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Acceleration of Disproportionation of Aromatic Alcohols through Self-Emulsification of Reactants in Water

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Exploration of new and effective routes to conduct organic reactions in water using the special properties of water/organics is of great importance. In this work, we performed the disproportionation of various aromatic alcohols in water and in different organic solvents. It was demonstrated that the disproportionation reactions of the alcohols were accelerated more effectively in water than organic-solvent-based or solvent-free reactions. A series of control experiments were conducted to study the mechanism of the accelerated reaction rate in water.

Introduction

In recent years, reactions using water as the medium have attracted considerable attention because it is abundantly available, inexpensive, non-toxic, and non-inflammable.^[1]A variety of organic reactions have been shown to have improved reactivity and selectivity in aqueous solutions. For example, Diels-Alder cycloadditions and Claisen rearrangements of nonpolar compounds in dilute aqueous solutions were accelerated significantly compared to the organic-solvent-based or solventfree reactions.^[2] The reactions of azodicarboxylates with various aldehydes to produce hydrazine imide products were performed very efficiently in water without the use of a catalyst.^[3] The asymmetric desymmetrization of meso-epoxides with amines showed a higher enantiomeric excess (ee) in water than in organic solvents.^[4] High yield and selectivity for the synthesis of ladder polyether moieties were achieved in water.^[5] Knoevenagel condensation of aromatic aldehydes in water could be accelerated dramatically by a cationic coordination cage under neutral conditions.^[6] 2-Naphthols and substituted phenols could be converted to the corresponding biaryl compounds efficiently in water using molecular oxygen as the oxidant.^[7] The direct alkyne–imine addition promoted by copper(I)-based catalysts showed a high ee and a good yield in water.^[8] Indium(0) could catalyze the allylation of ketones efficiently in water under mild conditions.^[9]

Interestingly, many reactions of hydrophobic reactants that are insoluble in water have been conducted more effectively in aqueous suspensions than in organic solvents, such as Diels– Alder reactions,^[10] Claisen rearrangements,^[10a,11] Passerini reaction,^[12] iodine transfer cyclization of α -iodoacetates,^[13] direct alkynylation of isatins,^[14] oxidation of aldehydes by using oxygen as the oxidant,^[15] and direct arylation of thiazoles.^[16] The term on-water has been used to describe the substantial rate accelerations in aqueous suspensions.^[10a] It was reported that onIt was shown that the reactants could emulsify the reactant/ water systems at the reaction conditions owing to their amphiphilic nature. The regularly orientated reactant molecules at the water/reactant droplet interface improved the contact probability of the reactive groups and the Pd nanocatalysts, which is one of the main reasons for the enhanced reaction rate in water. Controlling the self-emulsification of amphiphilic reactant/water systems has great application potential for optimizing the rate and/or selectivity of many organic reactions.

water nucleophilic substitution of alcohols obtained satisfactory results without the use of acidic catalysts.^[17] McErlean and co-workers developed a domino in-water-on-water process that shuttles molecules between the aqueous and organic phases based on the solubility difference of the reactants and products.^[18] It was also reported that diarylprolinolsilyl ether salts could be used as the catalysts for asymmetric Michael addition of aldehydes to nitroolefins on water with excellent diastereo- and enantioselectivities.^[19]

Various interactions and effects may exist in the aqueous reaction systems, such as electrostatic effects, polarization, hydrogen bonding, and hydrophobic effects. All of these interactions and effects can influence the reactions in water,^[1,10a] which factors are dominant depends on the natures of the reactants and reaction conditions. The mechanisms with which water enhances the efficiency of different reactions have been studied. For example, rate acceleration in water for the reaction with a negative activation volume, such as Diels-Alder reactions, was ascribed to the internal pressure from water wrapping the hydrophobic reactant aggregates.^[2b, 20] Hydrogen bonding could make an important contribution to the acceleration of Diels-Alder reactions in aqueous solution.^[21] It was suggested that a rate increase of the Diels-Alder reactions of diene carboxylate salts with dienophiles in aqueous suspensions originated from micellar catalysis, resulting in mutual

