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The Catalytic Reduction of Aldehydes and Ketones with 2-Propanol over Hydrous Zirconium Oxide

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Reduction of aldehydes with 2-propanol proceeded efficiently by catalysis with hydrous zirconium oxide to give the corresponding alcohols. Most ketones also were reduced efficiently, but conjugated or sterically hindered ketones resisted the reduction. The reduction was carried out with primary, secondary, or tertiary alcohols, and only secondary alcohols served as hydrogen donors. Kinetic experiments have indicated that the reaction rate is of first-order dependence on each of the concentrations of the carbonyl compound, 2-propanol, and the catalyst. An observation of the primary isotope effect has suggested that a step of hydride transfer from absorbed 2-propanol to absorbed carbonyl compound constitutes the rate-determining step for the reduction.

The reduction of multiple bonds using an organic molecule as a hydrogen donor in place of hydrogen gas or metal hydride is known as hydrogen-transfer reaction.[1] One example is the reduction of aldehydes and ketones with metal alkoxide and alcohol. This is called the Meerwein–Ponndorf–Verley reduction. It was discovered in 1925 and has been used successfully in a number of instances.[2] Aluminium isopropoxide has been found to be the best reagent for this reduction. However, this method calls for both addition of at least 100 to 200% excess aluminium isopropoxide and neutralization of alkoxide salt with strong acid. As other catalysts for this reduction, complexes of cobalt,[3] iridium,[4,5] rhodium,[6—8] ruthenium,[8,9] indium,[10] molybdenum,[11] and zirconium[12] have been reported. Although these catalysts have many advantages over conventional metal alkoxides, the isolation of products is always attended by tedious workups.

Heterogeneous methods for the reduction are known, and zeolite[13] and oxides of aluminium,[14] magnesium,[15] silicon,[15] calcium[15,17] barium,[15] strontium,[15] zirconium,[16] titanium,[16] vanadium,[16] molybdenum,[16] zinc,[16] thorium,[16] and lanthanoid groups[18] have been reported to be successful catalysts. These methods have several advantages in the isolation of products. However, they need to be carried out in the vapor phase, and require high reaction temperatures and flow reactor systems.

Posner et al.[19] reported that dried chromatographic alumina served as a catalyst in the liquid phase. Several aldehydes and ketones could be reduced by use of this catalyst, and products were easily isolated by filtering-off of catalyst and subsequent evaporation of solvent. However, this reduction requires water-free conditions and a large amount of catalyst. In our previous paper,[20] we briefly reported that the reduction of aldehydes and ketones with 2-propanol proceeded efficiently over hydrous zirconium oxide in the liquid phase. The hydrous oxide is available in the form of hard and translucent granules, of which X-ray diffraction analysis has shown to be amorphous.

Reduction with hydrous zirconium oxide has the following advantages: 1) the reduction does not call for strong acid treatment; 2) the products are easily isolated by filtering-off of catalyst and subsequent evaporation of solvent, because this catalyst is insoluble in any solvents; 3) hydrous zirconium oxide is stable at room temperature in air for 7 years, and can be used for repeated reductions; 4) hydrous zirconium oxide is not sensitive to air or water, and the reduction does not require water-free conditions.

In this paper, we will report the scope and limitation of the reduction of carbonyl compounds with alcohols catalyzed by hydrous zirconium oxide. A proposition of the mechanism of this reaction also will be described.

Experimental

Materials. Commercial reagents were used for the reduction without further purification. 2-Propan-2-*d*-ol was prepared by the reduction of acetone with sodium borodeuteride.

Hydrous Zirconium Oxide. To a solution of zirconium(IV) dichloride oxide ($ZrOCl_2 \cdot 8H_2O$) (200 g of solid in 10 dm^3 deionized water) was slowly added an aqueous solution of sodium hydroxide (1 mol dm^{-3}) at room temperature. Constant gentle stirring was maintained and the addition was continued until the pH of the resulting solution reached 6.80. The solution was allowed to stand for 48 h at room temperature. The resulting product was filtered and washed free from chloride ions. The gel was spread on a glass plate and dried in air at room temperature for 10 h and at 80 °C for 2 h. Fifty four grams of hydrous zirconium oxide was obtained in the form of granules, and was heated at 300 °C for 5 h.

