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Catalytic Hydrogenation of Glutamic Acid

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Abstract

Technology to convert biomass into chemical building blocks provides an opportunity to displace fossil fuels and increase the economic viability of biorefineries. Coupling fermentation capability with aqueous-phase catalysis provides novel routes to monomers and chemicals, including those not accessible from petrochemical routes. Glutamic acid provides a platform to numerous compounds through thermochemical approaches including hydrogenation, cyclization, decarboxylation, and deamination. Hydrogenation of amino acids also provides access to chiral compounds with high enantiopurity. This article details aqueous-phase hydrogenation reactions that we have developed that lead to valuable chemical intermediates from glutamic acid. In addition, ^{13}C nuclear magnetic resonance and matrix-assisted laser desorption ionization mass spectral data are presented that provide a mechanistic picture of the reactions. The results show that hydrogenation of glutamic acid has unique characteristics from other amino acids and that paradigms in the literature do not hold up for this transformation.

Index Entries: Glutamic acid; catalytic hydrogenation; pyroglutaminol; pyroglutamic acid; phosphoric acid; prolinol.

Introduction

Aqueous-phase thermochemical catalysis offers an important and complementary role to biocatalysis for the conversion of biomass feedstocks into products. The diversity of products offered from catalysis, including the chemical building blocks for polymers, is of growing interest and particularly important for the economic sustainability of biorefineries. Starch/glucose derived from corn provides a significant opportunity to produce large-scale commodity chemicals without a significant impact on the food supply or on the infrastructure. Currently, the cost for carbon derived from corn is only about 10–15% higher than carbon derived from

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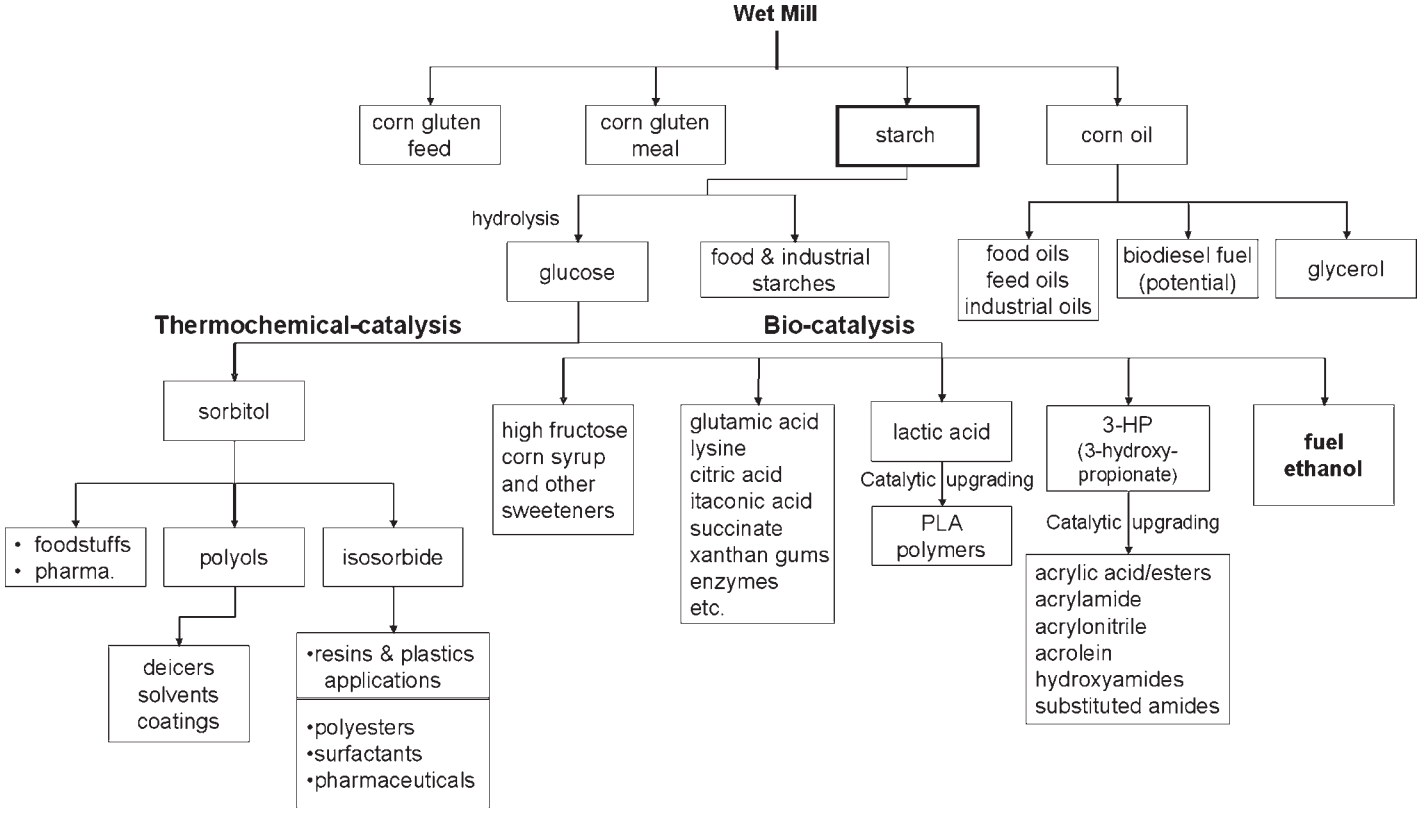


