Kinetic constraints on possible reaction pathways for osmium-catalysed asymmetric dihydroxylation

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Proposed mechanisms for the osmium-catalysed dihydroxylation are examined and kinetic rate laws derived in terms of various mechanistic rate constants. In light of the reported kinetic behaviour of these systems, particularly with asymmetric nitrogen base ligands, several constraints can be placed on the two major competing hypotheses. The chemical consequences of these constraints make stepwise formation of the two C–O bonds *via* an osmaoxetane the more plausible mechanistic model.

Introduction

The osmium-catalysed asymmetric dihydroxylation (AD) is one of the most general enantioselective processes known (Fig. 1).[1] A wide variety of alkenes can be dihydroxylated with good enantioselectivity under conditions that tolerate most other functional groups.

The mechanism of the basic reaction, dihydroxylation of alkenes by osmium tetroxide both in the absence and presence of rate accelerating amine ligands, has received considerable attention since its discovery. Böseken [2] first noted the similarity between osmium tetroxide and permanganate oxidations, and suggested a direct addition of two oxo groups to the alkene carbons, forming a five-membered metal diolate intermediate which was hydrolysed to yield *cis*-diol. Criegee investigated the stoichiometric reaction in the 1930s,[3] and noted such important phenomena as the ligand acceleration by pyridine. Later investigations have focused on electronic effects in the substrate,[4] as well as the kinetics of the reaction.[5,6] The early work on the osmylation has been reviewed.[7] The mechanism has since been the subject of frontier orbital studies.[8] The osmylation reaction has been shown to be sensitive to stereoelectronic effects in the absence of ligand.[9] The commonly held view of osmium tetroxide acting as an electrophile in the osmylation has been challenged based on reactivities of fluorinated alkenes.[10]

The outcome of these studies has been a controversy between two major competing hypotheses. The first mechanism to be proposed was the [3 + 2]-reaction, in which the observed primary product [an osmium(VI) diolate] is formed in one concerted step from an alkene approaching two oxo groups on either osmium tetroxide itself or its ligand complexes (Fig. 2).[2,3,7] This mechanism was challenged by Sharpless *et al.*[11] on the basis of relative reaction rates of electron rich and electron poor alkenes. Osmium tetroxide is thought to behave as an electrophile in this reaction, and the argument was that an electron deficient metal should be more electrophilic than an oxo group. The alternative mechanism involved initial bond formation between the metal and the alkene, forming a metallaoxetane, which in turn would rearrange to the observed primary product (Fig. 3). Metallaoxetanes have been proposed as intermediates in many metal-catalysed oxidations, but have usually not been observed.[12] However, several quantum chemical studies have indicated that they are energetically accessible.[13–15] In related systems with M=N and M=C double bonds, it has also been shown that a formal [2 + 2] addition of an alkene is a fast and reversible process.[16]

The debate over the basic osmylation mechanism has hampered clear understanding of the source of enantioselectivity and transmission of stereochemical effects in the AD reaction. Several models have been advanced for the stoichiometric asymmetric dihydroxylations promoted by chiral diamine ligands.[19,20] More recently, attempts have been made to find models able to predict the selectivity in reactions catalysed by

