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Exploiting Phase Behavior for Coupling Homogeneous Reactions with Heterogeneous Separations in Sustainable Production of Pharmaceuticals

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ABSTRACT: John Prausnitz was never content to measure new data solely because the data were new. He always had an application in mind—a separation or even a process that required the data for implementation. We present here an advance in using designed changes in phase equilibria to enable the facile recovery and recycle of homogeneous catalysts. We show a new application of organic-aqueous tunable solvents (OATS) to run homogeneous reactions (fast rates and high selectivities) followed by facile and efficient heterogeneous separations and the recycle of the homogeneous catalysts. This is done by using CO_2 to manipulate the phase behavior of monophasic organic−water mixtures to form heterogeneous organic-rich and aqueous-rich phases. The example shown is the hydroformylation of hydrophobic *p*-methylstyrene catalyzed by rhodium catalyst to which is attached a hydrophilic phosphorus ligand. The OATS method increases the conversion rate of styrene to the aldehyde products by an order of magnitude compared to heterogeneously reported reactions. Also, the selectivity toward the branched aldehyde (the desired product) increases by 30 %. The hydrophobic product partitions into the organic-rich phase with more than 99 % removal efficiency, and the hydrophilic catalyst is retained in the aqueous-rich phase with 99.9 % efficiency. In addition, we recycle the catalyst for five consecutive reactions without significant loss of catalytic activity.

INTRODUCTION

Organic-aqueous tunable solvents (OATS) are homogeneous solutions of water with aprotic polar organics (examples are acetonitrile (ACN), tetrahydrofuran (THF), and 1,4-dioxane (Diox)), which undergo a phase change when exposed to CO_2 pressures of (20 to 50) bar.[1,2] The resulting biphasic system consists of an aqueous-rich phase and an organic-rich phase.[3] This phase behavior is used to couple homogeneous reactions with heterogeneous separations. Thus it combines the benefits of homogeneous reactions—high rates and selectivities—with the ease of product separation and recycle of heterogeneous catalyst, as shown in the OATS process schematic in Figure 1.

Ideally, tunable solvent systems provide an attainable phase split (with lower pressures than supercritical conditions) with a relatively large liquid−liquid region and asymmetric composition distribution. Such a scenario would secure an efficient separation of the products from the catalyst, allowing the recycle of the catalyst.[4] Also, the solvents must have minimal interference with the chemistry of the process. Hallett et al.[5] reported the Rh catalyzed hydroformylation of 1-octene to produce the desired linear aldehyde 1-nonanal in THF-H_2O OATS (70 vol % organic). The hydrophilic ligands monosulfonated triphenylphosphine (TPPMS) and trisulfonated triphenylphosphine (TPPTS)—shown in Figure 2—were compared. Overall, TPPMS-Rh showed higher catalyst activity (turnover frequency (TOF) of 350) and comparable selectivity (linear to branched ratio of 2.3) compared to TPPTS-Rh (TOF of 115 and linear to branched ratio of 2.8). The rate of the homogeneously TPPMS-Rh catalyzed hydroformylation of 1-octene in OATS was approximately 2 orders of magnitude greater than the biphasic reaction. The postreaction application of CO_2 (3 MPa) induces a phase split with the water-rich phase containing 99.5 % of TPPMS and the organic-rich phase containing 99 % of the 1-nonanal. The recycle of the TPPMS-Rh catalyst for three consecutive reactions was successfully conducted with consistent catalytic activity and TOFs of $51 \pm 3\ h^{-1}$. The leaching of rhodium in the organic-phase was less than 1 ppm as determined by atomic absorption spectroscopy. OATS have also been utilized for enzyme-catalyzed reactions of hydrophobic substrates. An example is the kinetic resolution of *rac*-1-phenylethyl acetate to (*R*)-1-phenylethanol using *Candida antarctica* lipase B (CAL B)[6] and CAL B catalyzed hydrolysis of 2-phenylethyl acetate (2PEA) to 2-phenylethanol (2PE).[7]