Fig. 1. Examples of products available from corn wet milling, one embodiment of a biorefinery.

Table 1
Chemical Building Blocks Derived from Crude Oil[a]

Carbon no.	Name	Example products
1	Methane	Methanol, methylene chloride, acetylene, cyanamide
2	Ethane/ethylene	Ethylene oxide, ethylene glycol, poly-ethylene
3	Propylene	Propylene oxide, propylene glycol, acrylonitrile
4	Butane	Maleic acid, THF, GBL, MTBE
5	N/A	N/A
6	Benzene/xylene	Styrene, adipic acid, phenol, acetone, toluene

[a] N/A, not available; THF, tetrahydrofuran; GBL, γ-butyrolactone; MTBE, methyl-t-butyl ether.

petrochemical sources. Coupled with low-temperature efficient processing, this makes chemicals derived from corn economically competitive with chemicals derived from nonrenewable petrochemical resources. Today glucose is converted into numerous compounds using fermentation, enzymatic catalysis, and thermochemical catalysis as depicted in a composite wet-mill operation shown in Fig. 1. Fermentation products can be further modified by catalysis to provide new polymers and monomers. The development of a diverse portfolio of products for economic sustainability is equally important to other biorefineries as it is for corn wet-milling operations.

The products developed by the petrochemical industry over the past 75 yr are based on feedstock supply and not necessarily the result of "products by design." The same opportunity exists for using a renewable feedstock. The petrochemical industry has several basic building blocks from which it derives products. Example building blocks from the refining of petroleum are presented in Table 1.

What is interesting, however, is some of the chemistry that is not present. For example, the petrochemical industry does not have a basic feedstock in the five-carbon area and thus we see few products derived from or based on five-carbon chemistry. Optical active compounds are also missing from the petrochemical-derived product list. For example, lactic acid is now made exclusively from glucose, with the reason being that the fermentation route provides stereochemical purity that is difficult to achieve from petrochemical building blocks.

The strategy for the development of products from biomass needs to be twofold. One approach is to identify those opportunities where we can compete economically with existing petrochemical products. Succinic acid–derived materials fit into this category (Fig. 1). The second approach must include the identification of products with novel functionality that cannot easily or cost effectively be derived from petrochemical building blocks. The challenge with developing new materials is that the market for these products must also be developed and the time and cost can be significant; however, the reward may also be substantial.

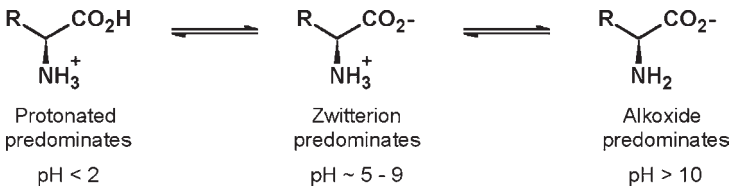
Amino acids, such as glutamic acid, derived from fermentation provide an excellent example of a "next-generation" platform intermediate beyond succinate. Recently, Ichimaru Pharcos announced the "volume production" of γ-polyglutamic acid for use in cosmetics, paints, water purification, and biodegradable plastics *([1])*. Aside from polyglutamic acid products, there are numerous monomeric intermediates that are possible to derive from glutamic acid. Such products offer unique functionality not provided by petrochemical intermediates including the five-carbon motif and chirality. In this article, we report our initial findings of the thermochemical conversion of glutamic acid into products and intermediates.

