

Noncatalytic kinetic study on site-selective H/D exchange reaction of phenol in sub- and supercritical water

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The site-selective H/D exchange reaction of phenol in sub- and supercritical water is studied without added catalysts. In subcritical water in equilibrium with steam at 210–240 °C, the H/D exchange proceeds both at the ortho and para sites in the phenyl ring, with no exchange observed at the meta site. The pseudo-first-order rate constants are of the order of 10^{-4} s^{-1} ; 50% larger for the ortho than for the para site. In supercritical water, the exchange is observed also at the meta site with the rate constant in the range of 10^{-6} – 10^{-4} s^{-1} . As the bulk density decreases, the exchange slows down and the site selectivity toward the ortho is enhanced. The enhancement is due to the phenol–water interaction preference at the atomic resolution. The site selectivity toward the ortho is further enhanced when the reaction is carried out in benzene/water solution. Using such selectivity control and the reversible nature of the hydrothermal deuteration/protonation process, it is feasible to synthesize phenyl compounds that are deuterated at any topological combination of ortho, meta, and para sites. © 2004 American Institute of Physics. [DOI: 10.1063/1.1753551]

I. INTRODUCTION

Water at high temperature and pressure exhibits some characteristic features that are significantly different from those of ambient water. The advantages of sub- and supercritical water for the application purposes are related to such drastic changes in its chemical and physical properties as a solvent.^{1–9} Water in hydrothermal conditions is a good medium for many organic compounds. Many chemical reactions that involve organic compounds can be carried out without any organic solvents which are often hazardous to the environment. Thus sub- and supercritical water can be used as a novel and clean medium for chemical reactions of environmental and industrial importance.^{10–21}

In this study, we investigate the H/D exchange reaction on the phenyl ring of phenol in sub- and supercritical water under noncatalytic condition. The H/D exchange reaction is one of the simplest forms of chemical reaction, involving no substitution in functional groups, and is thus suited for the fundamental study of the nature of hydrothermal chemical reactions. In addition, it is of wide interest ranging from basic physical chemistry to many application purposes; deuterium-labeled compounds are frequently used for the elucidation of reaction mechanisms, including the activation processes of C–H bonds with or without catalysts. A number of investigations have in fact been conducted since the 1960s on the synthesis of labeled compounds for such purposes, as some of them were reviewed by Junk and Catallo.²²

The H/D exchange reactions under ambient conditions are typically carried out in acid-catalyzed, base-catalyzed, or metal-catalyzed conditions. The acid-catalyzed H/D exchange reactions are generally performed for the synthesis of

arylic and alkylic labeled compounds; here we focus on a former homologue. This type of reaction is typical in benzene, involving the aryllic π -complex (arenium ion) as an intermediate structure. Generally speaking, however, the reactions catalyzed by Lewis acids show little site selectivity.²² The base-catalyzed H/D exchange reactions, on the other hand, are often carried out for the synthesis of more labile carbonyl compounds. The base-catalyzed reaction is believed to proceed as the base removes a proton from the reactant. The base-catalyzed H/D exchange reaction in phenol by heat reflux has also been examined by Small and Wolfenden.²³ They have reached approximately 70% of the exchange yield after 17 d of heat reflux with 23 m (mol/kg) KOH at 100 °C, without any exclusive studies of the site selectivity. Metal-catalyzed H/D exchange reactions are another pathway for the synthesis of labeled compounds.²⁴ Among the commonly used homogeneous metallic catalysts, PtCl_4^{2-} involves a π -complex during the reaction process. However, the metal catalysts are often hazardous to the environment, and therefore alternative synthesis pathways with desired site selectivity and without harmful catalysts are keenly awaited. Thus for both the basic and application purposes, it is insightful and meaningful to achieve the site selectivity without utilizing any catalysts.

The reaction under hydrothermal conditions is a possible answer to the clean H/D conversion with desired site selectivity. The H/D exchange reaction under hydrothermal conditions have been investigated recently for various chemicals with or without catalysts,^{25–35} as reviewed in brief by Savage.¹⁶ Hot water is a convenient and effective reaction medium since it serves both as a reactive species and as a solvent by surrounding the reactant and lowering the activation energy of the transition state.²¹ The role of supercritical water can be assessed when a wide range of water density is

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systematically investigated. Above the critical temperature, the density can be continuously controlled from the gas-like isolated state to the liquid-like condensed one, and the effect of solvation can be scrutinized without changing solvent species. Here lies the reason why the density effect needs to be investigated.

Although many of the previous studies have achieved the selective exchange to a certain degree, few have stepped into the topological control of the site selectivity by changing the solvent properties. For example, Hoffman and Conradi reported a kinetic study on the H/D exchange between the hydrogens of 4-ethylphenol and the solvent D₂O at 460 °C and 250 bar (converted to H₂O mass density of 0.11 g/cm³).³³ In the case of 4-ethylphenol, the site selectivity among the hydrogens can be achieved as the reactivities at the ortho, meta, and aliphatic hydrogens differ considerably on the basis of the electronic structure. As an example of the compounds that have similarly reactive phenyl protons, the deuteration of resorcinol (1,3-benzenediol) in hydrothermal D₂O was investigated recently.³⁵ In that study, however, the site-selective deuteration of similarly reactive protons at α and α' positions were not achieved at supercritical temperatures as high as 450 °C. The topological control of the site-selective deuteration is then desirable to be established for the sites that have similar reactivities in monosubstituted benzenes such as phenol, by taking advantage of the unique nature of supercritical aqueous medium. Furthermore, the evaluation of the effect of the reactant–water interaction on the reaction kinetics is needed. For that purpose, we choose the H/D exchange reaction in phenol as a model study, and focus on how supercritical water under noncatalytic condition controls the reaction.

In fact, there have been a few studies on the H/D exchange of phenol in hot water. For example, Werstuijk and Ju have obtained some degree (~20%) of exchange at the ortho and para at 130 °C for 70 h.³⁶ More recently, Boix and Poliakov have achieved the total deuteration (90%) at 325 °C for 24 h, catalyzed by Deloxan, a polymer-supported sulphonic acid.³⁴ However, none of them have achieved the selectivity between the ortho and para. We believe that the site selectivity can be more easily achieved by the interaction control available at supercritical conditions. In addition, the noncatalytic H/D exchange reaction in hot water in the present study is found to yield only small amounts of by-products and to attain reversibility. In other words, after the deuteration process, the deuterated phenol can be reprotonated when it is treated in H₂O. Taking advantage of such a reversible nature of the reaction, we have a way to manipulate the deuteration topology. The kinetics of the H/D exchange at each site of the phenyl ring of phenol is investigated by employing a 600 MHz NMR apparatus, and the dependence on the hydrothermal states, especially on the density of supercritical water, is discussed.

