Catalytic Reductive Aminolysis of Reducing Sugars: Elucidation of Reaction Mechanism

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S Supporting Information

ABSTRACT: A catalytic reductive aminolysis of reducing monosaccharides into short ethylene diamines (or C₂ diamines) was recently communicated by our group (Pelckmans et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 14540–14544). Here, a general mechanism for this novel reaction is proposed based on the results of a combined experimental and theoretical study. The mechanism involves hemiaminal formation and subsequent dehydration to produce a zwitterionic iminium intermediate, which undergoes fast C–C cleavage as a result of intramolecular deprotonation, followed by hydrogenation of the formed unsaturated amine intermediate. The role of the amine in facilitating the C–C scission is explained in detail and supported by DFT calculations. Different catalysts, carbohydrate substrates, and reaction conditions were tested to validate the proposed reaction mechanism. Reductive aminolysis of sugars is preferably carried out in the presence of a passivated silica(-alumina) supported Ni catalyst and an alkyl amine using 75–85 bar H₂ at 125–130 °C. The water content in the reaction mixture should be kept below 33 wt % to favor dehydration equilibria in the mechanism, while the amine-to-glucose molar ratio should be kept high, preferably larger than 6, to favor the amination equilibria. The reaction rate experiences a strong solvent dependency. For instance, the presence of MeOH enhances the rate of C₂ diamine formation, as compared to the use of tetrahydrofuran (THF). DFT calculations shows that presence of MeOH beneficially affects both the kinetics of the nucleophilic amine attack and the C–C bond scission. These selective rate enhancements result in a 2- to 3-fold increase of the C₂ diamine yield. Among a series of aminating agent, reductive aminolysis with *N*-methylethanolamine (MEOA) shows a 92 C% yield to the corresponding C₂ diamine (BEDHMEDA). The high yield is explained by the formation of a heterocyclic oxazolidine intermediate. Since its formation occurs H₂ free, a two-step one-pot production protocol, decoupling C–C scission and hydrogenation, is proposed to achieve highest C₂ diamine yield.

KEYWORDS: reductive aminolysis, mechanism, biomass, amines, heterogeneous catalysis

1. INTRODUCTION

Short amines are a group of versatile chemicals that are intensively used in today's chemical industry.¹ Ethylene diamines (C₂ amines) are for instance used as curing agents in epoxy resins and as catalysts in polyurethane synthesis.² Unfortunately, fossil-based ethylene is the common carbon source for the current industrial manufacture of these C₂ amines.³ The alternative production of amines from biomass is a strongly growing field of interest, though still in its infancy.⁴ Our group recently demonstrated that glucose can be converted with an amine into 51 C% of the corresponding C₂ diamine in one step.⁵ For instance, it was demonstrated that glucose can be converted into *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in the presence of hydrogen and dimethyl amine (DMA), forming water as byproduct, according to the following reaction equation:

This so-called reductive aminolysis process was carried out at surprisingly low temperature (<150 °C) of a recyclable heterogeneous Ru-based metal catalyst. Usually, such retro-aldol type of catalysis with carbohydrates requires a much higher temperature, at least when carried out in the absence of amines.⁶

To provide a better understanding of this novel amination reaction and to pinpoint the role of the amine in facilitating C–C cleavage in sugars, a mechanistic study is undertaken here using both experimental and theoretical tools. Therefore, details of the reaction evolution (in terms of P, T, and products) will

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be presented for the first time. Additionally, the catalytic outcome of different sugar substrates (reduced and non-reduced; mono-, di-, and polysaccharides), alkyl amines (and their molar ratio to the sugar), and varying reaction conditions (T, P, solvent, and catalyst types) were evaluated with regard to product variation and reaction rates. The collective information is used to propose a general reductive aminolysis mechanism, which is fully supported by associated density functional theory (DFT) calculations. Next to the mechanistic insights and the role of the amine, the study also shows an interesting (unexpected) solvent effect and addresses a peculiar two-step protocol to enhance C₂ diamines formation with particular alkyl amines.

2. EXPERIMENTAL SECTION

2.1. Reagents and Catalysts. Nitrogen sources: DMA 60 wt % aq. and MMA 40 wt % aq. (Eastman); DMA 2 M in MeOH, 2 M in THF and 5.6 M in EtOH (Sigma-Aldrich). Carbon sources: D-glucose (Fisher Chemical); sorbitol (Janssen Chimica); starch (UCB); sucrose, cellobiose, maltose, glyceraldehyde dimer, D,L-glyceraldehyde, D-xylose, and D-mannose (Sigma-Aldrich); maltotriose and ethylene glycol (Acros Organics); D-galactose and D-ribose (Fluka Chemie). Catalysts: Pt/C (1 wt %), Ru/C (5 wt %) and 65 wt % Ni/SiO₂Al₂O₃ (Sigma-Aldrich); Ru/Al₂O₃ (5 wt %, Alfa Aesar); Ni-6458P (56 wt %), Ni-5249P (64 wt %), Ni-3354E (60 wt %), Co-0164, Cu-1132 and Pd/C (5 wt %; Engelhard); Ni KL6565-TL1.2 (CRI), Pricat Ni 60/15, Pricat Ni 52/35, Ni HTC 102B, Co HTC 2000 and Sponge Cu–Cr A3B00 (Johnson Matthey); Raney Ni-4200, Raney Ni-5601, Raney Ni-6800, and Raney Co-2724 (Grace); Pd/Cu (5/30 wt./wt., Eastman).

2.2. Catalyst Activation. After the catalyst was loaded into a U-tube, the system was purged with N₂. Next, a H₂ flow of 300 mL min⁻¹ per g catalyst was established and temperature was increased (2 °C min⁻¹) to 120 °C (240 °C for Ni HTC 102B) and held for 60 min. Next, the temperature was increased (2 °C min⁻¹) to 230 °C (400 °C for Ni HTC 102B) and held for 60 min. Finally the catalyst bed was cooled to room temperature (RT) before loading into the reaction vessel under inert atmosphere using a N₂ bag.

2.3. Reaction, Instrumentation, and Analysis. Aqueous reductive aminolysis reactions were carried out using the previously reported procedures and instrumentation.⁵ For the reactions in other solvents than H₂O, a true batch setup was used without H₂ feed below 75 bar. Because lower glucose loadings were applied, less reactants were consumed, and hence, the total pressure reduction in the course of the experiment was less pronounced. Gas chromatographic (GC) analysis with N-methylpyrrolidone (NMP) as the standard was used for the quantification of the volatile reaction products.⁵ However, no aminoethylpiperazine (AEP) was required for the nonaqueous product mixtures to reduce the thermal expansion volume in the GC-liner. Derivatization with acetic anhydride was used to quantify hexitols, C₄ sugar alcohols, (N,N-di)-methylglucamine and 4-dimethylamino-butane-1,2,3-triol. A small amount of H₂O was added to initiate the acetylation in nonaqueous product mixtures. Carbon nuclear magnetic resonance (¹³C NMR) analysis with dioxane as the standard was used for the quantification of N,N'-bis(2-hydroxyethyl)-N,N'-dimethylethylenediamine (BHEDMEDA) and its oxazolidinic C₂ diamine precursor (OXAZOL).

2.4. CO Chemisorption. The metal dispersion of selected supported redox catalysts was determined via CO chemisorp-

tion experiments. A total of 100 mg of the catalyst was loaded in a tubular sample holder and pretreated with H₂ (20 mL min⁻¹) for 1 h at 125 °C (5 °C min⁻¹). Next, the sample was purged with He and cooled to RT. Pulses of pure CO were then added to a He flow (20 mL min⁻¹) with an interval of 2 min via a calibrated loop (5 μL). The CO concentration in the outlet stream was monitored (m/z = 28) with a Pfeiffer Omnistar quadrupole mass spectrometer.

