

Review

Catalytic conversion of chitin-based biomass to nitrogen-containing chemicals

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SUMMARY

The exploration of renewable alternatives to fossil fuels for chemical production is indispensable to achieve the ultimate goals of sustainable development. Chitin biomass is an abundant platform feedstock that naturally bears both nitrogen and carbon atoms to produce nitrogen-containing chemicals (including organonitrogen ones and inorganic ammonia). The expansion of biobased chemicals toward nitrogen-containing ones can elevate the economic competitiveness and benefit the biorefinery scheme. This review aims to provide an up-to-date summary on the overall advances of the chitin biorefinery for nitrogen-containing chemical production, with an emphasis on the design of the catalytic systems. Catalyst design, solvent selection, parametric effect, and reaction mechanisms have been scrutinized for different transformation strategies. Future perspectives on chitin biorefinery have also been outlined.

INTRODUCTION

The modern civilization utilizes an enormous amount of energy and consumer products of the chemical industry, from large-volume transportation fuels and polymers to high-value-added herbicides and pharmaceuticals. So far, more than 130 million synthetic chemical substances, which have not existed in nature before, have been produced in the last ca. 100 years¹ The utilization of fossil resources received only occasional applications until the Industrial Revolution when coal, and later crude oil and natural gas, became the primary feedstock for providing energy and carbon-based chemicals. Today, oil refinery processing continuously provides bulk raw materials for the chemical industry, which produces value-added consumer end-products that maintain our living standards. Due to the increased utilization of nonrenewable carbon resources, the atmospheric carbon dioxide concentration has increased by >50% from ~280 ppm since the Industrial Revolution to ca. 420 ppm in 2023,² resulting in severe environmental concerns including global warming and climate change. These issues have directed scientists to investigate a replacement of petroleum-derived carbon-based resources and fuels by renewable and carbon-neutral alternatives.

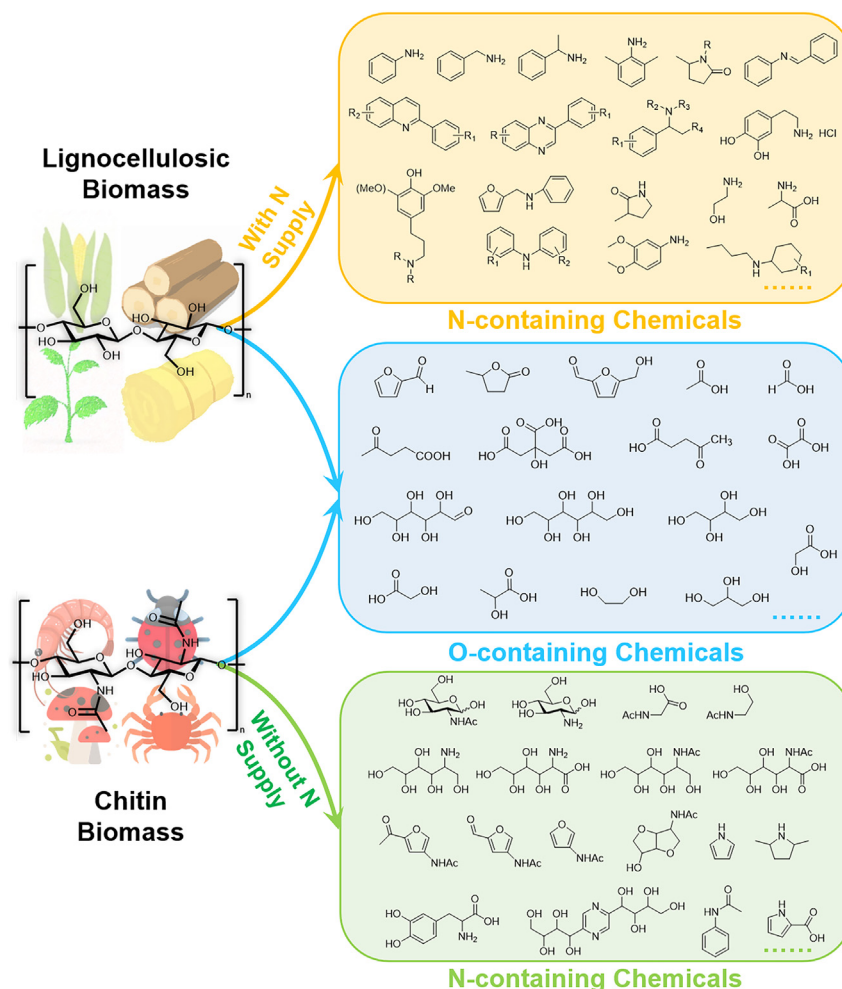
Biomass has been considered a globally available and inexpensive feedstock that will be the ultimate sustainable resource of all carbon-based consumer products of chemical industries in the future.^{3–8} Accordingly, intensive research activities have been directed toward the valorization of biomass and biomass-based waste streams to establish a conversion path of biomass materials into fuels and platform chemicals.^{9–17}

Among the various bioresources, as the most abundant biomass on earth, lignocellulosic biomass is most widely investigated. In comparison to crude oil, lignocellulosic biomass comprising cellulose, hemicellulose, and lignin, has significantly higher oxygen content with ample functional groups. Thus, transforming these materials requires different process strategies compared to integrated refineries, where the fractions of crude oil are separated by simple fractional distillation, and the low-value fractions are chemically upgraded via cracking or isomerizing processes, for example. Lignocellulosic biomass resources have been extensively used to produce renewable carbohydrate or hydrocarbon products either through whole utilization of the three components or through the fractionation-conversion strategy (Scheme 1). A variety of such products including 5-hydroxymethylfurfural (5-HMF), furfural, furfuryl alcohol, levulinic acid (LA), lactic acid, formic acid (FA), γ -valerolactone (GVL), etc.,^{9,10,18,19} could be obtained by different transformation routes. Furthermore, the coupling of ammonia or organic amines as the external nitrogen source with lignocellulose or lignocellulose-derived biomass feedstocks to produce high-value nitrogen-containing chemicals is an emerging hot field.^{20–23} Typical reactions include the amination of platform chemicals derived from lignocellulosic biomass into corresponding amines.^{24,25} For example, pyrrolidinone can be synthesized in one pot through the reductive amination of cellulose-derived platform chemical LA using hydrogen gas.²⁶ Efficient production of benzylamine is also achievable from lignin β -O-4 model compounds.²⁷ In addition, *N*-alkylation of amines with alcohols via transfer hydrogenation is a more environmentally benign method to produce *N*-alkylamines.²⁸ Notably, Ma et al. devised a single-step approach that directly transformed wood lignin into phenolic amines through reductive fractionation in an aqueous ammonia-alcohol mixture over a Ru catalyst, introducing a transformative route in lignin-first biomass

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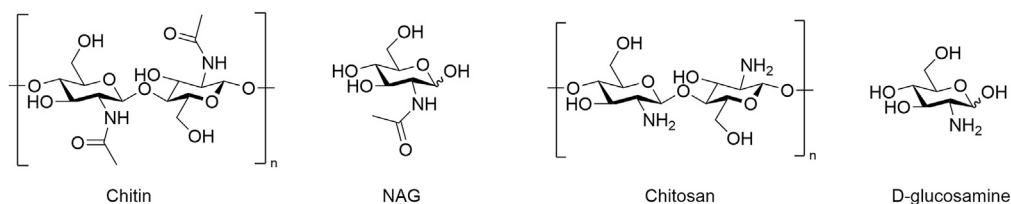


Scheme 1. Roadmap of lignocellulose and chitin biomass refinery for sustainable chemical supply

refinery.²⁹ Similarly, Lin et al. successfully used softwood lignin as raw material for directly producing hydrochloride dopamine through sequential steps of acid-catalyzed depolymerization, deprotection, hydrogen-borrowing amination, and methoxy group hydrolysis, which yielded overall 6.4 wt. % product with a high purity of 98%, offering a novel way to valorize lignin for nitrogen-containing chemicals.¹³

However, although the carbon source is sustainable, the conversion of lignocellulose or its derived feedstocks to nitrogen-containing compounds still requires the consumption of nonrenewable external nitrogen source from Haber-Bosch process. A fully sustainable production way on both carbon and nitrogen sources would be more attractive and environmentally beneficial. Following cellulose, chitin stands as the second most abundant biopolymer in nature,³⁰ with an annual biosynthesis estimated at approximately 100 billion tons.³¹ Primarily found in the exoskeletons of crustaceans and insects, chitin consists of *N*-acetyl-D-glucosamine (NAG) units, which are structural analogs of glucose with the substitution of the C2 hydroxyl group by an *N*-acetylamino group, linked together by the $\beta(1\rightarrow4)$ glycosidic bonds forming a linear and relatively uniform nitrogen-containing polymer.^{32,33} In general, chitin with a degree of acetylation below 50% is regarded as chitosan, which is mainly composed of D-glucosamine. (Scheme 2) Compared to lignocellulosic biomass, chitin not only naturally bears C, H and O atoms but also preserves 7 wt % of biologically fixed nitrogen. This unique feature enables chitin to be part of the current biorefinery to produce carbohydrates that are presently accessible from lignocellulosic biomass, as well as to open alternative and sustainable strategies to obtain biobased organonitrogen compounds, bypassing the Haber-Bosch ammonia production route.^{34–36} Hence, the valorization of chitin could further enlarge the biobased chemical pool and improve the economic competitiveness of the biorefinery concept. Meanwhile, it will mitigate the deforestation and secondary environmental risks of massive consumption of land-based biomass materials.

Most of the recent applications of chitin or chitosan have been limited to its polymeric form after stoichiometric chemical modification on the substitution groups^{37–39} for the generation of wound dressing material,⁴⁰ absorbent for heavy metals^{41,42} and dye,^{43,44} heterogeneous catalyst immobilizer,⁴⁵ and ingredient for skin and hair care product.⁴⁶ Its pyrolysis and hydrothermal liquefaction to obtain aromatic heterocycle compounds i.e., furans, were reported with low or moderate yields.^{47–49}



Scheme 2. Structure of chitin biomass

Nitrogen-containing compounds are often high-value chemical products including various pharmaceuticals, agrochemicals, etc. However, the current manufacture of these compounds is usually tedious with multiple transformations and with high carbon footprints due to the use of fossil carbon sources and ammonia. It should be noted that the synthesis of ammonia is a relatively highly energy-intensive process. This simple reaction accounts for ca. 2% of the total energy needs of humankind.⁵⁰ Valorizing the chitin-based biomass for nitrogen-containing chemicals could open up more sustainable and shortened pathways by utilizing the functional groups in chitin that expand the traditional boundaries of biorefinery and toward nitrogen-containing materials,^{51–53} and thus close the carbon and nitrogen cycle (Scheme 3).

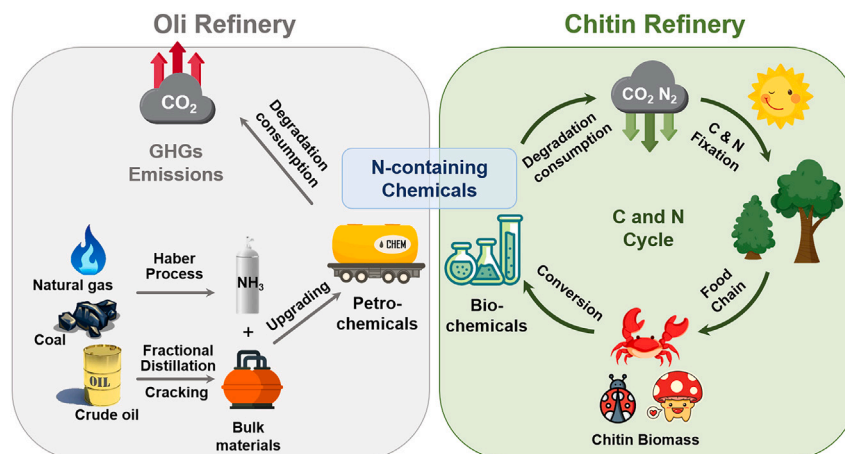
With the critical elements (C, H, O, N) in the structure, chitin could be selectively transformed into a variety of valuable organonitrogen chemicals through different strategies such as amino sugars, etc., as well as inorganic ammonia and organooxygen chemicals, to achieve high atom economy and a diverse product stream for broad uses. Natural chitin polymers usually possess high-molecular-weight, high crystallinity, and broad hydrogen bonding networks, and the robust structure makes its transformation relatively challenging. Hence, efficient and multifunctional catalytic systems are required to induce the cleavage/connection of different types of bonds for direct chitin conversion into target products, or chitin could be first depolymerized into soluble oligomers or monomers for further transformations in two-step manners. Chitin depolymerization is often aided by pretreatment methods and/or solvent effects to promote the cleavage of glycosidic bonds in a faster and milder way. The reaction is usually catalyzed by a mineral acid such as sulfuric acid. For chitin depolymerization, the selective cleavage of glycosidic bonds could produce amide sugars, while the simultaneous cleavage of glycosidic and the acetamido bonds could produce amine sugars. The monomeric amide sugar NAG could further undergo ring rearrangement and dehydration to produce a nitrogen-containing furanic compound in the presence of suitable Brønsted or Lewis acid catalysts. Hydrogenation or oxidation of the chitin biomass by heterogeneous noble metal catalysts will lead to the formation of amine/amide polyols or amino acids. Meanwhile, hydrodeoxygenation (HDO) could open new avenues to produce alkyl amines. As a result, different transformation strategies are indispensable to enable the generation of a variety of nitrogen-containing chemicals from chitin. So far, most of the transformations could be realized in one step, whereas multiple chemo-catalytic steps existed to obtain more diversified nitrogen-containing products. Aside from chemo-catalytic methods, the enzymatic methods could furnish opportunities to obtain value-added organonitrogen products with remarkably different structures from chitin.

Although several excellent reviews and feature articles have previously been reported on crustacean shell and chitin utilization, a timely and comprehensive summary on the rational design of the catalytic systems for chitin biorefinery to produce nitrogen-containing chemicals still lacks. In this review, the catalyst design, solvent selection, parameter optimization, reaction mechanism, etc. will be illustrated and examined respectively by the different transformation strategies. The key challenges and future directions on chitin-based biorefinery will also be outlooked. We anticipate this review will offer valuable insights and guidance for future studies contributing to chitin-based biomass valorization.

DEPOLYMERIZATION

The natural chitin boasts a very robust structure with the high crystallinity, high molecular weight and extensive hydrogen bonding networks. The depolymerization of chitin into soluble oligomers or sugar monomers is usually favorable for the subsequent transformations, besides, the oligomers or monomers themselves are also high-value nitrogen-containing products. The selective production of NAG requires the catalytic systems to promote the cleavage of glycosidic bonds while inhibiting the deacetylation. Hydrolysis of both bond types is necessary to favor D-glucosamine production. (Scheme 4). However, during depolymerization, the hydrolysis of the glycosidic bonds and the acetamide bonds will often happen non-selectively, especially in diluted acid, leading to unsatisfactory yields of NAG and D-glucosamine. The hydrolysis of glycosidic bonds is a S_N1 reaction with the formation of the carbonium ion as the rate-determining step (RDS), dependent on the H_3O^+ activity. On the contrary, the hydrolysis of acetamide bonds under acid-catalyzed conditions is a S_N2 reaction involving a nucleophilic substitution, where the RDS is the water activity in the reaction system. Water attacks the carbon center of the acetamide bonds, resulting in deacetylation. Therefore, conventional chitin depolymerization method utilizes concentrated acid solutions (e.g., 35% HCl)^{54,55} to promote glycosidic bond hydrolysis while limiting acetamide bond hydrolysis. In concentrated acid, the limited water content in the reaction system can suppress the deacetylation process while favoring the generation of carbonium ion intermediate, facilitating the glycosidic bonds cleavage to obtain NAG. However, these harsh conditions suffer from problems such as negative environmental impacts, rigorous requirements on equipment, great safety risks and low product selectivity.

In this regard, environmentally friendly and economically viable depolymerization approaches to transform chitin into the monomer sugars are imperative, as the primary step and entry point for chitin valorization.