In this work, we extend the use of OATS to the hydroformylation of *p*-methylstyrene—shown in Figure 3—catalyzed with rhodium/TPPMS. We chose *p*-methylstyrene as model compound as it structurally mimics *p*-isobutylstyrene, a key synthetic precursor to ibuprofen.[8,9] This is particularly important as ibuprofen is a widely used nonsteroidal anti-inflammatory drug with production of more than 12 million kg per annum.[10] *p*-methylstyrene reacts with syngas (CO and H_2, 3 MPa) to produce the branched (2-*p*-tolyl-propanal)

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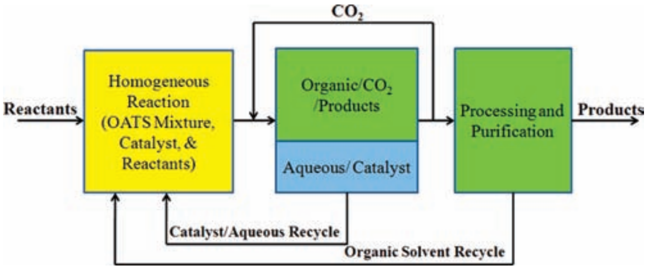

Figure 1. Schematic of catalyzed reaction with OATS mediated separation.

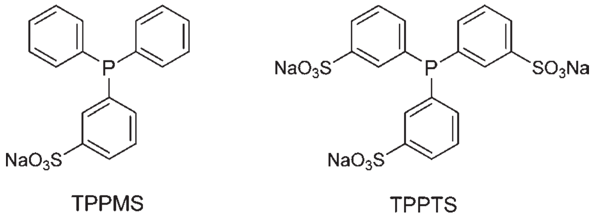

Figure 2. Hydrophilic ligands for hydroformylation reactions.

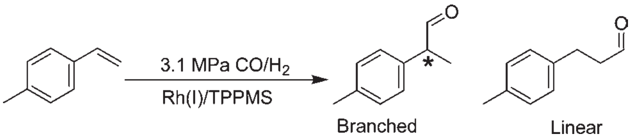

Figure 3. Hydroformylation of *p*-methylstyrene with Rh/TPPMS to produce branched (desired) and linear aldehydes.

and linear aldehyde; the branched aldehyde is the desired product. We show a comparison of the three OATS systems in terms of their effect on the reaction and the subsequent separation. There is a significant improvement in the rate of conversion and the yield of the desired product with OATS compared to reported heterogeneous catalysis.[11−14] We were able to isolate 99 % of the products while recovering and recycling 99.9 % of the catalyst using 3 MPa of CO$_2$ pressures. Therefore, OATS can improve the sustainability of hydroformylation processes by improving the rate, increasing product yield, reducing byproduct, and providing a facile and efficient separation, while also enabling recycle of the homogeneous catalyst. These benefits translate to economical advantages, which make OATS an attractive technique for selected applications in the pharmaceutical industry.

■ MATERIALS AND EXPERIMENTAL METHODS

Materials. The following solvents were degassed by the freeze−pump−thaw method: HPLC grade ACN (Sigma-Aldrich, ≥ 99.9 %), Diox (Fischer Scientific, 99.9 %), HPLC grade THF (Sigma-Aldrich, ≥ 99.9 %, inhibitor free), BHT stabilized THF (Sigma-Aldrich, ≥ 99.9 %, 250 ppm BHT) HPLC grade water (Sigma-Aldrich), and *p*-methylstyrene (Alfa Aesar, > 98 %). Carbon dioxide with supercritical fluid chromatography grade (SFC grade, Air Gas, 99.999 %) was purified via a Matheson gas purifier and filter cartridge (model 450B, Type 451 filter) and synthesis gas (syngas, 1:1 molar ratio of H_2:CO) was used as received. The following materials were used as received from the suppliers and stored in a nitrogen filled glovebox: triphenylphosphine-3-sulfonic acid sodium salt (TPPMS, TCI America, > 90 %) and rhodium(I) dicarbonyl acetylacetonate (Rh(acac), Sigma-Aldrich, 98 %).

