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Recovery of Ammonia in the Dipeptide Manufacturing Processes

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Abstract:

An example of an improvement in recovering ammonia in a dipeptide manufacturing process is described. The synthetic method, which makes use of the ammonolysis reaction, has been studied and found to produce dipeptides of satisfactory quality in high yield on a large scale. However, the treatment of unreacted ammonia in the ammonolysis reaction caused a reduction in the productivity and increased the production cost during actual manufacture. Therefore, a method to recover the unreacted ammonia has been investigated through simulations and trial runs using model solutions. Consequently, the modified process provided an improvement in the productivity and cost savings. In addition, the recovered ammonia could possibly be used for recycling. It was verified in a lab experiment that the reused ammonia did not lower the quality of the dipeptide.

Introduction

The synthetic production of the dipeptides, glycyl-L-glutamine (**3a**; GlyGln) and L-alanyl-L-glutamine (**3b**; AlaGln), has already been studied.[1] The established process of **3a** and **3b**, which was slightly different in terms of reaction conditions and work-up procedures, consisted of the reaction of α-halogenated acid with thionyl chloride and the Schotten−Baumann reaction with L-glutamine followed by an ammonolysis reaction (Figure 1). This method was selected as the best for dipeptide manufacturing from the viewpoint of quality and yield. Therefore, the production was successfully scaled-up.[1] However, there was a problem about the treatment of wastewater during the actual production. In the ammonolysis reaction, an excess of ammonia was required to reduce the byproduct formation, and the unreacted ammonia generated the wastewater. Its treatment resulted in a decrease in productivity and extra cost. Therefore, we started to investigate how to recover the unreacted ammonia by simulations and trial runs in the plant. In this paper, the following is an example of the improvement mainly focused on the GlyGln process, but a similar improvement will be applicable to the AlaGln process as well.

Problem of Ammonia Wastewater. The reagents of the ammonolysis reaction in the GlyGln process are 28 wt % aqueous ammonia and ammonium bicarbonate (Figure 2). The total ammonia source is 14 mol equiv to **2a**. It is the optimized value by the experiments in the tradeoff between the yield and the cost of ammonia. If the ammonia mol equiv is reduced, byproducts will increase.

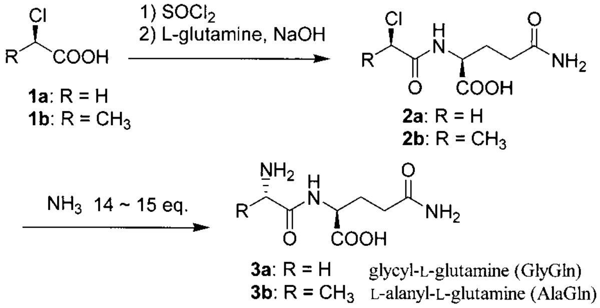

Figure 1. **Synthetic routes of dipeptides 3a and 3b.**

$$\mathbf{2a} \xrightarrow[\text{NH}_4\text{HCO}_3 \quad 5\text{ eq.}]{28\text{ wt\% aq. NH}_3 \quad 9\text{ eq.}} \mathbf{3a}$$

Figure 2. **Ammonolysis reaction in the GlyGln 3a process.**

The mechanism for the ammonia wastewater generation is as follows: After the reaction, the reaction mixture was continuously concentrated in a vacuum evaporator, and then the unreacted ammonia was evaporated and dissolved in the circulating water of the ejector pump. In the pump, freshwater was added to the circulating water to maintain the vacuum, and the overflow liquid from the water pit was discarded as wastewater. The ammonia concentration of the wastewater was about 4000 ppm. However, it had to be controlled under 200 ppm, according to the plant bylaws which were based on the allowable nitrogen concentration per the city regulation of 240 ppm. Thus, the wastewater had to be diluted with freshwater, and also stored until the treatment was finished. This treatment process required unexpected time and money (fee for putting wasting water in city sewer) and affected the productivity and the total production cost of the GlyGln process.

