Interconversion of Monohydride Intermediates in Rh(I)-Catalyzed Asymmetric Hydrogenation of Dimethyl 1-Benzoyloxyethenephosphonate

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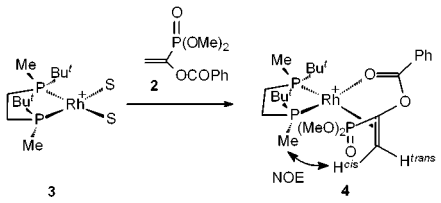
Received January 31, 2001
Revised Manuscript Received April 7, 2001

Recently, the interest in the exact mechanism of stereoselection in the Rh(I)-catalyzed asymmetric hydrogenation of activated double bonds is renewed due to both the development of the computational techniques[1−3] and the new experimental findings.[4−7] Thus, the extensive ab initio DFT calculations were used by Landis et al. to support the possibility of enantioselection during the oxidative addition of dihydrogen to a catalyst−substrate complex of a model Rh-diphosphine complex[1] and the real Rh-DuPHOS catalytic system.[2,3] On the other hand, we have observed almost perfect enantioselection in the low-temperature reaction of a solvate dihydride $[RhH_2(t\text{-Bu-BisP*})(CD_3OD)_2]BF_4$ (**1**) with methyl (*Z*)-α-acetamidocinnamate,[4] demonstrating that a dihydride pathway can also operate in the Rh(I)-catalyzed asymmetric hydrogenation. This result was reproduced for other BisP*-Rh complexes and a series of substrates.[5] Dihydride pathway is also in accord with the dramatic difference of the sense of enantioselection in catalytic asymmetric hydrogenation of aryl- and alkyl-substituted enamides.[6] Brown et al. reported recently the detection of an agostic intermediate in the asymmetric hydrogenation of dehydroamino acids catalyzed by the Rh-PHANEPHOS complex.[7] Interestingly, this intermediate was computationally predicted to be inaccessible via the unsaturated pathway;[2,3,7] however, its appearance via the dihydride mechanism is quite possible. In addition, the reversibility of the formation of the agostic intermediate with respective to substrate reported by Brown et al.[7] is also best explained if the relative stability of the solvate dihydride derived from the Rh-PHANEPHOS catalyst is proposed.

We report here the first observation of the structural rearrangement of monohydride intermediates in Rh(I)-catalyzed asymmetric hydrogenation, and demonstrate the interplay of two possible reaction pathways in this theoretically and practically important reaction.

Recently, the asymmetric hydrogenation of protected α,*β*-unsaturated α-acyloxyphosphonates was shown to be synthetically useful.[8] We found that the catalytic hydrogenation of dimethyl 1-benzoyloxyethenephosphonate (**2**) using Rh-(*S*,*S*)-*t*-Bu-BisP* catalyst gave the corresponding product with 88% ee (*S*),[9] which is comparable to the best results obtained by Burk et al.[8] On the other hand, the not perfect stereoselectivity observed in this hydrogenation allows one to analyze minor diastereomers of the intermediates, which are the precursors of the product with the opposite chirality.

Scheme 1. Formation of Catalyst−Substrate Complex **4**



Addition of a 2-fold excess of the phosphonate **2** to a deuteriomethanol solution of **3** yielded a catalyst−substrate complex **4** (Scheme 1), which displayed a single set of signals in the ^{31}P NMR spectrum within the temperature range from −100 to +60 °C. Complexation was fast even at −100 °C; no detectable equilibrium amounts of free solvate **3** were found in the spectra even at elevated temperatures. The chemical shift of the carbonyl carbon atom in **4** (δ = 178.9, compare to δ = 165.1 in uncoordinated substrate) and two vicinal C−P couplings observed for this signal (5 and 8 Hz) confirm the mode of chelating coordination by the double bond and the benzoyloxy group of the substrate. The solution structure of the observed diastereomer of **4** was determined from the NOE and EXSY data.

We carried out the reaction of dihydride **1**[4] with 2-fold excess of phosphonate **2** at −100 °C. The signals of two monohydride intermediates **5a**,**b** in the ratio 100:5 were detected in the hydride region of the ^1H NMR spectra (Figure 1a).[10] Raising the temperature of the sample to −30 °C resulted in disappearance of the signals of **5a**,**b** and simultaneous growth of new hydride signals at δ = −19.7 (**6a**) and −19.3 (**6b**); the ratio of **6a**:**6b** was the same as that of **5a**:**5b** within the experimental accuracy (Figure 1b−d). Recooling of the sample to −60 °C gave an additional low-intensity hydride signal at δ = −22.0 (**7a**) (Figure 1e).