2.5. DFT Calculations. All geometry optimizations and frequency calculations were performed in gas-phase (T = 298.15 K, p = 1 atm) with the hybrid meta-GGA functional M06-2X,⁷ corrected with Grimme's atom-pairwise dispersion correction (D3),⁸ and 6-311+G(2df,2p) basis sets. To verify that the located transition states (TSs) connect the expected minima on the potential energy surface (PES) intrinsic reaction coordinate (IRC) calculations were performed. Solvent effects were accounted for by means of the SMD⁹ continuum solvent model in a single-point calculations at the M05-2X/6-31+G(d,p) level of theory⁹ using the gas-phase optimized structures. For the liquid-phase reactions a standard state of 1 mol L⁻¹ was used for all species.¹⁰ In the cases where methanol is both a solvent and a reactant (such as in the solvent assisted TSs) a concentration correction term accounting for the standard state concentration of methanol in the liquid phase, 24.7 mol L⁻¹, was also added to the computed free energies.¹⁰ All calculations were carried out with the Gaussian 09 package.¹¹

3. RESULTS AND DISCUSSION

The production of N,N,N',N'-tetramethylethylenediamine (TMEDA) and the corresponding evolution of the reaction temperature and total pressure are presented in Figure 1 for both the reductive aminolysis of glucose (diamonds) and for the reaction of sorbitol (squares) with dimethylamine (DMA) 151

Figure 1. Evolution of temperature (hollow) and total pressure (full) for the reductive aminolysis of 5 g of glucose (diamonds) and 5 g of sorbitol (squares) with 25 g of dimethylamine (DMA, 60 wt % aq.) and 0.5 g of Ru/C (5 wt %) at 125 °C and 75 bar H₂. N,N,N',N'-Tetramethylethylenediamine (TMEDA, black) yield is given in carbon % (C%).

in the presence of Ru/C under hydrogen atmosphere. The product yield, given in C%, represents the fraction of carbon originating from the sugar substrate that is found in the final product.

Clearly, no TMEDA was formed from sorbitol, which largely remained unconverted under the catalytic conditions. The temperature is too low to initiate amination of sorbitol, which usually requires 200 °C or more.¹² Evolution of temperature and pressure for the sorbitol reaction is therefore considered as reference of inactivity. Formation of TMEDA from glucose clearly occurred rapidly. During the first minutes of the glucose reaction, the temperature was increased and the total pressure in the reaction vessel increased due to thermal expansion of H₂O, DMA, and H₂. Production of TMEDA from glucose initiated already after 15 min, i.e. at a temperature of 105 °C and a total pressure of 84 bar. From this point on, pressure in the reaction vessel dropped to 73 bar as a result of reactant (H₂ and DMA) consumption. Simultaneously the temperature profile showed an overshoot of 6 °C (up to 134 °C compared to 128 °C for the sorbitol reaction). This temperature increase is in line with the exothermicity of reactions such as the hydrogenation of unsaturated reaction intermediates (IMs).¹³ Hereafter, total reaction pressure leveled at the set-point pressure of 75 bar, since 75 bar H₂ was automatically fed into the reaction vessel via a back-pressure valve (at 75 bar; see the Experimental Section). This operation mode was employed to maintain sufficient hydrogenating capacity during the entire reductive aminolysis reaction.

Since sorbitol remains unconverted, no DMA or H₂ were consumed and, hence, the obvious absence of a total pressure decrease. For glucose, a maximum yield of 51 C% was reached already after 30 min (124 °C, 75 bar). From here on the reaction temperature reached the set-point value of 125 °C and remained unaltered. The TMEDA yield of 51 C% was maintained throughout the remaining of the reaction time, suggesting a high TMEDA product stability under reaction conditions.

3.1. Carbohydrate Substrate Scope. Apart from glucose, di-, tri-, and polymeric carbohydrates were evaluated. The main results are summarized in Figure 2.

As discussed above, reductive aminolysis of glucose with DMA shows about 54% C₂ amines, TMEDA as main product and some *N,N*-dimethylaminoethanol (DMAE). Next to the C₂ products, also C₃ products, viz. *N,N,N',N'*-tetramethyl-1,2-propanediamine (TMPDA), *N,N*-dimethylamino-2-propanol

and *N,N*-dimethylamino-2-propanone (DMA-2-propanone) were obtained. Reaction with the disaccharides, cellobiose and maltose, forms the same products, albeit at somewhat lower yields, viz. 38 C%. Trimeric maltotriose is also converted, but the product yield is only 22%. These data indicate that hydrolysis of both $\alpha(1-4)$ and $\beta(1-4)$ glycosidic linkages occurs during the reductive aminolysis, but not efficiently. Since hydrolysis of glycosidic linkages is typically catalyzed by Brønsted acids, the slow hydrolysis is likely attributed to the high alkalinity (pH 13–14) of the reaction medium resulting from the high DMA concentration. Accordingly, almost no TMEDA (<1 C%) was obtained from the reaction with polysaccharides such as starch, even after 240 min at 175 °C.

The lower amount of C₂ (and C₃ amines) obtained for substrates with high degree of polymerization (DP) further indicates that the reductive aminolysis is initiated from the reducing end of the sugar molecule. Indeed, at the low temperature (125 °C), the absence of a free carbonyl functional group prevents conversion of nonreducing substrates like sucrose (Figure S1, SI) into C₂ amines. Instead, only a trace amount of *N,N*-dimethylformamide (DMF, < 1 C%) was obtained. Interestingly, relatively more *N,N*-dimethylformamide (DMF) is produced from the higher DP substrates. For instance, more than twice the amount of DMF (10 C%) was obtained as a side-product from maltotriose, compared to 4 C% DMF from glucose. Given that DMF formation benefits from inefficient hydrolysis, it suggests that DMF formation proceeds in parallel to the production of C₂ (and C₃) amines.

3.2. Effect of the Metal Catalyst. Different commercial heterogeneous metal catalysts were explored for their performance in the catalytic reductive aminolysis of glucose with aqueous DMA. A standard amount of 2 wt % catalyst was used in the reaction mixture (see Table S1, SI), regardless of the metal loading. The results are summarized in Table 1.

As can be seen from this table, Pt, Ru, and Ni catalysts afford to produce more than 45 C% of the main TMEDA product. The maximum TMEDA yield is obtained with Ru/C (51 C%, entry 3), followed by Pt/C (48 C%, entry 2), Ni-6458P (47 C%, entry 5) and Ni/SiO₂-Al₂O₃ (47 C%, entry 6). Interestingly, the nature of the support material appears crucial for selective production of C₂ amines. The use of a 5 wt % carbon supported Ru catalyst resulted for instance in more than twice the TMEDA yield (51 C%) compared to the 5 wt % alumina supported Ru catalyst (22 C%). The Ru dispersion of the carbon supported catalyst is significantly higher (37%) compared to the alumina supported catalyst (25%), which probably attributes to the increased TMEDA yield for Ru/C. Other effects like adsorption phenomena are acid/base catalyzed interventions and cannot be excluded, but they are not investigated here.