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binding of the reactants in an aggregate.^[10b,c] Engberts and Blokzijl provided evidence that some Diels–Alder reactions were accelerated by an enforced hydrophobic effect, which resulted in the destabilization of the reactants as well as a hydrogen-bonding stabilization of the polarizable activated complex.^[22] The on-water effect has also been explained by an acid-catalysis mechanism facilitated by the strong adsorption of the hydroxide ion at the oil/water interface, leading to acid catalysis and an enhanced rate.^[23] Transition-state theory and energy-minimization studies of the on-water cycloaddition of

quadricyclane and dimethyl azodicarboxylate showed that the reaction rate was accelerated because the free OH⁻ groups of interfacial water molecules formed stronger hydrogen bonds with the transition state than with the reactants.^[24]



Scheme 1. Disproportionation of alcohols.

Mixed quantum and molecular mechanical methodology studies indicated that on-water rate enhancement for Claisen rearrangements was derived from the ability of the interfacial water to stabilize the polar transition state.^[25] A quantum mechanical/molecular mechanical modeling study indicated that some Diels–Alder reactions are accelerated less on the surface of water than in water.^[26] The origins of water improving the efficiency of different reactions are very complex and still need to be studied further.

A surfactant molecule consists of a polar head and apolar tail.^[27] Oil/water systems can form oil-in-water emulsions at suitable conditions with the aid of surfactants, and the surfactant molecules orientate regularly at the water/oil droplet interface, with polar groups facing the water phase and the apolar tails facing the oil phase,^[27] as shown schematically in Figure 1. The regularly orientated polar groups of the surfactant molecules at the oil/water interface have a high local density.



Figure 1. Diagram of oil-in-water emulsions.

Exploration into effective routes to conduct organic reactions in water using the special properties of water/organic systems, as well as further studying the mechanism is of great importance. Some organic reactants are amphiphilic, and these types of reactants may also act as surfactants to emulsify the such as THF,^[28] methanol,^[29] toluene,^[30] and at solvent-free condition.^[31] Pd nanoparticles are efficient catalysts for the disproportionation reactions.^[29]

reactant/water systems at suitable conditions. Therefore, in the

reactant/water emulsions emulsified by the reactant(s) itself,

the reactant droplets are dispersed in water, the reactant mole-

cules oriented in a regular fashion at the interface, and the

special orientation of the reactant molecules is favorable to en-

hance the contact probability of the reactants, which may in-

fluence the reactions significantly. In this work, we performed

the first work to provide evidence for the validity of the idea

by conducting disproportionation of different alcohols

(Scheme 1) already extensively studied in different solvents,

Results and Discussion

Self-emulsification of the reactant/water systems

We first studied the phase behaviors of the reaction systems of the disproportionation of 1-phenylethanol ($R^1 = Ph$, $R^2 = CH_3$ in Scheme 1) in different solvents without the catalyst. The photographs are presented in Figure 2 as insets. It can be seen that the reactant was miscible with the organic solvents and transparent solutions were formed.. However, the reactant and water were not miscible, and the reactant/water mixture became milky after stirring. Our experiment indicated that the emulsion could be stable for at least 24 h. The stable emulsion was probably formed because the reactant has the nature of a surfactant with a polar group and apolar tail. The formation of the emulsion was further confirmed by laser scanning confocal microscopy (LSCM), which is a commonly used technique to study the droplet size of emulsions.^[32] According to Figure 2 the size of the droplets in the emulsion was in the range of 0.2–2 μm.

Disproportionation of 1-phenylethanol in different solvents

We studied the disproportionation of 1-phenylethanol in different solvents at the same condition for the phase behavior studied above, and a commercial Pd/C catalyst was used, which was characterized in detail previously.^[33] The results are also presented in Figure 2. It shows that the conversion of the reactant in water was substantially higher than in the organic solvents or solvent-free under the same reaction conditions. We also conducted the reaction at longer times in different solvents, and the conversion in water was also higher than those in organic solvents (entry 1, Table 1). In this work, no byproduct was detected in the reaction.