Background

Although catalytic hydrogenation has been part of the chemical landscape for many years, relatively little work has been directed toward the hydrogenation of amino acids *(2–7)* and even less directed toward the mechanism of hydrogenation *(8–9)*. On a practical level, the pioneering work of Adkin's group *(4)* in the 1930s and 1940s demonstrated that carboxylic acid esters can be converted into alcohols at mild temperatures (25–150°C) and high hydrogen pressures (>15 MPa). Important to this research group's work is the demonstration that carboxylic reduction can be done while maintaining a high degree of stereochemical purity. The catalyst systems of the day, nickel or copper and chromium oxides, worked well with esters but not with free acids. Development of ruthenium *(10)* and rhenium *(11)* catalysts in the 1950s solved this problem.

There has been a substantial body of work directed at hydrogenation of dicarboxylic acids *(12,13)*, particularly maleic and succinic acids *(14)*. An example is the development of 1,4-butanediol and tetrahydrofuran from butane-based maleic anhydride in the 1970s. The simple C_5 dicarboxylic acid, glutaric acid, and its alkyl esters have been the subject of numerous studies to produce 1,5-pentanediol as a product. Catalysts used include copper chromite *(15,16)*, palladium, and cobalt *(17)*. High selectivity (>95%) and high conversion (>98%) are achieved over the $CuCrO_x$ catalysts. Conversion over homogeneous ruthenium catalysts is also reported *(18,19)*. In general, achieving high selectivity to the diol product is easier with glutaric and adipic acids than with succinic acid, because of the thermodynamic favorability of succinic acid cyclization during reaction, which detracts from the formation of linear diol.

Direct hydrogenation of amino acids to amino alcohols was first examined by Bowden and Adkins *(4)* via the esters and recently was studied by Antons and colleagues *(5–7)* in a series of patents. Using Ru/C catalysts at high pressures (>14 MPa) and mild temperatures (70–150°C), Antons and colleagues demonstrated the conversion of carboxylic acids and amino acids with retention of optical activity in the product alcohols. High yields (>80%) and high enantiomeric purity (>97% in many cases) were achieved. In an earlier study, Broadbent et al. *(11)* demonstrated that under certain conditions hydrogenation of amino acids can be accompanied by deamination.



Scheme 1. Acidic, neutral, and basic forms of amino acids.

When we first considered glutamic acid, a search of the literature revealed no studies expressly directed at hydrogenating glutamic acid to a specific product. Indeed, the major role that glutamic acid plays in hydrogenation reactions is to act as an enantioselectivity enhancer *(20,21)*. Glutamic acid (or a number of other optically active amino acids) is added to solutions containing Raney nickel, supported nickel, palladium, or ruthenium catalysts and forms stereoselective complexes on the catalyst surface, leading to enantioselective hydrogenation of ketogroups to optically active alcohols. Under the reaction conditions used, no hydrogenation of glutamic acid takes place.

Since the inception of our work, Jere et al. *(22)* have published kinetic and stereochemical data on the hydrogenation of alanine. Important in their analysis is the observation that the amino acid must be in the protonated form to undergo facile hydrogenation. Since amino acids exist in their zwitterionic form, control of pH is important (*see* Scheme 1). A full equivalent of phosphoric acid was required to obtain high yields. Lower amounts resulted in a significant drop in yield since the product formed is basic.

Jere et al. *(22)* also reported the stereoretentive C-H bond activation in aqueous-phase catalytic hydrogenation of alanine. They demonstrated that hydrogenation of the carboxylic functionality is a stereoretentive process. Racemization occurs through a distinct process.

Also since the inception of our work, Antons at al. *(23)* reported the reduction of several amino acids including glutamic acid and pyroglutamic acid. Their study employed extremely high catalyst loadings of unsupported ruthenium and rhenium. The resultant products, glutaminol from glutamic acid and pyroglutaminol from pyroglutamic acid, were achieved in fair yields (58–65%) with high enantiomeric excess—i.e. high optical purity (*see* Fig. 2). However, the work clearly shows the need for catalyst improvement and leaves open the opportunity to identify other novel products. With these results in mind, we can now turn to our own work.

