ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Article
Cite This: Org. Process Res. Dev. XXXX, XXX, XXX–XXX
pubs.acs.org/OPRD

Investigating the Underappreciated Hydrolytic Instability of 1,8-Diazabicyclo[5.4.0]undec-7-ene and Related Unsaturated Nitrogenous Bases

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Supporting Information

ABSTRACT: The widespread use of amidine and guanidine bases in synthetic chemistry merits a thorough understanding of their chemical properties. The propensity of these reagents to hydrolyze under mild conditions and generate aminolactams and aminoureas, respectively, has not been adequately described previously. During the synthesis of uprifosbuvir (MK-3682), we became aware of this liability for 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) by observing the formation of an unexpected reaction impurity and traced the root cause to low levels of *N*-(3-aminopropyl)-ε-caprolactam present in the commercial bottle. A controlled stability study over a period of two months at 25 °C demonstrated that, above a threshold water content, DBU steadily hydrolyzed over time. Rates of hydrolysis for DBU, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and *N,N,N′,N′*-tetramethylguanidine (TMG) in organic, aqueous, and mixed solvent systems were then measured to gain a more general appreciation of what conditions to avoid in order to maintain their integrity. Our findings indicate that these bases are hydrolytically unstable in unbuffered and very basic solutions but become significantly more stable in buffered solutions at pH values below 11.6.

KEYWORDS: *hydrolysis, anhydrouridine, uprifosbuvir, DBU, DBN, MTBD*

INTRODUCTION

As synthetic reagents, nitrogen-containing organic bases offer many practical advantages over inorganic bases, such as having less source-to-source variability (i.e., being pure liquids as opposed to the variable hydrates and particles sizes associated with inorganic salts), high solubility of both the conjugate base and conjugate acid in organic solvents, and low water content. When carrying out reactions that require the deprotonating species to have a pK_a higher than amines, amidines[1] and guanidines[2] are indispensable. Compilations of pK_a values for these bases in common solvents including water,[3] DMSO,[4] THF,[5] and acetonitrile[6] aid in choosing an appropriate one.[7] In acetonitrile, for which there is the most complete data set, the pK_a values of tertiary amines fall below 20 (18.8 for triethylamine), while 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and *N,N,N′,N′*-tetramethylguanidine (TMG) have pK_a values ranging from 23.4 to 25.4 (Table 1). The high basicity of these reagents arises from a combination of factors including (1) sp^2-hybridization of the deprotonating nitrogen atom, (2) resonance stabilization of the conjugate acid, and (3) a bicyclic ring system (with the exception of TMG) that ties back the neighboring alkyl functionality and enforces overlap of lone pair electrons of the sp^3-hybridized nitrogen(s) into the neighboring π^* orbital, thereby increasing electron density at the sp^2-hybridized nitrogen.

The exceptional abilities of DBN[8a] and DBU[8b] to promote E2 eliminations of secondary and tertiary alkyl halides, without competing N-alkylation, were first described by Möller,[1d] with the scope later expanded upon by Wolkoff.[8c] Primary alkyl halides and tosylates are prone to competing N-alkylation but can be viable substrates if they have alpha-branching.[9] DBU in particular has found widespread utilization for base-mediated organic transformations including Horner–Wadsworth–Emmons reactions,[10] amide couplings,[11] and an array of other condensations, halogenations,[12] and alkylations.[1] While there are often several basic reagents capable of effecting these reactions, DBU can, in some cases, offer unique advantages. For example, in a recent publication it was shown that of the bases examined, DBU alone could promote 3′-selective functionalizations for a broad range of nucleosides, obviating the need for protecting the typically more reactive 5′ alcohol.[13a] This method was then applied to the stereoselective synthesis of a cyclic prodrug nucleoside linked to a P-chiral phosphoramidate through the 3′ and 5′ positions.[13b] The substitution of organic for inorganic bases can also allow for homogeneous reaction conditions that are more amenable to scale up and continuous flow conditions. As such, an increasing number of reports featuring transition metal-catalyzed transformations mediated by DBU have appeared.[14−16] For Pd-catalyzed cross couplings, the application of organic bases to C–N bond formation has proven more challenging than C–C bond formation, but, through recent advances in the design of supporting phosphine ligands and mechanistic insight, this too has been realized.[15] The implementation of flow-based

Received: April 29, 2019

DOI: 10.1021/acs.oprd.9b00187
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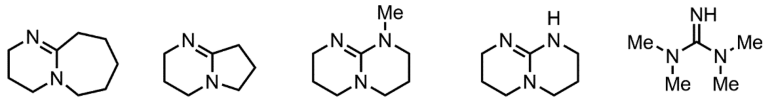
Table 1. pK_a Values of Commercially Available Amidine and Guanidine Bases in Common Solvents[3−6]



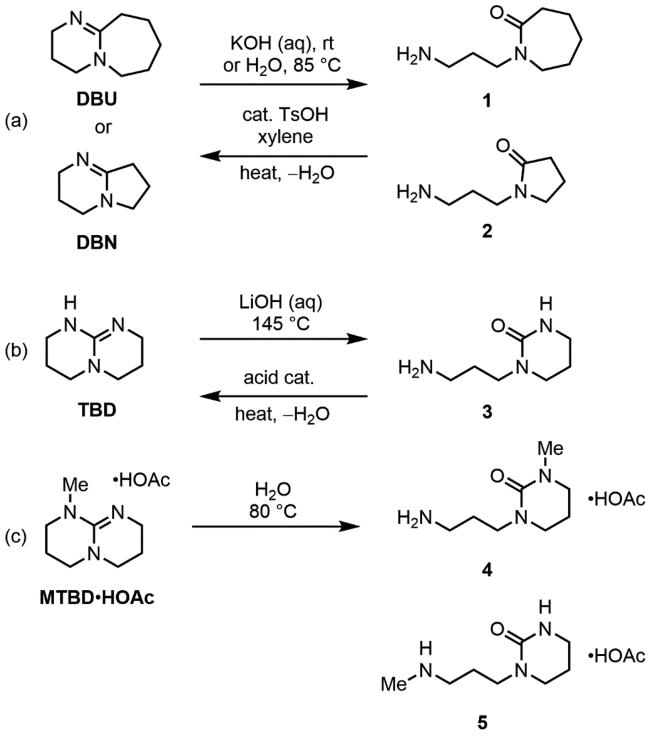
	DBU	DBN	MTBD	TBD	TMG
solvent					
MeCN	24.3	23.8	25.4	26.0	23.4
THF	16.8		17.9	21.0	15.3
DMSO	13.9				
H_2O (expt)	11.5		13.0	14.5	13.6
H_2O (calcd)	13.5		15.0	15.2	13.0

reaction conditions has been demonstrated for Suzuki−Miyaura cross couplings, carbonylative alkoxylations, and phenol alkylations.[16] DBU has also be used for the purification of C_{60} in the presence of higher fullerenes through selective charge-transfer complexation and precipitation.[17]