Figure 2. a) The conversion of the disproportionation of 1-phenylethanol in different solvents; reaction conditions: 1-phenylethanol 2 g (16 mmol), solvent 3 mL, Pd/C with 5 wt% Pd (23.5 µmol), 100 °C, 2 h; the insets are photographs of the corresponding reactant/water mixtures without the catalyst. b) LSCM image of 1-phenylethanol/ water emulsion at room temperature.

Table 1. Disproportionation of alcohols in water.					
Entry	Substrates	t [h]	Conversion heptane	[%] ^[c] propanol	water
1	OH	12	51.3 ^s	48.9 ^s	96.2 ^E
2	OH OH	4	68.5 ^s	67.3 ^s	94.9 ^E
3		12	60.7 ^s	58.0 ^s	98.8 ^E
4	OH	2	20.6 ^s	20.3 ^s	20.2 ^s
[a] Reaction conditions: substrate 16 mmol, solvent 3 mL, Pd/C with 5 wt % Pd (23.5 μ mol), 100 °C. [b] 1-phenylethanol 0.8 mmol, solvent 5 mL, Pd/C with 5 wt % Pd (4.7 μ mol), 100 °C. [c] All conversions were determined by GC; S=single phase; E=emulsion is formed.					

The catalytic reaction studied in this work involves two reactant molecules. The two hydroxyl groups and the Pd catalyst must contact for the reaction to proceed. The reaction rate probably depends mainly on two factors: the solvation effect and the contact probability of two hydroxyl groups with the Pd catalyst. Figure 2 indicates that the conversions in different organic solvents were similar, suggesting that the solvation effect was not dominant in the reaction. In this work, the disproportionation of 1-phenylethanol in different solvents was also conducted at a dilute reactant concentration, at which the reactant was also soluble in water. The results indicated that the conversions in the organic solvents and in water were nearlv the same (Table 1.

entry 4), which further supported the conclusion that the solvation effect was not the main factor for the reaction. Therefore, it can be postulated that the contact probability of two hydroxyl groups and the Pd catalyst was the dominant factor in the reaction. In the organic solvents and at the solvent-free condition, the reactant molecules were oriented randomly, whereas they were oriented in a regular fashion at the water/ reactant droplet interface in water, as shown schematically in Figure 3. In the aqueous system the contact probability of the two hydroxyl groups and the catalyst at the water/reactant droplet interface was much larger than in organic solvents and solvent-free conditions. This can be attributed to the ordered orientation, which leads to the larger reaction rate in water.

The reaction in 1-propanol-water mixed solvents

To further support the mechanism proposed above, in which water accelerates the reaction, we also performed the reaction in 1-propanol/water mixed solvents of different compositions. In combination with the phase behavior study of the reaction system, the results are illustrated in Figure 4. The reaction system experienced a transformation from a transparent single phase to a milky solution upon increasing the water volume fraction in the mixed solvent (V_w). This was caused by the in-



Figure 3. Schematic diagrams of the reactant orientation in organic solvents (a), solvent-free (b), and water (c).



Figure 4. Conversion and solubility of 1-phenylethanol in 1-propanol/water mixed solvents with different water volume fractions (V_w). Reaction conditions: 1-phenylethanol 2 g (16 mmol), solvent 3 mL, Pd/C with 5 wt% Pd (23.5 μ mol), 100 °C, 2 h. The insets are photographs of the reactant/1-propanol–water mixtures.

crease of the hydrophilicity of the mixed solvent. We also studied the solubility of the reactant in the mixed solvents, and the results are also presented in Figure 4. In the one phase region ($V_w < 0.33$), the conversion was nearly independent of the composition of the mixed solvent, indicating again that the solvation effect did not affect the reaction considerably. The conversion increased significantly with water content, since the reaction system started to self-emulsify as $V_{\rm w}$ approached 0.66. In the $V_{\rm w}$ range of 0.33 to 0.66, the solubility of the reactants decreased substantially with increasing V_{w} that is, the reactant molecules existing at the water/reactant interface increased with water content significantly, leading to dramatic increase of the conversion with V_w . The solubility of the reactant in the mixed solvent was very low in the $V_{\rm w}$ range of 0.66 to 1.00, and thus most of the reactants existed as dispersed droplets in water, and the reactant molecules at the interface did not change considerably with the variation in V_{w} . Therefore, the conversion was, again, almost independent of the water content. These results further support the proposed mechanism, in which the regular orientation of the reactant molecules at the interface enhanced the reaction significantly.



