This column provides examples of cases in which students have gained knowledge, insight, and experience in the practice of chemical engineering while in an industrial setting. Summer internships and co-op assignments typify such experiences; however, reports of more unusual cases are also welcome. Description of the analytical tools used and the skills developed during the project should be emphasized. These examples should stimulate innovative approaches for bringing real world tools and experiences back to campus for integration into the curriculum. Please submit manuscripts to Professor W. J. Koros, Chemical Engineering Department, University of Texas, Austin, Texas 78712.

CO-OP STUDENT CONTRIBUTION TO CHEMICAL PROCESS DEVELOPMENT AT DUPONT MERCK

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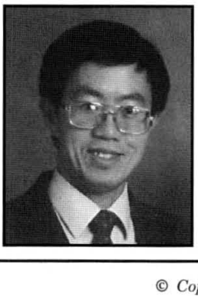
The chemical engineering group of DuPont Merck Pharmaceutical Company's Chemical Process R&D Department (CPR&D) began hiring co-op students for six-month assignments in 1994. The program is based on the belief that the arrangement would be mutually beneficial to both the student and the company.

THE COMPANY'S NEEDS

The Mission of CPR&D is to develop scalable processes for the preparation of candidate pharmaceutical chemical substances and to use the process to produce large quantities of candidate drug substance in the pilot plant to support clinical trial needs. During the early stages of the development of a new candidate drug substance, chemists work in the laboratory at small scales to devise multistep processes to synthesize intermediates and the final drug substance. Chemical engineers at this stage would provide early input to the chemist to ensure that the process could be practically scaled up to large scale in the plant and that it is safe, environmentally sound, and economical.

When pharmacology and toxicity studies show more evidence that the candidate drug is effective in treating the target disease and has minimal adverse side effects, a new phase of development is entered where a larger quantity of candidate drug substance is needed to begin clinical trials on humans. Thus, a pilot plant is now needed to produce the compound. At this stage, chemical engineers need to ensure the operability of the process at large scale. Effects of process parameters such as temperature, pressure, concentration, etc., need to be studied. Conditions need to be defined to ensure smooth and efficient unit operations, such as extraction, distillation, crystallization, filtration, drying, etc. Potentially hazardous conditions need to be identified and avoided. Procedures for the safe handling of hazardous materials need to be developed. Effluents and emissions need to be minimized and handled in compliance with environmental regulations.

As the pilot plant run approaches, the engineer needs to prepare operating instructions, to hold hazard and operability (HAZOP) reviews, and to develop plant equipment setups. During the actual pilot-plant run, the engineer is fully responsible for the operation of every step of the process and is constantly on the plant floor to monitor the progress of the operations and to give instructions when the run does not proceed as expected. Clearly, a tremendous amount of work



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is involved in taking a process from the bench to the plant, and an engineer can use a lot of assistance at any stage of the process development.

A co-op student is in a good position to provide the needed help. A "head count" may not exist for a permanent technical position since the industry as a whole is extremely cost conscious, and a temporary, six-month position can fill the gap. Co-op chemical engineering students are usually energetic, enthusiastic, and have a good technical background. Thus, important studies can be carried out that could not be done otherwise, and the company benefits greatly from the co-op student's employment.

BENEFITS TO THE STUDENT

Students gain industrial experience and have an opportunity to apply what has been learned from textbooks to solve real-world problems, reinforcing their learning experience. They can also encounter areas that stimulate interest, motivating them to pursue more in-depth learning or research on a particular subject, or they might even uncover deficiencies in their technical knowledge that can be reinforced upon their return to school. Furthermore, the students can observe and experience how people of various disciplines interact and cooperate to plan and execute a project and how safety and environmental compliance is emphasized in industry. Not least, the students are rewarded financially with a stipend.

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SELECTION OF A STUDENT

For the chemical engineering group of CPR&D, the co-op students selected so far have all been from Drexel University in Philadelphia. The school has a long tradition of co-op study for essentially every discipline. One advantage of employing students from Drexel is its close proximity to Du Pont Merck's Deepwater, New Jersey, Process Research Facility (PRF). The students are assumed to reside near the school; therefore, there is no need to find housing for them during the co-op period. Future co-op students, however, may very well be selected from more distant schools.

