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NAD(P)$^+$-NAD(P)H Models. 64. The Quantitative Elucidation of the Mechanistic Aspects in the Silica Gel-Catalyzed Reduction of α,β-Unsaturated Carbonyl Compounds by a Model of NAD(P)H

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Eight α,β-unsaturated carbonyl compounds, 1-(2′- or 4′-substituted phenyl)-3-phenyl-2-propen-1-ones (2′- or 4′-substituted chalcones), were subjected to the reduction by an NAD(P)H model in the presence of silica gel in benzene. All of these afforded quantitatively the corresponding saturated carbonyl compounds, whereas no 1,2-reduction took place. For 2′-methoxy, 4′-methyl, 4′-bromo, and 4′-nitro derivatives as well as the unsubstituted carbonyl compound, the apparent reactivity of the substrate increases with the increase in electron-withdrawing ability of the substituent, whereas the degree of the adsorption onto the surface of silica gel decreases. It is also apparent that the 4′-hydroxy derivative exerts lower reactivity than the 2′-hydroxy derivative in spite of much more efficient adsorption of the former. In order to uniformly interpret the apparent results, the data obtained were quantitatively analyzed in terms of kinetics as well as equilibrium constants for the adsorption of the substrates onto the surface of silica gel. It has been revealed that the silanol group on the surface of silica gel acts as a general-acid catalyst in the reduction.

Attentions have been paid recently upon the selective reductions by an NAD(P)H model with its advantage in mildness of reducing ability.[1-6] A certain catalyst sometimes plays a crucial role in such reductions, and there is no doubt that the success for highly selective reduction by an NAD(P)H model depends on a novel catalytic system. For example, we presented the rhodium complex-catalyzed reductive dehalogenation by an NAD(P)H model as a selective reaction applicable to organic halides of several types.[4] Recently, we found that silica gel acts as a catalyst in the selective hydrogenations of carbon–carbon multi-bonds in 1,2-bis(ethoxycarbonyl)alkenes and -alkynes with an NAD(P)H model although the yield of the reduction product was not satisfactory.[5] Semiquantitative analyses of the reduction have suggested that silanol groups on the surface of silica gel contribute to the reaction through general acid catalysis. The analysis was based on the comparisons of the reactivity and the equilibrium constant for the adsorption of these substrates onto the surface of silica gel. We also suggested a possibility that a hydride-equivalent transfers from the NAD(P)H model adsorbed on the surface of silica gel to the substrate in the bulk phase. Nevertheless, the role of silica gel could not be definitively clarified, because the structures of the substrates subjected to the reduction were largely different from each other and quantitative argument on the structure-reactivity relationship was little possible.[5]

More striking catalysis by silica gel was found in the 1,4-reduction of α,β-unsaturated carbonyl compound by an NAD(P)H model; the reduction brings about the corresponding saturated carbonyl compound in quantitative amount whereas no 1,2-reduction takes place.[6] Moreover, functional groups such as carbonyl and ester groups as well as isolated carbon–carbon double bond are inert under the conditions. Then, we intended to examine the reduction of a series of α,β-unsaturated carbonyl compounds by an NAD(P)H model in details to elucidate the role of silica gel.

In this article, we wish to report the results for the reduction of α,β-unsaturated carbonyl compounds, 1-(2′- or 4′-substituted phenyl)-3-phenyl-2-propen-1-ones (2′- or 4′-substituted chalcones) (**1a—h**), by an NAD(P)H model, 3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,6-dimethylpyridine (Hantzsch ester: HEH), in the presence of silica gel in benzene. The reduction of **1a—h** afforded the corresponding saturated carbonyl compounds, 1-(2′- or 4′-substituted phenyl)-3-phenyl-1-propanone (**2a—h**), respectively. No 1,2-reduction was detected. Detailed discussion on the mechanism will be presented based on kinetics and thermodynamics.

Results

In order to obtain reliable results in the product analyses, the kinetics, and equilibrium constants for the adsorption onto the surface of silica gel, silica gel of relatively large mesh, silica gel 60 with 35—70 mesh (Nakarai Chem. Co.), was employed as a catalyst.[5] As an NAD(P)H model, HEH was used because of its higher tolerance against self-decomposition in the presence of silica gel during the reaction.[6] It has been confirmed that water contained in commercial silica gel affects little both the reactivity and the equilibrium,[7] and then neither dryness nor purification of the silica gel is necessary prior to use. Benzene has been found to be the best in this reaction among the solvents examined.

Reduction with HEH. The reaction of 1.0×10^{-1}

mmol of **1** with 1.5×10^{-1} mmol of HEH in the presence of 0.2 g of the silica gel in 1 ml of benzene was carried out under the nitrogen atomosphere at 70 °C in the dark with mechanical stirring. After appropriate period, the reaction mixture was analyzed on VPC according to the procedure described previously.[5] The results are summarized in Table 1. From the viewpoint of amounts of the starting material and the product, it is obvious that the 1,4-reduction is almost exclusive process. The order of apparent reactivity is **1d<1e≃1c≤1f<1a<1g<1b<1h.**

Table 1. Reduction of **1** by HEH in the Presence of the Silica Gel[a]

