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Acceleration of Synthetic Organic Reactions Using Supercritical Water: Noncatalytic Beckmann and Pinacol Rearrangements

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Abstract: A high-pressure and high-temperature FTIR was used to study noncatalytic Beckmann and pinacol rearrangements using supercritical water (scH_2O). Significant acceleration of Beckmann and pinacol rearrangements can be achieved by using scH_2O, especially near the critical point, even in the absence of any acid catalysts. It has been demonstrated that scH_2O acts effectively in the place of conventional acid catalysts for both the rearrangements. The rate of pinacol rearrangement using scH_2O is significantly larger by a factor of 28200 than that in 0.871 M HCl solution at 46.7 MPa under distillation conditions. The activation energy for the former at 25 MPa was found to be markedly reduced to about one-third of that for the latter. The accelerated rates of reaction may be attributed to a great increase in the local proton concentration around the organic reactants. In addition, the nature of scH_2O can be adjustable to weak acidity in the near-critical region, and then it does not catalyze the pinacol rearrangement, but opens a new reaction pathway from pinacol through a completely dehydrated product and then to a Diels−Alder adduct between the dehydrated products.

I. Introduction

Currently, chemical manufacture is facing severe solvent problems coupled with environmental concerns. As industry is really interested in moving away from toxic or environmentally damaging solvents, the finding of an ideal replacement medium for conventional nonpolar solvents offers new opportunities in reaction engineering, environmental science and technology, materials science and so on. Supercritical fluids have great potential for attaining this goal, and much attention has been drawn to organic syntheses in supercritical fluids.[1−4] Supercritical carbon dioxide is a suitable medium in connection with "green" technology and has played a key role as a reaction medium or a reactant in several organometallic reactions.[5−12] Increasing attention to the protection of environment is further promoting the study for searching more "green" or environmentally friendly chemical processes. Supercritical water (scH_2O) should be a more useful replacement for organic solvents because water is most environmentally acceptable and its physicochemical properties can be changed widely with pressure and temperature;[13] for example, the static dielectric constant of water is about 80 for the liquid phase and dramatically decreases to 6.0 at 30 MPa and 673 K in the supercritical region,[14] and so nonpolar organic compounds are very soluble or miscible in scH_2O.[15] This nature along with high diffusivity and low viscosity is expected to function as an ideal replacement for nonpolar organic solvents.

Kinetics and mechanisms of organic and inorganic reactions in H_2O below 373 K belong to the most widely studied areas in chemistry.[16,17] Preparative organic syntheses have recently been investigated in superheated H_2O (e.g., below about 573 K), and a lot of examples have been presented;[17−22] Siskin et al. proved that superheated H_2O can be an effective solvent and

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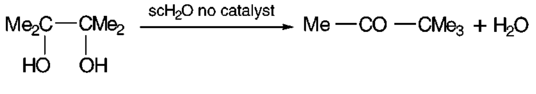
a reactant for organic synthesis.[18−23] Friedel−Crafts alkylation reactions have been investigated using superheated H_2O,[18,23] which was found to serve as both the medium and the catalyst. However, few research works have been reported on the use of scH_2O (e.g., above 648 K) for such “organic synthetic reactions”,[24,25] although scH_2O has been used mainly for “breakdown” of organic reactants such as destruction of waste and toxic organic compounds,[26−28] production of liquid and gaseous fuels from coal and biomass,[29,30] and geochemical reactions.[31] Therefore, the present work has been undertaken to explore the further possibility of performing organic synthesis in scH_2O.

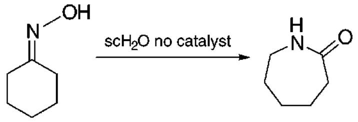
The ion product (K_w) for water increases with increasing temperature and pressure, reaches a maximum at a certain temperature, and then remarkably decreases beyond the critical point (or the critical temperature).[32] For example, as the temperature is increased at a fixed pressure of 25 MPa, log K_w, is −11.16 at 473 K, has a maximum value of −11.01 around 523 K, and then decreases to −19.43 at 673 K. The K_w for scH_2O is about 5 orders of magnitude lower than that for ambient liquid water, whereas the K_w for superheated H_2O at 523 K is about 3 orders of magnitude higher than the value for ambient water. Thus, it has been believed that superheated H_2O may promote acid-catalyzed reactions of organic compounds because of a sufficiently higher H^+ ion (proton) concentration than in liquid water. Several acid-catalyzed organic synthetic reactions were confirmed to actually proceed in superheated H_2O without any acid catalysts.[18,19,22,23]

Using an in situ Raman spectroscopy, we have recently found that the extent and strength of hydrogen bonding in scH_2O are reducing peculiarly near the critical point.[33] Raman studies can clarify microscopically intra- or intermolecular forces, and imply that the strength of hydrogen bonding weakens uniquely in the near-critical region on a short time scale, suggesting that the evolution of protons is significantly promoted, where dimers and monomers are predominant.[34−36] Some monomers could be further broken into protons near the critical point, and this dynamic change in the “local” water structure would induce the evolution of protons.[33,37] If the proton cannot escape, the “local” proton concentration would be high and might have a significant influence on reactivities in scH_2O region, especially in the near-critical region. Hence, we expect that acid-catalyzed organic syntheses can proceed under a scH_2O atmosphere even in the absence of any acid catalysts.

In this paper, we first report interesting examples of noncatalytic pinacol rearrangement with very excellent performance and of noncatalytic Beckmann rearrangement in the near-critical region in scH_2O, which are both well-known to be catalyzed by strong acids in conventional solutions. Beckmann rearrangement of cyclohexanone-oxime into ε-caprolactam is a commercially important reaction for the production of synthetic fibers, and the pinacol rearrangement is also important as a fundamental way of producing aldehydes and ketones. However, both reactions have disadvantages that highly concentrated monobasic acids or solid acids of short lifetime should be used as catalysts, and byproducts of low commercial value are formed frequently.[38,39] It would be significant if the use of scH_2O could promote these pinacol (eq 1) and Beckmann (eq 2) rearrangements. The reactions in scH_2O have been studied with an in situ high-pressure and high-temperature FTIR spectroscopy.



$$Me_2C(OH)-C(OH)Me_2 \xrightarrow{scH_2O\ \text{no catalyst}} Me-CO-CMe_3 + H_2O \tag{1}$$



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II. Results

H_2O Absorption. Although many of reactions in scH_2O were reported to be strongly affected by pressure and temperature changes,[24] these interesting effects have not been examined well. Recently the Raman spectra of H_2O in supercritical and superheated conditions have indicated a feature of the OH symmetric stretching at high pressures and temperatures.[33] Only the OH symmetric stretching (ν_1) around 3400−3600 cm^{-1} is active,[40] and detailed analysis of the ν_1 frequency can help us to better understand the features of H_2O molecules. Changes in temperature and pressure in the near-critical region were found to result in a uniquely weakening of the strength of the hydrogen bonding.[33] The present FTIR measurements show that liquid water has two main absorption bands in the mid-IR region which are attributed to intramolecular displacements, one having a very intense and broad band centered around 3400 cm^{-1} and corresponding to the OH symmetric and asymmetric stretching (ν_3) mode, and the other a maximum at 1645 cm^{-1} corresponding to the bending (ν_2) mode. The typical representative spectra of scH_2O in the mid-IR region are presented in Figure 1, where the temperature was raised from 603 to 708 K at a fixed pressure of 22.6 MPa just above the critical pressure (Figure 1a), and also the pressure was varied from 22.6 to 28.0 MPa at a fixed temperature of 650 K (Figure 1b). The integrated intensity of the bending mode decreases significantly in the near-critical region with decreasing pressure and increasing temperature, while the peak position (frequency) is insensitive to pressure and temperature. In the frequency region of stretching vibration, the absorption band weakens and blue shifts as the temperature is raised above the critical temperature. The large intensity of the stretching band points out the importance of intermolecular

