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Preview

Rational process design aids biomolecule-derived ethylene polyamine synthesis

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In this issue of *Chem Catalysis*, Vermeeren et al. develop a rich physical, intuitive understanding of the reaction network of ethylene polyamine production via the modeling and holistic synthesis of thermodynamic and kinetic handles hidden within process conditions.

Amines are critical platform chemicals for a wide range of applications, including CO_2-capture agents, antiseptics, epoxy resin additives, and pharmaceuticals.[1] However, many commercial amines are produced through fossil-derived ethylene oxide or ethylene dichloride precursors, which have large associated emissions. An alternative strategy is the use of bio-derived glycolaldehyde (GA)—generated in varying yields from the pyrolysis, hydrous thermolysis, or catalytic retro-aldol conversion of sugars—as a C_2 substrate for reductive amination.[2] Reductive aminations with GA have demonstrated success for ethanolamine and ethylene diamine formation with ammonia and methylated amine reagents.[3] Conversely, the synthesis of ethylene polyamines—formed via successive amination of ethylene diamines—has struggled with low selectivities and limits in understanding factors affecting reactivity for these more complex molecules. In this issue of *Chem Catalysis*, Vermeeren et al.[4] demonstrate a comprehensive strategy, informed by a rational-design-focused synthesis of thermodynamic and kinetic influences on the intermediate steps of the reaction pathway, for greatly improving generic ethylene polyamine synthesis with GA.

The specific chemistry analyzed was the reduction of *N*,*N*,*N*′-trimethylethylenediamine (TriMEDA) into the preferred *N*,*N*,*N*′,*N*″,*N*‴,*N*‴-hexamethyltriethylenetetramine (HMTriETA) over the side product *N*,*N*,*N*′-trimethylaminoethylethanolamine (TriMAEEA). An initial screen of commonly used hydrogenation catalysts and reaction conditions confirmed that the previously proposed mechanism for initial GA amination was also relevant here, although at optimized conditions only modest selectivity toward polyamines was achievable. This motivated further study of the pathway (Figure 1) in terms of intermediates isolated by low-temperature, inert-atmosphere reactions and characterized with gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance (NMR). In brief, nucleophilic addition of GA to TriMEDA forms IM1, which undergoes dehydration to IM2 followed by catalytic hydrogenation to TriMAEEA. Alternatively, IM2 can undergo tautomerization into IM3, which after nucleophilic addition and dehydration gives IM4 and ultimately HMTriETA (under hydrogenation conditions). From this framework, the authors identified three areas for improving yields: enhancing the secondary dehydration reaction via solvent choice, time separating IM4 formation from IM2 consumption, and improving IM2-to-IM3 conversion. Employing all strategies—and using ethylene glycol as the optimal solvent, 1 h at 30°C as the optimal pretreatment, and 10 mol % oxalic acid as an optimal additive—improved the final optimized process from 63% to 83% carbon yield and demonstrated it to be similarly effective for a variety of diamine reactants.

Solvent effects on chemical reactions are diverse, and effective description of their influence on the reaction is difficult to the degree that they are chemistry dependent. Here, Vermeeren et al. have admirably taken a holistic view in ascribing a specific physical phenomenon to each aspect of solvent dependence. Notable is the preference for the Dimroth-Reichardt parameter over the commonly used dielectric constant as a measure of polarity. Whereas the latter, a solvent-only property, has found success in early models between ionic reactions, the former probes the resulting energetics of a solute in solvent[5] and appears to pertain more to a reactive system. Of critical importance is the fact that solvation can alter thermodynamic behavior as well as kinetics, and here the effects are decoupled via variable contact-time studies, demonstrating kinetic-only effects for monohydric alcohols (dehydration mediated by solvent basicity) and both thermodynamic (favorable water activity) and kinetic (transition-state stabilization) effects for dihydric alcohols. In fact, "polarity" here is not the explanation for solvent behavior but merely another descriptor that correlates with mechanistically valuable information. The rich consideration of water structure in these systems—regularly incorporated in symmetric diols, clustered in asymmetric monohydric alcohols—epitomizes how much more complex the solvent choice is than polarity alone. Note that the article's