General Procedure for the Reduction of Aldehydes and Ketones with 2-Propanol. In a 25 cm^3 round-bottom flask equipped with a reflux condenser was placed hydrous zirconium oxide (24—60 mesh; 1.0 or 2.0 g), an aldehyde or ketone (5 mmol), 2-propanol (10 cm^3), and a hydrocarbon (0.5 mmol) as an internal standard. The contents were heated under gentle reflux. The reaction mixture was collected at appropriate times after refluxing, and the concentration of the products were analyzed by GLC (a capillary column PEG 20M 30 m). The identification of the products was made by comparison of retention times in gas chromatography with those of authentic samples.

Reduction of Hexanal with Several Alcohols. In a 10 cm^3 round-bottom flask equipped with a reflux condenser was placed hydrous zirconium oxide (24—60 mesh; 0.2 g), hexanal (1.0 mmol), an alcohol (2.0 cm^3), and dodecane (0.1 mmol) as an internal standard. The contents were placed in an oil bath kept at 78.0 °C (±0.1 °C). The analysis of the products was performed in a simlar manner as described above.

Kinetic Experiment. All experiments are carried out in a 10 cm^3 round-bottom flask equipped with a reflux condenser. The concentrations of a carbonyl compound and a hydrocarbon as an internal standard were always 0.5 and 0.05 mol dm^{-3}, respectively, and 2 cm^3 of 2-propanol was used as both reductant and solvent. In the case of the reduction of hexanal, benzaldehyde, cyclohexanone, and acetophenone, the amount of catalyst was usually 0.2, 0.2, 0.1, 0.4 g, respectively. The reaction was performed in a similar manner as described above.

Results and Discussion

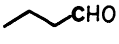
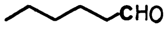
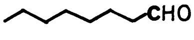
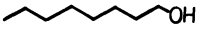
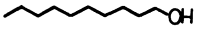
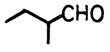
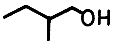
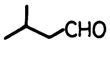
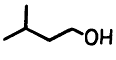
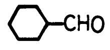
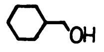
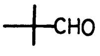
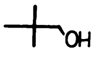
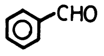
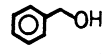
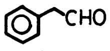
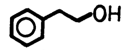
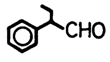
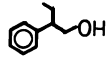
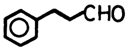
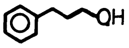
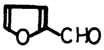
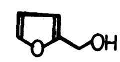
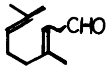
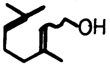
Reduction of Aldehydes. The reduction of aldehydes yielded the corresponding alcohols. Essentially no by-products could be detected. A linear correlation between the natural logarithm of the carbonyl concentration and the reaction time was obtained. This result indicates that the reduction rate is of pseudo-first-order in the carbonyl concentration. The rate of the reaction is represented by

$$r = k' \cdot [\mathrm{C}], \tag{1}$$

where k' and [C] are the pseude-first-order rate constant and the concentration of carbonyl compound, respectively. The rate constants and yields are listed in Table 1. Generally, the reduction of aldehydes proceeds efficiently, and the steric hindrance around the carbonyl group does not interfere with the reduction. The reduction of conjugated aldehydes also proceeds efficiently to give allylic alcohols selectively.

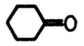
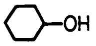
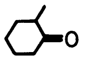
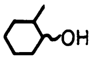
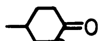
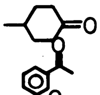
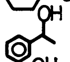
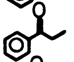
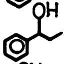
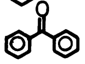
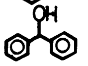
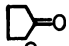
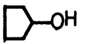
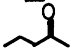
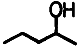
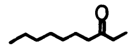
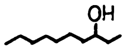
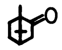
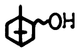
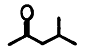
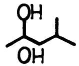
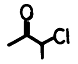
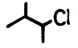
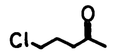
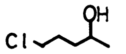
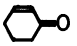
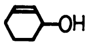
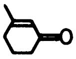
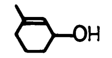
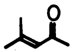
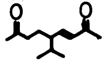
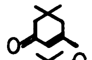
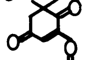
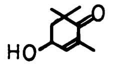
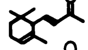
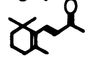
Reduction of Ketones. Rate constants for the reduction of ketones were obtained in the similar manner as those for aldehydes and are listed in Table 2. Cyclohexanone and 4-methylcyclohexanone were reduced faster than 2-methylcyclohexanone. An α-substituted methyl group seems to interfere with the access of a carbonyl group to the active site of the catalyst. The slow reduction of camphor, 3-decanone, and benzophenone can be attributed to the steric