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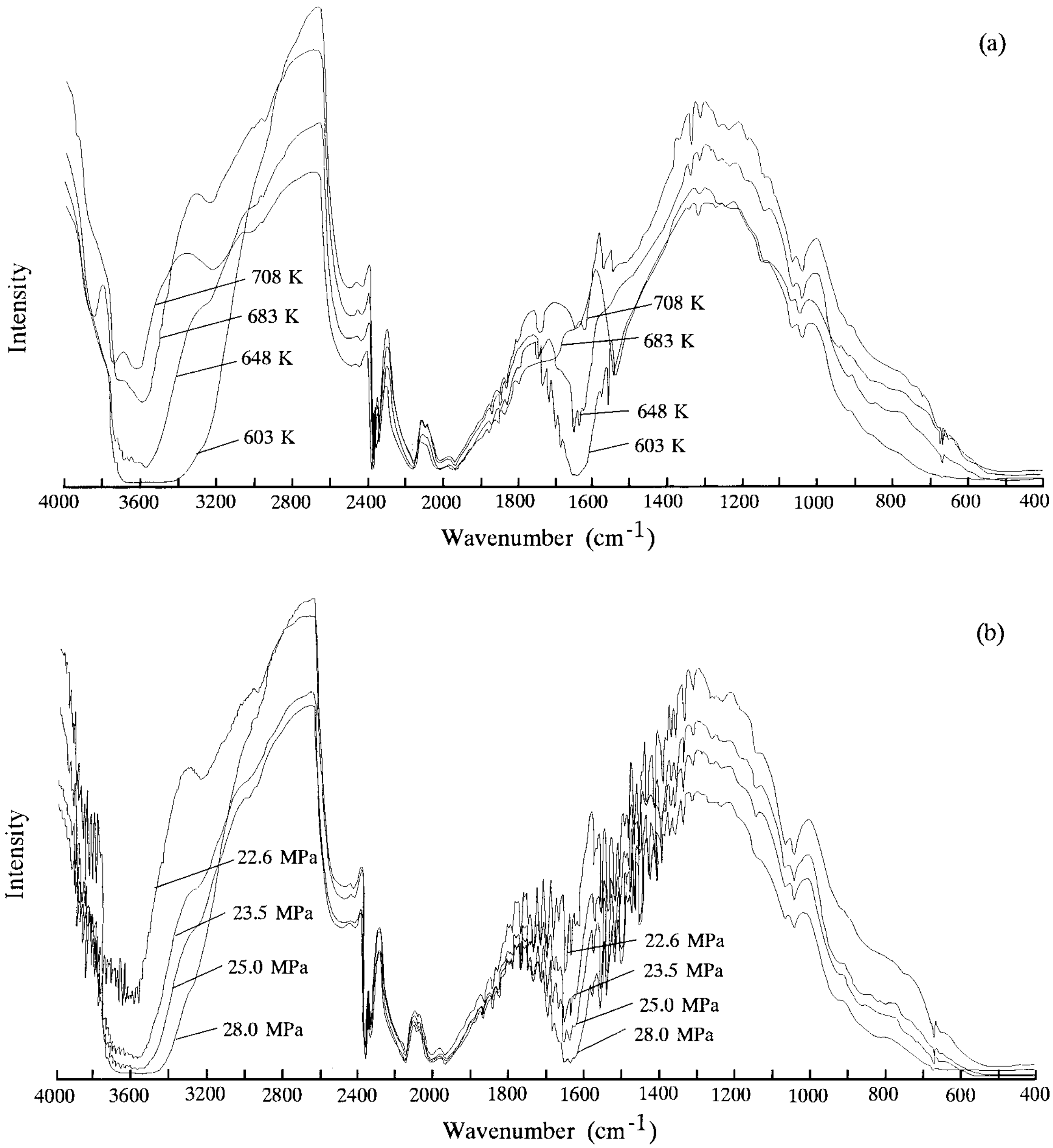

Figure 1. Spectra of scH_2O in the mid-IR region in the ranges of (a) 500−710 K at 22.6 MPa, and (b) 22.6 to 28.0 MPa at 650 K.

coupling through hydrogen bonding and suggests firm network of the hydrogen bonding,[41,42] and the decrease in the integrated intensity is an evidence of the breakdown of hydrogen bonding. The blue shift observed is due to the breakdown of hydrogen bond since a decrease in an O−H−O bridge strengthens the covalent O−H stretching. At a constant temperature of 650 K (Figure 1b), the OH stretching band becomes narrower and the peak position shows a slight blue shift with decreasing pressure.

Spectroscopic Measurements of Pinacol Rearrangement. The kinetic characteristics of the pinacol rearrangement are well-known in aqueous solution in the presence of monobasic acids at 298−393 K and at 0.1 MPa.[43−47] The rate of pinacol rearrangement to pinacolone can be improved by introducing acid catalysts at high concentrations, but quantitative formation of pinacolone from pinacol requires boiling in 25% H_2SO_4 for 3 h,[47] and it is very slow: for example, the first-order rate constant at 393 K is at best 3.0×10^{-3} s^{-1} and 2.9×10^{-3} s^{-1} in 0.71 M $HClO_4$ and 2.43 M H_2SO_4 aqueous solutions, respectively.[43,44] The selectivity of pinacolone is small, being only 65−72% even when the reaction is carried out in 6 N concentrated H_2SO_4 solution.[46] Previous studies were focused on the reactivity of pinacol rearrangement with a strong acid catalyst at atmospheric pressure. The effect of pressure up to 144.7 MPa on the rate of the acid-catalyzed pinacol rearrangement has been measured at 298−343 K in the presence of hydrochloric or sulfuric acid.[48] The first- and second-order rate constants decrease with increasing pressure at temperatures examined, and the rates at high pressures are fairly slow; for example, the first-order rate constants at 343 K are 1.24×10^{-5}, 1.10×10^{-5}, and 0.91 10^{-5} s^{-1} at 0.1, 46.7, and 144.7 MPa, respectively, in 0.87 M HCl aqueous solutions. Although the

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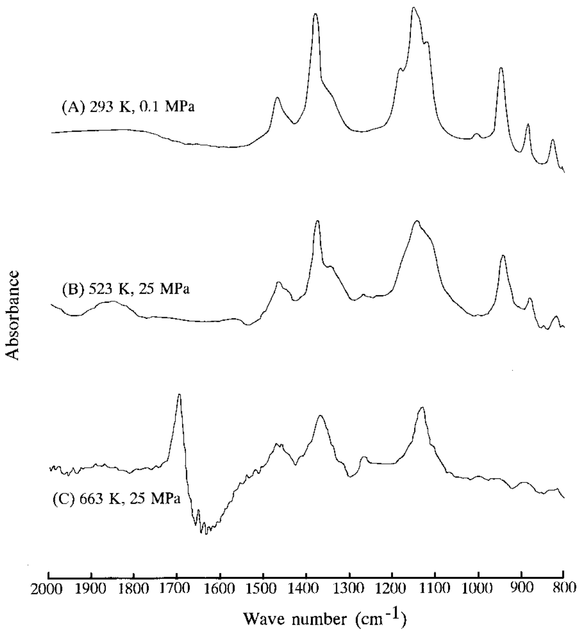

