

On the Nature of Rate Acceleration in the Synthesis and Fragmentation of Triazolines by Brønsted Acid: Secondary Catalysis by Water (Hydronium Triflate)

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Abstract: Rate acceleration of the addition of benzyl azide to an electron deficient olefin is characterized using in situ IR spectroscopy. Under strictly anhydrous conditions and at depressed temperature (-20 °C), a triazoline intermediate is selectively formed. The stability of this protonated triazoline intermediate at -20 °C is indefinite, but warming of the reaction mixture to 0 °C or above results in its conversion to the β-amino oxazolidine dione observed under conditions used in our earlier report. As an alternative to warming, the same conversion can be effected by the addition of a single equivalent of water. Our experiments collectively demonstrate the metastability of the protonated triazoline intermediate and secondary catalysis of triazolinium ring fragmentation by water. This behavior is attributed to the ability of water to transfer a proton from N3 to N1 of the triazoline, thereby allowing ring fragmentation and nitrogen expulsion.

Introduction

As part of a long-term goal to identify alternatives to osmiumbased methods for olefin aminohydroxylation,¹ we recently reported the conversion of electron deficient olefin 1 to β -amino oxazolidine diones 2 using an electron-rich azide.^{2,3} The overall reaction requires, and is therefore substantially accelerated by, Brønsted acid (eq 1).⁴ The rate acceleration is consistent with a mechanism in which the electron deficient olefin is activated by Lewis acid complexation, thereby lowering the activation barrier to reaction with the electron-rich (alkyl) azide. Azideolefin dipolar cycloadditions are often sluggish, but the desire to use Lewis acid acceleration is typically compromised by the strong, irreversible binding of azides to Lewis acids.^{5,6}

The overall reaction in eq 1 therefore stimulated our interest in dissecting its mechanistic underpinning as a prelude to broader



development of the reaction's scope with respect to the azide and olefin components. Moreover, knowledge of the transition state leading to formation of the first stereogenic carbon is a prerequisite for rational design of an enantioselective variant. In this first study of mechanism, we have successfully isolated one pathway connecting 1 and 2 that clearly defines the ability of acid to promote both [3+2] azide-olefin cycloaddition (regioselectively) and subsequent decomposition of the triazoline, an intermediate and/or resting state, cleanly to oxazolidine dione. Additionally, we have uncovered a secondary acceleration effect by molecular water in the triazoline ring opening step.⁷

Results and Discussion

Our initial studies of olefin aziridination using triflic acid were performed with commercial triflic acid and handling that followed standard laboratory protocols. Additionally, these reactions were initiated at -20 °C, but then allowed to warm slowly to room temperature at the reaction's end prior to quench and purification. After some scrutinization of the reaction variables, a new reaction product was observed, isolated, and structurally characterized as triazoline 3. This intermediate could be isolated as the sole product when the following constraints

⁽¹⁾ Li, G. G.; Chang, H. T.; Sharpless, K. B. Angew. Chem., Int. Ed. 1996, 35, Li, O. G., Chang, H. T., Sharpless, K. B. Angew. Chem., Int. Ed. 1990, 57, 451. Andersson, M. A.; Epple, R.; Fokin, V. V.; Sharpless, K. B. Angew. Chem., Int. Ed. 2002, 41, 472. Muniz, K. Chem. Soc. Rev. 2004, 33, 166. Donohoe, T. J.; Johnson, P. D.; Pye, R. J. Org. Biomol. Chem. 2003, 1, 2025. Bodkin, J. A.; McLeod, M. D. J. Chem. Soc., Perkins Trans. 1 2002, 7720. 2733.