About three months before the beginning of the co-op cycle (usually from April through September and from October through March), those engineers who feel they can benefit from a student's assistance and who can provide guidance and training to a student sign up to become a supervisor/mentor. They then participate in the selection of co-op students to fill the positions. A co-op student is usually chosen from a list of candidates provided by the engineering school's co-op program office. A preliminary selection is based on the resumes the students have submitted and the relevant courses they have taken; the student's GPA, and any prior co-op experience are also considered. A campus interview with as many as eight pre-selected students is then conducted, and an offer is extended to the student who is considered most likely to succeed in this six-month assignment.

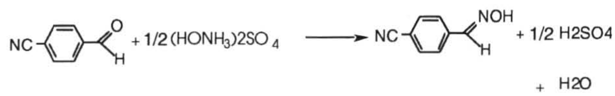
CASE HISTORY

A student was chosen from Drexel University to fill a co-op chemical engineer position at PRF from April through September of 1995. The student was entering his senior year and was scheduled to get his BS degree in June of 1996. Relevant courses he had taken included organic chemistry and lab, physical chemistry, thermodynamics, material balances, unit operations and lab, heat and mass transfer, process control, etc., and his grades were good. He had worked as a co-op student twice in previous years, first as an applications engineer in a pool treatment chemicals company, and the second as a supervisor in an environmental company handling hazardous materials. He expressed an interest in working in the pharmaceutical industry to gain additional experience.

The assignment for a co-op student is usually a balancing act. The assignment should be challenging enough to sustain the student's interest level and to allow him to use his training and intellectual powers to solve the problems, but not so difficult as to overwhelm and discourage him. Of course, the assignment can be changed or adjusted during the course of the assignment, based either on observation of the student's ability to perform or on his feedback.

The author was involved on a project to develop a candidate cardiovascular drug. The synthesis route required five steps. Like most pharmaceutical processes, the process steps were run in either batch or semi-batch mode. The process was to be scaled up from lab to the pilot plant for the first time. Although the basic steps had been worked out in the lab, there were parameters that had not been evaluated that could be problematic for large-scale operations. The co-op student was given the opportunity to evaluate these parameters.

First Assignment • The first assignment was purposely designed to be very simple, to provide the student with an easy transition to an industrial R&D setting. It involved evaluation of temperature and concentration effects on the reaction of the first step of synthesis. This first step involved the formation of a benzaldoxime from a benzaldehyde, using hydroxylamine sulfate as the reagent:



The reaction involves the protonation of the carbonyl oxygen of the aldehyde by the acid component of hydroxylamine sulfate, which makes carbonyl carbon more susceptible to nucleophilic attack by the basic nitrogen of the hydroxylamine. A water molecule is eliminated from the reaction intermediate to form a carbon-nitrogen double bond of the oxime molecule. At room temperature, the reaction was known to take more than six hours to complete. No additional information was available.

To shorten the reaction time, it is common to run the reaction at elevated temperatures, which was an easy concept for the student to grasp since he had already learned about chemical kinetics in his course work. The student and the author, together, defined the goals of a series of experiments to (1) verify that the reaction would indeed proceed at a faster rate at higher temperature, and (2) quantify the effect of temperature by evaluating the activation energy of the reaction.

The experimental setup consisted of a 3-neck round-bottom flask with a condenser and an overhead stirrer driven by an air motor. The flask was heated by a heating mantle, and the temperature of the reaction mixture was monitored by a thermocouple and controlled by a temperature controller. During the reaction, samples were periodically taken and analyzed by HPLC to monitor the progress of the reaction. Although it appeared to be a routine organic chemistry experiment, an undergraduate student can find it challenging to put together the apparatus to carry out experiments and to use instruments to monitor the reaction for the first time. Thus, for the first experiment the student acted principally as an observer/helper while the author assembled the glassware, conducted the actual experiment, ran instruments, and recorded observations and results in the lab notebook. For the second experiment, the roles were reversed; the author made sure that the student followed safety practices, ran the experiment properly, used instruments correctly, disposed of lab waste properly, and kept accurate records during the experiment.

A base run was first made at room temperature, and several samples of reaction mixture were taken from 0 through 5 hours. Another experiment was then run at 56°C. The reaction went to completion within a much shorter time, as expected.

With the assumption of a second-order kinetics for this reaction, the reaction can be expressed by[1]

$$\ell n\left[(M - X_A)/M(1 - X_A)\right] = (C_{B0} - C_{A0})kt$$

where C_{A0} and C_{B0} are the initial concentrations of reactants A and B; M is the ratio of the two initial concentrations; and X_A is the fractional conversion of A, defined as $X_A = (C_{A0}-C_A)/C_{A0})$.