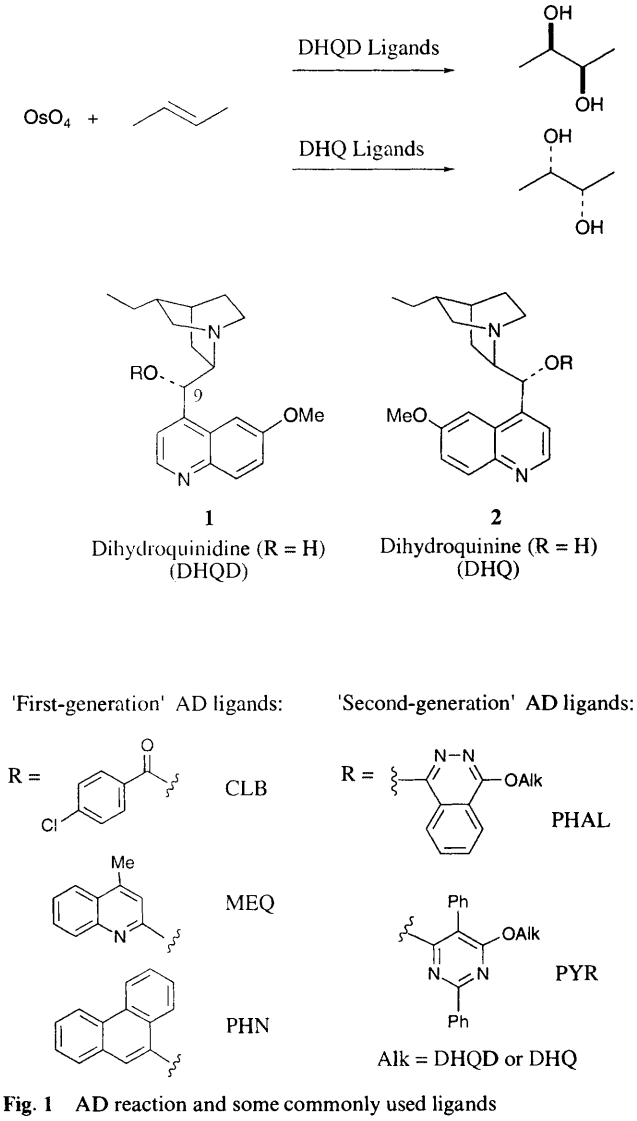

Fig. 1 AD reaction and some commonly used ligands

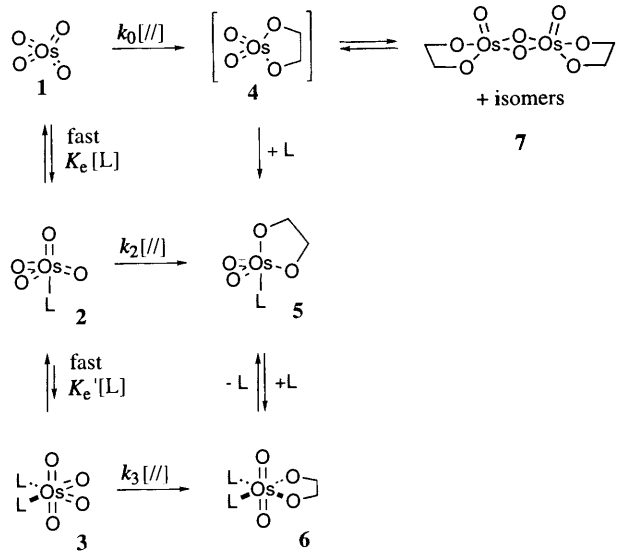

Fig. 2 Different possible [3 + 2] pathways for the osmylation reaction in the absence of ligand (k_0), for reactions that are first order in ligand (k_2, normal AD conditions)[17] and for reactions that have been suggested to be second order in ligand (k_3, *e.g.*, some pyridine accelerated reactions in water)[5,6]

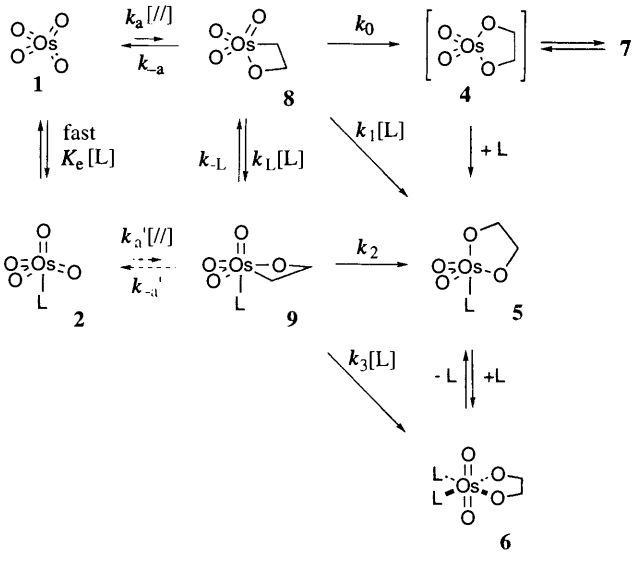

Fig. 3 Possible paths for the formal [2 + 2] mechanism, showing reaction in the absence of ligand (k_0), with ligand in sterically demanding situations (k_1, *e.g.*, tetrasubstituted alkenes and quinuclidine ligands),[18] under normal AD conditions (k_2)[17] and for reactions that are second order in ligand (k_3, *e.g.*, ammonia)[5,6]

cinchona-derived ligands (the AD reaction).[1,18,20–25] Sharpless and co-workers have developed methods for suppressing side reactions,[26] and also studied the effect of substrate and ligand structure upon relative and absolute reaction rates.[17,27–29] Göbel and Sharpless studied the effect of temperature upon enantioselectivity in the AD reaction and noticed the presence of isoinversion points.[30] The implications of this important finding will be discussed later. The dihydroxylation reaction has also been studied by high level quantum chemical methods.[13,14]

Both mechanisms have been elaborated to fit new observations, but definitive evidence for one mechanism has proved very elusive. However, many recent results have provided constraints on the possible mechanisms. It is our intention in this work to analyse the kinetic requirements of different pathways and find the 'minimal' mechanisms consistent with all available data. Further, we hope this analysis suggests fruitful areas of experimentation that might help resolve the current debate.

Initial conditions and assumptions

The aspect of this reaction that remains an issue of controversy is how the C–O bonds are formed. Any mechanistic model for osmylation must rationalize and reconcile the following experimental observations.

(1) Stereospecific *syn* addition to the alkene.

(2) Electron rich alkenes generally react faster than electron poor alkenes.

(3) In the absence of ligand, the rate for any alkene obeys the rate law (1).

$$-\frac{[\text{Alkene}]}{dt} = \frac{[\text{Diolate}]}{dt} = k_0[OsO_4][\text{Alkene}] \quad (1)$$

(4) Osmylation is strongly accelerated by most nitrogen bases.