Simulation

To recover the unreacted ammonia, a scheme to install a condenser between the evaporator and the ejector pump was considered. Thus, the unreacted ammonia was expected to be recovered as a condensed liquid from the condenser during the operation of concentrating the reaction mixture after the ammonolysis reaction. As for the condenser, the use of an idle condenser for another production area was desirable. Feasibility studies of this scheme were then carried out by simulations.

Simulation Method. The components, handled in the simulations, were water and ammonia. In the simulations, the nonvolatile components such as GlyGln were ignored. Ammonium bicarbonate was replaced with ammonia, because it was found to mostly decompose and vaporize in

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[1] Sano, T.; Sugaya, T.; Inoue, K.; Mizutaki, S.; Ono, Y.; Kasai, M. *Org. Process Res. Devel.* **2000**, *4*, 147.

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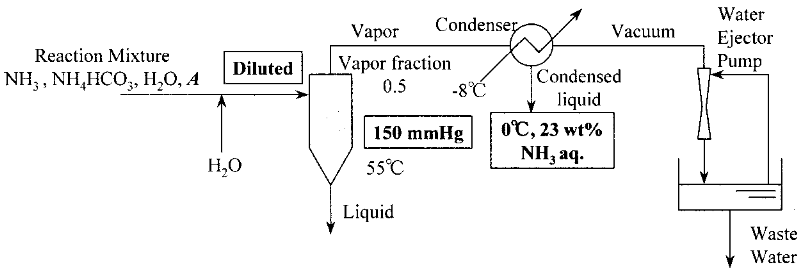

Figure 3. **Simulation result: optimal condition to recover ammonia.**

Table 1. **Result Summary**

	ammonia concentration[a] [wt %]				
	feed	residual	distillate	wastewater	recovery [%]
simulation	15	1	23	*b*	99
trial run 1[d]	14.4	2.4	21.5	<0.02[c]	99
trial run 2[e]	14.3	6.0	20.1	<0.02[c]	72
production	12.5	7.3	15	<0.02[c]	70
ref[f]	17	13	*g*	0.4	*g*

[a] Total concentration of ammonia and ammonium ion. [b] Not simulated. [c] Only confirmed to meet with the plant bylaws (<0.02 wt %). [d] Feed solution was aqueous ammonia. [e] Feed solution was aqueous ammonia with ammonium bicarbonate. [f] In the production before improvement. [g] No corresponding data because of the process difference

the same way as ammonia under heated conditions during the evaporation (35−55 °C).

Aspen Plus (product of Aspen Technology, Inc.) was used as the simulation tool, and built-in physical property methods were used.[2] However, the VLE (vapor liquid equilibrium) of the ammonia−water system was too complicated to be expressed by one model for a wide composition range. As a result, two types of methods were properly used, depending on the conditions. That is, the VLE models in the evaporator and the condenser were different. To evaluate which model was more appropriate, the previous experimental data[3] were referenced.

Simulation Results. The operation of concentrating the reaction mixture was simulated to investigate the best operational conditions, which should achieve the following results:

(1) Total Condensation of the Vapor. It was necessary to minimize the ammonia concentration in the wastewater from the ejector pump, so that the water could be directly disposed without any treatment. Thus, the vapor from the evaporator had to be cooled to under the boiling point and totally condensed to minimize any leakage into the pump.

(2) Maximizing the Ammonia Concentration of the Condensed Aqueous Ammonia. As the use of the recovered ammonia had not been determined, there were no target values for the ammonia concentration of the condensed liquid. However, as high a concentration as possible was desired to widen the use of the recovered ammonia and to reduce its volume.

