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Mechanism for the reduction of ketones to the corresponding alcohols using supercritical 2-propanol

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Abstract—The mechanism for the reduction of ketones into the corresponding alcohols using supercritical 2-propanol under non-catalytic conditions was investigated. The studies of the kinetic-isotope effect and isotopic-labeling for the reduction of benzophenone and acetophenone were carried out using $(CH_3)_2C\mathit{D}(OH)$, $(CH_3)_2CH(O\mathit{D})$, $(C\mathit{D}_3)_2CH(OH)$, and $(C\mathit{D}_3)_2C\mathit{D}(O\mathit{D})$. It was clarified that the α- and hydroxyl hydrogens on 2-propanol, respectively, transfer to the carbonyl C and O in the rate-determining step. These isotope studies also suggested that this reaction proceeds via a six-membered cyclic transition state analogous to that of the Meerwein–Ponndorf–Verley reduction. The fact that Hammett's reaction constant for this reaction was low, i.e., $\rho=0.33$, and that the reduction of the prochiral ketones using optically active alcohols at supercritical or high temperature provided optically active products also supported the existence of a six-membered cyclic transition state.

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1. Introduction

The reduction of carbonyl compounds to the corresponding alcohols is one of the most important transformations of functional groups not only in the laboratory but also in the chemical industry.[1] This reduction requires catalysts or hydride reagents. Heterogenous catalysts for these reductions are superior to homogenous ones from the viewpoint of cost and are utilized for the industrial scale reduction of carbonyls in many applications.[2] However, heterogenous catalysts are poor for the selective reduction of unsaturated carbonyls to unsaturated alcohols.[3] Homogenous catalysts are rarely used for the industrial scale reduction of carbonyls, except for the asymmetric reduction of prochiral ketones.[4] Hydride reagents are not suitable for the large-scale reduction, because the hydride reduction requires more than stoichiometric amounts of the reagents and produces much waste.[5] The mechanisms for the reduction with catalysts or hydride reagents have been determined by many research groups.[6]

The reduction of carbonyls using high temperature and supercritical 2-propanol (T_c=508 K, P_c=4.76 MPa, ρ_c=273 kg m^{-3}) under non-catalytic conditions is a promising process for the industrial production of alcohols from carbonyls, because the after-treatments are extremely simple, that is, removal of the 2-propanol and the formed acetone by evaporation. In 1983, Gubin et al. reported the reduction of benzaldehyde to benzyl alcohol using supercritical 2-propanol.[7] Bagnell et al. reported the reduction of ketones and aldehydes in high temperature ethanol and 1- and 2-propanol up to 500 K in the absence of catalysts.[8] Lermontov et al. reported that trifluoromethyl carbonyl compounds were reduced rather more smoothly than were non-fluorinated carbonyl compounds using high temperature alcohols.[9] We found that the substituted acetophenones can be reduced to the corresponding alcohols using supercritical 2-propanol.[10] Subsequently, Sominsky et al. reported that supercritical ethanol also functions as a reducing reagent for carbonyls, although it is less effective for carbonyl reduction than supercritical 2-propanol.[11] Daimon et al. investigated the reduction of unsaturated aldehydes using supercritical 2-propanol and found that supercritical 2-propanol is an efficient reagent for the selective reduction of conjugated or unconjugated unsaturated aldehydes to unsaturated alcohols.[12] They also reported that the reduction of 7-octenal to 7-octen-1-ol using 2-propanol proceeded very slowly at 473 K (below the critical temperature). The reduction rate increased with the rise in temperature, and at 523–573 K (above the critical temperature) the reduction proceeded smoothly. Their findings suggest that the use of supercritical 2-propanol as a reducing reagent for the C=O bond is a better choice than the use of high temperature 2-propanol (Scheme 1).

Keywords: Supercritical alcohol; Meerwein–Ponndorf–Verley reduction; Kinetic-isotope effect; Substituent effect; Concerted mechanism.

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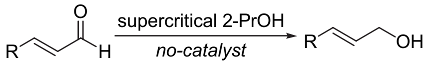


Scheme 1. Selective reduction of unsaturated aldehyde to the corresponding unsaturated alcohol.