Although amidines and guanidines are often touted as being non-nucleophilic,[1a,18] this description is only appropriate in relative terms, as when compared to anionic amide and alkoxide bases. Both classes of base are, in fact, quite reactive toward electrophiles as evidenced by their facile reaction with primary and benzylic alkyl halides,[19a,b] chlorophosphanes,[19c] chlorophosphates,[19d] acid chlorides and phenyl carbonates,[19e,f] and carbon dioxide.[19g] Quantitative data collected by Mayr for the reactions of DBU, DBN,[20a] and MTBD[20b] with benzhydrilium ions provides additional evidence of their high nucleophilicity and ranks them all above both DMAP and PPh_3. The rates of N-alkylation for a variety of strong nitrogen-containing bases with iodomethane were subsequently measured by Ronaldo and found to follow similar trends.[21] This inherent reactivity has been capitalized upon for the application of amidines and guanidines as nucleophilic catalysts in a broad array of settings including many types of acyl transfer chemistry, Morita−Baylis−Hillman reactions, carbonylations, silylations, and halogenations.[22] TBD, in particular, exhibits exceptional catalytic abilities owing to a close proximity of H-bond donor and acceptor nitrogens that provides for pathways involving bifunctional cooperativity.[23]

While unsaturated nitrogenous bases provide versatile and broad utility, they are susceptible to hydrolysis, which presents the possibility of generating reactive primary amines. This facet has been most widely recognized and studied for acyclic and aryl amidines.[24] For instance, *N*,*N*-dialkyl formamidines are useful protecting groups for primary alkyl and aromatic amines as they can be cleaved under very mild conditions in a water/alcohol mixture.[24d] In reference to acyclic amidines, de Wolfe has cautioned that they "often hydrolyze on standing in the presence of water, or when they are dissolved in water or an organic solvent containing water."[25] Unfortunately, only scant information is available for the aqueous stability of more commonly used, commercially available bicyclic amidines and guanidines. Half-lives for some of these bases in water at or near room temperature are reported in the online *Encyclopedia of Organic Reagents (e-EROS)*[26] and in a publication by Schwesinger,[27] but without any further supporting details. More widely appreciated is that for preparative purposes, DBU or DBN can be completely hydrolyzed by refluxing in water or at ambient temperature with KOH (Scheme 1a).[28] In the

Scheme 1. Published Conditions for the Hydrolysis of DBU, DBN, TBD, and MTBD·HOAc and Reverse Condensations[28,30−32]



reverse sense, DBU[8b,29] and DBN[8a] are typically prepared by a condensation reaction from their corresponding lactams (**1** and **2**) in the presence of catalytic acid while refluxing in xylene with azeotropic water removal. Similarly, TBD can be prepared from 1-(3-aminopropyl)tetrahydropyrimidin-2(1*H*)-one (**3**) in the presence of an acid catalyst (Scheme 1b).[30] TBD has been fully hydrolyzed with aqueous lithium hydroxide at 145 °C.[31] And in the context of ionic liquids, the resistance of DBN·HOAc and MTBD·HOAc to hydrolysis was studied under a range of temperatures and water contents (Scheme 1c).[32a] Of the two, MTBD·HOAc was found to be considerably more stable but, at 80 °C and above, did hydrolyze extensively to propylene ureas **4** and **5**.

In addition to the reactions shown in Scheme 1, there are sporadic reports of DBU or DBN decomposing by reactions with electrophiles to form N-functionalized products of **1** or **2**.[33] These products are expected to form through one of two pathways depicted in Scheme 2a. For Path A, an amidine is

DOI: 10.1021/acs.oprd.9b00187
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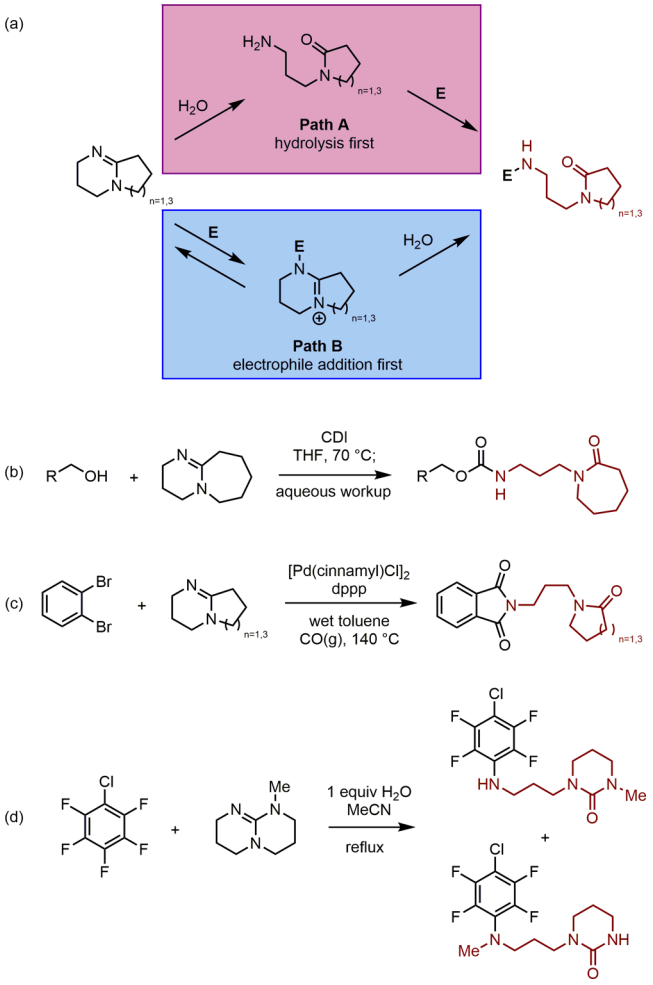
Scheme 2. (a) Two Potential Pathways for DBU or DBN Reacting with Electrophilic Functionality (E), (b) The Conversion of Alcohols to Carbamates with a Combination of CDI and DBU,[34a] (c) Pd-Catalyzed Carbonylative Amidation of 1,2-Dibromoarenes with DBU or DBN to Form Phthalimides,[34b] and (d) An S_NAr Reaction between MTBD and Pentafluorochlorobenzene[34f]



first hydrolyzed to generate a primary amine which can then react with an electrophile. In Path B, an amidine reversibly interacts with an electrophile to produce a cationic intermediate that then reacts with adventitious water or by an aqueous quench. Path A is expected when significant water is present, and Path B expected under strictly anhydrous conditions and/or when certain electrophiles are present. It may not be obvious which path is operative, and evidence that demonstrates the dominance of either pathway is not typically established, save for a few exceptions.[33j,k,m] In one insightful investigation by Wright and co-workers, they reported that when reacting $Pd(OAc)_2$ with a macrocyclic ligand in the presence of DBU and wet THF, a complex was formed with a Pd(II) center bound to ring-opened **1**.[33m] They first suspected Pd(II) was catalyzing the hydrolysis but found that it only occured when DBU was unbound to the metal. This latent reactivity has been capitalized upon to develop methods that produce ring-opened, N-functionalized products.[34] In one example, primary alcohols were treated with CDI and DBU to generate carbamates (Scheme 2b).[34a] It was proposed that DBU reversibly intercepts the intermediate acyl imidazole and subsequently reacts with adventitious water. DBU and DBN have been used as substrates for a palladium-catalyzed carbonylative amidation to form phthalimides from 1,2-dibromoarenes (Scheme 2c).[34b] Lastly, this reactivity manifold has been less developed for guanidines, but MTBD will react with pentafluorochlorobenzene in the presence of one equivalent of H_2O to form N-arylated aminopropylene ureas (Scheme 2d).[34f]

