# Heck reactions in hydrothermal, sub-critical water: water density as an important reaction variable

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**Abstract**—Heck coupling reactions of iodobenzene and cyclohexene in sub-critical water illustrate the importance of water density as a reaction variable. Altering the water density from 0.03 to 0.84 g/mL and the reaction pressure from 30 to greater than 213 bar at 225°C changed both product and isomer yields. The multiple physical effects of water density were also explored by the addition of ionic salts. Changing the isothermal state of the liquid water, measurably altered coupling reaction pathways suggesting that changes in solvent–solute interactions can influence transition states favoring some configurations and disfavoring others. © 2001 Elsevier Science Ltd. All rights reserved.

The last decade has seen significant growth in the development of water-based synthetic chemistry, reflecting a new appreciation for the unique characteristics of water as a solvent.[1] These important traits include low cost, improved safety, and environmental compatibility.[2] Recently, synthetic chemists have begun to move beyond traditional low-temperature, aqueous reactions ($T<100$°C) to exploit the physical changes that occur in water at higher temperatures and pressures. Although only a few groups are working directly in this area,[3] a variety of organic reactions have been demonstrated in sub-critical water including rearrangements, dehydrations, and carbon–carbon coupling reactions.[4]

At high temperatures and pressures, the physical properties of water change dramatically from those found under ambient conditions. For example, the dielectric constant of water decreases from $\varepsilon=80$ at STP, to $\varepsilon=31$ at 225°C, $P=100$ bar, and finally to $\varepsilon=6$ at the critical point, $T_c=374.15$°C, $P_c=221.2$ bar,[5] due to the steady decrease in the effectiveness of hydrogen bonds with increasing temperature.[6] This makes sub-critical water a realistic alternative to traditional organic solvents by removing important solubility barriers. Returning the system to ambient conditions restores the insolubility of organics, obviating the need for solvent-intensive extractions.

Characterizing hydrothermal water reactions, below the critical point ($100<T<373$°C) requires careful selection of temperature, pressure, and effective water density to control the aqueous phase behavior and insure the solubility of organics. Correlation between water density and physical properties, including pressure and dielectric constant, are documented in standard tables.[5] In supercritical water, the reaction rates and product distribution of cyclohexanol dehydration have been demonstrated to be very sensitive to water density.[7] However, water density has not previously been linked to synthetic results at sub-critical conditions. This paper examines the affect of altering water properties through changes in the water density, at 225°C, on Heck coupling reactions of iodobenzene and cyclohexene. In all the cases studied, only a single fluid phase was present so the effective water density corresponds exactly to the mass of water in grams charged internally to the reactor divided by the reactor volume in mL.
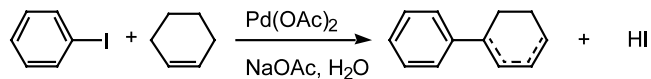
In a typical reaction, 12 mL 316 stainless steel reactors were loaded with 1 mmol of iodobenzene, 3 or 5 mmol of cyclohexene, 3 mmol of NaOAc, 0.06 mol of Pd(OAc)$_2$, and 0.36–10.1 g of water. In some experiments, either 55 (±0.5) bar N$_2$ at room temperature, or 0.1 $m$ of $n$-Bu$_4$NBr was also added. At 225°C, creation of a homogeneous, compressed aqueous phase required a minimum water density of 0.84 g/mL.[8] The water density was varied from 0.03 to 0.84 (±0.01) g/mL by

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changing the amount of loaded water. The reactors were sealed with a 1 mm titanium gasket, torqued to 140 ft/lb, attached to a shaker system, and heated to 225 (±1)°C for 20 min in a fluidized sandbath.[9] Reactions were quenched in an ice/water bath. Organics were extracted with toluene and identified by capillary GC–MS. Quantitation was performed by GC with naphthalene, added after reaction work-up as an internal standard. An optically transparent cell, fitted with a pressure transducer (±3 bar), was used to confirm the phase behavior of the reaction mixtures.[10]

At homogeneous, compressed aqueous phase conditions, the yield of the desired coupling products, phenylcyclohexenes, was 21% (entry 1). With a water density of 0.84 g/mL, the isomers were generated in 8:31:62 ratios (1-phenylcyclohexene, **1**:3-phenyl-cyclohexene, **2**:4-phenylcyclohexene, **3**). As the water density was reduced from 0.84 g/mL to 0.71 g/mL, the reaction pressure dropped from 114 to 45 bar and a two-phase reaction system, gas and liquid, was created. The product yield declined from 21 (entry 1) to 12% (entry 2). This yield remained constant for all the reactions with reduced water, 0.03–0.63 g/mL, $29<P<41$ bar (entry 3). The percentage of undesirable side-products increased concomitant with the decreased water density. Benzene yields increased from 4 to 9% and biphenyl increased from 3 to 8%. The isomer ratios were unaffected by changes in the water density and the yields were not improved by vigorous stirring. Overall results are summarized in Table 1.

