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Identification of Ammonium Chloride as an Effective Promoter of the Asymmetric Hydrogenation of a β-Enamine Amide

Andrew M. Clausen,* Brianne Dziadul, Kristine L. Cappuccio, Mahmoud Kaba, Cindy Starbuck, Yi Hsiao,† and Thomas M. Dowling

Merck & Co., Inc., Process Research & Development (Process Research), P.O. Box 2000, Rahway, New Jersey 07065, U.S.A.

Abstract:

An investigation into the cause of substrate specific hydrogenation performance variability was conducted. A significant and unexpected correlation was observed between apparent pH of a solution of the substrate and rate of conversion and enantioselectivity. This observation led to the examination of low and variable levels of native ammonium chloride in different lots of substrate. The presence of ammonium chloride was found to have a positive effect on reaction rate and enantioselectivity when controlled within a relatively narrow range. Optimal performance was achieved with a mole ratio of 1:1 ammonium chloride to catalyst.

Introduction

Sitagliptin phosphate is a dipeptidyl peptidase IV (DPP-IV) inhibitor which is being studied by Merck & Co., Inc. for the treatment of diabetes.[1] Commercial manufacture of the drug substance involves two isolated steps (see Scheme 1).[2,3] Obtaining the desired compound in high yield relies heavily on the novel enantioselective hydrogenation of an unprotected β-enamine amide. Such syntheses, while powerful, have not been completely characterized, making prediction of the effect of hydrogenation conditions and additives difficult.

During the development of this process, it was found that while individual lots of the starting material enamine amide gave consistent hydrogenation performance (i.e., rate and enantioselectivity) there was significant variability across lots. Results for the hydrogenation ranged from 82% conversion and 89% enantiomeric excess to 99% conversion and 95% enantiomeric excess. Process capabilities could tolerate these fluctuations, but such fluctuations would translate into yield swings of up to at least 21%. Therefore, an exhaustive investigation into the source of this variable performance was initiated.

This examination led us to conclude that the batches of substrate performing at the upper end of the range contained a species present in low concentration which promoted both conversion and desired enantioselectivity. This species was ultimately identified as ammonium chloride. The presence of a substoichiometric amount of ammonium chloride relative to the substrate had a tonic effect on the performance of the hydrogenation. Similar dependence on halide salt additives with the same and similar catalyst systems have been observed before, yet in those cases, the halide salt species were effective only when added in much higher concentrations.[4−6]

Experimental Section

Hydrogenation of Enamine Amide. Methanol (230 mL) is charged to a reactor with 25 g of enamine amide. The resulting slurry is degassed followed by the addition of 0.003 mol equiv (0.046 g) of $[(COD)RhCl]_2$ dimer and 0.0031 mol equiv (0.104 g) of Josiphos SL-J002-1 ligand (Solvias). The reaction mixture is heated to 50 °C and hydrogenated at 100 psig (or 115 psi). After 16 h at temperature and under hydrogen pressure, the batch is cooled to 20 °C and sampled to analyze for percent conversion and enantiomeric excess.

HPLC Method for Conversion. Percent conversion of enamine amide to the freebase of sitagliptin phosphate was analyzed by reverse phase HPLC on an Agilent 1100 according to the following conditions: column, Agilent Extend C-18, 150 mm × 4.6 mm i.d., 5 μm particles; eluent A, 1.21 g of TRIS (Sigma), 800 mL of water, 200 mL of methanol (EM Science), 90 μL of concentrated hydrochloric acid (Fisher); eluent B, 1.21 g of TRIS (Sigma), 200 mL of water, 800 mL of methanol (EM Science), 90 μL of concentrated hydrochloric acid (Fisher); gradient, eluent B, 45% at 0 min to 76% at 8 min held at 76% to 15 min, reequilibrated at initial conditions for 5 min prior to next injection.; flow rate 2.0 mL/min; UV detection at 215 nm; injection volume 5 μL; temperature, 23 °C. Typical retention times were: sitagliptin, 4.2 min; enamine amide, 5.9 min; dimer-like impurity, 12.3 min. Sample preparation: pipet 1 mL of hydrogenation stream into a 50-mL volumetric flask and dilute with eluent A.