Despite the indications outlined above, we believe that, based on anecdotal comments made in the literature, there is an underappreciation for the propensity of these bases to undergo hydrolysis under mild conditions. In addition to sharing our experience in relation to uprifosbuvir, we aim to educate the broader audience on factors to be cognizant of when using amidine and, to a lesser extent, guanidine bases. In the context of process research and development, a thorough understanding of reagent instabilities is crucial to avoid the generation of new impurities, maintain process robustness, and, when used catalytically, to achieve high turnover numbers. In addition to degradation by reactions with electrophiles as outlined above, it should be anticipated that these bases will hydrolyze to some degree for reactions run in the presence of water,[35] in aqueous workups, and for crystallizations from an aqueous mixture.[17]

Discovery of a DBU-Adduct During Process Development for Uprifosbuvir (MK-3682). One synthetic route to the hepatitis C NS5b inhibitor uprifosbuvir (MK-3682)[36,37] featured, as an intermediate step, the conversion of methyluridine **6** to anhydride **8a** through activation of the 2′-alcohol, followed by a base-mediated intramolecular displacement (Scheme 3).[38] This transformation was initially carried out by using a combination of CDI[39] and KOH but was plagued by inconsistent results due to precipitation and/or gumming of anionic intermediates. An examination of alternative bases revealed DBU to be very effective in promoting the reaction and, most importantly, providing for homogeneous conditions that imparted reproducibility and process robustness. Through a combination of LCMS and in situ NMR and IR studies, we discovered that the combination of **6** and CDI reacts to initially form a mixture of monomeric (**7a**) and dimeric (**7b**) carbonates, irrespective of the stoichiometry. Upon introduction of DBU at elevated temperature, deprotonation of the uracil N−H occurs, allowing for cyclization by way of attack of the adjacent uracil oxygen onto the 2′-position with concomitant loss of CO_2 and proton transfer to generate a mixture of anhydrides **8a** and **8b**. In the final step, anhydrous ethanol is introduced to cleave the remaining carbonate bonds and convert **8b** to **8a**, with generation of diethyl carbonate. Following crystallization, anhydrouridine **8a** is isolated in consistently high yield (avg. of 86%). While this revised process met all of our requirements in terms of reliability, it was accompanied by the generation of a new impurity, carbamate **9**, presumably arising from a side-reaction with DBU. The quantity of **9** generated was typically low, at around 0.1 LC area % (LCAP), and did not immediately pose a quality concern during scaleup, as it was adequately rejected in the crystallization. However, as the program progressed to the process characterization stage, we required greater confidence that neither **9** or its downstream counterparts would persist to API, since these impurities had not been qualified in animal safety studies. As such, we set out to understand its origin and implement a suitable control strategy.

DOI: 10.1021/acs.oprd.9b00187
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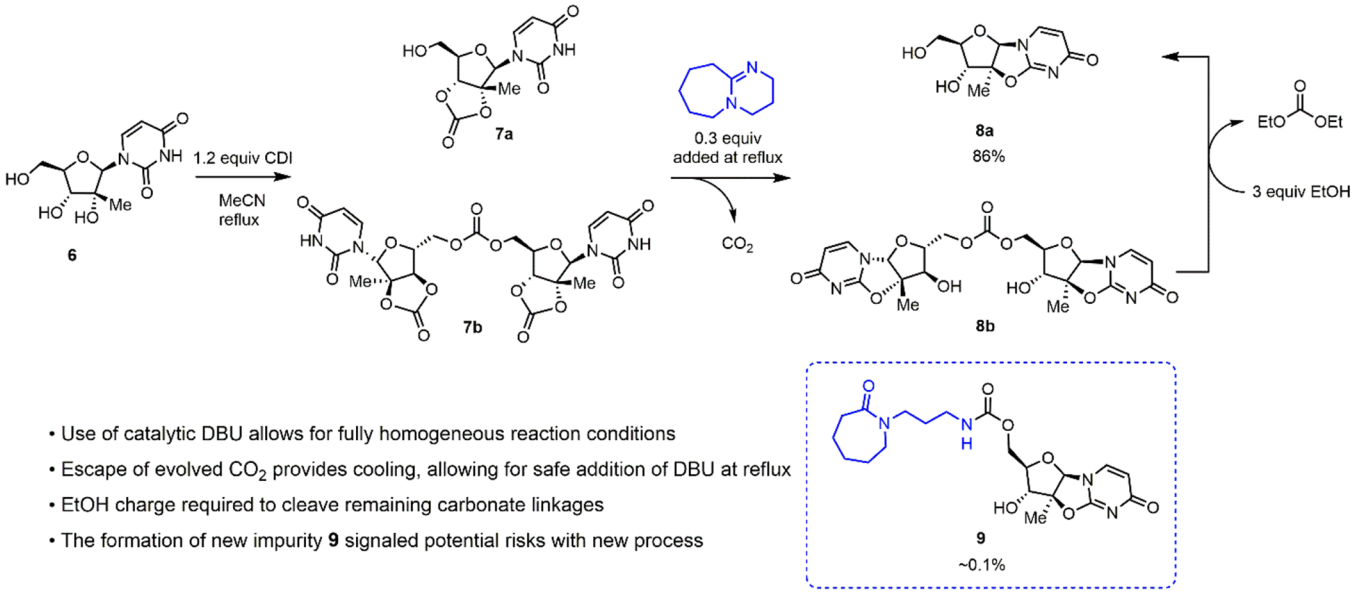
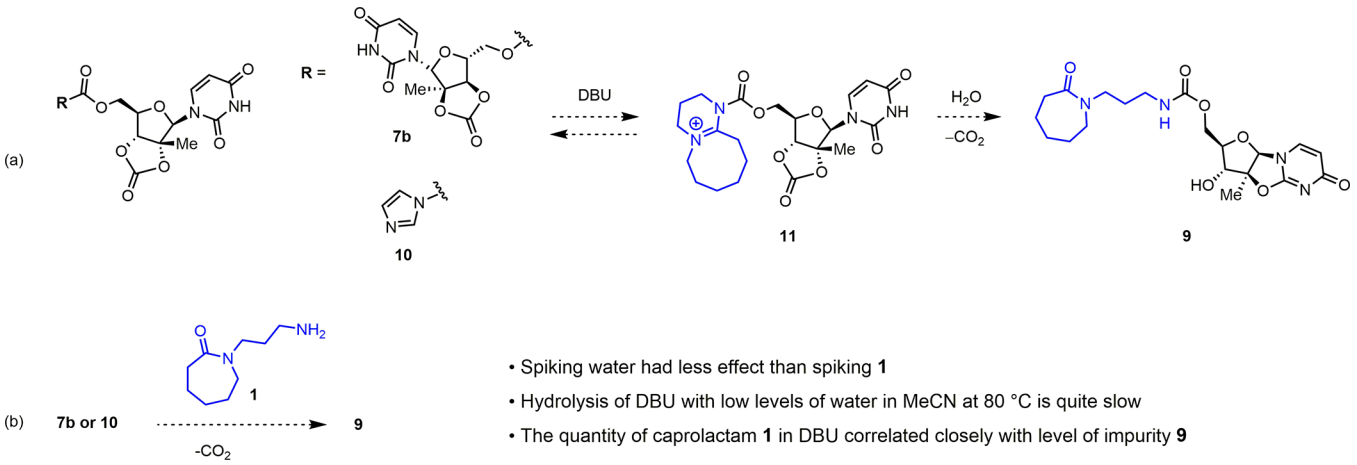
Scheme 3. CDI/DBU Promoted Ring Closure of Methyluridine 6 To Prepare Anhydrouridine 8a Accompanied by Carbamate Impurity 9