Materials and Methods

Glutamic acid, monosodium glutamate, pyroglutamic acid, and pyroglutaminol were purchased from commercial venders. Hydrogenation reactions were done using a 300-mL Parr autoclave using a continuous hydrogen gas feed at the pressure and temperature indicated. Reactant solutions contained 0.22 M substrate and 0–0.29 *M* phosphoric acid in deion-

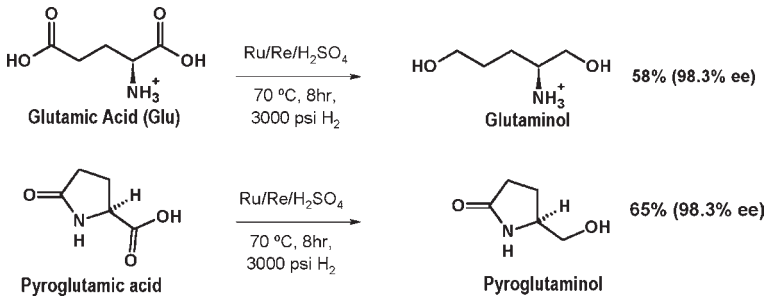
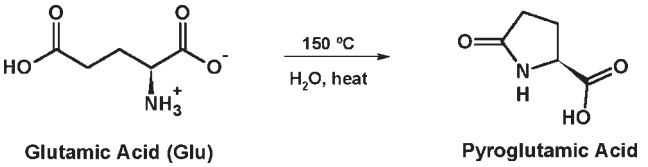


Fig. 2. Hydrogenation of glutamic acid and pyroglutamic acid (US patent no. 6,310,254; *see* ref. *23*).



Scheme 2. Glutamic acid.

ized water. The catalysts used were various precious metals on carbon supports as provided by Engelhard (Iselin, NJ), Degussa (Calvert City, KY), or prepared in house and generally added at 1% loading. Analysis was done on either a Waters high-performance liquid chromatograph (HPLC) with RID detector or an Agilent HPLC using ultraviolet detection with various columns. Nuclear magnetic resonance (NMR) spectra were taken on a VXR-300 MHz spectrometer. Matrix-assisted laser description ionization (MALDI) mass spectral data were obtained on a Perceptive Biosystems MALDI mass spectrometer.

Results

Early in our work, we discovered that at elevated temperatures glutamic acid has a strong propensity to cyclize, even under dilute neutral or acidic aqueous media (*see* Scheme 2). The reaction is thermal and does not require a catalyst. However, the cyclization rate appears to be enhanced using metal on carbon catalysts. Ring opening is possible but requires base. The propensity for ring closing to form substituted pyrrolidinones provides additional possible products. Furthermore, it provides a method for selectively protecting the pendant carboxylic acid, allowing one to selectively reduce the amino acid. At temperatures below 100°C, cyclization is slow and was not noted in Antons et al. *(23)* work. An important consideration is that the amino group of pyroglutamic acid is considerably less basic than the amino group of glutamic acid. Thus, hydrogenation of the pendant carboxylic group does not require additional acid. In fact, as we shall see, the addition of acid promotes further chemistry.

For hydrogenations at 150°C, essentially identical results were obtained whether starting with glutamic acid or pyroglutamic acid. Pyroglutamic acid shows much greater water solubility and thus was easier to work with.

Under hydrogenation conditions further unexpected chemistry occurs. The results of two hydrogenations are shown in Fig. 3. Both were run using 0.22 *M* substrate in water. The catalyst was a 5% ruthenium on carbon support, and the reaction was carried out at 150°C at 13.7 MPa of hydrogen. In one case, 0.29 *M* phosphoric acid was added, and in the other no additional acid was used.