II. RATE LAW AND ANALYSIS

The H/D exchange studied here occurs between the solute phenol and the solvent D₂O. D₂O is then present in excess, and it is possible to take the concentration of D₂O as a constant. In this case, the rate equation is given by

$$\frac{dC(t)}{dt} = -kC(t) + F(t), \quad (1)$$

where k is the pseudo-first-order rate constant, $C(t)$ stands for the concentration of proton at the ortho, para, or meta site of phenol, and $F(t)$ is the perturbation from the first-order kinetics due to the backward reaction. Although the pseudo-first-order rate constant k may be more customary to be taken as the product of the second-order rate constant k' and the concentration of D₂O, it will be treated as the “real” first-order rate constant hereafter. The term $F(t)$ includes the perturbation due to the backward reaction, as well as the coupled effects of the H/D exchanges at other sites in principle. Without specifying $F(t)$ explicitly, $C(t)$ is given by

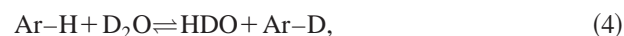
$$C(t) = C(0)e^{-kt} \left[1 + \int_0^t \frac{e^{ks}}{C(0)} F(s) ds \right]. \quad (2)$$

Since $F(t)$ mainly represents the contribution from the backward reaction and increases with t , the value of the integral in the above equation is estimated, using $C(\infty)$ as the hydrogen concentration at equilibrium, through

$$\begin{aligned} 0 \leq \int_0^t \frac{e^{ks}}{C(0)} F(s) ds &\leq (e^{kt} - 1) \frac{C(\infty)}{C(0)} \\ &\approx \left(\frac{C(0)}{C(t)} - 1 \right) \frac{C(\infty)}{C(0)}. \end{aligned} \quad (3)$$

In practice, when $C(t)$ at a particular t is large enough compared to the value at the longest reaction time during the experiment, the H/D exchange rate can be fitted to an exponential curve up to that t .

If the overall reaction rate is truly of first order, $C(t)$ should gradually and eventually reach a nondetectable level after a long enough reaction time. When the exchange reaction proceeds and the concentration of HDO reaches a certain level, however, the backward reaction can no longer be ignored. When the backward reaction is explicitly written, the chemical equation is expressed as



where “Ar-H” and “Ar-D” represent the proton and deuteron, respectively, at the ortho, para, or meta site. When $F(t)$ in Eq. (1) is explicitly spelled out, using the backward rate constant k_b , and with the assumption that the exchanges at different sites are totally uncoupled, the contribution from the backward reaction is given by

$$F(t) = k_b [\text{HDO}] C'(t), \quad (5)$$

where $C'(t)$ is the concentration of deuteron at the site of interest. As the exchange reaction proceeds, the concentration of HDO gradually increases. Therefore, after a long enough reaction time, it reaches the state where the effect of the backward reaction can no longer be ignored. If a careful investigation is conducted for both the forward and backward reactions over a long reaction time, it is possible to detect and isolate the isotope effect due to the difference of H and D. The determination of k_b is left for a subsequent study concerning the isotope effect.

III. EXPERIMENT

The ambient solution was made by dissolving phenol into D₂O at a concentration of 0.5 M (mol dm⁻³). The mole ratio of phenol to D₂O is kept at 1:112 for any phenol/D₂O samples throughout the present study. At this dilution, a phenol molecule is totally hydrated by D₂O, and the interaction between phenol molecules can be ignored. Phenol (guaranteed reagent grade for column chromatography, purity >99.5%), obtained from Nacalai, and D₂O (deuteration ratio of 99.9%), obtained from CEA, were used as received. A sealed glass or quartz tube was used as the reaction vessel. The solution was sealed into either a Pyrex NMR sample tube with 4.2 mm i.d. and 5.0 mm o.d. or a quartz capillary tube with 1.5 mm i.d. and 2.5 mm o.d. The height of the solution at ambient condition is kept at 4.0 cm whenever possible for a good spectral resolution. The total length of the capillary is varied according to the filling factor, which is the volume ratio of the sample solution to the entire vessel at room temperature. An NMR sample tube was used as the reaction vessel for the reactions at temperatures of 240 °C or lower, while a quartz capillary was used for the reactions at higher temperatures due to harsher experimental conditions. A glass tube is advantageous over a metal autoclave that is often used for studies of hydrothermal chemical reactions.^{37,38} The reasons are: (i) they can be easily processed and the reactions are visible from the outside, (ii) they can be used as containers for the gas- and liquid-phase NMR spectroscopic measurements without opening and transferring the samples, and (iii) the metal surface of an autoclave can often act as a reaction catalyst. It is essential to use materials without any catalytic functions, such as quartz, for the study of the solution reaction mechanism. Before the sample tube was sealed, the air inside the tube was substituted with argon in order to reduce a possible effect of oxygen to promote or modify the reaction.

The reaction was carried out within the sealed sample tube placed in an electric furnace (Denken KDF S-70). The furnace was initially preheated and kept at the reaction temperature before the sample insertion. The temperature in the furnace was controlled within 1 °C. After a fixed reaction time, the sample tube was removed from the furnace and the reaction was immediately quenched in a cold-water bath. After the quenching, a ¹H-NMR measurement was conducted at room temperature for the product identification and yield analysis. The NMR apparatuses (JEOL JNM-ECA600 and ECA400N), equipped with a superconducting magnet (14.09 and 9.39 T for 600 and 400 MHz, respectively), were used. The high resolution of the 600 MHz spectrometer was necessary for separating the ¹H peaks for the ortho and para sites of phenol. The spectra of 0.5 M phenol/D₂O solution, taken with the 600 MHz spectrometer, are shown at the bottom of Fig. 1(a). The peaks identified as the ortho and para sites are clearly separated, which enables the precise evaluation of the intensity for each peak. It is shown by the NMR information that there is no side reactions such as the phenyl ring disintegration.

Although D₂O was used as the solvent, the water density referred to in the present paper is always converted to the mass density of H₂O for convenience. The reactions were