Furthermore, use of the cheaper Ni catalysts instead of the noble Ru (or Pt) led to an insignificant reduction of TMEDA yield (<4 C%). Moreover, generally more aminoalcohols (DMAE and DMA-2-propOH) were produced with Ni compared to Ru and Pt, which is generally at the expense of the diamines TMEDA and TMPDA (compare entries 2–4 with 5–8). Especially the silica supported Ni-S249P is appropriate for the production of short aminoalcohols (up to 15 C%, entry 8). This catalyst was tested toward recyclability up to 3 times (entry 8a). After each reaction, the catalyst was recovered by filtration, rinsed with water, and dried overnight (60 °C). No reactivation procedures were carried out prior to the following reaction. Little to no deactivation takes place. Slightly more

Figure 2. Reductive aminolysis of sugar mono-, di-, tri-, and polymers with dimethylamine (DMA) and Ru/C (5 wt %) at 125 °C and 75 bar H₂. The reaction with starch was carried out at 175 °C.

Table 1. Screening of Different Heterogeneous Catalysts for the Aqueous Reductive Aminolysis of Glucose with Dimethylamine (DMA) at a Molar DMA-to-Glucose Ratio of 12^a

entry	catalyst	C ₂ amines		C ₃ amines			
		TMEDA ^b [C%]	DMAE ^c [C%]	TMPDA ^d [C%]	DMA-2-propOH ^e [C%]	DMA-2-propanone ^f [C%]	DMF ^g [C%]
1		0	0	0	0	11	9
2	Pt/C (1 wt %)	48	2	10	<1	6	4
3	Ru/C (5 wt %)	51	4	15	2	<1	4
4	Ru/Al ₂ O ₃ (5 wt %)	23	2	7	3	4	7
5	Ni-6458P (56 wt %)	47	4	2	5	7	5
6	Ni/SiO ₂ -Al ₂ O ₃ (65 wt %)	47	6	3	4	7	5
7	Ni-3354E (60 wt %)	44	3	2	3	7	4
8	Ni-5249P (64 wt %)	42	7	2	8	<1	4
8a	Ni-5249P (64 wt %) (3x)	45	2		2	8	5
9	Ni KL6565-TL1.2 ^{g,i}	32	1	2	6	5	6
10	Ni KL6565-TL1.2	21	1	<1	5	8	7
11	Pricat Ni 60/15 ^{g,i}	37	2	<1	4	8	6
12	Pricat Ni 52/35 ^{g,i}	35	2	1	11	2	6
13	Pricat Ni 52/35	25	<1	<1	5	7	9
14	Ni HTC 102B ^{h,i}	35	2	<1	2	13	7
15	Ni HTC 102B	2	<1	<1	<1	12	11
16	Raney Ni-4200 ⁱ	19	1	<1	1	8	7
17	Raney Ni-5601 ⁱ	23	2	<1	2	7	6
18	Raney Ni-6800 ⁱ	22	2	<1	<1	8	6
19	Raney Co-2724 ⁱ	19	2	<1	3	8	7
20	Co HTC 2000	19	<1	<1	4	8	10
21	Co-0164	9	1	<1	2	10	10
22	sponge Cu-Cr A3B00 ⁱ	19	<1	3	1	7	8
23	Cu-1132	13	<1	4	<1	8	18
24	Pd/Cu (5/30 wt/wt) ⁱ	11	<1	<1	<1	18	15
25	Pd/C (5 wt %)	14	2	3	<1	<1	<1

^aAll catalysts were loaded to the reaction vessel as a powder. Mass balance is not complete due to undesired competitive caramelisation and/or reactions of the Maillard type. Reaction conditions: 5 g glucose; 25 g aqueous DMA (60 wt %); 0.5 g catalyst; 125 °C; 75 bar H₂; 1 h reaction.

^bN,N,N',N'-Tetramethylethylenediamine. ^cN,N-Dimethylaminoethanol. ^dN,N,N',N'-Tetramethyl-1,2-propanediamine. ^eN,N-Dimethylamino-2-propanol. ^fN,N-Dimethylamino-2-propanone. ^gActivation prior to reductive aminolysis with H₂ at 230 °C. ^hActivation prior to reductive aminolysis with H₂ at 400 °C. ⁱCaution: pyrophoric.

TMEDA was formed after three reactions, at the expense of DMAE. This can be attributed to a slightly lower hydro-
genation rate. Likewise, more DMA-2-propanone was formed
at the expense of DMA-2-propOH.

Unlike the passivated Engelhard Ni-catalysts (entries 5, 7, and 8) which are reactivated in situ (see Figure S2 and Table S2, SI), passivated Ni-KL6565, Pricat Ni, and Ni HTC required reactivation with H₂ prior to efficient reductive aminolysis. This pretreatment was carried out in order to remove the oxide layer, thus obtaining the active Ni phase (entries 9–15).¹³ The beneficial effect of catalyst activation was most pronounced for the Ni HTC 102B, because this catalyst mainly consists of Ni-oxide. Hence, this catalyst showed a 33 C% TMEDA yield increase after pretreatment at 400 °C (entries 14–15). Pyrophoric sponge or Raney Ni (>90 wt % Ni) catalysts produced lower amount of C₂ amines (entries 16–18) compared to the supported Ni catalysts (entries 5–14). Instead, more DMA-2-propanone and DMF were produced, which are the main reaction products from glucose in the absence of metal catalyst (entry 1). The product mixtures were colored dark brown, due to undesired competitive caramelization¹⁴ and/or reactions of the Maillard type.¹⁵ Experiments with two and four times the amount of Raney Ni did not result in significantly higher TMEDA yields at full glucose conversion (see the SI, Figure S3), indicating that the low TMEDA selectivity is not attributed to catalyst poisoning.¹⁶

Of the tested catalysts, Cu, Co, and Pd showed the lowest selectivity toward C₂ diamines (entries 19–25). Again, more DMA-2-propanone and DMF were obtained instead, especially for the Cu and Co catalysts. For instance Cu-1132 produced 18 C% DMF and 8 C% DMA-2-propanone (entry 23) and Pd/Cu produced 15 C% DMF and 18 C% DMA-2-propanone (entry 24). The increased production of DMA-2-propanone and DMF in the presence of inefficient reductive aminolysis catalysts is in accord with our earlier suggestion that these products are produced through a competitive pathway.⁵ Alike for Raney Ni catalysts, product mixtures from the Co and Cu reactions were colored dark brown, due to undesired (noncatalytic) browning. The carbon supported Pd (entry 25), however, produced a translucent product mixture, indicating no competitive Maillard and/or caramelization. The main reaction product for this catalyst was N,N-dimethylglucamine (71 C%), which is the result of a reductive amination of glucose without C–C scission. In addition, 8 C% 4-dimethylamino-butane-1,2,3-triol was obtained, hereby completely closing the carbon balance.