(5) In the presence of most nitrogen bases, the rate shows saturation kinetics [eqn. (2)]. Here $[OsO_4]_T$ is the total

$$-\frac{[\text{Alkene}]}{dt} = \frac{k_0 + k_c K_{eq}[L]}{1 + K_{eq}[L]}[OsO_4]_T[\text{Alkene}] \quad (2)$$

concentration of osmium tetroxide, either free or ligated, $[OsO_4]_T = [OsO_4] + [OsO_4{\cdot}L]$; k_c is the ceiling rate at ligand saturation, $k_c \gg k_0$ [*cf.* condition (4)]; K_{eq} is the binding constant between ligand and OsO_4.

(6) In rare instances, a second-order dependence on ligand can be observed. So far, ligand reaction orders higher than one have only been indicated in aqueous solvent in the presence of certain small ligands (*e.g.*, ammonia[5] or pyridine[6]).

When osmylation is run in the presence of *cinchona*-derived ligands (AD reaction), the following observations must also be rationalized by any mechanistic proposal.

(7) Modified Eyring plots of enantioselectivity can show distinct non-linearity, with a change in slope usually taking place around 0 °C.[30] Non-linear Eyring behaviour of this type is usually associated with a change in rate determining step between two transition states with unequal temperature dependences.[31]

(8) In the AD reaction, the face selectivity is consistent over a wide range of alkenes, ligands and temperatures. Usually, the face selectivity can be rationalized by a simple mnemonic device (Fig. 4).[1,17,26]

(9) In certain cases, addition of bulky substituents to the substrate and ligand leads to a drastic rate *increase*,[17] not the decrease expected from crowding in the transition state. This is most notable when both the substrate and the ligand carry large aromatic substituents. The rate increase has been interpreted in terms of non-bonded attraction between the ligand and substrate in the transition state.[17,23] The proposed transition state geometry must allow such attractions between the indicated substituents.

Point (7) deserves some extra comment, since this recent finding implies some non-trivial corollaries.[30] Any single elementary rate process on the reaction pathway should follow the Eyring relationship.† Competitive, related processes (*e.g.*, formation of two stereoisomers from the same reactants) will show a linear relationship between $\ln(k_{rel})$ and $1/T$, with an energy term as the slope. This is the energy difference between the transition states for the two competing processes. All current reaction rate theories postulate that the energy barrier for a reaction is composed of both enthalpic and entropic components.[32] Furthermore, entropy and enthalpy as state

† $\ln(k) = -\Delta G^*/RT + \ln(k_B T/h)$; ref. 32. Note that all reaction rate theories (Arrhenius, collision, transition state) suppose a linear $\ln(k)$ *vs.* $1/T$ relationship; they differ mainly in whether there is an additional term. These additional terms cancel when comparing relative rates.

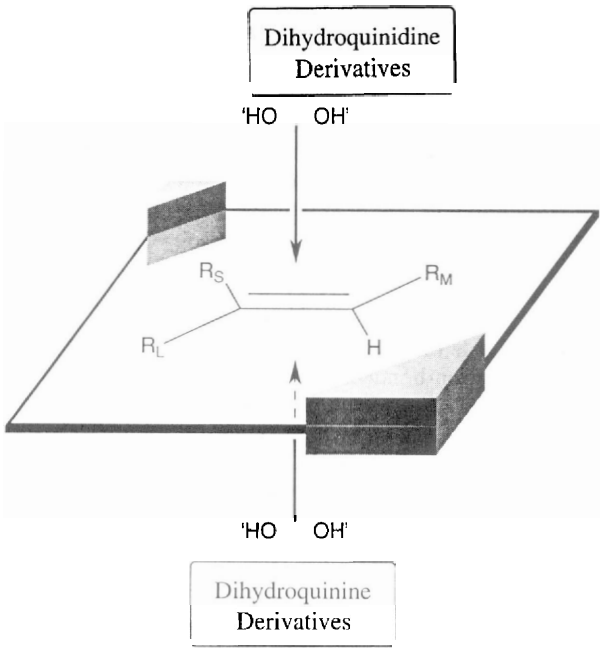

Fig. 4 Mnemonic device used to predict face selectivities in the AD reaction [1,17,26]

functions are temperature independent (at least over the 100–200 °C measurable range of most organic reactions). Thus, competing single-transition state paths leading to stereoisomers will show a single linear temperature dependence of the rate, which can be used to elucidate the enthalpy and entropy differences between the diastereoisomeric transition states. Any such relationship that shows two distinctly different linear portions can be used as evidence for two different transition state structures on each path, each with unique energetics compared to the ground state. The change in slope represents the change from one to the other being rate-limiting over the measured temperature range.

In the modified Eyring plots under consideration here, the slope is the relative activation enthalpy of the two paths, $\Delta\Delta H^*$. For a single pair of diastereoisomeric transition states, this is even less likely than an activation enthalpy to show a temperature dependence. It can therefore be concluded that at least two pairs of diastereoisomeric transition states exist, either on parallel pathways or flanking an intermediate. Furthermore, at the isoinversion temperature, the two pairs of transition states must have similar free energies of activation and substantially different entropies of activation. Below the isoinversion temperature one of these transition states must be overall selectivity determining, above the isoinversion temperature the other. An additional requirement comes from the fact that in all cases, there is no drastic change in enantioselectivity at the isoinversion point, just a change in the slope of the temperature dependence. This means that for a large range of alkenes, the interactions determining the enantioselectivity must be very similar in both pairs of transition states.