***p*-Methylstyrene Hydroformylation in OATS.** The hydroformylations were carried out in a 300 mL stainless steel Parr autoclave (Parr Instrument Company, model 4561). The reaction pressure was monitored with a calibrated digital pressure transducer (Heise, model 901B) providing a precision of ± 0.7 bar. A proportional−integral−derivative (PID) temperature controller and tachometer (Parr Instrument Company, model 4842) were used to control the temperature of the reactor to ± 2 °C and the stirring speed to ± 5 rpm. The temperature inside the reactor was monitored with a type J thermocouple, and heat was provided by a heating mantle. The catalyst solution was prepared by weighing the desired amounts of Rh(acac) and TPPMS in the glovebox, adding degassed solution of OATS, and then stirring for about 20 min to ensure complete solubility of the catalyst. The reactions were started by evacuating the Parr autoclave and flushing it with 3.5 bar of syngas. The degassed *p*-methylstyrene, the catalyst solution, and OATS solvents were added using gastight syringes (SGE Analytical Science). The total volume of the reaction mixture was 50 mL with a *p*-methylstyrene concentration of 0.15 M. The concentration equivalences of Rh(acac) and TPPMS are 0.0025 and 0.017, respectively. The reactor was heated to temperature, stirred at 300 rpm, and subsequently pressurized with 31 bar of syngas. After a one hour reaction period, a liquid phase sample was withdrawn, captured in acetone or methanol, and analyzed with an Agilent gas chromatography-flame ionization detector (GC-FID, model 6890) with an Agilent column (model HP-5MS). External standards of known concentrations were used to calibrate the FID response.

Separation of Substrates in OATS. A homogeneous OATS mixture (2.0 mL of *p*-methylstyrene or 2.3 mL of 2-(*p*-tolyl) propanal—0.15 M concentration of both—and 98 mL of 70/30 (v/v) organic/water OATS solution) was charged to the Parr autoclave described above, and CO$_2$ was added to the cell using an ISCO syringe pump until the desired pressure was reached. After equilibrium (we determined that mixtures reach equilibrium in 15 min of stirring and 30 min of settling), three samples each of the organic-rich and the aqueous-rich phases were taken using a six-way sample loop and analyzed using the Agilent GC-FID described above. We used a similar procedure for the separation experiments of TPPMS except that the samples were analyzed with a UV−vis to measure the concentration of the ligand.

Catalyst Recycle Experiments in OATS. To demonstrate catalyst recycle we ran homogeneous hydroformylation reactions at 60 °C for 1 h and sampled as above. After an ice quench of the reaction the syngas was vented. We flushed the reactor with CO$_2$ to remove any syngas and pressurized to 3.1 MPa of CO$_2$. A dip-tube removed products and unreacted starting material. This dip-tube was engineered to remove 85 % of the organic-rich phase, so that fresh *p*-methylstyrene and organic solvent could be added and the next reaction cycle started. Make-up catalyst was also added to compensate for catalyst removed during sampling and to maintain constant catalyst to substrate ratio.

■ RESULTS AND DISCUSSION

The OATS-mediated hydroformylation of *p*-methylstyrene allows the reaction to be conducted homogeneously followed by CO$_2$-induced heterogeneous separation. We compared the reaction and separation in three OATS systems and discuss the underlying effects that cause differences among these systems.

