MECHANISTIC STUDIES OF BORANE REDUCTION OF CARBOXYLIC ACID WITH INTEGRATED TECHNIQUE

Simon Leung, Paul Lobben and Srinivas Tummala, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, USA.

An integrated reactor with multiple monitoring tools is routinely used to study organic reactions. The acquired data, after kinetic and mechanistic analysis, provide essential understandings to improve process operation and safety. Borane reduction of carboxylic acid was investigated by this integrated technique. Mechanistic and scale-up issues will be discussed in this presentation.

Keywords: kinetic analysis, mechanistic analysis, borane reduction, simulation, kinetic modeling, scale-up.

Introduction

Reduction of carboxylic acids with borane is a common process in the pharmaceutical industry. In-situ generation of borane by reacting NaBH₄ with methanesulfonic acid in the presence of DME is a popular choice. However, in our development work, the scale-up of such a process generated a number of concerns. Firstly, use of DME in large scale is highly undesirable because of possible teratogenic activities. Secondly, the resulting reaction mixture is a very thick paste, which would be a potential problem in mixing and heat transfer. Finally, in this particular case, the reaction time for complete reduction was too long resulting in unacceptable levels of impurities.

As a result, use of commercially available BH₃·THF complex in THF was investigated and proved to be superior to in-situ preparation of borane. Additionally, the hydrogen off-gas is reduced by more than 50% and the process is greatly simplified.

Nevertheless, during the pilot plant campaign, a strong secondary exotherm was observed after the addition of borane over 45 minutes was completed. This observation necessitated the need to address some potential issues for further scale-up. First, the magnitude of the exotherm had to be measured accurately in order to predict the heat load on the cooling systems of different reactors and at different scales for future campaigns. Of particular concern was the observation that the peak of the exotherm occurred after the addition of BH₃·THF was completed; this translates into limited control of the process. This unusual exothermic behavior necessitated a detailed examination and understanding of the process to overcome the aforementioned issues.

Experiments and Results

The experiments discussed in this paper were all carried out with the integrated reactor, which consists of a RC1e reaction calorimeter (Mettler-Toledo GmbH) equipped with an in-situ FTIR system (ReactIR 1000 ASI systems, Millerville, NM) and a Brooks mass flow meter (GSI automation, Pine Brook NJ) to measure the hydrogen off-gas.

The starting carboxylic acid can react with BH₃ to form the mono, di or triacyloxyborane species (A, B or C respectively), as reported previously by Brown and Stocky (1). If triacyloxyborane is the intermediate, then 0.33 equivalent of BH₃·THF would be sufficient for generating one equivalent of hydrogen. If monoacyloxyborane is the intermediate, then one equivalent of BH₃·THF is required.
to liberate one equivalent of hydrogen. An experiment was performed where BH$_3$·THF was added in stages, and it was found that 0.5 equivalent BH$_3$·THF was required for the evolution of one equivalent of hydrogen (which translates into complete conversion of starting material) as measured by the mass flow meter of the integrated reactor. This suggested that diacyloxyborane is the key intermediate. The total heat liberated by the addition of 0.5 equivalent of the reagent was ~50 kJ/mol of starting material. This intermediate is finitely stable and was not reduced when held at 0°C overnight.

However, after another 0.5 equivalent of BH$_3$·THF was added, 88% of the intermediate was converted to the desired product overnight. This observation suggests the formation of the monoacyloxyborane intermediate by a redistribution mechanism and subsequently reduced to the product.