3.3. General Mechanism for the Reductive Aminolysis of Sugars. To rationalize the selective formation of C₂ amines from reducing sugars, we propose here a new reaction scheme, that is provided in Scheme 1. To our knowledge, we are the first to propose such an elementary mechanism for the catalyzed reductive aminolysis of sugars into C₂ amines. The essential reaction steps for the catalyzed reductive aminolysis of

Scheme 1. Proposed General Reaction Mechanism for the Low-Temperature Catalytic Reductive Aminolysis of Reducing Sugars into C₂ Amines^a

^aIntermediates indicated with a grey asterisk are prone to competitive reactions, like caramelization and reactions of the Maillard type, under the applied reductive aminolysis conditions. Cyclization to (14) is only possible if R₁ or R₂ = H.

glucose with DMA at a somewhat more global level have been identified as part of kinetic model development.¹⁷

The reaction starts with a nucleophilic attack of the aminating agent on the free carbonyl of the reducing sugar substrate (1). This results in the formation of a hemiaminal IM (2).¹⁸ It is important at this stage to suppress competitive hydrogenation of the sugar into the corresponding sugar alcohol (9),¹⁹ since amination of that polyol is difficult as demonstrated above in the reaction with sorbitol. At the low reaction temperature and elevated H₂ pressure, no dehydrogenation takes place to reactivate the sugar alcohol toward nucleophilic attack, and therefore no reaction with sorbitol was observed (see Figure 1). Next, the hemiaminal IM (2) reacts into a zwitterionic iminium species (3) via dehydration at the hemiaminal C atom. If the iminium species (3) is primary or secondary (R₁ = H), intramolecular proton transfer (PT) from the positive nitrogen ion to the negative oxygen ion results in the formation of a more stable imine (10).¹⁸ If the iminium species (3) is tertiary (R₁ ≠ H, R₂ ≠ H), intramolecular PT from the αC atom to the negative oxygen ion results in the formation of an enamine (10).¹⁸ These imine or enamine IMs may then undergo hydrogenation into the corresponding amino sugar alcohol (11), but they are susceptible to caramelization and complex browning of the Maillard type. The iminium species (3) is preferably fragmented by C–C cleavage into a C₂ enaminol IM (4) and a carbonyl compound (12), via a third possible intramolecular rearrangement route. Transfer of the electron lone pair from the negative oxygen ion to the βC atom leads to the formation of a βC=O carbonyl bond. Hereby, cleavage of the αC–βC is facilitated, which in turn neutralizes the positively charged N-ion of the iminium

IM. This amine-facilitated retro-aldol fragmentation is very similar to the working mechanism of Class 1 Aldolases that use a catalytic primary Schiff base IM to split C–C bonds even at body temperature.^{5,20} While the resulting carbonyl fragment (12) can re-enter the reaction pathway (dashed arrow), the C₂ enaminol (4) is hydrogenated into a C₂ aminoalcohol (13), or undergoes base-catalyzed keto–enol tautomerization into a C₂ aminoethanal (5). This reactive IM is susceptible to self-condensation (i.e., cyclization) to produce heterocyclic piperazine (14) or it may react with a second amine reactant to form the C₂ hemiaminal (6). This C₂ hemiaminal IM is eventually converted into the main C₂ diamine product (8) via H₂O elimination into the C₂ ene-diamine (7) and subsequent hydrogenation.²¹ Irreversible hydrogenation of the C₂ ene-diamine (7) and the C₂ enaminol (4) favors their formation equilibria. This way, high C₂ amines (e.g., TMEDA and DMAE) yield can be obtained.

In summary, for the conversion of 1 mol glucose into 3 mol of C₂ diamine (TMEDA), 3 mol of H₂, and 6 mol of amine (DMA) are net consumed, while 6 mol of H₂O is net produced (see the reaction equation).

To underpin the suggested reaction scheme and to obtain additional mechanistic insights, the reaction between glucose and DMA was investigated (in gas-phase) with DFT methods. Here, we consider only the first reaction steps related with the formation of the key compounds (4) and (10) rather than providing an exhaustive mechanistic investigation which is beyond the scope of the present work. The calculated gas-phase free energy profile is shown in Figure 3, and the optimized structures of the corresponding stationary-points can be found in Figure S4 of the Supporting Information (SI). The reaction

Figure 3. DFT calculated gas-phase free energy profile of the reaction between glucose and DMA into the C_6 enamine (10) or the C_2 enaminal (4) and C_4 carbonyl (12). Energy values are in kcal mol^{-1} .

of aminolysis is initiated by DMA addition to the $-\text{CHO}$ group of the substrate through TS1. In this transition state (TS) the formation of the $\text{C}-\text{N}$ bond and the PT to the carbonyl oxygen occur simultaneously, the latter process being mediated by a second DMA molecule. The free energy requirement for this step was calculated to be $19.2 \text{ kcal mol}^{-1}$. It has already been demonstrated that DMA or solvent mediated PT can significantly lower the energy barrier for the addition step as compared to the direct PT.²² TS₁ then collapses to the hemiaminal IM (2), which is thermodynamically more stable than the reactants by $5.3 \text{ kcal mol}^{-1}$. This IM (2) is connected, on the potential energy surface, to IM (3) via TS₂ by water release. The energy requirement for this step was calculated to be $25.9 \text{ kcal mol}^{-1}$. TS₂ involves direct PT from a neighboring $-\text{OH}$ group to the leaving group. Our modeling further demonstrated that DMA-mediated PT does not result in additional lowering of the energy barrier. The resulting iminium IM (3) is a high energy structure, which may further rearrange to give either enaminal (4), via TS₃, or enamine (10), via TS_{3s}. In agreement with the experimental results, the activation energy associated with the formation of enaminal ($22.8 \text{ kcal mol}^{-1}$) was calculated to be lower by about 8 kcal mol^{-1} as compared to the activation energy required for the formation of enamine ($31.2 \text{ kcal mol}^{-1}$). The low IM (3) $\rightarrow$ enaminal (4) barrier height associated with the $\alpha\text{C}-\beta\text{C}$ cleavage is most likely related with the finding that $\alpha\text{C}-\beta\text{C}$ bond is already weakened in the IM(3). The calculated $\alpha\text{C}-\beta\text{C}$ bond length in IM(3) is $1.581 \text{ \AA}$, while it is 1.535 and $1.525 \text{ \AA}$ in glucose and IM(2),

respectively. By using the linear correlation between $\text{C}-\text{C}$ bond length and bond dissociation energy (BDE) proposed by Zavitsas,²³ the $\alpha\text{C}-\beta\text{C}$ BDE in the iminium IM is estimated to be lower than that in glucose by about 19 kcal mol^{-1} . This can explain why iminium IM is more prone to $\alpha\text{C}-\beta\text{C}$ cleavage (via TS₃) than to a PT (via TS_{3s}) to enamine. Alternatively, enamine (10) can be obtained directly from (2) through dehydration, but this reaction route passes through a significantly higher energy barrier of about 57 kcal mol^{-1} . Thus, the DFT results support the proposed reaction scheme and provide a reasonable explanation for the obtained higher yield of the main C_2 amine products, viz. TMEDA and DMAE, that are preferably obtained instead of the amino sugar alcohol (11).

3.4. Evaluation of Reaction Conditions and Validation of the Proposed Mechanism. As can be seen from Scheme 1, it is evident that multiple reaction parameters must be carefully controlled in order to avoid undesired side reactions and to obtain C_2 amines with the highest selectivity:

- Selective hydrogenation of the desired IMs (5, 7) is crucial to obtain the targeted C_2 amines. Direct hydrogenation of the reducing sugar (1) or the corresponding imine/enamine (10) on the other hand results in the formation of the corresponding sugar alcohol (9) or the amino sugar alcohol (11), respectively. Also, selective electron and proton transfer is essential to facilitate the nucleophilic amine attack and promote the subsequent retro-aldol-type $\text{C}-\text{C}$ scission. Competitive

intramolecular proton transfer of the reactive iminium species, resulting in the formation of the imine or enamine (10), should be avoided.

- The amount of H₂O in the reaction system should be limited in order to maintain favorable dehydration equilibria, while a sufficient amount of DMA should be present in order to maintain favorable amination equilibria. By using DMA or any other secondary amine as the aminating agent, overalkylation and formation of heterocyclic PIPs (14) are avoided.

Since both H₂O and DMA affect the equilibria in the proposed reaction mechanism (Scheme 1), the effect of molar DMA-to-glucose excess should be assessed at constant H₂O-to-glucose ratio and vice versa. These results are summarized in Figure 4.

