

Mechanism of Ruthenium-Catalyzed Hydrogen Transfer Reactions. Concerted Transfer of OH and CH Hydrogens from an Alcohol to a (Cyclopentadienone)ruthenium Complex

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Kinetic studies of the ruthenium-catalyzed dehydrogenation of 1-(4-fluorophenyl)ethanol (4) by tetrafluorobenzoquinone (7) using the Shvo catalyst 1 at 70 °C show that the dehydrogenation by catalytic intermediate 2 is rate-determining with the rate = $k[4][1]^{1/2}$ and with $\Delta H^{\ddagger} = 17.7$ kcal mol⁻¹ and $\Delta S^{\ddagger} = -13.0$ eu. The use of specifically deuterated derivative 4-CHOD and 4-CDOH gave individual isotope effects of $k_{CHOH}/k_{CHOD} = 1.87 \pm 0.17$ and $k_{CHOH}/k_{CDOH} = 2.57 \pm 0.26$, respectively. Dideuterated derivative 4-CDOD gave a combined isotope effect of $k_{CHOH}/k_{CDOD} = 4.61 \pm 0.37$. These isotope effects are consistent with a concerted transfer of both hydrogens of the alcohol to ruthenium species 2.

Introduction

The use of transition metals that catalyze the transfer of hydrogen from alcohols has increased dramatically during the past decade.^{1,2} Systems such as Noyori's arene-Ru(II)-diamine catalyst and Shvo's hydroxycyclopentadienyl ruthenium(II) catalyst (1) have been used for the catalytic reduction of polarized unsaturated species,^{3,4} and Shvo's catalyst (1) has also been used for dynamic kinetic resolution.^{5,6} Unlike earlier systems, these hydrogen-transfer catalysts do not require the presence of base for the transfer of hydrogen from an alcohol to a ketone and have thus been suggested to operate through a mechanism different from the metal hydride mechanism common for transition-metal complexes^{1,2a} or the traditional Meerwein-Ponndorf-Verley mechanism common for main group elements.^{7,8} Noyori has proposed that hydrogen transfer occurs outside the

coordination sphere of the metal for the arene–Ru(II)– diamine system, and he and others have provided calculations that support this concerted mechanism.⁹ Casey has reported mechanistic evidence based on deuterium isotope effects that support a concerted transfer of hydrogen using the Shvo catalyst **1**.¹⁰

In dynamic kinetic resolution, the Shvo catalyst **1** is used to racemize a secondary alcohol (Scheme 1).^{5a} An enzyme, in the presence of an acyl donor, is employed to acylate one of the enantiomers of the racemic alcohol, while the other enantiomer is racemized in situ by the catalyst **1**. This process continues until all of the alcohol has been converted to a single enantiomer of the acylated product. The racemization proceeds via a dehydrogenation of the alcohol by the catalyst and readdition of the hydrogens to the intermediate ketone.

To address the mechanistic questions concerning the transfer of hydrogen and to better understand this process in dynamic kinetic resolution, we studied the kinetics of hydrogen transfer from an alcohol to ruthenium complex **2**. The results of our mechanistic study, including kinetic isotope effects, provide direct evidence for a mechanism involving simultaneous transfer of the C-H and O-H hydrogens from an alcohol to the unsaturated ruthenium catalyst **2**.

Results

Due to the high temperature necessary to dissociate the Shvo catalyst **1** and produce the unsaturated species

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SCHEME 1

SCHEME 2



2 that is capable of oxidizing an alcohol (Scheme 2), the stoichiometric reaction of ruthenium species **2** with an alcohol is too fast to monitor by NMR. We therefore chose to study the catalytic reaction. The use of tetrafluorobenzoquinone, **7**, as a hydrogen acceptor resulted in a catalytic system in which alcohol oxidation is the slowest step, and thus could be measured directly.