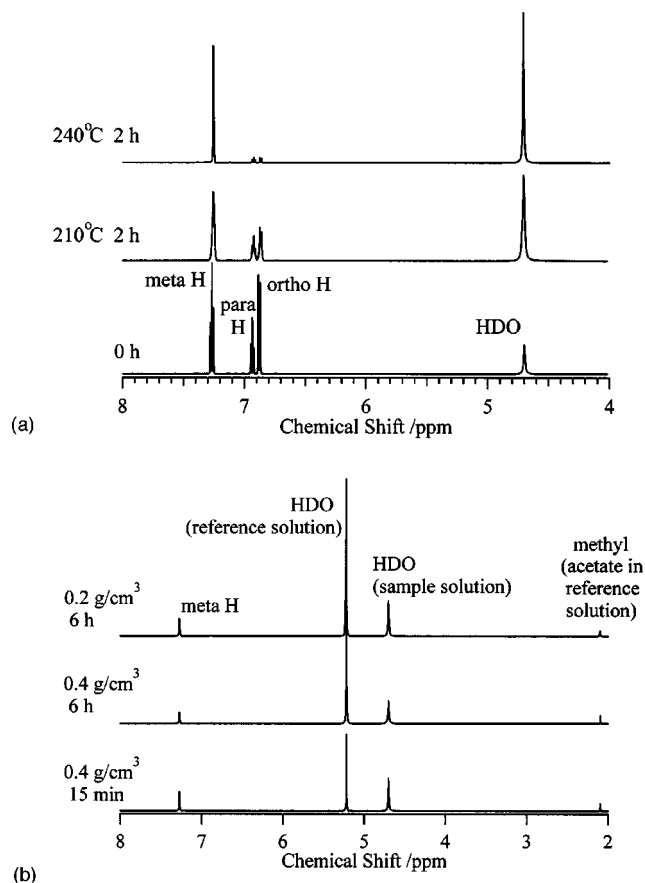


FIG. 1. ¹H-NMR spectra of phenol in D₂O. (a) Reactions are carried out at 210 (top) and at 240 °C (second from top) for 2 h. The spectra at the bottom are taken before the reaction proceeds (0 h). The intensity for the meta at 7.26 ppm is taken as the reference. (b) Reactions are carried out at 400 °C for 2 h, except for the spectra at bottom (15 min reaction). The water densities are 0.2 (top) and 0.4 (second from top and bottom) g/cm³. The intensity for the methyl group of sodium acetate at 2.09 ppm is taken as the external reference. The peaks of HDO are separated by adding 0.2 M of DCl/D₂O solution into the NMR sample tubes.

carried out on the liquid branch of the saturation curve at subcritical temperatures of 210, 220, 230, 240, 300, 350, and 370 °C. The corresponding water densities at the lower temperatures between 210 and 240 °C lie between 0.85 and 0.81 g/cm³. The water densities at the higher temperatures of 300, 350, and 370 °C are diminished, respectively, to 0.71, 0.57, and 0.45 g/cm³. The initial filling factor was kept at 40% for the samples reacted at any subcritical temperatures. On the other hand, the reactions at supercritical temperatures of 400 and 430 °C were carried out by varying the water densities over a wide range from 0.10 to 0.60 g/cm³ with an interval of 0.10 g/cm³. In addition, a low density of 0.07 g/cm³ was also studied at 430 °C, while the reactions at 460 °C were conducted only at 0.40 g/cm³. By changing the amount of the sample solution in the vessel when preparing the sample, the water density at supercritical states can be easily controlled. Actually, the water density in the supercritical condition is equal to the filling factor when converted to the corresponding mass density of H₂O and expressed in the unit of g/cm³.

Since an NMR sample tube was used as the reaction vessel for the reaction at temperatures between 210 and 240 °C, the ¹H spectrum was measured by placing the

sample tube directly into the NMR apparatus. No external reference was needed for the reactions at such temperatures because the meta peak intensity, virtually unchanged throughout the reaction, served as the internal reference. For the reaction at higher temperatures, the quartz capillary was dipped into an NMR sample tube with 4.2 mm i.d. and 5.0 mm o.d., filled with 0.2 M sodium acetate/D₂O solution for the external reference. Sodium acetate (guaranteed reagent) was obtained from Nacalai. The methyl peak of sodium acetate was used as an external reference. In order to separate the peaks of HDO inside and outside of the capillary, the external sodium acetate/D₂O solution was acidified with deuterated hydrochloride, making the $pH \sim 0$. DCI (deuteration ratio of 99.5%, 20% w/w in D₂O) was obtained from Cambridge Isotope Laboratories. With the pH of ~ 0 , the outside HDO peak shifts downfield by approximately 0.5 ppm. For the samples reacted at 300 °C or higher, the solution in the reaction vessel became slightly cloudy at the earliest stage of the heating process, probably due to the slight polymerization of phenol. To avoid the errors due to the polymerization, the sample was initially heated for 1 h at each intended temperature between 300 and 370 °C. Taking the pretreated sample as the starting reference, the reaction was further carried out to a desired reaction time. At the supercritical temperatures, the experimental procedure was the same as the one at the subcritical states using the quartz capillary, except (i) that smaller capillaries (inner:outer diameters of 0.7:1.5 and 0.3:0.7 mm) were also used in addition to the larger ones, and (ii) that the pretreatment of the sample was conveyed at 400 °C for any samples and was shortened to 15 min.

For the comprehensive understanding of the effect of water on the H/D exchange reaction, it is desirable to study a wide range of water density. Practically, however, it is nearly prohibitive to prepare a phenol/water solution with the filling factor corresponding to a very low water density. Instead, the reaction was also carried out in a benzene-*d*₆/D₂O mixture. Benzene-*d*₆ (deuteration ratio of 99.6%, containing 0.01% of H₂O) was used as received from Euriso-top. For the benzene/D₂O mixture, the water contents of 1.0×10^{-2} and 1.6×10^{-2} g/cm² in terms of the mass density converted to that of H₂O were examined. In all cases, the initial concentration of phenol was set to 28.5 mM, and the filling factor of the mixed solvent was set to 30% at room temperature. The reaction was carried out at 430 °C. A quartz capillary with 2.5 or 4.0 mm i.d. and length of 20 cm was used in this experiment. The organic phase produced was measured by ¹H-NMR.

Although the kinetics for the backward reaction was not thoroughly investigated in the present study, it is commendable to keep the initial concentration of HDO as low as possible in order to avoid the perturbation by the backward reaction which obscures the accurate measurements of the forward kinetics. Throughout this study, therefore, the initial HDO concentration was kept between 0.68 and 0.74 M and carefully monitored when preparing the sample.

IV. RESULTS AND DISCUSSION

A. H/D exchange rate analysis

1. Subcritical temperatures between 210 and 350 °C

We first illustrate the H/D exchange rate at the ortho, para, and meta sites through the ¹H-NMR spectra for the samples that were reacted at subcritical temperatures. Some representative ¹H-NMR spectra at 210 and 240 °C are shown in Fig. 1(a), along with the one before the reaction was initiated (0 h). In the subcritical temperature range between 210 and 240 °C, both the peaks representing the protons at the ortho and para sites diminish gradually along the reaction time relative to the peak intensity at 0 h, as the protons are replaced by deuterons. For the nonreactive meta site, in contrast, the peak changes from a triplet to a singlet along the reaction time due to the loss of the spin couplings with the protons at the ortho and para sites. The low reactivity of the meta site is further confirmed by the experiments conducted at higher temperatures. At the temperature as high as 300 °C, the proton peak intensity for the meta remains virtually constant even after a long reaction time of 17 d.³⁹ When the reaction temperature is raised to 350 °C, a slow substitution is observed at the meta site, requiring roughly 6 d for the 50% conversion. It is to be noted that the peak intensities for the ortho and para sites remain constant approximately at 5% of the original (0 h) intensities after a long reaction at both 300 and 350 °C. This suggests that it has reached the equilibrium for the H/D exchange; cf. Eq. (5). At this stage, the concentration of HDO is over 2 M.