In the presence of phosphoric acid, the substrate was rapidly consumed within 2 h. An initial product was formed, pyroglutaminol, but it was not stable to the reaction conditions. Under the HPLC analytical method employed, no other products were observed. By comparison, in the absence of phosphoric acid, pyroglutaminol was stable and not consumed. Interestingly, the reaction halted after 1 h, before the substrate was fully consumed. Further inquiry verified that the catalyst was still viable; that is, it had not been poisoned. It was also noted, however, that there had been a sharp rise in the pH of the solution from about 3.0 to 9.0. Formation of pyroglutaminol, a neutral compound, could not account for the rise in pH. The possibility that ammonia was being released during the reaction, as observed by Broadbent et al. *(11)*, was considered. However, analysis demonstrated that this was not the case. A second troublesome observation was the apparent poor mass balance of HPLC detected products in both reaction mixtures but worse for the reaction that contained phosphoric acid. Gas analysis showed no significant formation of methane or other overhydrogenation products in either experiment. In fact a total organic carbon analysis showed that essentially no carbon was lost from the solution.

The hydrogenation reaction was repeated this time using pyroglutaminol as substrate. Both neutral and acidic media were used as before. The results are presented in Fig. 4. The experiment verified the instability of pyroglutaminol under hydrogenation conditions in the presence of acid. Under neutral hydrogenation conditions, pyroglutaminol was stable. A small amount of hydrogenolysis, forming 5-methylpyrrolidinone and 2-pyrrolidinone, was noted (these products were not observed in the presence of phosphoric acid).

^{13}C NMR was helpful in determining what had occurred in the two experiments. Reaction solutions from the experiments shown in Fig. 3 were concentrated and examined by NMR without any further modification. The spectra are shown in Fig. 5.

The NMR data showed that the reaction was very clean when phosphoric acid was present. Essentially a single product was formed. The product did not contain carbonyl functionality. The spectrum, however, was not that of glutaminol (the expected ring opened compound) but rather of prolinol (*see* Fig. 5). The minor peaks in the spectrum corresponded to a small amount of unreacted pyroglutaminol. Conversely, when acid was not added, the resultant solution contained a complex mixture of products.

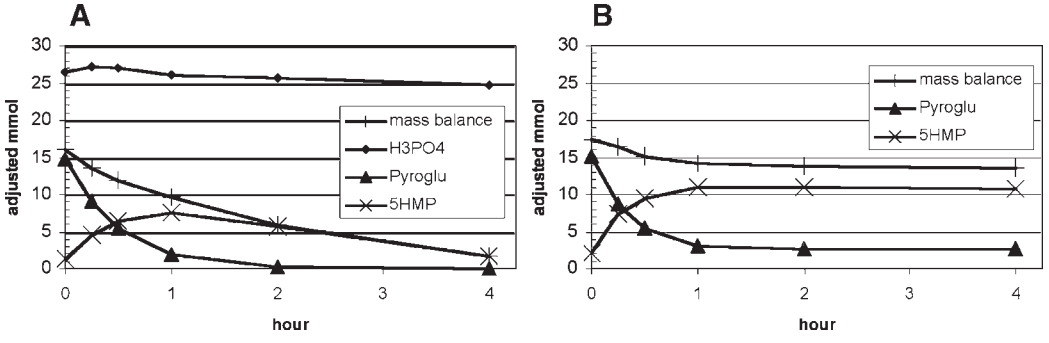


Fig. 3. Hydrogenation of pyroglutamic acid (0.22 *M*) in water at 150°C and 13.7 Mpa of H_2 with **(A)** 0.29 *M* phosphoric acid and **(B)** in absence of acid. 5HMP, pyroglutaminol (5-hydroxymethyl-2-pyrrolidinone). Note that small amounts of 2-pyrrolidinone and 5-methyl-2-pyrrolidinone were also formed. (Note: mass balance refers to HPLC identifiable product, not actual mass balance.)

