First determination of an activation volume for the osmium-catalyzed dihydroxylation of an alkene

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Received (in Cambridge) 10th May 1999, Accepted 3rd June 1999

The rate constants for the dihydroxylation of (*E*)-ethyl cinnamate with osmium tetroxide in toluene were determined at atmospheric and high pressure indicating a slight acceleration by high-pressure. The volume of activation was determined to be -12 ± 2 cm^3 mol^{-1} for this transformation. This relatively small negative value can not be explained with a simple [3 + 2]-mechanism for which a significantly more negative value should be expected.

Introduction

The application of high pressure[1] in organic synthesis can be useful for two reasons. First of all, high pressure can accelerate reactions having a negative activation volume, *i.e.* the volume of the transition state is smaller than the volume of the starting materials. This is in general the case for associative processes, and, not surprisingly, cycloadditions are most thoroughly investigated under high pressure. Typical volumes of activation for such reactions reach from -20 to -40 cm^3 mol^{-1} resulting in an acceleration of up to 10^5. Secondly, high pressure experiments can help to distinguish between reaction mechanisms if they have significantly different volumes of activation.[2] Only recently, the effect of high pressure on transition metal catalyzed reactions has been a matter of investigation.[3] Most notably, beneficial effects of pressure have been identified on reactivity and selectivity in the area of palladium catalysis.[4] Moreover, kinetic data obtained for such reactions helped to shed light on mechanistic pathways.[5]

In this paper we would like to describe the pressure effect on the osmium-catalyzed dihydroxylation of alkenes. Besides determining a possible activation of the process through pressure, we also hoped to gain new insights into the ongoing controversy being discussed in the literature between a possible [2 + 2]- or [3 + 2]-cycloaddition mechanism as the initial reaction step.

The osmium-catalyzed asymmetric dihydroxylation (AD)[6] of olefins developed by Sharpless is one of the best explored and most applied transformations in the field of asymmetric catalysis. Even though the reaction is well established, its mechanism is under heavy debate and to date a matter of ongoing research. During the last years, essentially two reaction pathways have been discussed, which differ in the way the osmium glycolate **3** is formed, *i.e.* in the way the two oxygen atoms are transferred to the alkene (Fig. 1). One hypothesis supported by Sharpless[7] assumes the rapid and reversible formation of an osmaoxetane[8] **2** in a [2 + 2]-cycloaddition from osmium tetroxide (**1**) and an alkene, followed by its rearrangement to the osmium glycolate **3** in the rate determining step. The other hypothesis supported by Corey[9] calls for a concerted [3 + 2]-cycloaddition of an alkene and osmium tetroxide (**1**) to give the osmium glycolate **3** in a single step.

Sharpless *et al.*[10] observed a non-linear relationship between enantioselectivity and temperature for the AD reaction, taking this observation as evidence against the [3 + 2]-mechanism as this could only be explained by postulating an intermediate on the way from the starting materials to the glycolate **3**.

