Quantitative Characterization of a Catalyzed PHIP Reaction

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TARGET AUDIENCE: Scientists interested in parahydrogen induced polarization (PHIP) for signal enhancement to measure metabolic processes and researchers interested in the scientific and technical aspects of developing agents for PHIP methods.

PURPOSE: Hyperpolarization by field cycling and RF transfer utilizing parahydrogen requires a fast addition of hydrogen to preserve the spin alignment of the parahydrogen.[1] To effectively utilize PHIP to produce the highest hyperpolarization, characterization of the reaction kinetics is required. The purpose of this research is to demonstrate how to systematically characterize the reaction kinetics to calibrate and evaluate instrument performance using a common PHIP standard, 2-hydroxyethyl acrylate (HEA). The exact timing for a 100% complete reaction can be predicted by determining the rate constants for temperature, hydrogen pressure, HEA concentration, and catalyst concentration. The objective is to define conditions for our instrumentation which will allow us to complete the reaction quicker than previously published data by other researchers with the end goal to be able to increase the efficiency of PHIP methods.

METHODS   Utilizing laboratory constructed equipment with controlling valves for mixing the reactants and Labview software for precise control of timing, we executed three variations of reaction conditions. (1) The reaction temperature was varied from $25^\circ \rightarrow 65^\circ$ Celsius with the following conditions: catalyst; 2.22 mM, H_2 pressure; 7.1 bar, HEA concentration; 16.8 mM HEA. (2) The hydrogen pressure was varied from $0.6 \rightarrow 7.1$ bar with the following conditions: catalyst; 2.22 mM, temperature; 45° Celsius, HEA concentration; 16.8 mM HEA. (3) The catalyst concentration was varied from $0.25 \rightarrow 1.5$ mM with the following conditions: temperature; 45° Celsius, H_2 pressure; 7.1 bar, HEA concentration; 16.8 mM HEA. All reactions were run for 4 seconds and quenched by removal of the hydrogen by degassing. Proton magnetic resonance spectroscopy was used to quantify the hydrogenation by chemical shift of the ethyl protons bound to the carbon adjacent to the oxygen. These protons have the largest shift resulting from the hydrogenation of the double bond of HEA. The hydrogenation percent was determined by measuring the ratio of the integrated intensity of the proton resonance of the product divided by the sum of the reactant plus the product integrated intensity (percentage; hydrogenation ratio x 100). The hydrogen pressure dependence was fit to the linear portion of the data. The other two reactions were linearly fit to all data points (the catalyst dependence was forced through the zero point to account for no reaction without the presence of the catalyst).

RESULTS

The hydrogenation rate constants for the temperature, pressure and catalyst concentration were: k_T = 0.10%/(sec · $^\circ$C), k_P = 1.1%/(sec · bar) and k_{cat} = 14.9%/(sec · mM) catalyst for a 16.8 mM concentration of HEA and four seconds of reaction time. These rates are dependent on the normalized conditions and serve to demonstrate the net contributions.
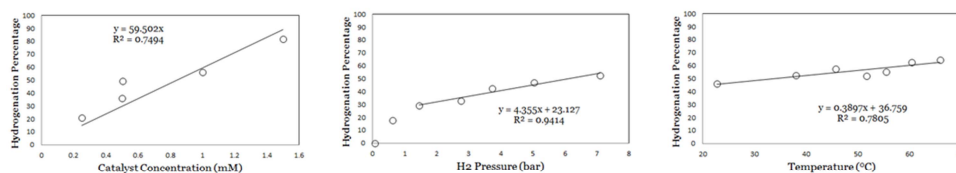

FIGURE 1: Hydrogenation percentage for 16.8 mM HEA for a 4 second reaction time. Other universal fixed conditions are 7.1 bar H_2 pressure, 2.2 mM catalyst, 45° Celsius and 4 second reaction time.

DISCUSSION

Prior researchers have varied the reaction conditions to maximize the polarization using a 4 second reaction time.[2-4] By determining the kinetics we defined the requirements to perform the chemical reaction in 2 seconds which should lead to increased polarization yields since less relaxation of the parahydrogen protons inserted can occur before the polarization transfer to the ^{13}C nucleus. Based on the catalyst concentration dependence this can be accomplished utilizing a 10 mM HEA sample with 2mM catalyst concentration (45 Celsius and 7.1 bar H_2). The nonlinear pressure increase for low pressures indicates that the solution volume limits the hydrogen concentration which results in a minimal increase in relaxation rate with increasing pressure (x2 pressure $\cong$ 20% increase in hydrogenation). Increases in temperature within the acceptable range for the equipment have little effect on increasing the hydrogenation.

CONCLUSION

Optimization of hyperpolarization of HEA is best accomplished through the variation of the catalyst concentration; other factors like hydrogen pressure and temperature only have minimal effects. This type of evaluation is crucial for understanding how to best control the chemical reaction to provide an effective hyperpolarization method.

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