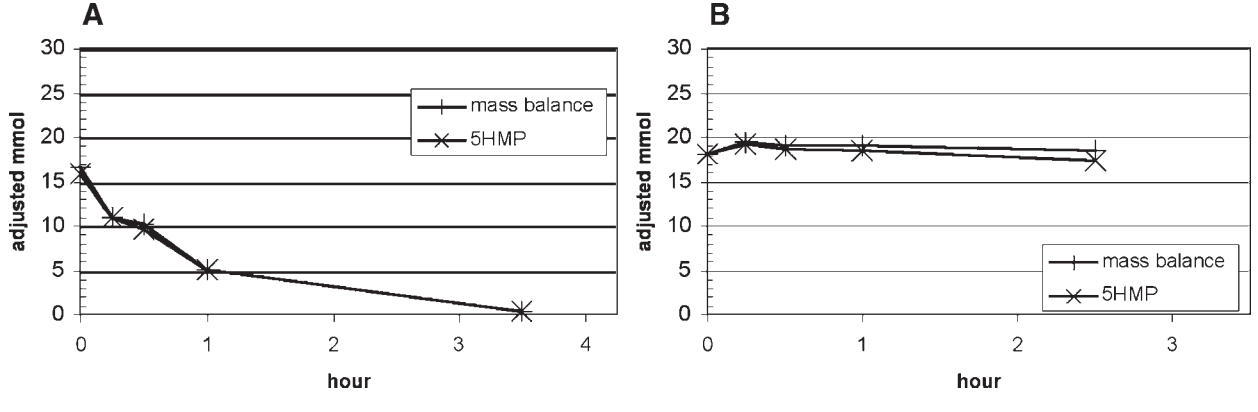


Fig. 4. Stability of pyroglutaminol (5HMP) (0.22 *M*) in water at 150°C. and 13.7 MPa of H_2 **(A)** in presence of 0.29 *M* phosphoric acid and **(B)** in absence of acid.

The spectrum showed resonances that we assigned to pyroglutamic acid and pyroglutaminol. In addition, there were resonances consistent with prolinol.

The ^{13}C NMR data were confirmed with MALDI mass spectral data. MALDI is a soft ionization technique able to transfer analytes into the gas phase as intact molecules without fragmentation. 2,5-Dihydroxybenzoic acid was used as the matrix to absorb nitrogen laser energy at 337 nm and assist in the ionization. The MALDI data verified the prolinol assignment (*see* Fig. 6). The data also showed that a minor amount of other pyrrolidines was formed including 2-methylpyrrolidine and pyrrolidine.

Discussion

The spectroscopic evidence provided the missing data required to explain the observations in Figs. 3 and 4. Key was the surprising observation that acid activates the lactam carbonyl toward reduction and thus produces prolinol *(24)*. Prolinol was not detectable using our HPLC method, which accounts for the apparent poor mass balance. A proposed mechanism for the transformation is shown in Fig. 7.

Under the reaction conditions, glutamic acid cyclizes to pyroglutamic acid. The cyclization can be done thermally, although the rate appears to be enhanced by the hydrogenation catalyst. The cyclization occurs at temperatures above 100°C even under dilute acidic conditions. Facile hydrogenation of pyroglutamic acid produces pyroglutaminol. Under strictly neutral conditions, pyroglutaminol is stable to the reaction conditions. However, in the presence of acid the carbonyl is activated. Hydrogenation of the resultant double bond followed by anchimeric assisted water loss and subsequent hydrogenation affords prolinol. Prolinol is a basic compound (pK_a of about 11.3). Under neutral conditions, pyroglutaminol is stable and the lactam carbonyl is not hydrogenated (Fig. 4). However, pyroglutamic acid is sufficiently acidic to promote a small level of lactam hydrogenation. In the absence of phosphoric acid, prolinol forms a salt with the substrate and the reaction halts before the pyroglutamic acid is fully converted. Phosphoric acid reprotonates the carboxylic acid, allowing high conversion to prolinol.

By careful control of reaction conditions and contact time, we were able to achieve high selectivity to either pyroglutaminol or prolinol. Under hydrogenation conditions in which phosphoric acid was present, prolinol was formed at about 98% selectivity with a 98% conversion (0.22 *M* glutamic acid, 0.29 *M* H_3PO_4, 5% Ru/C at 1% loading, 150°C, 2000 psig of H_2, 4 h). The absence of mineral acid, lower hydrogen pressure, and shorter residence time favor the formation of pyroglutaminol (0.22 *M* glutamic acid, 5% Ru/C at 1% loading, 150°C, 1000 psig of H_2, 1 h). The maximum selectivity we obtained was about 85% at 85–90% conversion. The major byproduct formed in this reaction was prolinol, which reacted with the substrate to inhibit higher conversion. Pyroglutamic acid can subsequently be ring opened under base-catalyzed conditions to form 4-amino-5-hydroxy pentanoic acid (*see* Fig. 8).