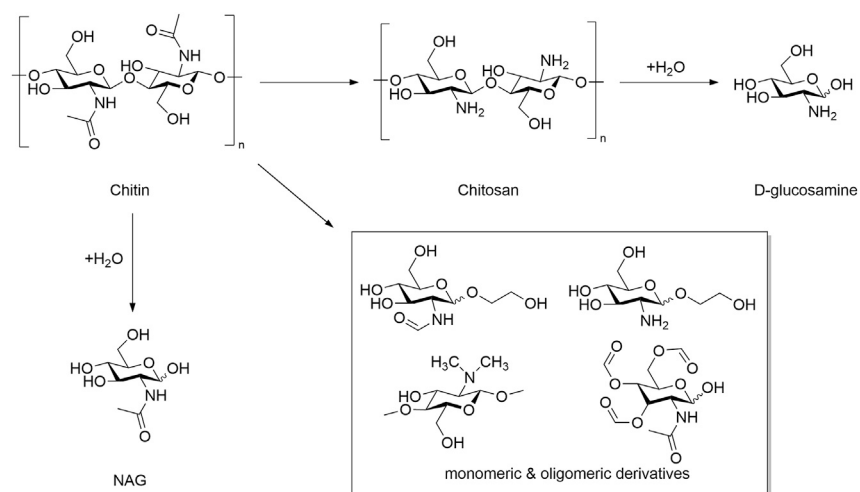
Scheme 3. Comparison of petroleum oil and chitin biomass refinery for nitrogen-containing chemicals

Thermochemical method

Chitin is insoluble in water and majority of common organic solvents. However, novel depolymerization routes have utilized several different solvents to “soften” the robust structure of chitin and facilitate the hydrolysis. Specifically, by employing various solvents that interact with the hydroxyl groups in chitin, its structural integrity can be altered, disrupting its hydrogen bonding networks or crystallinity, consequently impacting the thermodynamic driving forces of hydrolysis. Table 1 has summarized the reaction conditions and performances of the reported solvent systems for chitin depolymerization. Conventional methods which employ harsh conditions such as heating at high temperature of 200°C, may result in the carbonization and humification of oligosaccharides, leading to byproducts that inhibit the depolymerization. In contrast, solvent-mediated approaches significantly reduce the reaction temperature, eliminating the need for extensive energy input. Additionally, the acid amount considerably decreases by solvent effect, obviating the necessity for concentrated acid usage.

Pierson et al. reported the sulfuric acid-catalyzed liquefaction of chitin in EG with reduced acid dosage compared to conventional hydrolysis methods.⁵⁶ The EG functioned as both the solvent to interrupt the hydrogen bonding networks and decrease the crystallinity during the reaction, and the nucleophilic reagent to attack the glycosidic bonds and acetamide bonds for hydrolysis. Under optimal conditions, 75% conversion rate of chitin was achieved to produce EG-derived glucosamine (HADP), as the major product) and EG-derived NAG (HAADP) with an overall yield of 30% at 165°C for 90 min in the presence of 8 wt % sulfuric acid catalyst. It is found that the yields could not be further improved with prolonged reaction time because the acid catalyst was consumed and deactivated by the exposed amino group of the product. The proposed reaction mechanisms were as follow: HAADP was first formed by solvolysis and the sequential hydrolysis of the EG molecule as indicated by the Fourier Transform Infrared Spectroscopy spectra of recovered chitin solids (negligible deacetylation happened on chitin chains). Then, the acetamido side chain was cleaved to form HADP in a second step. The breakage of the glycosidic linkage is realized by the formation of an oxonium intermediate with the sulfuric acid which increases the electrophilicity on the C1 position. Next, a nucleophilic attack from the hydroxyl group of EG takes place to cleave the C-O bond and form HAADP. Afterward, the acetamido group could be solvolyzed after activation of the amide by the acid to afford HADP. Following this, the same group achieved efficient chitin liquefaction in FA.⁵⁷ The FA served as the solvent, the formylation reagent and the catalyst for the chitin conversion. The ball milled chitin became soluble in FA solvent due to the partial formylation of the -OH groups. Then, the oligomers and monomers were produced by the random cleavage of glycosidic bonds through a non-hydrolytic process. Concurrently, formylation reactions continuously undertook on both the hydroxyl and acetamide groups. As the reaction proceeded, the by-product water facilitated hydrolysis, and rehydrated products could form, thus products with a higher degree of depolymerization and formylation was obtained. About 44% yield of monomeric products (nitrogen-containing) were acquired at 100°C for 12 h in FA without a catalyst. They were further transformed to 5-(formyloxymethyl)furfural in 35% yield after an extended reaction duration.

More recently, Zhang et al.⁵⁸ developed a water/organic co-solvent system that could selectively convert ball milled chitin into D-glucosamine with 80% yield at 175°C in 1 h. The optimal co-solvent system was the 4:1 DGDE/water co-solvent. The mixture of water with the aprotic polar solvent displayed much superior performance than using pure water as solvent, as the sulfuric acid dosage was mitigated to only 0.1 M, but efficiently promoted the hydrolysis of both the glycosidic bonds and the acetamido bonds. This promotional effect was consistently observed with aprotic polar co-solvents, especially those with larger molecular structures. The key parameters in the co-solvent system for D-glucosamine production were identified as hydrogen-bond accepting basicity (β) and hydrogen-bonding interactions (δ_h). The solvent evaluation inferred that the organic co-solvent with large molecular structure exhibiting low β value and proper δ_h value. The low β value would improve apparent acidity while proper δ_h value facilitated better dissolution of the oligosaccharides, thereby sustaining the hydrolysis process under lower acid condition. Optimization of the solvent/water ratio was crucial, as water served both as a solvent and a reactant in the system, necessitating a certain amount of water addition, with a 4:1 ratio being determined as optimal. Very recently, Cheng et al. established a one-step production of *N,N*-dimethyl chitosan oligosaccharides (DMCOS) from chitin via an acid-catalyzed tandem



Scheme 4. Proposed reaction pathway of chitin depolymerization

depolymerization-deacetylation-*N*-methylation mechanism.⁵⁹ Chitin was converted to DMCOS in 5 wt % sulfuric acid solution with 10 wt % formaldehyde addition at 160°C. The maximal yield of DMCOS was 77% under optimal conditions, which has potential uses in anti-fungal applications. The acid catalyst promoted the hydrolysis and the formaldehyde served as the methylation reagent to functionalize the amino groups. The mechanistic study (Figure 1) indicated a non-conventional effect that the -OH groups have facilitated the reductive amination in the presence of a strong acid. Firstly, catalyzed by 5 wt % H₂SO₄, chitosan oligosaccharides (COS) were obtained through the depolymerization and deacetylation of chitin. Secondly, the authors proposed an adjacent hydroxyl group-assisted mechanism, which facilitated the reaction between the protonated amino group in COS and formaldehyde, leading to the formation of the imine intermediate in acidic environment. Subsequently, the imine intermediate underwent reduction via a direct hydrogen transfer mechanism, yielding *N*-methyl chitosan oligosaccharides. Finally, the synthesis of DMCOS was achieved by repeating the reductive amination process.

In the above studies, mineral acids were used as the acid catalyst for chitin depolymerization, but different organic solvent or co-solvent have been used to show different performances. The EG polyol solvent was involved in the acid-catalyzed depolymerization via solvolysis to favor both the cleavage of glycosidic and acetamido bonds, and the EG could interact with the hydroxyl group-rich chitin chains to mitigate its hydrogen bonding and crystallinity. FA and formaldehyde these small molecules with high activity could function as the derivatization reagents to react with the side groups of chitin polymers to solubilize chitin and make the transformation easier. The co-solvent systems usually consist of mainly dipolar aprotic solvent and a small amount of water. Such a co-solvent system could significantly reduce the acid dosage and selectively form glucosamine. It is believed that the solvent mixtures could create new solvent systems with desirable solvent parameters to enlarge the acidity and boost the solubility of oligosaccharides to lower down the acid dosage and efficiently promote the hydrolysis of both glycosidic and acetamido bonds.

The inorganic molten salt hydrates (MSHs) have recently been identified as effective and green solvents for selective chitin depolymerization into NAG. MSHs refer to salt aqueous solutions with the water-to-salt ratio close to the coordination number of the strongest hydrated cations, which could intensely interact with the -OH groups of the polysaccharides and favored the proton generation for acid-catalyzed reactions. Due to the coordination of MSHs with most water molecules, the amount of water molecules in the hydron solvation shell is reduced, greatly increasing the activity coefficient of the protons, allowing hydrolysis reactions to effectively occur under dilute acid conditions.⁶³ In addition, water-deficient environment may inhibit the S_N2 reaction between water molecules and the center carbon of the acetamido group.

Gökalp et al. employed the 60 wt % LiBr MSHs as the solvent in the presence of dilute acid (0.04 M HCl) to depolymerize chitin into NAG with the maximal yield of about 72% at 120°C for 30 min.⁶⁰ The reaction temperature and duration were correlated and played substantial roles in chitin hydrolysis, affecting the solubility, conversion, and yield. At lower temperatures (80°C and 100°C), chitin underwent either swelling or partial dissolution. For conversion, only 12.9% of chitin was converted at 80°C after a 30-min reaction, whereas the conversion rate gradually increased to 76.5% at 100°C. The yield of NAG continued to rise at both 80°C and 100°C within 180 min. Chitin's solubility in acidified MSHs was highly temperature-sensitive, resulting in a notably accelerated reaction rate at elevated temperatures. Complete dissolution of chitin was observed at 120°C, with conversion exceeding 90% within 30 min, and the yield of NAG peaked after 30 min at this temperature before declining. However, at 140°C, the solution became visibly dark-colored, suggesting the occurrence of side reactions and NAG decomposition at such elevated temperature. Additionally, the yield of NAG showed a monotonic decrease from 15 min onward. Therefore, a suitable temperature (e.g., 120°C) was required to initiate chitin hydrolysis within a brief duration and achieve a relatively higher product yield. The concentrated Li⁺ salt solution contributed to higher acidic strength and H⁺ activity, which not only significantly reduced the acid concentration but also improved the selectivity of chitin hydrolysis. The same group reported the chitin hydrolysis into NAG in the LiBr MSHs by using the solid acid catalysts of zeolites under similar reaction conditions.⁶¹ Nanosheet-like SAPO-34 crystals and commercial

Table 1. Summary of the reported solvent systems for chitin depolymerization

Entry	Substrate	Solvent	Catalyst	Temperature	Time	Main Product	Overall Yield	Reference
1	chitin	EG ^a	8wt % H ₂ SO ₄	165°C	1.5 h	EG-derived NAG & EG-derived glucosamine	30%	Pierson et al., ⁵⁶
2	ball-milled chitin	FA	\	100°C	12 h	monomeric product (nitrogen-containing)	44%	Zhang et al., ⁵⁷
3	chitin	4:1 DGDE ^b /water	0.1 M H ₂ SO ₄	175°C	1 h	D-glucosamine	80%	Zhang et al., ⁵⁸
4	chitin	10 wt % formaldehyde solution	5 wt % H ₂ SO ₄	160°C	4 h	DMCOS	77%	Cheng et al., ⁵⁹
5	chitin	60 wt % LiBr	0.04 M HCl	120°C	0.5 h	NAG	72%	Gözaydin et al., ⁶⁰
6	chitin	60 wt % LiBr	nanosheet-like SAPO-34	130°C	2 h	NAG	61%	Gözaydin et al., ⁶¹
			commercial microporous SAPO-34				63%	
7	H ₂ SO ₄ -aged chitin	50 wt % CaCl ₂	\	120°C	1 h	NAG	51%	Wang et al., ⁶²
		50 wt % CaCl ₂ -10 wt % ZnBr ₂					67%	

^aEG: ethylene glycol.

^bDGDE: diethylene glycol diethyl ether.

microporous SAPO-34 achieved 61% and 63% NAG yield under optimized conditions. In the reaction, the protons in zeolites exchanged with the Li⁺ in the solvent, and thus the hydrolysis is homogeneously catalyzed by the released protons. Hence, the hydrolysis rate was not related to the textual properties of zeolites but correlated with the acid site properties, and a strong negative correlation between Lewis acid density and NAG yield was observed.

Following this, Wang et al. devised an integrated aging-hydrolysis method to convert chitin into NAG in more abundant and inexpensive CaCl₂ MSHs.⁶² The mild and facile aging process (homogeneously coating a small amount of sulfuric acid onto chitin) at near room temperature (RT) for about 48 h induced a remarkable decrease in chitin molecular weight and improved the NAG yield. For the optimization of aging parameters, as shown in Figure 2, it was observed that increased acid dosage, elevated aging temperature, and prolonged aging time did not always result in improved aging efficiency. In fact, harsher aging conditions could potentially trigger NAG decomposition and reduce the monomer yields. Consequently, the optimal conditions were identified as aging with 8: 1 (chitin to acid ratio) sulfuric acid addition at 40°C for 48 h. The NAG yield increased to a 3-fold value from aged chitin compared to that of the non-aged sample. Under the optimal hydrolysis parameters, the aged solid powder (containing sulfuric acid, equal to 0.03 M in the solvent) was hydrolyzed in 50 wt % CaCl₂ MSHs at 120°C producing 51% yield of NAG. By adding 10 wt % ZnBr₂ as the co-salt, the optimal NAG yield of about 67% could be achieved. The CaCl₂ MSHs alone without an acid catalyst could notably promote chitin hydrolysis into shorter chain molecules at elevated temperature. The synergy of the aging step and the CaCl₂ MSHs was reckoned as the crucial reason for efficient hydrolysis into NAG. Based on the time-of-flight mass spectrometry, X-ray photoelectron spectroscopy and nuclear magnetic resonance (NMR) results, the Ca²⁺ cation coordinated with the carbonyl group (oxygen atom) and acetamido groups (nitrogen atom). While the Cl⁻ interacted with the -OH groups on the chains to shift the electrostatic states of chitin and stimulate the facile hydrolysis.

The MSHs solvents have been reported not only for the very efficient and selective depolymerization of chitin into NAG with high yields, but also successfully reduce the reaction temperature below 120°C compared to most organic solvents. The possible reasons of the boosting effects of MSHs could be ascribed to: 1) the deficiency of water in the solvation shells of the protons would considerably increase the apparent acidity of the system, 2) the strong interactions between the cations/anions of the salts and the chitin chains would favor the swelling and/or dissolution of chitin polymers, 3) such interactions with the oligosaccharide intermediates would further promote the depolymerization to produce NAG. The effects of different MSHs salt species were still unknown and under investigation, which deserves further clarification. Another challenge of chitin hydrolysis in MSHs is that the proton exchange will happen between the Brønsted sites on any heterogeneous solid catalyst and the salt cations. Thus, real heterogeneous acid catalyst is difficult to realize for chitin depolymerization into NAG monomer in MSHs solvent.