The kinetic derivations will be based on the assumption that ligation of nitrogen base ligands to OsO_4 is fast and reversible.[28] In our approach, we will also make the explicit assumption that the elementary reactions in which osmium tetroxide and its ligated analogues participate belong to a common unifying mechanism. One might imagine that subtle changes in ligand or substrate might change the mechanism from concerted to stepwise. However, we feel that so long as a single mechanism can rationalize all the experimental data, this is an unnecessary complication. We will examine the [3 + 2] and [2 + 2] models in turn and derive the limitations the experimental data places on either general process. Finally, we will compare these limitations to theoretical work on proposed intermediates and transition states.

I. Concerted [3 + 2] cycloaddition

This earliest mechanistic proposal is in many ways the simplest; its components are shown in Fig. 2. In the absence of ligand, direct bimolecular cycloaddition occurs to give **4**, which rapidly dimerizes to observed compound **7**, or is hydrolysed under the aqueous conditions. This gives the second-order rate law which is always present as a background reaction.

In the presence of Lewis base amine ligands, rapid association can occur to give known adduct **2**. Given the acceleration induced under such conditions, this species must be more reactive than OsO_4. The reversibility of ligation leads to saturation kinetics, and when essentially all of the osmium is ligated, additional ligand provides no additional acceleration.

For unhindered bases (*e.g.*, L = NH_3, pyridine or chelating diamines), a second equivalent of ligand can presumably bind to give **3**. This compound formally has 20 valence electrons (counting the oxos as dianionic double bonded ligands), but could conceivably exist as a highly reactive intermediate, especially when a formal negative charge on the oxygens can be stabilized (*e.g.*, in aqueous solution). Concerted cycloaddition of alkene to **3** would result in a third-order rate law in situations where $k_3K'_e[L] \gg k_2$.

Complex **2** contains two distinct types of oxo groups, one axial and three equatorial. It is generally assumed that the reaction takes place at one axial and one equatorial oxygen,[20,22] with a transition state geometry similar to the observed product, **5**. It has been shown that this arrangement can rationalize both the face selectivity and the non-bonded attractive acceleration in the AD reaction.[21,22,33] The possibility of reaction with two equatorial oxygens followed by rearrangement to **5** has not been as thoroughly addressed, but it has been indicated that the diequatorial mode would be expected to yield face selectivities quite different from those obtained by the axial-equatorial mode of reaction.[22,25] No complex similar to a diequatorial addition product has been observed, but this would be expected to interconvert rapidly to the more stable **5** through a pseudo-rotation or ligand exchange.

II. Stepwise [2 + 2] cycloaddition

It has long been known that electron rich alkenes generally react faster than electron deficient alkenes in osmium dihydroxylation. Osmium tetroxide has therefore been considered to act as an electrophile in osmylation reactions. However, ligand addition would then be expected to lower the reactivity of osmium tetroxide. This point was actually one of the main factors leading to the proposal of the formal [2 + 2] mechanism leading through an osmaoxetane intermediate (Fig. 3).[11]

Fig. 3 summarizes the possible pathways according to the formal [2 + 2] mechanism. As for the [3 + 2] mechanism, the top row outlines the reaction in the absence of ligand. Here an osmaoxetane (**8**) is reversibly formed and rearranges irreversibly in what is supposed to be the rate determining step to the same primary product as shown in Fig. 3. The situation gets more complicated when ligand is added. With strong ligands, most of the osmium is bound in complex **2**. There is some question about whether complex **9** can be formed by direct addition of an alkene to **2**, or if it is formed by addition of a ligand to preformed osmaoxetane **8**.[34] This question will be addressed further below. Under this model complex **9** is believed to be the species responsible for the high enantioselectivity in the AD reaction, due to the very close interaction between the moiety resulting from the alkene and the ligand.[13,18,23] Both complexes **8** and **9** have been shown to be plausible intermediates by quantum chemical calculations.[13,14] The normal reaction path for an AD reaction would

be direct rearrangement from **9** to **5**. This step has been calculated to be very exothermic.[13,14]

Based on the Hammond postulate, a predictive model for the AD reaction has been derived from a molecular mechanics model of **9**,[23] which should be similar in structure to the expected early rearrangement transition state.

Recent investigations have indicated that in sterically very demanding situations, that is, AD-reaction of tetrasubstituted alkenes, the energy of **9** is raised to a level where it cannot be considered a true intermediate.[18] The reaction is still strongly accelerated by ligands.[29] For these cases, we therefore expect the reaction to follow the k_1 path from **8** directly to **6** by ligand induced rearrangement. The transition state of this reaction would be structurally similar to **9**, but more loosely bound. The longer distances involved would result in weaker interactions and therefore a lower expected enantioselectivity for this class of alkenes, and this is indeed observed for most substrates. This proposal implies that the reaction goes either through path k_1 or path k_2, depending on the crowding in **8**. As the reaction is proposed to go through **9** in most AD-reactions, path k_1 will be ignored in the following derivations.

