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Lysinol: a renewably resourced alternative to petrochemical polyamines and aminoalcohols†

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This paper reports the preparation of lysinol (2,6-diamino-1-hexanol) by the hydrogenation of lysine and an example of its use as a replacement for petrochemical-derived amines. Lysine is presently manufactured by fermentation of sugars and other carbon sources at scale exceeding 10^9 kg per year. Therefore, lysinol is potentially a renewable, platform aminoalcohol of previously unrecognized potential. Lysine hydrogenation proceeds under relatively modest conditions with Ru/C catalyst in water (100–150 °C, 48–70 bar, pH 1.5–2) to give lysinol in good yield (100% conversion, >90% selectivity; 50–70% isolated yield after purification by distillation). The impact of the various reaction parameters on conversion and selectivity are presented and discussed. Lysine hydrogenation at higher temperatures provides a pathway to piperidines and other products *via* further reduction and elimination of lysinol. The feasibility of lysinol synthesis from commodity, animal feed-grade lysine sources is presented as well. An example of the potential utility of lysinol is demonstrated by its use as a diamine curing agent with a standard epoxy resin. The properties of the resulting thermoset are contrasted with that obtained with a typical petrochemical amine used in this application (diethylenetriamine, DETA).

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Introduction

The bulk of current research on renewable organic chemicals is directed at hydrocarbons and oxygenates. This is understandable as these classes of organic molecules dominate the organic petrochemical industry. However, there are other useful functional organics that also should be considered, amines being one particular example.

With respect to amines that can be considered renewable, the few available examples are limited to commercially-manufactured amino acids such as glutamic acid and lysine. Both of these amino acids are manufactured by fermentation of sugars (molasses, sucrose, corn steep liquor, *etc.*) although other carbon feeds (acetate or acetic acid, alcohols, paraffins) can also be used.[1–3] Glutamic acid is primarily used as a well-known flavor enhancer (monosodium glutamate) while lysine, being an essential amino acid, is used nearly exclusively as a dietary supplement in animal feed. These two renewable chemicals are produced at large, commodity-scale volumes. Nearly 3×10^9 kg of glutamic acid and 1.2×10^9 kg of lysine are produced annually, much larger volumes than any other amino acids. It should be further noted that lysine capacity is increasing at a significant rate, with a current annual volume growth of about 4%.[3] Significant current research efforts by lysine manufacturers continue to optimize the process to reduce costs and environmental impact. For example, Ajinomoto Co., the world's largest lysine manufacturer, has announced a multi-generational plan to this end and ultimately plan to convert their amino acid manufacturing to the fermentation of non-edible cellulose feedstock such as corn stover.[4]

Both glutamic acid and lysine have received attention as potential platform renewable chemicals.[5–7] The conversion of glutamic acid to potentially useful chemicals, for example by hydrogenation, decarboxylation, and cyclization chemistry, has been investigated.[8,9] Similarly, the conversion of lysine to 1,5-pentanediamine, caprolactam, and 5-aminovaleric acid has received recent attention.[10–13]

With respect to their reactivity, the zwitterionic nature of α-amino acids typically limits the amine-like reactivity of the α-amino group. Thus, lysine itself does not react like a typical organic diamine because under most conditions the α-amino group exists in the ammonium form. We reasoned that elimination of the zwitterion by reduction of the carboxylic acid functionality to a non-acidic hydroxymethyl group (Scheme 1) would provide a simple and scalable transformation to convert readily available lysine into the reactive, renewable diamine lysinol (Scheme 1).

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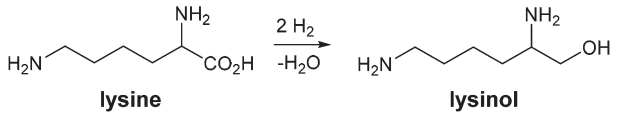
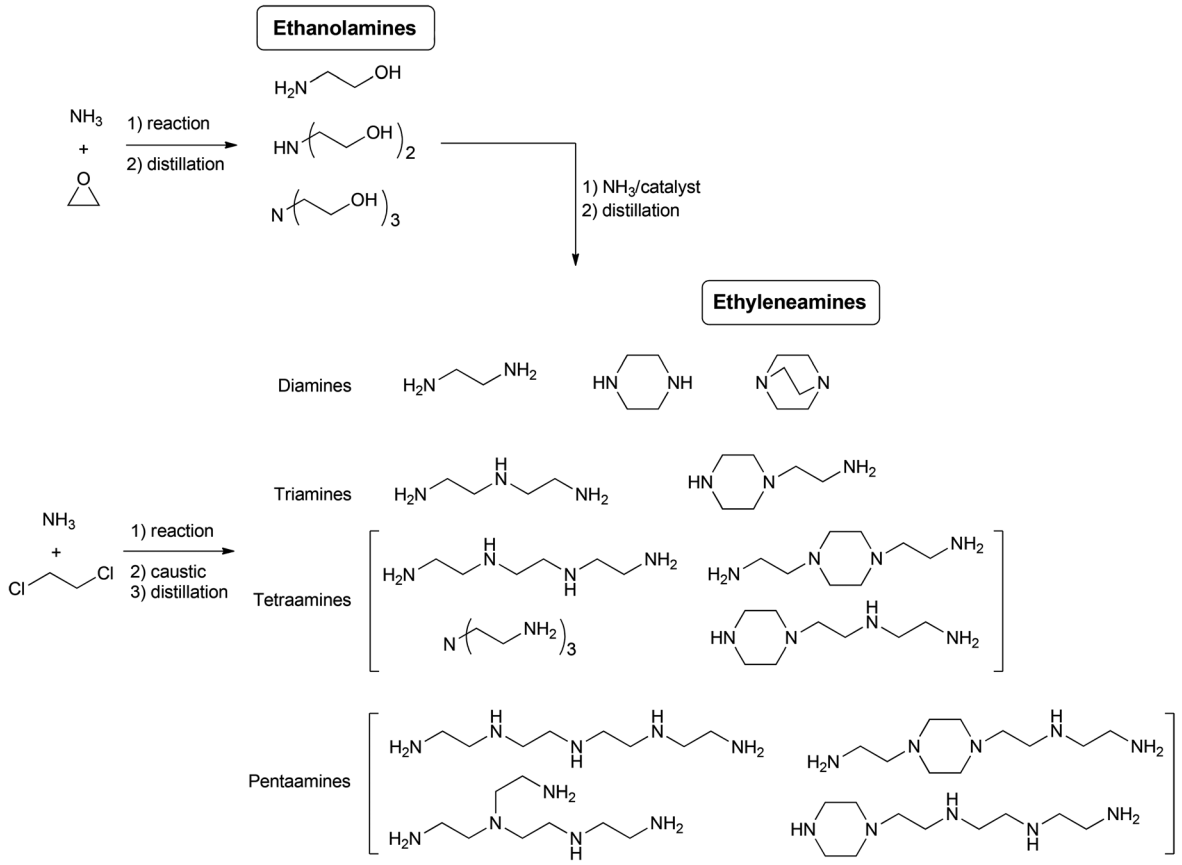


Scheme 1 Proposed conversion of lysine to lysinol.