Substrate	Reaction time/h	Yield[b]/% Recov.[c]	Redn.[d]	
1a	1	65	26	
	1.5	54	38	
	2.5	34	51	
	18	Trace	87	(56)
1b	0.5	74	21	
	1	49	51	
	1.5	32	68	
	2.5	20	80	
	4	ND[e]	95	(85)
	16[f]	81	13	
1c	1	85	15	
	2.5	58	42	
	18	ND[e]	100	(80)
1d	1	87	13	
	2.5	70	30	
	4	58	42	
	18	<8	92	(69)
1e	1	80	20	
	2.5	59	41	
	4	41	59	
	18	ND[e]	99	(93)
1f	1	76	24	
	2.5	51	47	
	4	35	61	
	5.5	23	77	
	18	ND[e]	96	(95)
1g	1	69	29	
	2.5	35	63	
	4	21	76	
	18	ND[e]	98	(88)
1h	0.5	57	43	
	1	25	74	
	2	8	92	
	4	ND[e]	100	(97)

a) 1.0×10^{-1} mmol of **1** and 1.5×10^{-1} mmol of HEH were used. The reaction was carried out in 1 ml of benzene at 70 °C in the dark under N_2 atmosphere in the presence of 0.2 g of the silica gel. b) The yield determined by VPC analysis based on the amount of the substrate used. The values in parentheses indicate the isolated yield from the reaction of 5.0×10^{-1} mmol of **1** and 7.5×10^{-1} mmol of HEH in the presence of 1.0 g of the silica gel in 5 ml of benzene. c) The yield of the recovered starting material. d) The yield of the reduction product, corresponding saturated carbonyl compound. e) Not detected. f) Without the silica gel.

Reduction products isolated from the run in larger scale after enough reaction period were analyzed on NMR and IR spectrometers. Importantly, all substrates examined afforded the corresponding saturated carbonyl compounds **2a—h** in quantitative yields along with 3,5-bis(ethoxycarbonyl)-2,6-dimethylpyridine (HE_{ox}), the oxidized form of HEH, in slightly more than theoretical amount, whereas no 1,2-reduction products were recognized.[8] Small portion of HE_{ox} may be resulted from autoxidation of HEH on the surface of silica gel although the details are not clear.

Adsorption onto the Surface of Silica Gel. As described previously,[5] the degree of the adsorption of **1** onto the surface of silica gel can be evaluated by an equilibrium constant K_{Ad} ($=S_{Ad}/(S_{Bulk}\cdot Q_{free})$) (Eq. 1)

$$S_{Bulk} + Q_{free} \overset{K_{Ad}}{\rightleftarrows} S_{Ad} \quad (1a)$$

$$Q_{free} = Q_0 - S_{Ad} \quad (1b)$$

where S_{Bulk} and S_{Ad} are the amounts (mmol) of **1** in bulk phase and adsorbed one, respectively. Q_0 is the "effective" amount (mmol) of adsorbing centers for **1** on the 0.2 g of silica gel, which can be counted as the maximum amount (mmol) of **1** to be adsorbed. The equilibrium constant K_{Ad} was obtained from the slope and the intercept of the plot of $1/S_{Ad}$ vs. $1/S_{Bulk}$ with the amount of **1** being variable, based on Eq. 2 derived from Eq. 1. Excellent linear correlations (correlation coefficients; $r>0.999$) were seen in the double-reciprocal plots for all substrates.

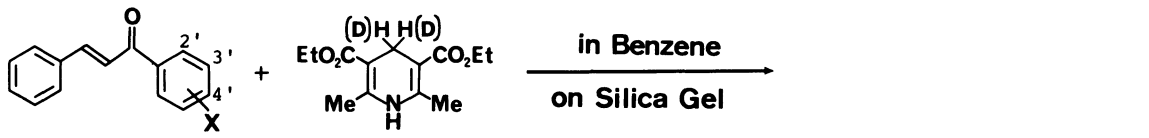
$$\frac{1}{S_{Ad}} = \frac{1}{K_{Ad}\cdot Q_0}\cdot\frac{1}{S_{Bulk}} + \frac{1}{Q_0} \quad (2)$$

Since the experiment was performed in 1 ml of benzene, each term with the dimension of mmol is equivalent to molarity (M (M=mol dm^{-3})) and the equilibrium constant K_{Ad} thus obtained has a

Table 2. Equilibrium Constants K_{Ad} for Adsorption of the Substrates into the Surface of the Silica Gel[a]

Substrate	K_{Ad}/M^{-1}	Substrate	K_{Ad}/M^{-1}
1a	693	**2f**	1.90
1b	3.33	HEH	51.1
1c	9.51	HE_{ox}	44.5
1d	9.64	**3**	21.3
1e	9.11	**4**	12.2
1f	6.81		
1g	5.49		
1h	4.25		

a) At 70 °C.