HPLC Method for Enantiomeric Excess. A normal phase chiral HPLC method was used to determine enantio-

* To whom correspondence should be addressed. E-mail: andrew_clausen@merck.com.

† Process Research.

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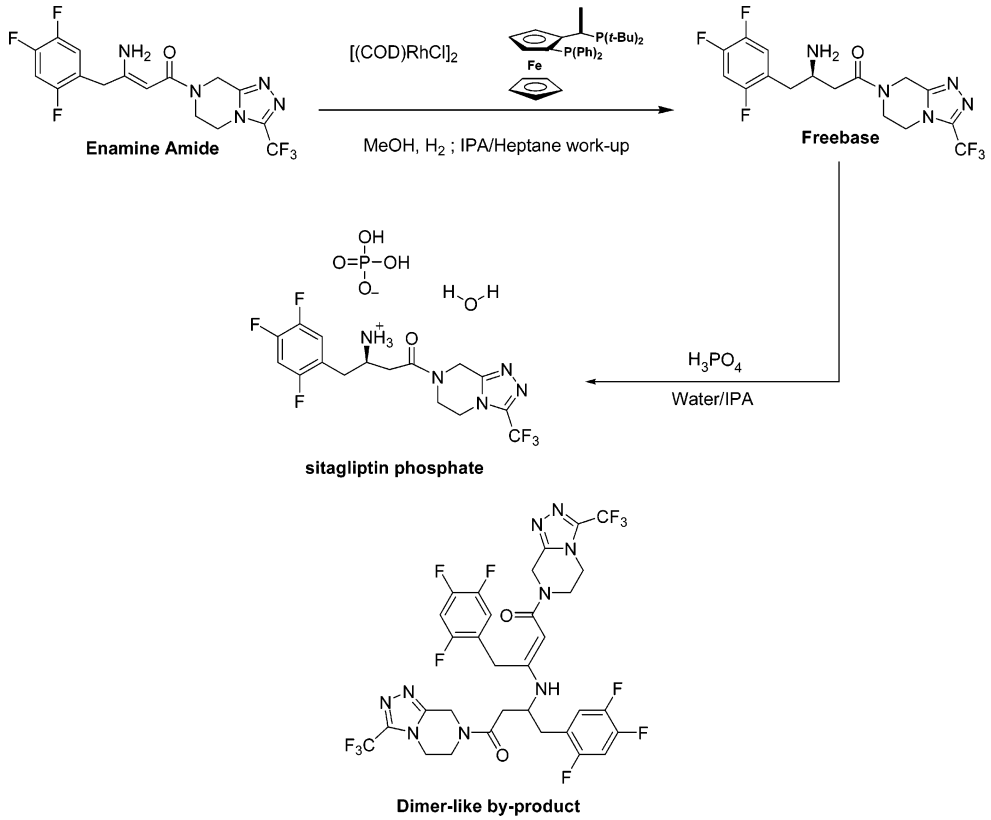
Scheme 1



meric selectivity of the reactions. All analyses were performed on an Agilent 1100 according to the following conditions: column, Diacel AD-H, 250 mm × 4.6 mm i.d., 5 μm particle size; eluent, 600 mL of ethanol (Pharmco), 400 mL of hexanes (EM Science), 0.1 mL of diethylamine (Aldrich), 0.1 mL of water; flow rate, 0.8 mL/min; UV detection at 268 nm; injection volume, 10 μL; temperature, 35 °C; diluent, 900 mL of methanol (EM Science) and 100 mL of water. Typical retention times were: minor enantiomer, 14.5 min; sitagliptin, 17.5 min. Samples were prepared: pipet 1 mL of hydrogenation stream into a 25-mL volumetric flask and dilute with diluent.

Apparent pH Measurement. Approximately 1 g of enamine amide sample was dissolved in 10 mL of dry dimethyl sulfoxide (EM Science). A combined pH electrode (Fisher) was first calibrated in an aqueous phosphate buffer at pH 7 (Fisher). After rinsing with water and dimethyl sulfoxide, the electrode was immersed in the sample until the reading stabilized. The electrode was washed with water prior to re-calibration. Each sample was analyzed three times, and the apparent pH of each solution was taken as the average of these three analyses. The electrode was calibrated prior to each measurement.