Using a 2.13×10^{-4} M solution of **1** in the presence of tetrafluorobenzoquinone (7) at 70 °C, the oxidation of 1-(4-fluorophenyl)ethanol (4) by the unsaturated ruthenium species 2 follows pseudo-first-order kinetics to over 90% conversion as determined by the observation of alcohol disappearance (δ 1.10–1.30) and ketone formation (δ 1.95–2.15) by ¹H NMR. This indicates a first-order dependence on the alcohol with $k_{\rm obs}$ = (7.57 \pm 0.40) \times 10^{-4} s⁻¹. The concentration of quinone 7 was varied above 1.5 equiv (versus alcohol, 0.24-0.36 M) with no resulting change in the observed rate of oxidation, indicating a zero-order dependence on quinone concentration. Variation of the catalyst concentration between 2.0×10^{-4} and 5.0×10^{-4} M led to the plot of ln[1] vs lnk_{obs}, which provided a line of slope 0.43, within experimental error of half-order dependence on the concentration of catalyst. This dependence is expected, as the catalyst must dissociate prior to catalytic activity. The rate law is provided in eq 1.

$$-\frac{d[4]}{dt} = k[4][1]^{1/2}$$
(1)

Reactions were carried out at several different alcohol concentrations, maintaining constant catalyst concentra-

TABLE 1. Rate Constants for Oxidation of Isotopomers of 4 at 70 $^{\circ}$ C in C₆D₆

	$k~(\mathrm{M}^{-1/2} \cdot \mathrm{s}^{-1}) imes 10^2$
k _{CHOH} k _{CHOD} kcDoh kcDod	$egin{array}{llllllllllllllllllllllllllllllllllll$

tion and pseudo-first-order kinetics. Under experimental conditions, the resting state of the catalytic cycle is the ruthenium species **1**, as observed by ¹H NMR. The observed rate was constant, within experimental error, for all alcohol concentrations tested. These concentrations were varied over the range of 0.12 to 0.24 M. Labeled derivatives of alcohol **4** specifically deuterated at the oxygen (**4-CHOD**; OH content < 1%), the α -carbon (**4-CDOH**; CH content < 5%), and at both the oxygen and the α -carbon (**4-CDOD**; CH content < 5%, OH content < 2%) were prepared by standard methods.¹¹ The reaction rate for each labeled alcohol was then independently determined. The rate constants were determined using the rate law in eq 1 and are shown in Table 1.

In determining the isotope effects using the ratios of rate constants, the equilibrium constant of the dissociation of the ruthenium species 1 must also be included in this expression (eq 2).

$$\frac{k_{\rm CHOH}}{k_{\rm CHOD}} = \frac{k_{\rm obs-CHOH} [1]^{1/2} \sqrt{K_{\rm eq}}}{k_{\rm obs-CHOD} [1]^{1/2} \sqrt{K_{\rm eq}}}$$
(2)

This equilibrium constant is extremely small, even at

TABLE 2. Kinetic Deuterium Isotope Effects for the Reaction of 2 with 4 at 70 $^{\circ}$ C in C₆D₆

<i>k</i> _{CHOH} / <i>k</i> _{CHOD} <i>k</i> _{CDOH} / <i>k</i> _{CDOD} <i>k</i> _{CHOH} / <i>k</i> _{CDOH} <i>k</i> _{CHOD} / <i>k</i> _{CDOD}	$\begin{array}{c} 1.87 \pm 0.17 \\ 1.80 \pm 0.19 \\ 2.57 \pm 0.26 \\ 2.47 \pm 0.24 \end{array}$
$k_{\rm CHOH}/k_{\rm CDOD}$	$\begin{array}{c} 1.11 \pm 0.01 \\ 4.61 \pm 0.37 \end{array}$

elevated temperatures, and has not been experimentally determined. With the use of labeled alcohols, the ruthenium species **1** incorporates deuterium, thus slightly changing the equilibrium constant for dissociation to **2** and **3**. The deueteriun isotope effect of this equilibrium constant is expected to be small. Because there was no detectable change in rate over the progression of the oxidation of the labeled alcohols, the differences in equilibrium constants were assumed to be negligible, thus simplifying the kinetic isotope effect determination to the ratio of the rate constants from eq 1.

We found primary deuterium isotope effects of 1.8-1.9 for the breaking of the OH bond of the alcohol **4** and of 2.5-2.6 for the breaking of the CH bond. The doubly labeled alcohol showed an isotope effect of 4.6 (Table 2). These isotope effects are consistent with a mechanism involving concerted transfer of both hydrogens of the alcohol to ruthenium species **2**.