1a; X = 4'-OH
b; X = 2'-OH
c; X = 4'-OMe
d; X = 2'-OMe
e; X = 4'-Me
f; X = H
g; X = 4'-Br
h; X = 4'-NO_2

HEH

2

HE_{ox}

dimension of M^{-1}. The values of K_{Ad} for **1a—h** are summarized in Table 2 together with that for HEH reported previously.[5] Table 2 also involves the values for 4-phenyl-3-buten-2-one (**3**), 4-phenyl-2-butanone (**4**), and **2f** as well as HE_{ox}. It should be emphasized that, as expected from the Eq. 2, each plot gave the identical value for the intercept within experimental error. Since the substrates have wide range of K_{Ad} values (from 3.33 M^{-1} for **1b** to 693 M^{-1} for **1a**), Q_0 of $(7.25\pm0.25)\times10^{-2}$ mmol was obtained with an excellent accuracy. The value of Q_0 elucidated here is well coincident with that previously calculated-($(7.37\pm0.28)\times10^{-2}$ mmol) based on the same method for diethyl maleate, fumarate, and acetylenedicarboxylate as well as for HEH.[5] Recently, the amount of acidic active sites on a silica gel as well as its B.E.T. surface area was reported based on a measurement by means of titration with pyridine.[9] From the values reported, the amount of acidic active sites on the 0.2 g of silica gel is calculated to be 7.0×10^{-2} mmol, which excellently agrees with Q_0 elucidated in the present study, suggesting that the "adsorbing center" defined above corresponds to the "acidic active site" in the literature.

Kinetics. The data listed in Table 1 were kinetically investigated. Since no reduction of **1** with HEH takes place in the absence of silica gel, there remains no doubt that the reaction proceeds according to any one of Eqs. 3—5:

$$\mathbf{1}_{Ad} + HEH_{Ad} \xrightarrow{k_{AA}} \text{Products} \quad (3)$$

$$\mathbf{1}_{Bulk} + HEH_{Ad} \xrightarrow{k_{BA}} \text{Products} \quad (4)$$

$$\mathbf{1}_{Ad} + HEH_{Bulk} \xrightarrow{k_{AB}} \text{Products} \quad (5)$$

The corresponding rate expressions are those shown in Eqs. 6—8, respectively.

$$\text{rate} = k_{AA}[\mathbf{1}]_{Ad}[HEH]_{Ad} \quad (6)$$

$$\text{rate} = k_{BA}[\mathbf{1}]_{Bulk}[HEH]_{Ad} \quad (7)$$

$$\text{rate} = k_{AB}[\mathbf{1}]_{Ad}[HEH]_{Bulk} \quad (8)$$

It is not straightforward to obtain second-order rate constants k_{AA}, k_{BA}, and k_{AB} because each concentration term is governed by complex functions of either equilibrium constants K_{Ad} for coexisting components, **1**, **2**, HEH, and HE_{ox}, or their stoichiometric concentrations, which change complicatedly during the reaction. Here, it may be profitable to simulate the change of $[\mathbf{1}]_{Ad}$, $[\mathbf{1}]_{Bulk}$, $[HEH]_{Ad}$, and $[HEH]_{Bulk}$ as a function of stoichiometric concentration of **1**, $[\mathbf{1}]_{Total}$ ($=[\mathbf{1}]_{Ad}+[\mathbf{1}]_{Bulk}$). The computer-assisted simulation was performed by using the K_{Ad} values for **1**, **2**, HEH, and HE_{ox}.[10] The K_{Ad} values for the reduction products **2** were not obtained experimentally except for that for **2f**. However, arbitrary change in K_{Ad} for **2** from one-fifth to twice of that for the corresponding **1** scarcely affected the simulations.[11] The simulation curves for the reactions of 1.0×10^{-1} mmol of the substrate with 1.5×10^{-1} mmol of HEH in 1 ml of the solvent (the reaction conditions in the present study) are depicted in Figs. 1 and 2.

The simulations for **1b—h** afforded the results with a similar propensity as exemplified in Fig. 1 for **1f**, where $[\mathbf{1}]_{Ad}$, $[\mathbf{1}]_{Bulk}$, $[HEH]_{Ad}$, and $[HEH]_{Bulk}$ are linearly correlated with $[\mathbf{1}]_{Total}$ approximately. Then, for **1b—h** Eqs. 6—8 can be analyzed in terms of second-order rate equations with respect to $[\mathbf{1}]_{total}$.[12] The second-order rate equations thus derived from Eqs. 6—8, respectively, are mathematically equivalent. Accordingly, the data in Table 1 afforded kineticaly indistinguishable three sets of second-order rate constants for the reactions of **1b—h**. The data after long reaction period in Table 1 were, unfortunately, not available for the kinetic analyses, because the reaction gives rise to the decomposition of HEH and/or the change in the activity of the silica gel after long period. However, that the rate constant were obtained with moderate reliability (correlation

coefficients; $r>0.99$) demonstrates the validity of the treatment at least at an early stage of the reaction. Table 3 summarizes the second-order rate constants k_{AA}, k_{BA}, and k_{AB} corresponding to Eqs. 6—8, respectively, for **1b—h**.

On the other hand, Fig. 2 shows that during the decrease in $[\mathbf{1a}]_{Total}$ from 1.0×10^{-1} M to ca. 0.4×10^{-1} M, $[HEH]_{Ad}$ was kept almost constant (1.34×10^{-2} M$\simeq$ 1.40×10^{-2} M under the assumption that K_{Ad} for **2a** is 139 M^{-1}), whereas $[HEH]_{Bulk}$ dramatically decreased. In fact, it was found that the observed rate for the reduction of **1a** obeys a first-order rate equation with respect to $\mathbf{1a}_{Ad}$ or $\mathbf{1a}_{Bulk}$ with an excellent linear correlation at least before ca. 50% of **1a** was consumed