The studies on the mechanism for the reduction of carbonyls using supercritical alcohols are required to clarify the scope and the limitations of this reaction. Based on the results of the experiments using supercritical deuterated 2-propanols and the Hammett's plots for the reduction of acetophenones using supercritical 2-propanol, we preliminarily reported that the reaction proceeds via a six-membered cyclic transition state[10] similar to that of the Meerwein–Ponndorf–Verley (MPV) reduction.[13] Sominsky et al. carried out the reduction of benzaldehyde to benzyl alcohol using *O*-deuterio-2-propanol and found that no *D* atoms were incorporated into the benzylic position.[11] Mainly based on this finding, they concluded that the transition state of the rate-determining step is cyclic. However, in order to demonstrate that the reduction proceeds via a cyclic transition state, it is essential to reveal that the hydrogen transfer from 2-propanol to the carbonyl carbon of the substrate simultaneously proceeds with that to the carbonyl oxygen. In this paper, we report our detailed results supporting the existence of a cyclic transition state for the reduction of ketones using supercritical 2-propanol.

2. Results and discussion

2.1. Kinetics of the reduction of ketone using supercritical 2-propanol

The reduction of acetophenone using supercritical 2-propanol was carried out at 573 K for 1–15 h to determine the rate of this reaction. The rate of this reaction should depend on the concentrations of both acetophenone and 2-propanol. However, there is a large amount of 2-propanol compared to that of acetophenone in this reaction system (the mole ratio of 2-propanol to the substrate is ca. 50). Thus, this reaction will obey pseudo-first-order kinetics with respect to acetophenone. According to this assumption, we conceived a kinetic law expressed in the form of Eq. 1, where $[A]_0$ and $[A]$ represent the concentrations of the substrate during the first stage and at the reaction time t, respectively. The letter k represents the pseudo-first-order rate constant.

$$\ln\left([A]_0/[A]\right) = kt \qquad (1)$$

2.2. Kinetic-isotope effect and deuterium labeling experiment

The 2-propanol molecule has three kinds of hydrogens: the methyl, the α-, and the hydroxyl hydrogens. Studies on the behavior of these three kinds of hydrogens during the reaction are required for the clarification of the reaction mechanism. The reduction of benzophenone and acetophenone using deuterated 2-propanol (($(CD_3)_2CH(OH)$, $(CH_3)_2CD(OH)$, $(CH_3)_2CH(OD)$, or $(CD_3)_2CD(OD)$) was carried out in the present work, in which the effects of the isotope labeling of 2-propanol on the reduction rate and the incorporation of *D* atoms into the product were investigated.

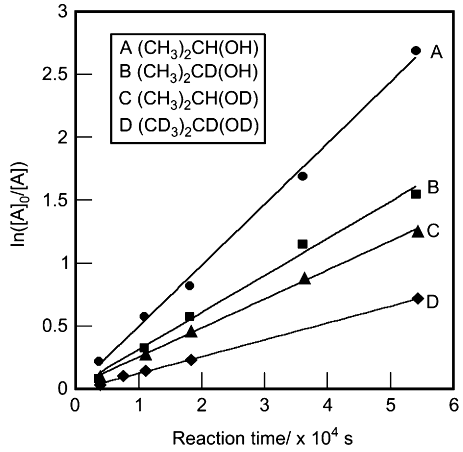


Figure 1. Pseudo-first-order plots for the reduction of acetophenone using deuterated 2-propanols at 573 K.

Five to seven experimental data were used to evaluate the rate constant for each deuterated 2-propanol. Figure 1 shows the plots of $\ln([A]_0/[A])$ against t, when the reduction of acetophenone was carried out using supercritical 2-propanol or deuterated 2-propanols. The plots are found to be linear. The pseudo-first-order reaction rate constants were calculated based on the slopes of these linear rate plots. Table 1 shows the k_H/k_D values for the reduction of benzophenone and acetophenone using deuterated 2-propanols.

When $(CH_3)_2CD(OH)$ or $(CH_3)_2CH(OD)$ was used as the reducing reagent instead of $(CH_3)_2CH(OH)$, the reduction of benzophenone and acetophenone was found to proceed more slowly except for the reduction using supercritical $(CD_3)_2CH(OH)$, and the k_H/k_D values were 1.4–2.1 at 573 K, as shown in Table 1. Therefore, the substantial kinetic-isotope effects for the reduction using supercritical $(CH_3)_2CD(OH)$ or $(CH_3)_2CH(OD)$ imply that the transfers of the α- and OH hydrogens proceed at a rate-determining step.