<sup>2735.
(2)</sup> For examples of Lewis acid promoted azide-carbonyl reactions, see: (a) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. J. Org. Chem. 2005, 70, 10645. (b) Zeng, Y. B.; Reddy, D. S.; Hirt, E.; Aube, J. Org. Lett. 2004, 6, 4993. (c) Hewlett, N. D.; Aube, J.; Radkiewicz-Poutsma, J. L. J.
Control (1997) 400. (2004) (c) Actor (Z003, (6) HOWERT N. D., Rube, J., Rube, J. J. Am. Chem. Soc.
 Org, Chem. 2004, 69, 3439. (d) Katz, C. E.; Aube, J. J. Am. Chem. Soc.
 2003, 125, 13948. (e) Reddy, D. S.; Judd, W. R.; Aube, J. Org. Lett. 2003,
 5, 3899. (f) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.;
 Milligan, G. L.; Aube, J. J. Am. Chem. Soc. 2000, 122, 7226. (g) Rostami,
 A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. Org. Lett. 2007, 9, 703

 ⁽³⁾ For examples of the reaction of azides with carbenium ions, see: (a) Pearson, W. H.; Fang, W. K. J. Org. Chem. 2001, 66, 6838. (b) Pearson, W. H. J. Heterocycl. Chem. 1996, 33, 1489. (c) Pearson, W. H.; Fang, W. K. J. Org. Chem. 1995, 60, 4960.

⁽⁴⁾ Mahoney, J. M.; Smith, C. R.; Johnston, J. N. J. Am. Chem. Soc. 2005, 127, 1354

Lewis acid-azide binding: Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; (5)Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234. (6) L'Abbe, G. *Chem. Rev.* **1969**, *69*, 345.

For a recent demonstration of water catalysis in the gas phase, see: Vohringer-Martinez, E.; Hansmann, B.; Hernandez, H.; Francisco, J. S.; Troe, J.; Abel, B. Science 2007, 315, 497. Smith, I. Science 2007, 315, 470





^{*a*} General conditions: BnN₃ (1.5 equiv) and the olefin (1 equiv) in CH₃CN (0.33 M) were treated with triflic acid at -20 °C. The triflic acid was first premixed with the indicated amount of water to create a stock solution. ^{*b*} Measured by ¹H NMR analysis of the crude reaction mixture after reaction quench (Et₃N, 2 equiv) at the reaction temperature and removal of volatiles by high vacuum. ^{*c*} Reaction mixture was warmed to room-temperature prior to quench.

were carefully followed: (1) the triflic acid was dried and distilled (from Tf₂O)⁸ prior to use, (2) transfer of the triflic acid prevented absorption of ambient humidity, (3) the reaction temperature was carefully maintained at -20 °C or below, and (4) reaction quenching by anhydrous triethylamine was performed at -20 °C.⁹ Following the reaction quench, the exclusion of water was not as critical, but purification by flash chromatography (SiO₂) immediately followed with the removal of volatiles *in vacuo* as the only intervening step. This procedure reproducibly furnishes the analytically pure triazoline **3** in 54% yield.¹⁰

This behavior suggested that adventitious water promoted the formation of 2, and this hypothesis was confirmed by several experiments in which water was intentionally added to reactions that otherwise followed the procedure outlined above (Table 1). We first verified our earlier observation that warming of the reaction mixture, even with strictly anhydrous conditions, produces the oxazolidine dione selectively (Table 1, entry 1) as measured by ¹H NMR of the crude reaction mixture after reaction quench by the addition of dry triethylamine. The protocol involving maintenance of the reaction and quench (triethylamine) at -20 °C, however, provided solely triazoline 3 when no water is added to the reaction, and again using anhydrous triflic acid (Table 1, entry 2). Increasing amounts of added water provided a corresponding shift in the ratio toward oxazolidine dione formation when reaction time was held constant (Table 1, entries 3-5), and oxazolidine dione eventually became the sole product. Addition of water beyond the 200 mol % level ultimately led to complete hydrolysis of 1 without production of either 2 or 3. This result highlighted the direct correlation between water and a three-way balance of the product distribution (triazoline, oxazolidine dione, and hydrolysis products).11



Figure 1. Reaction course observed by *in situ* IR spectroscopy (thermal, anhydrous variation).