Lysinol, an aliphatic diamino alcohol, possesses clear structural and functional similarity to two major classes of petrochemical-derived amines, the ethyleneamines and the ethanolamines. World production of these two classes of polyfunctional amines exceeds 1.5×10^9 kg per year (ethyleneamines: 3.9×10^8 kg per year in 2001;[14,15] ethanolamines: 1.1×10^9 kg per year in 1999[16,17]). The processes used to manufacture these amines are shown in Scheme 2.[18] The ethanolamines are manufactured exclusively from ethylene oxide (EO) and ammonia. The ethyleneamines are manufactured by two routes, reaction of ammonia with either 1,2-dichloroethane (DCE) or with the ethanolamines, primarily monoethanolamine. An inherent selectivity problem plaguing many amine syntheses is readily exemplified by the chemistry depicted in Scheme 2. These reactions rely on nucleophilic attack of nitrogen on an alkylating agent (EO, DCE) and nitrogen becomes more nucleophilic with increasing alkyl substitution. Therefore, the alkylated amine intermediates are more reactive than ammonia, and dialkyl amines are more reactive than monoalkyl amines. As a result, nucleophilic reactions of ammonia with EO produce a mixture of mono-, di-, and triethanolamine. Reaction of ammonia with DCE produces a more complex mixture of isomeric, cyclic, and oligomeric polyalkylated amines. This reactivity pattern also impacts the metal-catalysed amination of ethanolamines to produce ethyleneamines, as these reactions proceed *via* attack of nitrogen nucleophiles on carbonyl intermediates generated by reversible dehydrogenation.[19] In commercial practice, the product distributions can be and are shifted to some extent by the process parameters (for example, reactant ratios) but ultimately rely on fractional distillation to separate the resulting product mixtures. In the case of the ethyleneamines, the di- and triamines are isolated as pure, single components. However, the heavier tetra- and pentaamines are generally not separated as pure components and are sold and used as technical-grade mixtures owing to the similar boiling points of the individual components. In addition to the non-selective nature of the chemistry to manufacture these amines, these processes utilize hazardous starting materials (EO, DCE) and, where DCE is used, generate large quantities of by-product salts. Clearly, a renewable alternative replacement to these petrochemically-derived amines and aminoalcohols, manufactured by the efficient conversion of a renewable feedstock, is of



Scheme 2 Ethanolamine and ethyleneamine manufacturing processes.

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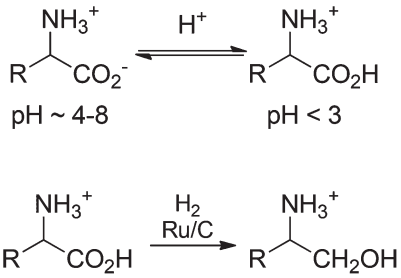

Scheme 3 Hydrogenation of α-aminoacids.

significant interest and potential utility in a wide range of applications.§

The catalytic hydrogenation of α-amino acids to the corresponding 1,2-aminoalcohols is known.[20–30] In general, carboxylic acids can be hydrogenated to alcohols but require fairly extreme conditions (≥200 °C, 50–140 bar) even with the most active catalysts.[31] However, the carboxylic acid group in α-amino acids can be hydrogenated under significantly milder conditions (100–150 °C, 17–70 bar) when performed at acidic pH. Below approximately pH 3, α-aminoacids are largely present as the cation and not the familiar zwitterion (Scheme 3). It is speculated that the electron-withdrawing effect of the adjacent ammonium cation renders the carboxylic acid functionality more reactive towards reduction.

While the hydrogenation of several amino acids to alcohols has been reported, there are, surprisingly, no reports describing the direct hydrogenation of lysine to lysinol.¶ The synthesis of lysinol from lysine has been reported but involves nitrogen protection, hydride-reagent reduction, and nitrogen deprotection.[32] Multi-step, stoichiometric chemistry such as this is obviously impractical to be considered for large scale application and also entirely negates the green advantages of using a renewable feedstock. It is possibly for these reasons that there are surprisingly few literature citations to lysinol or its derivatives. Lysinol derivatives have been employed primarily in pharmaceutical applications in addition to a few studies of chiral dendrimers and polymers.[32–38]

In this contribution, we describe our efforts to develop a practical preparation of lysinol by the catalytic, aqueous phase hydrogenation of lysine salts (sulphate, phosphate, chloride). We then show a comparison of lysinol with a petrochemically-derived ethyleneamine in a prototypical application, as a hardener/curing agent in epoxy thermosets.

Experimental

Materials

Lysine was obtained from multiple sources. L-Lysine (free base), L-lysine monohydrochloride, D-lysine monohydrochloride, and DL-lysine monohydrochloride were purchased from Sigma Aldrich®. Commercial animal-feed grade lysine samples were provided by Archer Daniels Midland Co., Decatur, Illinois, USA (Liquid lysine 50% feed grade, a dark brown 50% aqueous solution of L-lysine free base; L-lysine HCl, 98.5% feed grade monohydrochloride as off-white granules) and Evonik Industries AG, Essen, Germany (BioLys®, feed grade lysine sulfate as brown granules containing the equivalent of 50.7% by weight L-lysine free base).

Several catalysts were screened for the hydrogenation of lysine to lysinol. For most of the reactions discussed in this work, 5% ruthenium on carbon (Product no. 206180) powder obtained from Sigma-Aldrich® was used. Catalysts were also obtained from Johnson Matthey®. All the catalysts were obtained in powder form.

Various reference standards including 2-piperidinemethanol, 2-(aminomethyl)piperidine, 2-amino-1-hexanol, and 6-amino-1-hexanol were used for GC, LC, and NMR analysis and were obtained from Sigma-Aldrich®.

Product analysis

The reaction/product mixtures were analyzed using GC, GCMS, LCMS, and NMR. The high-pressure liquid chromatography (HPLC) instrument (Hewlett-Packard 1100) was equipped with a mass spectrum detector. The separation was carried out on a Zorbax Eclipse AAA column (4.6 × 150 mm) operating at a flow rate of 1 mL min^{-1} at 60 °C. The mobile phase consisted of a mixture of water and 0.1% formic acid (Phase A) and acetonitrile and 0.1% formic acid (Phase B) at a gradient of 95% A/5%B to 0% A/100%B over 10 min, followed by a 4 min hold. Gas chromatography was conducted with a Hewlett-Packard 5890 (FID detection) or a Hewlett-Packard 6890 (MS detection) and a 30 m × 0.32 mm × 0.25 μm ZB-5 column. Sample injec-

§ Relevant to this discussion are the relative prices of the ethylene- and ethanolamines compared to lysine and lysinol. While current pricing information is not readily or easily obtainable the available data suggest that they may be comparable. For example, 1999 ethyleneamines market prices were US$ 3–4 kg^{-1}.[15] In the early to mid-1990s the manufacturing cost for lysine monohydrochloride was estimated at US$ 1.5–1.8 kg^{-1}, equivalent to US$ 1.9–2.3 kg^{-1} on a lysine content basis (J. M. Connor, *Rev. Ind. Org.*, 2001, **18**, 5–21). L-Lysine prices during the infamous 1990s price-fixing case reached US$ 2.2 kg^{-1} (equal to US$ 2.7 kg^{-1} free base).