Generally, when the C–H–C configuration in the transition state of the H transfer is sufficiently nonlinear, it is well known that the k_H/k_D value is unusually low.[14] Therefore, the low k_H/k_D value for the reduction using supercritical 2-propanol may imply a non-liner transition state during the hydrogen-transfer step. Recently, Cohen et al. studied the kinetic-isotope effect for the aluminum alkoxide-catalyzed MPV reduction using $(CH_3)_2CH(OH)$ and $(CH_3)_2CD(OH)$ as the hydrogen sources.[13d] They reported a low k_H/k_D value of 2.33 at room temperature and suggested that the α-C–H bond of 2-propanol is broken in the rate-determining step. The rather low k_H/k_D value (2.33) will reflect the nonlinear configuration of the six-membered cyclic transition state of the MPV reduction. The lower k_H/k_D value for the reduction of acetophenone and benzophenone using supercritical $(CH_3)_2CD(OH)$ (entries 2 and 6 in Table 1) than that for the MPV reduction at room temperature may reflect the high reaction temperature, 573 K. The k_H/k_D value for the reduction of acetophenone using supercritical $(CD_3)_2CD(OD)$ (entry 8 in Table 1) is higher than that using supercritical $(CH_3)_2CD(OH)$ (entry 6) or $(CH_3)_2CH(OD)$ (entry 7).

Table 1. Pseudo-first-order rate constants and the k_H/k_D values for the reduction of benzophenone or acetophenone using supercritical deuterated 2-propanols

Entry	Substrate	2-Propanol	Rate constant k ($\times 10^{-5}$ s^{-1})	Fit parameter R^2	k_H/k_D
1	$Ph_2C{=}O$	$(CH_3)_2CH(OH)$	4.35±0.11	0.997	—
2	$Ph_2C{=}O$	$(CH_3)_2C\mathit{D}(OH)$	3.09±0.06	0.997	1.41±0.04
3	$Ph_2C{=}O$	$(CH_3)_2CH(O\mathit{D})$	2.42±0.07	0.995	1.80±0.07
4	$Ph_2C{=}O$	$(C\mathit{D}_3)_2CH(OH)$	4.62±0.13	0.996	0.94±0.04
5	$PhC({=}O)CH_3$	$(CH_3)_2CH(OH)$	4.84±0.17	0.996	—
6	$PhC({=}O)CH_3$	$(CH_3)_2C\mathit{D}(OH)$	2.93±0.21	0.992	1.65±0.17
7	$PhC({=}O)CH_3$	$(CH_3)_2CH(O\mathit{D})$	2.30±0.05	0.998	2.10±0.11
8	$PhC({=}O)CH_3$	$(C\mathit{D}_3)_2C\mathit{D}(O\mathit{D})$	1.33±0.03	0.998	3.63±0.20

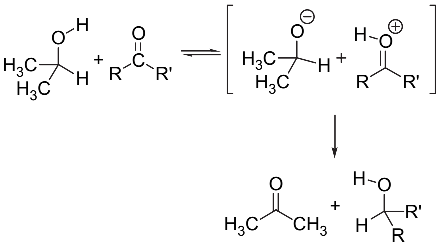
Reaction conditions: the concentration of the 2-propanol solution of substrate was 0.25 mol dm^{-3}, the density of 2-propanol during the reaction was 340 kg m^{-3}, and the reaction temperature was 573 K.

Based on the above facts, two types of hydrogen-transfer mechanisms are possible for this reaction: (i) a concerted hydrogen-transfer analogous to the MPV reduction (Scheme 2) and (ii) a stepwise mechanism in which both the steps are rate-determining (Scheme 3).

For the concerted mechanism, the product of individual isotope effects for the reduction using supercritical $(CH_3)_2C\mathit{D}(OH)$ and $(CH_3)_2CH(O\mathit{D})$ should be equal to the isotope effect for that using $(C\mathit{D}_3)_2C\mathit{D}(O\mathit{D})$. The product of individual isotope effects (1.65×2.10=3.46) is almost the same as the isotope effect for the reduction using $(C\mathit{D}_3)_2C\mathit{D}(O\mathit{D})$ (3.63). Within the experimental error, this is the result observed. For the two-step mechanism shown in Scheme 3, the isotope effect observed for doubly labeled 2-propanol should be smaller than the product of the individual isotope effect.[15] Thus the two-step mechanism can be excluded and the concerted mechanism is reasonable for the supercritical 2-propanol reduction.

