chart 1

1 ΔH‡ = 3.2 kcal/mol   **2** ΔH‡ = 3.1 kcal/mol   **3** ΔH‡ = 3.4 kcal/mol   **4** ΔH‡ = 44.1 kcal/mol   **5** ΔH‡ = 43.6 kcal/mol

6 ΔH‡ = 41.5 kcal/mol   **7** ΔH‡ = 41.6 kcal/mol   **8** ΔH‡ = 42.0 kcal/mol   **9** ΔH‡ = 30.6 kcal/mol   **10** ΔH‡ = 28.8 kcal/mol

of excess Na_2SO_3, and the unreacted *tert*-butylethylene was recovered after an extractive workup (rinsing the organic phase multiple times with water) by vacuum transfer followed by vacuum distillation. The resulting material was analyzed by ^{13}C and ^2H NMR compared to a standard sample of the original *tert*-butylethylene.[13] The changes in ^{13}C and ^2H isotopic composition were calculated by using the methyl groups of the *tert*-butylethylene as "internal standard" with the assumption that their isotopic composition does not change. From the changes in isotopic composition the KIEs were calculated in the previously reported fashion (Table 1).[11]

The model reaction of $OsO_4{\cdot}NH_3$ with ethylene and propene was investigated in Becke3LYP calculations[14] by using an effective core potential for osmium[15] with a (341/321/21) basis set for the "valence" electrons in conjunction with a 6-31G* basis set for all other atoms. Transition structures were located for (3 + 2) cycloadditions with ethylene (**1**) and propene (**2**, **3**), formation of an intermediate osmaoxetane with ethylene (**4**, **5**) and propene (**6**–**8**),[16] and ring-expansions of the osmaoxetane derived from ethylene (**9**, **10**). As has been found in other recent calculations,[9] the (3 + 2) pathway is predicted to be facile with activation barriers of 3.1–3.4 kcal/mol for **1**–**3**, in reasonable agreement with experimental values. In contrast, the activation barriers for the located transition structures (among multiple possibilities) along the stepwise pathway are predicted to be prohibitively high (41–44 kcal/mol for formation of the osmaoxetane and 29 - 31 kcal/mol for the ring expansion).

Theoretical KIEs based on these transition structures were calculated as previously described[10,17] and are summarized along with the experimental KIEs in Table 1. The predicted KIEs based on the (3 + 2) transition structures **2** and **3** are in evident qualitative and quantitative agreement with the observed values. Eight of the ten experimental KIEs differ from the predicted

KIEs by less than a standard deviation, and the root-mean-square differences between the experimental KIEs and those predicted for **2** are only 0.4% and 0.2% for deuterium and ^{13}C KIEs, respectively. Considering the differences between the experiment and theoretical model—(DHQD)₂-PYR vs NH_3, solution vs gas phase, *tert*-butylethylene vs propene—the agreement between experimental and predicted KIEs is remarkable.

In contrast, the KIEs predicted for the transition structures for two possible rate-limiting steps along the stepwise pathway do not match up at all with the experimental KIEs. The ^{13}C KIEs predicted for **9** and **10** are in accord with qualitative arguments made by Corey[12] that only one carbon of the alkene should exhibit a KIE significantly greater than 1.00 if ring expansion were rate limiting. The calculated KIEs and the experimental use of *tert*-butylethylene here greatly strengthens the argument against rate-limiting ring expansion. It is difficult to completely exclude rate-limiting formation of an osmaoxetane if one accepts the premise that the theoretical results here could be both energetically and geometrically unusually inaccurate—the idea being that some alternative transition state geometry could in principle result in the observed KIEs. It should also be noted that a one-step (3 + 2) cycloaddition does not provide an explanation for observations on electronic effects in these reactions[6] or temperature effects on the enantioselectivity[5] that support a complex overall mechanism. Furthermore, Gable's studies on a reversible rhenium analog seem to require a stepwise mechanism.[18] Despite these facts and the caveat on the exclusion of the osmaoxetane, the agreement between experimental KIEs and those predicted for **2** and **3** is evidence of an affirmative nature that is consistent with and *supports* a (3 + 2) cycloaddition as the rate-limiting step in these reactions.

(13) As described in the Supporting Information and previously,[10b–d,11] a number of precautions were taken to minimize both random and systematic errors in the NMR analysis.

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(16) Three regioisomeric transition structures were found with the methyl group on the carbon next to osmium, but these were 4–5 kcal higher in energy. See Supporting Information for details.

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