Attempts to hydrogenate the catalyst−substrate complex **4** in the temperature interval from −100 to −60 °C were unsuccessful; no reaction occurred under these conditions. The hydrogenation of **4** with 2 atm of H_2 carried out for 10 min at −30 °C gave a mixture of the monohydride intermediates **5**−**7** (Figure 1f) together with the hydrogenation product. Comparing the spectrum to that obtained in the previous experiment (Figure 1e), one can see two main differences: the ratio of **6a**:**6b** changed to 5:1 and an additional signal at δ = −21.8 (**7b**) appeared.

Both experiments were reproduced three times to give essentially the same results. The overnight EXSY experiment carried out at −60 °C (Figure 2) showed that **6a** is interconverting with **7a**, and **6b** is interconverting with **7b**, but no exchange between **6a** and **6b** or **7a** and **7b** takes place. These data together with the correlation of ee values obtained from the NMR samples[11] and relative integral intensities of the monohydride signals in the NMR spectra testify that the monohydrides **5a**, **6a**, and **7a** are the precursors of the *S*-hydrogenation product, whereas **5b**, **6b**, and **7b** give minor *R*-product after the reductive elimination. The hydrogenation of the catalyst−substrate complex **4** always gave markedly lower ee values compared to those observed in the low-

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(9) The detailed account on the asymmetric hydrogenation of α,*β*-unsaturated phosphonates using Rh-BisP* and Rh-MiniPHOS catalysts is in preparation.
(10) In the ^{13}C and ^{31}P NMR spectra taken at −95 °C an additional intermediate was detected. Its spectra resemble those of **4**, but it is not the second diastereomer of the catalyst−substrate complex, since it does not form in the absence of hydrogen under the same conditions. A molecular hydrogen complex (see refs 1−3) with a broad undetectable signal in ^1H NMR is possible.
(11) The ee of the product in both experiments was determined by HPLC analysis after warming the sample to room temperature to complete the reductive elimination (NMR control) and removing Rh complexes by filtration through silica gel.

10.1021/ja015611l CCC: $20.00
Published on Web 04/19/2001

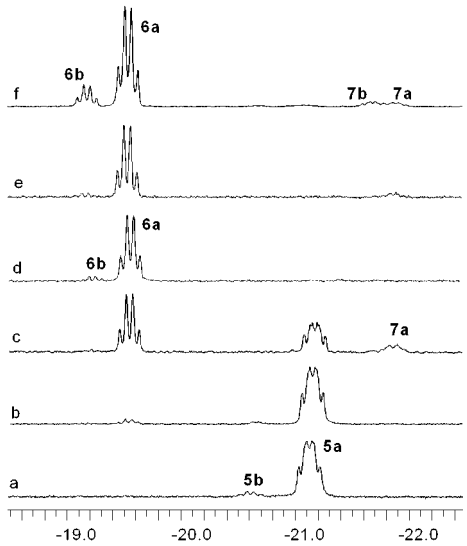


Figure 1. Hydride region of the ^{1}H NMR spectra (400 MHz, CD_3OD): (a) the sample obtained by mixing the CD_3OD solutions of **1** and **2** at −100 °C, spectrum taken at −95 °C; (b) the same sample after raising the temperature to −70 °C, (c) to −50 °C, (d) and to −30 °C; (e) the sample after recooling to −60 °C; (f) the sample obtained by hydrogenation of the CD_3OD solution of **4** for 10 min at −30 °C, spectrum taken at −60 °C.

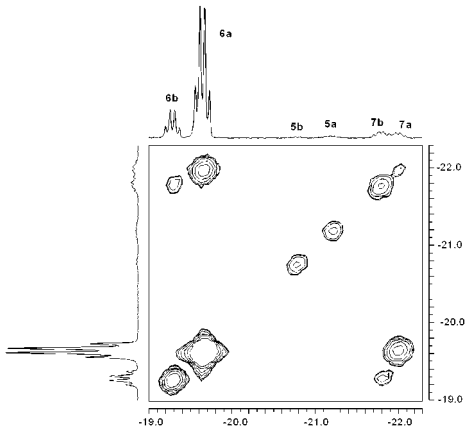


Figure 2. Phase-sensitive ^{1}H−^{1}H EXSY spectrum (400 MHz, CD_3OD, −60 °C) of the equilibrium mixture of monohydride intermediates **5**−**7**.