Figure 4. (A) Effect of DMA-to-glucose molar excess on the yield of C₂ amines (H₂O-to-glucose = 20, Ni-6458P). (B) Effect of molar H₂O-to-glucose excess on the yield of C₂ amines (DMA-to-glucose ratio = 12, Ni-6458P). (C) Effect of H₂ pressure on the yield of C₂ amines (Ru/C). (D) Effect of H₂ pressure on the yield of C₃ amines (Ru/C). The temperature is 125 °C for each reaction.

For instance, it can be seen from Figure 4A that the amount of DMA strongly affects TMEDA yield. At a molar DMA excess of 4.8 only 13 C% TMEDA is produced, while 47 C% TMEDA is obtained at a molar DMA-excess of 12.3. This agrees with the proposed mechanism (Scheme 1), since both formation of intermediates (2) and (6) are favored at high DMA concentration. At a molar DMA excess below 6, TMEDA cannot be efficiently produced, and hence, the product mixtures are colored brown as a result of competitive caramelization and Maillard type reactions.

In contrast, the yield of DMAE remains almost unaffected (3 C% to 4 C%) with increasing DMA excess. This is likely because only 1 mol of DMA is consumed in the formation of 1 mol of DMAE, which means only 3 mol of DMA instead of 6 should be available per mol of glucose in the reaction mixture. Also, at a DMA excess above 4, increasing amount of DMA selectively favors the formation of TMEDA and not DMAE. This indicates that the base-catalyzed keto–enol tautomerization of the C₂ enaminol (4) and subsequent attack of a second DMA into (6) is preferred over hydrogenation into the C₂ aminoalcohol (13), especially at high DMA concentration.

Per mol of TMEDA that is formed, 2 mol of H₂O is coproduced. The presence of too much H₂O may negatively affect the dehydration equilibria, ultimately lowering the C₂ amine product yield. Figure 4B illustrates that TMEDA yield decreases steeply from 47 C% at molar H₂O excess of 20 (i.e., 33 wt % H₂O) to less than 16 C% TMEDA at a molar H₂O

excess above 80 (i.e., above 66 wt % H₂O). Increasing the H₂O amount indeed resulted in more brown-coloring as a sign of substantial occurrence of undesired reactions. As for higher DMA concentrations, the DMAE yield is less affected by increasing H₂O amount. Only 1 mol of H₂O is produced per mol of DMAE, instead of the 2 mol of H₂O for each mol of TMEDA. Also, at the high molar DMA-to-glucose ratio of 12, formation of TMEDA is favored over DMAE (Figure 4A), which impedes true evaluation of the H₂O effect on DMAE. At lower DMA loading, selectivity toward C₂ amines is generally low, due to more competitive browning (Figure 4A).

The effect of H₂ pressure was also investigated (Figure 4C–D). In accord with Scheme 1, no TMEDA is obtained in absence of H₂ (Figure 4C). Furthermore, yield for both TMEDA and DMAE increase with increasing H₂ pressure. Scheme 1 indeed shows that 1 mol of H₂ is consumed for the production of 1 mol of TMEDA or 1 mol of DMAE. Notably, for the reaction at 100 bar H₂, less TMEDA (44 C%) is obtained, compared to 75 bar H₂ (51 C%). This is the result of a more competitive sugar hydrogenation. Indeed, 4 C% hexitols (9), 2 C% C₄ sugar alcohols (9), and 2 C% 4-dimethylamino-butane-1,2,3-triol (11) were obtained at 100 bar H₂, whereas only 1 C% hexitols, 1 C% C₄ sugar alcohols, and 1 C% 4-dimethylamino-butane-1,2,3-triol were observed at 75 bar H₂. Selectivity toward *N,N*-dimethylglucamine (11) was the same (2%) at 75 and 100 bar H₂. Considering the C₃ amine products, which are beyond the scope of the proposed reaction mechanism (Scheme 1), DMA-2-propanone is the only C₃ product in absence of H₂. This product was also observed by Safariamin and co-workers for the acid-catalyzed hydroamination of glycerol with DMA under inert atmosphere.²⁴ At higher H₂ pressure, more TMPDA and DMA-2-propOH are produced at the expense of DMA-2-propanone. This corresponds to the suggestion in our earlier work that DMA-2-propanone is the precursor for both TMPDA and DMA-2-propOH.⁵ Selectivity toward either the C₃ diamine or the C₃ aminoalcohol is affected by catalyst choice, as evidenced by the data in Table 1.

According to Scheme 1, competitive intramolecular PT of the iminium IM (3) contributes to more amino sugar alcohol (11). When secondary amines (R1 ≠ H, R2 ≠ H) are used as the N-source, deprotonation at the αC atom results in formation of the corresponding enamine (10), since no H atom is available at the positive N-ion for deprotonation to occur. However, when primary aminating agents (or ammonia) are used (R1 = H), PT from the positive nitrogen ion to the negative oxygen ion leading to the corresponding imine (10) exhibits a lower activation barrier. This can be seen from the theoretical calculations as presented in Figure 5 (optimized geometries of the species along the reaction of glucose with monomethylamine (MMA) can be found in Figure S5, SI). As expected, the calculated TS energies for the reaction with MMA associated with the formation of iminium intermediate (TS₂, 26.7 kcal mol^{−1}) and enaminol (TS₃, 24.4 kcal mol^{−1}) were very similar to those for the reaction with DMA (see also Figure 3). However, with MMA a second PT via TS_{2s} resulting in the formation of imine is preferred by about 3 kcal mol^{−1}. The free energy of this compound lays below the energy of the C₂ enaminol cleavage product (4) by about 10 kcal mol^{−1} implying that in the case of MMA the side-product (10) is not only kinetically but also thermodynamically favored.

Competitive reaction aside, the imine or enamine IM (10) is converted into the corresponding amino sugar alcohol (11) via

Figure 5. Reaction profile for enaminol and imine formation between glucose and MMA into the C₆ (10) imine or into the C₂ enaminol (4) and C₄ carbonyl (12). Energy values are in kcal mol⁻¹.

Table 2. Different Monomeric Substrates for the Reductive Aminolysis with Dimethylamine (DMA 2M in MeOH)^a

entry	substrate	C ₂ amines		C ₃ amines			DMF [C%]
		TMEDA [C%]	DMAE [C%]	TMPDA [C%]	DMA-2-propOH [C%]	DMA-2-propanone [C%]	
1	ethylene glycol	0	0	0	0	0	0
2	TMEDA	100	0	0	0	0	0
3	DMAE	0	100	0	0	0	0
4	glycolaldehyde dimer	63	30	0	0	0	0
5	D,L-glyceraldehyde	4	1	6	14	8	2
6	D-xylose	34	2	7	13	4	2
7	D-arabinose	30	2	6	13	6	2
8	D-ribose	24	2	6	11	6	2
9	D-mannose	52	4	6	4	2	4
10	D-galactose	57	6	5	4	1	3
11	D-glucose	66	4	7	5	1	4
12	sorbitol	0	0	0	0	0	0

^aReaction conditions: 1 g of substrate; 20 g of DMA (2 M in MeOH); 0.3 g of Ni-6458P; 130 °C; 85 bar H₂; 60 min reaction. Mass balance is not complete due to undesired competitive caramelisation and/or reactions of the Maillard type.

hydrogenation (Scheme 1). At a molar DMA-to-glucose ratio of 12, only 2 C% *N,N*-dimethylglucamine (11) was obtained from the Ru/C catalyzed conversion of glucose with DMA. Using the same molar excess of MMA instead of DMA, up to 22 C% of the corresponding *N*-methylglucamine (11) was obtained. This explains why the reductive aminolysis process that involves catalytic trapping of the N atoms via hydrogenation is preferably carried out with secondary amines, while (retro-)Aldolases that catalyze the C–C bond scission without

N-incorporation by catalytic hydrogenation use a catalytic primary amino group in their catalytic motif.^{20b}

3.5. Reductive Aminolysis of Selected Monomeric Substrates to Validate the Proposed Mechanism. To further validate the proposed reductive aminolysis reaction mechanism (Scheme 1), a selection of monomeric sugars, sugar alcohols, as well as TMEDA and DMAE were evaluated as the carbon source (Table 2). This series of reactions was carried out in methanol (MeOH) instead of H₂O. TMEDA and DMAE (entries 2–3) are stable under the reductive aminolysis

conditions, confirming the irreversibility of the hydrogenation reaction. This explains for the yield plateaus that are observed shortly after the temperature set-point was reached.