Figure 2. Infrared spectra of reaction mixture in noncatalytic pinacol rearrangement in H_2O medium at different pressures and temperatures. The bands at 1701 and 945 cm^{-1} correspond to CO stretching (ν_1) of pinacolone and OH bending (ν_2) of pinacol, respectively. The reaction time is 108 s.

previous data do not indicate the superiority of pressure effect in the pinacol rearrangement, quantitative rearrangement of pinacol, 1,1′-dihydroxy-1,1′-dicyclopentyl, and 1,1′-dihydroxy-1,1′-dicyclohexyl to the corresponding ketones was recently proved to occur in superheated D_2O alone at 548 K,[19] suggesting that pure superheated H_2O provides an environment that can maintain to some extent cationic intermediates. However, quantitative formation of the ketones requires a long time of 30 min under the above-mentioned superheated condition, and the rate is still very slow. We have suggested that the evolution of protons is significantly promoted in the near-critical region in scH_2O from in situ spectroscopic measurements.[33,37] Then, we have tried the pinacol rearrangement from superheated to supercritical conditions, and the kinetic determination was conducted spectroscopically at 473−723 K and 20−35 MPa.

A 0.40 M solution of pinacol in H_2O was introduced into the flow reactor with a high-pressure, high-temperature FTIR. Figure 2 shows the background-corrected IR spectra for a mixture of the straightforward pinacol rearrangement in scH_2O (663 K, 25 MPa), superheated H_2O (523 K, 25 MPa), and ordinary water (293 K, 0.1 MPa) at a constant reaction time of 108.0 s measured with our real time, in situ FTIR. A great change is seen in the spectrum obtained in scH_2O (trace C), in which a new strong band appears at 1701 cm^{-1}. This strong band can be assigned to CO stretching (ν_1) of pinacolone formed, which cannot be observed in the superheated (trace B) and ordinary water (trace A) phases, and the band for OH bending (ν_2) of pinacol at 945 cm^{-1} disappears completely in scH_2O. This in situ observation first demonstrates that the pinacol rearrangement to pinacolone proceeds very rapidly in scH_2O even in the absence of any acid catalysts, strongly supporting the function of scH_2O as an acid catalyst. The selectivity of pinacolone was found to reach 100% at 663 K and 25 MPa.

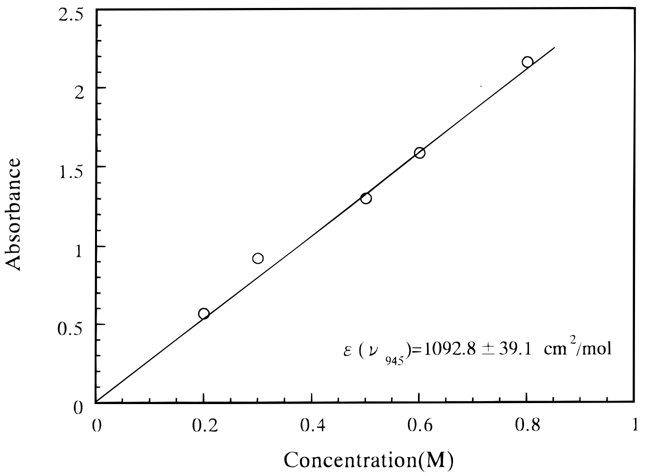

Figure 3. IR absorbance of ν_2 (OH) of pinacol as a function of concentration at 298 K.

Figure 3 shows the IR absorbance of ν_2(OH) of pinacol as a function of concentration at 298 K. The data points follow a straight line with a correlation coefficient of 0.9997 calculated by the least-squares method. We measured the absorptivity of pinacol at a constant concentration of 0.40 M in H_2O over 0.1−35 MPa and 298−423 K, but pressure and temperature had no influence on the absorbance. The molecular extinction coefficient, ϵ, of the ν_2(OH) determined using the slope of the line in Figure 3 through the Lambert−Beer law is 1092.8 ± 39.1 cm^2/mol. The extinction coefficient of ν_2(OH) was assumed to be also independent of temperature above 423 K, although such high temperatures will cause the reaction.[18,19] The effect of water density on the extinction coefficient of pinacol is also important; however, it is not possible to measure it under the reaction conditions used in the present work, and no such data can be found in the literature. So, we made measurements in liquid water at different pressures to confirm no effect of pressure on the extinction coefficient of pinacol. Thus, the concentration of pinacol was obtained from Figure 3, while quantifying pinacolone in H_2O was not able to be effected because pinacolone can be hardly dissolved in H_2O at ambient condition. Hence the rate of loss of pinacol, not the rate of formation of pinacolone, was employed in this study; the two rates were identical within the limits of experimental errors.[44] The change of pinacol concentration was monitored by the decrease in the FTIR absorbance of ν_2(OH) of pinacol. The reaction was reported to be kinetically of the first[43−45,48] or second[48] order in pinacol. In this study the first-order rate constants have been determined at temperatures of 298−723 K and pressures of 0.1−35 MPa. The first-order rate constants were obtained graphically by plotting $-\ln \alpha/(\alpha - x)$ against time t, where α is the initial concentration of pinacol and x is the amount of pinacol reacted in time t. Figure 4 shows an example at temperatures of 658, 673, and 723 K at 25 MPa in scH_2O. An approximately linear relationship indicates that the reaction follows kinetically the first order in pinacol.

Table 1 compares the first-order rate constants for the pinacol rearrangement under various conditions: scH_2O, superheated H_2O, and aqueous concentrated acid solutions. A dramatic enhancement in the reaction rate is seen with scH_2O even in the absence of any acid catalysts. The reaction in scH_2O at 25 MPa and 773 K is over 100 times faster than those in 2.43 M H_2SO_4[43] and 0.71 M $HClO_4$[44] solutions under distillation conditions, and it is further 28200 times faster than that in 0.871 M HCl solution at 46.7 MPa and 343 K.[48] Quantitative formation of pinacolone from pinacol via a classical method requires boiling in 25% H_2SO_4 for 3 h.[47] The reaction is significantly accelerated by raising temperature in subcritical and scH_2O region; however, in superheated H_2O below 573 K and at a

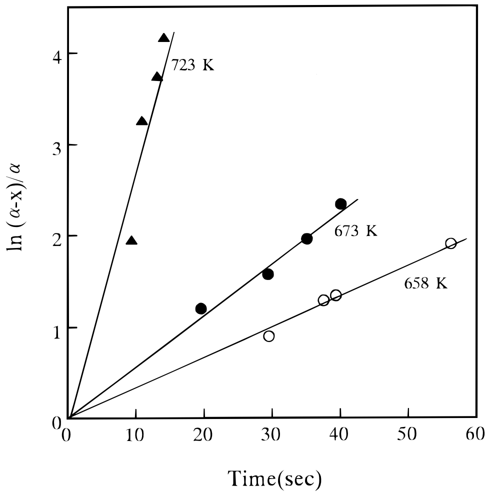

Figure 4. A plot of $-\ln \alpha/(\alpha - x)$ against reaction time at temperatures of 658, 673, and 723 K and at 25 MPa for the pinacol rearrangement using scH_2O. α: initial concentration of pinacol, x: amount of pinacol reacted in time t.

