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Reduction of acetophenone using supercritical 2-propanol: the substituent effect and the deuterium kinetic isotope effect

Takashi Kamitanaka, Tomoko Matsuda and Tadao Harada*

Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University, Otsu, Shiga 520-2194, Japan

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Abstract—The reductions of several substituted acetophenones using supercritical 2-propanol were carried out to estimate the Hammett's reaction constant ($\rho = 0.33$). Also, the reduction of acetophenone using supercritical deuteriated 2-propanol was carried out to determine the rate-determining step. The kinetic isotope effects were observed in the reduction using 2-deuterio-2-propanol ($k_H/k_D = 1.6$) and *O*-deuterio-2-propanol ($k_H/k_D = 2.0$). These findings suggest that the reaction proceeds via a cyclic transition state between acetophenone and 2-propanol similar to that of the Meerwein–Ponndorf–Verley reduction. © 2003 Elsevier Science Ltd. All rights reserved.

Supercritical fluids have been of significant interest to organic chemists due to their unique properties. The physicochemical properties of supercritical fluids, such as diffusivities and polarities, can be continuously tuned by adjusting their pressure and temperature. These tunabilities make it possible to use them as unique organic reaction media.[1] Recently, organic reactions using supercritical fluids not only as media but also as reagents have been reported.[2] Gubin reported that benzaldehyde was reduced to benzyl alcohol using supercritical 2-propanol ($T_c = 235°C$) without catalysts or reagents other than 2-propanol: during the reduction of benzaldehyde, the 2-propanol was found to be oxidized to acetone.[3] Generally, the traditional procedures to reduce the carbonyl group, such as the reduction with hydride reagents[4] and with hydrogenation catalysts,[5] require complicated after-treatments. In contrast, supercritical 2-propanol reduction requires no reagents except for 2-propanol. Therefore, the after-treatment is extremely easy; that is, only to remove the 2-propanol and the produced acetone by evaporation. Although this reaction is useful for synthetic chemistry, the reaction mechanism has not yet been clarified. In this communication, we report the results of studies on the substituent effects and the deuterium kinetic isotope effects for the reduction of acetophenone using supercritical 2-propanol.

The representative experimental procedures are as follows. All reactions were carried out in sealed Pyrex tubes (ca. 2 mm inner diameter and ca. 70 mm length) to eliminate the effect of the metal vessel. A portion of the 2-propanol solution containing the substrate (0.25 mol dm^{-3}, 140 μl) was placed in a Pyrex tube with one closed end. The air in the tube was replaced by argon gas and the other end of the tube was fused shut under reduced pressure. After sealing, the tube was placed in an autoclave (SUS316) with methanol, which prevents the tube from breaking during the reaction. The autoclave was heated to 300°C and the temperature was maintained for 1–15 h. After a specific time, the autoclave was cooled using an air stream to quench the reaction. After the removal of the 2-propanol and the acetone in vacuo at 30°C, the products in the tube were subjected to the identification by GC, ^{1}H NMR and IR. Conversions were determined by GC analysis using the internal standard method.

The reaction rates of the reduction of acetophenone using supercritical 2-propanol may depend on both the concentrations of acetophenone and 2-propanol. However, there is large excess of 2-propanol to the acetophenone in the reaction system. Thus, this reaction can be regarded as a pseudo-first order reaction with respect to the concentration of acetophenone. Table 1 summarizes the rate constants of the reduction of the substituted acetophenones using supercritical 2-propanol. The rate constants depend on the type and the position of the substituents. Obviously, the introduction of the electron-withdrawing CF_3 or Cl group to the benzene ring enhances the reduction rate of the

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Keywords: supercritical 2-propanol; reduction; Meerwein–Ponndorf–Verley reduction; Hammett equation; kinetic isotope effect; acetophenone.

* Corresponding author. Tel.: +81-77-543-7461; fax: +81-77-543-7483; e-mail: harada@rins.ryukoku.ac.jp

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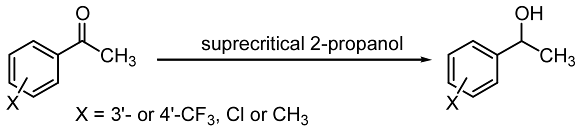
Table 1. The pseudo-first order rate constants of the reduction of various substituted acetophenones using supercritical 2-propanol[a]



	3′-Substituted				4′-Substituted		
Substituent	H	CF_3	Cl	CH_3	CF_3	Cl	CH_3
Rate constant×10^5 (s^{-1})	4.9	6.4	6.0	4.6	7.3	5.6	3.9

[a] Reaction conditions are described in the text. Mole ratio of substrate to 2-propanol is ca. 1:50.