Interestingly, the reductive aminolysis of glucose runs more efficiently with MeOH as the solvent, compared to H₂O, even at the lower DMA excess (8 instead of 12). With the Ni-6458P catalyst, up to 70 C% C₂ amines were obtained (entry 11) of which 66 C% TMEDA and 4 C% DMAE. With the same catalyst, only 51 C% C₂ amines was obtained in H₂O (see before: Table 1, entry 5). Indeed, no C₄ or C₆ (amino) sugar alcohols were detected in the product mixture for reaction in MeOH, indicative of a more efficient C–C scission. This peculiar solvent effect will be handled below in more detail. Furthermore, sugar alcohols (entries 1 and 12) remain unconverted also in MeOH (see also Figure S6, SI). Because of the low reaction temperature, no alcohol dehydrogenation or hydrogenolysis take place. The controlled fashion of the retro-aldol-type C–C scission therefore affords high selectivity to the desired C₂ amines.

In Scheme 1, glycolaldehyde (GA) was proposed as a reaction intermediate (12). From Table 2 (entry 4), it can be seen that GA was indeed efficiently converted into 63 C% TMEDA and 30 C% DMAE. Aldopentoses such as xylose, arabinose, and ribose were also converted into TMEDA (34 C%, 30 C%, and 24 C% respectively), albeit with lower yields than the hexoses (compare entries 6–8 to 9–11). Instead, more C₃ amines were formed because the C₅ sugar is split into C₂ and C₃ fragments in agreement with the proposed mechanism (Scheme 1). However, more C₂ amines (36 C% vs 29 C%) and less C₃ amines (24 C% vs 31 C%) were produced from xylose for the MeOH reaction, compared to the H₂O reaction.⁵ Considering that the C₃ carbonyl fragment (12) originating from the pentose after retro-aldol scission still contains a βC–OH functional group, it remains a suitable substrate to re-enter the reductive aminolysis pathway (see Scheme S1, dashed arrow and also Scheme S1, SI). Indeed, about 4 C% of TMEDA was obtained from the reductive aminolysis of glyceraldehyde (entry 3). DMA-2-propOH, DMA-2-propanone, and TMPDA (and DMF) were the main products from glyceraldehyde, which indicates that glyceraldehyde is the likely precursor for the observed C₃ amines (and DMF) that are coproduced during reductive aminolysis of glucose into C₂ amines.

Table 2 furthermore shows that different hexose and pentose epimers yield different amounts of the main TMEDA product. For instance mannose yields only 52 C% TMEDA in MeOH, while glucose yields up to 66 C% TMEDA (compare entries 9 and 11). Likewise xylose yields 34 C% TMEDA (entry 6), while ribose only yields 24 C% TMEDA (entry 8). A tentative working hypothesis is that the relative orientation of the βC–OH bond in the hemiaminal species (Scheme 1, (2)) with respect to the hydroxyl group from HO–C–N determines the feasibility of iminium (3) formation, which in turn affects the efficiency of the retro-aldol-type C–C scission. This could explain for the varying TMEDA yield that is obtained for different sugar epimers, but more research is required to support the explanation.

3.6. Effect of the Reaction Solvent. At first glance, the improved TMEDA yield for the reductive glucose aminolysis in MeOH, compared to H₂O, could be explained by the absence of H₂O, which favors the dehydration steps. It should be also taken into account that, in H₂O, DMA (pK_a 10.7) is partially present as ammonium salt. As a consequence of its protonation,

its nucleophilicity is reduced. Also, the conjugated OH[−] nucleophiles may give rise to additional side reactions, which could explain why better results are obtained in MeOH.

To further examine the effect of the solvent, reductive glucose aminolysis was carried out under exactly the same reaction conditions, but in THF instead of MeOH. Surprisingly, only 23 C% TMEDA could be obtained for the THF reaction at full glucose conversion, compared to 66 C% for the same reaction in MeOH. The major side products in THF were *N,N*-dimethylglucamine (19 C%) and 4-dimethylamino-butane-1,2,3-triol (5 C%), as a result from inefficient C–C scission.

Kinetic experiments, presented in Figure 6, demonstrate that formation of TMEDA is faster in the presence MeOH

Figure 6. Solvent effect on reductive glucose aminolysis with DMA. (A) Evolution of TMEDA formation in time for 5 g of additional tetrahydrofuran (THF) or 5 g of additional methanol (MeOH) in the conversion of 1 g of glucose with 20 g of DMA (2 M in THF) and 0.3 g of Ni-6458P at 130 °C and 85 bar H₂. (B) Evolution of TMEDA and total amount of cleavage products upon systematic replacement of THF with MeOH as reaction solvent, while other reaction parameters were kept constant.

compared to in THF alone. Upon replacing 5 g of THF into 5 g of MeOH, without altering the molar DMA excess, TMEDA is indeed produced considerably faster (Figure 6A). In presence of MeOH, 30 C% TMEDA is obtained already after 25 min, instead of 12 C% TMEDA in the absence of MeOH. For THF alone, 23 C% TMEDA was obtained after 1 h. Extension of the reaction time to 2 h did not result in higher TMEDA yield (see Figure S7, SI). Instead, 52 C% TMEDA was obtained in the presence of MeOH after 1 h. Figure 6B shows the same trend for reactions with a gradual increase of the methanol content.

Thanks to the rapid TMEDA formation, extensive formation of side-products from glucose, like *N,N*-dimethylglucamine and 4-dimethylamino-butane-1,2,3-triol, but also undesired caramelization and complex Maillard reactions are avoided. Interestingly, the amount of C₃ products that are produced remained almost constant upon the systematic replacement of THF by MeOH (Figure 6B).

Apparently, only the C₂ products benefit from the solvent-depending reductive aminolysis efficiency, which was at the expense of *N,N*-dimethylglucamine and 4-dimethylamino-butane-1,2,3-triol. This observation further concurs with the statement that the formation of the C₃ compounds occurs mechanistically parallel to formation of the C₂ products, the latter resulting from a true reductive aminolysis reaction, as presented in Scheme 1.

Figure 7. Free energy profile of the reaction between glucose and DMA in methanol (black lines) and in THF (blue lines). Energy values are in kcal mol⁻¹.

To rationalize the solvent effect, the reaction between glucose and DMA was examined theoretically both in MeOH and in THF by means of a continuum solvent model. Because of its aprotic nature, THF is unable to mediate PT and therefore the mechanism of aminolysis in THF largely resembles the gas-phase mechanism (Figure 3) as the main energy contribution will be due to bulk solvent effects. Instead, MeOH mediated/assisted PT reactions are expected to be more efficient as compared to DMA.²² To account for this in the calculations, all TSs along the reaction were modeled with one or two explicit MeOH molecules. The results are presented in Figure 7. DFT optimized structures can be found in Figure S8 (SI).