Table 1. First-Order Rate Constants of Pinacol Rearrangement to Pinacolone

system	temp (K)	pressure (MPa)	10^3k_1 (s^{-1})
2.43 M H_2SO_4 aq solution	373	0.1	2.9^a
0.871 M HCl aq solution	343	46.7	$1.1 \times 10^{-2\,b}$
no catalyst, scH_2O	648	25.0	35 ± 2^c
no catalyst, scH_2O	673	25.0	57 ± 5^c
no catalyst, scH_2O	723	25.0	310 ± 40^c
no catalyst, scH_2O	673	25.0	89 ± 6^c
no catalyst, superheated scH_2O	673	22.5	32 ± 3^c

[a] Reference 44. [b] Reference 47. [c] 95% confidence limit.

fixed pressure of 25 or 30 MPa the reaction was not observed to occur. Quantitative rearrangement of pinacol in superheated D_2O at 548 K required 60 min.[19] In the literature, no pinacol rearrangement has been done in aqueous acid solutions at such high temperatures and pressures where the environment should be changed into a very corrosive state in superheated H_2O.[49] The usual acid solutions do not appear to function as a catalyst at high pressures and temperatures because the ionic behavior including dynamics at high pressures and temperatures should be entirely different from that at ambient conditions.[50,51] The change in the molecular extinction coefficient of pinacol with water density might influence on the rate of constants. Wada et al. reported the change of the extinction coefficient of some substituted benzene compounds in pressurized CO_2.[52] Their data show that the extinction coefficients increase with the CO_2 density by about 50%. Of particular interest to us, in the case of pinacol in water, its extinction coefficient would change with the water density. From our results in liquid water and data of Wada et al., however, we can think that this change is not so large compared with the marked enhancement of the rate of reaction by one- or two-orders of magnitude by using scH_2O as shown in Table 1. There is some uncertainty in the absolute values of the rate constants determined, as the extinction coefficient may change with the water density. However, this does not prevent us from concluding that the use of scH_2O can significantly promote the rate of the organic reaction.

Spectroscopic Measurements of Beckmann Rearrangement in scH_2O. To demonstrate that this type of nucleophilic rearrangement is triggered by using scH_2O even in the absence of acid catalyst, we have further attempted a Beckmann rearrangement of cyclohexanone-oxime into ϵ-caprolactam in superheated and scH_2O conditions. A 0.15 M solution of cyclohexanone-oxime dissolved in H_2O was introduced into the flow reactor at the desired temperature and pressure, and then in situ observation was carried out at 623−673 K at the critical pressure of 22.1 MPa. Our attention has been focused on the chemical reactivities changing through the critical point from superheated H_2O to scH_2O conditions because the rate of reaction in the pinacol rearrangement is promoted peculiarly near the critical pressure at a given temperature. Figure 5 depicts the background-corrected IR absorption spectra of the solution in scH_2O (647.5 K), superheated H_2O (623 K) at the critical pressure of 22.1 MPa and at a constant reaction time of 133.0 s, and also of ordinary cyclohexanone-oxime and ϵ-caprolactam aqueous solutions (293 K, 0.1 MPa). Significant changes are seen in the spectrum observed in scH_2O at the critical point (trace D) as well as that in superheated H_2O (trace C), compared with that of cyclohexanone-oxime solution (trace A). In the scH_2O a new broad band was seen at around 1630 cm^{-1} with a discernible shoulder at 1705 cm^{-1}, whereas in the superheated H_2O a new intense band appeared at 1705 cm^{-1}, but the absorption band assigned to CO stretching (ν_1) of ϵ-caprolactam at 1625 cm^{-1} was not observed. The absorption band at 1705 cm^{-1} was unambiguously assignable to CO stretching of cyclohexanone that is the expected hydrolysis product of cyclohexanone-oxime, and in superheated H_2O the hydrolysis of cyclohexanone-oxime, not the Beckmann rearrangement, was found to proceed under the conditions examined. In scH_2O, however, a new absorption band around 1630 cm^{-1} clearly shows the Beckmann rearrangement to ϵ-caprolactam. The ^1H NMR spectrum of the purified chief product obtained at 22.1 MPa and 647 K is in fair agreement with that of the authentic sample. It is interesting that as the reaction conditions approach the supercritical state, the reaction is significantly accelerated by an increase in temperature. Under scH_2O conditions, a broad band in the 3300−3500 cm^{-1} region assignable to NH stretching of cyclohexanone-oxime and shoulder at 1705 cm^{-1} are also observable, demonstrating incompletion of the Beckmann rearrangement and occurrence of the hydrolysis of cyclohexanone-oxime. As a result, in analogy with the pinacol rearrangement, the Beckmann rearrangement can also proceed in scH_2O without acid catalysts, although the above-described data do not indicate the superiority of the Beckmann rearrangement over the pinacol rearrangement with respect to the rate of reaction and the selectivity.

Spectra shown in Figure 5 were collected for 5−6 flow rates at each of 6 temperatures between 573.1 and 667.6 K at 22.1 MPa. The area corresponding to ϵ-caprolactam was resolved by using curve-fitting method[53] and was converted into concentration based on the above-mentioned calibration method. Pressure and temperature had no effect on the absorbance as proved by the unchanged absorptivity of ν_1(CO) of ϵ-caprolactam in H_2O over 298−623 K at 22.1 MPa. Hence the molecular extinction coefficient of the ν_1(CO) through the Lambert−Beer law was determined to be 2499.2 ± 124.5 cm^2/mol. In this study the first-order rate constants for the formation of ϵ-caprolactam were obtained in the same manner as in the pinacol rearrange-

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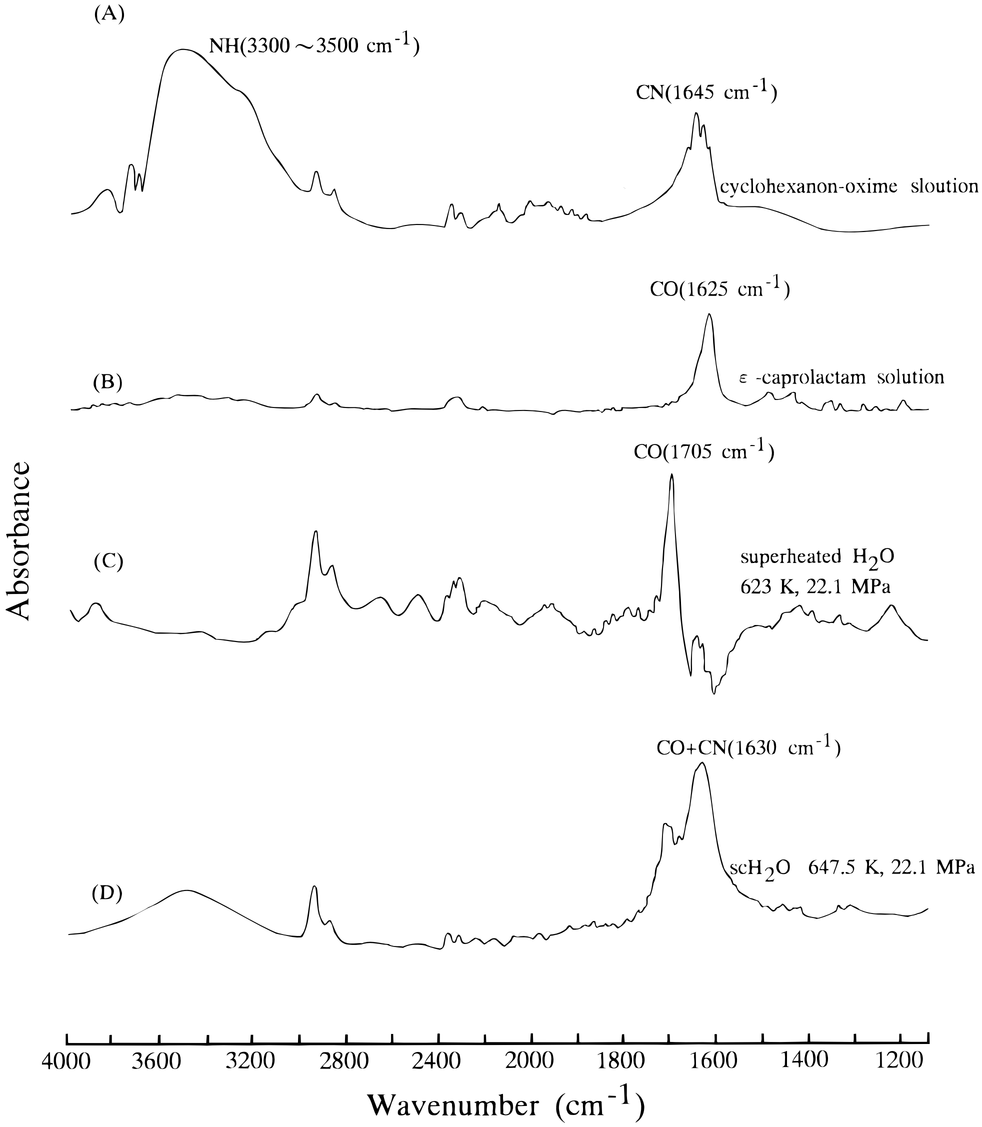