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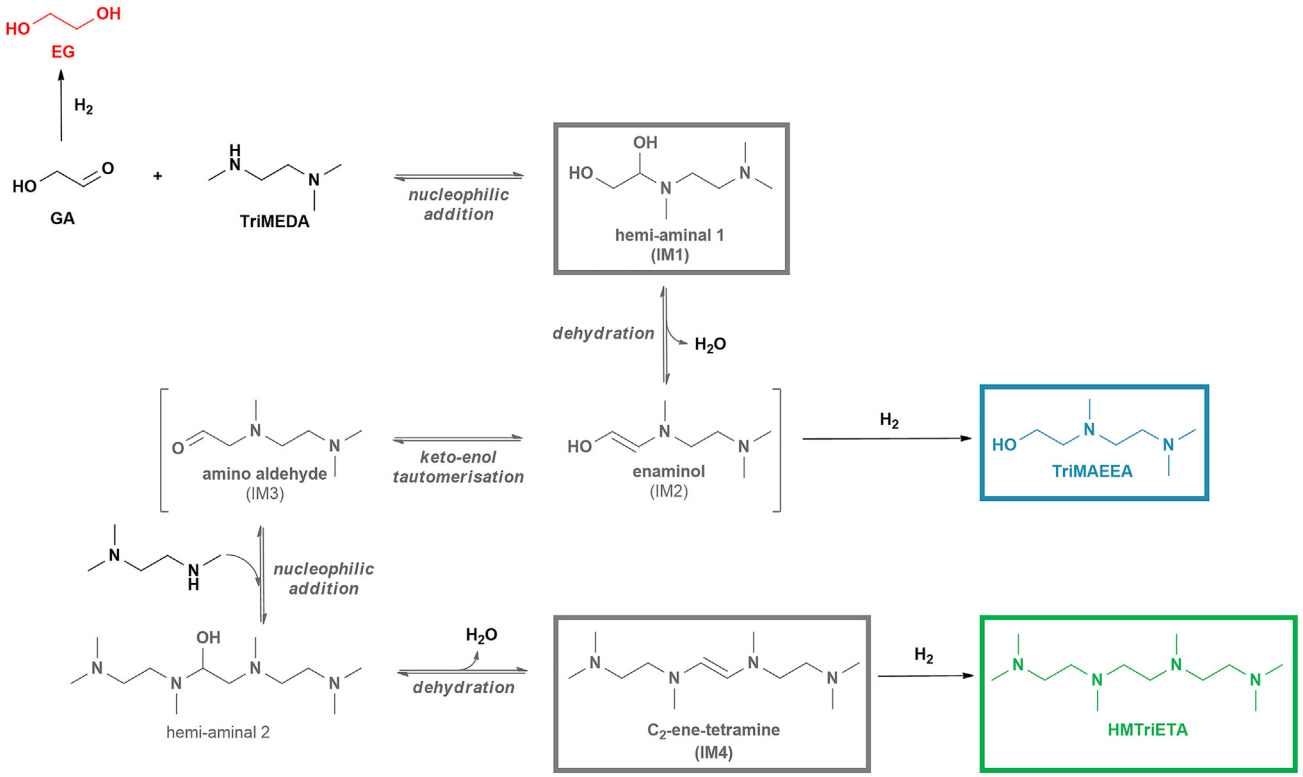

Figure 1. Proposed reaction pathway for the catalytic reductive amination of GA with TriMEDA

Pathway demonstrating routes to the formation of ethylene polyamine (HMTriETA [green outline]) and ethanolamine (TriMAEEA [blue outline]). Identified intermediates (IM1 and IM4 [gray outline]) and proposed unidentified intermediates (IM2 and IM3) are shown for context of reaction control strategies. Reprinted from Vermeeren et al.[4]

supplemental information also shows work characterizing the system for polar aprotic solvents, which appear superficially similar to dihydric alcohols and present further interesting avenues for comparison studies. Key points from this in-depth analysis are that process conditions, especially in multistep pathways, do not necessarily demonstrate straightforward relationships with overall yields and that complex networks can display multifaceted behavior. A strong chemical picture of the pathway allows for hypothesis testing on the exact action of myriad "solvent effects."