Scheme 1. Triazoline Synthesis and Fragmentation Catalyzed by Triflic Acid



To more accurately characterize the effect of water as an additive, the mechanistic picture outlined in Scheme 1 was hypothesized on the basis of the behavior described to this point and in Table 1. We turned to *in situ* IR spectroscopy as a means to monitor the reaction course across a series of procedural changes. Two of the key experiments characterized spectroscopically are summarized in Figures 1-3.¹²

The first experiment focused on the findings that anhydrous conditions lead to the formation of **2** when the reaction is warmed to room temperature prior to quench, but that the presence of water at -20 °C also allowed isolation of **2**. Complexation of imide **1** was evident from the shift of the carbamate carbonyl from 1739 to 1788 cm⁻¹ upon addition of triflic acid to a cold (-20 °C) acetonitrile solution of **1** (Figure 1). Once benzyl azide is added, immediate movement of this absorption to 1747 cm⁻¹ was observed, and complete conversion was achieved within a matter of minutes. Assignment of this new species to triazoline salt **5** is consistent with absorptions at 1711 cm⁻¹ (amide C=O) and 1747 cm⁻¹ (carbamate C=O).

⁽⁸⁾ Sagl, D. J.; Martin, J. C. J. Am. Chem. Soc. 1988, 110, 5827.

⁽⁹⁾ In this discussion, quenching (anhydrous Et₃N) temperature and reaction temperature are always identical.

⁽¹⁰⁾ Azide-olefin cycloadditions (thermal): Huisgen, R.; Szeimies, G.; Mobius, L. Chem. Ber. 1966, 99, 475. Broeckx, W.; Overberg, N.; Samyn, C.; Smets, G.; Labbe, G. Tetrahedron 1971, 27, 3527. Kadaba, P. K. J. Heterocycl. Chem. 1976, 13, 1153.

⁽¹¹⁾ See the Supporting Information for the analogous series of experiments with the crotonate derivative.

⁽¹²⁾ A Mettler-Toledo iC-10 instrument was used for these studies. In situ IR experiments for the following variations are provided in the Supporting Information: (1) thermal conversion, (2) H_2O^{16} catalyzed conversion, (3) H_2O^{18} catalyzed conversion, and (4) thermal conversion followed by H_2O^{18} addition.



Figure 2. Reaction course observed by in situ IR spectroscopy (water additive variation).



Figure 3. Reaction course observed by monitoring oxazolidine dione 2-TfOH formation (1830 cm⁻¹, in situ IR) from triazoline 5 using (a) thermal or (b) water-catalyzed conditions.

The corresponding absorptions in triazoline 3 are 1704 and 1740 cm⁻¹, respectively. Intermediate **5** is indefinitely stable at -20 °C in solution, and triazoline 3 was isolated when this reaction mixture was quenched with triethylamine. When the low temperature bath was replaced with a 25 °C water bath, a change in the IR spectrum occurs (Figure 1). The aforementioned peaks were replaced by new absorptions at 1830 and 1754 cm⁻¹ over the course of several minutes. Visually, gas evolution (N₂) occurred when the reaction temperature was in the 0-25 °C range (Figure 3a and Supporting Information, movie A). Importantly, nitrogen evolution consistently paired with the appearance of the $1830/1754 \text{ cm}^{-1}$ IR absorptions. The IR spectrum of the new species is consistent with product 2.HOTf, which was converted to its free base in the crude reaction mixture by triethylamine addition (examination by ¹H NMR).

In a separate experiment (Figure 2), the same conditions and procedures were applied until the stability of **5** was again apparent (Figure 3b, 0-10 min). Instead of warming the reaction mixture at this point, one equivalent of water was added to the reaction mixture ([H₂O]_{max} = 0.4 mM). The changes in the IR spectrum were both immediate and identical to those induced by warming of the reaction mixture to room temperature (Supporting Information, movie B). In most cases, the conversion was complete within several minutes, and no further change

Scheme 2. Secondary Catalysis by Water: Characterization



was observed by IR.¹³ Neutralization of the reaction mixture again led to observation of **2** by ¹H NMR.

Figure 3 charts the decomposition of **5**, and the formation of **2**·HOTf, as a function of time (a) when the temperature is raised and (b) when water is added to initiate the conversion but the temperature is maintained at -20 °C. Additional control experiments confirmed that isolated triazoline behaved identically to that formed *in situ* (as in the experiments above), and that water alone, without TfOH present, returned only unmodified triazoline even at room temperature. The role of water therefore, is secondary to triflic acid which can catalyze the conversion of **3**→**2** unassisted, if the proper amount of thermal energy (above -20 °C) is supplied. Water alone is not a competent catalyst, but the combination of triflic acid and water will promote the conversion at -20 °C, clearly requiring less thermal energy (Scheme 2).