During the simulation, there were some constraints to be followed besides achieving the above two objectives. The critical process variables under constraint were the heating temperature, the coolant temperature, and the GlyGln concentration of the liquid flow from the evaporator. The heating temperature, that is, the vapor and liquid temperature in the evaporator, had to be kept under 55 °C due to the instability of GlyGln. The lowest temperature of the available coolant was −8 °C. If the concentration of GlyGln in the liquid flow from the evaporator is higher than the solubility, GlyGln might crystallize in the pipeline. Thus, there was a limit in the degree of concentration. There were no solutions that met all of the requirements based on the results from a preliminary simulation. However, it was found that one of the key variables was the operating pressure, that is, the pressure in the evaporator and the condenser, as the pressure drop between them could be assumed negligible. High pressure causes a high temperature in the evaporator and decomposition of GlyGln, and low pressure leads to a low boiling point of the vapor and the leakage of ammonia vapor which cannot be condensed. After all, the appropriate pressure could not be obtained under any conditions which met all of the constraints described above, if the reaction mixture was directly fed to the evaporator.

As there were some ways considered to provide the appropriate pressure, a method to dilute the reaction mixture with water before concentration was selected from the viewpoint of cost and GMP, because there were no changes affecting the reaction. The amount of water to dilute the reaction mixture after the reaction and the optimal pressure were determined from the simulations. Finally, the result is shown in Figure 3; the ammonia concentration in the feed liquid is 15 wt %, the optimal pressure is 150 mmHg, the recovered ammonia as 23 wt % aqueous ammonia, and the heat transfer area of the condenser, which might be diverted, is large enough.

Results in the Plant

Results of the Trial Runs. As the simulation results were considered feasible, some trial runs were carried out in the plant. In the trial runs, model solutions of the reaction mixture were used. The model solutions were prepared with aqueous ammonia, NH_4HCO_3 and water. Thus, the GlyGln reaction product was not included in them.

The results are summarized in Table 1. The trials were divided into two types depending on whether NH_4HCO_3 was included (Table 1, "trial run 1") or not ("trial run 2").

In the trial when NH_4HCO_3 was not included, the model solution was equal to the aqueous ammonia, and the handled

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(2) The built-in methods "ELECNRTL" and "NRTL-RK" were used. While both methods basically consist of the NRTL activity coefficient model for the liquid phase and the Redlich−Kwong equation of state for the vapor phase, "ELECNRTL" is an enhanced method to handle electrolytes.

(3) Sherwood, T. K. *Ind. Eng. Chem.* **1925**, *17*, 745. The experimental solubility data of ammonia in water vs partial pressure of ammonia are described.

components were the same as in the simulations. Thus, the result of this trial run was in quite good agreement with the simulation result.

The result of the trial including NH_4HCO_3 was also in good agreement with the simulation result except for the residual concentration of ammonia (to be precise, ammonia and ammonium ion). The ammonia concentration of the liquid in the evaporator was higher than that of the simulation. The difference was considered as the pH became smaller when NH_4HCO_3 was included, and more ammonia was ionized which remained in the liquid phase. However, an accurate estimation of that concentration was not very important, because the first objective was to recover ammonia as a high concentration of aqueous ammonia and to reduce the leakage of ammonia vapor into the pump. In any case, 20−25 wt % aqueous ammonia was condensed, and it was confirmed that the leakage of ammonia vapor into the pump was so low that the ammonia concentration in the wastewater from the ejector pump could be low enough to meet the regulation for actual production.

Results of the Actual Production. After the trial runs, the operating conditions of concentrating the reaction mixture in the GlyGln manufacturing process was modified. One of the production results is shown in Table 1 (“production”). While the simulated optimal feed concentration of ammonia in Figure 3 was 15 wt %, that in the actual productions was 12−13 wt %, for example, 12.5 wt % in Table 1. The set value of the feed ammonia concentration was lowered for the following reasons:

- It was possible that the result in the actual production might be different from that in the trial runs as the model solution did not include solutes such as GlyGln.
- The feed concentration of 15 wt % was the upper limit concentration to achieve the total condensation of ammonia vapor, and the lower side was steadier.
- In the actual productions, a steadier process was desirable, and the frequent change of the condition in the process should be avoided from the viewpoint of GMP.