The change in the proton concentration at both the ortho and para sites at 210 °C is plotted against the reaction time in Fig. 2(a). The proton concentrations decrease exponentially along the reaction time until 4 h. As the protons at both sites are replaced with deuterons, in fact, the increase in the HDO concentration is observed. The total amount of hydrogens, estimated by the sum of the peak intensities for the meta, ortho, para, and HDO, is kept constant throughout the reaction time. This shows the absence of the side reactions. In order to follow the criteria for the first-order assumption that is described in Sec. II, the data beyond the point where $C(t)$ reduces below $5C(t_{\max})$ were disregarded, where t_{\max} is the longest reaction time examined, for the estimation of the rate constant k . For instance, t_{\max} is 75 h at temperatures of 210 and 220 °C, and 48 h at temperatures of 230 and 240 °C. Namely, the kinetic data up to 4, 2, 1.5, and 1 h of the reaction time were used accordingly at 210, 220, 230, and 240 °C for both the ortho and para sites. The logarithmic plot of the proton concentration ratio to the initial one against the reaction time t is linear in all cases when $C(t)$ is at least five times as large as $C(t_{\max})$. When the plot for the reaction is extended to longer reaction times, on the contrary, the data points at large t lie above the fitting curve. The deviation from the fitting curve indicates the influence of the backward reaction.

Table I summarizes the first-order rate constant k for the H/D exchange reaction at each site of the benzene ring under various hydrothermal conditions. The rate itself is always larger for the ortho than for the para site in this temperature range. The difference in the reactivity at each site will be

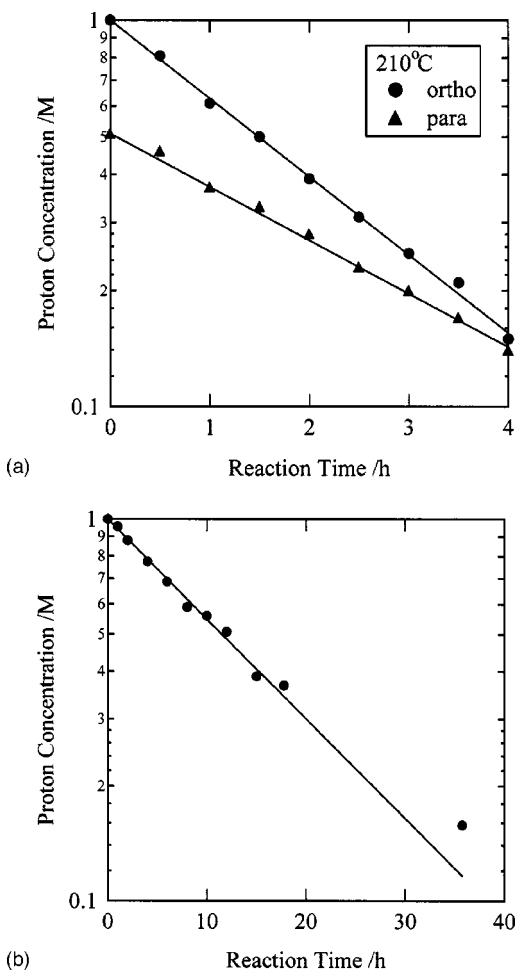


FIG. 2. The time evolutions of the proton concentration of (a) the ortho and para at 210 °C and (b) the meta at 400 °C and 0.4 g/cm³. At 210 °C, the concentrations for the ortho and para were logarithmically fitted to straight lines up to the reaction time of 4 h. At 400 °C, the logarithm of the concentration was fitted to a straight line up to 18 h.

discussed in Sec. IV B. The temperature dependence of the rate constant is larger for the para. With the calculated rate constants, the activation free energy ΔG^\ddagger of the H/D exchange reaction can be estimated from the standard relationship in the transition state theory, given by

$$k = \frac{k_B T}{h} \exp(-\Delta G^\ddagger/RT), \quad (6)$$

where k_B , T , h , and R are the Boltzmann constant, reaction temperature, Planck's constant, and the gas constant, respectively. The obtained ΔG^\ddagger for the ortho and para sites at 210 °C are, respectively, 156 and 158 kJ/mol. ΔG^\ddagger for both sites increase along the temperature.

Unlike ΔG^\ddagger , the activation enthalpy ΔH^\ddagger is a property that may be divergent at the critical point, and thus the Arrhenius analysis requires careful attention as the reaction state approaches the critical point. Such attention, however, need not be paid at temperatures between 210 and 240 °C, and the Arrhenius analyses are also conducted. Figure 3 shows the Arrhenius plots to estimate the "apparent" activation enthalpy. Straight lines are drawn for both the ortho and para at temperatures between 210 and 240 °C. The derived

TABLE I. Pseudo-first-order rate constants for deuteration of phenol in hydrothermal conditions. -: The reaction proceeds immeasurably fast within the time intervals of the present work. ~0: The reaction does not proceed within the time scales of the present work.

Temperature/°C	Water density/g cm ⁻³	Rate constant/10 ⁻⁵ s ⁻¹		
		ortho	para	meta
210	0.85	13	8.1	~0
220	0.84	19	13	~0
230	0.83	33	23	~0
240	0.81	51	36	~0
300	0.71	-	-	~0
350	0.57	-	-	0.16
370	0.45	-	-	0.46
400	0.10	-	27	0.087
	0.20	-	-	0.43
	0.30	-	-	0.95
	0.40	-	-	1.7
	0.50	-	-	2.9
	0.60	-	-	5.4
430	0.07	-	15	0.44
	0.10	-	-	0.60
	0.20	-	-	1.6
	0.25	-	-	3.4
	0.30	-	-	5.8
	0.40	-	-	8.5
	0.50	-	-	12
	0.60	-	-	25
460	0.40	-	-	17
430	1.0 × 10 ^{-2a}	10	~0	~0
	1.6 × 10 ^{-2a}	36	0.46	~0

^aExperiments are conducted in a benzene/water mixture. At subcritical temperatures, the measurements are on the liquid branch of the liquid-vapor coexistence curve.

activation enthalpies are 92 and 103 kJ/mol for the ortho and para sites, respectively. The estimated errors are less than 10 kJ/mol for both cases. It should be emphasized that the activation enthalpies derived from Fig. 3 are along the coexistence curve and that both the pressure and the density are

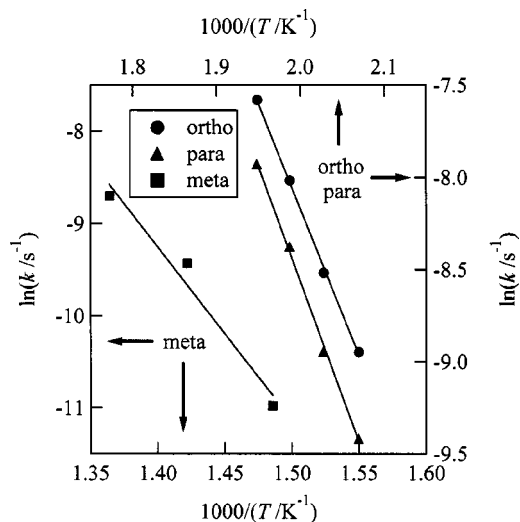


FIG. 3. Arrhenius plot for the H/D exchange reaction rate at each site of phenol. For the ortho and para, the data were taken at temperatures between 210 and 240 °C, while temperatures were between 350 and 460 °C for the meta. k and T stand for the pseudo-first-rate constant and the reaction temperature, respectively.