The first steps in the triazoline decomposition¹⁴ (isomerization of **5** to **6**, and of **6** to **7**) do not require consumption of water. However, formation of **2** can occur by either cleavage of the methyl–oxygen bond in **7** by S_N2 attack of a nucleophile (e.g., CH₃CN), or hydrolysis of **7** (leading to the production of MeOH). Since oxazolidine dione **2**·TfOH was the next spectroscopically observed and isolated product from both anhydrous-thermal and low temperature water catalyzed reactions, its formation under these very different conditions from putative intermediate salt **7** needed to be rectified. The operative pathways were identified using three experiments and the use of $H_2^{18}O$.

The thermal procedure for decomposition of the intermediate triazoline was applied, and $H_2^{18}O$ was added prior to the usual quench. In this case, the spectrum of **2** (¹⁶O) was observed (Figure 4a,c), as in the analogous case when $H_2^{16}O$ was used. This behavior is consistent with nucleophilic cleavage of the methyl–oxygen bond by acetonitrile solvent. Indeed, an absorption at 2418 cm⁻¹ in this experiment (*in situ* IR) prior to reaction quench is consistent with the formation of [CH₃NCCH₃]⁺.¹⁵ When the heavy isotope was used as the water additive at

⁽¹³⁾ Note that times and intensity in Figures 3 and 5 are relative to allow the overlay of separate experiments.

⁽¹⁴⁾ Smith, R. H.; Wladkowski, B. D.; Taylor, J. E.; Thompson, E. J.; Pruski, B.; Klose, J. R.; Andrews, A. W.; Michejda, C. J. J. Org. Chem. 1993, 58, 2097. Hunig, S.; Schmitt, M. Liebigs Ann. 1996, 559. Schmiedekamp, A.; Smith, R. H.; Michejda, C. J. J. Org. Chem. 1988, 53, 3433.



Figure 4. Comparison of 2 (¹⁶O) respectively 8 (¹⁸O:¹⁶O \approx 2:1), and H₂¹⁸O-catalyzed experiments (Scheme 3). ¹³C NMR (125 MHz) spectra of oxazolidine dione (a) 2 (¹⁶O) formed from thermal triazoline decomposition (H₂¹⁸O quench), and (b) 8 formed by H₂¹⁸O-catalyzed triazoline decomposition at -20 °C; (c) IR of oxazolidine diones formed from the thermal experiment and three variations, including H₂¹⁸O catalyzed triazoline decomposition decomposition leading to ¹⁸O incorporation.

-20 °C, the IR of the oxazolidine dione that resulted was similar to that observed when using H₂¹⁶O, but with the carbamate

Scheme 3. Isotope Labeling Experiments to Ascertain Role and Fate of Water in Both Thermal and Water-Catalyzed Triazolinium Fragmentations



C=O shifted from 1819 to 1799 cm⁻¹, consistent with **8** (Figure 4c). The ¹³C for **8** also exhibits the characteristic isotope-induced chemical shift for the carbamate oxygen, consistent with \sim 66% ¹⁸O enrichment (Figure 4b).¹⁶ The transformations depicted in Scheme 3 summarize this behavior in the context of mechanism following the triazolinium fragmentation.

We propose two roles for water in this reaction. A full equivalent is ultimately consumed in the hydrolysis of oxonium intermediate 7. Additionally, the evidence suggests that water accelerates the triazoline fragmentation, particularly by catalyzing the preceding isomerization (a nonhydrolytic process). The irreversible expulsion of nitrogen allows these two roles to be deconvoluted since the visual evolution of N₂ allows us to pinpoint rate acceleration at the triazoline ring-opening step (see movies A and B). Were this not the case, an alternate explanation for the observed water effect would normally be the existence of an equilibrium whose product is consumed by water in a chemical reaction, thereby leading to the disappearance of the monitored species through reconstitution of the equilibrium. These observations are consistent with secondary *catalysis* of the triazoline decomposition step by water.¹⁷ It is also important to note that reactions to which water is added at the beginning typically result in slower overall conversion of $1 \rightarrow 2$. Since the first step is Lewis acid catalyzed, this behavior is consistent with hydronium's lower Lewis acidity relative to triflic acid. This character is clearly reversed in the second step where the Lewis acidity of hydronium triflate and triflic acid are unchanged, but their mobility is the determinant of rate.