In general, the reaction in MeOH shows overall faster kinetics as compared to THF, in accord with the experimental results (see Figure 6). Upon replacement of THF with methanol the energy barrier for the nucleophilic DMA attack lowers dramatically from 20.3 to 8.7 kcal mol⁻¹. TS₂ and TS₃ are less affected in MeOH, with an energy lowering of about 3 kcal mol⁻¹. Unlike THF, where TS₁ is assisted by a second DMA molecule, DMA attack in MeOH is facilitated by a PT that involves two explicit solvent molecules. For TS₂ and TS₃/TS_{3s}, the reaction rate enhancement in MeOH can thus be attributed to its higher polarity, as compared to THF, i.e., improved stabilization of the charge separated states. Notably, the energy difference between TS₃ and TS_{3s} increases from 5.8 in THF to 7.0 kcal mol⁻¹ in methanol which could explain the difference in the TMEDA/*N,N*-dimethylglucamine ratio between the two solvents.

In our earlier work, we have also reported on the reductive aminolysis of glucose with *N*-methylethanolamine (MEOA).⁵ For this highly efficient solvent-free reaction, an exceptional

yield of 84 C% of the corresponding C₂ diamine *N,N'*-bis(2-hydroxyethyl)-*N,N'*-dimethyl-ethylenediamine (BHEDMEDA) was obtained in batch mode. Hereto we proposed a stabilization of the C₂ ene-diamine IM (Scheme 1, (7)), that favors the reaction equilibria toward this stable IM. We have successfully identified (see also Figure S9, SI) a stable, cyclic C₂ enamine IM adduct, which was synthesized in the absence of H₂. This oxazolidinic compound (OXAZOL) with a heterocyclic 5-membered ring structure is produced in situ via intramolecular cyclization, as demonstrated in Scheme 2.

Scheme 2. Proposed Stabilization Mechanism via Intramolecular Hydroxyl-Mediated Cyclization of the Unsaturated BHEDMEDA Ene-Diamine Precursor into a Heterocyclic Oxazolidine Compound (OXAZOL)

Thanks to the stability of the OXAZOL IM, its formation from the reaction of glucose and MEOA at 130 °C is highly selective. From Table 3 (entry 2) it can be seen that up to 75 C % OXAZOL was obtained under N₂ in the absence of a metal catalyst.

Formation of this unique stable cyclic IM enables retro-aldol fragmentation and hydrogenation to be decoupled in two separate reaction steps: first under N₂ and then under H₂. The yield of BHEDMEDA is maximized by the selective formation of the desired stabilized OXAZOL IM in the absence of H₂, hereby minimizing irreversible competitive hydrogenation of the enamine IMs (4) and (10) or the carbonyl compounds (1) 709

Table 3. Two-Step Optimization for the Reductive Aminolysis of Glucose with *N*-Methylethanolamine (MEOA) to *N,N'*-Bis(2-hydroxyethyl)-*N,N'*-dimethylethylenediamine (BHEDMEDA) and Its Cyclic Oxazolidine Precursor (OXAZOL)^a

entry	temp _{N2} [°C]	time _{N2} [min]	catalyst _{N2}	temp _{H2} [°C]	time _{H2} [min]	catalyst _{H2}	Y _{OXAZOL} ^b [C%]	Y _{BHEDMEDA} ^b [C%]	Y _{MDEOA} ^c [C%]
1				130	120	Ni-6458P	0	84	3
2	130	120					75	0	0
3	130	120	Ni-6458P	130	120	Ni-6458P	0	92	<1

^aReaction conditions: 1 g of glucose; 30 g of *N*-methylethanolamine (MEOA); 0.3 g of catalyst; 22 bar N₂ and/or 85 bar H₂. Mass balance is not complete due to undesired competitive caramelisation and/or reactions of the Maillard type. ^bProduct yield determined via ¹³C NMR with dioxane as the standard after. ^cProduct yield determined via GC with *N*-methylpyrrolidone (NMP) as the standard.

and (12), prior to the retro-aldol-type C–C scission. Indeed, when the reaction of glucose with MEOA was carried out in two steps, first under N₂ and then under H₂ (Table 3, entry 3), both at 130 °C in the presence of Ni-6458P and in the same reaction vessel, an impressive BHEDMEDA yield of 92 C% was obtained.

The reductive aminolysis with MEOA is a special case. For instance, the reaction of glucose with DMA under N₂ resulted in a dark colored product mixture due to caramelization and browning of the Maillard type.⁵ If no hydroxyethyl (or hydroxypropyl/-butyl) group is present at the N atom of the C₂ ene-diamine ((7), Scheme 1), the precursor is not prone to intramolecular stabilization. Hence, decoupling of retro-aldol and hydrogenation in two separate steps is less effective for DMA aminolysis reactions.

Finally, the detrimental effect of H₂O on the formation of the desired C₂ amines was further confirmed for the reductive aminolysis of glucose with MEOA. When the amount of H₂O in the reaction mixture was increased without changing the molar MEOA-to-glucose excess, systematically less BHEDMEDA was produced at higher H₂O loading. This is illustrated in Figure 8. In the absence of H₂O, 84 C% BHEDMEDA was

evidenced by the increased browning of the product mixture at higher H₂O loading.

4. CONCLUSION

In summary, a mechanism for the reductive aminolysis of reducing sugars with amines is proposed, to our knowledge, for the first time in terms of true elementary steps. This mechanism was validated experimentally, by kinetic and reactivity studies, and theoretically, by DFT calculations. Catalyst screening demonstrated that cheap silica or silica–alumina supported Ni catalysts are highly efficient for the production of the corresponding ethylenediamine (or C₂ diamine). In agreement with the proposed mechanism, it was demonstrated that efficient reductive glucose aminolysis into the corresponding diamine requires at least 6 mol of the aminating agent per mol glucose. The amount of H₂O in the reaction mixture should be kept low (<33 wt %) in order to maintain favorable dehydration equilibria. It was also demonstrated that MeOH selectively promotes the reductive aminolysis by lowering the activation barriers for nucleophilic amine attack, for the formation of the zwitterionic iminium key intermediate and for the subsequent retro-aldol-type C–C scission reaction.

Further research is needed in order to investigate the precise effect of solvent polarity and solvent proticity on the efficiency of reductive aminolysis. In addition, the mechanistic insights that were acquired allow for a detailed investigation of the reaction kinetics and thus for a future kinetic modeling of the presented aminolysis process. Ultimately, the highest yield of C₂ products is obtained from monomeric reducing sugar substrates, since hydrolysis of the glycosidic linkages is inefficient under typical (alkaline) reductive aminolysis conditions. With DMA, typical TMEDA yields of 66 C% are possible. When *N*-methylethanolamine (NMEOA) is used as the amine, intramolecular stabilization of the unsaturated C₂ diamine precursor affords to obtain an excellent 92 C% of the C₂ diamine product (BHEDMEDA). Thanks to the identification of a stable reaction intermediate, the process was optimized by carrying out the reaction in two steps. By supplying H₂ only in the second reaction step, competitive hydrogenation prior to retro-aldol-type C–C scission is eliminated, and hence, the BHEDMEDA yield was successfully improved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b00619.