Industrial amination processes can use complex catalyst formulations[6] or organic additives[7] that empirically improve yields, activity, or selectivity, but discerning their mechanistic impact is challenging. The authors here rationalize one such additive through systematic study of the impact of carboxylic acids on the catalyst, as well as rigorous controls, with carboxylic salts, esters, and mineral acids and bases. (This is in addition to the "control" of performing analyses under non-hydrogenating conditions, given that previously these acids were considered hydrogenation catalyst promoters.) Specifically, the protonated carboxylic acid is effective at catalyzing the accumulation of the IM3 intermediate, and naturally this (de)protonation has a strong dependence on solvent. In a pure screen of solvent and additives, the convolution of these effects might have obscured the chemical nature, and without a rigorous description of the pathway, it would be difficult to determine their action.

The kinetic modeling effort is an example of an elegant treatment leading to enriched, quantitative understanding. The reaction network here is complex, especially considering Maillard-type side reactions. However, the model captures the overall results quite well, and its single free parameter, *K*, is essentially the time-averaged balance of IM1–IM4. Thus, this model serves multiple functions well. First, most optimization strategies discussed focus on accumulating IM4. Therefore, the *K* parameter serves as an objective measure, for a given condition, of the success of that approach because it integrates more data for better resolution than a single-point, high-conversion estimate alone. In further optimization of the process, by these authors or others, the parameter *K* can serve as a useful benchmark. Second, if yields of HMTriETA are improved by process modifications while model fits report a low value of *K*, this indicates a deviation

from the pathway shown here—and an opportunity for more in-depth kinetic analysis. Third, the report of these *K* (and *k* for GA consumption rate) values can be used as predictive tools for future reaction models, and possibly incorporate side or tandem reactions, now decoupled from the specific experimental configuration used by the authors. Modeling work here has greatly improved the generalizability, accessibility, and quantitative chemical description of the work and is an important step for anyone contributing to the field.

An important lesson from this work is that process conditions can be significantly more variable than they appear—the exponential rate dependence of chemical reactions can mean that elements of reaction pathways can occur on starkly different timescales (as in intermediate accumulation versus direct hydrogenation), and the sensitivity of chemistries to shifting thermodynamics can further complicate matters (as in the solvent-effect study). Thus, a simple screening approach will not be sufficient because the interaction of process conditions could obscure key information. In the initial screen, for instance, Ru/C produced the highest yields, whereas Pd/C, with its preference for IM4 hydrogenation, was ultimately more successful in the optimized condition. Screening conditions on axes motivated by chemical intuition of the pathway greatly improves experimental efficacy and limits lost information. Similarly, it is critical for such screens to have a wide scope such that chemical influence is not erroneously ascribed to a single mechanistic effect. The authors here have performed several thoughtful sets of experiments that epitomize rational chemical design and have been rewarded with a robust chemistry.

Physical understanding of the system is key for ultimate commercialization and scale-up efforts; as such, this system represents a strong step forward toward the biorefinery paradigm for both commodity and specialty chemicals. Many restrictions are placed on pilot-scale reactors on the basis of market pricing, material compatibilities, logistics requirements, etc. If a process needs alteration, it is essential to have both an intuitive, physical understanding and quantitative predictive power. However, there are other advantages in moving toward larger or continuous processes—the "two-step, one-pot" approach might be unexpected in laboratory experiments, but in process chemistry this is the domain of unit operations. One could envision (for this chemistry) series or recycle reactors designed to precisely control the degree of intermediate accumulation by staged water removal or additive introduction prior to a secondary hydrogenation unit. In a typical hydrocarbon-processing refinery, dozens of interconnected reactors and separation units are employed to achieve high yields; there is no conceptual reason that a biorefinery must operate differently. As the authors note, there is already a degree of integration in this chemistry—carboxylic acids are already present known impurities in GA feeds produced from sugar thermolysis, and the hydrogenation of GA is a green route toward the synthesis of their preferred solvent, ethylene glycol.[2] The reactor-design optimization, however, is of limited use if the intermediate steps in a pathway are not well understood, reinforcing the need for their detailed study. Indeed, there might already be significant information in the patent literature to suggest mechanism-modifying additives or conditions. The diversity of bio-derived molecules (compared with their hydrocarbon counterparts) provides a wealth of flexibility for chemical integration and functionalization if transformations can be understood systematically to enable their more general application. The work here has made an important step in characterizing several key reactions in complex amine synthesis and will surely enable the integration of further biomolecules as successive reactions.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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