Figure 5. The photographs of the reaction mixtures of a) 1-indanol/*n*-heptane, b) 1-indanol/1-propanol, c) 1-indanol/water, d) 1-(4-meth-oxylphenyl)ethanol/*n*-heptane, e) 1-(4-methoxylphenyl)ethanol/1-propanol, f) 1-(4-methoxylphenyl)ethanol/water, and the LSCM images of g) 1-indanol/water and h) 1-(4-methoxylphenyl)ethanol/water.

The disproportionation of other aromatic alcohols

We also studied the disproportionation of other aromatic alcohols in different solvents, and the results are presented in Table 1. 1-Indanol (entry 2) and 1-(4-methoxylphenyl)ethanol (entry 3) were soluble in the organic solvents and could emulsify the aqueous reaction systems (Figure 5). The conversions of the reactions in water were much higher than those in organic solvents at the same conditions, further supporting the proposed mechanism, in which the larger contact probability, originating from self-emulsification, accelerated reactions substantially. Conversely, controlling self-emulsification is an effective tool to optimize the reaction conditions.

Conclusions

The disproportionation reactions of aromatic alcohols in water are faster than those in organic solvents, mainly because the reactants are amphiphilic and can emulsify the reactant/water systems. The regularly orientated reactant molecules at the water/reactant droplet interface give rise to a larger contact probability of the reactive groups with the catalyst, which is one of the main reasons for the accelerated reactions. We believe that the self-emulsification ability of amphiphilic reactant/water systems provides a useful tool to control the reaction rate and/or selectivity of many reactions in aqueous media, especially if the contact probability is a dominant factor in the reaction.

Experimental Section

Materials: The commercial Pd/C catalyst was provided by Baoji Rock Pharmachem Co., Ltd., China (5 wt% Pd, Product No. D_5L_3), which was the same as that used previously for the hydrogenation of phenol to cyclohexanone and was characterized in detail.^[33] *N*,*N*dimethylformamide (A. R. grade), toluene (A. R. grade), *n*-heptane (A. R. grade), 1-propanol (A. R. grade), were purchased from Beijing Chemical Reagent Company. 1-(4-Methoxylphenyl)ethanol (A. R. grade), 1-indanol (A. R. grade) and 1-phenylethanol (A. R. grade) were obtained from Alfa Aesar China (Tianjin).

Methods: All the reactions were performed under nitrogen (1 bar) in a stainless steel autoclave (15 mL), which was similar to that used previously.^[33] Only the procedures for the disproportionation of 1-phenylethanol are described because those of the other substrates were similar. In the experiment, suitable amounts of 1-phenylethanol (reactant) and Pd/C (catalyst) were loaded into the autoclave. The autoclave was sealed and placed in a silicon oil bath (100 °C), and the reaction mixture was stirred using a magnetic stirrer (400 rpm). After the desired reaction time, the autoclave was cooled in a cold water bath. If an organic solvent was used for the reaction, the reaction mixture was analyzed directly. If water was the reaction solvent, the reaction mixture was extracted with CH_2Cl_2 (20 mL). The organic layer was analyzed.

The quantitative analysis of the reaction mixture was performed using GC (Agilent 6820) equipped with a flame ionization detector (FID) and a PEG-20 μ capillary column (0.25 mm in diameter, 30 m

in length).Benzene was used as internal standard. Identification of the products and reactants was performed by using GC–MS (SHI-MADZU-QP2010) as well as by comparing the retention times to respective standards in GC traces. The conversion was calculated from the GC data.

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