In the above experiment, altering the water density affected both the pressure and the distribution of water, between compressed liquid and gaseous phases. In order to separately probe these physical factors, 55 bar of $N_2$ was added to increase internal reaction pressure. In reactions with reduced water density, $N_2$ increased the yield phenylcyclohexenes by about 60% (entries 5 and 6). The beneficial effect of the added nitrogen was optimized at a density of 0.75 g/mL, which resulted in

a yield of 22% phenylcyclohexenes (entry 5). However, the benefit of added pressure was lost in the homogeneous compressed aqueous systems, $d=0.84$ g/mL, where the reaction yield decreased from 22% (entry 5) to 15% (entry 4). The addition of $N_2$ restored the yield of phenylcyclohexenes by compensating for the pressure lost by reducing the water density. Very high pressures, 8 kbar, have been reported to improve Heck reaction yields in organic solvent systems, $T \leq 100°C$.[11] The increased yields were attributed to decreased catalyst precipitation due to catalyst stabilization by coordination of the solvent molecules. In the present work, reaction yields were improved with modest $N_2$ pressures but the effect was limited to two-phase aqueous systems. This result is consistent with water's superior coordinating ability compared to that of typical organic solvents.

In a separate series of experiments, the effect of multiple phases within the reactor was probed by examining the coupling of iodobenzene and cyclohexene in the presence of *n*-Bu_4NBr. In traditional Heck reactions in organic solvents, the presence of a quaternary ammonium salt is known to both increase yield and improve selectivity.[12] Systems containing nonvolatile, ionic salts should be particularly sensitive to the aqueous phase behavior. In homogeneous, compressed, aqueous phase reactions, $d=0.84$ g/mL, the addition of *n*-Bu_4NBr increased the yield of phenylcyclohexenes from 21 (entry 1) to 47% (entry 8) and changed the isomer distribution of the products. Without the quaternary ammonium salt, isomer **3** was preferred, 8:31:62 (**1:2:3**) (entry 1), while, after the addition of *n*-Bu_4NBr isomer **1** was preferred, 55:16:28 (**1:2:3**) (entry 8). These results at homogeneous, compressed aqueous conditions were surprisingly similar to the synthesis results from same reaction in typical organic solvents.[9]

The coupling of iodobenzene to cyclohexene in the presence of *n*-Bu_4NBr proved to be very sensitive to the amount of water in the reaction vessel. A modest

**Table 1.** Effect of water density at 225°C on coupling reactions of iodobenzene and cyclohexene with added pressure or ionic salts

| Entry | Reactant ratios (iodobenzene:cyclohexene) | Additives | Water density[a] | Internal pressure (bar) | % Yield[b] | Isomer ratios[c] (**1:2:3**) |
|---|---|---|---|---|---|---|
| 1 | 1:5 | – | 0.84 | 114 | 21 | 8:31:62 |
| 2 | 1:5 | – | 0.71 | 45 | 12 | 3:32:65 |
| 3 | 1:5 | – | 0.03–0.63 | 29–41 | 12 | 5:27:68 |
| 4 | 1:5 | 55 bar $N_2$ | 0.84 | >213 | 15 | 3:35:63 |
| 5 | 1:5 | 55 bar $N_2$ | 0.75 | 200 | 22 | 12:30:58 |
| 6 | 1:5 | 55 bar $N_2$ | 0.58 | 136 | 20 | 6:32:62 |
| 7 | 1:5 | 55 bar $N_2$ | 0.17–0.40 | 120–123 | 14 | 14:29:57 |
| 8 | 1:3 | 1 *m* *n*-Bu_4NBr | 0.84 | 130 | 47 | 55:16:28 |
| 9 | 1:3 | 1 *m* *n*-Bu_4NBr | 0.75 | 39 | 21 | 8:29:63 |
| 10 | 1:3 | 1 *m* *n*-Bu_4NBr | 0.67 | 38 | 18 | 8:30:62 |
| 11 | 1:3 | 1 *m* *n*-Bu_4NBr | 0.50 | 34 | 28 | 11:29:60 |
| 12 | 1:3 | 1 *m* *n*-Bu_4NBr | 0.33 | 32 | 25 | 14:28:58 |
| 13 | 1:3 | 1 *m* *n*-Bu_4NBr | 0.17 | 30 | 24 | 22:22:56 |

[a] Water density ($d$)=grams of water/mL of reactor volume.

[b] % Yield of phenylcyclohexenes.

[c] 1-Phenylcyclohexene (**1**):3-phenylcyclohexene (**2**):4-phenylcyclohexene (**3**).

reduction in water density from 0.84 g/mL to 0.75 g/mL, led to a 50% decrease in product yield. Interestingly, this reduction in water density caused the product isomer ratios (entry 9) to revert to those generated in reactions where the quaternary ammonium salt was absent (entries 2 and 3). Further reduction in water density caused an increase in the scrambling of the product isomers (entries 10–13). The preference for isomer **1** in the homogeneous compressed aqueous system was lost with lower water density, despite the presence of the quaternary ammonium salt. Even vigorous agitation failed to improve the conversion or isomer ratios. Experiments are presently underway to investigate the origin of this effect.

In summary, hydrothermal media at sub-critical conditions have been shown to influence chemical pathways for the model Heck reaction studied and may have an important future as a solvent for synthetic organic applications. In order to harness the potential of this unusual medium, it is critical to understand the reaction variables involved. This work has shown that water density must be carefully considered as a characterizing parameter in order to control reaction phase behavior and preferred reaction pathways for optimizing reaction yield and desired isomer distribution.

## Acknowledgements

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8. The phase behavior of water is *critically* dependent upon the temperature and water density. Calculations for homogeneous compressed water systems are based on data for pure water in Ref. 5.
9. **CAUTION**: High-temperature and high-pressure reactions should be approached with reasonable care.
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