Triazoline Stability and Additional Effects. Scheme 2 summarizes the behavior of the intermediate triazoline. The free

⁽¹⁵⁾ Booth, B. L.; Jibodu, K. O.; Proenca, M. F. J. Chem. Soc., Chem. Commun. 1980, 1151.

^{(16) 95%} H₂¹⁸O (Aldrich) was used. Both HRMS and ¹³C NMR indicated incorporation of ¹⁸O (ca. 65%: acetonitrile conversion of 7 to 2 is competitive with hydrolysis of 7). See Supporting Information for complete details. Isotope ¹³C induced shift: Risley, J. M.; Vanetten, R. I. J. Am. Chem. Soc. **1979**, 101, 252. Vederas, J. C. J. Am. Chem. Soc. **1980**, 102, 374.

⁽¹⁷⁾ For examples where added water modifies a catalyst, thereby adversely affecting reactivity and/or selectivity, see the following reviews: (a) Ribe, S.; Wipf, P. Chem. Commun. 2001, 940. (b) Lindstrom, U. M. Chem. Rev. 2002, 102, 2751. (c) Kobayashi, S.; Manabe, K. Acc. Chem. Res. 2002, 35, 209. Selected examples: (d) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. J. Am. Chem. Soc. 1987, 109, 5765. (e) Narasaka, K.; Tanaka, H.; Kanai, F. Bull. Chem. Soc. 1987, 109, 5765. (e) Narasaka, K.; Terada, M.; Nakai, T. J. Am. Chem. Soc. 1990, 112, 3949. (g) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. Org. Lett. 2004, 6, 1861. (h) Nyberg, A. I.; Usano, A.; Pihko, P. M. Synlett 2004, 1891. (i) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. Tetrahedron Lett. 1988, 29, 3967. (j) Tottie, L.; Baeckstrom, P.; Moberg, C.; Tegenfeldt, J.; Heumann, A. J. Org. Chem. 1992, 57, 6579. (k) Denmark, S. E.; Sweis, R. F. Org. Lett. 2002, 4, 3771. (l) Davis, F. A.; Zhang, Y.; Qiu, H. Org. Lett. 2007, 9, 833. (m) Xia, Y. Z.; Liang, Y.; Chen, Y. Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y. H.; Yu, Z. X. J. Am. Chem. Soc. 2007, 129, 3470.

base is indefinitely stable to water in the absence of added Brønsted acid. In our experience, the triazoline is also indefinitely thermally stable up to temperatures of (at least) 100 °C.¹⁸ This behavior contrasts that of the triflic acid salt, which is indefinitely stable at low temperature (-20 °C) when anhydrous, but will convert concomitant with nitrogen evolution when warmed to room temperature. These three behaviors indicate that the triazoline stability is primarily controlled by the polarization provided by Brønsted acid. However, the effect of water further accelerates the rate of triazoline decomposition, and this can be clearly quantified at -20 °C. The overall transformation produces oxonium ion 7, which then consumes one equivalent of water. Water is still a catalyst for the triazolinium fragmentation, since the isomerization and cyclization steps do not consume water. The evolution of nitrogen provides a corroborating indicator that fragmentation is catalyzed under these conditions.19

It was not clear to us why the triazolinium intermediate might exhibit this behavior, since its stability would need to be rationalized by a reluctant proton transfer. Calculations have determined N3-protonation can be favored over N1 by as much as 10 kcal/mol, but N1 protonation is in equilibrium and leads to irreversible triazoline decomposition in studies of the triazoline-aziridine interconversion.¹⁴ The stability of **5a/b** is therefore surprising, particularly since a number of capable proton carriers can be identified in the reaction mixture, including a second triazolinium or simply the abundant acetonitrile solvent. Proton "immobilization" is often perceived to require the design of special Brønsted bases^{20,21} that bear no resemblence to the intermediates at play here.