Mechanochemical method

Apart from thermochemical method, appropriate pretreatment methods can be very effective in improving the hydrolysis performance. Among these techniques, the mechanochemical method can be defined as the interaction between external mechanical forces and a chemical system, wherein force vectors are applied to activate chemical reactions, offering a complementary approach to traditional strategies. So far, the ball mill pretreatment method was identified as the most effective one to destruct the structural robustness of chitin, and the

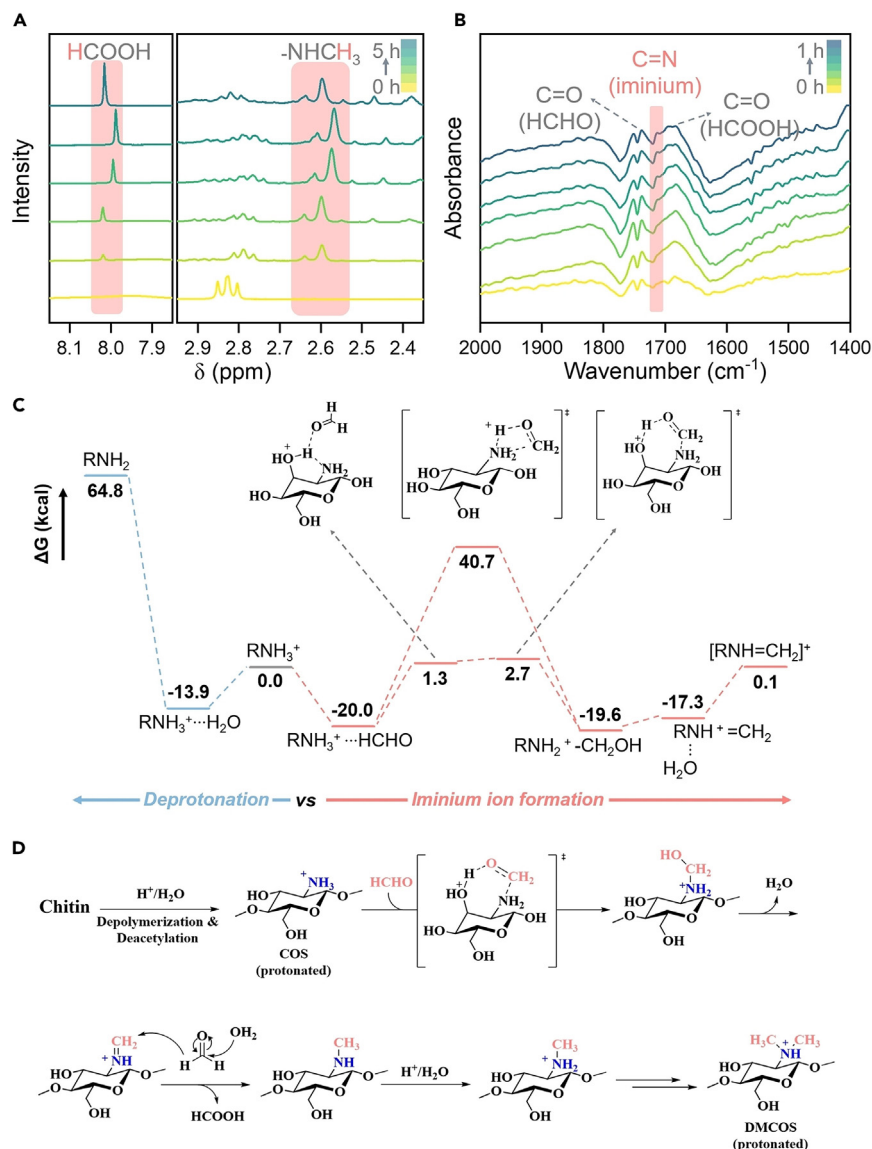


Figure 1. Mechanistic analysis of reaction from chitin to DMCOS

(A) ^1H NMR and (B) operando ATR-FTIR during reaction of GlcN in acidic formaldehyde solution. (C) DFT calculations of deprotonation process and iminium ion formation process at B3LYP/6-31+G(d) level of theory. (D) Proposed reaction pathway.

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mechanochemical depolymerization of chitin have been reported. Yabushita et al. ball milled the acid-impregnated chitin powders, in which the mechanical and chemical forces concurrently facilitated the depolymerization (Figure 3A).⁵⁴ Totally soluble short-chain oligomers could be obtained after ball milling at 500 rpm for 6 h. The reaction happened in solid-state without the addition of a solvent, but the physically adsorbed water on chitin was regarded as the reagent in the hydrolysis process. The as-obtained soluble oligomers were easily hydrolyzed into NAG (53% yield) or methanolized into 1-O-methyl-N-acetylglucosamine (70% yield) under relatively mild conditions. Compared with the conventional hydrolysis method, the mechanochemical method has significantly reduce the acid dosage, mitigate environmental burdens (solvent-free) and remarkably enhance the product selectivity. The high selectivity toward NAG monomers was ascribed to the reason that the mechanical forces primarily imposed on the chitin chains as an external pulling force to break the glycosidic bonds, whereas the acetamido side chain was negligibly influenced. The assumption was verified by the density functional theory (DFT) calculations (Figure 3B).⁶⁵ The conformation of NAG dimer greatly altered by the application of the external force, which facilitated the electron donation to the σ^* -orbital of the glycosidic bond, resulting in the increased Brønsted-Lowry basicity of the glycosidic oxygen. Consequently, the proton affinity and the reactivity increased, which induced the selective cleavage of glycosidic bond rather than acetamido group in low acid concentrations.

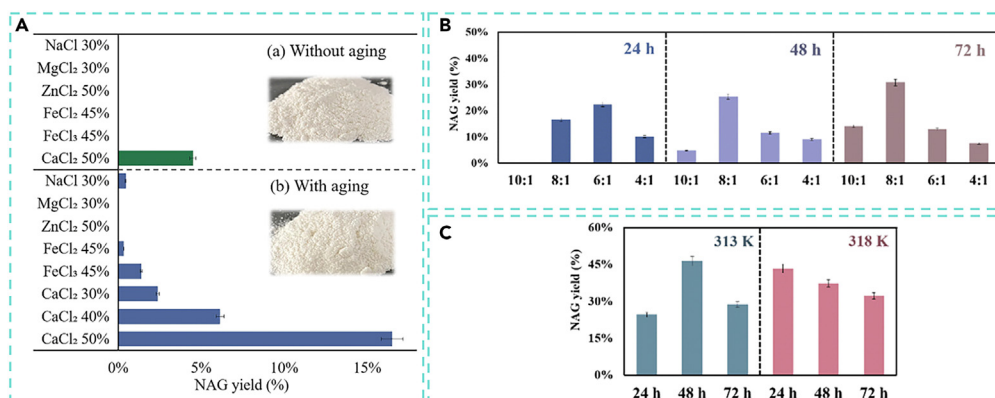


Figure 2. Aging effect on chitin hydrolysis into NAG

(A) Hydrolysis of (a) chitin without aging and (b) chitin with aging (aging 48 h at RT) in different types of salt solutions.

(B and C) The NAG yield under different chitin aging conditions. Reproduced with permission from ref.⁶². Copyright 2023 Royal Society of Chemistry.

In the presence of a base catalyst, the depolymerization and deacetylation could simultaneously occur to afford deacetylated chitosan products. Since a base catalyst is beneficial to the hydrolysis of the acetamido group, but inadequate for the hydrolysis of glycosidic bonds, the products were usually obtained as low-to-high molecular weight chitosan rather than oligomers. Chen et al. developed a facile solid-state mechanochemical method to quantitatively produce low molecular weight chitosan (LMWC), by ball milling a mixture of a base (e.g., NaOH) and chitin or the raw shrimp shell powders (Figure 3C).⁶⁶ The degree of deacetylation (DD) and molecular weight (MW) of the resulted products could be adjusted by varying the ball milling parameters such as the speed, time and ball number. Increasing the ball number from 50 to 140 (2 milling cycles) significantly enhanced the yield of water-soluble product from 21.6% to 96.4%. Maintaining a ball number of 100, the yield consistently hovered around 95% over 4 milling cycles and beyond, indicating that a minimum of 4 cycles is necessary for high conversion. Milling speed also played a pivotal role, with yields of the water-soluble product measured at 17.1%, 42.6%, and 96.4% for speeds of 500, 600, and 700 rpm, respectively. These findings underscored the substantial improvement in chitin transformation with increased mechanical power, leading to reduced crystallinity and enhanced chemical reactivity. Consequently, the conversion of chitin into water-soluble products was facilitated. The impact of ball milling time and speed on DD and MW values was also investigated. DD values increased gradually with longer milling times, reaching 39.1% after 2 cycles and further escalating to 83.3% after 12 cycles, signifying continuous deacetylation throughout the milling process. Additionally, MW values experienced a sharp decline to 12.8 kDa after 2 cycles and further plummeted to 7.7 kDa after 12 cycles. Achieving a product with an even lower MW necessitated a further round of ball milling. For instance, milling a sample in the presence of an equivalent amount of NaOH for 6 cycles reduced the MW significantly to 1.2 kDa. This revealed the synergistic effects between mechanical and chemical forces under appropriate ball milling conditions, leading to the efficient formation of LMWC products with tunable MW (ranging from 1.2 to 13 kDa) and varied DD values (from 40% to 83%). Compared to traditional methods, the mechanochemical method diminished base usage to one-tenth, and the obtained chitosan products had narrower weight distributions (with a polydispersity value of 1.1). Following this, Nardo et al. adopted the aging-mechanochemical approach to produce high molecular weight chitosan (HMWC) from chitin (Figure 3D).⁶⁷ In the first step, the chitin was slightly ball milled in a mixer milling machine using a ZrO₂ jar with one ball for 30 min, which led to the amorphization of chitin. Next, the amorphized chitin powders were blended with NaOH (5 equivalents) and milled in a PTFE jar for 5 min. The solid powders were then aged at RT with the relative humidity (RH) controlled at 98% for 6 days for deacetylation to yield about 73% HMWC products. The extent of depolymerization and deacetylation is strongly influenced by factors such as the ball mill type, the quantity and material of balls and environmental parameters. The mixer milling machine is less energy-intensive than the planetary milling machine used in previous works, so would not significantly reduce the molecular weights, which could obtain chitosan with distinct properties, namely high DD and high MW. Harder and denser materials like ZrO₂ and steel are more effective in disrupting chitin, leading to significant amorphization compared to polytetrafluoroethylene. High RH value provides more water for deacetylation and depolymerization reactions. Additionally, increasing aging temperatures accelerate hydroxy-induced reactions, with deacetylation reaching 90% at temperatures ranging from RT (22°C) to 30°C, accompanied by a 1-fold decrease in molecular weight. Regarding aging time, deacetylation increases from 53% at 3 days to 76% at 4 days at RT, plateauing thereafter. At 50°C, deacetylation reaches 90–95% between 3 and 6 days.

As previously mentioned, chitin has a robust structure and the depolymerization is challenging, and thus most of the hydrolysis reactions have been undertaken using a homogeneous acid catalyst. With the aid of mechanical forces, chitin depolymerization with a solid acid catalyst became viable. Kerton et al. investigated the mechanochemical treatment of chitin and a natural clay kaolinite (as a solid acid catalyst) in a mixer mill, and 75.8% of chitin became water-soluble after ball milling with a reaction time of 6 h.⁶⁸ The soluble products were identified as chitin oligomers with the degree of polymerization of 1–5, with the total NAG monomer and dimer yield of about 9%. Fukuoka et al. explored a carbon-based solid acid catalyst (named as AC-Air) to produce chitin oligomers from chitin by the

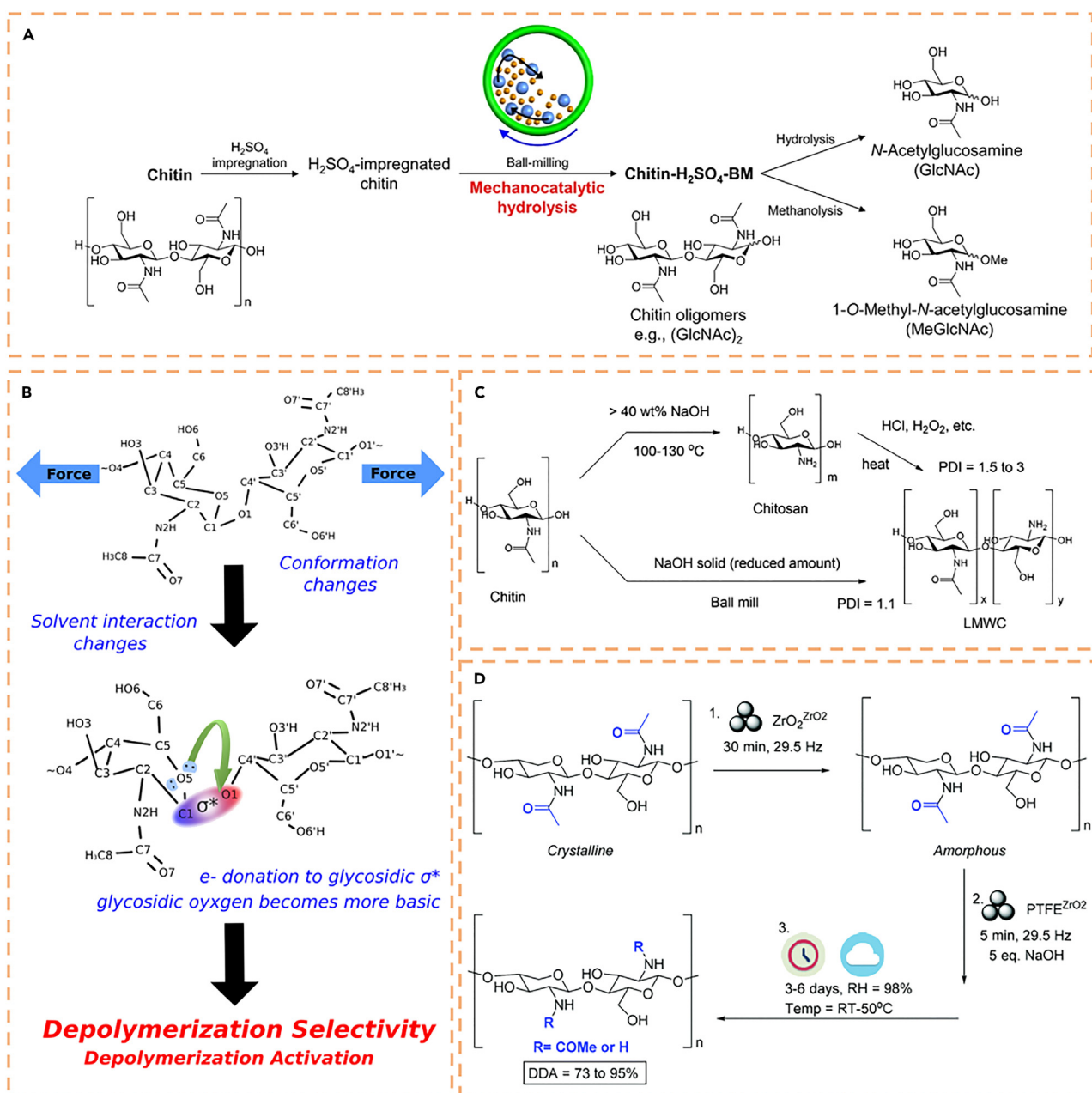


Figure 3. Chitin depolymerization under ball milling

(A) Two-step depolymerization of chitin to N-acetylated monomers, catalyzed by H₂SO₄. Reprinted with permission from ref.⁶⁴. Copyright 2015 Wiley.

(B) Scheme of mechanochemical activation toward chitin depolymerization. Reprinted with permission from ref.⁶⁵. Copyright 2020 American Chemical Society.

(C) The reaction scheme of the traditional, two-step method (top) and the proposed one-step, mechanochemical method (bottom). Reprinted with permission from ref.⁶⁶. Copyright 2017 Royal Society of Chemistry.

(D) Amorphization/aging based chitin deacetylation experiments. Reprinted with permission from ref.⁶⁷. Copyright 2019 Royal Society of Chemistry.

mechanochemical method.⁶⁹ The AC-Air catalyst was obtained by pyrolyzing the commercial AC at 425°C for 10 h in air, which promoted the generation of carboxylic and phenolic groups on the surface. The weak acid sites were effective at cleaving the glycosidic bonds chemically. The mechanical forces and the CH- π interactions between chitin and the carbon catalyst facilitated the contacts of the substrate and the catalyst to overcome mass transfer limitation. The highest oligomer yield and selectivity was 66% and 94% under optimal conditions. Monte Carlo simulations revealed that AC-Air could hydrolyze the glycosidic bonds of chitin at a similar rate, independent of molecular size. With CH- π interactions, the adsorbed long-chain polysaccharides were preferentially hydrolyzed by the weak acid sites

on the catalyst surface over the short-chain ones, leading a high yield and selectivity of oligosaccharides with specific degree of polymerization of 1–6.

Microwave method

Microwave technology is also an effective method for chitin depolymerization since microwave irradiation can disrupt the robust structure of chitin, thereby facilitating the subsequent enzymatic or catalytic hydrolysis.⁷⁰ Simultaneously, it functions as an energy source, providing rapid and uniform heating patterns that accelerate the depolymerization by enhanced molecular movements and collisions.