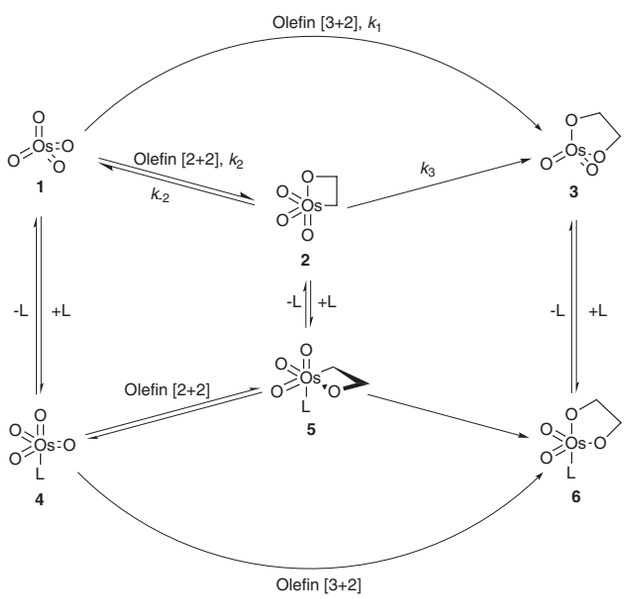

Fig. 1 The [2 + 2]- and [3 + 2]-pathway for the formation of the intermediate osmium glycolate **3**. If no amine ligand L is present only structures **1**–**3** are relevant. In the presence of L structures **4**–**6** should exist in equilibrium. k_1, k_2, k_{-2} and k_3 are the rate constants for the steps without base L.

However, Corey[11] determined that the AD reaction follows Michaelis–Menten kinetics and argues that this would account well for the observed enantioselectivity–temperature dependence. Furthermore, he developed a transition state model for the AD reaction which explains the observed asymmetric induction by assuming an enzyme-like U-shaped binding pocket. Also, ^{13}C- and ^{2}H-kinetic isotope effects for AD reactions support the [3 + 2]-mechanism.[12]

Density functional theory (DFT) calculations by Ziegler[13] as well as by Morokuma[14] showed that the activation barrier for the formation of an osmaoxetane **2** with no base present should be very high (Ziegler: +39.7 kcal mol^{-1}, Morokuma: +43.3 kcal mol^{-1}). On the other hand the activation barrier for the [3 + 2]-pathway was determined to be much smaller (Ziegler: 1.8 kcal mol^{-1}, Morokuma: 1.9 kcal mol^{-1}). Their calculations for the model system "ethylene + OsO_4 + NH_3" also reflected the known acceleration of the reaction by base.[15] *Ab initio* calculations by Frenking[16] showed that a reaction *via* a [2 + 2]-pathway is possible, however, this work provided no inform-

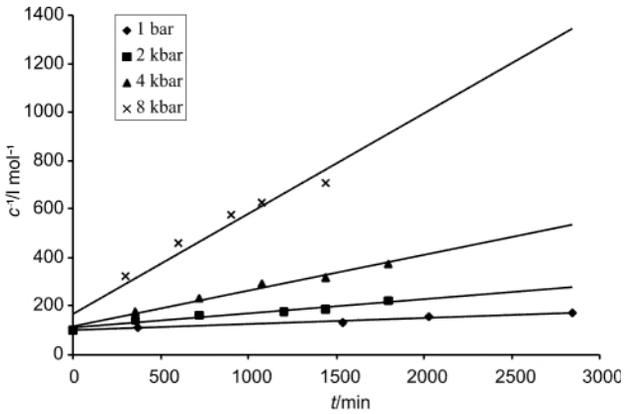

Fig. 2 Determination of rate constants for the dihydroxylation of (*E*)-ethyl cinnamate at different pressures from a plot of $[\text{Olefin}]_t^{-1}$ *vs.* *t* according to eqn. (8).

ation on transition state structures. Theoretical kinetic data of the AD reaction were calculated by Norrby and Gable[17] and seem to support the [2 + 2]-mechanism.

Results and discussion

For reasons of simplification we chose to perform our high pressure experiments without base ligands in order to minimize the number of pressure sensitive steps. According to DFT-calculations,[13,14] the reduction of the activation energies for both mechanisms by addition of base ligands is small compared to the difference of the activation barriers. Therefore, one can reason that the rate-determining steps of the alternative pathways are the same no matter whether accelerating ligands are present or not. The rate law for the formation of the glycolate **3** *via* the [3 + 2]-pathway is given by eqn. (1).

$$-\text{d[alkene]}/\text{d}t = \text{d[}\mathbf{3}\text{]}/\text{d}t = k_1[\text{OsO}_4][\text{alkene}] \quad (1)$$