Capillary Electrophoresis Method for Ammonium. The concentration of ammonium in enamine amide samples was determined via a nonaqueous capillary electrophoresis method.[7] Standards (0.0017, 0.0033, 0.0083, and 0.017 mg ammonium/mL) were prepared by dissolving ammonium chloride (EM Science) in methanol (EM Science). Samples of enamine amide (provided by Merck Process Research and Merck Chemical Engineering Research and Development and Lonza) were prepared by dissolving ~50 mg of each sample into 10 mL of methanol. The samples were vortexed thoroughly and filtered through a 1 μm PTFE syringe filter (Whatman) prior to analysis. All analyses were performed on an Agilent capillary electrophoresis instrument.

Purification of Enamine Amide. Enamine amide may be purified by adding approximately 190 mL of degassed methanol to a 500-mL three-neck flask. To this 23 g of enamine amide is added. The slurry is stirred at 25 °C for 60 min and then cooled to 2 °C over 1.25 h and held for 2 h at this temperature with continued stirring. The slurry is then filtered and the cake washed with methanol cooled to 2 °C. Solids, liquors, and washes are collected.

Results and Discussion

Quite often, when process difficulties are encountered and found to be substrate specific, the investigation will center on identifying contaminants with negative effects on the reaction, and initially, this examination followed this approach. Enamine amide is normally isolated at greater than 99.5% purity, and all lots described here met or exceeded this purity. Exhaustive chemical and physical analysis of numerous batches of enamine amide provided no obvious or distinct differences that would account for the observed differences in hydrogenation performance.

The first measurement that showed meaningful differentiation among enamine amide lots and appeared to correlate with hydrogenation performance was apparent pH (pH*). Enamine amide is not readily soluble in water, and it

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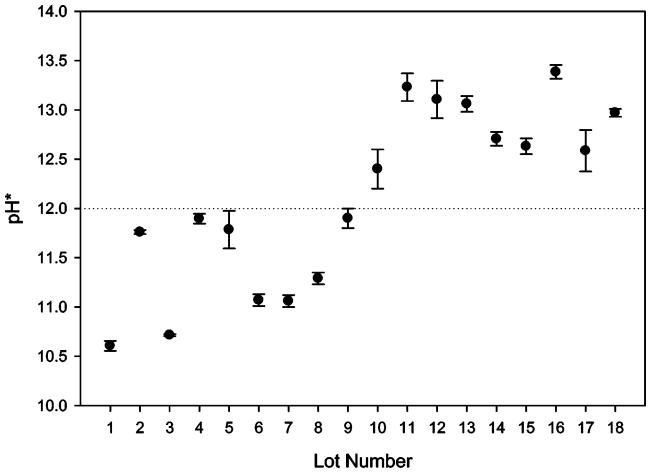

Figure 1. **Apparent pH of 10 mg/mL solutions of enamine amide in dimethyl sulfoxide. Error bars are the standard deviation obtained from triplicate analyses.**

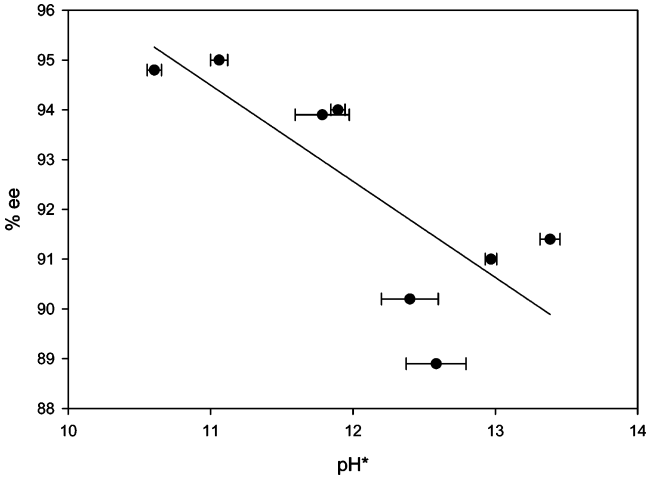

Figure 2. **Apparent pH of enamine amide lots versus the percent enantiomeric excess resulting from asymmetric hydrogenation. The solid line is a linear fit of the data. Error bars are the standard deviation obtained from triplicate analyses.**