Table 1. Reduction of Several Aldehydes[a]

Entry	Reductant	Product	Yield/% (h)[b]	k[c]/10^{-4} s^{-1}
1			93 (6)	1.236
2			88 (6)	0.972
3			93 (6)	1.306
4			81 (6)	0.764
5			80 (6)	0.744
6			82 (6)	0.778
7			99 (6)	1.894
8			99 (4)	3.128
9			98 (6)	1.902
10			90 (6)	1.083
11			81 (6)	0.781
12			96 (6)	1.586
13			99 (6)	2.108
14			92 (6)	1.186
15			97 (6)	1.689

a) Aldehyde 5 mmol, 2-propanol 10 cm^3, cat. 1.0 g, reflux temperature of 2-propanol. b) Reaction time. c) Rate constant.

Table 2. Reduction of Several Ketones[a)]

Entry	Reductant	Product	Yield/% (h)[b)]	$k^{c)}/10^{-4}\ \mathrm{s^{-1}}$
1			99 (2)	7.188
2			91 (6)	1.110
3			99 (2)	7.016
4			77 (6)	0.684
5			70 (10)	0.334
6			62 (20)	0.134
7			84 (6)	0.894
8			81 (10)	0.462
9			63 (20)	0.138
10			tr.	—[d)]
11			68 (20)	0.156
12			98 (6)	1.816
13			64 (10)	0.284
14			84 (10)	0.516
15			68 (20)	0.156
16		——	tr.	—[d)]
17		——	tr.	—[d)]
18		——	tr.	—[d)]
19			58 (10)	0.238
20		——	tr.	—[d)]
21		——	tr.	—[d)]

a) Ketone 5 mmol, 2-propanol 10 cm^3, cat. 1.0 g, reflux temperature of 2-propanol. b) Reaction time. c) Rate constant. d) Rate const. $<1\times10^{-6}\ \mathrm{s^{-1}}$.

hindrance. The presence of a double bond conjugated to the carbonyl group serves to slow down the rate of some reactions, although the reduction of 2-cyclohexen-1-one, 3-methyl-2-cyclohexen-1-one, and 2,6,6-trimethyl-2-cyclohexene-1,4-dione did proceed. The chloride substitution at the α-position increased the reduction rate, but at the γ-position it did not affect the rate. This suggests that electronic factors have some influence on the reaction.

Alcohols as Hydride Sources. The reduction of hexanal was carried out with some alcohols as well as with 2-propanol. The results are listed in Table 3. When primary alcohols were used, the acetalization proceeded faster than the reduction. Hexanal diethyl acetal and hexanal dimethyl acetal were obtained in 91 and 100% yields, respectively. Tertiary alcohol or methanol did not work as hydride donors. Basically, only secondary alcohols could be used.

Dependence on Catalyst Amount. For determining the order in catalyst amount, reduction rates of hexanal, cyclohexanone, and acetophenone were measured with 0.02—1.0 g of the catalyst. As shown in Fig. 1, the pseudo-first-order rate constants, k', were proportional directly to the amount of catalyst. Hence the specific rate constant, k, is to be introduced as

$$r = k'/[\mathrm{cat.}], \qquad (2)$$

where [cat.] is the concentration of catalyst.

Dependence on Reaction Temperature. In order to investigate the dependence on reaction temperature,

Table 3. Reduction of Hexanal with Several Alcohols[a)]

Entry	Reductant	$k^{b)}/10^{-4}\ s^{-1}$
1	$(CH_3)_2CHOH$	0.514
2	Cyclohexanol	0.116
3	$C_6H_5CH(OH)CH_3$	0.447
4	CH_3CH_2OH	—[c)]
5	CH_3OH	0[d)]
6	$(CH_3)_3COH$	0

a) Hexanal 1 mmol, alcohol 2 cm^3, cat. 0.2 g, 78.0 °C. b) Rate constant. c) Reduction was slow ($<10^{-6}\ s^{-1}$), and the main product was diethyl acetal (91% yield). d) Only dimethyl acetal was obtained (100% yield).