not constant. The isobaric activation enthalpy $(\Delta H^\ddagger)_p$ can be estimated from a thermodynamic relationship given by

$$\begin{aligned} (\Delta H^\ddagger)_{\text{coex}} &= \left(\frac{\partial(\Delta G^\ddagger/T)}{\partial(1/T)} \right)_{\text{coex}} \\ &= (\Delta H^\ddagger)_p - (\rho\kappa T) \left(\frac{\partial\Delta G^\ddagger}{\partial\rho} \right)_T \left(\frac{\partial P}{\partial T} \right)_{\text{coex}}, \quad (7) \end{aligned}$$

where the subscript ‘‘coex’’ represents ‘‘along the coexistence curve,’’ and ρ and κ stand for the water density and the isothermal compressibility, respectively. $(\partial\Delta G^\ddagger/\partial\rho)_T$ can be roughly provided from the density-dependent data obtained at supercritical states. In this case, however, the value of $(\partial\Delta G^\ddagger/\partial\rho)_T$ is not known either, as it is unavailable for the ortho and para at supercritical temperatures in the present work. An estimate can still be drawn by adopting the value for the meta and from the relationship in Eq. (6). With such rough procedures, the deviation of $(\Delta H^\ddagger)_{\text{coex}}$ from $(\Delta H^\ddagger)_p$ is ~ 10 kJ/mol, that is nearly the same as the experimental errors. Thus the activation enthalpy obtained along the coexistence curve can be regarded as the isobaric one in this temperature range.

2. Supercritical temperatures between 400 and 460 °C

A typical spectrum at the water density of 0.4 g/cm³, after 15 min of reaction at 400 °C, is shown in Fig. 1(b), in comparison with the spectrum after 6 h. After 15 min, the meta intensity decreases over 5%. Nearly all the hydrogens are replaced by deuterons at the ortho or para sites. At 400 °C, unlike the reactions at the subcritical temperatures mentioned above, the peak intensity for the meta gradually decreases along the reaction time; nearly 50% of hydrogens at the meta site are substituted by deuterons in 12.5 h of reaction. At 430 °C, 50% conversion occurs in less than 2.5 h.

The change in the proton concentration at 400 °C and 0.4 g/cm³ is plotted against the reaction time in Fig. 2(b). The proton concentration $C(t)$ at the meta site decreases exponentially along the reaction time until about 18 h. Beyond 18 h, however, the deviation from the logarithmic curve is observed. This suggests the effect of the backward reaction, as expected. The concentration of HDO at 18 h reaches nearly 3 M, roughly four times as much as the initial concentration. A non-negligible amount of HDO is present, so that the effect of the backward reaction can no longer be ignored. The derived first-order rate constant for the meta site is shown in Table I. Note that the exchange reactions for both the ortho and para sites, with the reaction interval of 15 min, proceed immeasurably fast.

From Eq. (6), the activation free energy for the H/D exchange at the meta site is estimated. At 400 °C and 0.4 g/cm³, the activation free energy ΔG^\ddagger becomes 231 kJ/mol. The plot of ΔG^\ddagger against the density gives a smooth downwardly concave curve with no apparent ‘‘anomaly,’’ as it is often referred to in many thermodynamic properties in the discussion of critical phenomena. It decreases along the density, and thus the activation volume also becomes negative despite the bond elongation in the transition state.⁴⁰ Re-

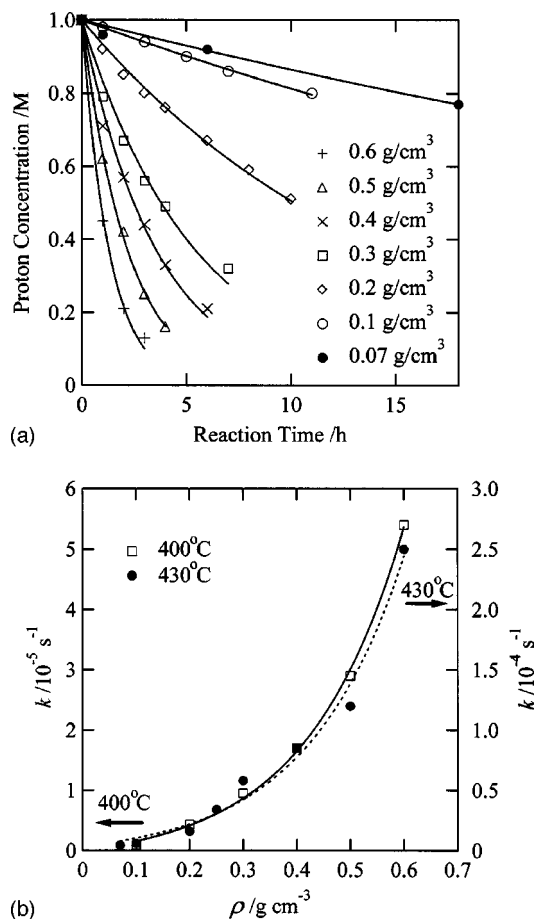


FIG. 4. (a) The time dependence of the meta proton concentration at densities between 0.07 and 0.60 g/cm³. The reactions were carried out at a supercritical temperature of 430 °C. (b) Density dependence of the rate constant for the H/D exchange reaction of phenol at the meta site. k and ρ in the figure stand for the pseudo-first-rate constant and the water density, respectively.

garding the temperature effect on ΔG^\ddagger at 0.4 g/cm³, it remains at similar values of 232 and 238 kJ/mol for the reactions at 430 and 460 °C, respectively, as shown in Fig. 3. Thus the temperature effect on the rate constant can be considered as the $k_B T$ effect in the range between 400 and 460 °C at the fixed density of 0.4 g/cm³.

Although the H/D exchange for the ortho and para sites at supercritical temperatures occurred immeasurably fast with the measurement interval of 15 min, they can be crudely estimated from the observed half-life of less than 10 s for both sites at 400 °C. The maximum possible values of ΔG^\ddagger for both the ortho and para at 400 °C are then found to be ~ 180 kJ/mol. This is significantly smaller than the one for the meta at any densities studied here, as expected.

