Non-catalytic Anti-Markovnikov Phenol Alkylation with Supercritical Water

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The anti-Markovnikov alkylation of phenol with *tert*-butyl alcohol could be achieved without catalyst in supercritical water at 673 K. The dehydration of *tert*-butyl alcohol gave isobutene and was followed by the reaction with phenol to form 2-isobutylphenol as an anti-Markovnikov product, 2-*tert*-butylphenol and 4-*tert*-butylphenol. The hydroxy group probably participated in the anti-Markovnikov alkylation and the increase in water density enhanced the formation of 2-isobutylphenol as well as 4-*tert*-butylphenol.

The Friedel–Crafts alkylation is one of the most important reactions to produce alkyl aromatics in the chemical industry. This reaction usually proceeds with strong acids under water-free condition, thus considerable waste treatments and highly closed systems are required. The chemistry of typical Friedel–Crafts reaction, which is governed by the carbocation, leads to regioselectivity for the alkyl side chain of aromatics and depends on the stability of the carbocation intermediates (Makovnikov rule). Therefore, it is difficult to synthesize lower branched alkylphenols because highly branched carbocation is favored. Catalysis with metal complexes is one of the methods to achieve anti-Markovnikov alkylation.[1] On the other hand, in the alkylation of phenol, the hydroxy group of phenol strongly activates the ring substituents at both the *ortho*- and *para*-positions. Various catalysis can change the ratio of *ortho*- and *para*-orientation for alkylation of phenol.[2–5] Solid catalysis of alkylation of phenol in supercritical carbon dioxide[6] and non-catalytic reaction in supercritical alcohols[7] give alkylphenols.

In high temperature water including the supercritical region ($Tc = 647$ K, $Pc = 22.1$ MPa), water acts as a solvent and many organic reactions have been shown to proceed without catalyst.[8–12] Chandler et al.[13,14] reported that alkylation of phenol with propan-2-ol and *tert*-butyl alcohol proceeded without catalyst in high temperature water at 548 K and the alkyl side chain of products were followed by Friedel–Crafts alkylation rule. For the alkylation of phenol, we have found that the highly *ortho* selective alkylation of phenol with propan-2-ol[10,11] and regioselective alkylation of phenol with propionaldehyde[12] occurs in supercritical water.

In this study, we conducted the alkylation of phenol with *tert*-butyl alcohol in sub- and supercritical water at 673 K without catalyst. We show that alkylphenol whose alkyl side chain being anti-Markovnikov type can be formed without catalyst and the orientation for *ortho*- and *para*-position can be controlled with water density in supercritical water.

Experiments were conducted in stainless 316 tube-bomb reactors (6 cm^3) with a forced convection oven at 673 K. The phenol and *tert*-butyl alcohol was purchased from Wako Pure Chemical Industries, Ltd., and their purities were both >99%. For the reaction of *tert*-butyl alcohol with phenol, 0.002 mol of *tert*-butyl alcohol and 0.010 mol of phenol and from 0 to 3 g of water were loaded into the reactor after purging the reactor with argon. This amount of water corresponded to water densities between 0 and 0.5 g/cm^3. After the reaction, liquid products were recovered with acetone and both qualitative and quantitative analyses of the products were performed with GC-MS with an internal standard. For some cases, we conducted experiments by using the reactors equipped with a high pressure valve to analyze gas products. For these cases, the gas products were analyzed by GC-TCD. Product yield was defined on a *tert*-butyl alcohol loaded basis, as: yield [%] = (moles of carbon atom of the alkyl side chain attached to the benzene ring)/(moles of carbon in *tert*-butyl alcohol loaded) × 100.

Figure 1 shows the yields of the main products in the alkylation of phenol with *tert*-butyl alcohol in water at 673 K and 0.5 g/cm^3 of water density. The liquid products were 2-isobutylphenol, 2-*tert*-butylphenol, and 4-*tert*-butylphenol. The 2-isopropylphenol was a minor product and its yield was below 1.1%. In some cases, several other small peaks such as butyl phenyl ether, 2-propylphenol were identified in the GC analysis, however, the yields of these compounds were trace (below 0.1%). We conducted the experiments for gas analysis for some runs at 80 min reaction time at 673 K and 0.5 g/cm^3 water density. For this case, almost all gas products were isobutene, whose molar proportion to other gases was 90.4%. The proportion of isobutane and propane was 6.6 and 2.4%, respectively. Propylene, methane, carbon dioxide, and hydrogen were formed below 1%. The yield of isobutene shown in Figure 1 was estimated from carbon balance and included other gases as well.