Table 1. ***p*-Methylstyrene Conversion and Branched Product Selectivity after 1 h of Reaction Time in Different Homogeneous Solvent Systems**

OATS mixture (70 vol % organic)	reaction temperature (°C)	conversion (%)	branched product yield (%)
ACN/H_2O[a]	40	17.2 ± 3.7	94.4 ± 0.9
	60	47.6 ± 3.0	95.9 ± 0.5
	80	100.0 ± 0.0	83.9 ± 4.7
	120	99.2 ± 0.9	66.2 ± 3.6
Diox/H_2O	40	10.0 ± 2.1	97.8 ± 1.3
	80	100.0 ± 0.0	82.0 ± 2.7
	120	99.0 ± 0.3	52.0 ± 1.9
THF/H_2O	40	10.7 ± 7.6	97.3 ± 2.2
	80	83.7 ± 7.4	87.5 ± 0.7
	120	93.3 ± 0.9	51.0 ± 2.6

[a] Reaction data were reported earlier.[1]

The hydroformylation of *p*-methylstyrene to produce *p*-tolylpropanal (branched product)—Figure 3—was conducted in ACN/H_2O, Diox/H_2O, and THF/H_2O. The conversions after one hour of reaction time and the branched product yields (as a percentage of total products) at different temperatures are shown in Table 1. The conversion and yield in ACN/H_2O and Diox/H_2O are similar; the reactions proceed slowly at 40 °C with *p*-methylstyrene conversion of less than 20 % after one hour and selectivity of about 95 %. As would be expected the conversion rises rapidly with temperature giving complete conversion of the starting materials after one hour at 80 °C. However, increasing the reaction temperature decreases the branched product yield; the 2-(*p*-tolyl)-propanal yield after 1 h of reaction time decreases to about 84 % at 80 °C and decreases further to about 50 % at 120 °C. The decrease in the branched product yield at elevated temperatures is attributed to the increase of β-hydride elimination.[15] The intermediate complex of the branched product with the rhodium catalyst reverts to the starting material at reaction temperatures greater than 60 °C as observed in the reactions in ACN/H_2O OATS.

Early in this research, it was observed that the reactions in THF/H_2O OATS mixtures worked only in 2,6-di-*tert*-butyl-*p*-cresol (BHT, free radical scavenger) stabilized THF. We speculate that the peroxides present in THF[16] may interfere with the reaction by causing catalyst poisoning. Also, we observed color change in catalyst solution from yellow to dark gray when using THF/H_2O OATS. In stabilized THF/H_2O, the reaction proceeds, but conversion rates are lower than those measured for ACN/H_2O and Diox/H_2O OATS. THF was therefore not investigated further, and we chose to focus on the Diox/H_2O and ACN/H_2O systems.

The conversion rate of *p*-methylstyrene in OATS is 2 to 10 times greater than the analogous heterogeneous hydroformylation using zeolites,[12] hydrotalcite clays,[11] ionic liquid modified silica sol—gel,[13] or inorganic supports.[14] Also, the selectivity toward the desired product in OATS increases by more than 30 % compared to these heterogeneous systems. The improvement in yield and conversion results from the mitigation of mass transfer limitations that are often a limiting factor in heterogeneous catalysis.

We assess the efficiency of product separation and catalyst recovery by measuring the concentrations of product and the catalyst in the organic-rich phase and the aqueous-rich phase.

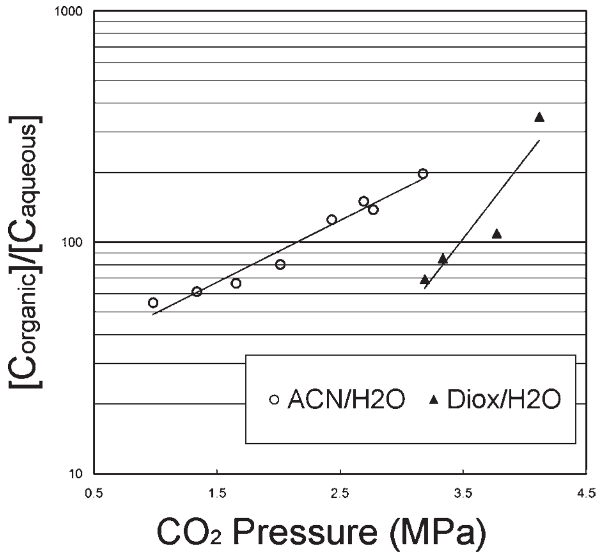

Figure 4. Differences in OATS on the separation of 2-(*p*-tolyl)-propanal in the organic phase as a function of CO_2 pressure.