In order to clarify the effect of hydration at supercritical states, the density dependence of the H/D exchange rate is investigated, ranging from 0.07 to 0.60 g/cm³, while the phenol/water ratio is kept constant at 1:112. The NMR spectrum after the 2 h reaction at 400 °C with the water density of 0.2 g/cm³ is shown in Fig. 1(b), along with the spectrum at 6 h with 400 °C and 0.4 g/cm³. Roughly a three fold increase in the conversion rate is seen when the water density is doubled. Figure 4(a) shows the degree of deuteration of the

meta site along the reaction time at 430 °C. The reaction rate gradually increases with the water density. The density dependence of the rate constant is shown in Fig. 4(b) at temperatures of 400 and 430 °C; the density dependencies are similar to each other. When the water density is increased from 0.1 to 0.6 g/cm³ (six fold increase), the rate constant increases roughly by 60-fold at both temperatures. The density effect is large and nonlinear, indicating the importance of the hydration. Such a nonlinear dependence of the reactivity on the water density originates from the microscopic hydration structure of the transition state. Because the C–H bond is elongated at the transition state, the charge separation of the bond also becomes larger than that of the original reactant. The hydration then plays a crucial role and stabilizes the transition state.⁴¹ Thus, the higher the water density, the faster the reaction.

B. Site selectivity

1. Dependence on the thermodynamic state

In Table I, we see that the H/D exchange reaction proceeds more selectively towards the ortho than the para without added catalysts. At subcritical temperatures between 210 and 240 °C, the difference in the rate constant between the ortho and para sites is roughly given by

$$k_{\text{ortho}} \approx 1.5k_{\text{para}}, \quad (8)$$

and no substitution is observed at the meta site. From these observations, the reactivity in the subcritical temperatures can be aligned in the decreasing order,

$$\text{ortho} > \text{para} \gg \text{meta}. \quad (9)$$

At supercritical temperatures, the effect of the phenol–water interaction at the atomic level could appear more evidently than at subcritical temperatures because the water density is drastically varied and the attractive interactions play a key role in controlling the hydration at low to medium densities. As mentioned earlier, one of the unique features of supercritical water is that its density can be easily and continuously changed from a liquid-like condensed state to a gas-like isolated one. Thus the environment surrounding phenol changes significantly by controlling the water density.

At medium- to high-water densities, the exchange reaction proceeds very quickly both at the ortho and para sites, as found in the previous section. On the other hand, when the water density is lowered to 0.10 g/cm³ at 400 °C, the rate constant for the para reduces to a measurable value within our time scale that is comparable to the rate constant for the para at 230 °C (0.83 g/cm³). The rate constant for the ortho, although the accurate measurements were difficult, are estimated to be roughly ten times as large as the one for the para at 400 °C with the density of 0.10 g/cm³, given the fact that over 90% of the protons at the ortho are substituted in less than 15 min. At higher densities, the site selectivity toward the ortho should be tuned to lie between the ratio found at subcritical temperatures and the one found at 0.10 g/cm³.

Compared to the ratio of $k_{\text{ortho}} \approx 1.5k_{\text{para}}$ at subcritical temperatures, the site selectivity toward the ortho is further enhanced at supercritical states studied here. When the water density is low, the water molecules are considered to be more

localized around the hydrophilic hydroxyl group than around the hydrophobic phenyl ring. It is therefore natural to expect in the initial stage of the reaction that the ortho site, which is closer to the hydroxyl group, is relatively more hydrated than the para. As a result of the topological aspect of the hydration, the ortho protons become more reactive than those at the para site. When the water density is higher, water surrounding phenol is abundant and relatively delocalized or random throughout the phenyl ring of phenol. Therefore the site selectivity is no longer significant by the phenol–water interaction at the initial state of the reaction.

2. Selectivity enhancement with hydrophobic–hydrophilic interaction control

In order to validate the preferential hydration effect in which the localization of D₂O around the reaction site enhances the site selectivity due to the phenol–water interaction, further investigations are performed to extend the accessible low density region. For that purpose, phenol is dissolved into a hydrophobic solvent, benzene, with a small amount of D₂O. Two samples are prepared at the water densities of 1.0×10^{-2} and 1.6×10^{-2} g/cm³, and the exchange reaction is examined at 430 °C. By dissolving phenol into a benzene/water mixture, we can accomplish a very low water density region, which is difficult to achieve with pure water in our method. This enables us to investigate the exchange kinetics at the ortho and para sites at supercritical states. Both water densities studied here are considerably lower than the phenol/pure D₂O samples of the lowest density (0.07 g/cm³) at the same temperature.

From the observations of the reactions in pure water, one would expect that the exchange rate decreases considerably in the benzene/water mixture due to weak hydration effect. In fact, the H/D exchange at the ortho site, which occurred immeasurably fast for our observation interval of 15 min in pure supercritical water, was observable at such low water densities, as shown at the bottom of Table I. In contrast, almost no H/D exchange was observed at the para and meta sites after 1.5 h of reaction at 430 °C for both benzene/water mixed solvents. The reaction was further continued as long as 48 h, when 55% of the proton at the para site was finally substituted at the higher water content of 1.6×10^{-2} g/cm³. No exchange was observed at the meta site even after 48 h of reaction. The ratio of the obtained reaction rate for the ortho to the para is roughly $k_{\text{ortho}} \approx 75k_{\text{para}}$. Thus the site selectivity of the H/D exchange reaction is markedly enhanced in the benzene mixture than in pure supercritical water by a factor of 5 to 15. In practice, the nearly perfect site selectivity is accomplished in the supercritical water–benzene mixture.

The ratio of the reaction rate at the ortho to the para site, $R = k_{\text{ortho}}/k_{\text{para}}$, is

$$R_{\text{sub}} < R_{\text{scw/low } \rho} < R_{\text{benz}}, \quad (10)$$

where the subscripts sub, scw/low ρ , and benz denote the conditions at subcritical, supercritical in the low-density region, and in the benzene/water mixture, respectively. At subcritical temperatures, the entire phenol molecule is surrounded by water molecules as the water density is high. When the bulk water density is low, as is the case with pure

D₂O at supercritical temperatures studied here, the water molecules are more localized near the hydroxyl group of phenol. As a result, the site selectivity is more enhanced toward the ortho site. The site-selective localization of water can be amplified by reducing the water density. In the benzene–water solution, the bulk water concentration is even lower than the lowest density studied with pure D₂O, and thus fewer water molecules are statistically available for the meta and para sites. Thus the H/D exchange between the phenyl proton of phenol and deuterium of D₂O becomes more site-selective toward the ortho site.

Previous studies on the H/D exchange of phenol, with or without any types of catalysts, have not achieved the site selectivity to the degree that is comparable to the present study.^{34,36} Regarding the electrophilic substitution of mono-substituted benzenes, the compounds that bear an ortho-para-directing group such as toluene or phenol generally show the reactivity in the order of decreasing trend, para > ortho >> meta at typical reaction conditions.^{42,43} This is not in agreement with our results, except that the meta is far less reactive in both cases. If the steric hindrance can be ignored, as is the case for the present study, the discrepancy may be due to the enhanced localization of water around the ortho site in the hydrothermal conditions. A few studies have been conducted on the H/D exchange reactions of related compounds at hydrothermal conditions. For example, Yao and Evilia have investigated several substituted benzenes under hydrothermal conditions.²⁸ Although they have obtained a highly efficient substitution of several compounds, no effective methods for the site selectivity were employed. For other related compounds, Junk and Catalo have also investigated arenes and heteroarenes under metal- or base-catalyzed supercritical conditions,³⁰ although the site selectivity was not attained in their approach either.