Inspections of models of complex **9** with *cinchona*-type ligands show that there is substantial crowding between the metal-bound carbon and the ligand. This should make the intermediate unstable and in fact facilitate the rearrangement of the carbon to the axial oxygen, leading to the observed product **5**. With less sterically demanding ligands (*e.g.*, pyridines), complex **9** should be much more long-lived. If, for any reason, the rearrangement of **9** to **5** is inhibited, a competing pathway with nucleophile-induced rearrangement directly to **6** is plausible (pathway k_3). This could be a rationalization for the high order in ligand sometimes found with electron deficient alkenes in aqueous systems.

Kinetics for the [3 + 2] reaction

The kinetics of the [3 + 2] reaction are easily worked out from the reaction scheme in Fig. 2.‡[,17,27,28] The equilibrium between OsO_4 and OsO_4·L is fast, so the discrete complex concentrations may be expressed in terms of the total Os(VIII) concentration $[Os]_T$ [eqns. (3) and (4)].

$$[OsO_4] = \frac{[Os]_T}{1 + K_{eq}[L]} \quad (3)$$

$$[OsO_4{\cdot}L] = \frac{[Os]_T K_{eq}[L]}{1 + K_{eq}[L]} \quad (4)$$

The overall rate is a sum over the three possible irreversible steps. In case of the AD reaction, the component which is second-order in ligand can be ignored, and we reach the final eqn. (5).

$$r = \underbrace{\frac{k_0 + k_2 K_{eq}[L]}{1 + K_{eq}[L]}}_{k_{obs}} [Os]_T[Alkene] \quad (5)$$

We define the ceiling rate constant k_c as k_{obs} at complete ligand saturation, $k_c = \lim_{[L]\to\infty} k_{obs}$. For the simple case above, $k_c = k_2$. Obviously, because k_2 is expected to obey the Eyring equation, the simple eqn. (5) cannot explain the observed non-linear temperature-enantioselectivity relationship. The reaction mechanism is required to contain at least one more distinct step involving both the chiral ligand and the alkene in a pair of diastereoisomeric transition states. The two possible 'minimal' choices are (1) two distinct, parallel [3 + 2] reaction pathways of type **2** to **5** and (2) a precomplexation of the alkene to the osmium tetroxide–ligand complex **2**. The implications of both these possibilities will now be discussed.

Examining the structure of the trigonal bipyramidal complex **2**, there are two obvious choices for parallel [3 + 2] reactions. The common assumption is that the axial and one equatorial oxo react with the incoming alkene, but it is plausible to assume that a [3 + 2] reaction can also take place at two equatorial oxygens. Two different trajectories have been advanced for the reaction of one axial and one equatorial oxygen.[33] Both these models are able to rationalize the observed enantioselectivities by selective non-bonded interaction between the incoming alkene and the alkaloid moiety. However, attempts to use the interactions in these models to predict enantioselectivities in a diequatorial reaction leads to very different results from the normal axial–equatorial mode, sometimes even predicting the opposite face selectivity.[22,25] A non-linear temperature dependence from such a system would be expected to show an S-curve, with radically different enantioselectivities above and below the inversion point. Instead, the observed curves take the shape of two lines with different slope intersecting at the inversion point. This problem is quite general for all attempts to explain the observed behaviour by parallel pathways, as the two transition states must give almost identical enantioselectivities and yet different thermodynamic activation parameters for a wide range of alkenes.

A second general problem with parallel paths is that similar reaction types would be expected to have similar activation entropies. The expected Eyring plot in such a case would be a smooth transition curve. Only with a substantial difference in activation entropy will the transition range be small and the break well defined.

Ignoring the background reaction and possible interference from pathways that are second-order in ligand, a pathway involving a precomplexation of alkene to the osmium tetroxide ligand complex is shown in Fig. 5.

This is the simplest general path that can rationalize the observed non-linear temperature behaviour. Assuming a steady state of the intermediate complex, the observed rate constant is given by eqn. (6).

$$k_{obs} = \frac{k_a k_2}{k_{-a} + k_2} \times \frac{K_{eq}[L]}{1 + K_{eq}[L]} \quad (6)$$

The easiest way to recognize a rate expression capable of giving rise to temperature breaks in Eyring type diagrams is that it must contain a factor that in turn is a sum of at least two independent rate constants with unequal temperature dependencies. At the inversion point, these two rate constants have equal values. In the linear regions at temperatures far removed from the inversion point, one of these rate constants dominates the factor. If substantial enantioselectivity is observed in one linear region, the corresponding rate constant must have different values for the paths leading to the diastereomeric primary products (**5**). Both transition states in Fig. 5 contain both the chiral ligand and the alkene, and can therefore exist as pairs of diastereoisomers. Using lower indices R and S for the paths leading to the two diastereoisomeric primary products, the expression for the ratio of the enantiomers (Y) can be obtained by dividing the enantiomeric versions of eqn. (6) with each other:

$$Y = \frac{k_{aR} k_{2R}}{k_{aS} k_{2S}} \times \frac{k_{-aS} + k_{2S}}{k_{-aR} + k_{2R}} \quad (7)$$

Eqn. (7) allows for a non-linear enantioselectivity–temperature relationship when $k_2 \approx k_{-a}$. The activation entropies

‡ Derivation details are available on request from Per-Ola Norrby, e-mail peon@medchem.dfh.dk.