Scheme 4. (a, b) Potential Mechanisms for the Formation of Impurity 9



There are two general pathways by which DBU could become incorporated into byproduct **9** as previously outlined in Scheme 2a. If DBU reacts directly with carbonate **7b** or acyl imidazole **10**,[34a] this would generate cationic intermediate **11**, which would subsequently hydrolyze to form carbamate **9** (Scheme 4a). Alternatively, if DBU undergoes hydrolysis in solution or already contains *N*-(3-aminopropyl)-*ε*-caprolactam **1**, this could also react with **7b** or **10** and lead to impurity **9** (Scheme 4b).

The commercial bottle of DBU we were using was analyzed for **1**, and it was found to be present at 0.3 wt % (0.09 mol %). Accounting for a 30 mol % DBU charge, this translates to 0.09 mol % relative to methyluridine **3** and correlates well with the 0.09 mol % of **9** that was generated in the reaction (Table 2, entry 1). The effect of water at multiple stages of this reaction on the formation of **9** was studied. In the first stage of the reaction before addition of DBU, added water has little effect as it likely reacts with CDI. In contrast, spiking water in the second stage along with the DBU (Table 2, entry 2) or the third stage along with the EtOH (Table 2, entry 3) did have a measurable effect on the quantity of **9** formed compared to the standard process conditions in entry 1. Even more strikingly, spiking **1** at four times the amount initially present had the greatest effect, increasing the amount of **9** to 0.51% (Table 2, entry 4). We also examined the stability of DBU to reaction conditions with high water (5600 ppm of H_2O, 80 °C) and found, by ^1H NMR spectroscopy in MeCN-d_3, less than 0.5% hydrolysis over a period of 15 h.

Having several manufacturing campaigns planned to prepare uprifosbuvir, we deemed it necessary to understand the

Table 2. Spiking Experiments To Study the Impact of Water and Amino Lactam 1 on the Formation of Impurity 9

entry	experiment	mol % **9** formed
1	standard conditions[a]	0.09
2	1.4 mol % H_2O added with DBU	0.12
3	5.0 mol % H_2O added with EtOH	0.27
4	0.42 mol % **1** added with DBU	0.51

[a]DBU contained 1100 ppm of H_2O (0.28 mol %/charge) + 0.3 wt % **1** (0.09 mol %/charge).

DOI: 10.1021/acs.oprd.9b00187
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stability of neat DBU to trace water over a period of two months. Accordingly, six stability experiments were run with low (400 ppm), moderate (1900 ppm), and high (4200 ppm) water content at both 25 and 40 °C.[40] These solutions were aged in tightly closed vials with periodic sampling and GC analysis. As shown in Figure 1, there was a steady rise in **1** over time with the largest quantities formed at high water and elevated temperature (up to 3.5% over 2 months).

On the basis of internal quality guidelines, we aimed to limit the maximum amount of impurity **9** in isolated **8a** at 0.15 LCAP. We determined, through a series of crystallization experiments, that up to 0.5% (by GC area) of **1** could be present in the system without exceeding the limit set for **9**. In view of our stability data, we were confident that if we limited exposure to atmospheric water, long-term reagent stability would not be a problem, and the quality standard would be met.

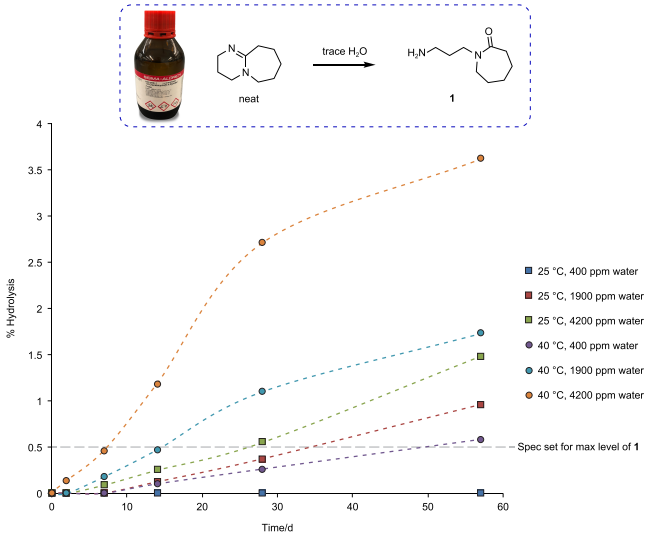

Figure 1. Stability study of neat DBU with variable H_2O content over two months as measured by GC.

Stability of Unsaturated Nitrogenous Bases in Aqueous Mixtures. Having established the sensitivity of DBU to small amounts of water in a MeCN-d_3 solution, we sought a broader understanding of its stability in the presence of larger amounts of water. Gas chromatography was not suitable for monitoring dilute solutions in real time, so we turned to in situ ^{1}H NMR analysis.