¶ During the course of our work a patent published (P. Ouyang, K. Guo, H. Zhong and Z. Fang, *CN Pat*, 102 617 364, 2012) that claims the hydrogenation of a variety of α-amino acids and esters bearing pendant amino groups to produce diaminoalcohols. The patent further describes the preparation of various polymers, including epoxy thermosets, from these diaminoalcohols. The preparation and use of lysinol is included. Careful translation and consideration of this work indicate that it is in error. For example, the patent describes lysinol only as a colorless solid that is purified by washing with a mixture of water and ethanol. No analytical or spectroscopic information is provided. However, as demonstrated by others[32] and in this present work, lysinol is a liquid and completely miscible with water and ethanol. Furthermore, the patent claims the hydrogenation of lysine methyl ester with RANEY® nickel (6 bar H_2, 60 °C, 6 h, H_2O). These exceptionally mild hydrogenation conditions are suspect. RANEY® nickel is a poor catalyst for the hydrogenation of esters to alcohols, requiring much higher temperature and pressure, and is strongly basic. As discussed in this report, acidic conditions, incompatible with RANEY® nickel, are required for amino acid hydrogenation under mild conditions. These suspicions were confirmed by exactly repeating the patent example using lysine methyl ester. A colorless solid was indeed isolated as described. Analysis (NMR, LCMS) clearly proved the product is lysine, resulting from saponification of the methyl ester starting material, presumably from the base introduced with the RANEY® nickel. No hydrogenation product or gas uptake was observed. Polymers, including epoxy thermosets, prepared with this solid are, unsurprisingly, dramatically different than those prepared from authentic lysinol as described in this paper.

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tions were made at a 40 °C initial column temperature and after a 4 min hold were ramped to 300 °C at 20 °C min^{-1}. ^1H NMR analysis was performed on an Agilent DD2 Spectrometer operating at 500 MHz equipped with a room temperature 4-nucleus probe. The data were collected with 64 transients, 45° pulse width, a 12.9 kHz spectral width, 3.2 s acquisition time, and a 45 s recycle delay. Samples for product composition analysis were prepared with *ca.* 20 mg sample in 0.8 g D_2O stock solution containing a known concentration of 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) as internal reference.

Reactors

Small scale reactions were conducted in a custom high pressure reactor of Hastelloy C construction (50 mL liquid capacity). Mixing was achieved with a Teflon® coated stir bar and magnetic stirring; the stir bar length was matched to the reactor inner diameter to ensure catalyst fluidization. Reaction progress was monitored by pressure drop using a Setra Systems Model 206 Pressure Transducer (0–138 bar range) and digital readout. Larger scale reactions were conducted in a 600 mL Parr® (Model no. 4563) Hastelloy C276 batch reactor equipped with a magnetically-driven impeller, heating mantle (Temperature Controller Model 4848), and a liquid sampling system. Preparative scale reactions were performed in 4 or 19 L autoclaves.

Hydrogenation screening

The evaluation of reaction parameters such as catalyst and pH were performed as described by the following procedure. The 50 mL pressure reactor was charged with catalyst (1–3 g), 30 g reaction solution, and a stir bar. A typical reaction solution contained 10 wt% lysine (free base), with the remaining balance the requisite amounts of water and H_2SO_4. Catalyst screening was conducted at an initial pH of about 2.1. The reactor was then sealed and pressure tested. The vessel was then pressurized with 34.5 bar H_2 followed by heating to 120 °C. Upon reaching this temperature the reactor pressure was adjusted to 55.2 bar by introducing additional H_2. The pressure drop was monitored regularly and the reactor was re-pressurized once the pressure dropped below 48.3 bar. The typical total reaction times were 24 h. The reactor was then cooled and vented, and the catalyst was separated from the reaction mixture by filtration with a 0.45 μm filter. The filtrate was analyzed using LCMS and NMR techniques as described earlier.

Mass transfer

The rate of lysine hydrogenation is subject to mass transfer limitations in the case of inefficient stirring. At 600 mL scale the hydrogenation rate was found to increase with increasing stirrer speed over the range 300–900 rpm. Above approximately 900 rpm the hydrogenation rate was observed to plateau. Therefore, experiments were conducted at this higher stirrer speed to ensure that experiments were not operated under H_2-starved conditions.

Lysinol synthesis and isolation, representative procedure

L-Lysine (420.0 g, 2.79 mol) and 2.2 L of deionized water were charged to a container. Concentrated sulfuric acid (160 mL, 2.94 mol) was added gradually with stirring, and using ice cooling as required to maintain temperature <30 °C. The mixture was stirred until all of the lysine had dissolved and the temperature had returned to ambient. The resulting solution and 100.0 g of powdered 5% ruthenium on carbon were charged to a 4 L Hastelloy autoclave. The vessel was purged with hydrogen and then brought to 120 °C and 69 bar hydrogen pressure with vigorous stirring, recharging with hydrogen as needed until the hydrogen uptake ceased. After 22.5 hours the reactor was cooled and depressurized. The catalyst was removed by filtration, rinsed twice with deionized water, dried under nitrogen, and saved for later reuse. LCMS (API-ES+) of the combined filtrates showed lysinol (M + H = 133) and no unreacted lysine (M + H = 147), as well as small amounts of byproducts. The filtrate pH was increased to 12.2 by dropwise addition of 50% NaOH (*ca*. 300 mL, 5.7 mole). Water was removed by vacuum distillation to give a mixture of lysinol and sodium sulfate as a colorless semi-solid. This material was extracted with ethanol (2 × 500 mL) and then warm MeOH (500 mL). The extracts were combined and concentrated to give a light amber liquid. The product was fractionally distilled to give 62 g of an impure forecut boiling at *ca.* 40–100 °C and 0.1 mm. Pure lysinol was then distilled at 105–118 °C and 0.1 mm. Yield of distilled lysinol: 259.8 g, 1.97 mol, 71%.

NMR (ppm, D_2O/DSS): ^{13}C: 68.5 (C1), 53.8 (C2), 42.8 (C6), 34.7, 34.2 (C3, C5), 24.8 (C4). ^1H: 3.52 (1H, dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 4.5 Hz), 3.35 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 7.0 Hz), 2.78 (1H, m), 2.58 (2H, t, J = 6.8 Hz), 1.45–1.3 (4H, m), 1.3–1.2 (2H, m).

Preparation of Mosher amides and determination of lysinol enantiopurity – representative example

A vial was charged with a micro stir bar, *S*-lysinol (4 mg, 0.03 mmol, prepared by hydrogenation of *S*-lysine), diisopropylethylamine (10 μL, 8 mg, 6 mmol), and 0.5 mL of CD_2Cl_2. (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride [(*S*)-(+)-MTPA-Cl, *S*-Mosher's acid chloride; 11 μL, 15 mg, 0.06 mmol] was added by syringe. After 2 h at room temperature another 0.3 mL CD_2Cl_2 and 1 drop of hexafluorobenzene internal standard (δ −164.90) were added. The solution was filtered through a 0.2 μ filter into a 5 mm NMR tube and analyzed by ^1H and ^{19}F NMR. Enantiopurity was determined by both integration and peak deconvolution of the CF_3 resonances in the ^{19}F NMR. Peak assignments were made by preparing solutions of all combinations of *R*-, *S*-, and racemic lysinol (in turn prepared by hydrogenation of *R*-, *S*-, and racemic lysine) and *R*- and *S*-Mosher acid chloride.

Epoxy thermoset preparation and evaluation – instrumentation

Epoxy thermosets were prepared from lysinol or DETA and bisphenol-A-diglycidyl ether (BADGE) using stoichiometries of 1 equiv. N–H per 1 equiv. epoxide. Nanoindentation evalu-

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ations were performed with a CSM Instruments Ultra Nano-Hardness Tester equipped with a Berkovich indenter. Compression and lap shear tests were conducted on a screw-driven universal mechanical tester under standard conditions (23 °C and 50% RH). Evaluations were conducted in accordance with established ASTM methods (see ESI†).