Additional ¹³C NMR spectra, TPR profiles, DFT optimized geometries, pathway for C₃ amine formation, and additional screening of reaction parameters. (PDF)

Figure 8. Detrimental effect of H₂O on the formation of BHEDMEDA obtained from the reductive aminolysis of glucose with MEOA (at MEOA-to-glucose of 72) and Ni-6458P at 130 °C and 75 bar H₂ after 2 h reaction. Photos of the six product samples illustrate the increased browning at higher H₂O loading.

obtained. Only 69 C% BHEDMEDA was produced in the presence of 19 wt % H₂O. After increasing the H₂O content in the reaction mixture to 32 wt %, the yield of the desired C₂ diamine further decreased to 59 C%. Instead, the yield of the corresponding C₂ aminoalcohol, viz. *N*-methyl-diethanolamine (MDEOA), increased to a limiting extent from 2 C%, in the absence of H₂O, to 3 C% in the presence of 32 wt % H₂O. The major side products that are formed upon addition of H₂O result from caramelization or reactions of the Maillard-type, as

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, U.K., 2004.
- (2) Eller, K.; Henkes, E.; Rossbacher, R.; Höke, H. Amines, Aliphatic. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2012; pp 647–698.
- (3) (a) Weissmehl, K.; Arpe, H.-J. Olefins. In *Industrial Organic Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2007; pp 59–89. (b) Rossberg, M.; Lendle, W.; Pfeiderer, G.; Tögel, A.; Dreher, E.-L.; Langer, E.; Rassaerts, H.; Kleinschmidt, P.; Strack, H.; Cook, R.; Beck, U.; Lipper, K.-A.; Torkelson, T. R.; Löser, E.; Beutel, K. K.; Mann, T. Chlorinated Hydrocarbons. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2000.
- (4) (a) Pelckmans, M.; Renders, T.; Van de Vyver, S.; Sels, B. F. Bio-based amines through sustainable heterogeneous catalysis. *Green Chem.* **2017**, *19* (22), 5303–5331. (b) Froidevaux, V.; Negrell, C.; Caillol, S.; Pascault, J.-P.; Boutevin, B. Biobased Amines: From Synthesis to Polymers; Present and Future. *Chem. Rev.* **2016**, *116*, 14181–14224.
- (5) Pelckmans, M.; Vermandel, W.; Van Waes, F.; Moonen, K.; Sels, B. F. Low-Temperature Reductive Aminolysis of Carbohydrates to Diamines and Aminoalcohols by Heterogeneous Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56* (46), 14540–14544.
- (6) Wang, H.; Ben, H.; Ruan, H.; Zhang, L.; Pu, Y.; Feng, M.; Ragauskas, A. J.; Yang, B. Effects of Lignin Structure on Hydrodeoxygenation Reactivity of Pine Wood Lignin to Valuable Chemicals. *ACS Sustainable Chem. Eng.* **2017**, *5* (2), 1824–1830.
- (7) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
- (8) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H–Pu. *J. Chem. Phys.* **2010**, *132* (15), 154104.
- (9) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
- (10) (a) Pliego, J. R., Jr.; Riveros, J. M. The Cluster-Continuum Model for the Calculation of the Solvation Free Energy of Ionic Species. *J. Phys. Chem. A* **2001**, *105*, 7241–7247. (b) Bryantsev, V. S.; Diallo, M. S.; Goddard, W. A., III Calculation of Solvation Free Energies of Charged Solutes Using Mixed Cluster/Continuum Models. *J. Phys. Chem. B* **2008**, *112*, 9709–9719.
- (11) Frisch, M. J.; et al. *Gaussian 09*, revision E.01; Gaussian, Inc.: Wallingford, CT, 2013.
- (12) Ernst, M.; Hoffer, B. W.; Melder, J. P. Verfahren zur herstellung von aminen aus zuckeralkoholen, WO2009027249 A2, 2009.
- (13) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley: New York, 2001.
- (14) (a) Kroh, L. W. Caramelisation in food and beverages. *Food Chem.* **1994**, *51* (4), 373–379. (b) de Bruijn, J. M.; Kieboom, A. P. G.; Van Bekkum, H.; Van Der Poel, P. W. Reactions of monosaccharides in aqueous alkaline solutions. *Sugar Technol. Rev.* **1986**, *13*, 21–52.
- (15) (a) Hodge, J. E. Dehydrated Foods, Chemistry of Browning Reactions in Model Systems. *J. Agric. Food Chem.* **1953**, *1* (15), 928–943. (b) Martins, S. I. F. S.; Jongen, W. M. F.; van Boekel, M. A. J. S. A review of Maillard reaction in food and implications to kinetic modelling. *Trends Food Sci. Technol.* **2000**, *11* (9–10), 364–373. (c) Nursten, H. The Chemistry of Nonenzymic Browning. In *The Maillard Reaction: Chemistry, Biochemistry and Implications*; The Royal Society of Chemistry: London, 2005; pp 5–30.
- (16) Kennema, M.; de Castro, I. B. D.; Meemken, F.; Rinaldi, R. Liquid-Phase H-Transfer from 2-Propanol to Phenol on Raney Ni: Surface Processes and Inhibition. *ACS Catal.* **2017**, *7*, 2437–2445.
- (17) Poissonnier, J.; Pelckmans, M.; Van Waes, F.; Moonen, K.; Sels, B. F.; Thybaut, J. W.; Marin, G. B. Kinetics of Homogeneous and Heterogeneous Reactions in the Reductive Aminolysis of Glucose with Dimethylamine. *Appl. Catal., B* **2018**, *227*, 161.
- (18) March, J. *Advanced Organic Chemistry* 4th ed.; Wiley: Weinheim, Germany, 1992; pp 896–900.
- (19) Kusserow, B.; Schimpf, S.; Claus, P. Hydrogenation of Glucose to Sorbitol over Nickel and Ruthenium Catalysts. *Adv. Synth. Catal.* **2003**, *345* (1–2), 289–299.
- (20) (a) Jiang, L.; Althoff, E. A.; Clemente, F. R.; Doyle, L.; Röthlisberger, D.; Zanghellini, A.; Gallaher, J. L.; Betker, J. L.; Tanaka, F.; Barbas, C. F.; Hilvert, D.; Houk, K. N.; Stoddard, B. L.; Baker, D. De Novo Computational Design of Retro-Aldol Enzymes. *Science* **2008**, *319* (5868), 1387–1391. (b) Althoff, E. A.; Wang, L.; Jiang, L.; Giger, L.; Lassila, J. K.; Wang, Z.; Smith, M.; Hari, S.; Kast, P.; Herschlag, D.; Hilvert, D.; Baker, D. Robust design and optimization of retroaldol enzymes. *Protein Sci.* **2012**, *21* (5), 717–726. (c) Giger, L.; Caner, S.; Obexer, R.; Kast, P.; Baker, D.; Ban, N.; Hilvert, D. Evolution of a designed retro-aldolase leads to complete active site remodeling. *Nat. Chem. Biol.* **2013**, *9* (8), 494–498.
- (21) Runeberg, J.; Baiker, A.; Kijenski, J. Copper catalyzed amination of ethylene glycol. *Appl. Catal.* **1985**, *17* (2), 309–319.
- (22) Patil, M. P.; Sunoj, R. B. Insights on co-catalyst-promoted enamine formation between dimethylamine and propanal through ab initio and density functional theory study. *J. Org. Chem.* **2007**, *72* (22), 8202–15.
- (23) Zavitsas, A. A. The Relation between Bond Lengths and Dissociation Energies of Carbon–Carbon Bonds. *J. Phys. Chem. A* **2003**, *107* (6), 897–898.
- (24) Safarimian, M.; Paul, S.; Moonen, K.; Ulrichs, D.; Dumeignil, F.; Katryniok, B. Novel direct amination of glycerol over heteropolyacid-based catalysts. *Catal. Sci. Technol.* **2016**, *6*, 2129–2135.