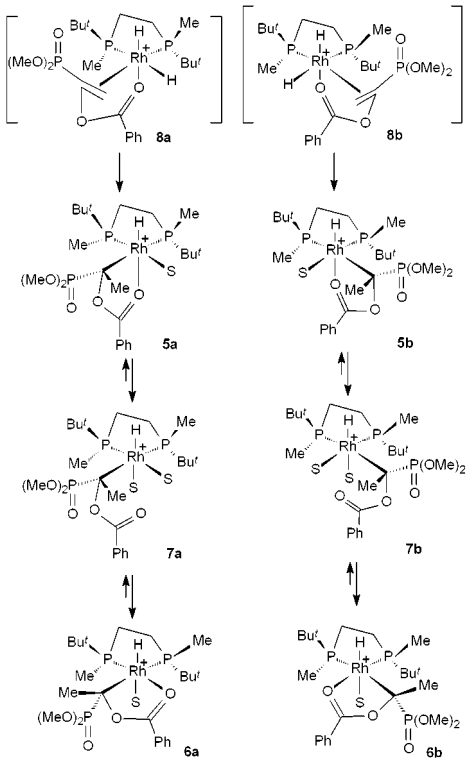
temperature reaction of **2** with **1**, which corresponded to the different ratios of **5**−**7a**:**5**−**7b** in these experiments.

The structures of the monohydride intermediates **5**−**7** were elucidated on the basis of their NMR spectra. The chemical shifts of their hydride protons confirm that in all six compounds the hydrides are disposed cis respective to both phosphorus atoms. Experiments applying the α-^{13}C labeled phosphonate **2*** proved that in all observed monohydride intermediates the α-carbon atom is bound to the rhodium atom. The detailed signal assignments and measurement of coupling constants were made with the use of 2D NMR correlation techniques and selective decoupling experiments. Structures of **5**−**7** elucidated from these data are shown in Scheme 2.[12]

We suggest the following sequence of processes explaining our experimental data (see Scheme 2). The dihydride intermediates

(12) The low concentration of **7a** retarded the observation of the signal of the carbonyl carbon atom in the ^{13}C NMR spectrum. Nevertheless, in both **5a** and **6a** the benzoyloxy group is coordinated, and the fast exchange between **6a** and **7a** gives a strong support for the suggested structure of **7a**.

Scheme 2. Formation and Transformations of Monohydride Intermediates **5**−**7**



8a and **8b** are the most probable unobservable intermediates formed by complexation of the substrate to the two interconverting isomers of solvate dihydride **1**.[4] The failure to observe these intermediates is in accord with the recent computational data, which predict extremely low barriers of migratory insertion in the dihydrides of similar structure.[2,3] The occurrence of migratory insertion through the dihydride intermediate **8a** is more favorable compared to the reaction of **8b** due to steric reasons.[4]

Monohydride intermediates **5a**,**b** are the direct products of the migratory insertion in **8a**,**b**; in these intermediates the dimethoxyphosphinoyl group is located in the trans-position to the vacant coordination site, and they rearrange to **6a**,**b** in which the additional coordination of the $P(O)(OMe)_2$ group is possible. Rearrangement proceeds through the equilibrium amounts of nonchelating complexes **7a**,**b**, which were also detected in our experiments. We have suggested such transformation in our previous work. However, this is the first experimental observation of this type of rearrangement, as well as of the interconversion between monohydride intermediates.

Calculations suggest that the oxidative addition of dihydrogen to **4** should directly lead to **6**.[2,3] Therefore, when **4** was hydrogenated at −30 °C, **6a**,**b** might be partially produced via this pathway. The lower selectivities observed in these experiments are therefore attributable to the lesser effectivity of enantioselection in the unsaturated pathway compared to dihydride in this catalytic hydrogenation.

Acknowledgment. This work was supported by the Research for the Future program, the Japan Society for the Promotion of Science.

Supporting Information Available: NMR charts of all important intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015611L