Results and discussion

Lysine hydrogenation

As discussed earlier, the catalytic hydrogenation of α-amino acids to the corresponding 1,2-aminoalcohols has been reported.[22,24,25,28–30] In particular, Jere *et al.* reported a detailed kinetic study of the hydrogenation of alanine to alaninol.[26] That report addresses the impact of a number of important reaction parameters on amino acid hydrogenation such as temperature, pressure, and acid concentration. The hydrogenation of lysine to lysinol has not been reported and therefore the impact of the additional pendant amino group is unknown. We undertook an investigation of this hydrogenation, including a cursory study of the hydrogenation conditions to develop a semi-quantitative understanding of the key parameters to allow for the synthesis of lysinol on a preparative (*ca*. 0.1–1.0 kg) laboratory scale.

Lysine hydrogenation was first investigated using the reaction conditions reported in the literature as guidance: 5% Ru/C, 120–160 °C, 48–69 bar, aqueous H_3PO_4.[26,27] Two molar equivalents of H_3PO_4 were used to ensure protonation of both of amino groups (*vide infra*). Under these conditions lysine is indeed hydrogenated to give lysinol as the major product. Lysine conversions of 100% are easily achieved at unoptimized productivities on the order of *ca.* 0.5 M h^{-1}. Lysinol is the major product, exceeding 90% selectivity under some reaction conditions. The primary by-products are the result of cyclization to produce piperidines. For example, 2-hydroxymethylpiperidine, 2-aminomethylpiperidine, 2-methylpiperidine, and piperidine are observed.

After establishing that lysinol could be prepared in excellent conversion and selectivity, modifications to the original conditions were explored. First, the lysine concentration was increased to 10–20 wt% from the 2–4 wt% amino acid and phosphoric acid was replaced with sulfuric acid. In addition, in our hands the catalyst preactivation step described (13.8 bar H_2, 200 °C, 15–18 h) prior to hydrogenation is not necessary; we observe no difference in activity or selectivity between experiments using preactivated catalyst and those with no preactivation and therefore this step was omitted. Apparently, any requisite activation of the 5% Ru/C catalyst is rapid and complete when the reaction solutions reach the target temperature and pressure.

Further examination of the reaction parameters was conducted. First, commercially-available hydrogenation catalysts were screened for lysine hydrogenation under a standard set of conditions: 30 g 10 wt% aqueous L-lysine (free base), 0.74 equiv. H_2SO_4, 3 g catalyst, 120 °C. 55.2 bar H_2, 24 h. The 5% Ru/C catalyst performed much better than any of the others examined. The analogous 5% Rh/C catalyst showed marginal activity (*ca*. 60% conversion), while carbon-supported Re, Ir, Ni, Pd, and Pt catalysts showed little to no activity. Bimetallic catalysts were not examined but have been reported in the patent literature for the hydrogenation of other amino acids.[29,30]

Alumina and silica were investigated as alternative supports to carbon, limiting the supported metal to ruthenium and to 5 wt% metal loading. Both 5% Ru/alumina and 5% Ru/silica catalysts hydrogenate lysine but with lower activity than the carbon support. In addition, lysinol selectivities are much poorer with these oxides than that obtained with the carbon support. While lysinol remains the primary product, the oxides produce larger amounts of piperidines (2-(hydroxymethyl)-piperidine, 2-(aminomethyl)piperidine, 2-methylpiperidine) as well as 1-hexylamine.

We have not performed a detailed kinetic analysis but the following observations are notable. Representative gas uptake data are provided in Fig. 1. These hydrogenations exhibit linear hydrogen uptake with time for the majority of the reaction as is seen by the linear least-squares fits to the initial uptake rates of these data sets. The uptake rate abruptly decreases and then stops. Analysis of the reaction solution shows quantitative lysine conversion at the cessation of hydrogen uptake.

A few conclusions can be drawn from these data. Under these conditions the hydrogenation can be considered to be approximately pseudo-first order in hydrogen pressure through a substantial portion of the reaction. Thus, at initial pressures P_i of about 69 bar (Fig. 1, curves b and c), the total

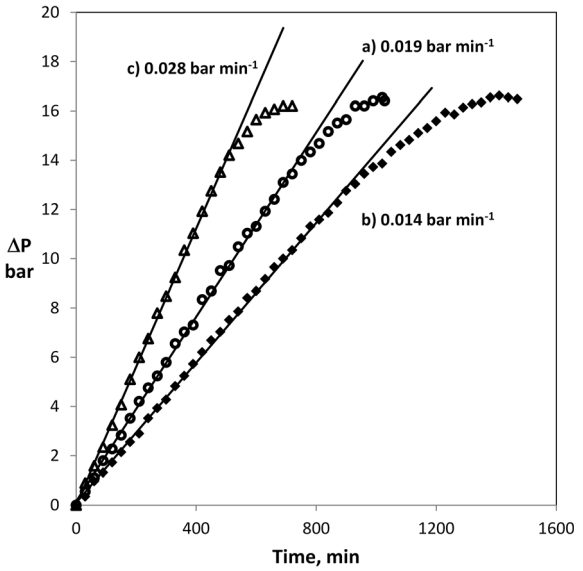

Fig. 1 Representative hydrogen uptake rate for the lysine hydrogenation reaction. All experiments were carried out with 2.1 g (14.4 mmol) L-lysine, 11.0 g H_2O, 1.0–1.3 equiv. H_2SO_4, 120 °C. (a) Diamonds: 0.253 g 5% Ru/C, 52.0 bar P_i H_2; (b) circles: 0.25 g 5% Ru/C, 69.7 bar P_i H_2; (c) triangles: 0.50 g 5% Ru/C, 68.8 bar P_i H_2.

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pressure drop to complete lysine consumption is 16 bar, or 23% of the initial pressure. However, the uptake rate is linear for over 90% of the total uptake and thus lysine conversion. That may be contrasted with a hydrogenation at lower initial pressure (P_i 52.0 bar, Fig. 1 curve a) where the initial uptake rate begins to deviate from linearity at 75% conversion. The change in initial gas uptake rates in experiments a and b of Fig. 1, varying only in P_i, is consistent with first-order behavior in hydrogen pressure. Thus the initial rate at P_i 52.0 bar (0.014 bar min^{-1}) is decreased from that obtained at P_i 69.7 bar (0.019 bar min^{-1}) by exactly the same amount expected for first order dependence.

Unlike hydrogen, lysine is completely consumed in these reactions. Therefore, the linearity of the gas uptake through 3–4 half-lives (>90% lysine conversion) is consistent with zero order dependence on lysine concentration. Finally, comparison of experiments b and c in Fig. 1 indicate a first order dependence on catalyst.

These observations are consistent with the literature which, for other amino acids, have shown dependencies on hydrogen that are approximately first order below 69 bar but change to zero order at higher pressures.[26] The previously reported rate dependencies on amino acid concentration are complex and structure dependent, but zero order behavior has been observed with some amino acids. The lysine hydrogenation rates reported compare favorably with those reported for other amino acids, for example alanine.‖

Lysine hydrogenation is pH dependent. From the foregoing discussion it would be expected that a minimum pH must be achieved to establish a substantial concentration of the requisite lysine dication substrate. As shown in Fig. 2 this is indeed observed, and the initial pH must be below 1.8–2.0 to achieve high lysine conversion. At higher pH the conversion drops, but not completely at intermediate pH, and has been attributed to the action of acid sites present on the carbon support.