acetophenone, whereas the electron-releasing CH_3 group lowers the rate. These results indicate that the reaction rates depend on the electron densities on the carbonyl carbon of the acetophenones. The Hammett equation[6] has been well documented to evaluate the effect of a substituent on the kinetics of many organic reactions.[7] Figure 1 shows the Hammett plots for the reduction of acetophenones using supercritical 2-propanol, where k_0, k and σ are the pseudo-first order rate constants of acetophenone and substituted acetophenones, and the Hammett's substituent constants, respectively. The Hammett plots give a straight line with a positive slope (the Hammett's reaction constant ρ is 0.33). The small positive reaction constant suggests that this reaction involves a nucleophilic attack on the carbonyl carbon by a slightly negative charged reagent. It also suggests that this reaction contains no strongly ionized intermediate or transition state.

Next, we examined the reduction of acetophenone using supercritical 2-deuterio-2-propanol or *O*-deuterio-2-propanol. The kinetic isotope effect was observed during both reductions using these deuteriated 2-propanols. The k_H/k_D values were 1.6 (2-deuterio-2-propanol) and 2.0 (*O*-deuterio-2-propanol), respectively. These results suggest that the eliminations of the α- and *O*-hydrogens in 2-propanol are the rate determining step and simultaneously occur. During the reduction of acetophenone using supercritical 2-deuterio-2-propanol, the deuterium is exclusively transferred to the carbonyl carbon of acetophenone to give 1-deuterio-1-phenylethanol: mass spectrum of the product reveals that no H/D exchange at the phenyl and the methyl of acetophenone occurs during the reaction.[8] It is also showed that no H/D exchange in the product occurred when it was treated with supercritical 2-deuterio-2-propanol.

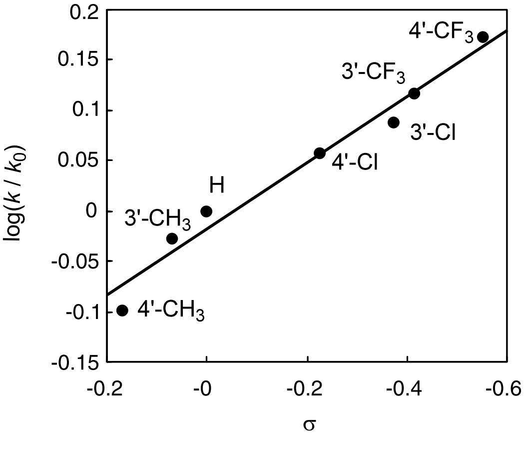
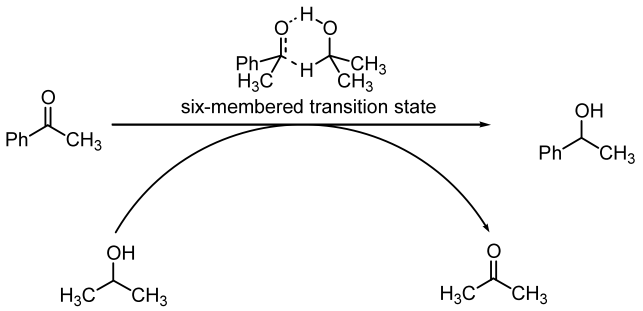


Figure 1. Hammett plots of the reduction of substituted acetophenones using supercritical 2-propanol.



Scheme 1.

Based on the present results, we postulate that the reduction of the carbonyl group using supercritical 2-propanol proceeds via a six-membered cyclic transition state similar to that of the Meerwein–Ponndorf–Verley reduction,[9] as shown in Scheme 1. During the first step, 2-propanol coordinates to the carbonyl group of acetophenone through the two hydrogens to form the six-membered cyclic transition state. The donation of the α- and *O*-hydrogens of 2-propanol to acetophenone then takes place. As a result, the acetophenone is reduced to 1-phenylethanol and the 2-propanol is oxidized to acetone.

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8. Transfer of the deuterium from 2-deutero-2-propanol to acetophenone was confirmed by ^{1}H NMR and GC–MS. In the ^{1}H NMR spectrum, the authentic 1-phenylethanol exhibits a one-proton quartet signal of the benzyl proton at δ 4.84, whereas the signal was not observed for the product. The spectrum of the product: (400 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.85 (br, s, 1H), 7.26–7.39 (m, 5H); MS (EI) m/z 123 (M^+). For 1-phenylethanol: δ 1.46 (d, $J=6.5$ Hz, 3H), 2.24 (br, s, 1H), 4.84 (q, $J=6.4$ Hz), 7.23–7.33 (m, 5H); MS (EI) m/z 122 (M^+).
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