Therefore, the amount of added water for the dilution of the reaction mixture was set to a larger value than that required to adjust the feed concentration to 15 wt %. In each later GlyGln manufacturing batch, the concentration procedure has been operated under the same conditions. The concentration of the wastewater from the pump was low enough to meet the regulation, and it can be directly disposed. As it became unnecessary to keep and treat the wastewater, the productivity increased, and cost for the sewage charges was reduced.

As a result, about 70% of the charged ammonia has been recovered in about 15 wt % aqueous ammonia for each batch. The concentration of the recovered ammonia was lower than those in the trial runs. Some of the reasons are that the feed concentration was lower as described above and that the residual concentration was higher probably due to the existence of GlyGln, which is an acid.

Further Development

As described above, the process to recover ammonia has been successfully established to save cost and time. The recovered ammonia still must be disposed of eventually. Therefore, the beneficial reuse of recovered ammonia has been desired. Recycling does not significantly contribute to the cost reduction because ammonia is not as expensive as some other ingredients, but it is environmentally desirable. The possibility of recycling has been examined.

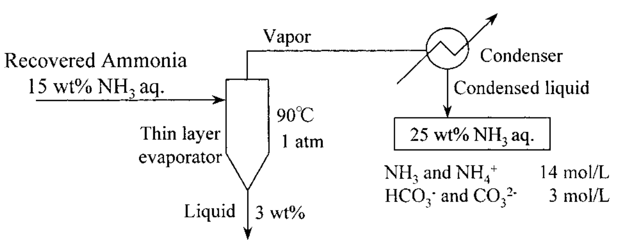

Figure 4. **Optimal condition to enrich the recovered ammonia.**

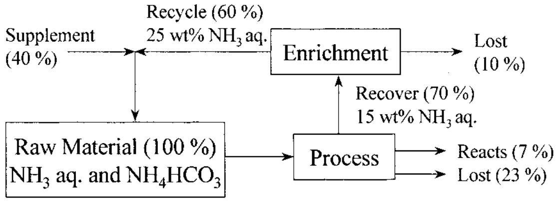

Figure 5. **Prospect for recycling: 60% of the ammonia source can be recycled.**

To be recycled, it is necessary to enrich the recovered ammonia up to a minimum of 25 wt %. At first, we tried to reconcentrate the recovered ammonia during the actual production facilities. The operating condition was decided on the basis of the results of the simulation. In this case, there are no constraints on the temperature of the evaporator as GlyGln is not contained. As the operating condition, which was decided by simulation, and shown in Figure 4, the trial run was operated at atmospheric pressure. The result of the trial run was in good agreement with the simulation results, and 25 wt % aqueous ammonia was obtained. It was a possible sample for recycled ammonia. Using this sample,[4] a lab experiment was carried out according to the reported procedures.[1] It was verified that the quality of synthesized GlyGln using the sample met the specification for GlyGln. Thus, recycling was considered to be feasible from the viewpoint of its quality.

Figure 5 shows the prospect for the recycling derived from the current process and the result of the trial. As a result, 60% of the source of ammonia can be recycled, and 33% is lost. The lost ammonia mainly remains in the evaporation residue. This is difficult to evaporate as it is almost ionized. However, there are some ways being considered to decrease the percentage, for example, the addition of acid, the use of a multi-stage distillation tower, and so on.

Summary

The ammonia recovery system in dipeptide manufacturing processes, utilizing the ammonolysis reaction, has been established. The optimal operational conditions were estab-

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(4) As the analytical result of this sample is shown in Figure 4, the mole ratio of N:C was 14:3. In the lab experiment, NH_4HCO_3 was supplemented in the preparation of the reaction solution so that the ratio became 14:5, the original condition shown in Figure 2.

lished mainly by simulation. The implementation of recovering ammonia contributed to cost and time savings by simplifying the treatment of wastewater. The prospect for recycling of ammonia was also developed. From the viewpoint of quality, recycling was considered to be feasible from the results of the lab experiments.

The results during the actual production showed that the employed simulation methods are proper and will be applicable to the similar reaction system, for example other dipeptide processes.

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