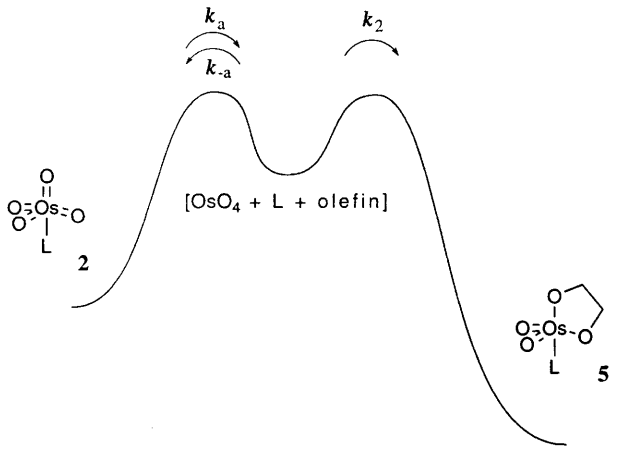

Fig. 5 Reaction path involving precomplexation of alkene to the ligated osmium tetroxide

should be substantially different, since k_{-a} is the rate of dissociation of the intermediate complex (with a strongly positive expected ΔS^*) whereas k_2 is the rate of a simple rearrangement (with a small, possibly negative expected ΔS^*). The reaction would therefore be expected to switch from a rate determining complexation to a rate determining rearrangement in a fairly narrow temperature range.

The observed systems all show substantial enantioselectivity in the linear regions away from the inversion point, when either k_2 or k_{-a} is dominating the expression. Any precomplex must therefore in one temperature region be formed irreversibly, with a high face selectivity for several alkenes. This strongly implies that any such intermediate complexes must contain covalent bonds or other very strong interactions between the alkene moiety and the ligated osmium tetroxide. To our knowledge, the only such intermediate that has been suggested to date is the osmaoxetane complex (*vide infra*). A strong π-complex between the alkene and the osmium cannot be excluded from this data. However, complexes of osmium tetroxide with hindered alkenes[35] and arenes[36] have been shown to be present in the reaction mixture but at very low concentrations. We predict that the best way to differentiate between these two possibilities is to investigate the possibility of regio-asymmetric binding of the complex in the intermediate from differential substituent effects.

Kinetics for the formal [2 + 2] reaction

The kinetic equations for the formal [2 + 2] reaction are much more complex than the corresponding [3 + 2] equations. All attempts to isolate or observe an osmaoxetane so far have failed. The concentration of osmaoxetanes at any given time will therefore be assumed to be much smaller than the total concentration of OsO_4 species, [**8**] or [**9**] $\ll$ $[Os^{VIII}]_T$. The problem can be greatly simplified by assuming either fast and reversible formation of free osmaoxetane **8** from osmium tetroxide and alkene or fast and reversible equilibrium between osmaoxetanes **8** and **9**. A third possibility is to assume that alkene addition cannot occur to the formal 18-electron complex **2**. These assumptions and their implications will be investigated below.

Case (1) assumes that metallooxetane formation is fast and reversible. Thus, we can write $K_a = k_a/k_{-a}$ = [**8**]/[**1**][Alkene] $\ll$ 1. By assuming steady state for the ligated oxetane **9**, we get the expressions (8) and (9) for the observed rate constant and the ceiling rate.

$$k_{obs} = \frac{K_a k_0 + k_2 \dfrac{k_L K_a[L] + k'_a K_{eq}[L]}{k'_{-a} + k_{-L} + k_2}}{1 + K_{eq}[L]} \qquad (8)$$

$$k_c = k_2 \frac{k_L K_a/K_{eq} + k'_a}{k'_{-a} + k_{-L} + k_2} \qquad (9)$$

Eqn. (9) is able to rationalize the observed behaviour by either k'_{-a} or k_{-L} being equal to k_2 at the inversion temperature. Mathematically, different combinations of parallel paths with equal rates could also be constructed from eqn. (9), but as was pointed out in the discussion on the [3 + 2] mechanism, it is not probable that the observed behaviour could be due to competing reactions. For a direct ligand-promoted rearrangement from **8** to **5** (path k_1, Fig. 2), k_c would simply be $K_a k_1/K_{eq}$, and no temperature breaks would be possible.