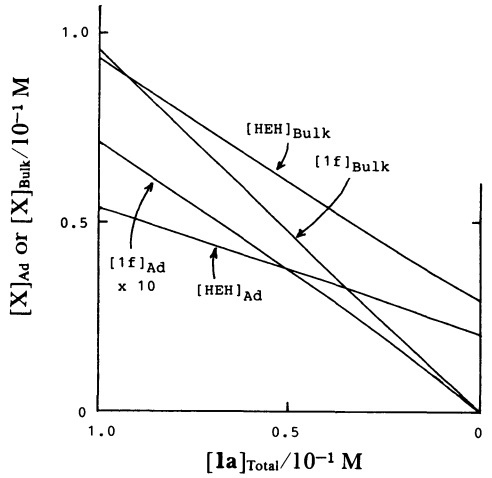


Fig. 1. The simulation curves of $[\mathbf{1f}]_{Ad}$, $[\mathbf{1f}]_{Bulk}$, $[HEH]_{Ad}$, and $[HEH]_{Bulk}$ as a function of $[\mathbf{1f}]_{Total}$.

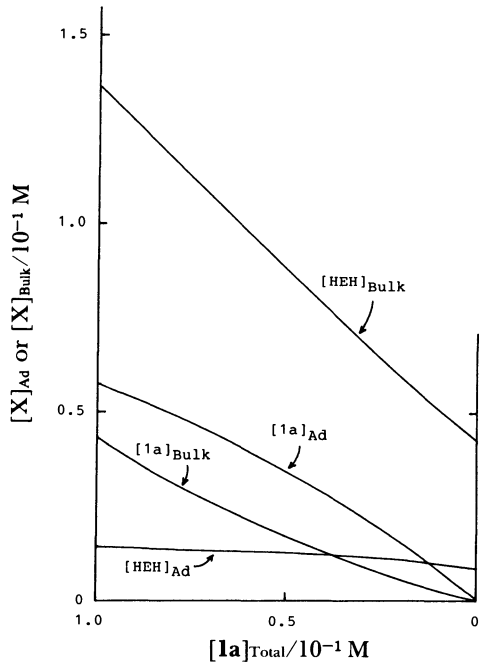


Fig. 2. The simulation curves of $[\mathbf{1a}]_{Ad}$, $[\mathbf{1a}]_{Bulk}$, $[HEH]_{Ad}$, and $[HEH]_{Bulk}$ as a function of $[\mathbf{1a}]_{Total}$.

(correlation coefficients; $r>0.999$). The finding manifests invalidity of Eq. 8 composed of two varying terms ($[\mathbf{1a}]_{Ad}$ and $[HEH]_{Bulk}$), and in turn excludes Eq. 5 as a possible reaction path. Therefore, we obtained second-order rate constants k_{AA} and k_{BA} for the reaction of **1a** by dividing the observed first-order rate constants by 1.3×10^{-2} M (=$[HEH]_{Ad}$ in Fig. 2). The results are listed in Table 3.

Deuterium Isotope Effect. In the reduction of **1f** by 3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,6-dimethylpyridine-4,4-d_2 (HEH-4,4-d_2), the NMR spectrum of the product **2f** confirmed the incorporation of quantitative amount of a deuterium into the β-position. Thus, Michael-type migration of a hydride-equivalent occurs in this reaction. Interestingly, it has been confirmed that the hydrogen at the 4-position of 1-benzyl-1,4-dihydronicotinamide, an NAD(P)H model, also migrates onto the β-position of 4-(unsubstituted or *p*-bromo- and *p*-nitrocinnamoyl)-pyridines in the presence of magnesium perchlorate in acetonitrile.[13]

Reductions of **1a**, **b**, **f**, and **g** by HEH-4,4-d_2 were kinetically followed, and primary kinetic deuterium isotope effects calculated for k_{AA} are listed in Table 4. The values indicate that a hydride-equivalent transfers from HEH to **1** in the rate-determining step.

Discussion

In Fig. 3, $\log(K^{X}_{Ad}/K^{H}_{Ad})$ derived from the values in Table 2 are plotted against the substituent σ-values. The σ-values for the 4′-substituents are tentatively

Table 3. Second-Order Rate Constants for the Reduction of **1** by HEH[a]

Substrate	k_{AA}[b] min^{-1} M^{-1}	k_{BA}[b] $\times10^{-1}$ min^{-1} M^{-1}	k_{AB}[b] min^{-1} M^{-1}
1a	0.526±0.083	6.02 ±1.55	—
1b	0.06 ±0.92	3.20 ±0.37	5.06 ±0.75
1c	0.910±0.143	0.599±0.037	0.496±0.066
1d	0.555±0.034	0.965±0.097	0.304±0.011
1e	1.03 ±0.11	1.00 ±0.11	0.568±0.037
1f	1.71 ±0.09	1.29 ±0.07	0.790±0.004
1g	3.17 ±0.33	2.08 ±0.22	1.67 ±0.18
1h	15.1 ±2.1	7.50 ±1.04	9.23 ±1.18

a) Derived from the data in Table 2. b) Errors contain those originated from uncertainty of K_{Ad} for **2** along with standard deviation; see text for details.