Using this equation and the experimental data, the reaction rate constant, k, and the activation energy could be calculated, and the rate expression becomes

$$\text{Rate} = k[A][B]$$

$$k = 74900\exp(-8050/RT)$$

To verify this model, the student ran a third experiment,

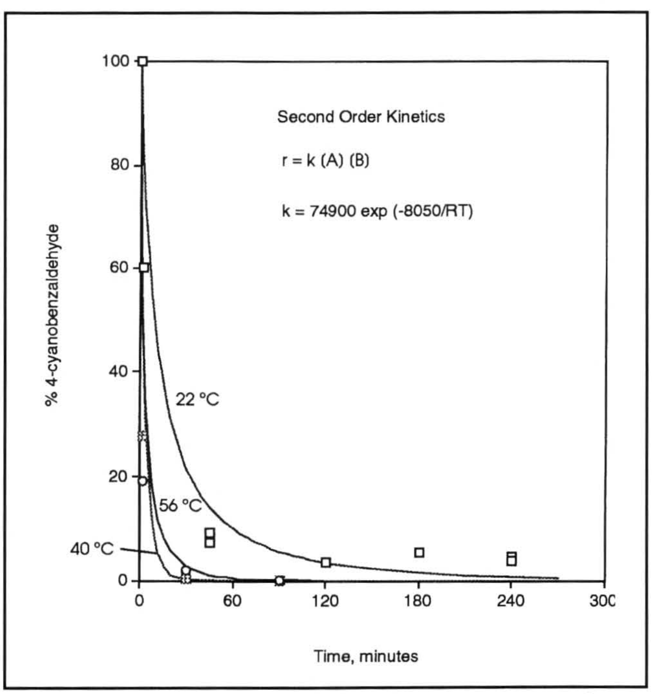


Figure 1. *Oximation at different temperature and concentration.*

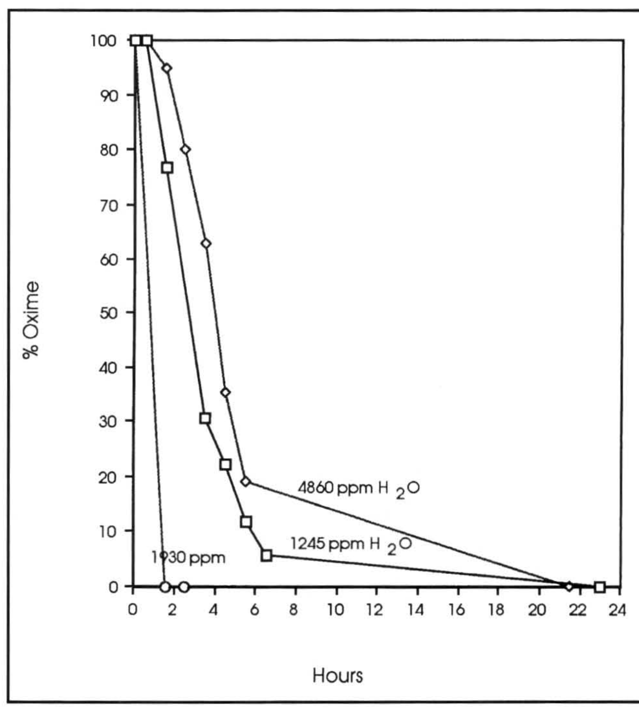


Figure 2. *Effect of water on chlorination rate of oxime.*

now independently, at a different concentration of reagent B (hydroxylamine sulfate) and at a different temperature. The model prediction and the experimental data appeared to agree very well. The results of these three sets of experiments, as well as the model prediction, are shown in Figure 1.

Although simplistic, this information proved to be very useful in practical application to our Step 1 reaction. The simple model enabled us to predict how fast the reaction proceeded at different temperatures and concentrations. We could easily control the reaction rate in a very predictable way by changing reaction temperature or the concentration of the reactants. In fact, we decided to raise the batch temperature to 50 °C in the pilot-plant run to shorten the reaction time and to ensure complete reaction.

To the co-op student, it was exciting to take part in a simple experiment that yielded results with real-world applications. The kinetic equation derivation also served as a preview of the kinetics course he was going to take when he returned to school. Additionally, the student had become familiar with the equipment setup, the lab procedures, and the instrument use; he could work independently with minimal supervision and was ready to take on the second task.