We first examined the rate of DBU hydrolysis in pure D_2O at 27 °C. By ^{1}H NMR spectroscopy, peaks corresponding to the CH_2 groups adjacent to the sp^2-hybridized nitrogen in DBU and the amide nitrogen of **1** were clearly resolved (Figure 2). Plotting the reaction progress against time (Figure 3) revealed rapid hydrolysis initially, but then the rate slowed more than expected for pseudo-first-order kinetics, as assessed from a nonlinear relation of ln[DBU] and time (Supporting Information, Figure S2). This kinetic behavior is suggestive of either product inhibition or approaching an equilibrium. A shift in peak position over time suggested that the pD was changing, and this was confirmed by periodic measurement of the solution pH*.[41] At the beginning, we measured a pH* of 13.20, which dropped quickly to 12.98 after 5 h and to 12.62 by 46 h.[42] This pH* drop, because of the conversion of DBU to a less basic primary amine, results in a decreasing pseudo-

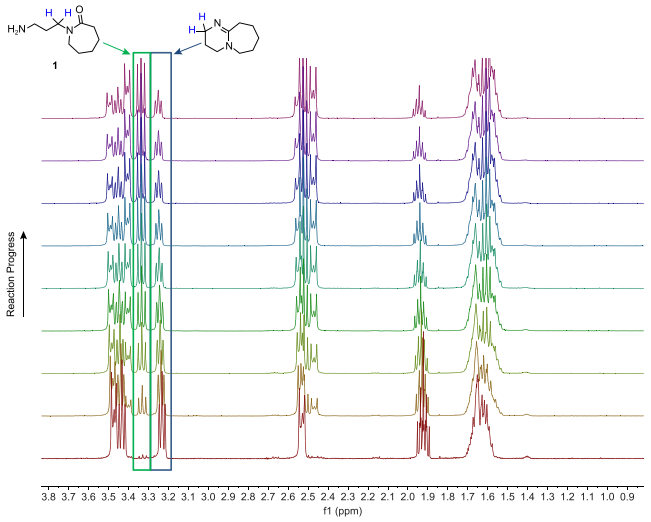

Figure 2. ^{1}H NMR signals for DBU and lactam **1** used to measure % hydrolysis in D_2O.

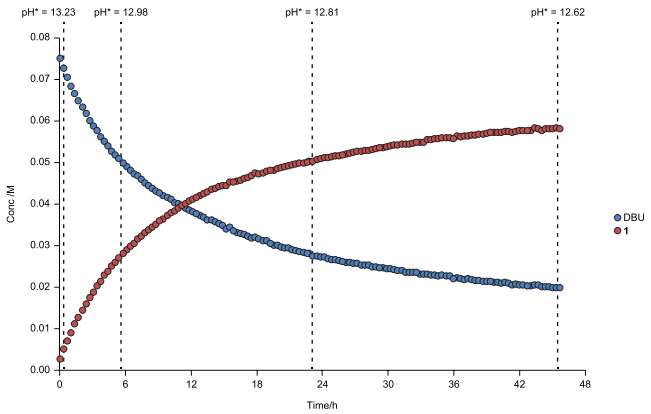

Figure 3. Temporal concentration and pH* profile for DBU hydrolysis in D_2O at 27 °C as measured by ^{1}H NMR spectroscopy.

first-order rate constant over the course of the reaction. For this reason, it is not accurate to state a half-life for this reaction (vide supra) without holding the pH constant.

With the aim to characterize more typical scenarios encountered by organic chemists, we measured the rate of hydrolysis for DBU in aqueous/organic mixtures of D_2O with THF-d_8, MeCN-d_3, EtOH-d_6, DMSO-d_6, or DMF-d_7.[43] In aqueous DMF-d_7 mixtures, hydrolysis was quite sluggish, and, on the basis of a large downfield shift of the peaks, it was evident that there was significant hydrolysis of the solvent.[44] Figure 4 illustrates that, for THF-d_8 and MeCN-d_3, similar rates were measured for aqueous fractions ranging from 100 to 30%, but hydrolysis slowed considerably with less D_2O. We found an unusual profile for EtOH-d_6, in which the rate decreased significantly when a small amount of EtOH-d_6 was added, and then the rate increased for intermediate levels and decreased again for a low volume fraction of D_2O. For DMSO-d_6/D_2O mixtures, up to 50% aqueous fraction had a minimal impact on the rate, and with less D_2O, the rate fell precipitously. There are several potential explanations for these solvent trends: (1) variable water activity as a function of solvent composition,[45] (2) differences in solvent stabilization of water−adduct transition states or intermediates, and (3) variable pD in the different solvent mixtures.[46] It is quite likely

DOI: 10.1021/acs.oprd.9b00187
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

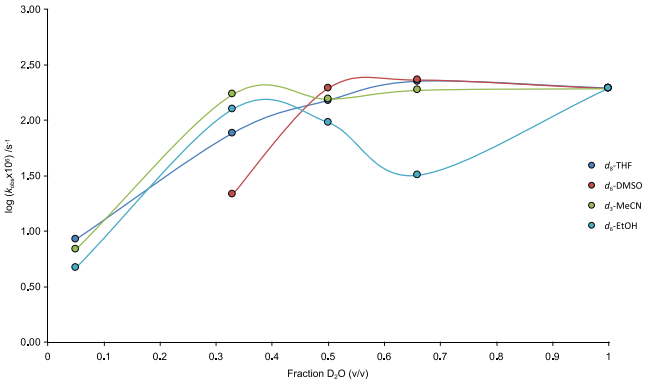

Figure 4. Log ($k_{obs} \times 10^6$) for DBU hydrolysis at 27 °C as a function of solvent composition as measured by ^{1}H NMR spectroscopy.

that all three of these factors are contributing to the rate, but a thorough accounting is beyond the scope of this paper.

Strikingly, a new set of peaks appeared in the ^{1}H NMR traces for these mixed solvent systems, which had been barely detectable in the fully aqueous samples (Figure 5). This species

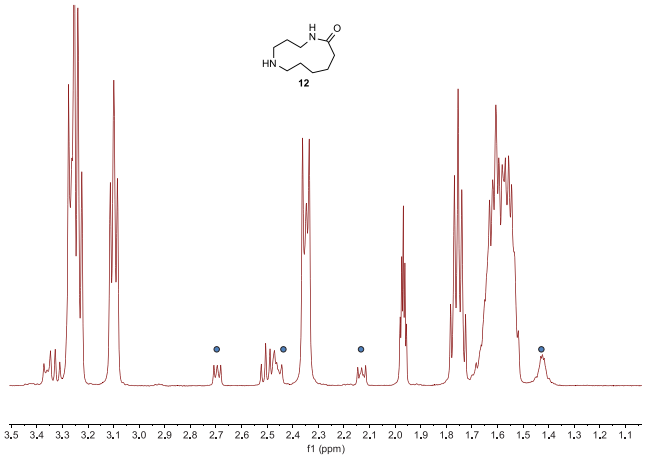

Figure 5. Detection of macrocycle **12** while aging DBU in a solution of 2:1 MeCN-d_3/D_2O at 27 °C by ^{1}H NMR spectroscopy.

grew in quickly, reached a steady state throughout most of the reaction, and then disappeared at the end (see Supporting Information, Figure S4). By tracking and accounting for the concentration of all species, we determined that this compound is ultimately converted to **1**. Through a combination of 2D NMR spectroscopy experiments on the mixture, we assigned the structure to macrocycle **12**. Notably, adducts of this compound have been reported when reacting DBU with benzyl halides in the presence of water.[34c] We tabulated the maximum buildup as a function of solvent composition, presented in Table 3. Two general trends are evident: (1) this intermediate is formed in the largest quantities, at 4.7−8.1% (entries 1−6), when an organic cosolvent is present; (2) in purely aqueous solutions (entries 7−12), there is a maximum buildup at pH* 13.5 (3.1%), and the relative amount decreases sharply at lower pH values.