Ajavakom et al. demonstrated that under the microwave heating with an irradiation power of 850 W, the hydrolysis duration significantly reduced to merely 12 min from 120 min under conventional heating conditions, with 57% yield of glucosamine hydrochloride as the product.⁷¹ The faster heating rate under microwaves promoted reaction kinetics while achieving yield comparable to traditional heating methods. Yan et al. revealed a synergistic effect between microwave heating and a solid catalyst graphene oxide (GO).⁷² They added GO catalysts into microwave-assisted depolymerization systems, which increased the heating rate by 0.37 K/s and 0.26 K/s in chitin and chitosan depolymerization systems, respectively, at a microwave power of 5 W/g. Simultaneously, the functional groups on the GO surface facilitated the dehydration reaction and subsequent production of 5-HMF. Specifically, the -COOH functional groups played a crucial role in cleaving glycosidic bonds to produce oligomers and monomers, while the -OH groups induced alterations in the conformation of monosaccharides. Moreover, microwave heating has proven highly effective for nonspecific enzymatic hydrolysis of chitin into oligosaccharides. In a 5-h process with pepsin, a chitin oligosaccharide content of 37.58 mg/g was achieved, including 13.76 mg/g of NAG.⁷³ Combining microwaves with enzymes, especially pepsin, a 35.59% increase in the conversion rate compared to individual pretreatment of chitin or enzyme could be realized, mainly because microwave technology broke down the crystalline structure of chitin, improved the enzyme stability and enhanced chitin-enzyme interaction probability.

Microbial method

Microbial technology has emerged as a promising pretreatment approach to produce NAG. Chen et al. pioneered a bacterial fermentation method for pretreating chitin powder under optimized condition at 25°C, 200 rpm and an initial pH of 7.5 for 12 h, which resulted in a well-treated chitin termed CBF.⁷⁴ CBF displayed distinctive structural changes, including a visible fleecy structure, reduced crystallinity and decreased average molecular weight. The bacterial fermentation proved comparable performance to high-pressure homogenization and superior to grinding and ultrasonication technologies. Subsequent enzymatic reaction yielded 19.2 g/L NAG from 20 g/L CBF, representing an impressive 96% yield. The scalability of CBF preparation further suggests its viability for large-scale industrial enzymatic production of NAG.

Besides, microorganisms are one of the most important natural sources of chitinases. Bacteria produce chitinase to utilize chitin's components as essential carbon and nitrogen sources for microbial growth.⁷⁵ In fungi, chitinases play a fundamental role in synthesizing cellular structures.⁷⁶ Remarkably, microbial chitinases, distinguished by their intrinsic abundance, robust enzymatic activity and facile accessibility, are valuable tools for transforming chitin into NAG or its oligosaccharides. Chitinases have been successfully extracted from various bacterial strains, such as *Serratia proteamaculans* NJ303, *Aeromonas hydrophila* NJ303, *Chitinolyticbacter meiyuanensis* SYBC-H1 and *Chitinibacter* sp. GC72, for the depolymerization of chitin,^{77–80} highlighting the availability of microbial technology in sustainable NAG production. To improve efficiency, it is necessary to further develop the chitinases separation and purification technologies. The elucidation of the enzymatic hydrolysis mechanism and design of recombinant enzymes systems are still lacking in current research.

DEHYDRATION

Chitin biomass possesses multiple hydroxyl groups, and its dehydration steps (removal of water molecules) will often generate carbon-carbon double bonds and/or furanic ring structure, producing different products including 3-acetamido-5-acetylfuran (3A5AF), 2-acetamido-2,3-dideoxy-D-erythro-hex-2-enofuranose (Chromogen I), 3-acetamido-5-(1',2'-dihydroxyethyl)furan (Chromogen III)/dihydroxyethyl acetamidofuran (Di-HAF), 3-acetamido-5-furfuryl aldehyde (3A5F) and 3-acetamidofuran (3AF). Table 2 has summarized the reaction conditions and catalytic performances of the reported catalytic systems for chitin biomass dehydration into these products. So far, most of the developed catalytic systems can efficiently dehydrate NAG, whereas only a few can convert chitin into the target products directly. For the reaction pathway (Scheme 5), it is reckoned that the NAG first undergoes ring-opening to afford the straight-chain form (aldehyde-N-acetyl-D-glucosamine). Starting from the chain form, two possible pathways have been proposed.^{81,82} Both proposed pathways involve dehydration and furan ring formation, but the sequence was different. The NAG chain could first dehydrate into an unsaturated chain intermediate and then form the furan ring, or conversely undergo ring formation-dehydration, to produce the Chromogen I product. Further dehydration (eliminating one more water molecule) would generate the Chromogen III (or named as Di-HAF) product. 3A5AF would be formed after the elimination of three water molecules from NAG. The oxidative cleavage of the C-C bond in the acetyl group would result in 3A5F product (with a more reactive aldehyde group). In addition, the combinational use of a base and the dehydration catalysts (usually Brønsted or Lewis acids) would induce a retro-aldol condensation-dehydration route to give 3AF.

3A5AF

3A5AF is a high-value organonitrogen chemical that can be obtained by NAG dehydration. This furanic amide is a versatile building block which can be upgraded into important biomedical, pharmaceuticals, dyes, etc.^{104–107} The Kerton group first reported the boric

Table 2. Summary of dehydration of chitin biomass into different products

Entry	Substrate	Solvent	Catalyst	Additive	Temperature	Time	Product	Yield	Reference
1	NAG	[BMim]Cl ^a	Boric Acid	\	180°C	3 min (Microwave)	3A5AF	60%	Drover et al., ⁸³
2	NAG	DMA ^b	Boric Acid	NaCl	220°C	15 min (Microwave)	3A5AF	62%	Omari et al., ⁸⁴
3	chitin	NMP ^c	Boric Acid	NaCl	215°C	120 min	3A5AF	8%	Chen et al., ⁸¹
4	chitin	[BMim]Cl	Boric Acid	HCl	180°C	60 min	3A5AF	6%	Chen et al., ⁸⁵
5	ball-milled chitin	[BMim]Cl	Boric Acid	HCl	180°C	10 min	3A5AF	29%	Chen et al., ⁸⁶
6	NAG	DMF ^d	AlCl ₃ ·6H ₂ O	\	120°C	30 min	3A5AF	30%	Padovan et al., ⁸⁷
7	NAG	DMA	[Gly]Cl ^e	CaCl ₂	200°C	10 min	3A5AF	53%	Wang et al., ⁸⁸
8	NAG	DMA	[Pyz]Cl ^f	Boric Acid CaCl ₂	190°C	60 min	3A5AF	70%	Du et al., ⁸⁹
9	NAG	DMA	[TEA]Cl ^g	Boric Acid	170°C	20 min	3A5AF	62%	Zang et al., ⁹⁰
10	NAG	NMP	[PDCMPi]Cl ^h	\	180°C	20 min	3A5AF	43%	Zang et al., ⁹¹
11	NAG	NMP	[CMpy]Cl ⁱ	B ₂ O ₃ +CaCl ₂	180°C	20 min	3A5AF	67%	Zang et al., ⁹²
12	NAG	DMF	NH ₄ Cl	LiCl	160°C	5 min	3A5AF	43%	Wang et al., ⁹³
13	NAG	DMA	NH ₄ SCN	CaCl ₂ ·2H ₂ O	180°C	10 min	3A5AF	57%	Chen et al., ⁹⁴
14	NAG	DMA	CCCA DES ^j	CaCl ₂ ·2H ₂ O	210°C	20 min	3A5AF	47%	Wu et al., ⁹⁵
15	NAG	DMA	ChCl-Gly DES ^k ChCl-Gly-B(OH) ₃ DES ^l	\	140°C	140 min 160 min	Chromogen III 3A5AF	31% 39%	Zhao et al., ⁹⁶
16	NAG	choline chloride/ PEG-200/ boric acid DES	\	\	180°C	15 min	3A5AF	18%	Wang et al., ⁹⁷
17	NAG	GVL	NH ₄ SCN	HCl	140°C	120 min	3A5AF	75%	Ji et al., ⁹⁸
18	NAG	Water	\	\	180°C 240°C	33 s 8 s	Chromogen I Chromogen III	37.00% 34.50%	Osada et al., ⁹⁹
19	NAG	pyridine	phenylboronic acid triflic acid	\	115°C	30 min	Di-HAF	73%	van der Loo et al., ¹⁰⁰
20	NAG	pyridine	boric acid triflic acid	NaIO ₄	116°C	30 min	3A5F	92%	Gomes et al., ¹⁰¹
21	NAG	NMP	Ba(OH) ₂ -H ₃ BO ₃ - NaCl	\	180°C	20 min	3AF	74%	Lin et al., ¹⁰²
22	NAG	dioxane	La ₂ O ₃	\	180°C	180 min	3AF 3A5AF	50% 21%	Shaikh et al., ¹⁰³

^a[BMim]Cl: 1-butyl-3-methylimidazolium chloride.

^bDMA: *N,N*-dimethylacetamide.

^cNMP: *N*-methyl-2-pyrrolidone.

^dDMF: *N,N*-dimethylformamide.

^e[Gly]Cl: glycine chloride.

^f[Pyz]Cl: pyrazine hydrochloride.

^g[TEA]Cl: triethanolamine hydrochloride.

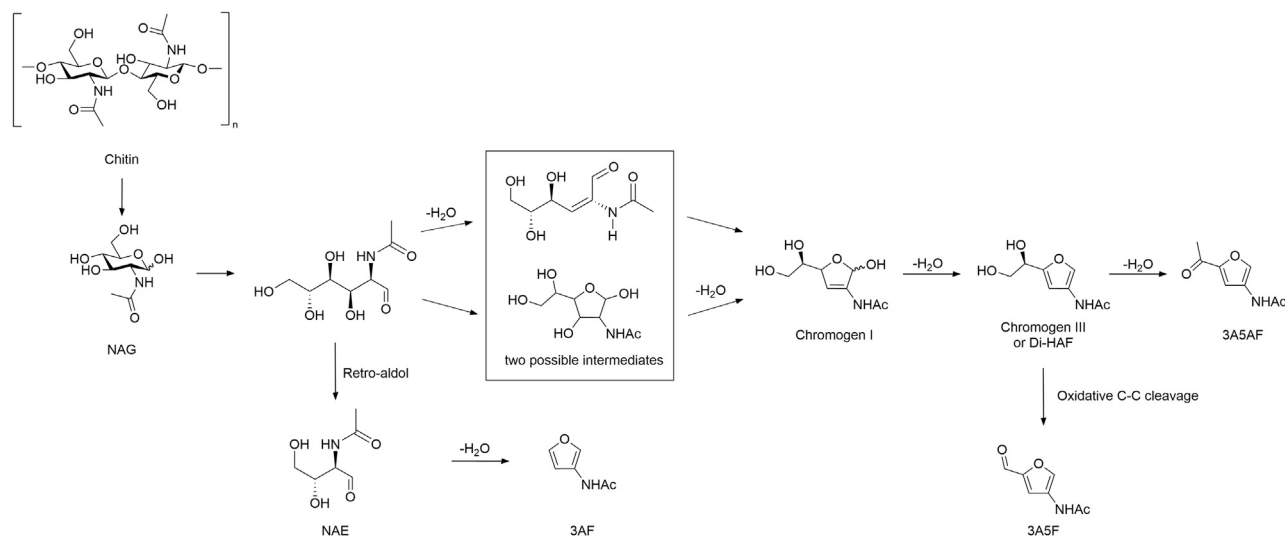
^h[PDCMPi]Cl: 4,4'-(propane-1,3-diyl)bis(1-(carboxymethyl)piperidin-1-ium) chloride.

ⁱ[CMpy]Cl: 1-carboxymethyl pyridinium chloride.

^jCCCA DES: choline chloride/citric acid deep eutectic solvent.

^kChCl-Gly DES: choline chloride-glycerin deep eutectic solvent.

^lChCl-Gly-B(OH)₃ DES: choline chloride-glycerol-B(OH)₃ deep eutectic solvent.



Scheme 5. Proposed reaction pathway of chitin dehydration into different products (NAE: N-acetylerthrosamine)

acid-catalyzed dehydration of NAG to selectively produce 3A5AF (>60% yield) under microwave-assisted heating at 180°C–220°C in [BMIm][Cl] ionic liquid⁸³ or DMA.⁸⁴ Yan et al. pioneered the direct conversion of chitin polymer into 3A5AF by coupling depolymerization and dehydration in one step.^{81,85} Combinational uses of Brønsted and Lewis acids as the promoters were beneficial to facilitate the hydrolysis and dehydration simultaneously, and chitin pretreatments have been employed to further enhance the hydrolysis efficiency. The highest 3A5AF yield of 29% was obtained directly from chitin polymer under conventional heating at 180°C for 10 min in [BMIm]Cl.⁸⁶ Besides, the mechanistic studies by poisoning tests and NMR analyses (Figure 4) have probed the promotional effects of boric acid.⁸¹ In the poisoning experiments (Figure 4A), when adding the EG and 1,3-propanediol (1,3-PG) to the chitin conversion system, the 3A5AF yield dropped by 75% and 95%, respectively. But the decrease in yield was less obvious when adding ethanol. It is shown that the boric acid preferably formed five- or six-membered ring with the chitin monomer sugar by coordinating with two hydroxyl groups to produce a relatively stable intermediate. The EG and 1,3-PG could compete with NAG and led to considerable yield drop in the poisoning tests. The hypothesis was further verified by NMR studies. Most new peaks observed in the ¹³C NMR spectrum (Figure 4B) underwent a downfield shift, which occurs when saccharides form a complex with the boron atom. In addition, a new broad peak appeared in ¹¹B NMR (Figure 4C) in contrast with the spectrum of pure boric acid. These changes indicated the formation of a six-membered ring NAG-boron complex, which was further speculated to be coordination between boric acid and two -OH groups on C4 and C6 positions of NAG as evidenced by the disappearance of two peaks on the ¹H NMR spectra (Figure 4D). As the reaction temperature increased, the intensity of the peak assigned to NAG-boron complex continued to decrease. This complex was identified as the intermediate in 3A5AF production and boric acid may shift the equilibrium toward aldose¹⁰⁸ (straight-chain form of NAG), initiating dehydration reaction. The boric acid catalyst presumably could function as both Brønsted and Lewis acid sites to promote both the furan ring formation and dehydration to produce 3A5AF.

Aside from boric acid, other catalysts have been explored for NAG dehydration. It is worth noting that Lewis acids, particularly metal chlorides and ammonium salts, or Brønsted acidic chloride-ion based ionic liquids, play a dominant role in the dehydration. Brønsted acids can release acidic protons, thereby leading to more effective dehydration by eliminating water molecules. For metal chlorides, a series of them have been identified as beneficial for chitin dehydration, possibly because the metal center functions as the Lewis acid site to induce ring rearrangement while the chloride ion could interact with the hydrogen bonding networks to aid the reaction. Several ammonium salts have been proved remarkably efficient for chitin dehydration possibly because ammonium is a Brønsted acid. The counter anions in the ammonium salts are crucial for the dehydration but future studies are required to elucidate the effects. Fukuoka et al. demonstrated that AlCl₃ catalyzed NAG dehydration under a milder temperature of 120°C in DMF and ~30% 3A5AF yield could be obtained within 30 min.⁸⁷ Their process temperature is the lowest one reported to date, since majority of current systems employed high temperatures of 170°C–220°C. Zang et al. identified the promotional effects of several recyclable ILs such as [Gly]Cl,⁸⁸ [Pyz]Cl,⁸⁹ [TEA]Cl,⁹⁰ etc.^{91,92} on NAG dehydration to produce 3A5AF in DMA or NMP at 170°C–190°C. The highest 3A5AF yield of ~70% was achieved using [Pyz]Cl, boric acid and CaCl₂ as the promoters at 190°C for 60 min.⁸⁹ Zhang and co-workers have employed ammonium salts as the promoters for NAG dehydration⁹³ and achieved chitin dehydration via an enzymatic hydrolysis-dehydration two-step approach.⁹⁴ With NH₄Cl and LiCl as the additives, NAG was converted into 3A5AF at 160°C in 5 min with about 43% yield in DMF.⁹³ For chitin dehydration, an affinity adsorption-enzymatic method was first used to hydrolyze chitin into the NAG monomer, and then the separated NAG was converted under the catalysis of NH₄SCN and CaCl₂ to afford 3A5AF with 57% yield at 180°C.⁹⁴ As the thiocyanate group is regarded as halogen-like ions, NH₄SCN has similar chemical properties to NH₄Cl. Process scaling-ups and product purification were performed in these works. The scaling-up of solvent volume from 5 mL to 500 mL has been conducted, and the 3A5AF product with 99% purity and needle-like shapes could be obtained by crystallization purification.