The deuterium labeling study was carried out to confirm the existence of the transition state shown in Scheme 2. For this experiment, $(C\mathit{D}_3)_2CH(OH)$, $(CH_3)_2C\mathit{D}(OH)$, and $(CH_3)_2CH(O\mathit{D})$ were used as the deuterated 2-propanols, and benzophenone was used as the substrate. The deuterium distributions in the product were determined by the ^{1}H NMR analyses of the products. If the reaction using supercritical $(CH_3)_2C\mathit{D}(OH)$ proceeds via a cyclic transition state shown in Scheme 2, the deuterium atom should be incorporated into the benzylic position of the product. The results are shown in Table 2.

The deuterium atom of $(CH_3)_2C\mathit{D}(OH)$ was exclusively transferred to the carbonyl carbon of the substrate. On the other hand, no deuterium atom was transferred to the carbonyl carbon during the reaction using $(CH_3)_2CH(O\mathit{D})$, as Sominsky et al. reported for the reduction of benzaldehyde.[11] In this study, the incorporation of a deuterium atom of $(CH_3)_2CH(O\mathit{D})$ into the carbonyl oxygen of the substrate could not be confirmed because an easy H/D exchange occurred on the hydroxyl group of the product during the after-treatment (separation of the product and the substrate by thin layer chromatography). However, it is reasonable to assume that the origin of the hydroxyl hydrogen of the product is the hydroxyl hydrogen of the 2-propanol, based on the kinetic-isotope effect for the reaction using $(CH_3)_2CH(O\mathit{D})$. This indicates that the reaction proceeds via a cyclic transition state. The cyclic transition state is also supported by the inverse isotope effect shown in Table 1 (entry 4). The reduction of benzophenone using $(C\mathit{D}_3)_2CH(OH)$ proceeds rather more smoothly than that using $(CH_3)_2CH(OH)$. Considering the fact that the $C\mathit{D}_3$ group is slightly less bulky than the CH_3 group,[16] the inverse isotope effect may reflect a steric repulsion between the methyl group(s) of 2-propanol and the phenyl group(s) of benzophenone. In the transition state, the phenyl groups of benzophenone are located in the immediate

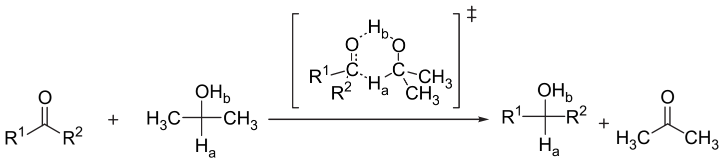


Scheme 3. Two-step hydrogen-transfer from 2-propanol to the carbonyl group.

Table 2. The incorporation of deuterium atoms into the product of the reduction of benzophenone using 2-propanols

Hydrogen source	Signal at 5.8 ppm[a]	Product
$(CH_3)_2C\mathit{D}(OH)$	–	$Ph_2C\mathit{D}(OH)$
$(CH_3)_2CH(O\mathit{D})$	+	$Ph_2CH(OH/\mathit{D})$
$(C\mathit{D}_3)_2CH(OH)$	+	$Ph_2CH(OH)$
$(C\mathit{D}_3)_2C\mathit{D}(O\mathit{D})$	–	$Ph_2C\mathit{D}(OH/\mathit{D})$

[a] A signal at 5.8 ppm is assigned to the proton on the benzylic position of benzhydrol based on the ^{1}H NMR analysis.



Scheme 2. Possible concerted mechanism for the reduction of carbonyl group using supercritical 2-propanol.

neighborhood of the methyl groups of 2-propanol. A similar six-membered cyclic transition state has been proposed for the MPV reduction. During the MPV reduction, the lone-pair electrons on the carbonyl oxygen coordinate to the aluminum ion of the catalyst to activate the carbonyl carbon. Although there are no aluminum ions in the supercritical reaction system, the reduction of ketones using supercritical 2-propanol smoothly proceeded. This suggests that the OH hydrogen in supercritical 2-propanol has a Lewis acidity as strong as that of the Al^{3+} ion in $Al(O^{i}Pr)_3$ used as the catalyst in the MPV reduction. Recently, some research groups reported that the alcohol molecules in the supercritical state exist in the monomeric or dimeric form, whereas, at ordinary temperature, alcohol molecules combine with their neighbors through a hydrogen bond network.[17] Therefore, the hydrogen atom of the OH group in supercritical 2-propanol is relatively naked and supercritical 2-propanol has a high Lewis acidity. This may be one of the reasons why it is easy to form the six-membered cyclic transition state without the aluminum catalyst. The hydroxyl hydrogen would also serve as a template by holding the ketone and 2-propanol in the appropriate orientation. When there are no templates, it is unlikely that two hydrogens ($H^{\delta+}$ and $H^{\delta-}$) approach a carbonyl group simultaneously in the appropriate orientations. Thus, we might rule out a transition state in which two independent alcohols donate their hydrogens simultaneously to a ketone molecule.