Figure 5. Infrared spectra of reaction mixture in noncatalytic Beckmann rearrangement at temperatures of 623 and 647 K and at a constant pressure of 22.1 MPa. The bands at 1705 and 1625 cm $^{-1}$ correspond to CO stretching (ν_1) of cyclohexanone and ϵ-caprolactam, respectively. The band at 1645 cm^{-1} is assigned to CN stretching (ν_1) of cyclohexanone-oxime.

Table 2. First-Order Rate Constants for the Formation of ϵ-Caprolactame in 0.15 M Cyclohexanone-Oxime Solutions at 22.1 MPa

temp (K)	10^3k_1 (s^{-1})
623.0	not detectable
637.5	0.35×0.02^a
647.5	2.46 ± 0.36^a
652.5	8.16 ± 0.75^a
667.5	1.40 ± 0.17^a

[a] 95% confidence limit.

ment because neither the compressibility nor the pressure dependence of the acidity is available. The best-fit values for the first-order rate constant at each temperature are listed in Table 2. One can also see an interesting temperature dependence. The Beckmann rearrangement in superheated H_2O below 623 K at 22.1 MPa was not observed to occur by the IR observation; however, the ϵ-caprolactam was found to be synthesized peculiarly in the limited temperature range around the critical temperature. The rate constant significantly increases as the temperature approaches the critical temperature, above which it decreases greatly.

III. Discussion

Effect of Hydrogen Bonding on Reactivities. The most important factor for the high rates obtained in scH_2O may be the change in the nature of hydrogen bonding of H_2O. Recent neutron diffraction data demonstrate that the hydrogen bonding is still present in scH_2O;[54] however, the cooperative nature of the hydrogen bonding network disappears, and only dimers and monomers are predominant species.[34−36] Large fluctuations of the structure near the critical point might allow further breakdown of monomers, leading to the evolution of protons from scH_2O medium itself.[33,37,55,56] This makes it possible to conduct pinacol and Beckmann rearrangements using scH_2O, which can be promoted by acid catalysts in conventional solvents: this point will be discussed in more detail below. Less obvious but potentially important to the high rate are other factors such as compressibility near the critical point and rapid diffusion in the supercritical phase.

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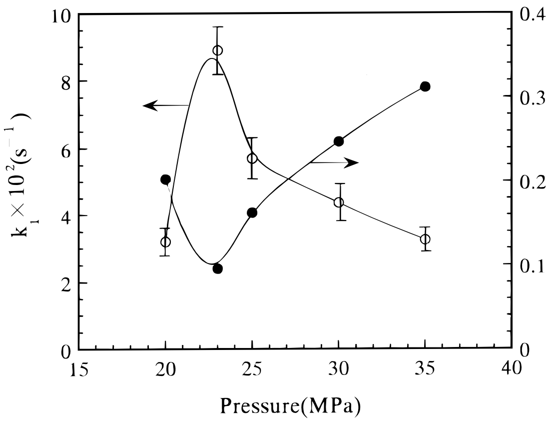

Figure 6. Relationship between the extent of hydrogen bonding, η (filled symbols), and the first-order-rate constant, k_1 (open symbols), for the pinacol rearrangement as a function of pressure at a fixed temperature of 673 K.

Figure 6 shows the change in the rate constant of pinacol rearrangement with pressure at a fixed temperature of 673 K. The rate constant becomes maximized at the near-critical pressure of 22.5 MPa, and then decreases with increasing pressure. Steeper et al. also observed a maximum in the rate of methane oxidation at a particular pressure in scH_2O as the system pressure was varied.[57] The specific increase in the rate of reaction may be due to a marked increase in the proton concentration in the near-critical pressure. For acid-catalyzed reactions in superheated H_2O, the ion product (K_w) is of importance.[18,19,22−24] However, the present result under the supercritical state cannot be explained by the change in K_w. At a constant temperature of 673 K, K_w is $10^{-33.18}$ at 5 MPa and it increases with increasing pressure; for example, $K_w = 10^{-19.43}$ at 25 MPa near the critical pressure.[32] The pressure dependence of K_w is entirely different from the data of Figure 6, and we should consider other microscopic factors on a short time scale such as dynamically changing structures of scH_2O, especially in the near-critical region rather than macroscopic/static properties such as the K_w.

In Figure 6 the extent of hydrogen bonding (η) of water is also presented, where $\eta = 0$ in the limit of no hydrogen bonds for hot, low-density vapor and $\eta = 1$ for water at 298 K and 0.1 MPa. Our Raman data concerning the hydrogen bonding of water has been successfully converted to the η scale,[33] by applying a linear relation between the NMR chemical shift (δ) of water and the η value.[34−36] This simple η-scale model, in which hydrogen nuclei are either involved or not involved in a hydrogen bond, can give an estimate of the probability of formation of the hydrogen bonding relative to that for water at ambient conditions. For example, the η values calculated at densities of 0.52, 0.20, and 0.12 g/cm^3 for scH_2O are 26%, 15%, and 10%, respectively, being in good agreement with the above-mentioned NMR values. In Figure 6, the η value shows a minimum at the near-critical pressure and is remarkably lower compared with other superheated or supercritical water. This peculiarity of the strength of hydrogen bonding was not obtained by NMR studies.[34−36] It was thus demonstrated that the extent of hydrogen bonding is reducing uniquely near the critical pressure, where dimers and/or monomers are predominant, but some monomers are further broken into protons due to large fluctuations of the structure of water.[33,37] A similar explanation for this phenomenon resulting from structural fluctuations has been reported by other researchers.[55,56] The organization of 4−10 water molecules is required to solvate the transferred protons,[58] and the water structure near the critical pressure becomes less able to accommodate the ejected protons. That is, the "local" proton concentration would be extremely high when the transferring proton cannot escape.