Table 4. Primary Kinetic Deuterium Isotope Effect

Substrate	k^{H}_{AA}/k^{D}_{AA}
1a	5.2±0.6
1b	5.5±0.9
1f	5.1±0.7
1g	5.4±1.0

used for the corresponding 2′-substituents, because the electronic effects of substituents at the 2′- and 4′-positions upon a side chain are reasonably assumed to be equivalent. The plot for **1a** locates far above the area, so it is omitted. For **1c—g**, a linear correlation (correlation coefficient; r=0.990) is seen with ρ=−0.50, indicating that, for these substrates, the more electron-releasing the substituent, the larger the K_{Ad} value. That **1c** and **1d** has almost identical K_{Ad} suggests that an ortho-substituent exerts no steric effect on the adsorption. The K_{Ad} value for **1b** is much smaller than expected from its σ-value. The finding supports the importance of carbonyl oxygen for the adsorption. That is, the adsorption through the carbonyl oxygen would be prevented in **1b** by its strong coordination with the 2′-hydroxyl group through a hydrogen-bonding to form a stable six-membered ring, which can be recognized by anomalously low chemical shift (δ from TMS=12.8 in $CDCl_3$) of the 2′-hydroxyl proton in the NMR spectrum of **1b**. The absence of appreciable absorption in the 3500—3600 cm^{-1} range in the IR spectrum also supports the proposal. The K_{Ad} for **1a** is unexpectedly large, which seems to be mainly attributed to the extremely low solubility of **1a** in benzene. Interestingly, the nitro group in **1h** is likely to result in an additional contribution to the adsorption. Smaller K_{Ad} values for the saturated carbonyl compounds **2f** and **4** than those for the corresponding α,β-unsaturated carbonyl compounds **1f** and **3**, respectively, may be due to thermodynamically less stable coordination of the former compounds than those of the latter compounds, respectively. That is, the induced small positive charge on the carbonyl group is not mesomerically stabilized by the phenyl ring on the β-position in saturated compounds. Alternatively, the π-bond in the carbon-carbon double bond of an α,β-unsaturated carbonyl compound may contribute to the adsorption.

All data listed in Table 2 reveals that electrostatic interaction between the carbonyl oxygen of **1** and the silanol group on the surface of silica gel is a predominant factor in the adsorption of **1**, as proposed previously for diethyl maleate, fumarate, and acetylenedicarboxylate.[5]

Figure 4 shows an excellent linear correlation between $\log(k^X_{AA}/k^H_{AA})$ derived from the data in Table 3 and the Hammett σ-value (ρ=1.22: correlation coefficient; r=0.998) except for **1b** and **1d**, where points for 2′-substituted derivatives are plotted against σ-values of the corresponding 4′-substituents (vide supra). As will be described later, there are convincing reasons against the deviations of plots for **1b** and **1d**. On the other hand, rather a U-shaped correlation between $\log(k^X_{BA}/k^H_{BA})$ and the σ-values can be seen in Fig. 5, with the plot for **1a** being largely deviated positively. There is no reason for the reaction between **1** in the solution and HEH on the surface of silica gel to exert a U-shaped Hammett relationship. The Hammett plot for k^X_{AB}/k^H_{AB} shows slightly positive deviations for **1c** and **1e** as seen in Fig. 6. Thus, the correlation in k^X_{AB}/k^H_{AB} is poorer than that in k^X_{AA}/k^H_{AA}. Note that the definition of k_{AB} is impossible for the reaction of **1a** as mentioned above. Finally, we infer that the reactions in the present study are most reasonably interpreted in terms of the kinetics represented by Eq. 6 instead of those in Eqs. 7 and 8.

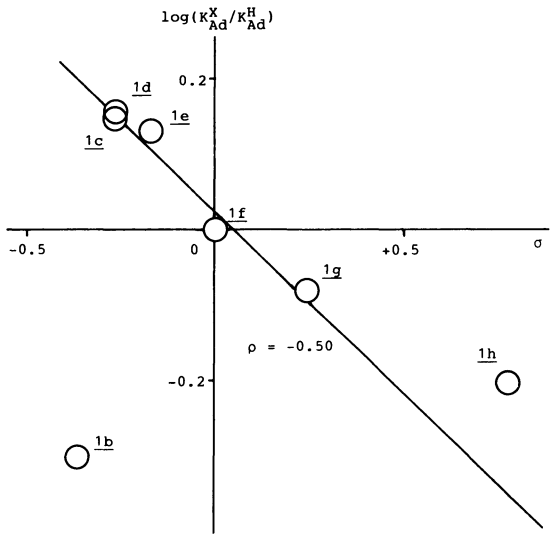


Fig. 3. The Hammett plot of $\log(K^X_{Ad}/K^H_{Ad})$ vs. σ-value.

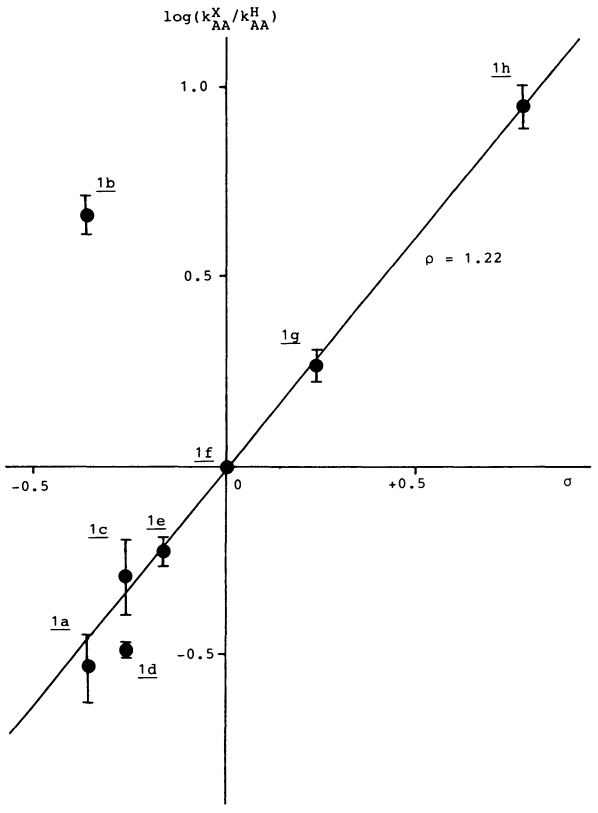


Fig. 4. The Hammett plot of $\log(k^X_{AA}/k^H_{AA})$ vs. σ-value.