For the [2 + 2]-pathway eqns. (2)–(4) provide the rate laws of the present species.[18]

$$\text{d[alkene]}/\text{d}t = -k_2[\text{OsO}_4][\text{alkene}] + k_{-2}[\mathbf{2}] \quad (2)$$

$$\text{d[}\mathbf{2}\text{]}/\text{d}t = k_2[\text{OsO}_4][\text{alkene}] - k_{-2}[\mathbf{2}] - k_3[\mathbf{2}] \quad (3)$$

$$\text{d[}\mathbf{3}\text{]}/\text{d}t = k_3[\mathbf{2}] \quad (4)$$

Steady-state approximation for the osmaoxetane **2** (d[**2**]/d*t* = 0) and combination with eqn. (2) leads to eqn. (5). As the

$$\text{d[}\mathbf{3}\text{]}/\text{d}t = -\text{d[alkene]}/\text{d}t = k_3[\mathbf{2}] \quad (5)$$

[2 + 2]-model postulates the rapid and reversible formation of the osmaoxetane **2** its formation and decomposition occur at the same speed, *i.e.* eqn. (6). From the combination of eqns. (5) and (6) we obtain eqn. (7).

$$k_2[\text{OsO}_4][\text{alkene}] = k_{-2}[\mathbf{2}] \quad (6)$$

$$\text{d[}\mathbf{3}\text{]}/\text{d}t = -\text{d[alkene]}/\text{d}t = K_{eq}k_3[\text{OsO}_4][\text{alkene}] \quad \text{with } K_{eq} = k_2/k_{-2} \quad (7)$$

The formation of the glycolate **3** can be treated as a reaction of type A + B → C. If the initial concentrations $[\text{OsO}_4]_0$ and $[\text{Olefin}]_0$ are equal it follows that after the reaction time *t* has passed $[\text{OsO}_4]_t$ also equals $[\text{Olefin}]_t$. This fact greatly simplifies the integration of the rate laws and leads to eqn. (8), with $k = k_1$

$$[\text{A}]_t^{-1} = [\text{A}]_0^{-1} + kt \quad (8)$$

for the [3 + 2]-mechanism and $k = K_{eq}k_3$ for the [2 + 2]-mechanism. Therefore the dihydroxylations described in this article were run with stoichiometric amounts of OsO_4. As the solvent for our experiments we chose toluene as it does neither solidify in the pressure range of 1 bar to 8 kbar which we applied nor does it give rise to side reactions. The dihydroxylation of (*E*)-ethyl cinnamate was carried out at 4 different pressures, monitoring the decrease of the alkene concentration with time. Plotting of $[\text{Olefin}]_t^{-1}$ *vs.* time (Fig. 2) according to eqn. (8) allowed determination of the rate constants for the reaction which revealed a modest pressure acceleration (Table 1).

Table 1 Rate constants *k* and k_{rel} and corresponding correlation coefficients R^2 for the dihydroxylation of (*E*)-ethyl cinnamate at various pressures in toluene at 23 °C

p/bar	*k*/1 mol^{-1} min^{-1}	k_{rel}	R^2
1	0.0255	1	0.98
2000	0.0598	2.3	0.95
4000	0.148	5.8	0.98
8000	0.414	16.2	0.95

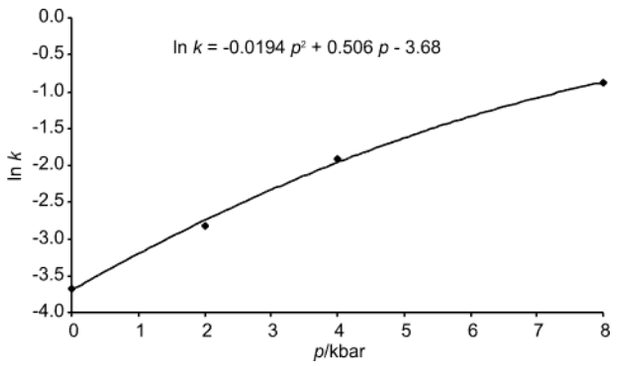

Fig. 3 Determination of the activation volume according to eqn. (10).