hydrolyzes, making an aqueous pH measurement impossible; therefore, measurement of pH* of a rather concentrated solution of the substrate was made in dimethyl sulfoxide. Inspection of Figure 1 shows a tenuous but observable distinction between lots. Lots 1−9 produced solutions with pH* less than 12. More distinctive is when pH* of a subset (those batches which were hydrogenated alone, not part of a mixture) of these data is plotted versus percent enantiomeric excess (% ee). Figure 2 clearly shows that those batches which gave a lower solution pH* performed better in this hydrogenation.

Here we note an important feature of Figure 1. Lots 10−18 had all been subjected to a purification operation in the form of a slurry wash, recrystallization, or recrystallization and carbon treatment. The significance of an additional purification step led us to two possible conclusions: either a poison was being concentrated by the purification, or a substance which promoted the hydrogenation was being washed out.

A simple "crossover" experiment was completed to assess whether the stochastic nature of the performance of the

Table 1. **Results from "crossover" experiment**

	lot 1	purified lot 1	lot 10	lot 10 with liquors from lot 1 slurry wash
% conversion	95	91	91	95
% ee	95	91	91	95

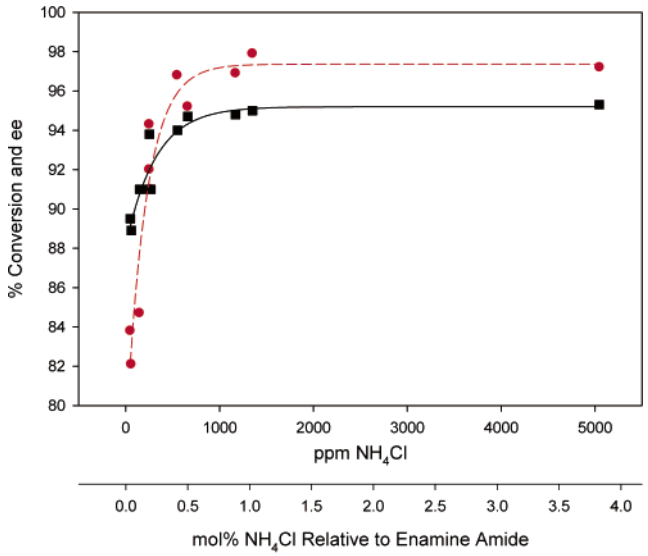

Figure 3. **Results of hydrogenation of enamine amide lots containing various amounts of ammonium chloride. Data points marked by (●) correspond to percent conversion as measured by LC (100 × (area of the peak corresponding to enamine amide)/(sum of the areas for the peaks corresponding to enamine amide and sitagliptin freebase). Data points marked by (■) correspond to percent enantiomeric excess as measured by LC (100 × (area of the peak corresponding to enamine amide − area of the peak corresponding to the sitagliptin freebase)/(sum of the areas for the peaks corresponding to the *S*-enantiomer of sitagliptin freebase and sitagliptin freebase). Curves are added solely to illustrate trends and do not represent a fit of the data.**

reaction was due to a poison or a promoter. A portion of Lot 1 which displayed desirable performance characteristics was purified via a slurry wash with methanol. The enamine amide solids were collected from the slurry wash and hydrogenated. The liquors and washes were collected and used as the solvent for the hydrogenation of Lot 10 which in its native state performed poorly in the hydrogenation. Results of these hydrogenations appear in Table 1. As expected, the performance of Lot 1 in the hydrogenation degraded upon purification, but the performance of Lot 10 improved to that of unpurified Lot 1. These data provided evidence that lack of an unidentified promoter was the cause of the poorer conversion and enantioselectivity of Lots 10−18.