Given how quickly DBU decomposes in D_2O at 27 °C, we became interested in measuring the relative rates of hydrolysis for DBN and commercially available guanidine bases, as they could potentially serve as substitutes in some situations. In all cases, we were able to monitor the disappearance of starting

Table 3. Maximum Concentration of Macrocycle 12 as a Function of Solvent Composition and pH*

entry	D_2O/organic solutions	% buildup of **12**	entry	D_2O solutions	% buildup of **12**
1	66% EtOH-d_6	6.2	7	unbuffered	1.5
2	66% DMSO-d_6	8.1	8	pH* 12.0	nd[a]
3	66% THF-d_8	6.0	9	pH* 12.5	0.8
4	66% MeCN-d_3	6.4	10	pH* 13.0	2.1
5	50% MeCN-d_3	6.0	11	pH* 13.5	3.1
6	33% MeCN-d_3	4.7	12	pH* 14.0	2.0

[a]nd = not detected.

material over time by ^{1}H NMR spectroscopy (see Supporting Information for product distributions). As seen in Figure 6,

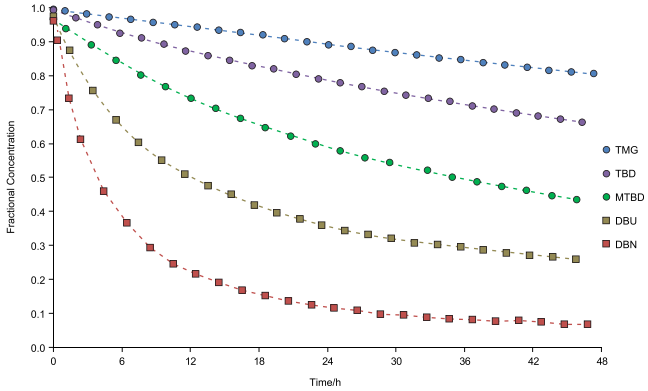

Figure 6. Temporal fractional concentration profiles of amidines and guanidines in D_2O measured at 27 °C by ^{1}H NMR spectroscopy.

DBN is substantially less stable in D_2O than DBU, likely arising from a relief of ring strain upon hydrolysis.[47] As expected, guanidines were more stable due to their greater electron density at the sp^2-hybridized carbon. Of the guanidine series, MTBD hydrolyzed fastest, followed by TBD and then TMG. In contrast to DBU, analogous macrocycles of DBN, MTBD, or TBD were not detected, even in mixed aqueous/organic solvent systems.[48] We also examined Barton's base (2-*tert*-butyl-1,1,3,3-tetramethylguanidine), but no measurable hydrolysis was detected after 24 h. To bridge this data with rates to be expected in protiated water, we measured the solvent kinetic isotope effect (k_{obs} H_2O/k_{obs} D_2O) for each base (Table 4). The values range from 0.32 to 0.71, signaling inverse secondary isotope effects and is consistent with a step other than proton transfer being rate-determining.[49]

Table 4. Solvent Kinetic Isotope Effects ($k_{obs}H_2O/k_{obs}D_2O$)

	DBU	DBN	MTBD	TBD	TMG
solvent KIE	0.71	0.66	0.32	0.48	0.70

Rates of Amidine and Guanidine Hydrolysis as a Function of pH. A firm understanding of the effect of pH is critical in order to avoid operating conditions that will increase the risk of hydrolyzing these reagents. Of relevance to this subject, Wolfenden recently published a study on the hydrolysis of acetamidine, pivalamidine, methylguanidine, and *N*,*N*,*N*′,*N*′-tetramethylguanidine in the pH range of 3.6−10. A linear increase of log k_{obs} versus increasing pH was measured, but high temperatures (140 °C) were needed to

DOI: 10.1021/acs.oprd.9b00187
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achieve reasonable rates.[24a] In contrast, Halliday and Symons studied *N*,*N*′-dimethyl formamidine in the pH range of 11.5−13.5, and in all of the experiments hydrolysis was quite rapid, requiring subambient temperatures (10 °C) to obtain sufficient data density.[24b] In order to deconvolute the pH* effect noted for Figure 3, we measured the rate of hydrolysis in a series of buffer solutions. Consistent with Wolfenden's observations, aging DBU in buffer solutions with pH* values ranging from 0 to 11.6, at 27 °C, did not result in any measurable hydrolysis over a period of 24 h. We also examined the behavior of DBU in the presence of an excess of $MgCl_2$, $CaCl_2$, CuCl, $FeCl_2$, $FeCl_3$, $ZnCl_2$, and in each case, minimal or no hydrolysis was detected. At pH* 11.6 and above, measurable rates were observed, and, in all cases, a linear correlation of log[DBU] vs time was found, indicating that the reaction follows the expected pseudo-first-order kinetics (Supporting Information, Figure S3). We plotted the log of ($k_{obs} \times 10^6$), which ranged from 0.88 s^{-1} to 3.55 s^{-1}, against pH* (Figure 7). On the

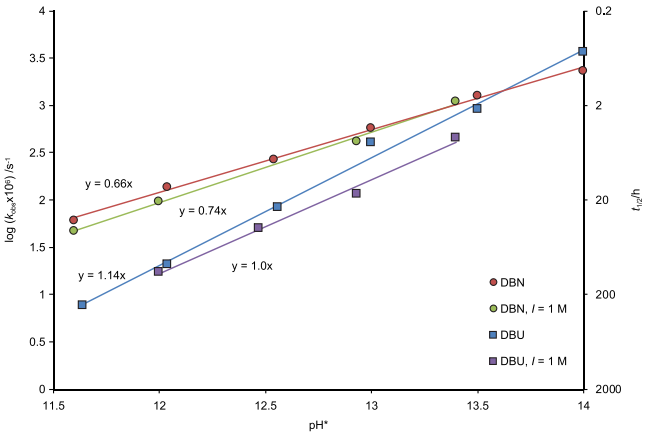

Figure 7. pH*−rate profiles for DBU and DBN measured at 27 °C by ^{1}H NMR spectroscopy.