The ratio of the branched product concentration in the organic phase to that in the aqueous phase (partitioning coefficient) is shown in Figure 4 for Diox/H_2O and ACN/H_2O OATS at 20 °C. The partition coefficient of *p*-(2-toly)-propanal in ACN/H_2O OATS increases exponentially as CO_2 pressure increases, and more than 99 % of the desired product is separated in the organic phase at 2.5 MPa of CO_2. The partition coefficient in Diox/H_2O shows a similar trend, but more CO_2 pressure is required to achieve comparable separations; 99 % of the desired product is separated in the dioxane phase at 4 MPa of CO_2. The difference in separation efficiency between ACN/H_2O and Diox/H_2O OATS is explained by examining the molecular interactions between H_2O with dioxane and H_2O with ACN. Goats et al.[17] reported favorable interactions between dioxane and water and hypothesized the possibility of H-bonded complexes ranging from $1C_4H_8O_2{:}3H_2O$ to $2C_4H_8O_2{:}1H_2O$ in a dioxane mole fraction range of 0.25 to 0.60 (the Diox/H_2O OATS system has a dioxane mole fraction of 0.33); the favorable interactions between dioxane and water require greater amounts of CO_2 to yield an efficient phase separation. In ACN/H_2O binary mixture and in the range of water mole fraction of 0.2 to 0.7 (the ACN/H_2O OATS system has a water mole fraction of 0.55), water—water interactions are dominant,[18] and the separation of acetonitrile from water with CO_2 is achieved with relatively low pressures.

The phase separation temperature is another variable that we have studied. Increasing the temperature could result in improved separation due to reduction of hydrogen bonding between the branched product and water. However, the increase in temperature also results in solubility enhancement of the product in the water and solubility decrease of gases in liquids; the overall effect of these competing effects results in diminished partitioning at 40 °C when compared to 20 °C as shown in Figure 5.

The efficiency of TPPMS retention in the aqueous phase is shown in Figure 6. We measured the concentration of the TPPMS in both the aqueous-rich and the acetonitrile-rich phases at 20 °C and different CO_2 pressures. The partitioning of TPPMS in the aqueous phase increases exponentially with CO_2 pressure, and 99.9 % of the TPPMS is retained in the aqueous phase at 4 MPa of

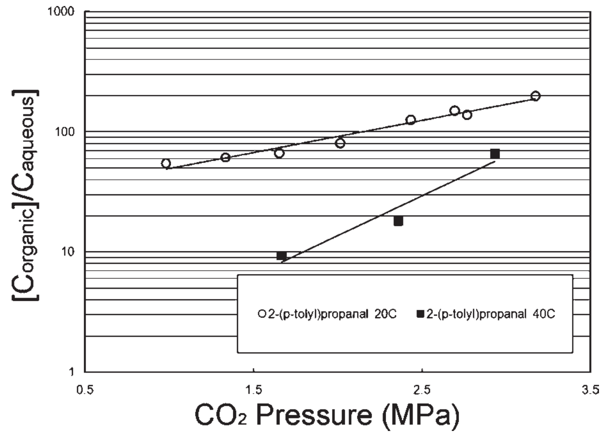

Figure 5. Effect of temperature on the separation of 2-(*p*-tolyl)-propanal in the organic-rich phase in ACN/H_2O OATS.