It is possible to mention another factor that may be related to the maximum rate of reaction observed near the critical pressure. It has been noted that the local concentration of organic solute in supercritical carbon dioxide becomes maximized in the near-critical region,[59,60] where the rate of reaction is significantly large.[61−64] For example, in noncatalytic esterification of phthalic anhydride and methanol in supercritical carbon dioxide, the rate of reaction was markedly enhanced with an increase in the local concentration of phthalic anhydride molecules around a methanol molecule.[62] This effect may explain the observed enhancement of the rate of reaction in scH_2O as well. In the present noncatalytic pinacol rearrangement in scH_2O, the "local" concentration of pinacol around protons would be very large near the critical pressure, leading to the promotion of the reaction. In addition, one cannot deny the possible role of the proton from the organic reactant itself, and in this study we have further examined the Beckmann rearrangement as an alternative type of acid-catalyzed reaction using a flow reaction system with FTIR because this in situ observation would be helpful for the discussion of the origin of the products.

As shown in Figure 5 and Table 2, the conversion of cyclohexanone-oxime was accelerated with increasing temperature, especially near the critical temperature, while the cyclohexanone obtained by the hydrolysis of cyclohexanone-oxime decreased markedly above the critical temperature. Even under the same scH_2O conditions, a certain amount of cyclohexanone other than ϵ-caprolactam has been produced in the Beckmann rearrangement. However, application of the flow reaction system which can shorten considerably heating time up to scH_2O conditions was found to depress the formation of cyclohexanone, compared with that of a bath reaction system[25] ranging in heating time from 30 to 60 s. Thus, cyclohexanone-oxime should be hydrolyzed to cyclohexanone within a residence period of only a few seconds in superheated H_2O during heating to scH_2O conditions.

Figure 7 depicts the first-order rate constant for the formation of ϵ-caprolactam against temperature at the critical pressure (22.1 MPa) of H_2O. For acid-catalyzed reactions, the K_w has been considered to be of importance;[18,22−24] however, the K_w of bulk scH_2O near the critical point is similar to the values at ambient conditions (10^{-14}),[32] and one cannot give a reasonable explanation of the maximized rate using the K_w data alone. It is likely that microscopically dynamic behavior in a shorter time domain is more important in discussing the reactivity. In Figure 7 the extent of hydrogen bonding (η) of water based on our Raman data[33] is represented as well. The η value shows a significant decrease over 643 K and shows a minimal value at the critical

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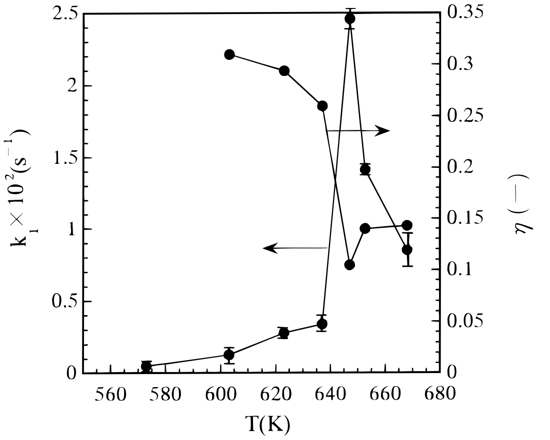

Figure 7. Relationship between the extent of hydrogen bonding, η (filled symbols), and the first-order-rate constant, k_1 (open symbols), for the Beckmann rearrangement of cyclohexanone-oxime to ϵ-caprolactam as a function of temperature at the critical pressure of 22.1 MPa.

temperature, strongly supporting that the strength of hydrogen bonding is significantly weakened near the critical point. As a result, both in the pinacol and Beckmann rearrangements, the temperature dependence of the rate of reaction corresponds to the opposite dependence of the η value (Figures 6 and 7). Furthermore, a small temperature increase up to the supercritical state that leads to a marked decrease in the η value opened such a new reaction path to the ϵ-caprolactam, although cyclohexanone-oxime was hydrolyzed at 623 K in superheated H_2O (Figure 5). Therefore, the protons responsible for the rearrangement are supplied from H_2O itself under supercritical state, not from organic reactants. One can thus believe that a marked loss in the ability of water to accept protons evolved from H_2O molecules near the critical point is an important cause for the promotion of the Beckmann rearrangement as well as the pinacol rearrangement.

Reaction Pathway to a Cyclic Compound. In the pinacol rearrangement, the selectivity of pinacolone reaches 100% in scH_2O, e.g., at 673 K and 25 MPa; pinacolone is the sole product under scH_2O and superheated H_2O reaction conditions. However, further analysis of the reaction products shows the formation of an interesting type of product. In very limited near-critical region of 648−653 K at 22.5 MPa, the route to 1,2,5-trimethyl-5-isopropenyl-1-cyclohexene (**IV**) from pinacol (**I**) other than that to pinacolone (**II**), as shown in Figure 8, was found for the first time. The formation of **IV** was identified when the near-critical conditions were established, but then it sharply decreases with increasing temperature. Hence the new pathway very strongly depends on the properties of scH_2O near its critical point. The conversion of **I** to **IV** is around 30−50%. We think that pinacol is thoroughly dehydrated into 2,3-dimethyl-1,3-butadiene (**III**), and then the ring closure between **III** brings about the formation of **IV**. The production of such a cyclic compound in scH_2O is similar to other reactions reported previously,[65] in which a variety of Diels−Alder reactions were confirmed to occur in high yields in scH_2O even in the absence of acid catalysts. It is also known that the complete dehydration of **I** to **III** is consistent with a mechanism proposed for relatively weaker acids such as HBr.[66] This dehydration should proceed through a mechanism different from that in the above-mentioned pinacol−pinacolone rearrangement. The formation of **IV** from this Diels−Alder type of reaction occurs at the critical density, and this may be associated with a clustering behavior. Thus, not only the "local" concentration of protons as described above but also the "acidity" itself of scH_2O can be adjustable, especially in the near-critical region, so scH_2O will find more important potential application for organic synthesis. In a very compressible medium such as a supercritical fluid it may be possible by controlling pressure and temperature to adjust the mean distance between a solvent and a more massive solute species within a range where the mutual pair function is significantly varying.[67] It appears that the alternate path in dehydration may be associated with tuning of the average distance between the protons generated and the substrate molecules, which results in the change in the solvation energy of the substrate. The solvation energy of the substrate can therefore be controlled by pressure and temperature, leading to the alternation in product distribution of a chemical reaction.

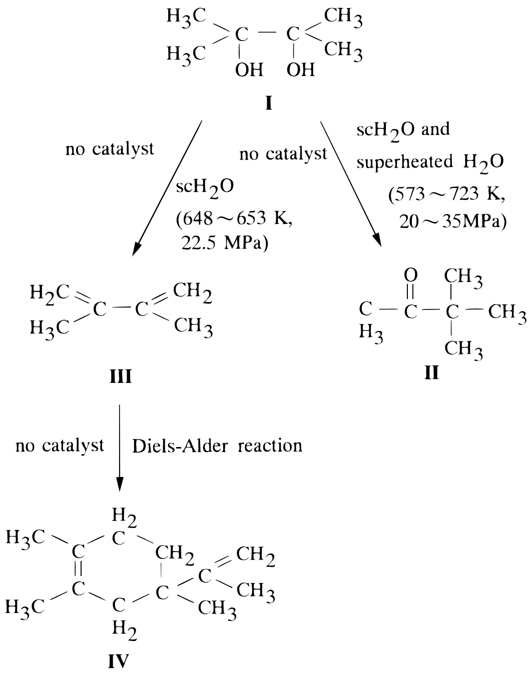

Figure 8. Noncatalytic reaction paths producing pinacol (rearrangement) and 1,2,5-trimethyl-5-isopropenyl-1-cyclohexene (Diels−Alder reaction) in scH_2O.