Namely, since the equilibration is much faster process than the reduction,[5] the transfer of a hydride-equivalent appears to take place between HEH and **1**, both adsorbed on the surface of silica gel.

Nevertheless, our previous study on the reductions of diethyl maleate, fumarate, and acetylenedicarboxylate by HEH in the presence of silica gel has postulated that the transfer of a hydride-equivalent takes place from the HEH adsorbed on the surface of silica gel to the substrate in bulk phase.[5] First-order dependency of the reaction rate on both $[\mathbf{1}]_{Ad}$ and $[HEH]_{Ad}$ in the present reaction (Eq. 6) does not necessarily require the transfer of a hydride-equivalent between HEH and **1**, both adsorbed on the surface of silica gel, at the rate-determining step. Alternatively, we can take into account the local concentration(s) of **1** and/or HEH in the outer sphere of the silica gel. Since adsorption and desorption of the materials are in rapid equilibrium at the interface of the silica gel and the bulk phase, the local concentrations of HEH and **1** in the outer sphere would be approximately proportional to $[HEH]_{Ad}$ and $[\mathbf{1}]_{Ad}$, respectively. If this is the case, kinetic results obtained from the present study might accommodate the transfer of a hydride-equivalent from HEH to **1** in the outer sphere of the silica gel. As proposed previously, it is also possible that one of the two components, perhaps HEH counterpart, exists on the surface of silica gel during the transfer of a hydride-equivalent.[5]

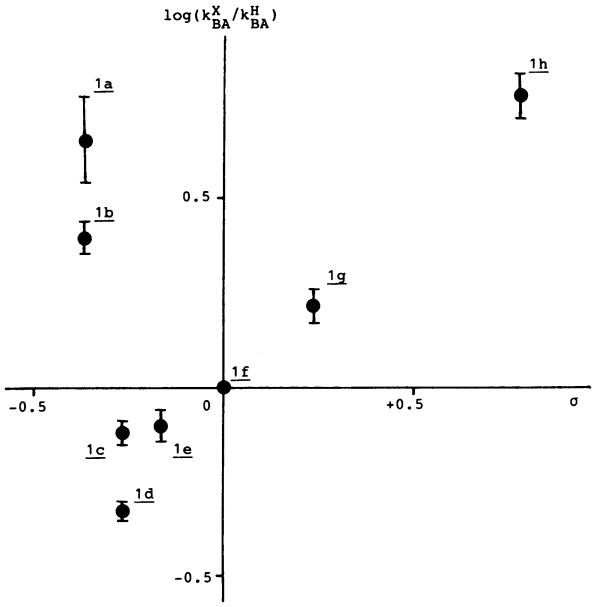


Fig. 5. The Hammett plot of $\log(k^X_{BA}/k^H_{BA})$ vs. σ-value.

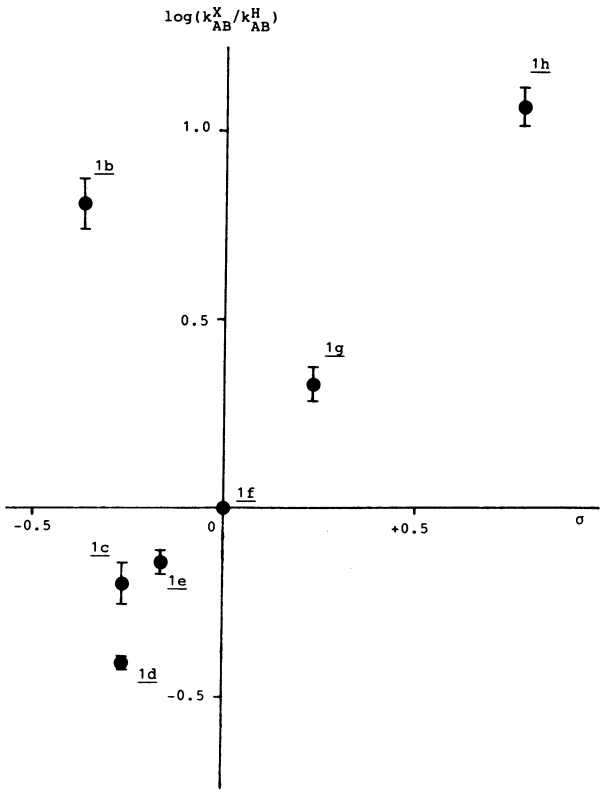


Fig. 6. The Hammett plot of $\log(k^X_{AB}/k^H_{AB})$ vs. σ-value.

