The Discovery and Development of a Safe, Practical Synthesis of ABT-869

Albert W. Krugerc,* Michael J. Rozema, Alexander Chu-Kung, Jorge Gandarilla, Anthony R. Haight, Brian J. Kotecki, Steven M. Richter, Albert M. Schwartz and Zhe Wang

Abbott, Process Research and Development, 1401 Sheridan Road, North Chicago, Illinois 60064

Supplementary Information:

Measurement of Dissolved Oxygen in Ethanol: Two Liquid Methods

Although many vendors have oxygen meters for headspace analysis, a dissolved oxygen probe would allow for a direct measurement of dissolved oxygen with time and would easily allow the calculation of the volumetric mass transfer coefficient \( (k_{La}) \) for our solvent system. In searching for probes that were capable of measuring dissolved oxygen in solvents an optical probe developed by In Situ, Inc. for aqueous environments (TROLL 9500) was found to work in pure ethanol. The probe works by measuring the amount of red light produced by a luminescent film that is excited by an internal blue laser. The amount of red light produced is inversely proportional to the amount of oxygen present in the solvent in contact with the luminescent film.

Since this probe was designed for aqueous measurements and the solubility of oxygen in water is 10,000 ppm\(^1\), a second method of verifying the probe readings in ethanol, which has a dissolved oxygen solubility of about 60,000 ppm\(^2\), was necessary. A UV-Vis colorimetric method described by Franco\(^3\) was used to verify the probe response to the level of oxygen in the ethanol solvent system. The dissolved oxygen probe response is not linear with respect to oxygen present in the ethanol (see calibration curve, Figure 1). As the concentration of dissolved oxygen in ethanol reaches about 20,000 ppm, the sensitivity of the probe drops and plateaus to probe reading of about 10,000 ppm. Though the UV-Vis method was found to be more sensitive to the amount of oxygen present, it was also inherently more difficult to use, as glove bag sampling techniques were necessary. Therefore, the relationship depicted in the figure above was used as a standard calibration to transpose TROLL 9500 probe-generated values into actual values of dissolved oxygen in ethanol.

---


Experimental for the Determination of Catalyst Oxygen Sensitivity

The Pd(OAc)$_2$ and ligand 12 were charged as solids to a reactor and degassed by purging with nitrogen sweep. A separate flask containing the required amount of ethanol was purged with nitrogen (bubbling). The amount of dissolved oxygen was monitored via the TROLL 9500 probe (In-situ Inc.) and at predetermined values of dissolved oxygen the required amount of ethanol would be passed to the flask containing the catalyst components. Once the ethanol was transferred, the catalyst solution was heated to 50 °C for 30 min. A separate flask containing 10, 6, and K$_3$PO$_4$ and ethanol/water was degassed to <10 ppm (bubbling), once the catalyst preparation was complete, the flasks were combined and warmed to 55 °C according to the Second Generation Process to 1. (Experimental section). Samples at 2 and 24 h were analyzed for conversion by HPLC.

Kinetic Evaluation of Nitrogen Sparge to remove Oxygen at the Laboratory Scale

The TROLL 9500 dissolved oxygen probe was placed into a 250 mL glass reactor with retreat curve impeller. A nitrogen line was fed into the bottom of the reactor via a 14-inch stainless steel syringe. The mixing was controlled at either 100 rpm (Low) or 500 rpm (High). The nitrogen purge rate was controlled using a Gilmont Flow meter between 0.1 L/min and 2 L/min. The reactor was filled with 200 mL of ethanol saturated with oxygen; then the nitrogen purge was started. The dissolved oxygen probe was programmed to take a measurement every 10 seconds. The data was transformed using the calibration curve (Figure 1). The dissolved oxygen data was then treated as a first order process and plotted in Figure 2. The resulting first order equation is as follows:

\[ \ln \left( \frac{O_2(t)}{O_2(initial)} \right) = (k_2a)t \]
Measurement of Oxygen at the Pilot Scale: Mass Transfer upon Scale-up