From the results in Figure 1, we propose the main reaction pathway. In Figure 1, the yield of *tert*-butyl alcohol (**1**) rapidly decreased with reaction time and the yield of isobutene (**2**) in-

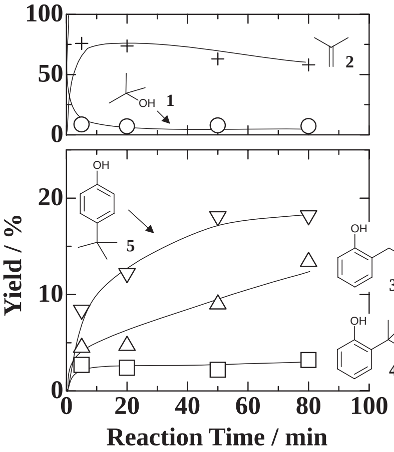

Figure 1. Yield of (+) isobutene (**2**), (△) 2-isobutylphenol (**3**), (□) 2-*tert*-butylphenol (**4**), (▽) 4-*tert*-butylphenol (**5**) for reaction of phenol with *tert*-butyl alcohol (○) at 0.5 g/cm^3 of water density and 673 K.

creased corresponding to the decrease of *tert*-butyl alcohol. Xu et al.[15] reported that *tert*-butyl alcohol decomposed to isobutene without catalyst in high temperature water and acid accelerated the dehydration. In supercritical water, the higher temperatures used probably caused rapid dehydration of *tert*-butyl alcohol to isobutene. After that, the alkylation of phenol with isobutene proceeded to form 4-*tert*-butylphenol (**5**), 2-isobutylphenol (**3**), and 2-*tert*-butylphenol (**4**) whose yields were in this order. At 140 min of reaction time, the yield of 2-isobutylphenol was 12.6% as the same level at 80 min (not shown), which indicates that the reaction probably attained equilibrium at longer reaction time. Interestingly, 2-isobutylphenol whose alkyl side chain was lower branched was formed at yields as high as 13%. Further, we conducted the decomposition of 2-*tert*-butylphenol at 673 K and 0.3 g/cm^3 of water density for 80 min. The phenol is main product and 2-isobutylphenol was formed at 2.3% of yield. The anti-Markovnikov phenol alkylation occurred in supercritical water in the absence of catalyst.

Table 1. Effect of water density on the alkylation of phenol with *tert*-butyl alcohol for 80 min at 673 K, $[\textit{tert}\text{-butyl alcohol}]_0 = 0.33\,\text{mol/L}$, $[\text{phenol}]_0 = 1.65\,\text{mol/L}$

Water density /g cm^{-3}	Yield/%				
	1	**3**	**4**	**5**	Sum of **3**, **4**, **5**
0	103.0	3.4	1.1	0.0	4.5
0.2	18.9	2.8	4.9	0.0	7.7
0.3	8.9	10.1	1.5	2.9	14.5
0.4	9.1	9.7	3.8	9.6	23.1
0.5	7.2	13.4	3.2	18.2	34.8

Next, we evaluated the effect of water density on the alkylation as shown in Table 1. In supercritical water, both dielectric constant and ion product are known to increase with increasing water density. Further, phenol dissociates to form proton and its dissociation constants changes with water density.[16] For example, the dissociation constants of phenol increases by about two orders of magnitude for water density changing from 0.3 to 0.4 g/cm^3. The higher dissociation constant of phenol makes proton concentrations higher, which promoted the dehydration of *tert*-butyl alcohol through protonation of alcohol. In the experimental results, the increase in water density decreased the residual amount of *tert*-butyl alcohol, even in 103% yield of *tert*-butyl alcohol implying experimental error.

The yield of 2-*tert*-butylphenol was almost constant below 4.9% between 0 and 0.5 g/cm^3 of water density and that of 4-*tert*-butylphenol greatly increased with increasing water density up to 18.2%. In the typical Friedel–Crafts alkylation, the *tert*-butyl positive ion attacks both *ortho*- and *para*-position of hydroxy group and the structure of the alkyl side chain becomes highly branched according to Markovnikov rule. The increase of water density promotes typical Friedel–Crafts alkylation by the increase in proton concentration. In water, the solvation of water molecules around the hydroxy group of phenol occurs.[17] Therefore, in the lower water density region, the local proton concentration around the hydroxy group was relatively larger than the bulk proton concentration. As a result, the alkylation occurred mainly at the *ortho* position and 2-*tert*-butylphenol preferred to form in lower water density region. In the high water density region, the yield of 4-*tert*-butylphenol was larger than that of 2-*tert*-butylphenol because the steric hindrance of *tert*-butyl group was probably high.

On the other hand, the yield of 2-isobutylphenol was lower than 3.4% below 0.2 g/cm^3 of water density, increased to 10% at 0.3 g/cm^3 of water density and was attained 13.4% at 0.5 g/cm^3 of water density. Sato et al.[11,12] reported that the hydroxy group participated in the alkylation of phenol to form a carbon–carbon bond between carbon of aromatic ring and the alkene (OH-catalyzed reaction). In the case of phenol alkylation in supercritical water, alkylation proceeds through both typical Friedel–Crafts alkylation and above OH-catalyzed alkylation. The reaction field of OH-catalyzed reaction seemed to be limited around *ortho*-position of hydroxy group, which causes no formation of 4-isobutylphenol. The increase in water density influenced the solvation around OH group of phenol and enhanced OH-catalyzed reaction[11] to form anti-Markovnikov alkylphenol.

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