Because lysinol is a stronger base than lysine (Table 1), it is expected that the solution pH should increase as the hydrogenation progresses. As shown in Table 2, this is in fact observed, where the pH increases by 2–4 units upon reaction completion. This result has significant implications for batch hydrogenations conducted without *in situ* pH control such as those reported here. If insufficient acid is present at the beginning of the hydrogenation the pH rise will eventually cause the lysine dication concentration to decrease to the point that hydrogenation ceases and incomplete conversion occurs; this phenomenon has been examined in more detail in the case of alanine. Unlike the case of alanine, while we are able to achieve quantitative lysine conversion at an initial pH of 1.6–1.8 it is also the case that lysinol selectivity is pH dependent. Thus, at very low initial pH (<1.3–1.5) the selectivity decreases due to increased cyclization to form piperidines. An improved process would maintain constant and higher pH range by continuously feeding acid during the hydrogenation. This concept requires further study and demonstration.

The data in Table 1 also provide guidance with respect to optimum acids to use for pH control. Our initial investigation of lysine hydrogenation employed phosphoric acid, using guidance from the literature. Examination of the pK_a data indicates that two equivalents of H_3PO_4 are required to convert lysine to substantial concentrations of the requisite dication $[lysineH_2]^{2+}$. On the other hand, the acidity of HSO_4^- is sufficient to generate lysine dication and therefore only a single equivalent of H_2SO_4 is needed to achieve complete

‖ From Fig. 1 of ref. 24 we estimate alanine hydrogenation rates of *ca.* 4–8 mmol (g-cat hour)$^{-1}$ at 100–125 °C (69 bar, 100% conversion). The rate of lysine hydrogenation at 120 °C in the present work is *ca.* 3–4 mmol (g-cat hour)$^{-1}$ (69 bar, 100% conversion).

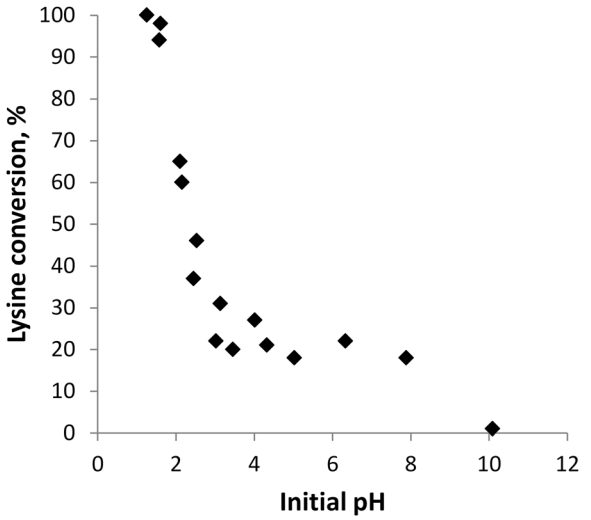

Fig. 2 Dependence of lysine conversion on initial pH. Reaction conditions – feed: 10 wt% lysine (aqueous free base or monohydrochloride), 3 wt% Ru/C catalyst, H_2SO_4 as required to achieve the indicated initial pH, Temperature – 120 °C, pressure – 55.2 bar. Reaction time – 24 h.

Table 1 pK_a data

Compound	pK_{a1}	pK_{a2}	pK_{a3}
Lysine	2.2	8.8	10.5
Lysinol[a]	10.5	12.8	
H_3PO_4	2.2	7.2	12.4
H_2SO_4	−3	2.0	

[a] Estimated pK_a obtained from: *Scifinder*, Chemical Abstracts Service: Columbus, OH, 2014; RN 25441-01-4 (accessed 6 May 2014); calculated using ACD/Labs Software version 11.02; ACD/Labs 1994–2011.

Table 2 pH shift during lysine hydrogenation – representative examples[a]

Initial pH	Final pH	Lysine conv. %
2.2	6.9	75
1.7	5.7	Not determined
1.3	3.5	>99

[a] Conditions: 20 wt% L-lysine, H_2SO_4 as required, 8 wt% Ru/C, 120 °C, 48.3 bar, 7–24 h.

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lysine conversion. The choice of acid also has significant implications in product isolation, which involves the addition of base to convert the aqueous lysinol salt to the free base. Phosphoric acid is triprotic and requires at least two molar equivalents to effect lysine hydrogenation, thus requiring at least 6 molar equivalents of base to liberate free base lysinol. Sulfuric acid, diprotic and requiring a single molar equivalent, requires only 2 equivalents of base for neutralization and therefore generates far less salt byproduct. As discussed in further detail below, it is notable that lysine manufacturers produce the chloride and sulfate salts directly from their fermentation processes.

Lysinol selectivity decreases with increasing temperature as shown in Fig. 3. At 100 °C the lysinol selectivity exceeds 95%, dropping slightly to 93–95% at 120 °C. The primary by-product observed by ^{1}H NMR is 1,5-diaminohexane, characterized by the doublet at δ 1.29 (J = 6.7 Hz) and supported by LCMS ([MH$^+$] = 117 amu). Trace amounts of other products such as 2-hydroxymethylpiperidine ([MH$^+$] = 116 amu), 2-aminomethylpiperidine ([MH$^+$] = 114 amu) 1-hexylamine ([MH$^+$] = 102 amu) are also observed by LCMS and confirmed by comparison to authentic samples. At 150 °C the selectivity drops more severely to 65–70%, with increasing amounts of these byproducts in addition to 2-methylpiperidine (δ 1.28 d, J = 6.6 Hz; [MH$^+$] = 100 amu)) and piperidine (δ 3.15 d, 1.77 quin, 5.8 Hz; [MH$^+$] = 85 amu). At 180 °C no lysinol is observed and the primary products are 2-methylpiperidine and piperidine. Most of the experiments shown in Fig. 3 were conducted for 24 h, sufficient time to ensure complete lysine conversion although gas uptake ceased well before this time (120 °C, 10 h; 150 °C, 6 h; 180 °C, 3 h); the 100 °C experiment was held at that temperature for 45 h prior to analysis. Additional details (NMR, LCMS) may be found in the ESI.†

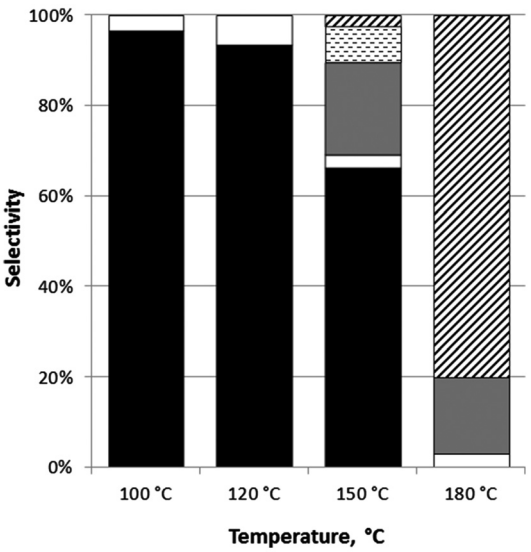

Fig. 3 Lysine hydrogenation product distribution (selectivity in %) at different temperatures. Experimental conditions: 14 wt% aqueous L-lysine, 1.0 equiv. H_2SO_4, 3.4 wt% Ru/C catalyst, 68.9 bar H_2, temperature as indicated. Lysinol, black; 1,5-diaminohexane, white; 2-substituted pyridines, gray; piperidine, diagonals; other, dash fill. Reaction time – 24 h for runs at 120–180 °C; 45 h at 100 °C run.