Second Assignment • The next chemical step was to chlorinate the oxime using N-chlorosuccinimide as the chlorinating agent:

Oxime N-chlorosuccinimide Chloro-Oxime Succinimide

In earlier experiments, the reaction was found to be very exothermic, and under adiabatic conditions the temperature rise was estimated to be nearly 70 °C. Thus, the reaction rate needed to be controlled to avoid the temperature runaway. But there was not enough information on what catalyzed the reaction. There were experiments that took overnight (about sixteen hours) for the reaction to complete, while there were also runs that went to completion within one hour (with considerable temperature rise). The speculation was that a free radical mechanism was involved and that water catalyzed the reaction, because those batches that showed fast reaction appeared to contain more water than the others. But without definitive experimental data to prove it, this hypothesis alone was not satisfactory for scaling up to the pilot scale, because heat removal at large-scale units is generally less efficient than at small scale due to a decrease in the heat transfer area/volume ratio as the volume increases. An out-of-control exothermic event could lead to a hazardous situation. Thus, the second task for the co-op student was to find the dominant factor that determined the reaction rate.

The student and the author agreed that the "water theory" should be tested first. Two experiments were run, using the same lot of oxime. The student deliberately added a small amount of water to the reaction mixture and used Karl-Fischer titration to determine the water level in the reaction mixture. He found that the increased water level did not increase the reaction rate, as shown in Figure 2, where the results of the two experiments (at 1245 ppm and 4860 ppm water, respectively) were plotted.

The student was puzzled by the result of a third experiment using a different lot of oxime, also shown in Figure 2. The starting mixture had a water content of 1930 ppm (between the water levels of the first two experiments), but the reaction went so fast that it was complete in less than two hours. Thus it became clear to the student that some other factors were involved in accelerating the reaction rate.

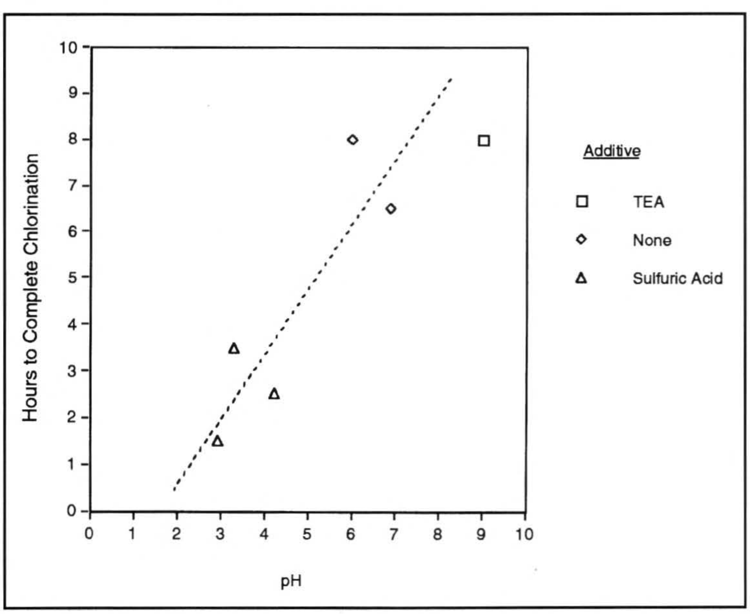


Figure 3. *Chlorination rate increases with decreasing pH.*

The author showed the student that some of the literature[2] indicates that acid catalyzes the chlorination reaction through the activation of a chlorine atom of N-chlorosuccinimide. The author suggested that a series of experiments be run at different pH levels to see the effect on reaction rate, using sulfuric acid to lower the pH of the solution and triethylamine to raise the pH. The student was now very skilled in running these experiments, and he generated the data shown in Figure 3. It shows that acid indeed catalyzes the reaction, because the reaction took less time to complete at lower pH values. The observation was interesting because it offered a plausible explanation why some lots of oxime reacted faster than others; when oxime was prepared using hydroxylamine sulfate in the previous step, the by-product was sulfuric acid. Thus, if the acid was washed away by water to a different degree during oxime isolation, these different lots of oxime would contain different amounts of residual acid and would be chlorinated at different rates.

This hypothesis had one flaw, however. Some experiments showed very fast chlorination of oxime while the pH of the system was not low at all. There is also literature[3-5] that shows that base catalyzed the chlorination. So we discussed the possibility that the hydroxylamine sulfate itself, rather than the by-product sulfuric acid, had the dominant effect on the reaction rate. We planned more experiments, each with a different amount of hydroxylamine sulfate added. The result, shown in Figure 4, shows that hydroxylamine sulfate indeed had the most pronounced effect on the reaction rate; even a very low level (0.7% by weight of oxime) catalyzed the reaction to completion in less than fifteen minutes.