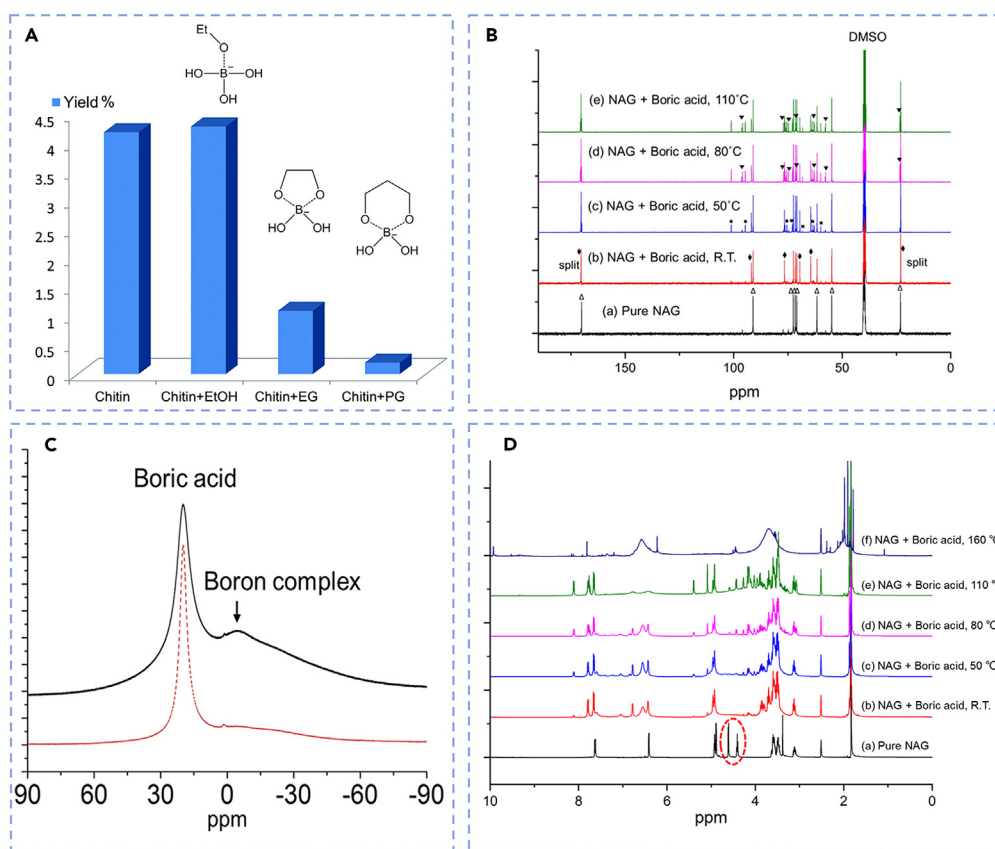


Figure 4. Mechanistic studies of boric acid catalyzed dehydration from NAG to 3A5AF

(A) The inhibition effect of different alcohols as additives. (B) ^1H NMR spectra of pure NAG and NAG-boric acid at different temperatures in dimethyl sulfoxide- d_6 ($\text{DMSO}-d_6$). (C) ^{13}C NMR of pure NAG and with boric acid at different temperatures. (D) ^{11}B NMR of boric acid (dash line) and boric acid with NAG (solid line) at RT.

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The Zhang group has also reported the use of deep eutectic solvents (DESs) as the catalyst for NAG dehydration into 3A5AF.⁹⁵ The catalyst screening has shown that the CCCA was the most effective one among the attempted DESs. With CCCA and CaCl_2 as the additive, 3A5AF was obtained with 47% yield at 210°C in DMA solvent. Wang et al. devised a switchable reaction system based on the DESs as the catalyst in the DMA solvent to selectively produce 3A5AF or Chromogen III.⁹⁶ With the binary DESs of ChCl-Gly as the catalyst, Chromogen III was formed as the major product with the highest yield of about 31% obtained at 140°C. With the ternary DESs of ChCl-Gly-B(OH)_3 , the reaction pathway was shifted to produce 3A5AF as the dominant product with the yield of 39% obtained at 140°C. The *in situ* NMR analyses have identified Chromogen I as the intermediate for 3A5AF formation. The current DES catalysts are made with ChCl as hydrogen bonding acceptor and it suggests that chloride-based DESs are conducive to NAG dehydration due to their interaction with NAG. The ^1H NMR chemical shift titration indicated that the ChCl-Gly interacted with the two -OH groups on C3 and C4 position of NAG. In addition, the ^{35}Cl NMR results indicated the presence of a strong interaction between Cl and NAG. However, the reaction mechanism still requires further elucidation to explain the formation and interaction of reaction intermediates.

Most of the above studies have employed toxic organic solvents such as DMF, DMA, etc. Greener solvent systems are highly desirable to improve the environmental friendliness of the dehydration reactions. Zang et al. reported the dehydration of NAG in DESs of choline chloride/PEG-200/boric acid (1/1/0.5) without any additional catalyst or additive.⁹⁷ 3A5AF was produced in 18.3% yield at 180°C within 15 min. Chen et al. utilized the biobased GVL for NAG dehydration with NH_4SCN and HCl as the catalysts.⁹⁸ A remarkably high 3A5AF yield of 75% was obtained at 140°C in 2 h. The dissolution-dehydration effect was unraveled which played a key role in the effective and selective dehydration. NAG was barely soluble in GVL at room or elevated temperatures, but 100% dissolution could be observed in the presence of NH_4SCN . In contrast to previous studies employing catalyst loading ranging from 50 to 200 mol % to NAG, NH_4SCN addition was increased to 400 mol % in this study, as this super-stoichiometric quantity proved essential for enhancing NAG dissolution and subsequent dehydration to produce 3A5AF effectively. To investigate the solvent effect, reactions in various solvents were conducted. The yield of 3A5AF in the green solvent PC was promising, slightly lower than that in GVL. However, the yields were below 5% in conventional solvents such as DMF, DMA, and dimethyl sulfoxide (DMSO), commonly used in previous reports. Despite these solvents' ability to dissolve NAG at RT, their dehydration

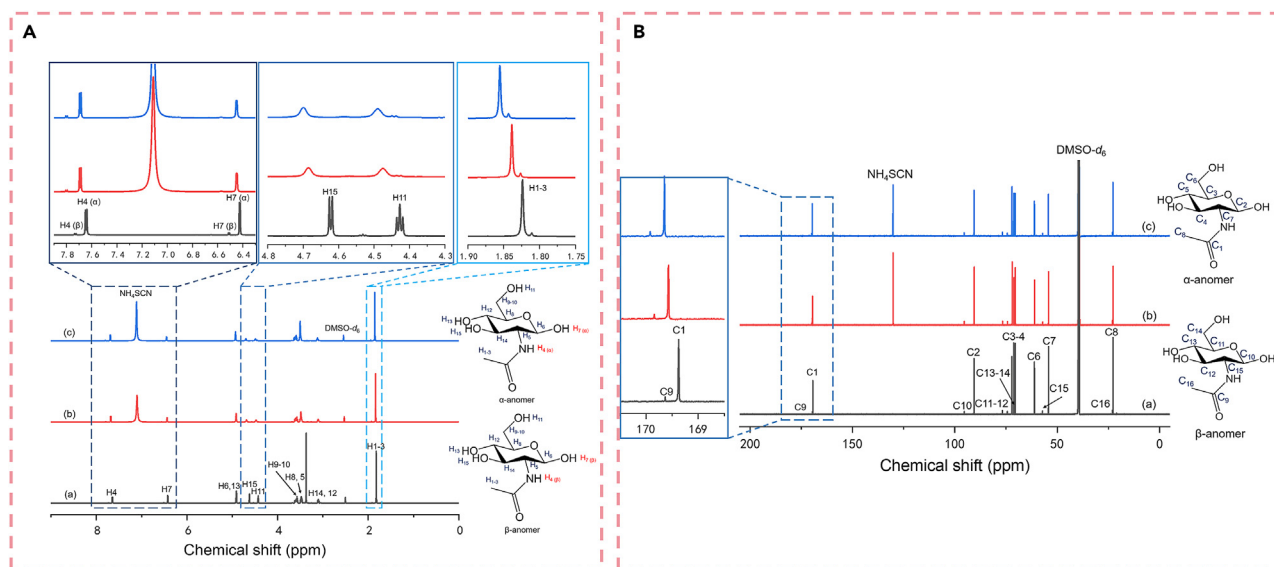


Figure 5. NMR studies of NAG dehydration into 3A5AF in GVL catalyzed by NH₄SCN

(A) ¹H NMR spectra of (a) NAG, (b) NAG with NH₄SCN (400 mol %) in DMSO-*d*₆ (4 mL) at RT, (c) NAG with NH₄SCN (400 mol %) in DMSO-*d*₆ (4 mL) at 80°C for 5 min.

(B) ¹³C NMR spectra of (a) NAG, (b) NAG with NH₄SCN (400 mol %) in DMSO-*d*₆ (4 mL) at RT, (c) NAG with NH₄SCN (400 mol %) in DMSO-*d*₆ (4 mL) at 80°C for 5 min. Reproduced with permission from ref.⁹⁸. Copyright 20203 Elsevier.

performance was not satisfactory. It is inferred that conventional solvents only promote NAG dehydration at higher temperature ranges (>180°C). Through the addition of NH₄SCN, the solvation environment for NAG was notably enhanced, addressing the dissolution issue in GVL and facilitating efficient NAG dehydration under milder temperature conditions. According to the mass spectrometry and NMR studies (Figure 5), the NH₄SCN has induced an extremely rapid conversion of NAG within several minutes possibly because the ammonium salts intensely coordinated with the acetamido and -OH groups. Chromogen I and Chromogen III were identified as the intermediates, which substantiated that 3A5AF was obtained through a sequential dehydration pathway (the gradual elimination of the three water molecules). This work put forward an efficient and selective NAG dehydration method to produce 3A5AF in a cheaper and greener solvent compared to previous studies.

Most 3A5AF studies have focused on homogeneous catalysts, which may offer better control over reaction conditions and selectivity, but require more difficult procedures for the separation and recovery of the catalyst. Some researchers have recycled the catalyst in a filtration-extraction-rotary evaporation manner, where the resulting solids/mixtures were directly subjected to the next round of dehydration reaction. Although after five rounds, the catalytic performance maintained 63–94% of the first round,^{88,90,93–95,97} the loss of catalyst is inevitable. The heterogeneous catalysts may be easier to recover and recycle, but they suffer from mass transfer limitations and lower activity, which is a challenge that needs to be addressed in NAG dehydration in the future. Despite numerous endeavors being constantly made on the efficient 3A5AF production from NAG in the laboratory, the direct conversion of chitin into 3A5AF in a large-scale pattern remains a challenge. For catalyst design, the developed catalysts mainly involved Brønsted and Lewis acids such as boric acid, metal chlorides and ammonium salts. The presence of both Brønsted and Lewis acids was also found more efficient for chitin dehydration. Therefore, more catalysts belong to the category and the combinational uses of Brønsted and Lewis acids could be investigated in the future. The heterogenized Brønsted and Lewis acids such as immobilizing boric acid on a support could be attempted for the development of heterogeneous catalysts.

Other furan derivatives

The elimination of one or two molecules of water from NAG will lead to the formation of Chromogen I and Chromogen III (Scheme 5) respectively, which were usually regarded as the intermediates during NAG dehydration to 3A5AF. Osada et al. reported the non-catalytic conversion of NAG in water as the green solvent at high temperature. At elevated temperatures of above 200°C, the extent of self-ionization of water increased significantly, enabling the promotion of dehydration reactions by the free protons and hydroxide ions. 23.0% yield of Chromogen I was achieved at 190°C within a rapid reaction time of 22 s in a continuous flow reactor, with its isomers (3,6-anhydro-GNF and 3,6-anhydro-MNF) produced as the minor products.⁸² Chromogen III could be obtained with 23.1% yield at a higher temperature of 220°C for 13 s. With further parameter optimizations, the Chromogen I and III were obtained with the highest yields of 37.0% and 34.5% at 180°C for 33 s and 240°C for 8 s respectively.⁹⁹ To explore the specific function of H⁺ and OH⁻ ions generated from water dissociation, acetic acid or sodium hydroxide was added to the reaction system. The results revealed that acid plays a negative role in the dehydration from NAG to Chromogen I but a positive role in the dehydration from Chromogen I to Chromogen III, while the base has the opposite effect. The non-catalytic

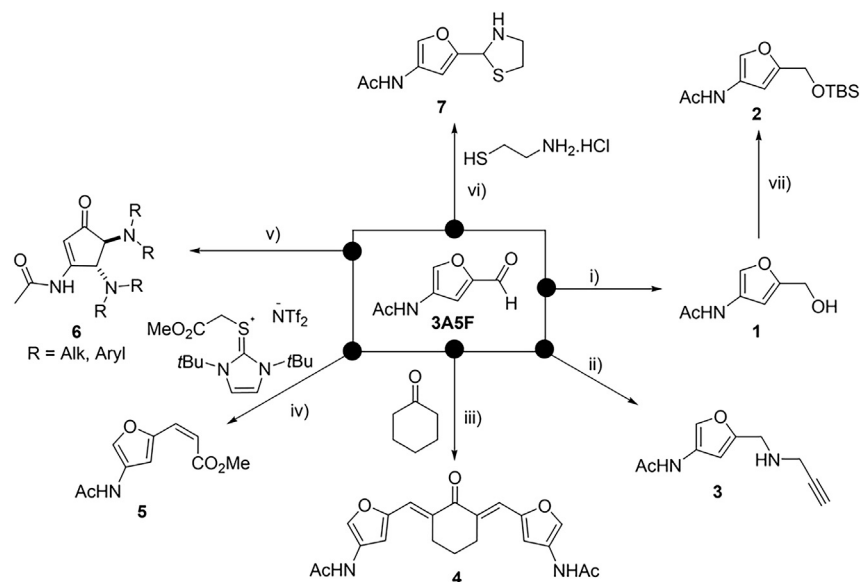


Figure 6. The downstream upgrading of 3A5F into various organonitrogen compounds

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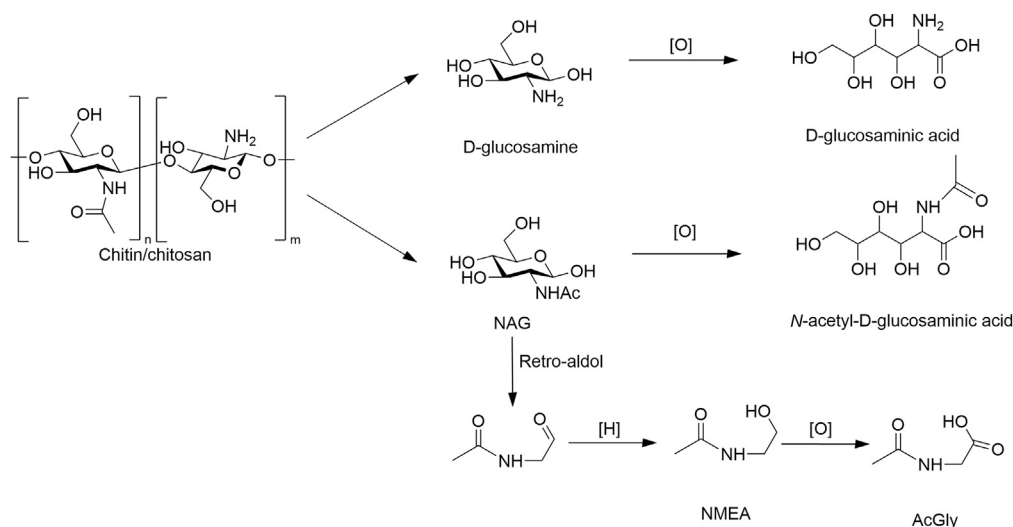
hydrothermal method has also been applied for the dehydration of chitin dimer¹⁰⁹ and chitin polymer.¹¹⁰ However, the chromogen products were negligibly obtained, possibly because the high temperature water medium was inadequate to effectively cleave the glycosidic bonds without a catalyst.