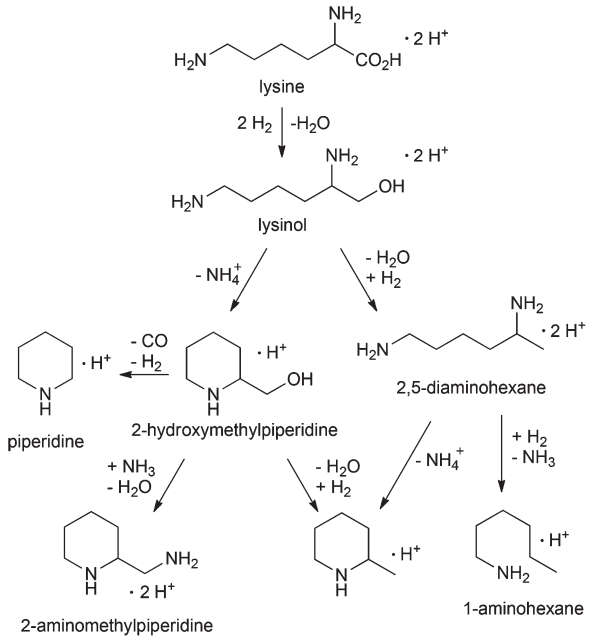

Fig. 4 Proposed reaction scheme for the by-product pathways during lysine hydrogenation reaction.

A reaction scheme consistent with these observations is shown in Fig. 4 and is supported by the following observations. First, treating aqueous lysinol at 180 °C, 70 bar H_2, and pH 3.1 in the presence of 5% Ru/C resulted in gas uptake for approximately 7 h before halting. Analysis at this time showed complete lysinol consumption and formation of 2-methylpiperidine (80%) and piperidine (10%) as the major products, in addition to smaller amounts of 1-hexylamine and 2-amino-1-hexanol. A similar reaction, again starting with lysinol but at 150 °C, resulted in *ca.* 15% lysinol conversion with 2-hydroxymethylpiperidine obtained as the major product (selectivity – 70%) and piperidine (20%) and 2-methylpiperidine (10%) as side products. Finally, treating 2-hydroxymethylpiperidine with H_2 (69 bar) at 180 °C produced largely piperidine (84%), 2-methylpiperidine (5%), and the usual slate of other trace products as observed with lysinol. These experiments are consistent with and support the reaction scheme proposed in Fig. 4.

Catalyst lifetime is critical in any process and was considered in the present study. A series of batch lysine hydrogenations was performed wherein the 5% Ru/C was separated from the aqueous reaction solution by filtration, rinsed with water, dried, and then added back to the reactor for another hydrogenation. No attempt was made to replenish catalyst losses due to physical handling during the filtration or other manipulations involved. Lysine conversions and selectivities were unchanged over 6 batch hydrogenations conducted in this manner (experimental details are provided in the ESI†). Analyses of the filtrates from these experiments showed no detectable ruthenium (<1 ppm). Catalyst lifetimes for a com-

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mercially viable process will likely be on the order of weeks to months and therefore these encouraging results should be considered as preliminary.

Lysinol from commercial lysine

The experiments described to this point provide an insight regarding experimental conditions (*e.g.*, catalyst, acidity/pH, temperature, *etc.*) required for the effective conversion of lysine to lysinol. All of these experiments were carried out using high purity L-lysine free base obtained from Sigma-Aldrich®. As discussed earlier, more than 1.2×10^9 kg of lysine are produced annually throughout the world. This commercially manufactured material is almost entirely in the form of salts, usually the monohydrochloride but more recently the sulfate has also become available. Much smaller amounts of free base lysine are available as a 50% aqueous solution. In all cases this lysine is of adequate purity for animal feed but is not laboratory reagent or pharmaceutical grade. For example, the color of these feed grade products varies from off-white to dark brown. To assess the feasibility of lysinol production, it is important to determine if commodity lysine is a suitable raw material and that impurities and the chloride counterion found in most commercial material do not interfere with the hydrogenation.

Three samples of commercial, feed-grade L-lysine were evaluated: L-lysine-HCl (off-white granules) and lysine (50 wt%) free base (dark coffee-colored liquid) were obtained from ADM. BioLys®, L-lysine sulfate, was obtained from Evonik and received in the form of brown granules. These three samples were each tested under typical hydrogenation conditions after adjusting the solution to pH ~ 1.5 as needed with H_2SO_4 (30 g of 10 wt% aqueous lysine, 3 g 5% Ru/C, 120 °C, 55.2 bar, 24 h). All three commercial samples were cleanly hydrogenated to lysinol with quantitative lysine conversion and selectivities of approximately 95% and thus showed no difference in activity or selectivity compared to high purity lysine.

Lysinol synthesis and isolation

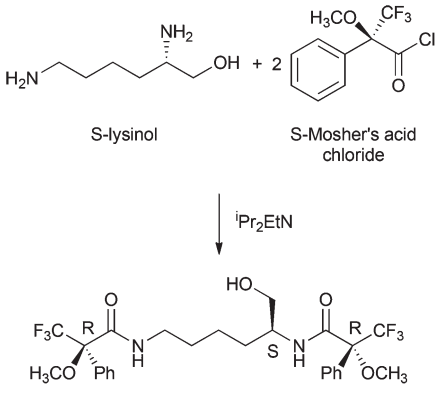
Once the hydrogenation conditions became well-understood the reaction was scaled up to produce sufficient quantities for evaluation in various applications. As described in the Experimental section, this hydrogenation has been conducted at multi-liter scale (typically 15–20 wt% aq. lysine, 1.05 equiv. H_2SO_4, 120 °C, 48.3 bar, 5% Ru/C, 4–20 L autoclave). Although the catalyst loadings relative to lysine substrate are somewhat large (20–25 wt/wt%), the catalyst from large scale preparations is routinely isolated and reused with little to no loss in activity.

Lysinol isolation involves catalyst filtration and adjustment to high pH (*ca.* 12) by the addition of NaOH. Calcium hydroxide and strong base ion exchange resins may also be used to generate the free base solution. Water is then removed by distillation and the resulting semi-solid, a mixture of Na_2SO_4 and lysinol free base, is extracted with an alcohol (EtOH, MeOH) to separate the lysinol from the insoluble salt. After solvent removal the resulting liquid is fractionally distilled to provide, after a forecut containing the aforementioned piperidines, pure lysinol in 50–70% isolated yields. Given the high lysine conversion and lysinol selectivity observed by analyses (GC, LC, NMR) of the raw hydrogenation solutions, higher isolated yields should be possible. The efficiency with which free base lysinol is extracted from the sulfate salt mass has been identified as one critical parameter impacting the final yield. Another yield loss occurs during the vacuum fractional distillation of the crude lysinol where an as yet unidentified decomposition reaction occurs in the distillation pot. Pure lysinol can be redistilled with very high recovery, suggesting that an impurity or impurities present in the crude product result in decomposition when exposed to the high temperatures in the distillation pot. Process optimization and yield improvement are the subject of future study.