2.3. Substituent effect

Evaluation of the substituent effects on the reaction rates is one of the most available tools for a mechanistic study and has been applied to many organic reactions. The substituent effects on the reaction rates were evaluated by the substituent constant σ and the reaction constant ρ in the Hammett's equation. For the MPV reduction of benzophenone using aluminum tri(*tert*-butoxide), Hammett's reaction constant ρ was reported to be +1.296.[18] This rather small value of ρ is based on the six-membered cyclic transition state of the MPV reduction. Nucleophilic hydrogen attack on the carbonyl carbon of the substrate produces a moderate positive ρ value (about 2–3),[19] but the simultaneous nucleophilic attack of the carbonyl oxygen on Al^{3+} lowers the ρ value. A small reaction constant has also been documented for the acid-catalyzed hydrolysis of alkyl benzoate ($A_{AC}2$ mechanism). This reaction consists of the protonation of the carbonyl oxygen and a subsequent nucleophilic attack of water on the carbonyl carbon of the ester. The competing substituent effects in these two steps result in a low ρ value (ρ=0.1 for the acid-catalyzed hydrolysis of ethyl benzoate).[20] In this study, we investigated the substituent effects on the reduction of acetophenone using supercritical 2-propanol. Some substituents, such as nitro,[21] acyl,[10,11] formyl,[7,8,12,21] and amino[22] groups, cannot be employed in this study because they are reduced or/and alkylated by supercritical alcohols. We employed trifluoromethyl, chloro, and methyl groups as the substituents at the *meta*- and *para*-position of the phenyl ring of acetophenone because they are stable in supercritical 2-propanol. Figure 2 shows the relationship between Hammett's substituent constant σ and $\log(k_S/k_H)$, where k_S and k_H represent the rate constant for the reduction of the substituted acetophenones and non-substituted one, respectively. These plots exhibit a good linear relationship. From the slope of the Hammett's plots, the reaction constant ρ was determined to be +0.33. The low ρ value indicates that this reaction is not sensitive to the substituent effects. As for the reduction with supercritical 2-propanol, the 2-propanol simultaneously donates two hydrogens to the substrate, that is, the C–H hydrogen (nucleophilic) and O–H hydrogen (electrophilic). The competing characteristics of these two hydrogens should be one of the reasons for the low ρ value. Another reason will be the high reaction temperature (573 K), because the ρ value is temperature dependent, that is, the ρ value decreases with increasing reaction temperature.

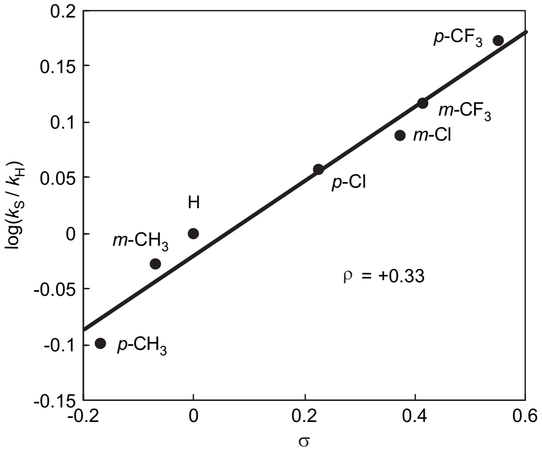


Figure 2. Hammett's plot for the reduction of substituted acetophenone using supercritical 2-propanol at 573 K.

2.4. Reduction of acetophenone using optically active alcohols

For the MPV reduction, asymmetric reductions have been well documented using aluminum alkoxide catalysts prepared from optically active alcohols.[23] During the MPV-type asymmetric reductions, two diastereomeric cyclic transition states have been proposed to predict the predominant configuration of the product (Fig. 3).