Chromogen III has a chiral center and was named Di-HAF as a more general acronym by Minnaard et al.¹⁰⁰ NAG was dehydrated in pyridine solvent in the presence of phenylboronic acid and triflic acid to produce Di-HAF in 73% yield with 99% ee at 115°C in 30 min on a multi-gram scale.¹⁰⁰ The phenylboronic acid was superior to boronic acid for furanose formation and suppressed further dehydration to 3A5AF, while the triflic acid could significantly increase the dehydration rate. Inspired by the study, Gomes et al. demonstrated the oxidative cleavage of the obtained Di-HAF using NaO₄ to produce 3A5F. Furthermore, they achieved the two-step dehydration-oxidative cleavage of NAG to obtain 3A5F.¹⁰¹ In the first step, NAG was reacted in pyridine with boric acid and triflic acid at 116°C for 30 min. During the second step, water and NaO₄ were added, and the reaction took place at RT for 1.5 h. An overall yield of 92% 3A5F was obtained under optimal conditions. With an aldehyde group instead of an acetyl group, 3A5F was more reactive and was upgraded into a variety of valuable organonitrogen compounds (Figure 6).

Lin et al. discovered a ternary Ba(OH)₂-H₃BO₃-NaCl catalytic system to convert NAG to 3AF.¹⁰² According to the control experiments and the high performance liquid chromatography-mass spectrometry analyses, 3A5AF was not the intermediate for 3AF. On the contrary, it is deduced that the NAG first underwent retro-aldol condensation at the C4-C5 position to afford glycolaldehyde and NAE. Then, NAE was dehydrated to produce 3AF by the eliminating two water molecules. The basic environment plays a significant role in the conversion of NAG into 3AF rather than 3A5AF because this environment is more conducive to the retro-aldol condensation. Ba(OH)₂ was responsible to promote the retro-aldol condensation at the C4-C5 position, while NaCl and boric acid stimulated the dehydration. The maximal 3AF yield of 74% was obtained in NMP at 180°C for 20 min. Shaikh et al. reported the first heterogeneous catalyst (La₂O₃)-promoted NAG dehydration. 3AF and 3A5AF were identified as the major products with 50% and 21% yields in dioxane under optimal conditions.¹⁰³ La₂O₃ displayed a nano-pore structure and acted as a weak Brønsted base, which conducted the dehydration pathway to the 3AF. It was regenerated after successive filtration, wash, dry and calcination. 3AF yield was only slightly decreased by 3% after four cycles. This attempt demonstrated the potentials of heterogeneous catalysis for NAG dehydration in the future. Overall, with non-catalytic aqueous environments (less acidic), Chromogens will form instead of 3A5AF because dehydration was difficult to occur without an efficient dehydration catalyst (Brønsted or Lewis acids) in aqueous solution. When adding the dehydration catalyst such as boric acid together with a base, retro-aldol condensation and dehydration could happen simultaneously to afford 3AF. The roles of heterogeneous catalysts were less studied, but the Brønsted basicity was assumed beneficial to convert chitin biomass into 3AF and 3A5AF. More studies on heterogeneous catalysis should be undertaken.

OXIDATION

The oxidation of the aldehyde group in NAG and glucosamine to produce the corresponding amino/amide acids is typically facile due to the high reactivity of the aldehyde group (Scheme 6). In the literatures, supported Au nanoparticles (NPs) are the most-commonly used catalysts for the oxidation, because of their high selectivity and activity. Ebitani et al.¹¹¹ first reported the oxidation of chitin monomer sugars into the corresponding amino acids by using Au NPs on basic supports such as MgO and HT. D-glucosaminic acid could be obtained from



Scheme 6. Proposed reaction pathway of chitin oxidation into D-glucosaminic acid, N-acetyl-D-glucosaminic acid or N-acetyl glycine (AcGly) (intermediate NMEA: N-acetyl monoethanolamine)

glucosamine with 93% yield at 40°C under O₂ flow in 3 h in the presence of Au/MgO, and N-acetyl-D-glucosaminic acid could be afforded from NAG with 95% yield at RT in 5 h in the presence of Au/HT. The MgO-supported Au NPs boasted better recycling ability than the HT-supported ones, and negligible decrease in yield was noticed for three runs. The basic sites on the surface of MgO may strongly interact with Au NPs to prevent Au particle growth and maintained good reusability and catalytic activity. Both the basicity of the support and the Au particle size were found crucial for the oxidation ability. An optimal size seemed to be 1–2 nm as indicated by the characterizations and support with basic sites was favorable. Gu et al. utilized a Pd-Bi/AC catalyst to convert D-glucosamine hydrochloride to D-glucosaminic acid with about 70% yield in water with NaOH and KHCO₃ as a basic additive under O₂ flow at 30°C.¹¹² Compared to the supported Au catalysts, the Pb-Bi/AC was inferior in terms of product yield and selectivity. Besides, external bases were needed to boost the oxidation. As a result, Au-based catalysts were still the most suitable ones for the oxidation. Table 3 has summarized the reaction conditions and catalytic performances of the reported catalytic systems for chitin biomass oxidation into corresponding products.

Zheng et al. fabricated the Au/ZnO catalyst (Au loading 1 wt %) to oxidize D-glucosamine into D-glucosaminic acid at 35°C under atmospheric air in base-free water.¹¹³ The catalyst preparation method was influential on the catalytic activity to affect the Au structure. By using the deposition-precipitation (DP) method rather than the deposition-reduction (DR) method, more than 2-fold increase in product yield could be realized possibly due to a declined apparent activation energy of the Au/ZnO-DP. The control experiments and characterization results indicated that the two factors of particle size and surface oxygen vacancy significantly affect the oxidation performances. With control tests and characterization, the Au/ZnO-DP boasts smaller Au particle size and more oxygen vacancy sites compared to the other synthesis method. Meanwhile, the metal loading and calcination temperature were critical to affect the particle size. The transmission electron microscopy (TEM) analysis indicated a very slight growth of the average particle size from 1.57 nm to 2.43 nm with the Au loading from 1 wt % to 10 wt %. A linear relationship was established between particle size and turnover frequency (TOF). The smaller the particle size, the higher the TOF value. While the increase in calcination temperature will first decrease then increase the particle size, and 300°C was the most suitable temperature. The study demonstrates a mild, simple and efficient method for glucosamine oxidation in air. The change of support material could result in direct air oxidation with proper synthetic method. For catalyst design, the exploration of new support materials and non-noble metal center sites should be taken into consideration. Overall, the Au on MgO or HT could afford the highest yield of the amino acids without the addition of a base under O₂ gas. Au/ZnO synthesized by the DP method could achieve direct air oxidation of the chitin monomer sugar into the amino acid with satisfactory yields. The Pd-Bi/AC was not as good as Au-based ones, and lower product yield was obtained. Besides, external bases were required.

Although the oxidation of their monomers is relatively facile, the direct oxidation of chitin or chitosan into the amino acids was rather challenging. Dai et al. reported a hydrolysis-detoxication-oxidation tandem approach to convert chitosan polymers into D-glucosaminic acid.¹¹⁴ First, the solid acid catalyst Amberlyst-15 was employed to facilitate the hydrolysis of chitosan in the presence of an equivalent amount of sulfuric acid in water at 160°C for 2 h, to afford glucosamine with 58% yield. Next, the activated carbon was adopted to remove the humins that were poisonous to Au catalyst, after the hydrolysis, and the detoxicated solutions (named AC-LMCH) were used for the subsequent oxidation by the Au/MgO catalyst. This detoxication technology resulted in a 3.7-fold on the yield. In the parameter optimization experiments using glucosamine-HCl as the model compound, a zero-order reaction kinetics relationship between D-glucosaminic acid yield and oxygen pressure was observed. The acid yield remained consistent within the range 2.5–7.5 bar range. The oxidation reaction can easily occur at near RT due to the high activity of the aldehyde group. The highest yield was achieved at merely 40°C lasting for 3 h with a nearly 100% conversion, however, upon the temperature increasing to 160°C, the yield dropped dramatically to 6% from 88%, which is mainly attributed to the

Table 3. Summary of oxidation of chitin biomass into D-glucosaminic acid, N-acetyl-D-glucosaminic acid and AcGly

En-try	Substrate	Catalyst	Oxidant	Solvent	Additive	Tempe- rature	Time	Product	Yield	Reference
1	Glucosamine-HCl	Pd (3.04 wt %)-Bi (1.74 wt %)/AC	O ₂ flow	water	NaOH KHCO ₃	30°C	6 h	D-glucosaminic acid	70%	Wen-xiu et al., ¹¹²
2	Glucosamine-HCl	0.9 wt % Au/MgO 2.0 wt % Au/HT 1.1 wt % Au/CaO 1.8 wt % Au/Al ₂ O ₃	O ₂ flow (50 mL/min)	water	\	40°C	3 h	D-glucosaminic acid	93% 89% 81% 22%	Ohmi et al., ¹¹¹
	NAG	2.0 wt % Au/HT	O ₂ flow (30 mL/min)	water	\	25°C	5 h	N-acetyl-D-glucosaminic acid	95%	
3	Glucosamine-HCl	1 wt % Au/ZnO	atmospheric air	water	\	35°C	2 h	D-glucosaminic acid	85%	Zheng et al., ¹¹³
4	AC-LMCH	0.1 wt % Au/MgO	5 bar O ₂	water	\	40°C	3 h	D-glucosaminic acid	67%	Dai et al., ¹¹⁴
5	NMEA	Ru/C	10 bar O ₂	water	NaHCO ₃	120°C	1 h	AcGly	21%	Techikawara et al., ¹¹⁵
6	NMEA	Fe(NO ₃) ₃ /TEMPO/KCl	20 bar O ₂	1,2-dichloroethane	\	35°C	16 h	AcGly	62%	Dai et al., ¹¹⁶

overoxidation of glucosamine-HCl at higher temperature. Consequently, under optimal conditions, the D-glucosaminic acid was obtained from chitosan polymers with an overall yield of 36%. Compared with previous studies, the Au loading was reduced to 0.1 wt % in this work, which exhibited an extremely high turnover number of 780.

Apart from the long-chain amino sugars, shorter-chain amino acid product was obtained from NAG in a tandem reaction. Techikawara et al. employed Ru/C (5 wt %) to promote the retro-aldol condensation and hydrogenation of NAG to produce NMEA in the first step by adopting a H₂ pressure control technique with NaHCO₃ as the additive at 120°C for 1 h.¹¹⁵ Next, the same catalyst and additive were used for the oxidation of NMEA to produce AcGly, by changing the atmosphere from H₂ to 10 bar O₂ (Scheme 6). The optimal oxidation temperature was determined to be 120°C, at which NMEA was fully converted and AcGly reached a highest yield of 21% for 1 h and did not decompose with prolonged time. Originally, the authors intended to directly couple retro-aldol condensation with oxidation to produce AcGly, nonetheless, the product yield was extremely low and such transformation route was not successful. The X-ray diffraction and TEM results suggested that the Ru NPs were highly dispersed on the AC support with 1–3 nm particle size. The X-ray absorption fine structure analyses show that the Ru was in the oxidized form with the fitted Ru-O coordination number of about 5.1, and the Ru-Ru coordination number was fitted to be about 1.2. The Ru species structure on carbon support could influence the oxidation alcohol to acid. It is believed that the low coordination number of Ru and the rich Ru-OH groups of the catalyst are beneficial for the high catalytic activity. The study revealed that the Ru/C could promote both hydrogenation and oxidation under different atmospheres. However, the direct retro-aldol condensation and oxidation of chitin into AcGly would be more economically favorable and deserves research efforts in the future. Besides, the overall yield of major byproducts, including acetamide, acetic acid, and FA, exceeded 50%, indicating insufficient selectivity of this catalytic system for AcGly production. Both Pd/C and Au/C were found to be inactive for the oxidation of NMEA, underscoring the need for the development of new catalysts. Dai et al. conducted the aerobic oxidation of NMEA into AcGly in 1,2-dichloroethane solvent with Fe(NO₃)₃, TEMPO and KCl (10 mol % of the substrate respectively) under 20 bar O₂ gas.¹¹⁶ The maximal 62% yield of AcGly could be obtained at 35°C with a reaction time of 16 h from NMEA. None of the three catalysts alone can produce AcGly. Among them, Fe(NO₃)₃ and TEMPO exhibit a more significant impact on the catalytic oxidation of NMEA compared to KCl. In this system, both reaction temperature and oxygen pressure exhibited a volcano-shaped effect on the AcGly yield to fully stimulate oxidation reaction and prevent the excessive oxidation of NMEA at the same time. For the reaction mechanism, it is presumed that TEMPO, Fe³⁺ and Cl⁻ coupled to form an adduct intermediate (Int 1) to oxidize NMEA to Int 2. Acetylacetaldehyde amine was formed from the decomposition of Int 2. The NO₃⁻ offered a circulation system, in which NO₂ could oxidize Fe²⁺Cl to Fe³⁺Cl and the formed NO could be converted to NO₂ by O₂. The generated water attacked the ketone group in acetylacetaldehyde amine to produce Int 3 which was further oxidized into Int 4. Final elimination reactions facilitated the formation of the AcGly product (Figure 7).