Determination of lysinol enantiopurity

Jere *et al.*[27] report that the hydrogenation of alanine to alaninol under similar conditions to those reported here proceeds with a high degree of stereoretention. For example, hydrogenation of L-alanine at 100 °C gives L-alaninol with the enantiomeric excess ranging from 83% to above 99% depending on the specific reaction conditions. It was therefore of interest to determine the enantiopurity of lysinol prepared by lysine hydrogenation.

As expected, lysinol is rapidly and cleanly converted to the bis-Mosher amides upon treatment with the Mosher acid chloride (Scheme 4), presenting the use of NMR as a method to determine enantiopurity.[39,40] The reaction is selective for the amine groups; the alcohol group reacts much more slowly to form the ester, even in the presence of excess acid chloride reagent. This allowed for the rapid and simple *in situ* generation of the bis-amide and subsequent evaluation by NMR, in particular by ^{19}F NMR. Fig. 5 shows representative ^{19}F NMR spectra of the bis-Mosher amides generated from reaction of *S*-Mosher acid chloride with lysinol prepared from *S*-lysine (top), racemic lysine (middle), and *R*-lysine (bottom). These spectra clearly indicate a significant degree of enantiopurity in these hydrogenation products. The top and bottom spectra are the non-mirror image diastereomers RSR (top) and RRR (bottom). The product prepared from racemic lysine is, as expected, an



Scheme 4 Formation of RSR lysinol Mosher amide.

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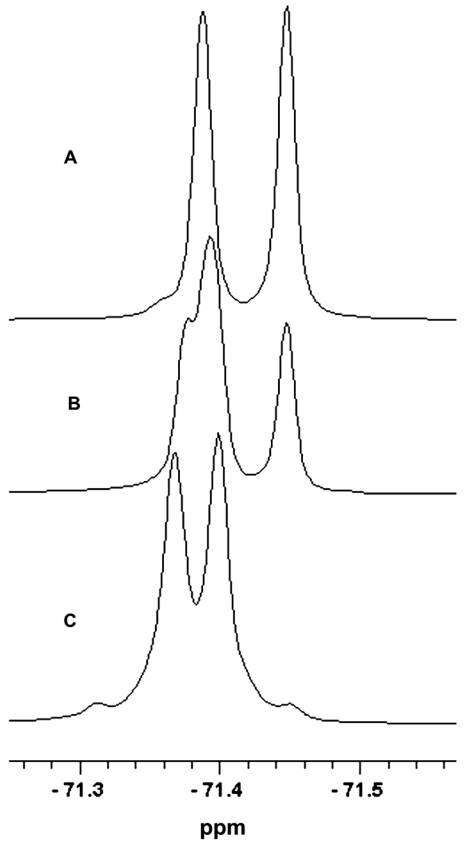
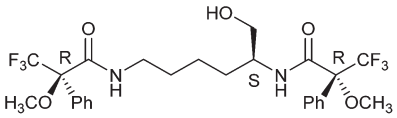


Fig. 5 ^{19}F NMR (377 MHz) spectra of lysinol bis-Mosher amide diastereomers. Legend: A: Product of reaction of *S*-Mosher acid chloride and lysinol prepared by *S*-lysine hydrogenation and assigned to RSR diastereomer (refer to Scheme 4 and text for diastereomer designations); B, racemic mixture of RSR and RRR obtained from *S*-Mosher acid chloride and lysinol prepared by *S,R*-lysine hydrogenation; C, RRR diastereomer obtained from *S*-Mosher acid chloride and lysinol prepared by *R*-lysine hydrogenation.

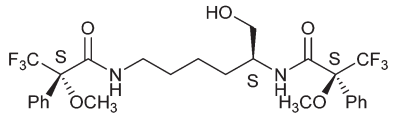
equal mixture of this diastereomeric pair. The results were further confirmed by ^{19}F NMR evaluation of the products of reaction of enantioenriched and racemic lysinol with *R*-Mosher acid chloride.

The enantiopurity was determined by peak deconvolution (details provided in ESI†) or integration of the ^{19}F NMR spectra and indicate 88–96% ee for lysinol prepared under these conditions. These results are entirely consistent with those reported previously, where alanine hydrogenation at 125 °C provided alaninol with ee's spanning 83–98% depending on the other reaction parameters.[27]

The absolute configurations of these derivatives can be deduced from the ^{1}H and ^{19}F NMR chemical shift data following the analysis developed by Sullivan *et al.*[41–44] Consider, for example, stereoisomers **1** and **2**, differing in the configuration of the α-methoxy-α-trifluoromethylphenyl groups only. If the configuration at C2 is S as indicated, and assuming that the hydroxymethyl group at C2 is sterically smaller than the $(CH_2)_4NH(COR)$ group, the Mosher analysis predicts that the hydroxymethyl methylene protons will be shifted upfield in diastereomer **2** (SSS) relative to diastereomer **1** (RSR). Indeed, the diastereotopic methylene protons shift upfield by 0.0131 and 0.0604 ppm in **2** relative to **1**. The ^{19}F NMR chemical shifts are also diagnostic. Thus, the CF_3 in diastereomer **2** is shifted 0.090 ppm downfield relative to that in **1**, again exactly as predicted by the Mosher analysis. These results demonstrate retention of configuration in the hydrogenation.



1, RSR



2, SSS

Epoxy thermosets

As previously discussed, the ethyleneamines and ethanolamines are used in a number of applications. One of the more familiar applications is in epoxy thermosets commonly used as adhesives and coatings. In this application, an epoxy resin is combined with a "hardener" to produce the thermoset.[45] Polyamines such as diethylenetriamine (DETA) and triethylenetetramine (TETA) are common hardeners and, for example are employed in consumer two-part epoxy adhesives. Besides being petrochemical-based, non-renewable materials, DETA and TETA are potent skin irritants and sensitizers,[15,46] providing additional incentive for alternatives. For these reasons, as well as the obvious structural and functional group similarity, the use of lysinol as an epoxy hardener was investigated and its performance was compared to DETA.

Bisphenol A diglycidyl ether (BADGE, Fig. 6) was chosen as the epoxy resin due to its ubiquitous presence in amine-cured epoxy thermosets. Indeed, over 75% of epoxy thermosets employ BADGE as the epoxy resin.[45] During thermoset formation each N–H bond in the amine hardener ring opens an epoxide to give a 1,2-aminoalcohol group. It is for this reason that the stoichiometry of these epoxy thermosets is typically set at two epoxy groups per primary amine (RNH_2). The multiple number of amine and epoxy groups in the hardener and resin, respectively, results in a highly cross-linked three dimensional network as depicted in Scheme 5.

In commercial applications epoxy thermosets are often complex formulations tailored to their intended application. These formulations may include, besides the epoxy resin and hardener, curing catalysts, fillers, strengthening agents such as silica and fiberglass, and diluents for rheology control. For

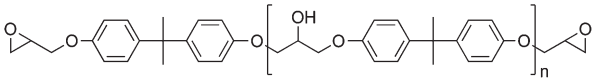


Fig. 6 Structure of BADGE.