Case (1) leads to the corollary that k_{-L} must be either rate determining or negligible. In case (2) we will instead assume that ligand addition to **8** is fast and reversible. This is certainly reasonable intuitively, since **8** formally is a 16-electron complex similar to **1**, but the steric interactions upon ligand addition are expected to be much larger for **8** than for **1**, so the assumption is by no means certain. The rate expression is solved by assuming a combined steady state for **8** and **9**, leading to expression (10).

$$k_{obs} = \frac{(k_0 + k_2 K_L[L])(k_a + k'_a K_{eq}[L])}{(1 + K_{eq}[L])\{k_{-a} + k_0 + (k'_{-a} + k_2)K_L[L]\}} \qquad (10)$$

Deriving the expression for k_c is not as easy here as for the previous expressions. It can be safely assumed that k_0 can be ignored even at modest ligand concentrations. However, k_{-a} must be assumed to be very large, and it is by no means certain that it can be neglected at any attainable ligand concentration. It is even possible that k_{-a} dominates the denominator. In order to explain ligand saturation behaviour, both possibilities must be considered.

If k_{-a} can be neglected at very high ligand concentrations, the expression for k_c is greatly simplified to eqn. (11).

$$k_c = \frac{k_2 k'_a}{k'_{-a} + k_2} \qquad (11)$$

This expression rationalizes saturation behaviour and also gives the possibility of selectivity breaks, but only if $k'_{-a} = k_2$ at the inversion temperature. On the other hand, assuming that k_{-a} dominates the denominator at any attainable ligand concentrations, the following expression is derived for the ceiling rate (12).

$$k_c = \frac{k_2 K_L}{k_{-a}}\left(\frac{k_a}{K_{eq}} + k'_a[L]\right) \qquad (12)$$

This equation cannot be reconciled with observed experimental results. In order for this equation to exhibit saturation behaviour, k'_a must be negligible. The simple resulting equation can then no longer result in selectivity breaks. The conclusion then from case (2) is that fast and reversible ligand addition to **8** requires that alkene can add directly to **2** [eqn. (11)].

Case (3) assumes that alkene cannot add to the formal 18-electron complex **2**. In this case, the rate expression is solved by assuming steady state for both osmaoxetane complexes [eqn. (13)].

$$k_{obs} = \frac{k_0(k_2 + k_{-L}) + k_2 k_L[L]}{(k_0 + k_{-a})(k_2 + k_{-L}) + k_2 k_L[L]} \times \frac{k_a}{1 + K_{eq}[L]} \qquad (13)$$

The denominator of this equation is second-order in the ligand whereas the numerator is first-order. In order to

rationalize the observed saturation behaviour, it is now necessary to assume that k_{-a} will dominate over $k_L[L]$ for all attainable ligand concentrations (otherwise ligand inhibition is expected). We can then again assume a very fast equilibrium between **1** and **8**. As usual, the background reaction can be ignored ($k_0 \approx 0$). The expression for the ceiling rate constant then becomes eqn. (14).

$$k_c = \frac{k_2 k_L K_a}{K_{eq}(k_2 + k_{-L})} \quad (14)$$

As expected, eqn. (14) can also be obtained by setting both k'_a and k'_{-a} to zero in eqn. (9). This expression allows selectivity breaks when $k_{-L} \approx k_2$. As opposed to case (2) above, ligand addition to the osmaoxetane (8) must now be rate determining in the low temperature regime. This can be rationalized by the extensive steric crowding necessary to allow ligand addition to **8**. Thus, the currently available data cannot differentiate between different modes of formation of **9**.

Discussion

The preceding treatment shows quite clearly that an intermediate incorporating the three principal reagents (osmium tetroxide, ligand and alkene) is a necessary part of the reaction pathway. This is a consequence of having to reconcile the rate law (particularly saturation kinetics) and the observed temperature behaviour for the AD reaction. Detection of this elusive species has been attempted, but the only reported success[37] was shown to be incorrect.[38] However, high level quantum chemical studies of metal catalysed oxidations have indeed shown that metallaoxetane intermediates are energetically accessible.[13-15] For the osmium and ruthenium tetroxide oxidations, three possible intermediates have been identified so far,[13,14] **8**, **9** and an isomer of **9** where the ring occupies the axial position. Attempts to find other plausible intermediates, for example a π-complex between **2** and an alkene, have failed.[39] The 'axial' isomer of **9** has been excluded as a significant contributor in the high-ee cases on the basis of negligible interactions between the ligand and alkene moieties in the complex. We are therefore left with **9** as the only plausible candidate for an intermediate which can rationalize the observed enantioselectivities. Molecular mechanics calculations based on **9** have indeed been successful in rationalizing observed selectivities in the AD reaction.[23]

At ambient temperatures (above the isoinversion temperature for the AD reaction[30]), the rate and selectivity determining step is very probably the rearrangement of **9**. In Fig. 3, **9** can be formed by two possible paths. Both of these paths are potentially capable of rationalizing all observations in the AD reaction (*vide supra*). In a recent experiment, Lohray *et al.*[34] used two equivalents of OsO_4 together with one equivalent of a dimeric *cinchona* ligand and showed that the first equivalent of OsO_4 reacted much faster than the second equivalent with cyclohexene. The results were interpreted to mean that all OsO_4 was bound to the dimeric ligand, but only one was able to react. It was concluded that since the second equivalent of OsO_4 reacted only very slowly, it must be bound and unreactive. This was interpreted to mean that reaction *via* ligand-free oxetane **8** cannot take place. However, no comparison was made with the rate of the background reaction in the absence of ligand. It is also known that the binding constant of OsO_4 with the type of ligand employed is quite low.[17] The results can just as easily be interpreted to mean that only one quinuclidine moiety in the dimeric ligand is able to add to **8** in an efficient manner. When the ligand is locked in one equivalent of diolate complex, the reaction would be expected to proceed with the rate of the background reaction, which is two or three orders of magnitude slower.[29] The results are interesting in that they point out that the two moieties of the dimeric ligand do not react independently, but cannot be used as an argument for the direct addition of alkene to **2**.