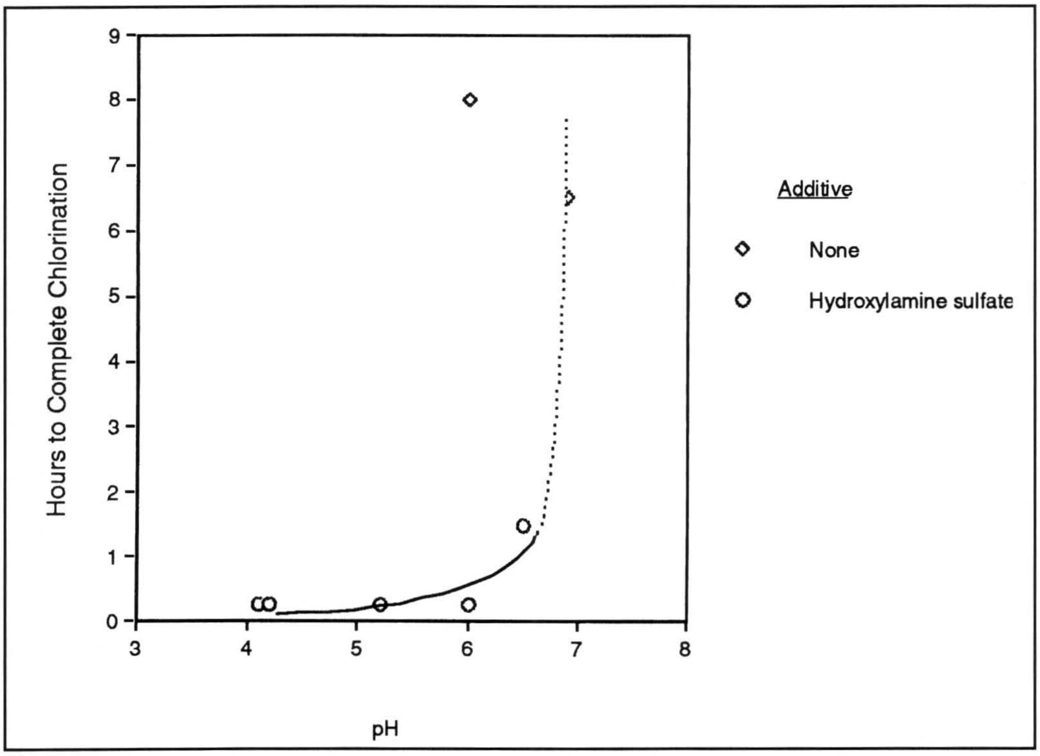


Figure 4. *Chlorination rate strongly depends on hydroxylamine sulfate.*

These results proved extremely useful for the scaleup of the process. It showed how important it is to remove residual sulfuric acid and hydroxylamine sulfate from the previous step. A more stringent specification could now be set to assure that the residual level of hydroxylamine sulfate is low enough in the oxime for the next step. A method also became available to shorten the reaction time by the controlled addition of this catalyst.

During the actual pilot-plant runs, samples of oxime were taken, and the student conducted use tests of the oxime to predict how the material would behave in the pilot reactor in the next step.

Other Assignments • The student was subsequently assigned additional tasks. One was to investigate various variables affecting the efficiency of an enzymatic resolution process. The process employed an enzyme to resolve a racemic ester into (R)-acid (desired product), leaving behind the "wrong" isomer, (S)-ester. The variables included enzyme loading, pH, organic solvent, surfactant concentration, etc. Another assignment was to evaluate various organic bases for the racemization of the wrong isomer for recycle purposes. Important experimental data were obtained that would prove useful for the further development of the process.

The student also participated in the preparation for pilot-plant runs, including gathering information on the hazardous properties of various chemicals to be used, vent-size calculations, heat-transfer calculations, material-balance calculations, etc., that required application of his chemical and engineering knowledge.

CONCLUSION

With clearly defined scope and objectives, along with a properly designed assignment, the co-op student was able to adapt quickly to the industrial R&D environment. He was able to learn various aspects of process development, acquire good lab skills, to interact with various personnel in the industrial organization, and was exposed to various challenges in the scale-up of chemical processes . At the same time, the company obtained important experimental data and kinetic correlations that were used to successfully scale up an important process. The experience was highly beneficial to both the student and the company.

ACKNOWLEDGMENT

Greg Flyte of Drexel University was the co-op student in this assignment. His work made a valuable contribution to the project.

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