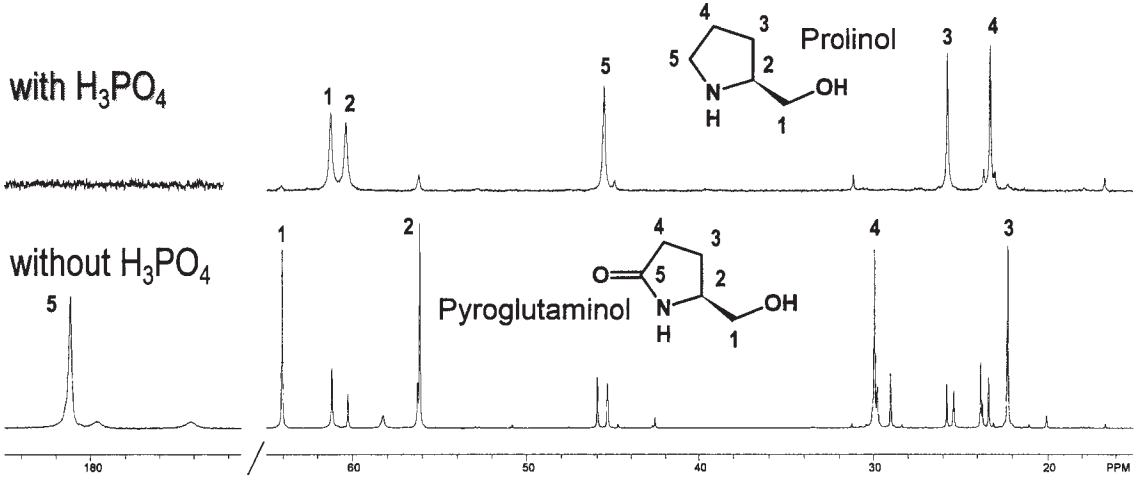


Fig. 5. ^{13}C NMR data of reaction solutions from Fig. 3.

