

# 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  $(\text{CH}_3)_2\text{CD}(\text{OH})$ ,  $(\text{CH}_3)_2\text{CH}(\text{OD})$ ,  $(\text{CD}_3)_2\text{CH}(\text{OH})$ , and  $(\text{CD}_3)_2\text{CD}(\text{OD})$ . It was clarified that the  $\alpha$ - 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.<sup>1</sup> 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.<sup>2</sup> However, heterogenous catalysts are poor for the selective reduction of unsaturated carbonyls to unsaturated alcohols.<sup>3</sup> Homogenous catalysts are rarely used for the industrial scale reduction of carbonyls, except for the asymmetric reduction of prochiral ketones.<sup>4</sup> 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.<sup>5</sup> The mechanisms for the reduction with catalysts or hydride reagents have been determined by many research groups.<sup>6</sup>

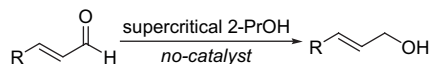
The reduction of carbonyls using high temperature and supercritical 2-propanol ( $T_c=508$  K,  $P_c=4.76$  MPa,  $\rho_c=273$  kg m<sup>-3</sup>) under non-catalytic conditions is a

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.<sup>7</sup> 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.<sup>8</sup> Lermontov et al. reported that trifluoromethyl carbonyl compounds were reduced rather more smoothly than were non-fluorinated carbonyl compounds using high temperature alcohols.<sup>9</sup> We found that the substituted acetophenones can be reduced to the corresponding alcohols using supercritical 2-propanol.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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<sup>10</sup> similar to that of the Meerwein–Ponndorf–Verley (MPV) reduction.<sup>13</sup> 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.<sup>11</sup> 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

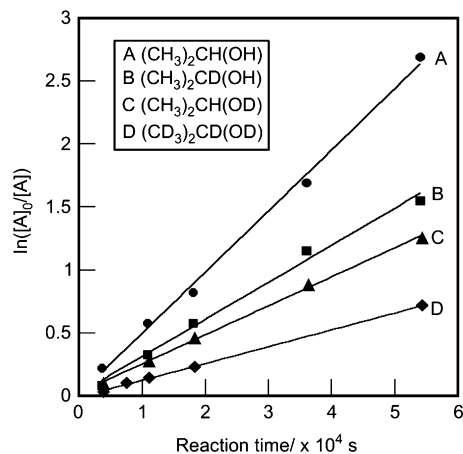
### 2.1. Kinetics of the reduction of ketone using supercritical 2-propanol

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.

$$\ln([A]_0/[A]) = kt \quad (1)$$

### 2.2. Kinetic-isotope effect and deuterium labeling experiment

The 2-propanol molecule has three kinds of hydrogens: the methyl, the  $\alpha$ -, 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  $\alpha$ - 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.<sup>14</sup> Therefore, the low  $k_H/k_D$  value for the reduction using supercritical 2-propanol may imply a non-linear 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.<sup>13d</sup> They reported a low  $k_H/k_D$  value of 2.33 at room temperature and suggested that the  $\alpha$ -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).

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