Figure 1 shows another integrated reactor experiment where 1.5 equivalent of BH$_3$·THF was added to the carboxylic acid over a 90 minute addition time. The total heat liberated from the reaction was ~280 kJ/mol of starting material. The hydrogen off-gas clearly indicated the consumption of the starting material, and the formation of trialkoxyboroxine was monitored by in situ FTIR. The presence of trialkoxyboroxine was confirmed by the IR signal at 718 cm$^{-1}$, which is the diagnostic value of a boroxine skeleton. In this experiment, the use of 1.5 equivalent of BH$_3$·THF reduced the reaction time to 3 hours. This result coupled with previous observations suggests that the monoacyloxyborane can reduce to the product in two ways: either by reacting with another monoacyloxyborane or by reacting with the excess BH$_3$. Based on the above results the following mechanism was proposed.
**Kinetic Model and Simulation**

The proposed mechanism was used to develop a five-step kinetic model. The starting carboxylic acid (SM) reacts with BH$_3$ to form the monoacyloxyborane A followed by subsequent transformation to the diacyloxyborane intermediate B by reacting with another molecule of the starting acid. Then the diacyloxyborane B reacts with another 0.5 equation of BH$_3$ to transform back to monoacyloxyborane A. Intermediate A has two major pathways to convert to product, namely reduction by the reactive B–H bonds of A or by excess BH$_3$. The reactive B–H bonds of A are represented by a pseudo species (B–H). The five steps and the associated rate expressions are,

\[
\begin{align*}
\text{(SM)} + (\text{BH}_3) & \rightarrow (A) + (\text{H}_2) \quad \text{Rate: } k_1 (\text{SM})(\text{BH}_3) \\
(A) + (\text{SM}) & \rightarrow (B) + (\text{H}_2) \quad \text{Rate: } k_2 (\text{SM})(A) \\
(B) + (\text{BH}_3) & \rightarrow 2(A) \quad \text{Rate: } k_3 (B)(\text{BH}_3) \\
\end{align*}
\]

Reduced by reactive BH bonds of (A)

\[
\begin{align*}
(A) + 2(\text{B–H}) & \rightarrow (\text{Product}) \quad \text{Rate: } k_4 (A)(\text{B–H}) \\
\text{Reduction by excess BH}_3 \\
(A) + (\text{BH}_3) & \rightarrow (\text{Product}) + (\text{B–H}) \quad \text{Rate: } k_5 (A)(\text{BH}_3)
\end{align*}
\]

This model was used along with the heats of reaction, off-gas data and in situ FTIR data to develop a thorough understanding of the kinetic and mechanistic details of the reaction. Kinetic rate constants were regressed using the software Batch-CAD, (Version 7, GSE systems, MD) on the experimental data of the 90 Minute addition run. The following rate constants were estimated,

\[
\begin{align*}
 k_1 & = 13.9 \text{ kmol m}^{-3} \text{ min}^{-1}, \\
 k_2 & = 2.08 \text{ kmol m}^{-3} \text{ min}^{-1}, \\
 k_3 & = 459 \text{ kmol m}^{-3} \text{ min}^{-1}, \\
 k_4 & = 0.0129 \text{ kmol m}^{-3} \text{ min}^{-1}, \\
 k_5 & = 0.245 \text{ kmol m}^{-3} \text{ min}^{-1}
\end{align*}
\]

The model was then used to simulate the experiment with the 45 minute addition time and was found to predict the experimental results with reasonable accuracy.

**Conclusions**

This investigation has clearly demonstrated the advantages of expanding the concept of integrated technique to include mechanistic studies and kinetic modeling. By performing a limited number of integrated reactor runs, the pilot plant observation was accurately reproduced and a better mechanistic understanding of the process was obtained. Based on the proposed mechanism a kinetic model was developed and the rate constants for the various steps have been estimated. Furthermore, the experimental runs were simulated using the kinetic model and it was shown that the model predicted the experimental results reasonably well. The model can now be used to simulate different reaction conditions, which would enable elucidation of scenarios for better control of the process for further scale-up.

**References**


Simon Leung, Paul Lobben and Srinivas Tummala, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, USA.

This lecture was held at the 10th RXE User Forum Europe in Lucerne, Switzerland, in November 2001.

Mettler-Toledo GmbH, CH-8603 Schwerzenbach.

Layout by Regula Rellstab.