Kinetic measurements performed between 65 and 80 °C allowed the determination of activation parameters. The rate constants are $3.69 \times 10^{-2} \text{ M}^{-1/2} \text{ s}^{-1}$ at 65 °C, $5.33 \times 10^{-2} \text{ M}^{-1/2} \text{ s}^{-1}$ at 70 °C, $8.15 \times 10^{-2} \text{ M}^{-1/2} \text{ s}^{-1}$ at 75 °C, and $11.61 \times 10^{-2} \text{ M}^{-1/2} \text{ s}^{-1}$ at 80 °C. The subsequent Eyring plot provided the values $\Delta H^{\ddagger} = 17.7 \pm 3.7$ kcal mol⁻¹ and $\Delta S^{\ddagger} = -13.0 \pm 1.1$ eu.

Discussion

The intermediate negative entropy of activation determined in this study ($\Delta S^{t} = -13.0 \pm 1.1$ eu) is much less negative then the entropy of activation for the hydrogenation of benzaldehyde by the bis-tolyl derivative of ruthenium hydride **3** ($\Delta S^{t} = -28$ eu). The intermediate negative ΔS^{t} is consistent with the mechanism proposed for the hydrogen transfer. From the resting state of this cycle, the dimeric ruthenium species **1** must initially dissociate to form **2**, prior to reacting with the alcohol through an associative process during the slow step of the catalytic cycle (Scheme 2). This combination of dissociative and associative steps results in the intermediate negative ΔS^{t} value.

The kinetic isotope effects observed for the transfer of hydrogen from the alcohol oxygen to the cyclopentadienone ligand of ruthenium ($k_{\text{CHOH}}/k_{\text{CHOD}} = 1.87 \pm 0.17$) and from carbon to ruthenium ($k_{\text{CHOH}}/k_{\text{CDOH}} = 2.57 \pm 0.26$) provide strong evidence for a concerted mechanism. For a concerted reaction in which both hydrogens are transferred in a single step, the kinetic isotope effect for the doubly labeled material should be the product of the two individual isotope effects. The combined isotope effect ($k_{\text{CHOH}}/k_{\text{CDOD}} = 4.61 \pm 0.37$) for transfer of hydrogen from both carbon and oxygen to the unsaturated ruthenium

SCHEME 3



species **2** is within experimental error of the product of the individual isotope effects $(2.57 \times 1.87 = 4.80)$. This observation provides strong evidence that both hydrogens are transferred in a concerted manner.

Two mechanisms have been suggested for the concerted transfer of hydrogen from ruthenium species **3** to an aldehyde and can be applied to the reversed reaction, the dehydrogenation of an alcohol. Bäckvall¹² and Shvo¹³ have both proposed mechanisms involving initial coordination of the alcohol to the metal center. This coordination forms alcohol complex **8**, which undergoes simultaneous β -hydride elimination and proton transfer to produce the resulting ketone (Scheme 3).^{12,14} Because complex **8** is formally an 18-electron complex, this species must undergo a $\eta^4 \rightarrow \eta^2$ ring slip to form the open coordination and proton transfer, to produce **9**. Dissociation of the ketone from **9** and $\eta^3 \rightarrow \eta^5$ ring slip forms ruthenium hydride **3**.

Casey has proposed that hydrogen transfer takes place outside of the coordination sphere of the metal (Scheme 4).¹⁰ Although the alcohol may reversibly coordinate to the metal center to form complex **8**, no alcohol complex has thus far been isolated.¹⁵ As only a single coordination site is necessary for the concerted transfer of hydride and proton outside the coordination sphere, this transfer is thought to proceed without ring slippage. Upon reaction, the ketone and ruthenium species **3** are subsequently formed free in solution. Experiments to differentiate these two mechanisms are currently in progress.