The volume of activation is defined by eqn. (9). To describe

$$(\delta \ln k/\delta p)_T = -\Delta V^{\ddagger}/RT \quad (9)$$

the pressure dependence of the activation volume the second-order polynome (10) has been used successfully in many cases[19]

$$\ln k(p) = a + bp + cp^2 \text{ with } \Delta V^{\ddagger} = -bRT \quad (10)$$

to account for the increased viscosity of the solvent at high pressure. The activation volume for this reaction was therefore determined from a plot of ln *k* *vs.* *p* as -12 ± 2 cm^3 mol^{-1} (Fig. 3).

Since no activation volumes are published for transition metal mediated cycloadditions, the only comparison possible is that to metal-free ones, which are reported in the literature.[1c] Nevertheless, since the activation volume is mainly dependent on geometrical factors,[20] such a comparison should be feasible.

Typical activation volumes for 1,3-dipolar cycloadditions range from −20 to −30 cm^3 mol^{-1}. The value -12 ± 2 cm^3 mol^{-1} that we have obtained in this study is significantly lower and can therefore not support the [3 + 2]-pathway.[21] On the other hand, it is difficult to say whether our results are compatible with a [2 + 2]-pathway as the corresponding activation volume is influenced by the reversible cycloaddition and the subsequent rearrangement. However, since the latter reaction as the rate determining step should have a volume of activation close to 0 cm^3 mol^{-1},[4b] one would expect for the [2 + 2]-pathway an overall smaller negative value than for typical metal-free cycloadditions (−20 to −40 cm^3 mol^{-1}). Nevertheless, these arguments have to be considered with great care, since it is not clear that one can compare the volumes of activation of conventional cycloadditions with those having transition-metal species involved.

Experimental

High pressure experiments were performed using a Laboratory Hydraulic Press U101 with Liquid Vessel LV/30/16 by Unipress, Warszawa, Poland. The conversion in each dihydroxylation reaction was determined using gas chromatography with phenyl ethylacetate as internal standard. GC analysis was carried out on a Carlo Erba Mega 8560 chromatograph with split injection at 0.4 bar H_2. Temperature program: 60 °C/1 iso/10 °C min^{-1}/200 °C. Column: permethylated β-cyclodextrin bound covalently to permethylated polysiloxane, id = 0.3 mm, 0.2 μm film, 20 m.[22]

Dihydroxylation of (*E*)-ethyl cinnamate at high pressure

In a volumetric flask 0.50 ml (0.050 mmol, *c*(alkene) = *c*(standard) = 0.10 mol l^{-1}) of a solution of (*E*)-ethyl cinnamate and ethyl phenylacetate in toluene were mixed with 0.54 ml (0.050 mmol, $c(OsO_4)$ = 93 mmol l^{-1}) of a solution of OsO_4 in toluene. The solution was diluted to a total volume of 5 ml with toluene. 1 ml of the solution was filled in a Teflon™ tube and left in the high pressure apparatus at 2, 4 or 8 kbar for the requested time at 23 °C. Then the reaction mixture was poured into 1 ml of a 1 M sodium sulfite solution and stirred for 15 min. 0.2 ml of the organic layer were filtered through a silica gel pad with a thickness of 1 cm in a pasteur pipette. The silica gel pad was washed with 4 ml of a dichloromethane–methanol mixture (20:1) and the filtrate was analyzed *via* GC. Retention times: ethyl phenylacetate: 8.29 min; (*E*)-ethyl cinnamate: 11.55 min; diol: 14.22/14.39.

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft (Re 948/3-1 and Schm 1012/2) and the Fonds der Chemischen Industrie for financial support. R. R. thanks the Fonds der Chemischen Industrie and the BmBF for a Kekulé fellowship. M. N. thanks the EU for an ERASMUS scholarship.

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Paper 9/03706C