Following the discussion and model by Garcia-Ochoa,\textsuperscript{2} estimated mass transfer coefficients were calculated for varying conditions of mixing, nitrogen flow, and liquid level in 300 and 750-gallon tanks. The parametric investigation presented\textsuperscript{2} as well as our calculations indicate that under our normal pilot operating conditions mixing has the dominant effect upon the mass transfer coefficient. Under the assumptions of 5-10% hold-up\textsuperscript{4}, fully developed mixing with a power number of $N_p=0.65$, effective bubble diameter\textsuperscript{4}, and volumetric nitrogen flow rate of 50 L/min through a 1-inch orifice, mass transfer coefficients for the removal of oxygen from ethanol were estimated for the pilot plant scale between 0.003 s\textsuperscript{-1} and 0.005 s\textsuperscript{-1} for mixing of 30 rpm and 60 rpm, respectively. Based upon the early lab data generated in the dissolve oxygen section of this report, these mass transfer coefficients were within the right order of magnitude.

Since the TROLL 9500 dissolved oxygen monitor was not rated for use in the pilot plant an Alpha Omega Instruments headspace analyzer (Series 3000) was used to monitor the progression of the oxygen removal. The 3000 series instrument is designed to monitor trace amounts of oxygen, but has an upper limit of 1000 ppm. The monitor was set-up to measure a side stream of the headspace gas and was used to determine when the amount of oxygen was less than 1000 ppm, as most of the time the monitor would be off-scale. Once the headspace value fell below 1000 ppm the time and oxygen

\begin{footnotesize}
\end{footnotesize}
values were recorded until the readings were below 10 ppm. A mass transfer coefficient was fit to the data and the amount of dissolved oxygen was then calculated from the headspace values.

The operating conditions used to purge oxygen from the ethanol/water system were a mixing speed of 30 rpm and 50 L/min nitrogen purge rate. The mass transfer coefficient that was measured was 0.0023 s\(^{-1}\), which is in good agreement with the predicted value. This leads to a removal time for 99% of the oxygen in 33 minutes, which is far less than the direction specified time of 1 hour. The mass transfer correlation\(^3\) used to estimate mass transfer at varying operation conditions is adequate to describe the ABT 869 solvent system and can be used as a tool to determine purge times for technical transfer to other sites or other reactors on site. Additionally, the headspace oxygen analyzer has proven to be an effective means of monitoring the oxygen purging procedure as a PAT tool.

**Extension into Pilot Equipment**

Measurement of the oxygen level at pilot scale required a transition to head-space monitoring.\(^6\) A complicating factor was that the Alpha-Omega headspace detector (series 3000) only functioned at below 1000 ppm oxygen levels. That being the case, a 500 gal reactor was charged with an ethanol/water solution and sparged at a rate of 50 L/min through the bottom valve at 30 rpm. After the oxygen level had reached <1000 ppm, the rate of oxygen removal from the headspace was measured (Figure 2). The rate constant for oxygen removal using the same model as above was determined to be 0.0023 s\(^{-1}\) for the portion of the degassing below 1000 ppm. This was in good agreement with that observed in the lab (see Table 7) and indicated that the lab-scale degassing parameters (100 rpm stirring, 0.3 L/min nitrogen flow) and pilot scale 500 gal reactor (30 rpm stirring, 50 L/min nitrogen flow) gave similar absolute rates of oxygen removal. This specific rate constant (0.0023 s\(^{-1}\)) corresponds to the removal of approximately 99% of the oxygen from the ethanol/water solution over 33 min of sparging (200000 ppm down to 2000 ppm). The first order lab model that was developed scaled well to the pilot scale de-oxygenation in the EtOH/water solvent system, and thus similar time parameters could be used to scale degassing operations from the lab to the pilot plant (assuming proper accounting for nitrogen flow and mixing speed).

Even with some success in developing a model that will allow us to predict the time needed to degas a specific solution in a specific vessel, there are limitations to developing general models, due to the impact of headspace, vessel shape and bubble size to the mass transfer of oxygen out of the system.\(^2\) Perhaps the most advantageous use of an oxygen head-space analyzer is as a Process Analytical Technology (PAT), so that real-time measurement of the oxygen level can be determined. Instead of a typical time-bound parameter to scale the degassing operation, a more direct oxygen-level measurement can be used to give maximum operational flexibility and confidence in the scale-up operation.

---

\(^6\) The solution oxygen monitor was not explosion proof (XP), so could not be used in the pilot plant.