HYDROGENATION

The hydrogenation of chitin biomass could produce various valuable amine/amide polyols which are key precursors for a diversity of functional polymers, and the hydrogenation of C=O bond as well as the cleavage of C-C bond are crucial in this transformation strategy. The hydrogenation of the end aldehyde group and/or deacetylation will produce several C₆ amine/amide polyols, which could be further

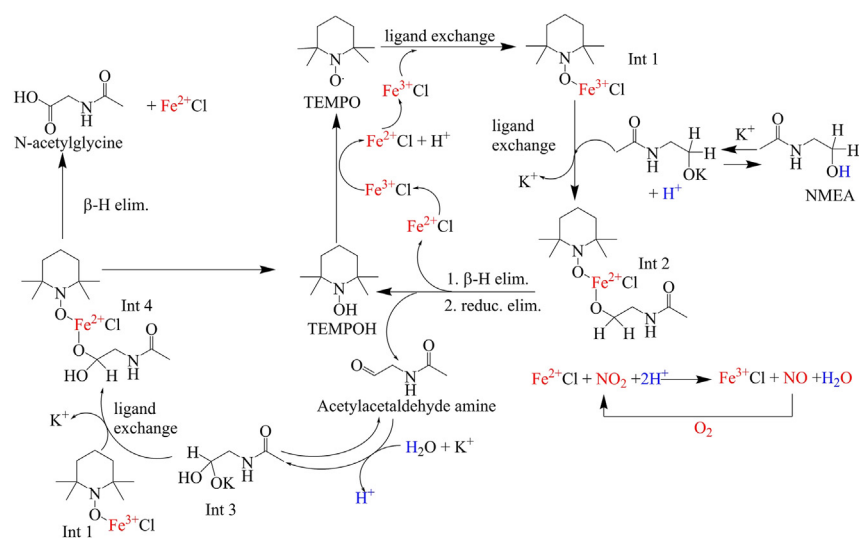


Figure 7. Possible reaction mechanism for the oxidation of NMEA to AcGly

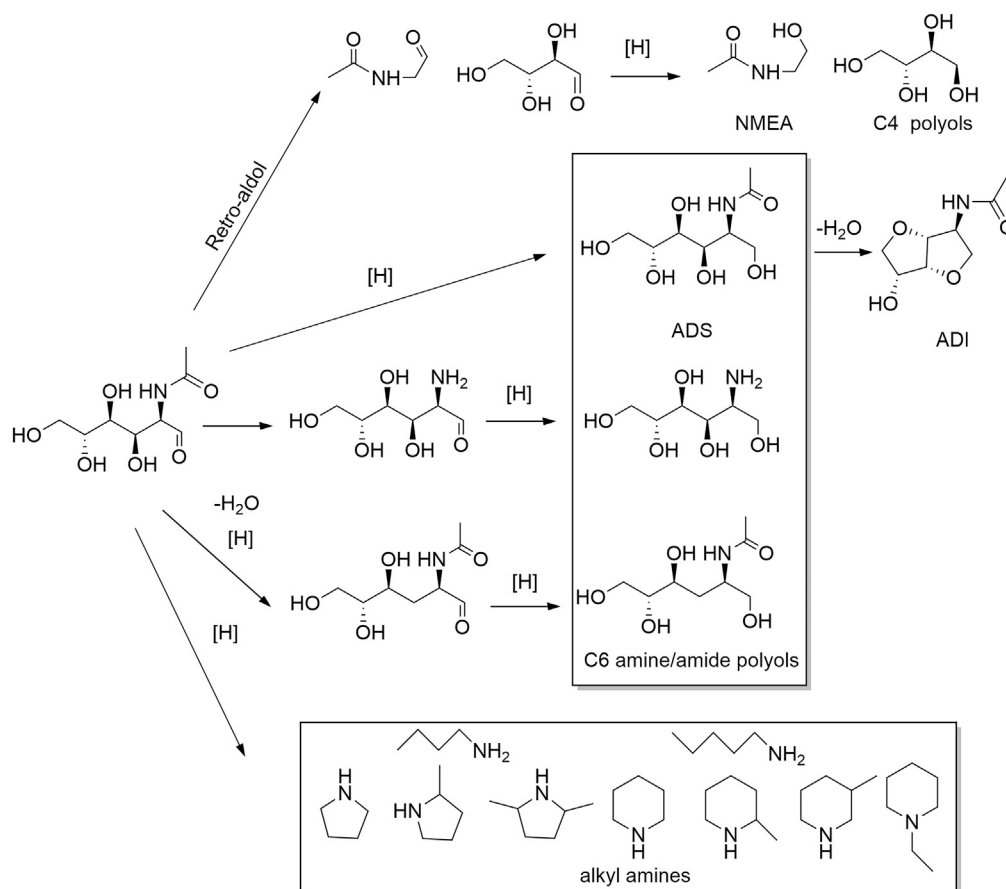
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dehydrated into an amide containing isosorbide analog. The retro-aldol condensation of NAG into aldehyde fragments and the subsequent hydrogenation will produce shorter-chain amide polyols such as NMEA. Apart from polyols, NAG can undergo HDO reaction to produce alkyl amines (Scheme 7).

The initial study on NAG hydrogenation was conducted by Yan et al.¹¹⁷ The aldehyde group of NAG was easily hydrogenated, and 100% NAG conversion into 97.7% yield of the hydrogenated NAG, ADS, was achieved at 80°C under 40 bar H₂ with 5 wt % Ru/C catalyst in water. At elevated temperature, the cleavage of C-C bond on the sugar chain started to occur possibly through a retro-aldol condensation pathway. About 8% NMEA, 6% C₄ polyols and 72% C₆ amine/amide polyols were obtained at 180°C under 40 bar H₂ with the 1 wt % Ru/C. The NMEA yield was slightly increased to about 11% in the presence of 0.1 equivalent NaOH additive. After being recycled through centrifugation, filtration, and washing, the catalyst maintained its activity well for at least three cycles. The hydrogenation activity and selectivity of Ru were superior to other noble metals (Pd, Pt, and Rh, etc.), a finding consistent with the hydrogenation of cellulose. Additionally, Ru can effectively inhibit the noncatalytic side reactions in thermal conditions. Ru may promote the generation of the active hydrogen species and produce acidic ions (H⁺ and [Ru(H₂O)₅(OH)]²⁺) in hot water. These acids could potentially mitigate the poison effect of the amine functionality on metal catalysts during NAG conversion to facilitate the hydrogenation process. The product distribution is correlated to the Ru loading on carbon support. At elevated loading, there was a notable increase in the production of the direct hydrogenation product, accompanied by a suppression in the formation of small polyols. This suggests that retro-aldol condensation is the primary route to produce small polyols, occurring prior to the initial hydrogenation. Four primary pathways are proposed. Initially, NAG undergoes retro-aldol reaction to produce erythrose and acetamidoacetaldehyde intermediates, which are unstable under the employed conditions and thus further converted into C₄ polyols and NMEA, respectively. In the second pathway, NAG is directly hydrogenated into the corresponding sugar alcohol. In the third pathway, NAG is deacetylated into glucosamine and acetic acid. Glucosamine, being less reactive in the retro-aldol reaction due to the absence of the electron-withdrawing acetyl group, is readily hydrogenated into a C₆ amine sugar alcohol. The last pathway entails the dehydration of NAG succeeded, by hydrogenation, leading to the formation of partially deoxygenated product. The authors also attempted the direct hydrogenation of chitin and chitosan at 260°C but the product yields were relatively low. The major obstacle perhaps is that the cleavage of glycosidic bonds requires higher temperature or more acidic medium, but the harsh conditions would induce severe side reactions for the aldehyde intermediates and thus direct hydrogenation of chitin was not successful.

To achieve the formation of a monomeric nitrogen-containing compound from chitin through hydrogenation, Fukuoka et al. devised a pretreatment-hydrolysis-hydrogenation to convert chitin into ADS in multiple steps also using the Ru/TiO₂ catalyst (Figure 8A).¹¹⁸ First, chitin was ball milled together with sulfuric acid catalyst and the mechanochemical treatment would lead to the formation of NAG (19% yield) and oligomers (64% yield). Next, the obtained soluble solution containing the NAG, oligomers and sulfuric acid (named *Oligomer-H₂SO₄*) was conventionally heated at about 175°C to further promote the depolymerization to produce NAG in 61% yield. The NAG will be then hydrogenated at 120°C with the Ru/TiO₂ catalyst and the NaHCO₃ additive (to adjust pH to 3) to produce ADS with 52% yield. This study demonstrated that chitin hydrolysis undergoes advantageously at high temperature and low pH (2.0), whereas the hydrogenation step is favorable at a lower temperature and a pH range of 3–4. Hence, it is necessary to conduct the steps separately under their optimal conditions to achieve the efficient and selective conversion of chitin into ADS.

Following this, the same group upgraded the chitin-derived ADS into ADI, which is an amide containing isosorbide analog (Figure 8B).¹²¹ ADI is synthesized via a two-step dehydration of ADS. A super strong acid, triflic acid (CF₃SO₃H), was used to catalyze the condensation



Scheme 7. Proposed reaction pathways of chitin hydrogenation into NMEA and C6 amine/amide polyols or alkyl amines (ADS: 2-acetamido-2-deoxyisorbitol; ADI: 2-acetamide-2-deoxyisorbide)

reaction at 150°C without a solvent under vacuum, and about 33% ADI was produced under optimal conditions. DFT calculations suggested the trapping of acidic protons by the acetamide side chain of ADS which explains the high loading of the acid catalyst. The vacuum condition favored the removal of water and suppressed the deacetylation side reaction. The combinational use of the Lewis acid $\text{Yb}(\text{OTf})_3$ and the Brønsted acid $\text{CF}_3\text{SO}_3\text{H}$ did not only decrease the reaction time but also increased the ADI yield to about 40% by altering regioselectivity of the reaction.¹¹⁹ $\text{Yb}(\text{OTf})_3$ not only accelerated the dehydration reaction rate, but also coordinated the amide groups of ADS, which prevented the protons trapping and made the apparent activation energy decrease by 30 kJ/mol. To replace the expensive and strongly acidic catalyst, the same group discovered a weak acid H_3PO_3 to efficiently promote this reaction.¹²⁰ About 25% yield of ADI could be obtained at 130°C for 3 h under vacuum conditions with this acidic catalyst. It is possible that the H_3PO_3 catalyst has changed the reaction mechanism from the acid-catalyzed dehydration cyclization to the cyclization via the phosphite ester intermediates as indicated by the DFT calculations. The activation energy for dehydration of 1,4-anhydro-ADS to ADI in a simple acid-catalyzed system was 118 kJ/mol, which was 36 kJ/mol higher than that in phosphite ester system. Compared to the hydroxy group (1024 kJ/mol), the phosphite ester formed by 1,4-anhydro-ADS and H_3PO_3 has a P=O group (1066 kJ/mol) with a higher proton affinity, which was more readily protonated to overcome the proton trapping problem (Figure 8C).

Besides ADS, the synthesis of the shorter-chain nitrogen-containing polyols with broad applications such as the NMEA is extremely desirable. To improve the NMEA yield, Fukuoka et al. conceived an H_2 pressure control technique.¹¹⁵ It is assumed that NAG was easily hydrogenated into ADS under employed conditions which would inhibit the retro-aldol condensation and make the C-C chain cleavage demanding. As a result, the NAG solution with the NaHCO_3 additive and Ru/C catalyst was heated to 120°C under merely 1 bar H_2 gas to suppress the direct hydrogenation of the aldehyde group. Then, the H_2 pressure was elevated to 40 bar at 120°C and NMEA was obtained in 15% yield (29% yield on the nitrogen basis) with a reaction time of 1 h. The catalytic hydrogenation ability of base metal has been tested. Zheng et al. fabricated the Ni/CeO₂ catalyst to selectively convert NAG into NMEA.¹²² About 21% NMEA yield (42% on the nitrogen basis) was achieved with Ni supported on cubic CeO₂ materials as the catalyst at 120°C for 8 h under 40 bar H_2 gas in water with the addition of NaHCO_3 . The relatively stable catalytic performance is attributed to high susceptibility to reduction, lower oxygen vacancies, and a lower surface area.

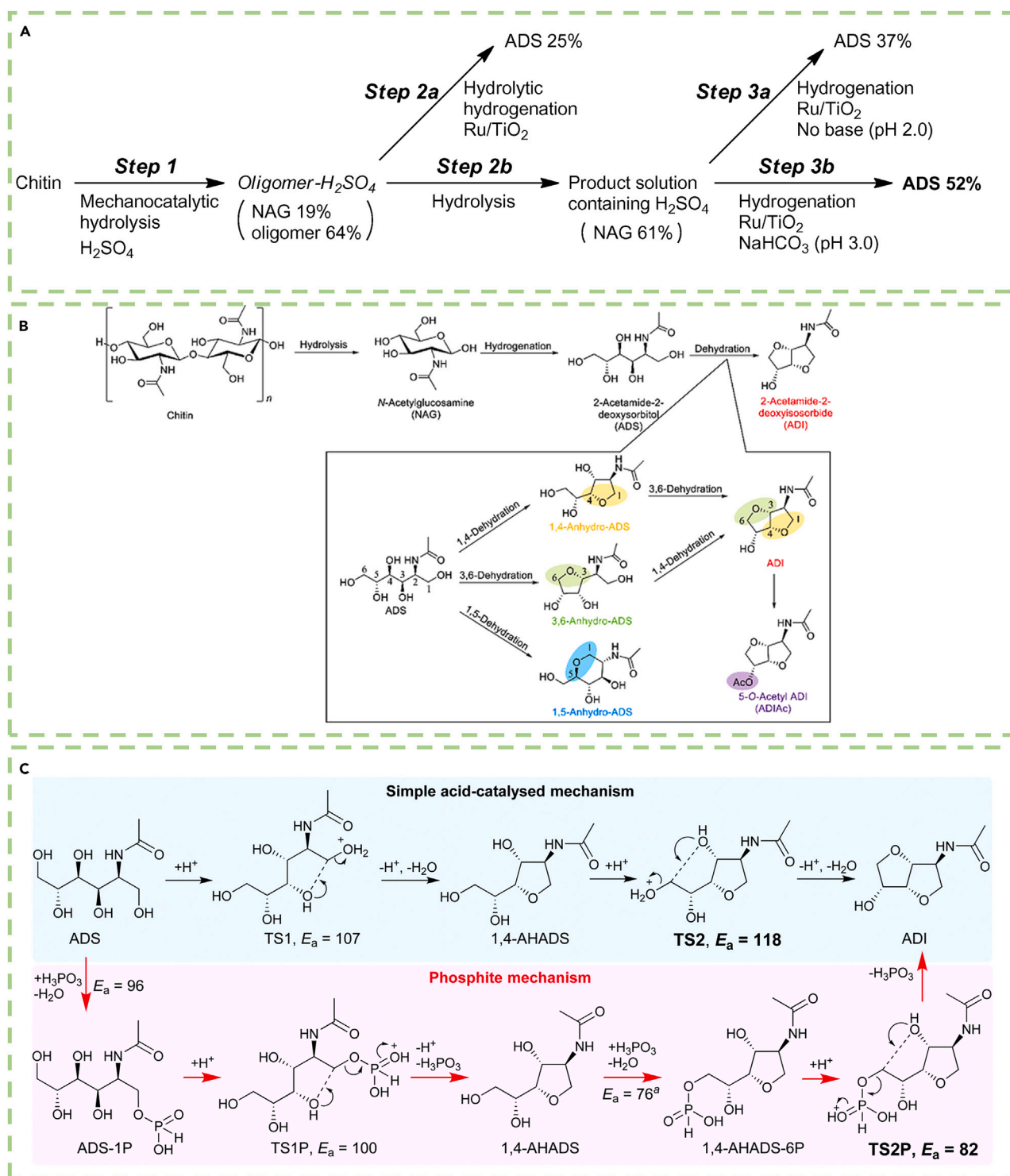


Figure 8. Production of ADI via ADS from chitin

(A) Catalytic conversion of chitin to ADS. Reprinted with permission from ref.¹¹⁸. Copyright 2017 Royal Society of Chemistry.

(B) Synthetic route of ADI from chitin. Reprinted with permission from ref.¹¹⁹. Copyright 2020 Elsevier.

(C) Speculated reaction pathways for the conversion of ADS to ADI. Reprinted with permission from ref.¹²⁰. Copyright 2021 Royal Society of Chemistry.

Table 4. Summary of hydrogenation of chitin biomass into C6 amine/amide polyols or alkyl amines

Entry	Substrate	Catalyst	Hydrogen		Additive	Temperature	Time	Product	Yield	Reference
			Pressures	Solvent						
1	NAG	5 wt % Ru/C	40 bar	water	\	80°C	1 h	ADS	97.7%	Bobbink et al., ¹¹⁷
	NAG	1 wt % Ru/C	40 bar	water	\	180°C	1 h	C6 polyols	71.9%	
								C4 polyols	6.1%	
								NMEA	8.7%	
2	Oligomer-H ₂ SO ₄	5 wt % Ru/TiO ₂	40 bar	water	\	120°C	2 h	ADS	37%	Kobayashi et al., ¹¹⁸
								ADS	52%	
3	NAG	5 wt % Ru/C	1→40 bar	water	NaHCO ₃	120°C	1 h	NMEA	15%	Techikawara et al., ¹¹⁵
4	NAG	10.4 wt % Ni/CeO ₂	40 bar	water	NaHCO ₃	120°C	8 h	NMEA	21%	Zheng et al., ¹²²
5	NAG	3 wt % Ru/C	33 bar	water	H ₃ PO ₄	250°C	2 h	alkyl amines	50%	Xie et al., ¹²³

The authors conjectured that the NMEA was formed via the retro-aldol condensation and hydrogenation route as well as the hydrogenation-cleavage route (the Ni-catalyzed C-C cleavage of ADS as the intermediate).