3. Site-specific control of deuteration

As discussed earlier, hydrothermal solution provides a novel reaction medium for the deuteration of phenol. In particular, even the meta site, where otherwise it is difficult to proceed with the H/D exchange, can be effectively deuterated in supercritical water at above 400 °C. If the site selectivity is not concerned, deuteration at both the ortho and para sites can be achieved under either typical acidic or basic conditions.^{22–24} The site selectivity at the ortho or para is, however, low under such conditions. Using a supercritical organic–water mixture as a solvent, as shown in this study, only the ortho site can be selectively deuterated. This is an example of the reaction control which utilizes an advantageous feature of supercritical water that the mixing with organic solvents can be precisely tuned. Taking advantage of such selectivity control, as well as the reversible nature of the hydrothermal deuteration/protonation process, the synthesis of phenol that is deuterated at any combination of the phenyl hydrogens is now possible.

Phenol that is deuterated at both the ortho and para can be synthesized by the reaction in D₂O at a subcritical temperature of 300 °C. When phenol deuterated at all the ortho, meta, and para sites is needed, the reaction temperature can be raised to 400 °C, where the deuteration even at the meta site readily proceeds. If the distinction between the ortho and para is required, the reaction can be carried out in benzene/D₂O mixture at supercritical temperature. Using such methodology, ortho-only-deuterated phenol can be selectively obtained.

Phenols with other combinations of deuterated sites require more than one reaction step by taking advantage of the reversibility of the H/D exchange reaction under hydrothermal conditions. For example, phenol that is deuterated only at the meta site is attained by treating the totally deuterated

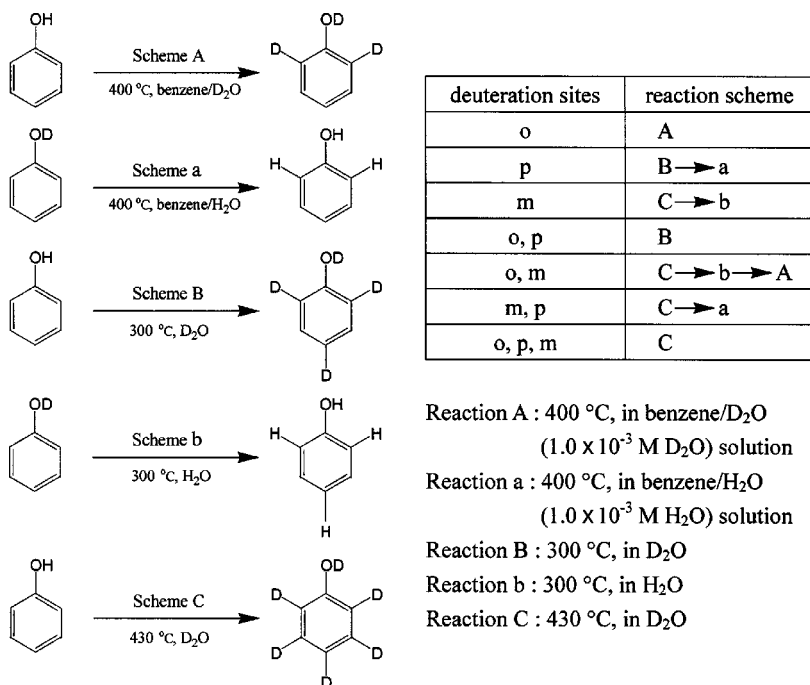


FIG. 5. The reaction scheme for the site-selective deuteration of phenol. Note that only the hydrogens (protons or deuterons) which are substituted through the scheme are exclusively drawn in the figure. The lowercase-lettered reaction is the backward reaction of the uppercased one (cf. reaction a vs reaction A), and only differs in the solvent water (cf. H₂O vs D₂O).

phenol with H₂O at subcritical temperatures. Highly pure para-deuterated phenol can be isolated with a supercritical benzene/H₂O mixture by protonating the ortho site of phenol that is initially deuterated at both the ortho and para sites. Likewise, deuteration at both the para and meta sites can be achieved by treating totally deuterated phenol with a supercritical benzene/H₂O mixture. The synthesis of phenol that is deuterated at the ortho and meta sites can be achieved by treating meta-deuterated phenol with a supercritical benzene/D₂O mixture. The synthesis scheme for the site-specific deuteration of phenol is summarized in Fig. 5. Note that in every scheme, the hydrogen of the hydroxyl group coincides with that of the solvent at any reaction condition.

V. CONCLUDING REMARKS

The site-selective H/D exchange reaction of phenol in sub- and supercritical water is investigated without any catalysts as a model study of site-selective reactions in hydrothermal conditions. In the subcritical temperatures ranging from 210 to 240 °C, the order of the reactivity is ortho > para without any exchanges observed at the meta site. The reaction rate is roughly 50% as large for the ortho as for the para site. In supercritical water at low densities, the ratio of the rate constant ($k_{\text{ortho}}/k_{\text{para}}$) increases to roughly 10, while it becomes even much larger in a supercritical benzene/water mixture. In higher solvent density regions such as the subcritical regime on the liquid–vapor coexistence curve, a large amount of water molecules exist and surround phenol. As a result, the difference in the reactivities between the ortho and para sites is not significant. In supercritical water with low bulk densities, on the other hand, water is more localized near the hydroxyl group of phenol. Thus, the reactivity at the ortho, being closer to the hydroxyl group, is more enhanced than at the para site. At the meta site, the exchange rate increases as the bulk density of supercritical water increases, and the dependence is stronger than linear. When the reaction rate is plotted against the bulk density, it is downwardly concave, suggesting that the chemical species at the transition state is more stabilized by the hydration due to the increased dipole moment. In conclusion, the site-selective deuteration is now possible by adjusting the reaction conditions; i.e., temperature, density, reaction time, and/or solvent.

In order to assess the origin of the site selectivity, *ab initio* quantum calculations are conducted with the GAUSSIAN 98 program.⁴⁴ The highest occupied molecular orbital (HOMO) electron density computed at HF/6-31+G(*d,p*) level is the highest at the para site while it is the lowest at the meta. Although the obtained values of the HOMO electron densities depend upon the computational scheme, the para clearly has a higher HOMO electron density than the ortho; this does not coincide with the order of the observed rate constant. Thus the specific phenol–water interaction affects the reactivity, beyond the treatment of phenol as an isolated quantum-chemical object.⁴⁵ The phenol–water interaction plays a key role in the reaction selectivity and overturns the HOMO order of the reactivity toward the ortho.