Activation Energies and Entropies. We have estimated the apparent activation energy (E_a) for the pinacol rearrangement in scH_2O. It can be obtained from the following Arrhenius equation using the k_1 values determined above.

$$\ln k_1 = \ln A_o - E_a/RT \tag{3}$$

where A_o is the Arrhenius preexponential factor. An Arrhenius plot for this rearrangement in the range of 553 to 723 K at a fixed pressure of 25 MPa yields a straight line as shown in Figure 9. The E_a was determined to be 55.7 ± 4.1 kJ/mol. Table 3 shows the values of activation parameters calculated from these plots for the rearrangement at pressures of 22.5, 25, 30, and 35 MPa in superheated H_2O and scH_2O. In Table 3, literature values for the acid-catalyzed pinacol rearrangement at room temperature or around 373 K and at high pressures up to 144.7 MPa are given as well.[42−44,48] We note that our E_a values are reduced to one-half or one-fourth of the literature

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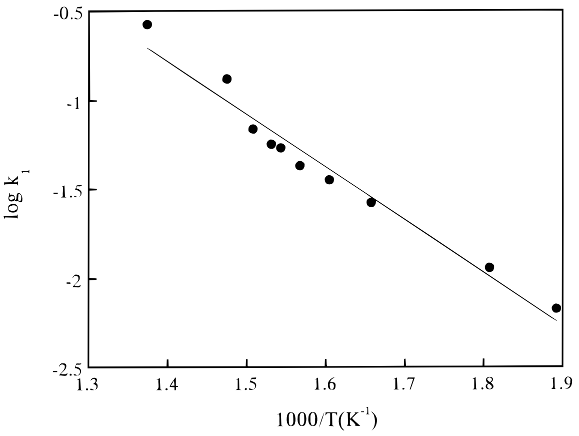

Figure 9. An Arrhenius plot for the pinacol rearrangement using scH_2O in the range of 553 to 723 K at 25 MPa.

Table 3. Activation Energies and Entropies for the Pinacol Rearrangement

P (MPa)	E_a (kJ/mol)	$\Delta S^‡$ (J/k mol)
22.5	28.3 ± 2.1^b	-246.7 ± 13.3^b
25.0	55.7 ± 4.1^b	-202.0 ± 11.3^b
30.0	80.9 ± 5.5^b	-161.0 ± 9.0^b
35.0	93.4 ± 2.0^b	-142.0 ± 6.7^b
0.1[a]	151.3	93.4
46.7[a]	155.0	103.1
95.5[a]	158.8	113.1
144.7[a]	162.2	121.9

[a] In 47.5 wt % H_2SO_4 aq solution at 343 K.[65] [b] 95% confidence limit.

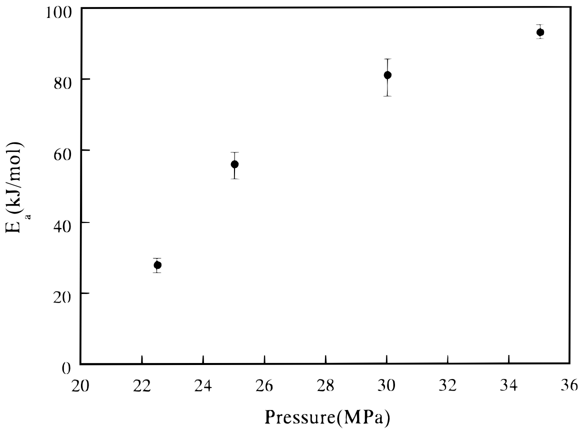

Figure 10. Pressure dependence of the activation energy for the pinacol rearrangement using scH_2O.

values of "acid-catalyzed" rearrangement. In addition, the literature value of E_a very slightly increases with increasing pressure over the wide range of 0.1 to 144.7 MPa, whereas the E_a values for the scH_2O rearrangement are greatly enhanced by the small gain in pressure from 22.5 to 35 MPa. Figure 10 shows the pressure dependence of our E_a value. The E_a value at 22.5 MPa above the critical pressure was found to be prominently lower compared with the other E_a values at higher pressures of 25, 30, and 35 MPa. The lower E_a value is associated with the maximized rate constant at the near-critical pressure shown in Figure 6. Our results indicate significantly lower activation energies for the "noncatalytic" reaction process using scH_2O. Although these results could run counter to the usual conception of catalysis as a process by which activation energies are reduced, the protons evolved from the monomers under scH_2O conditions could function as a catalyst instead of the usual acid catalysts, and an enhancement in the local proton concentration near the critical point would greatly increase the rate of reaction in the "noncatalytic" rearrangement using scH_2O.

For the "acid-catalyzed" pinacol rearrangement at high pressures, previously determined activation entropies are positive and increase with increasing pressure as shown in Table 3. Figure 11 represents a possible mechanism[68] proceeding through an carbonium ion intermediate to the transition state for the usual acid-catalyzed rearrangement. This mechanism comprises the inference from analogy with alcohol dehydration and can reasonably account for the oxygen exchange and the migration tendencies of alkyl groups. If this is indeed an equilibrium process, we can use the apparent equilibrium constant to extract thermodynamic information about the process. To obtain the equilibrium constant for activated-complex formation, we can use the van't Hoff equation:

$$\Delta G^‡ = -RT \ln K^‡ \tag{4}$$

Since the $\Delta S^‡$ for activated-complex formation is positive in concentrated acid solution, the complex formation is thermodynamically favored due to an increase in the spatially degree of freedom, leading to an enhancement in the "effective concentration" of the complex. Hence the rate-determining step is considered to be the process of dehydration of the carbonium ion intermediate (**III**), leading to $k_{-e} \gg k_{x.}$ This is consistent with the kinetic results.[48] Furthermore, as shown in Table 4 the $\Delta H^‡$ is positive, and we infer that the transformation of **III** → **IV** in Figure 11 is an endothermic equilibrium process shifting to the right at higher temperatures in usual acid solution.

To estimate the entropic cost of the pinacol rearrangement using scH_2O, we use the following relationships according to the transition-state theory.

$$k_1 = s(k_BT/h)\exp(-\Delta G^‡/RT) \tag{5}$$

$$\Delta G^‡ = \Delta H^‡ - T\Delta S^‡ \tag{6}$$

$$k_1 = s(k_BT/h)\exp(\Delta S^‡/R)\exp(-\Delta H^‡/RT) \tag{7}$$

where k_B and h are Boltzmann's constant and Planck's constant, respectively. s is the transmission coefficient and usually assumed to be unity. From thermodynamic relations the following equation is obtained:

$$E_a = RT + \Delta E^‡ \tag{8}$$

Furthermore, at a constant pressure the following equation is given:

$$\Delta H^‡ = \Delta E^‡ + P(\Delta V^‡) \tag{9}$$

In a monomolecular-type of reaction such as the present pinacol rearrangement, one can see no change in the number of molecules through the transition state from the initial state, and $\Delta V^‡$ is assumed to be negligibly small, being actually supported by small values of $\Delta V^‡$ obtained in earlier kinetic investigation.[48] Thus, from eqs 8 and 9

$$E_a = \Delta H^‡ + RT \tag{10}$$

We estimated the activation entropy for the pinacol rearrangement in scH_2O using eqs 6 and 10. The $\Delta S^‡$ at each pressure is negative as shown in Table 3, in contrast to the positive $\Delta S^‡$ values for the acid-catalyzed rearrangement. This implies that scH_2O conditions do not thermodynamically favor

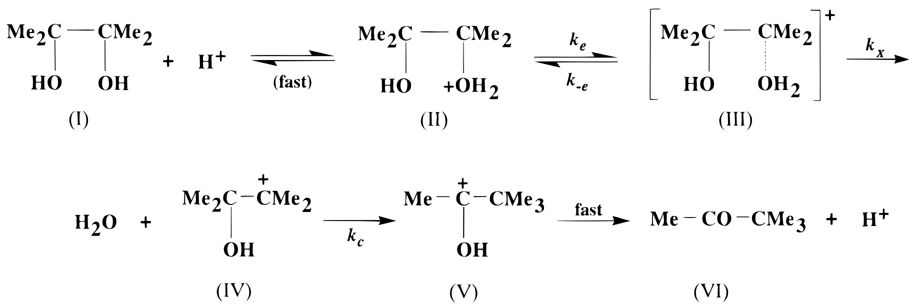

Figure 11. Possible mechanism for the usual acid-catalyzed pinacol rearrangement.