Table 4 has summarized the reaction conditions and catalytic performances of the reported catalytic systems for chitin biomass hydrogenation into amine/amide polyols or alkyl amines. The studies mentioned above indicate that reaction parameters, particularly temperature and pH, play significant roles in the hydrogenation selectivity toward ADS or NMEA. The hydrogenation process is highly temperature-sensitive. Specifically, the direct hydrogenation of NAG to ADS initiates at relatively lower temperatures, where the presence of ADS may not favor the formation of NMEA. Conversely, NMEA production tends to occur at higher temperatures due to the higher activation energy of the retro-aldol condensation. Therefore, applying high pressure at the beginning of the reaction may direct the synthesis toward ADS, while increasing the hydrogen pressure after reaching a specific temperature would promote the production of NMEA. Regarding pH, a low level could inhibit hydrogenation activity and trigger side reactions involving amide and hemiacetal groups. In contrast, a slightly acidic condition is conducive to ADS synthesis, whereas a higher pH (e.g., 6.8) may facilitate the retro-aldol condensation of NAG to generate NMEA due to the presence of basic species such as HCO₃⁻. Thus, a basic environment is more suitable for NMEA production.

Apart from polyols, the conversion of NAG into alkyl amines over noble metal catalysts has been reported. Lin et al. achieved the HDO of NAG to generate various widely used alkyl amines of high-economic values, by using the H₃PO₄ and 3 wt % Ru/C catalysts.¹²³ H₃PO₄ served as a bifunctional reagent in this system, initially catalyzing the deacetylation of NAG into acetic acid and D-glucosamine, and subsequently coordinating with and stabilizing the exposed -NH₂ group, thereby suppressing the deamination side reactions and facilitating the formation of nitrogen-containing chemicals. The amount of H₃PO₄ greatly influenced the yield of amines. Increasing the H₃PO₄ to D-glucosamine ratio to ~4.5 resulted in the highest yield of amines, which remained relatively unchanged as the ratio was further increased to 8.0, indicating that the -NH₂ group has been sufficiently protonated and thus well protected. The higher amount of H₃PO₄ favored the production of long-chain piperidine derivatives. However, an excessive ratio (H₃PO₄ to D-glucosamine ratio = 12) may result in the formation of ammonium phosphate, which negatively affected the amines yield. Since D-glucosamine contains numerous hydroxyl groups, complete deoxygenation is anticipated at elevated temperatures and hydrogen pressures. With the temperature increased to 250°C and hydrogen pressure to 33 bars, the oxygen atoms in the D-glucosamine intermediate were largely eliminated in the forms of H₂O and/or CO/CO₂, thus enhancing the yield of cyclic amine products. But extending the reaction time or raising the reaction temperature beyond a certain point did not lead to further improvements in yield. The Ru/C loading is also the key factor in determining hydrogenation activity. Lower loading was ineffective in stimulating the hydrogenation reaction while higher loading could cleavage C-C and C-N bonds simultaneously. Consequently, 3 mol % Ru/C was identified as the most suitable loading, contributing to the highest overall yield of various amines (about 50%) under optimal conditions. Optimizing reaction parameters is crucial for the HDO reaction to fully remove the oxygen atoms while avoiding the cleavage of the C-N bond, resulting in the selective production of alkyl amines. The study opens a new route to generate alkyl amines with existing grand market size from chitin.

OTHER STRATEGIES

Other novel strategies are being explored to synthesize more diversified nitrogen-containing chemicals with high economic values and wide applications. The concept of an integrated biorefinery through biological method has been proposed to directly upgrade the shrimp shell waste (SSW) into valuable organonitrogen chemicals. In addition, transamidation, hydrothermal oxidation, self-condensation, deamination, etc. have been developed. Moreover, automated analysis methods have been introduced to uncover novel synthesis routes and extend the scope of biobased nitrogen-containing chemicals.

Ma et al. utilized an integrated biorefinery process that consisted of SSW pretreatment and fermentative bioconversion (Figure 9).¹²⁴ Two highly valuable aromatic organonitrogen chemicals in the biomedical fields, tyrosine and the L-DOPA, were obtained from the SSW, which are highly valuable products with important applications in biomedical fields. The SSW pretreatment step employed mechanochemical technology to promote acid-catalyzed depolymerization of chitin and proteins in the SSW, realizing the full recovery of chitin biomass. Then, the

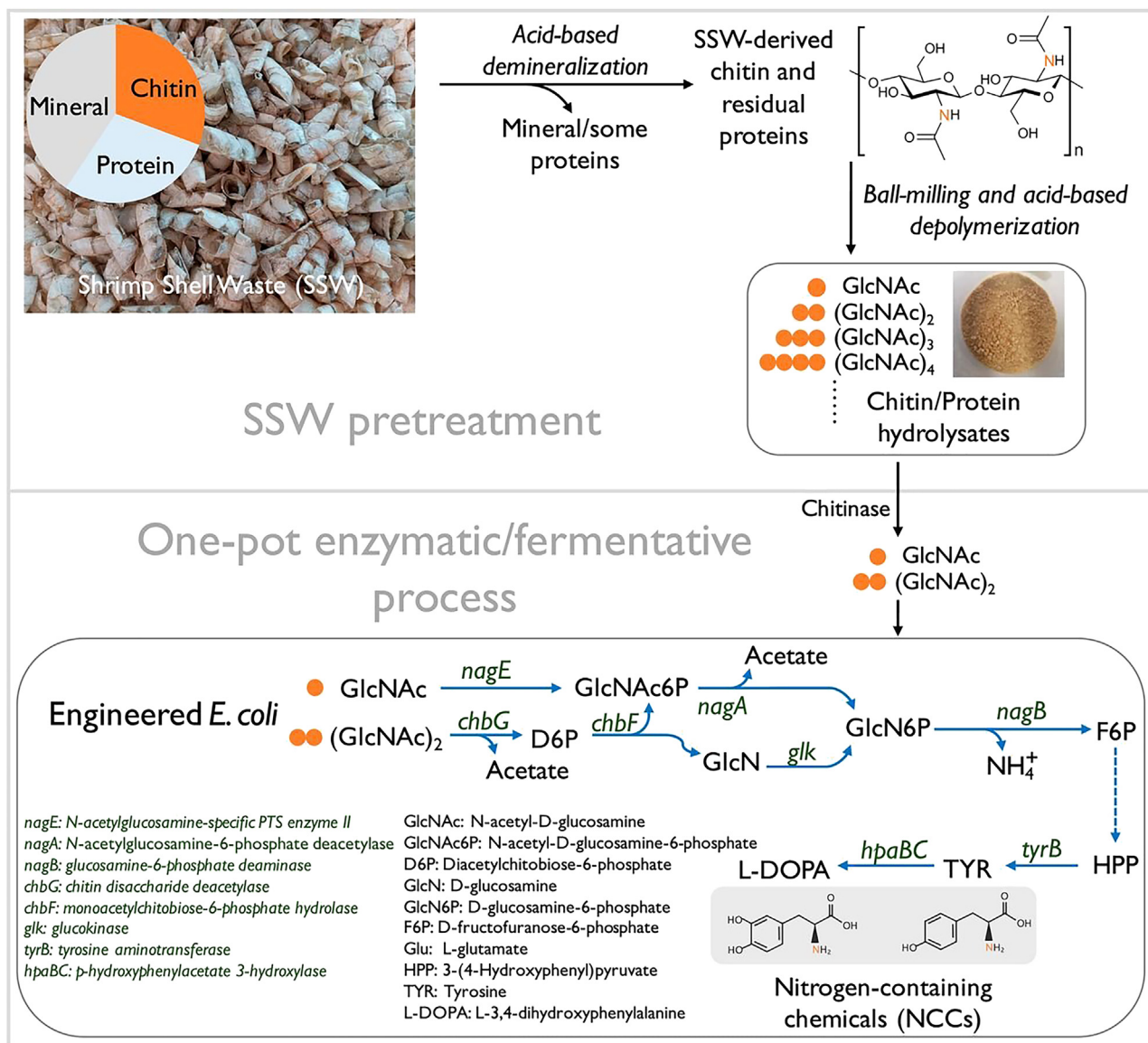


Figure 9. An integrated shell biorefinery process for upcycling SSW-derived chitin into NCCs

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soluble hydrolysates were fermented by the engineered *Escherichia coli* strains to produce 0.9 g/L and 0.4 g/L tyrosine and L-DOPA respectively from 22.5 g/L unpurified SSW-derived hydrolysates.

Xin et al. put forward a transamidation strategy in which chitin transfers the acetyl group on the side chain to amines, and thus amides and deacetylated chitin would be obtained as the organonitrogen products.¹²⁵ Using Cu(OAc)₂ as the catalyst, the aniline substrate could be converted to acetanilide in 87% yield by borrowing the acetyl groups from chitin in DMF at 140°C for 12 h. The transamidation strategy can be generalized to a wide scope of aliphatic, cyclic and functionalized aromatic amines to produce the corresponding pharmaceutical-related amide products with satisfactory yields (51–94%). The proposed reaction mechanism involves the coordination of C=O group in the side chain with the Cu(OAc)₂ catalyst, followed by a nucleophilic attack from the amine group to generate a tetrahedral intermediate. Subsequently, proton transfer and the cleavage of C-N bond occurred to produce the corresponding amides and completed the catalytic cycle. On the other hand, the deacetylated chitin could be used as a solid base catalyst to promote the aldol condensation between furfural and acetone to generate fuel precursors.

Gao et al. employed a hydrothermal method to convert chitin in NaOH solution at above 300°C. Without the addition of a catalyst, organonitrogen products including pyrroles, pyrazines, pyridines, amides, etc.¹²⁶ were identified. Pyrrole as a major product was obtained with about 4% yield at 325°C for 5 min in 1 M NaOH aqueous solution. The yield could be enhanced to 12% by supplying ammonia as the external

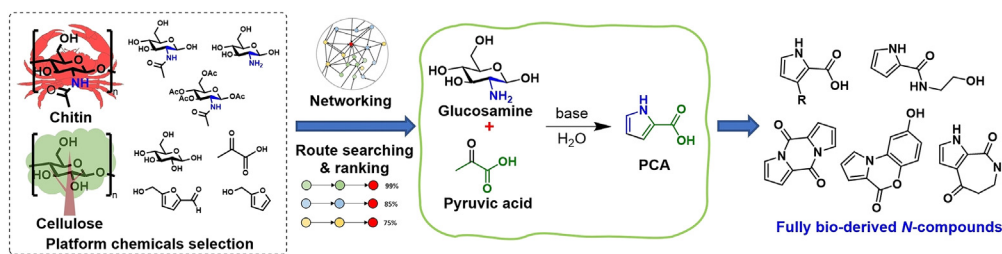


Figure 10. Synthesis of pyrrole-2-carboxylic acid from cellulose- and chitin-based feedstocks discovered by the automated route search
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nitrogen source. It was deduced that the chitin underwent depolymerization and retro-aldol cleavage to form acetyl furan intermediates, and oxygen-to-nitrogen exchange happened on the furan ring followed by side chain cleavage to afford the pyrrole product.

Two molecules of D-glucosamine can undergo a self-condensation reaction to obtain *N*-heterocycles (pyrazine derivatives), including deoxyfructosazine (DOF) and fructosazine (FZ), accompanied by the elimination of water molecules.¹²⁷ In this process, D-glucosamine molecules initially convert to an open-chain form, followed by intermolecular nucleophilic addition and dehydration, leading to the formation of the intermediate dihydrofructosazine, ultimately resulting in DOF or FZ after additional dehydration or dehydrogenation step. Recent researchers explored catalysts like ionic liquids and deep eutectic solvents to enhance the activity of this reaction.^{128–130} A one-pot dehydration by utilizing 1-butyl-3-methylimidazolium hydroxide ([BMIM]OH) as both solvent and catalyst was first reported, yielding up to 49% of DOF and FZ at 120°C for 180 min, with the assistance of DMSO as a co-solvent.¹²⁸ Additionally, choline chloride/urea catalyst was synthesized, which achieved 13.5% yield of DOF through condensation reaction at 100°C for 150 min.¹²⁹ When introducing amino acids as cocatalysts, particularly arginine, the DOF yield significantly increased to 30.1% under optimal conditions. Mechanistically, hydrogen bonding plays a pivotal role in D-glucosamine activation and product selectivity, accordingly driving the condensation reaction and pathway to DOF or FZ, as evidenced by strong interactions observed between ionic liquids or amino acids and functional groups on D-glucosamine using techniques such as NMR spectroscopy,^{129,130} which provides promising directions for the catalyst design of the selective production of pyrazine derivatives.

In addition to organonitrogen products, the conversion of chitin feedstock to ammonia has been determined to be feasible, thereby opening the possibility of large-scale production of this indispensable chemical at relatively low temperatures. In their study on the conversion of chitosan to 5-HMF (and LA), Kerton et al. proposed a key mechanism involving a deamination step that generated ammonia.¹³¹ In a recent study, Horváth et al. successfully detected and quantified ammonium ions using the ¹H NMR technique in the acidolysis of crustacean shells and chitin to 5-HMF, LA, and GVL at 130°C to 150°C.¹³² A highly favorable maximum yield of 83% ammonium from chitin was achieved in their reaction system, with the remaining nitrogen contents being incorporated into humins. The acid-catalyzed deamination step could be attained following cleavage of the amide bond through hydrolysis.

Pham et al. introduced an automated analysis approach based on reaction networks evaluation through datamining Reaxys, with the aim to find potential synthetic routes to pyrrole-2-carboxylic acid (PCA) using cellulose and chitin as sustainable feedstocks¹³³ (Figure 10). First, a forward search (from reactants to products) from cellulose and chitin for two reaction steps was conducted, identifying a collection of 357 platform chemicals. Subsequently, synthetic routes to PCA were searched in the backward direction at maximum five steps. Then, all possible routes linking platform chemicals associated with PCA and derivable from cellulose and chitin were collected, filtered, and ranked. Ultimately, five routes emerged as prominent choices. Among them, the most promising route involved synthesizing PCA from D-glucosamine and pyruvic acid, achieving a maximum yield of 50% and a PCA-based chemical space was established. This study offers insights into synthesizing new renewable chemicals based on artificial intelligence tools.

TECHNICAL CHALLENGES

Chitin biorefinery is a relatively new field with significant advancements made since 2012. In the past decade, a variety of transformation strategies have been developed to obtain different types of chemicals and diversify the product stream from chitin biomass. As it is still in its preliminary stage, there are still many key challenges to overcome toward the economically viable commercialization of chitin biorefinery for chemical production. The first concern could be the source of chitin, although currently most of the chitin was industrially extracted from crustacean shells, chitin naturally exists in other forms such as the skeletons of insects and the cell walls of fungi. With the future expansion of the chitin industry, more feasible and effective methods to extract chitin from these other sources are anticipated. Such technologies are under investigation and hold great potentials. From the upstream, the collection/transportation as well as the fractionation of shell waste could be crucial. Establishing inexpensive and efficient protocols to collect and transport crustacean shells will not only ensure a steady supply but also streamline the subsequent valorization process. As the starting point, the seafood processing companies (such as lobster canning plants) would be good centralizing sites for shell collection to save the capital costs. Following this, supports are necessary from the governments to put forward relevant policies on crustacean shell sorting which could be integrated into the current waste sorting systems. For shell fractionation, the current industrial method using concentrated corrosive acid and base reagents suffers from major environmental problems and is expensive. Alternative fractionation methods are continuously being explored, to achieve green but efficient fractionation. Besides, the full utilization

of the shell components including chitin, calcium carbonate, astaxanthin and proteins is beneficial to enhance the economic competitiveness, which is also one of the aims of the new fractionation methods. Apart from these challenges, scalable, green, and inexpensive catalytic systems to convert chitin into nitrogen-containing products with high economic values in high yield and selectivity are highly desirable. In addition, more attention should be given to product purification as practical applications are likely hindered by the use of costly separation methods.

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AUTHOR CONTRIBUTIONS

Conceptualization: X.C., X.J., L.T.M., and M.Y.L.; investigation: X.J. and Y.Z.; project administration: X.C.; supervision: X.C.; writing – original draft: X.J., Y.Z., X.C., L.T.M., and M.Y.L.; writing – review and editing: X.J., Y.Z., and X.C.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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