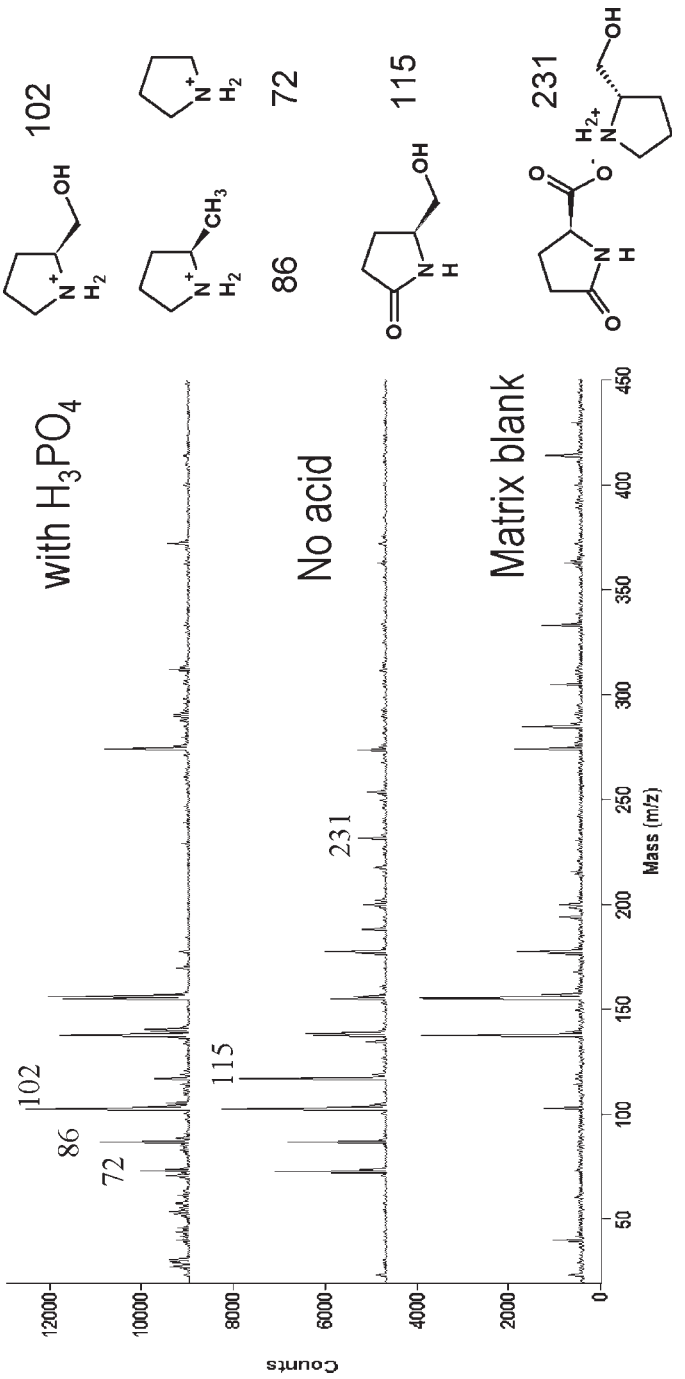


Fig. 6. MALDI mass spectral data confirming formation of prolinol.

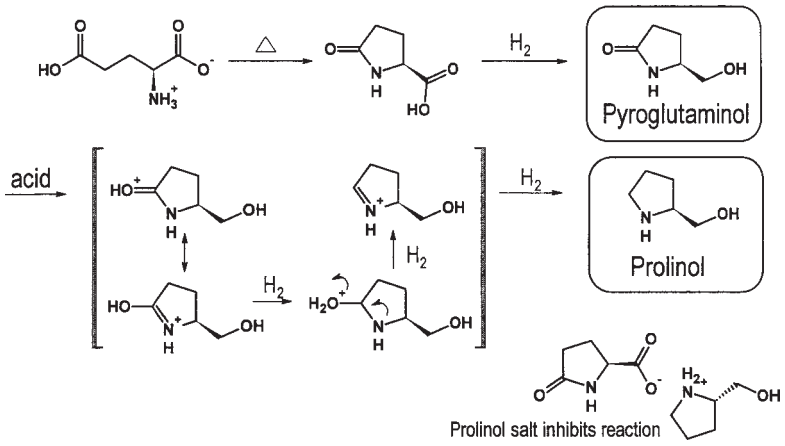


Fig. 7. Proposed reaction mechanism and products observed.

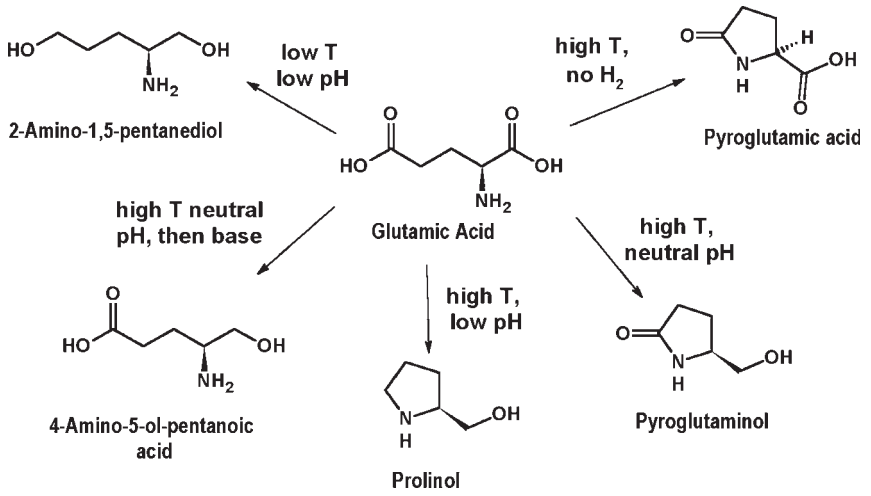


Fig. 8. Products demonstrated from glutamic acid.

In conclusion, we have presented various molecules available from glutamic acid via aqueous-phase thermochemical transformations. The chemistry highlights the dual role of acid in amino acid hydrogenation. Initially a catalytic amount of acid is required to protonate the zwitterionic amino acid. However, if a basic product is formed, stoichiometric amounts of acid are required to achieve high conversion. A caveat is present for glutamic acid: cyclization results in a lactam nitrogen that is significantly less basic than the amine. In this case, the addition of acid is not only unnecessary but in fact surprisingly promotes the subsequent hydrogenation of the less reactive lactam carbonyl. The various products that have been demonstrated thus far are shown in Fig. 8. Other products will be the subject of further research.

Acknowledgments

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