A mechanistic alternative to a concerted hydrogentransfer process is a two-step mechanism in which the barriers for proton transfer followed by hydride transfer

⁽¹¹⁾ Alcohol **4-CDOH** was prepared by LiAlD₄ reduction of 4-fluoroacetophenone. Alcohols **4-CHOD** and **4-CDOD** were obtained from **4** and **4-CDOH**, respectively, by exchange of the OH proton with D_2O and MeOD (see Supporting Information)

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SCHEME 4



SCHEME 5



(or vice versa) are approximately equal. This type of mechanism would display kinetic isotope effects for transfer both from oxygen and from carbon (Scheme 5). For a mechanism of this type, the kinetic isotope effect of the doubly labeled material should be smaller than the product of the individual isotope effects.

Assuming no equilibrium isotope effect on the first step and equal barriers for both proton and hydride transfer, one must employ isotope effects of 2.70 for proton transfer and 4.26 for hydride transfer to obtain the observed isotope effects ($k_{CHOH}/k_{CHOD} = 1.87 \pm 0.17$) and ($k_{CHOH}/k_{CDOH} = 2.57 \pm 0.26$) (see Supporting Information). The combination of these isotope effects would result in a doubly labeled isotope effect of 3.57, significantly smaller than the observed 4.61 \pm 0.37. Thus a two-step mechanism with equal barriers can be excluded.¹⁶

Another mechanistic possibility is reversible proton transfer from the alcohol to ruthenium complex 2, followed by a rate-determining hydride transfer. The first step would display an equilibrium isotope effect, while the second would display a kinetic isotope effect. The transfer of a proton from an O-H bond in the alcohol to an O-H bond in the resulting ruthenium complex would be expected to show a very small equilibrium isotope effect, much smaller than the observed isotope effect of 1.87. A two-step mechanism with fast and reversible proton transfer can therefore be excluded.

The conclusion that the transfer of hydrogen from an alcohol to the unsaturated ruthenium catalyst occurs through a concerted mechanism is in good agreement with the findings of Casey for the stoichiometric reduction of benzaldehyde.¹⁰ Recently, Casey and Johnson reported isotope effects for dehydrogenation of 2-propanol using chiral Ru(*p*-cymene)(diamino)catalyst that are very similar to those obtained in the present work ($k_{CHOH}/k_{CHOD} =$ 1.79, $k_{CHOH}/k_{CDOH} = 2.86$, and $k_{CHOH}/k_{CDOD} = 4.88$).¹⁷ Continued work in this area contributes to the overall understanding of this catalytic process and to its use in hydrogenation and dynamic kinetic resolution.

Experimental Section

The general kinetic procedure is illustrated by a specific example. Tetrafluoro-1,4-benzoquinone 7 (45 mg) was measured into a screw cap NMR tube that had been flushed with argon. A standard solution of Shvo catalyst 1 (0.1 mL, 2.13 \times 10^{-4} M, prepared under argon from 2.31 mg of 1, ~5 mg of ferrocene, and 1.0 mL of C₆D₆) was added by 100 μ L syringe through a septum in the cap of the NMR tube. The sample was then diluted to 0.75 mL total volume by addition of dry benzene- d_6 . The sample was placed into the NMR spectrometer prewarmed to 70 °C and the benzoquinone was allowed to completely dissolve. The sample tube was ejected and $15.2 \,\mu\text{L}$ (0.12 M) of the alcohol 4 was added by 25 μ L syringe. The tube was reinserted and timing begun. All kinetic runs were carried out to at least 2.5 half-lives and monitored by ¹H NMR spectroscopy by following the disappearance of the methyl resonance of the alcohol (δ 1.10–1.30) and the appearance of the methyl resonance of the ketone (δ 1.95–2.15). Integrations were recorded in comparison to a ferrocene internal standard. Determination of the observed rate was accomplished by plotting the concentration of 4 versus time and fitting the disappearance to a nonlinear first squares fit.

Supporting Information Available: Experimental procedures and characterization for deuterated alcohols and kinetic results and calculation of stepwise isotope effects. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁶⁾ One referee suggested that there is a possibility that both kinetic isotope effects (KIEs) are large but that there is a step after the isotope-sensitive steps that is partly rate-limiting thus masking both KIEs. Although we cannot completely rule out this possibility, it seems unlikely, since we have shown that the rate-limiting step is the dehydrogenation of **4** by **2** to give **5** and **3**. The possible masking step after the isotope-sensitive steps, reaction of **3** with quinine **7**, was shown to be fast.

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