Table 4. Reaction Rate Constants, Activation Eathalpies, and Reactants-to-Activated Complex Equilibrium Constants for the Pinacol Rearrangement

P (MPa)	k_1 (s^{-1})	$\Delta H^{\ddagger}$ (kJ/mol)	$K^{\ddagger}$
22.5[a]	3.2×10^{-2}	28.0	2.11×10^{-15}
25.0[a]	3.5×10^{-2}	55.4	2.59×10^{-15}
30.0[a]	3.3×10^{-2}	80.6	3.34×10^{-15}
35.0[a]	2.5×10^{-2}	93.1	3.22×10^{-15}
0.1[b]	1.2×10^{-5}	8.5	1.98×10^{-18}
46.7[b]	1.1×10^{-5}	8.7	1.74×10^{-18}
95.5[b]	1.0×10^{-5}	8.9	1.9528×10^{-18}
144.7[b]	0.9×10^{-5}	9.1	1.33×10^{-18}

[a] In H_2O at 648 K. [b] In 47.5 wt % H_2SO_4 aq solution at 343 K.

the activated complex formation, although an increase in pressure shows slight symptom to be preferable to the complex formation because of an increase in the $\Delta S^{\ddagger}$. If the noncatalytic rearrangement using scH_2O follows the mechanism shown in Figure 11 as well, the rate-determining step may be regarded to be the pathway to the carbonium ion intermediate (**III**) from the ion species (**II**), not the dehydration of **III** because the internal degree of freedom of **II** increases upon the shift from **II** to **III**, resulting in a decrease in the $\Delta S^{\ddagger}$. At present, one cannot deny some other possibilities, and further work is needed to elucidate the mechanism for the rearrangement using scH_2O.

The scH_2O rearrangement is less favorable than the acid-catalyzed rearrangement from the standpoint of entropic cost, although the former was kinetically more advantageous than the latter as shown in Table 1. The large increment in heat content at higher temperatures under scH_2O conditions would more than compensate for the unfavorable entropy change. However, the thermal energy alone cannot explain the unique specificity of the reactivities near the critical point as indicated in Figures 6 and 7.

Hence we have further estimated activation enthalpy and apparent equilibrium constant for the activated complex formation for the pinacol rearrangement in scH_2O using eqs 4, 6, and 10. The $\Delta H^{\ddagger}$ and $K^{\ddagger}$ values at pressures of 22.5, 25, 30, and 35 MPa and at a constant temperature of 648 K are shown in Table 4. The $\Delta H^{\ddagger}$ values are positive, and the reaction in scH_2O is regarded to follow an endothermic process similarly to the usual acid-catalyzed rearrangement. However, the $\Delta H^{\ddagger}$ values are remarkably larger than those in concentrated acid solution, and the activated complex formation is thermodynamically less favorable at ambient temperature. The $K^{\ddagger}$ values are about 1000 times larger than those in acid solution, and the activated complex should be more stable under scH_2O conditions.

The relationship between the equilibrium constant and the rate constant is given as $k_1 = (k_B T/h)K^{\ddagger}$, and one can expect $(k_1/k_1')/(K^{\ddagger}/K^{\ddagger\prime}) \approx 1$ for some comparable reactions such as the pinacol rearrangements in scH_2O and acid solution; however, as shown in Table 4 $(k_1/k_1')/(K^{\ddagger}/K^{\ddagger\prime})$ reaches maximally ca. 2.5. So, we should consider other factors than the stability of the activated complex. A significant enhancement in the local proton concentration or in the local concentration of reactant molecules attributable to a compressibility near the critical point is likely to contribute peculiarly to the promotion of the rate of reaction in scH_2O. The dependence of reactivities on the structure and/or dynamics of scH_2O, especially in the near-critical region, will be clarified in more detail by various spectroscopic analyses and computer simulations.

IV. Conclusions

We have demonstrated that nucleophilic organic synthesis such as pinacol and Beckmann rearrangements can be achieved using scH_2O in the absence of acid catalysts. Our real time, in situ FTIR measurements for the pinacol rearrangement under ordinary to scH_2O conditions show a great change in the spectrum in scH_2O, in which a new strong band at 1701 cm^{-1} assigned to CO stretching of pinacolone appears and the band for OH bending of pinacol at 945 cm^{-1} completely disappears. A dramatic enhancement in the rate constant was seen for scH_2O. For example, the reaction in scH_2O at 25 MPa and 723 K is over 28000 times faster than that in 0.871 M HCl solution at 46.7 MPa and 343 K. Thus, this in situ observation first demonstrates that the pinacol rearrangement proceeds very rapidly in scH_2O even in the absence of any acid catalysts. We have further attempted a Beckmann rearrangement of cyclohexanone-oxime into ϵ-caprolactam as an another type of nucleophilic reaction without acid catalysts in superheated H_2O and scH_2O. In the IR spectrum near the critical point a new band of CO stretching assigned to ϵ -caprolactam appeared, whereas any bands for cyclohexanone was not observed. The rate constant for the formation of ϵ-caprolactam greatly increases as the temperature approaches the critical temperature of H_2O.

Both in the pinacol and Beckmann rearrangements the rate constants are in fairly agreement with the opposite dependence of the extent of hydrogen bonding derived from our Raman results in which the extent of hydrogen bonding is reducing uniquely near the critical point and H_2O monomers are further broken into protons due to large fluctuations of the structure of water. One can thus believe that a marked loss in the ability of water to accept protons evolved from H_2O molecules near the critical point leads to a significant cause for the promotion of the rearrangements.

Analysis of the reaction products in the pinacol rearrangement at the near-critical point indicated an interesting possibility that another mechanism not involving pinacolone is responsible for the production of cyclic ring systems without catalysts. In the very limited region of 648−653 K at 22.5 MPa, the route to 1,2,5-trimethyl-5-isopropenyl-1-cyclohexene was found to be opened. The complete dehydration can be achieved with relatively weaker acids, and the alternate path may be associated with tuning of the average distance between the protons generated and the substrate molecules in such a very compressible medium in which the change in the solvation energy of the substrate takes place.

The activation energies for the pinacol rearrangement using scH_2O are reduced to one-half or one-fourth of those for the usual acid-catalyzed rearrangement. Not only the high stability of the activated complex and an increase in the complex concentration but an enhancement in the local proton concentration would bring about the great increase in the rate of reaction using scH_2O near the critical point.

The processes described in this work are well suited to ecofriendly industrial application. The high rates of reaction revealed in this report are ideal for larger scale continuous flow systems. It is hoped that the high efficiency of the reactions mentioned herein will encourage the use of scH_2O-based processes in the place of strong acid-catalyzed processes.

Supporting Information Available: The details of experimental apparatus and procedures including materials, high-pressure and high-pressure IR cell, and methods are described. This material is available free of charge via the Internet at http://pubs.acs.org.

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