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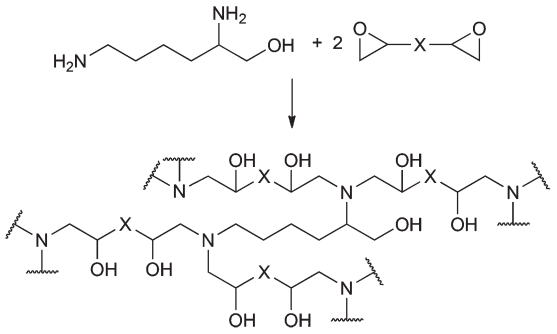

Scheme 5 Depiction of epoxy thermoset formation between lysinol and a generic bis-epoxide.

the purposes of this investigation, which is simply to compare lysinol with DETA, thermosets were prepared from these amines and BADGE only and no optimization or formulation development was performed. The thermosets were prepared using stoichiometrically precise amounts of amine and BADGE, thus 1 mole lysinol (4 moles N–H) per 2 moles of resin (4 moles epoxide; see Scheme 5), and 1 mole DETA (5 moles N–H) per 2.5 moles resin (5 moles epoxide). After mixing the two components thoroughly at room temperature the resulting viscous liquid were poured into a mold or applied to coupons as required. The samples were allowed to set at ambient temperature for up to 24 h. The resulting tack-free solids were then cured at 60–100 °C. This procedure gave clear, colorless, thermosets in the case of both lysinol and DETA. Samples with stoichiometrically unbalanced amounts of hardener and epoxy (±15%) were also prepared and evaluated to determine the sensitivity of the properties investigated to this parameter. Although some variation was observed, within this range of stoichiometry the effects were small and of no impact or importance to the purposes of this evaluation and comparison.

The resulting thermosets were subjected to a number of tests to evaluate their mechanical and adhesive properties, and chemical resistance, as described in the Experimental section. The results are summarized in Table 3. Within the experimental errors, the thermosets prepared from lysinol and DETA are indistinguishable.

The thermal stabilities of the two thermosets were also evaluated using TGA, and the results are provided in Fig. 7. Although these data indicate a slightly lower thermal stability for the lysinol thermoset it shows excellent stability to 300–310 °C, as compared to 350–360 °C observed for DETA.

Table 3 Physical property comparison of epoxy thermosets derived from renewable lysinol and petrochemical DETA[a]

	Lysinol	DETA
Lap shear		
Tensile strength (MPa)	4.6(1.1)	4.7(0.5)
Compression		
Compression modulus (MPa)	1678(133)	1489(69)
Strain at yield (%)	11.6(0.5)	16.3(0.4)
Stress at yield (MPa)	103(1)	104(1)
Nanoindentation		
Instrumented hardness (MPa)	228(48)	199(35)
Reduced modulus (MPa)	3506(412)	3287(279)
Chemical resistance		
% Mass gain		
50% aq. NaOH	5.5(2.5)	5.0(1.1)
30% aq. H_2SO_4	3.8(1.0)	4.4(0.5)
H_2O	2.4(0.2)	2.3(0.4)
3.5% aq. NaCl	2.6(0.3)	1.9(1.5)
Acetone	6.9(2.3)	5.4(1.9)
Toluene	0.4(0.1)	0.2(0.4)

[a] Value in parentheses is one standard deviation.

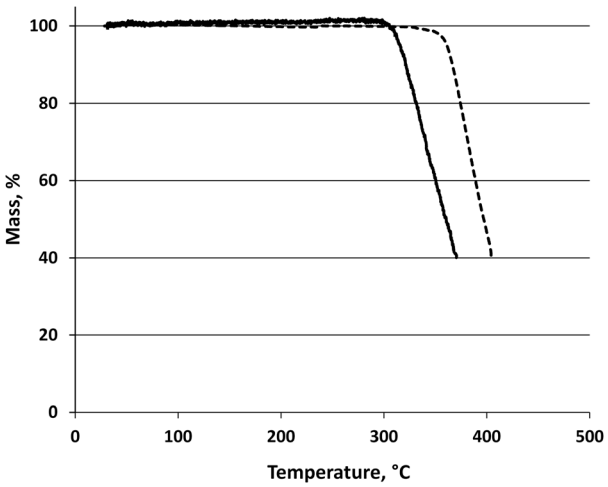

Fig. 7 Thermogravimetric analyses (TGA) of lysinol and DETA epoxy thermosets. Experimental conditions: initial temperature: 30 °C; temperature ramp: 10 °C min^{-1}. Solid line: lysinol thermoset; dashed line: DETA thermoset.

Conclusions

A comprehensive experimental study of lysinol synthesis from lysine, a renewably sourced large scale commodity amino acid, has been conducted. Lysine hydrogenation occurs under relatively modest conditions (100–150 °C, 48–70 bar, pH 1.5–2) in benign water solvent and yields water as the only direct reaction byproduct. Amongst the various catalysts screened for this hydrogenation reaction, Ru/C gives the highest lysinol yields. Lysine hydrogenation at higher temperature results in the formation of piperidines. The feasibility of lysinol synthesis from commercially available animal feed-grade lysine sources is shown.

Structurally and chemically lysinol resembles di- and polyfunctional petrochemical amines, particularly ethyleneamines and ethanolamines. These amines, besides being derived from non-renewable resources, are manufactured from toxic and hazardous raw materials *via* processes that produce complex mixtures of products requiring energy-intensive fractional distillation. These facts alone suggest the potential for lysinol as a

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replacement for ethylene- and ethanolamines. This point is further underscored by the demonstration that an epoxy thermoset prepared from lysinol possesses properties indistinguishable from one derived from a commercial ethyleneamine. Bio-based epoxy thermosets have received considerable recent attention but in all cases the focus has been on renewably sourced epoxy resins and not the hardeners.[47–53] Lysinol provides a bio-based amine hardener to complement bio-based epoxy resins and thus advances the area closer to a fully bio-based, renewable thermoset.

The concept and results presented here address most of the 12 Principles of Green Chemistry.[54] Conversion and selectivity to lysinol from lysine is high (Principle 1), a renewable feedstock is used as raw material (Principle 7), and the use of highly toxic and explosive starting materials (EO, EDC) is avoided (Principles 3, 4, and 12). The catalytic hydrogenation is conducted using water as solvent under relatively mild conditions (Principles 5, 6 and 9), although reduced pressure and catalyst loadings represent significant potential improvements. The *E*-factor (Principle 2) for lysine hydrogenation is 1.0–1.2, in the range of bulk chemical processes. Besides co-product water this value takes into account the salt formation (Na_2SO_4 or 2 NaCl) resulting from the counterion introduced with the lysine starting material and required to achieve the low pH conditions for the hydrogenation and the resulting neutralization. Because the fermentation process produces lysine as a salt almost all downstream uses of lysine to manufacture other chemicals will generate salt co-products. Nonetheless, this value compares favorably with the current processes to manufacture ethyleneamines with *E*-factors ranging from theoretical maxima of 0.3 ($2EO + 3NH_3 = DETA + H_2O$) to 2.3 ($2EDC + 3NH_3 + 4NaOH = DETA + 4NaCl$). Note that the latter calculations do not attempt to include correction for the complex product mixtures generated by these processes in practice, but instead assume direct conversion to a single product. Recycle or treatment of the water used and generated in this process also must eventually be considered. We have conducted lysine hydrogenation at up to 35 wt% lysine concentration without difficulty, thus demonstrating minimum water use. Finally, the toxicity, biodegradation, and environmental fate characteristics of lysinol require investigation.

To the best of our knowledge, this is the first study reporting a potentially scalable and economical lysinol synthesis and demonstration of the potential of both lysine and lysinol as a replacement for petrochemical amines. The use of lysinol in the dozens of other applications currently addressed by petrochemical amines awaits further exploration and exploitation.

Acknowledgements

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