The values of primary kinetic deuterium isotope effects listed in Table 4 clearly indicate that a hydrogen is migrating more or less in the rate-determining step.[14] It is also evident that these are approximately identical in magnitude irrespective of the reactivity of the substrate, which would postulate that the same mechanism persists for a hydride-equivalent transfer steps for **1a**, **f**, and **g**, as that for **1b**.[15] Unexpectedly high reactivity of **1b** is reasonably attributable to the intramolecular acid catalysis by the 2′-phenolic hydrogen in **1b**. Indeed, **1b** is reduced to **2b** by HEH in benzene without silica gel although the yield is low (Table 1). The transition state for the other substrates may stabilized as well by a hydroxylic proton of silanol group on the surface of silica gel. Considering that **1** is absorbed onto the surface of silica gel through the interaction of its carbonyl oxygen with a proton of a silanol group, a participation of the silanol group to the carbonyl oxygen of **1** in the outer sphere would be reasonably anticipated. Such a participation of the acidic silanol group may be not specific- but general-acid catalysis in view of extremely low basicity of the carbonyl oxygen of **1**[16] and moderate acidity of the silanol group,[17] although it cannot be demonstrated at present that the protonation is partially rate-determining. The positive ρ-value in this reaction shows the predominance of the hydride-equivalent transfer from HEH compared with the proton transfer from the silanol group at the transition state. Interestingly, in the reduction of *p*-methoxybenzaldehyde by NADH-dependent yeast alcohol dehydrogenase, the transfer of a proton from a water molecule onto the carbonyl oxygen does not participate in the rate-determining step, whereas the

transfer of a hydride equivalent onto the carbonyl carbon constitutes the sole rate-determining step.[18]

The present simulation has predicted that a large amount of silanol groups remain free during the reaction. It should be noted that the value of Q_0 does not represent the amount of all silanol groups on the surface, but it merely designates the "effective" amount of adsorbing centers on the surface for the materials used in the present study. A previous report has shown that only "free" silanol groups on the convex outer surface, the amount of which is calculated from the reported data to be 0.64 mmol per 0.2 g of silica gel, is ethoxylated by treating silica gel with ethanol. 2-Propoxylation and 2-methyl-2-propoxylation of silanol groups takes place, to the extents of two-third and one-third of that of ethoxylation, respectively, when silica gel is treated with 2-propanol and 2-methyl-2-propanol under the same conditions.[19] In addition, note that benzene molecule as a solvent in the present study does not perturb the silanol group because of its nonpolarity. Thus, during the present reaction, quite numerous silanol groups on the surface of silica gel possibly act as general-acid catalysts.

The mechanism is partly supported by the fact that k_{AA} for **1d** is smaller than that for **1c** even though these compounds have practically identical K_{Ad}. The ortho-substituent in **1d** may intervene an assistance by a silanol group during the process for the transfer of a hydride-equivalent.

Our previous study has revealed that active aluminas give rise to no reduction in spite of comparable adsorption of both a substrate and HEH onto their surfaces as those onto silica gel.[5] This fact indicates that silica gel not only adsorbs the materials but also plays a crucial role such as general-acid catalysis by the silanol group on the surface, as shown schematically in Fig. 7. Interestingly, an infrared spectroscopic study has revealed that when ethanol is adsorbed through hydrogen bonding, the silanol groups of silica gel act as proton donors, whereas on alumina the surface oxygen atoms play a dominant role as proton acceptors.[20]

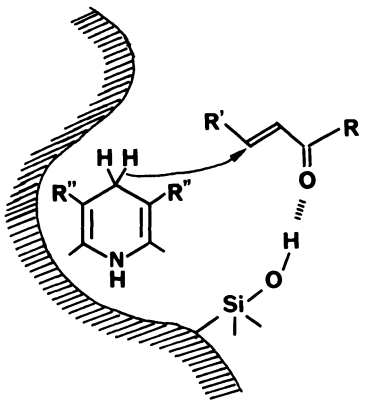


Fig. 7. Schematic representation of the reaction of **1** with HEH in the presence of silica gel.

In conclusion, we believe that the quantitative analysis in the present study has proven general-acid catalysis by silanol groups on the surface of silica gel in the reduction of α,β-unsaturated carbonyl compounds by an NAD(P)H model. Moreover, the silica gel unambiguously withdraws the materials subjected to the reduction closer to its surface. The dual roles of silica gel may be claimed as "enzyme-like." There are several examples for enzymatic hydrogenation of carbon–carbon double bond with a coenzyme NADH or NADPH, a redox potential of which is known to be equivalent to that of NAD(P)H models so far studied.[21] Thus, in a mimetic system an enzyme-like catalyst which exerts the dual ability, binding and catalysis, is required.

Finally, we wish to emphasize that the reduction system composed of HEH and silica gel is an excellent tool for chemo- and regio-selective reduction of α,β-unsaturated carbonyl compound due to its simplicity relative to other systems described in the recent reports.[22]

Experimental

Apparatus. VPC analyses and elemental analyses were performed on a Yanaco G-180 gas chromatograph and a Yanaco MT-3 elemental analyzer, respectively. ^{1}H NMR and IR spectra were recorded on a JEOL GX 400 FT NMR spectrometer and a Hitachi 260-10 infrared spectrophotometer, respectively. Computer-assisted simulations were run on an NEC PC-9801 VM2 personal computer with an N$_{88}$ BASIC program.