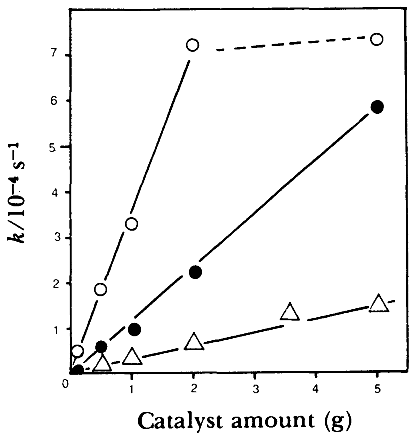


Fig. 1. The dependence of catalyst amount.
Carbonyl compound 5 mmol, 2-propanol 10 cm^3, reaction temperature 78.0 °C.
●; Hexanal. ○; Cyclohexanone. △; Acetophenone.

the reduction of hexanal, benzaldehyde, cyclohexanone, or acetophenone was carried out at 59.0—82.5 °C. The natural logarithm of the specific rate constant, *k*, vs. the reciprocal of the absolute temperature, that is, the Arrhenius plot, is shown in Fig. 2. As can be seen from the figure, a good straight line is obtained. From the inclination of the line, the activation energies of these reductions were estimated, which are listed in Table 4.

Effect of Alcohol Concentration. The influence of the concentration of 2-propanol upon the reduction rate was investigated for the reduction of hexanal, benzaldehyde, cyclohexanone, and acetophenone under the following conditions: the amount of 2-propanol was changed in the range from 2 to 0.5 cm^3 and toluene as a diluent was added in order to keep the volume of reaction mixture constant. The correlation between the concentration of 2-propanol and the specific rate constant, *k*, is shown in Fig. 3. In all cases, similar rate constants were obtained, and the concentration of 2-propanol did not affect the reaction rate under the present experimental conditions. However, decreasing the ratio of 2-propanol to the carbonyl compound changed the reaction rate. When the ratio of 2-propanol to hexanal, benzaldehyde, cyclohexanone, or acetophenone was 1 to 1, a linear correlation between the reciprocal of the concentra-

Table 4. Activation Energies[a)]

Carbonyl compound	Cat./g	ΔE^{*}/kcal mol^{-1}
Hexanal	0.2	13.7
Cyclohexanone	0.1	12.3
Benzaldehyde	0.2	10.5
Acetophenone	0.4	12.5

a) Carbonyl compound 1 mmol, 2-propanol 2 cm^3 reaction temperature 60.0—85.0 °C.

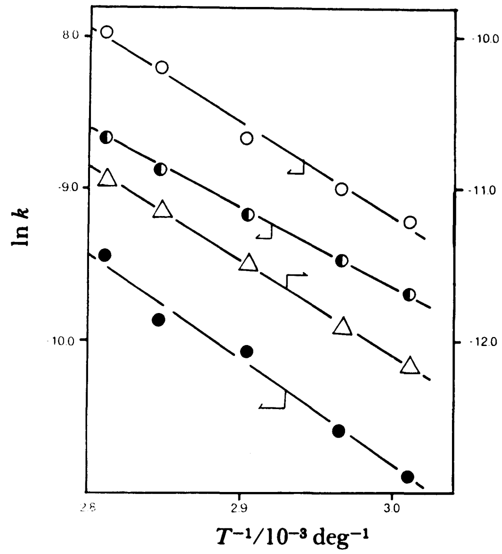


Fig. 2. Arrhenius plot.
Carbonyl compound 1 mmol, 2-propanol 2 cm^3.
●; Hexanal (cat. 0.2 g). ○; Cyclohexanone (cat. 0.1 g). ◐; Benzaldehyde (cat. 0.2 g). △; Acetophenone (cat. 0.4 g).

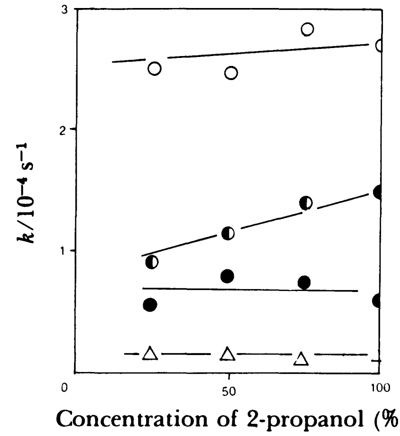


Fig. 3. The dependence of the concentration of 2-propanol.
Carbonyl compound 1 mmol, reaction temperature 78.0 °C. ●; Hexanal (cat. 0.2 g). ○; Cyclohexanone (cat. 0.1 g). ◐; Benzaldehyde (cat. 0.2 g). △; Acetophenone (cat. 0.4 g).