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- ¹F. N. Spiess, K. C. Macdonald, T. Atwater *et al.*, *Science* **207**, 1421 (1980).
- ²R. W. Shaw, T. B. Brill, A. A. Clifford, C. A. Eckert, and E. U. Franck, *Chem. Eng. News* **69**(51), 26 (1991).
- ³J. S. Seewald, *Nature (London)* **370**, 285 (1994).
- ⁴D. M. Pfund, J. G. Darab, J. L. Fulton, and Y. Ma, *J. Phys. Chem.* **98**, 13102 (1994).
- ⁵P. B. Balbuena, K. P. Johnston, and P. J. Rossky, *J. Phys. Chem.* **100**, 2706 (1996).
- ⁶M. Nakahara, T. Yamaguchi, and H. Ohtaki, *Recent Res. Dev. Phys. Chem.* **1**, 17 (1997).
- ⁷O. Kajimoto, *Chem. Rev. (Washington, D.C.)* **99**, 355 (1999).
- ⁸N. Matubayasi and M. Nakahara, *J. Chem. Phys.* **112**, 8089 (2000).
- ⁹N. Matubayasi and M. Nakahara, *J. Chem. Phys.* **117**, 3605 (2002); **118**, 2446 (2003).
- ¹⁰N. Yamasaki, T. Yasui, and K. Masuoka, *Environ. Sci. Technol.* **14**, 550 (1980).
- ¹¹M. Siskin and A. R. Katrizky, *Science* **254**, 231 (1991).
- ¹²P. E. Savage, S. Gopalan, T. I. Mizan, C. J. Martino, and E. E. Brock, *AIChE J.* **41**, 1723 (1995).
- ¹³M. Nakahara, T. Tanno, C. Wakai, E. Fujita, and H. Enomoto, *Chem. Lett.* **2**, 163 (1997).
- ¹⁴P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice* (Oxford University Press, New York, 1998).
- ¹⁵Y. Tsujino, C. Wakai, N. Matubayasi, and M. Nakahara, *Chem. Lett.* **28**, 287 (1999).
- ¹⁶P. E. Savage, *Chem. Rev. (Washington, D.C.)* **99**, 603 (1999).
- ¹⁷Y. Yamasaki, H. Enomoto, N. Yamasaki, and M. Nakahara, *Bull. Chem. Soc. Jpn.* **73**, 2687 (2000).
- ¹⁸P. T. Anastas, L. G. Heine, and T. C. Williamson, *Green Chemical Syntheses and Processes* (American Chemical Society, Washington, D.C., 2000).
- ¹⁹N. Akiya and P. E. Savage, *Chem. Rev. (Washington, D.C.)* **102**, 2725 (2002).
- ²⁰Y. Nagai, C. Wakai, N. Matubayasi, and M. Nakahara, *Chem. Lett.* **32**, 310 (2003).
- ²¹Y. Nagai, N. Matubayasi, and M. Nakahara, *Bull. Chem. Soc. Jpn.* **77**, 691 (2004).
- ²²T. Junk and W. J. Catallo, *Chem. Soc. Rev.* **26**, 401 (1997).
- ²³P. A. Small and J. H. Wolfenden, *J. Chem. Soc.* **2**, 1811 (1936).
- ²⁴C. Lutterloh, J. Biener, A. Schenk, and J. Küppers, *J. Chem. Phys.* **104**, 2392 (1996).
- ²⁵N. H. Werstiuk and G. Timmins, *Can. J. Chem.* **67**, 1744 (1989).
- ²⁶B. Kuhlmann, E. M. Arnett, and M. Siskin, *J. Org. Chem.* **59**, 3098 (1994).
- ²⁷B. Kuhlmann, E. M. Arnett, and M. Siskin, *J. Org. Chem.* **59**, 5377 (1994).
- ²⁸J. Yao and R. F. Evilia, *J. Am. Chem. Soc.* **116**, 11229 (1994).
- ²⁹Y. Yang and R. F. Evilia, *J. Supercrit. Fluids* **15**, 165 (1999).
- ³⁰T. Junk and W. J. Catallo, *Tetrahedron Lett.* **37**, 3445 (1996).
- ³¹T. Junk, W. J. Catallo, and L. D. Civils, *J. Labelled Compd. Radiopharm.* **39**, 625 (1997).
- ³²M. Nakahara, H. Enomoto, A. Kishita, K. Tsuda, T. Tanno, and E. Fujita, *US Patent No.* 5,733,984 (1998).
- ³³M. M. Hoffmann and M. S. Conradi, *J. Supercrit. Fluids* **14**, 31 (1998).
- ³⁴C. Boix and M. Poliakoff, *Tetrahedron Lett.* **40**, 4433 (1999).
- ³⁵S. Bai, B. J. Palmer, and C. R. Yonker, *J. Phys. Chem. A* **104**, 53 (2000).
- ³⁶N. H. Werstiuk and C. Ju, *Can. J. Chem.* **67**, 812 (1989).

- ³⁷J. L. Bell, D. A. Palmer, H. L. Barnes, and S. E. Drummond, *Geochim. Cosmochim. Acta* **58**, 4155 (1994).
- ³⁸T. Arita, K. Nakahara, K. Nagami, and O. Kajimoto, *Tetrahedron Lett.* **44**, 1083 (2003).
- ³⁹At 300 °C, the meta peak diminishes by approximately 10% in 1 h of reaction, due to the polymerization of phenol. After 1 h, the intensity of the meta peak remains virtually constant at least as long as 312 h (13 d) of reaction.
- ⁴⁰For comparison, the isochoric activation enthalpy $(\Delta H^\ddagger)_v$ for the meta site is estimated from the data at supercritical temperatures between 400 and 460 °C at 0.4 g/cm³, according to the Arrhenius plot shown in Fig. 3. The obtained $(\Delta H^\ddagger)_v$ is 160 ± 15 kJ/mol. When it is converted to the isobaric value, following a similar scheme adopted for the ortho and para at temperatures between 210 and 240 °C described in Eq. (7), $(\Delta H^\ddagger)_p$ becomes ~ -70 kJ/mol at 0.4 g/cm³ and 400 °C. This is because the pressure changes significantly with the density. Further investigation was not attempted in the present study.
- ⁴¹J. March, *Advanced Organic Chemistry*, 3rd ed. (Wiley, New York, 1985).
- ⁴²F. P. Bailey and R. Taylor, *J. Chem. Soc. B* **1971**, 1446 (1971).
- ⁴³H. V. Ansell, J. Le Guen, and R. Taylor, *Tetrahedron Lett.* **4**, 13 (1973).
- ⁴⁴M. Frisch, G. Trucks, H. Schlegel *et al.*, GAUSSIAN 98, Gaussian Inc., Pittsburgh, PA, 2001.
- ⁴⁵Similarly, the lowest unoccupied molecular orbital (LUMO) was also computed. The obtained LUMO is nearly equally localized at the ortho and meta positions, while it is negligibly small at the para. We believe that the hydrothermal H/D exchange reaction is not nucleophilic, as the meta is far less reactive than both the ortho and para positions.