The transition state **A**, in which the smaller group R_S of the substrate is adjacent to the larger group R'_L from the aluminum alkoxide and the larger group R_L of the substrate is adjacent to the smaller group R'_S from the aluminum alkoxide, will be favored over the diastereomeric transition state **B**, in which the two larger groups and the two smaller groups are on the same side of the six-membered ring. It is postulated that the activation energy for the formation of **A** would be lower than that for **B**. Based on this concept, we can predict the predominant configuration of the product from the MPV reduction of prochiral ketones.[23] The same concept could be

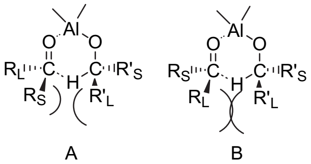


Figure 3. Two possible transition states of the asymmetric MPV reduction.

Table 3. The reduction of acetophenone using chiral secondary alcohols

Entry	Hydrogen source	ee[a] of hydrogen source (%)	Reaction time (h)	Conversion[b] (%)	ee[b] of 1-phenylethanol (%)
1	(*R*)-2-Butanol	94	3	40	3.1(*R*)
2	(*R*)-2-Butanol	94	10	78	3.0(*R*)
3	(*S*)-2-Butanol	95	3	41	3.4(*S*)
4	(*S*)-2-Butanol	95	10	80	3.4(*S*)
5	*racemic* 2-Butanol	0	3	42	0(−)
6	*racemic* 2-Butanol	0	10	80	0(−)
7[c]	(*S*)-3-Methyl-2-butanol	99	6	21	9.3(*S*)
8	(*S*)-3,3-Dimethyl-2-butanol	58	3	20	10(*S*)

Reaction conditions: the concentration of the alcoholic solution of acetophenone was 0.25 mol dm^{-3}, reaction temperature was 573 K.

[a] The ee of the hydrogen sources did not change during the courses of the reaction.

[b] Based on GC analysis.

[c] The reaction was carried out at 553 K.

applied to the prediction of the predominant enantiomer from the reduction of prochiral ketones using optically active supercritical alcohol. The results for the reduction of acetophenone using several optically active alcohols are shown in Table 3.

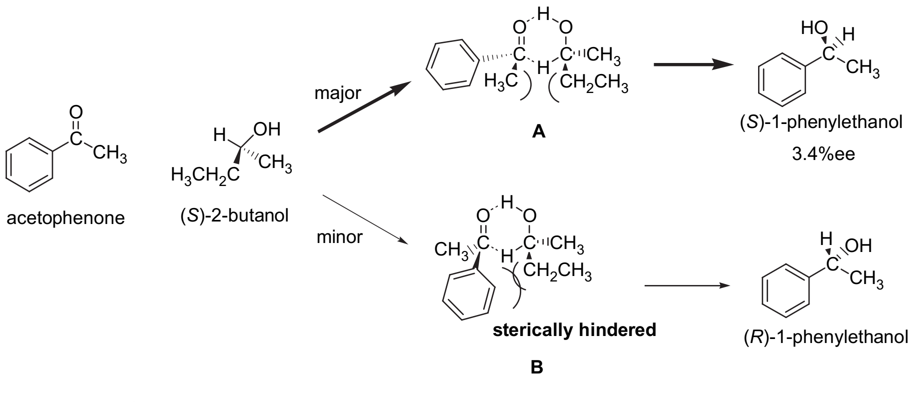
The reduction of acetophenone using (*R*)-2-butanol produced (*R*)-1-phenylethanol with a 3.1% ee (entries 1 and 2). On the other hand, the reduction of acetophenone using (*S*)-2-butanol gave (*S*)-1-phenylethanol with a 3.4% ee (entries 3 and 4). The ee values were independent of the conversion of the substrate. This indicated that the enantioselectivities were not changed during the course of the reaction. The reduction by the *racemic* 2-butanol produced the *racemic* 1-phenylethanol (entries 5 and 6).

As shown in Scheme 4, two transition states can be proposed for the reduction of acetophenone using (*S*)-2-butanol.