Table 5. Isotope Effect[a)]

Carbonyl compound	Cat./g	k_H/k_D
Hexanal	0.2	2.32
Cyclohexanone	0.1	2.16
Benzaldehyde	0.2	2.29
Acetophenone	0.4	2.46

a) Carbonyl compound 1 mmol, alcohol 2 cm^3 reaction temperature 78.0 °C.

tion of the carbonyl compound and the reaction time was observed in the early stage of reaction. This result indicates that the initial reaction rate is of second order under these conditions. Furthermore, when their ratio was 2 to 1, the following relationship was obtained:

$$\log_e\{([C_0]-[C])/(2\cdot[C_0]-[C])\} = k''\cdot[C_0]\cdot t, \tag{3}$$

where $[C_0]$, $[C]$, and k'' are the initial carbonyl concentration, the carbonyl concentration, and the pseude-second-order rate constant, respectively.

Isotope Effect. The reduction of hexanal, benzaldehyde, cyclohexanone, and acetophenone was performed with 2-propan-2-*d*-ol in place of 2-propanol. The primary isotope effects k_H/k_D of the reactions, which are listed in Table 5, are larger than 2, which indicates that the C–H bond at the 2-position in 2-propanol is broken in the transition state.

Kinetic Discussion. As described above, the reaction rate is of first-order dependence on each of the concentrations of the carbonyl compound, 2-propanol, and the catalyst, as represented by

$$r = k\cdot[C]\cdot[A]\cdot[\text{cat.}], \tag{4}$$

where k, $[C]$, $[A]$, and $[\text{cat.}]$ are the rate constant and the concentrations of the carbonyl compound, 2-propanol, and the catalyst, respectively. These results suggest that the rate-determining step is to be assigned to the step subsequent to the adsorption of 2-propanol and carbonyl on the catalyst. Taking the mechanism into account, we should like to propose a scheme. Based on the proposed scheme, the reduction rate is expressed by

$$r = \frac{k_1\cdot k_2\cdot k_3\cdot[C]\cdot[A]\cdot[\text{cat.}]}{k_{-1}\cdot(k_2+k_{-2})+k_2\cdot k_3[C]}. \tag{5}$$

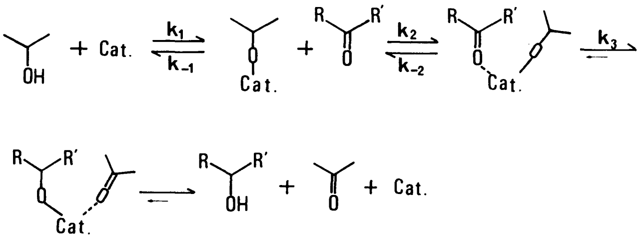
The observation of the primary isotope effect suggests that the step of the hydride transfer from 2-propanol to a carbonyl compound, that is, the third step in the scheme, constitutes the rate-determining step. Therefore, k_3 is far less than k_{-2}, and the rate equation is rewritten to

$$r = \frac{k_1\cdot k_3\cdot[C]\cdot[A]\cdot[\text{cat.}]}{k_{-1}/K_2+k_{-3}\cdot[C]}. \tag{6}$$

where $K_2=k_2/k_{-2}$. Furthermore, $k_{-1}/K_2 \gg k_3\cdot[C]$, hence the rate equation becomes

$$r = K_1\cdot K_2\cdot k_3\cdot[C]\cdot[A]\cdot[\text{cat.}], \tag{7}$$

where $K_1=k_1/k_{-1}$. This equation apparently corresponds to Eq. 4, and the proposed scheme may be concluded to be reasonable. A similar mechanism[17)] has been proposed for the Meerwein–Ponndorf–Verley reduction with hydroapatite catalyst, leading to estimation of its activation energy as 12±2 kcal mol^{-1}, which is the same with our case (see Table 4).



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