The formal [2 + 2] reaction can be viewed as a co-ordination of alkene as a ligand to the metal.[40] The formally 16-electron OsO_4 easily adds one ligand,[41] but attempts to detect complexes with two ligands have been unsuccessful. On the other hand, an alkene is such a weak ligand that even the complex between one alkene and OsO_4 can seldom be detected.[35,36,42] From this viewpoint, adding an alkene to free OsO_4 seems feasible, but adding alkene to already ligated OsO_4 would be much harder. We therefore favour case (3) above [eqns. (13)–(14)] as the most rational [2 + 2] mechanism for the AD reaction. However, no evidence known to us can exclude the direct addition of alkene to **2** as a possible mechanism.

It is also useful to compare the proposed mechanisms to other known chemistry, particularly of transition metal oxo compounds, in order to place this system in a larger context. If the [3 + 2] process is operative, then it is possible to extend pericyclic reactivity directly to metal-containing systems. Additional new reactivity for metal complexes may thus lie undiscovered. Furthermore, it would confirm that controlling C–O bond formation is fundamentally a matter of tailoring the reactivity of oxygen in metal oxo complexes, and that the participation of the metal is primarily electronic, through its bond to oxygen. The high stereoinduction observed in this system may be quite fortuitous; extension to other bond-forming processes in a systematic manner may be difficult. On the other hand, the [2 + 2] mechanism proposes a discrete covalent interaction between metal and substrate. Understanding the reaction energetics (and particularly the stereoinduction) becomes more complex since there are more intermediates to consider, but the manner in which steric and electronic factors interact might be extended to other processes.

One source for the Criegee mechanism (and a substantial reason for its continued popularity) is the analogy to pericyclic [3 + 2] cycloadditions such as ozonation and other 1,3-dipolar cycloadditions to alkenes.[43] Several hypotheses have been put forward to explain why such reactions occur (and do so in a concerted fashion). These bimolecular cycloadditions must develop enough bonding at the transition state to overcome the highly negative entropic barrier imposed by the alignment necessary for orbital overlap. One approach has been to note that the proper arrangement of molecules gives rise to electronic interactions somewhat akin to 'aromatic stabilization' in the transition state.[44] Another approach has suggested that concerted bond formation is a way for the molecule to avoid an energetically unfavourable intermediate (biradical or zwitterion)[45] in an otherwise thermodynamically favourable process. The latter explanation has been extended to concerted (but non-pericyclic) organometallic rearrangements.[46] However, a metal in the reacting cycle of orbitals is likely to decrease either effect: either by decreasing the aromatic stabilization possible in a metallacycle,[47] or by stabilizing other intermediates. It is worth noting here that one of the most common reactions of M=X multiple bonds (particularly where X = CR_2) is a [2 + 2] cycloaddition;[40,48] the different kinds of bonding available to the metal allow it to circumvent the restrictions of orbital symmetry requirements.

The formation of a metallaoxetane is not only an expected reaction of metal oxo complexes; such reactions with unsaturated molecules have ample precedent.[16,49] There is some evidence that such an intermediate can form from OsO_4,[50] though this does not necessarily place that intermediate on the reaction coordinate for bishydroxylation. The alkyl-to-oxo migration step in the multistep pathway is more speculative, particularly given the growing number of stable alkyl-oxo compounds.[51] However, circumstantial evidence for such a transformation has been seen,[52] and a photochemical version has recently been reported.[53] The

reverse process, migration from oxygen to metal, has ample precedent as well.[54] In a system closely related to osmylation by microscopic reversibility, a concerted mechanism has been ruled out for fragmentation of rhenium diolates.[55] Again, positive evidence that alkyl migration is rate-determining is limited, but circumstantial arguments favour a metallaoxetane intermediate.

Our view, then, is that the [2 + 2] mechanism is more consistent with known reactivity of metal complexes. Further more, it better rationalizes the available experimental and theoretical evidence from osmylation chemistry than does the [3 + 2] mechanism. This is particularly true for the asymmetric version of the osmium-catalysed dihydroxylation reaction.

Conclusions

It seems very improbable that the osmylation reaction can be rationalized by a pathway involving simultaneous formation of both C–O bonds. The only remaining possibility seems to be formation of a precomplex of the three principal reaction components. From this precomplex, the barrier to osmylation must be as low as the barrier to decomplexation, whereas the barrier to osmylation for non-complexed alkene must be high. The formal [2 + 2] pathway, on the other hand, can rationalize all available data. Contrary to a previous suggestion,[34] available data cannot differentiate between the two main [2 + 2] proposals. However, from chemical precedence we favour the path where complex **9** is formed by ligand addition to free osmaoxetane **8**.

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