The transition state **A**, in which the methyl group of acetophenone and the ethyl group of (*S*)-2-butanol are on the same side, is more stable than **B**. However, the ee values were low, as shown in Table 3. It is reasonable to assume that the differences in the bulkiness between the methyl and the ethyl groups of 2-butanol are not sufficient to permit distinguishing between the methyl and the phenyl groups of the substrate, acetophenone. Based on this idea, we carried out the reduction of acetophenone using supercritical (*S*)-3,3-dimethyl-2-butanol, which has a bulkier branched alkyl group on the chiral carbon than an ethyl group. We also attempted the reduction of acetophenone using subcritical (*S*)-3-methyl-2-butanol (T_c=556 K, P_c=3.87 MPa) (entry 7 in Table 3). The employment of these branched 2-butanols resulted in attaining higher ee.

3. Conclusions

The mechanism for the reduction of ketones to the corresponding alcohols using supercritical 2-propanol was investigated. The deuterium kinetic-isotope effects were recognized in the reduction of ketones using $(CH_3)_2CD(OH)$ or $(CH_3)_2CH(OD)$. The product of the individual k_H/k_D values for the reductions of acetophenone using supercritical $(CH_3)_2CD(OH)$ and $(CH_3)_2CH(OD)$ (1.65×2.10=3.46) was equal, within the experimental error, to that of supercritical $(CD_3)_2CD(OD)$ (3.63±0.20). The deuterium labeling experiments using $(CH_3)_2CD(OH)$, $(CH_3)_2CH(OD)$, $(CD_3)_2CH(OH)$, or $(CD_3)_2CD(OD)$, indicated that the hydrogens on the α-C and the O of 2-propanol transfer to the carbonyl C and O of the substrate, respectively. These results revealed that the reduction of ketones to the corresponding alcohols using supercritical 2-propanol proceeds via a six-membered cyclic transition state analogous to that of the MPV reduction. The fact that the Hammett's reaction constant ρ was found to be low for this reaction and that the reduction of prochiral ketones using supercritical (*R*)- or (*S*)-alcohols provided optically active products also supported the existence of the six-membered cyclic transition state during the reduction.



Scheme 4. Enantioselective reduction of acetophenone using supercritical (*S*)-2-butanol.

4. Experimental section

4.1. General aspects

The chemicals used in this study were obtained from commercial sources except for some chiral alcohols. The ^1H NMR spectra were recorded on a Bruker DPX400 (400 MHz) spectrometer with $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million with TMS as an internal standard. Conversions were evaluated by gas chromatography (GC-15A, Shimadzu; flame ionization detector and 30-m capillary column DB-17, J&W) with the internal standard method.

4.2. Representative procedure for the reduction using supercritical 2-propanol

All reactions were carried out in sealed Pyrex tubes (0.2 cm inner diameter and 7.0 cm length) to eliminate the effect of the metal. A portion of the 2-propanol solution of the substrate (0.25 mol dm^{-3}, 140 μl) was placed in a Pyrex tube with one end closed. The air in the tube was replaced by argon gas and the other end of the tube was fused shut under reduced pressure. The tube was then placed in an autoclave with methanol, which prevented the tube from breaking during the reaction. For the kinetic-isotope effect study on the reduction of benzophenone, four tubes enclosing $(CH_3)_2CH(OH)$, $(CH_3)_2C\mathit{D}(OH)$, $(CH_3)_2CH(O\mathit{D})$, or $(C\mathit{D}_3)_2CH(OH)$ solution of benzophenone were placed in an autoclave together. The autoclave was heated to 573 K and the temperature was maintained for 1–15 h. The temperature in the autoclave was regulated with a precision of about ±1 K during the reaction. After a specific time, the autoclave was cooled using an air stream to quench the reaction. The solutions in the tube were then subjected to GC analyses for identification of the products and the estimation of the product distribution. The GC analyses involved more than two determinations for each run and gave the conversion values with a relative error of the order of a few percent.

4.3. Preparation of chiral alcohols and the analyses of the enantiomer excess. The (*R*), (*S*), and *racemic* 2-butanols were purchased from commercial sources and used as received. (*S*)-3-Methyl-2-butanol and (*S*)-3,3-dimethyl-2-butanol were prepared by a reported method.[24] The enantiomer excess (ee) values of these alcohols were estimated by gas chromatography (GC-14B, Shimadzu; flame ionization detector and 25-m capillary column Chirasil-DEX CB, Chrompack). In the cases of 2-butanol and 3-methyl-2-butanol, the samples acetylated with acetyl chloride and pyridine were subjected to the GC analyses. The absolute configurations of the products were determined by comparing the GC retention time with those of the authentic samples. The ee values of the products were estimated by the same method as the ee estimation of the chiral alcohols.

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