secondary axis, we show the corresponding half-lives for decomposition, which ranged between 0.53 and 253 h, to aid in interpreting the data. Slopes of 1.1 and 0.66 were found for DBU and DBN, respectively, which directly indicates the order in deuteroxide. It is quite unusual for reaction involving base catalysis to have orders in hydroxide or deuteroxide concentration other than one (specific base catalysis) or zero (general base catalysis).[50] Since the buffer solutions used for experiments had variable ionic strengths,[51] measurements were repeated with solutions having a constant ionic strength of 1 M. A slope of 1.00 was now found for DBU and 0.74 for DBN. Although we did not gather conclusive evidence, we suspect the data collected for DBN is indicative of overlapping mechanisms.[52]

Gathering similar pH*−rate profiles for MTBD and TBD (without strict control of ionic strength) revealed nearly identical slopes of 0.88 and 0.89, respectively (Figure 8, slopes not shown). For TMG however, we see more complicated behavior. Above pH 13.5, the rate begins to become insensitive to deuteroxide concentration. This is often the case for specific base catalysis, in which the tetrahedral intermediate is fully converted to its conjugate base.[42] There is another near-zero dependence on deuteroxide concentration between pH* 12.5 and 13.0 with a decreasing rate below that. A complete mechanistic interpretation was not undertaken, but, the reader

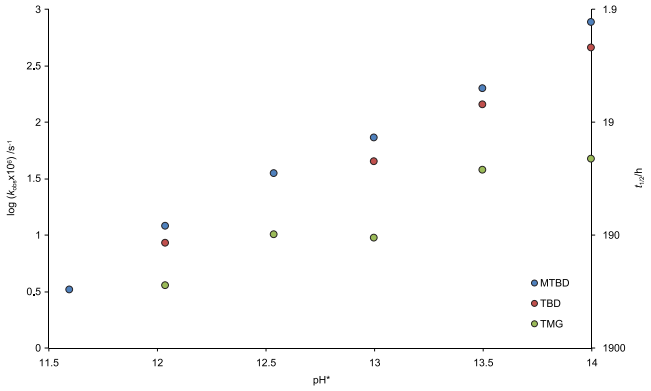

Figure 8. pH*−rate profiles for MTBD, TBD, and TMG at 27 °C measured by ^{1}H NMR spectroscopy.

is directed to literature examples, in which similar behavior for other substrates has been studied in great detail.[53]

CONCLUSION

A summary of our experiments is shown in Table 5, which is meant to provide guidance on conditions when these bases are expected to be stable or not. The first data column shows that neat DBU and DBN (Supporting Information, Figure S1) are stable for extended periods if kept dry, but that even modest amounts of water, which could be present in an old bottle, will cause appreciable hydrolysis over time. The next column is of relevance to running reactions in organic solvents, as it was found that the rate of hydrolysis at 80 °C for 0.07 M solutions of DBU, MTBD, or TMG in MeCN-d_3, containing 5600 ppm of H_2O is negligible. A small amount of hydrolysis was observed for DBN (∼2%) under these same conditions. The next column indicates that all of the bases tested will readily hydrolyze in unbuffered aqueous solutions with the following relative rates: DBN > DBU > MTBD > TBD > TMG. However, as indicated in the final column, if the pH is controlled at 11.2 or below for DBU, DBN, or MTBD, 12.0 for TBD, or 12.5 for TMG, and then hydrolysis at 27 °C is halted. These findings indicate that when these bases are removed from a reaction mixture by aqueous workup, the aqueous phase should be neutral or acidic to limit the risk of hydrolysis and formation of reactive primary amines.

Collectively, the stability data we obtained provided us with confidence that, with the revised procedures for converting methyluridine **6** to anhydrouridine **8a** using a combination of CDI and DBU, the formation of carbamate impurity **9** could be controlled. A root cause analysis for its formation pointed to the major source being the presence of *N*-(3-aminopropyl)-ε-caprolactam **1** in DBU. In addition to characterizing the risks for DBU in this process, we sought a broader understanding of reagent stability for DBU as well as other amidine and guanidine bases. Collectively, our data show that these reagents will readily hydrolyze under mild conditions, and this fact should be considered when designing processes that utilize them.

EXPERIMENTAL SECTION

General. *Reagents and Materials.* Reagents were purchased from commercial suppliers and used without further purification, unless otherwise described. The following were obtained from Sigma-Aldrich: CDI (97%), DBU (≥99%), DBN (≥98%), TBD (98%), MTBD (98%), 2-*tert*-butyl-

DOI: 10.1021/acs.oprd.9b00187
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Table 5. Summary of Base Stability Experiments

	hydrolysis of neat samples 25 °C, 28 days					
	water content (ppm)					
base	400	1500	4000	hydrolysis in d_3-MeCN with 5600 ppm of H_2O 80 °C, 15 h	hydrolysis in H_2O 27 °C, 4 h (%)	pH at which base is stable (<1% decomp) 27 °C, 4 h
DBU	<0.1%	0.37%	0.55%	<0.5%	18	≤11.2
DBN	<0.1%	0.20%	0.37%	~2%	32	≤11.2
MTBD		nd[a]		<0.5%	3.4	≤11.2
TBD		nd		nd[b]	3.8	≤12.0
TMG		nd		<0.5%	1.9	≤12.5

[a]nd = not determined. [b]TBD was not soluble in MeCN-d_3.

1,1,3,3-tetramethylguanidine (≥97%), TMG (99%), glycine, sodium chloride, MOPS (≥99.5%), CAPS (≥98%), CABS (≥98%), 40 wt % sodium deuteroxide in D_2O (99+ atom % D). The following were obtained from Fisher Scientific: Na_2HPO_4 (certified ACS), pH 1.00, 7.00, 8.00, and 10.00 certified buffer solutions. Ethanol-d_6 (99 atom % D) was obtained from Acros. The following were obtained from Cambridge Isotope Laboratories: DMF-d_7 (99.5 atom % D), DMSO-d_6 (99.9 atom % D), MeCN-d_3 (99.8 atom % D). 1-(3-Aminopropyl)azepan-2-one (95%) was obtained from Enamine. D_2O (99.9 atom % D) and THF-d_8 (>99.5 atom %) were obtained from Oakwood. pH 13.00 buffer solution was obtained from Ricca Chemical.

Glycine, NaCl, and Na_2HPO_4 were dried in a vacuum oven at 140−150 °C for 24 h before use. All other reagents were used as received.