Materials. 3,5-Bis(ethoxycarbonyl)-1,4-dihydro-2,6-dimethylpyridine (HEH) was prepared as reported previously.[23] HEH-4,4-d_2 was synthesized according to the same procedure as described for HEH using paraformaldehyde-d_6 in place of formaldehyde. 400 MHz ^{1}H NMR spectrum confirmed deuterium content at the 4-position to be 98%. 2′- or 4′-Substituted chalcones **1a—h** were obtained by condensation of benzaldehyde with the corresponding 2′- or 4′-substituted acetophenone followed by recrystalization from ethanol.[24] Spectral data as well as the results of elemental analyses of these compounds were satisfactory. Silica gel 60 (35—70 mesh) (Nakarai Chem. Co.) was commercially available.

Procedures. Measurements of adsorption onto the surface of the silica gel and product analyses were succeeded according to the procedures described previously.[5]

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7) The content of water in the silica gel 60 has been measured to be 4.6±0.2 mmol g^{-1} on a Kirl-Fisher moisture content meter. See Ref. 5.

8) No reduction of nitro group was detected.

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10) Each concentration term is simulated by resolving the following equations simultaneously without any approximation,

$$K^{1}_{Ad} = [\mathbf{1}]_{Ad}/(([\mathbf{1}]_{Total}-[\mathbf{1}]_{Ad})\cdot[Q]_{free})$$
$$K^{2}_{Ad} = [\mathbf{2}]_{Ad}/(([\mathbf{2}]_{Total}-[\mathbf{2}]_{Ad})\cdot[Q]_{free})$$
$$K^{HEH}_{Ad} = [HEH]_{Ad}/(([HEH]_{Total}-[HEH]_{Ad})\cdot[Q]_{free})$$
$$K^{HE\text{-}ox}_{Ad} = [HE_{ox}]_{Ad}/(([HE_{ox}]_{Total}-[HE_{ox}]_{Ad})\cdot[Q]_{free})$$
$$[Q]_{free} = [Q^{0.2}_{0}]-[\mathbf{1}]_{Ad}-[\mathbf{2}]_{Ad}-[HEH]_{Ad}-[HE_{ox}]_{Ad}$$

and

$$[\mathbf{1}]_{Total}+[\mathbf{2}]_{Total} = 1.0\times10^{-1}\ M$$
$$[HEH]_{Total}+[HE_{ox}]_{Total} = 1.5\times10^{-1}\ M$$
$$[\mathbf{1}]_{Total}-[\mathbf{2}]_{Total} = [HEH]_{Total}-[HE_{ox}]_{Total}$$

where superscripts **1**, **2**, HEH, and HEox denote the values referred to **1**, **2**, HEH, and HE_{ox}, respectively.

11) The approximations may be reasonable considering that the observed K_{Ad} values for saturated carbonyl compounds **2f** and **4** are 1/3.57 and 1/1.75 of those for the corresponding α,β-unsaturated carbonyl compounds **1f** and **3**, respectively (Table 2).

12) The simulation allows the following approximations:

$$[\mathbf{1}]_{Ad} = A[\mathbf{1}]_{Total}$$
$$[\mathbf{1}]_{Bulk} = A'[\mathbf{1}]_{Total}$$
$$[HEH]_{Ad} = B[\mathbf{1}]_{Total}+C$$
$$[HEH]_{Bulk} = B'[\mathbf{1}]_{Total}+C'$$

where the parameters A, A', B, B', C, and C' are constants directly given by the correlation plotted in Fig. 1. Discrepancy between concentrations simulated and thus approximated is ca. 4×10^{-4} M (<1%) in maximum (for **1d**; when $[\mathbf{1d}]_{Total}=0.5\times10^{-1}$ M under the assumption of K_{Ad} (for **2d**)=1.93 M^{-1}.) Based on these approximations, Eqs. 6—8 afford a second-order rate equation with respect to $[\mathbf{1}]_{Total}$ as a following formula:

$$kt = c_1\cdot\ln\{(c_2\cdot(c_3[\mathbf{1}]_{Total}+c_4))/([\mathbf{1}]_{Total}\cdot(c_2\cdot c_3+c_4))\}$$

where c_1, c_2, c_3, and c_4 are constants, and in the equation derived from Eq. 6 where $k=k_{AA}$, for example, they are put as $c_1=1/(A\times C)$, $c_2=0.1$ (an initial concentration of **1**), $c_3=B$, and $c_4=C$, respectively.

13) S. Yasui and A. Ohno, unpublished result.

14) The mechanism of the transfer of a hydride-equivalent in the present study may be investigated in terms of successive transfers of an electron and a hydrogen atom (or an electron, a proton, and an electron) as proposed in NAD(P)H model-mediated reductions of several types of the substrates. Unfortunately, the present data in our hands provide no informations in this respect. Note that since **1** is supposed to be a strongly electron-deficient substrate under the silica gel catalysis, the step of an initial electron transfer would not be experimentally appreciable. See: S. Yasui and A. Ohno, *Bioorganic Chem.*, **14**, 70 (1986).

15) The theory demands, of course, identical values of kinetic primary deuterium isotope effect only when the position of the transition state along the reaction coordinate are exactly the same. There is no reason at all that the values of k^{H}_{AA}/k^{D}_{AA} obtained here must be identical. We only note that the values are roughly identical in the magnitude, which would certify the consideration in this place at least qualitatively.

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