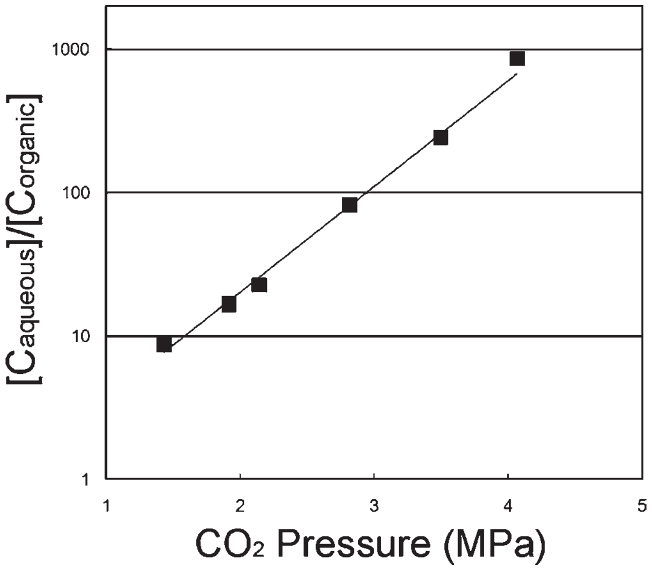

Figure 6. Retention of the ligand TPPMS in the aqueous phase in ACN/H_2O OATS as a function of CO_2 pressure.

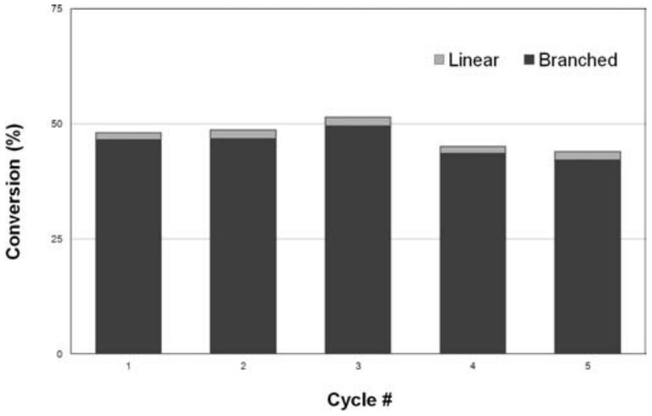

Figure 7. Hydroformylation catalyst recycles in ACN/H_2O OATS with 3.1 MPa of CO_2.

CO_2. The concentration of TPPMS in the ACN-rich phase is below 1 ppm at 3.5 MPa of CO_2. At the same pressure, the calculated amount of rhodium leaching is less than 100 ppb (rhodium leaching is calculated by assuming that one rhodium molecule coordinates with three molecules of TPPMS). The TPPMS retention and Rh leaching measurement are comparable to those reported by Hallett et al. in THF/H_2O OATS.[5]

The recycling of catalyst for five consecutive reactions is demonstrated in Figure 7. We ran the reaction for 1 h at 60 °C and then used 3.1 MPa of CO_2 (same as reaction pressure) to cause phase separation; we then removed 85 vol % of the organic-rich layer. The average *p*-methylstyrene conversion of the five recycle experiments is 47.6 ± 3.0 %, and the branched product selectivity is 95.9 ± 0.5 %. The recycle experiments reflect constant catalytic activity with an average TOF of 193.2 ± 12.3.

■ CONCLUSIONS

We have demonstrated the use of phase equilibria for creating sustainable processes. In the work we report the use of organic-aqueous tunable solvents for a pharmaceutically relevant reaction, the hydroformylation of *p*-alkylstyrene (with *p*-methylstyrene as model compound). The homogeneous reactions provide an order of magnitude improvement in rate and more than 30 % increase in the desired product selectivity when compared to their heterogeneous analogues. The CO_2-induced heterogeneous separation of the product from the catalyst provides and efficient and simple way to remove 99 % of the product and to recover 99.9 % of the catalyst, which was then successfully recycled for five consecutive reactions.

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