(2*R*,3*R*,3a*S*,9a*R*)-3-Hydroxy-2-(hydroxymethyl)-3a-methyl-2,3,3a,9a-tetrahydro-6*H*-furo[2′,3′:4,5]oxazolo[3,2-*a*]-pyrimidin-6-one (**8a**): A 1 L jacketed cylindrical vessel was charged with 180 mL of dry acetonitrile followed by anhydrouridine **6** (35.0 g, 136 mmol). The vessel was charged with CDI (29.3 g, 163 mmol) and rinsed with an additional 50 mL of acetonitrile. After an endotherm, there was a brief exotherm, and the solids dissolved after about 30 min. The solution was heated to reflux with the internal temperature ranging from 80 to 83 °C and aged for 30 min. DBU (6.13 mL, 40.7 mmol) was then added over 30 min via syringe pump (Safety Note: As CO_2 is liberated, this provides adequate cooling such that the reaction is maintained at a safe temperature. As such, it is imperative to allow for the escape of evolved gas). After refluxing for 4−5 h, seed crystals of **8a** (1 wt %) were added followed by addition of punctilious ethanol (1.58 mL, 27.1 mmol). After aging for 2 h to grow the seed bed, an additional charge of punctilious ethanol (15.83 mL, 271 mmol) was added over 3 h via syringe pump. The reaction was aged for an additional 9−12 h and then cooled to room temp over 2 h. The solids were filtered and washed with ethanol. The product was dried under a vacuum at 50 °C. Yield = 28.04 g, 86%. m.p. = 222 °C (DSC) ^{1}H NMR (DMSO-d_6, 600 MHz) δ: 7.86 (d, J = 7.2 Hz, 1H), 6.08 (brs, 1H), 5.94−5.91 (m, 2H), 5.03 (brs, 1H), 4.24 (m, 1H), 4.01 (m, 1H), 1.59 (s, 3H); ^{13}C NMR (d_6-DMSO, 150 MHz) δ: 171.14, 159.19, 137.02, 108.75, 95.28, 92.95, 87.54, 75.69, 60.57, 17.04.

Buffer Preparation.[54] A 10 or 25 mL wide-neck volumetric flask equipped with a magnetic stir bar was charged with the buffer salt and sodium chloride if needed to control the ionic strength. The flask was filled to just below the indicator line with D_2O. With magnetic stirring, the pH* was adjusted with a NaOD solution in D_2O. The stir bar was removed by use of a magnet, and the solution was topped off with D_2O to the indicator level. When calculating ionic strengths of buffers based on the degree of dissociation, pK_a's were corrected for nonideality by use of the Davies equation and for the effect of D_2O (instead of H_2O) according to the method of Bal[41c] (see Supporting Information for complete calculations).

The following buffers were prepared at 0.2 M concentration in D_2O for NMR experiments: pH 2.0 phosphoric acid, pH 4.75 acetic acid, pH 7.0 MOPS, pH 8.4 tris, pH 10.8 CAPS, pH 11.2 CABS, pH 11.6 CABS, pH 11.6 sodium phosphate, pH 12.0 sodium phosphate, pH 12.5 sodium phosphate, pH 13.0 sodium deuteroxide, pH 13.5 sodium deuteroxide, and pH 14.0 sodium deuteroxide.

Analytical Methods. *pH Measurements.* An accumet AP110 pH meter from Fisher Scientific was used in conjunction with a Mettler-Toledo InLab micro pH probe that was calibrated by bracketing with two freshly opened buffer solutions.

KF Measurements. To measure water content in DBU and DBN, a direct injection coulometric KF from Metrohm AG was used following typical procedures as outlined in USP <921> for water determination. System suitability was confirmed prior to use with a fresh 1000 ppm water standard.

GC Measurements. To monitor the conversion of DBU to **1** or DBN to **2** in neat samples, an Agilent DB-5 MS UI bonded phase capillary column (30 m × 0.25 mm, 0.5 μm film) was utilized. Temperature program: 45 °C for 0.5 min; 20 °C/min to 300 °C; hold at 300 °C for 5 min. Injector: 300 °C; 400:1 split Detector: FID at 250 °C Carrier gas: helium, constant flow, 1.3 mL/min. Injection volume: 1 μL. DBU and DBN samples were undiluted.

HPLC Measurements. The conversion of methyluridine **6** to anhydrouridine **8a** and formation of intermediates and impurities were monitored using an Agilent 1190 HPLC with Atlantis T3 column (3 μm, 4.6 mm × 150 mm), part number 186003729. Column temp: 20 °C. Flow rate: 1.5 mL/min detection: 210 nm DAD. Run time: 35 min, 5 min equilibration time. Mobile phase: A: 0.1% H_3PO_4 (aq), B: Acetonitrile. Gradient: 0% solvent B from 0 to 2 min, 0−10% solvent B from 2 to 10 min, 10−95% solvent B from 10 to 30 min, 95% solvent B from 30 to 35 min. Sample diluent: 20:80 methanol/water. Anhydrouridine **8a** has limited solution stability; keep refrigerated. We prepared a dilution of approximately 20x and injected 1 μL. If the cyclic carbonate dimer **7b** was present, we predissolved the sample in a minimal volume of DMSO and then diluted to volume using normal diluent.

DOI: 10.1021/acs.oprd.9b00187
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NMR Measurements. Structure elucidation of the hydrolysis intermediates was performed on a Bruker Avance III 600 MHz spectrometer equipped with a 5 mm TCI cryogenic probe. ^{1}H NMR spectra for kinetic studies were recorded on a Bruker 400 MHz NMR Spectrometer. Chemical shifts are reported in ppm relative to the residual deuterated solvent. A tared 1 mL volumetric flask was charged with the organic base, and the weight was recorded. The volumetric flask was then diluted with the indicated buffer solution to the fill line and shaken until homogeneous. This reaction solution was transferred to a 5 mm NMR tube which was then inserted into the spectrometer for measurements. A delay time of 10 s was used for all kinetics experiments. For experiments in H_2O, a capillary containing D_2O was added for locking purpose, and presaturation was applied on the water frequency (1889 Hz/4.721 ppm) with the following parameters: NS = 8, DS = 4, SW = 8.0 ppm, TD = 32768, AQ = 5.1 s, D1 = 10.

NMR data were aggregated and processed using MestReNova v.12.0.3. Pseudo-first-order rate constants (k_{obs}) were calculated from initial rates using Excel 2010.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00187.

Base screening for the conversion of **6** to **8a**, additional kinetic data, calculated energies of DBU, DBN and hydrolysis products, procedures for the preparation of reaction impurities, NMR spectra for process intermediates and impurities (PDF)

Details on buffer compositions (XLSX)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Pete Dormer, Ryan Cohen, and Alexei Buevich for NMR assistance. We are also grateful to Tom Vickery for assistance with RC1 calorimetry measurements to ascertain the reaction safety. We acknowledge Eugene Kwan, Patrick Fier, Scott Pollack, Ben Sherry, Jon Naber, Rebecca Ruck, and Bill Morris for valuable comments and/or discussions.

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DOI: 10.1021/acs.oprd.9b00187
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