With this in mind, we revisited data which we had collected earlier during in depth chemical and physical examination of all lots of enamine amide studied. Our approach in developing this chemistry had been to supply the hydrogenation step with the most pure enamine amide feasible. As such, we had monitored, among many other characteristics, the residual ammonium chloride which had

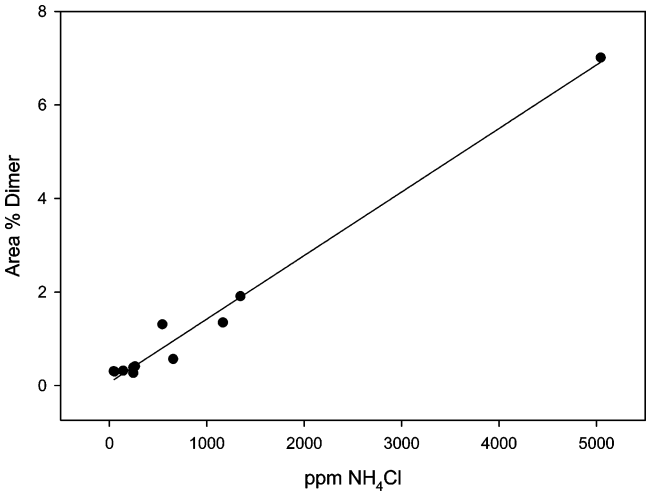

Figure 4. **Dimer levels observed with increasing concentration of ammonium chloride present in the hydrogenation solution. Area percent as measured by LC (100 × (area of the peak corresponding to dimer-like impurity)/(sum of all peaks detected in the chromatogram which were not present in a blank injection). The line represents a linear fit to the data.**

carried through during enamine amide synthesis.[8] Ammonium chloride had been controlled at maximum 0.1 wt %; yet since this was the most probable source of a weak acid "contaminant" in the substrate and thus related to pH*, we more closely evaluated its level in the individual batches.

Using the nonaqueous capillary electrophoresis method described above, we measured the level of ammonium in enamine amide. Assuming that all ammonium was in the form of the chloride salt, the native presence of this compound ranged from 60 to 1400 ppm. These values of native ammonium chloride along with a spike of 0.5 wt % ammonium chloride into a hydrogenation were then plotted versus percent conversion and percent enantiomeric excess (see Figure 3). A very strong correlation exists between the concentration of ammonium chloride until approximately 500 ppm at which time diminishing improvement is observed. In fact, Figure 4 shows that if the amount of ammonium chloride present in the reaction is too high the formation of a dimer-like side product between enamine amide and sitagliptin reaches a level at which yield is curtailed.

To achieve optimum reaction performance, the level of ammonium chloride in the reaction must be maintained between 500 and 1500 ppm (0.38−1.14 mol % relative to enamine amide). This is done by controlling the amount of ammonium chloride in the enamine amide raw material at a maximum of 0.1 wt % and adding 0.05 wt % to the reaction. Such treatment rendered the reaction very reproducible and no longer dependent on the source of substrate.

Conclusions

We have demonstrated that the performance and consistency of the asymmetric hydrogenation of an unprotected β-enamine amide was significantly affected by the apparent pH of the reaction solution. Hsiao et al.[2] observed deuterium was integrated only in the β-position when a model compound related to the enamine amide discussed here was hydrogenated with the same catalyst and solvent system in a deuterium atmosphere. The authors note that this may imply that tautomerization plays a role in this reaction.[2,9,10]

The correlation of apparent pH and reaction performance may be due to positive perturbations of the enamine−imine tautomerization such that the equilibrium is shifted in a subtle but positive way. The addition of substoichiometric quantities of ammonium chloride adjusts the apparent pH of the reaction solution to a range that gives optimum conversion and enantioselectivity without over-promoting the formation of a dimer-like side product. Studies are ongoing to better understand the mechanism by which ammonium chloride fosters the desired reaction and to elucidate the effect of changing the protic source and salt anion.

Overall, the addition of ammonium chloride has improved yield, cycle time, and consistency of this novel asymmetric hydrogenation. In a broader scope, there may be some processes whose reactant-dependent performance, still unexplained, may be revaluated in the light of identifying an as yet unknown promoter.

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