A final test of this reasoning was made by monitoring the water catalysis phenomenon under conditions of excess triflic acid. If protonation at N3 is nonlabile and electronically stabilizes the triazoline toward N1-N2 fragmentation, then excess triflic acid would not be expected to overcome this effect; although protonation at N1 might be possible (to form the doubly protonated triazoline), protonation at N3 would prevent proper polarization for N1-N2 fragmentation. Furthermore, addition of water to the bis(salt) would enhance proton mobility, but oxazolidine dione formation might be slower because of protonation of the carbamate oxygen in the cyclization step or because of slower triazoline fragmentation (via formation of monosalt 5c from a bis(salt). Both of these predictions were confirmed by experiment (Figure 5). The triazoline was indefinitely stable toward two equivalents of triflic acid at -20 °C in the absence of water. And addition of water promoted triazoline fragmentation again, but oxazolidine dione formation was markedly slower (Figure 5b) than the rate observed with a single equivalent of triflic acid (Figure 5a).



Figure 5. Comparison of water catalyzed triazolinium fragmentations (monitoring oxazolidine dione formation at 1830 cm⁻¹) using (a) 1 equiv and (b) 2 equiv of triflic acid (water added at 10 min).

Water Catalysis. Water may specifically lower the barrier to isomerization of **5b** to **5c**.^{14c,22} The stability of **5b** may be a general phenomenon of anhydrous triazoline salts or may be due to a bidentate proton chelate.²³ It is not possible to further discriminate details of the isomerization process. For example, the water molecule could shuttle the proton (as hydronium) from N3 to N1 of the triazoline. Alternatively, it could competitively bind to the carbamate system, allowing an agent such as solvent to play the role of shuttle.²⁴

Although the mechanism advanced in Scheme 1 suggests a discrete diazonium ion 6, we cannot exclude the possibility that this intermediate is bypassed by a single transition state in which carbon-oxygen bond formation is concomitant with triazoline fragmentation. The depressed rate of formation of oxazolidine dione observed when using excess triflic acid is consistent with this possibility as well.

The role of water in chemical transformations has been studied under innumerable circumstances, leading to a broad range of effects.^{17,19} In particular, scrutiny of the integrated behavior of water, as both substrate and ancillary catalyst, in the hydrolysis of ester derivatives has been studied in numerous contexts as well, and with methods both experimental²⁵ and computational²⁶ in nature. Furthermore, studies of protontransfer catalysis range from mechanistic²⁷ to biochemical²⁸ contexts and have been used as a basis to explain a wide range of phenomena. The case described here is unique to our knowledge in that water catalyzes a nonhydrolytic step in a nonaqueous solvent. The circumstances allow a clear demon-

- (27)Chou, P. T.; Yu, W. S.; Wei, C. Y.; Cheng, Y. M.; Yang, C. Y. J. Am. Chem. Soc. 2001, 123, 3599.
- (28) Derat, E.; Shaik, S.; Rovira, C.; Vidossich, P.; Alfonso-Prieto, M. J. Am. Chem. Soc. 2007, 129, 6346.

⁽¹⁸⁾ Rejzek, M.; Stockman, R. A.; van Maarseveen, J. H.; Hughes, D. L. Chem. Commun. 2005, 4661. Dahl, R. S.; Finney, N. S. J. Am. Chem. Soc. 2004, 126, 8356. Allemann, S.; Vogel, P. Synthesis 1991, 923.

⁽¹⁹⁾ Water can generally provide varying effects in catalysis different from the Water can generary provide varying enects in catalysis different non-the secondary catalysis described here, for example: Hayashi, Y. Angew. Chem., Int. Ed. 2006, 45, 8103. Kjaer, A. M.; Sorensen, P. E.; Ulstrup, J. J. Chem. Soc., Perkins Trans. 2 1978, 51. Pirrung, M. C.; Das Sarma, K. J. Am. Chem. Soc. 2004, 126, 444. Pirrung, M. C. Chem.—Eur. J. 2006, 12, 1312. Kleiner, C. M.; Schreiner, P. R. Chem. Commun. 2006, 4315. Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. Angew. Chem., Int. Ed. 2007, 46, 3798. Brogan, A. P.; Dickerson, T. J.; Janda, K. D. Angew.

^{Chem., Int. Ed. 2007, 40, 5785. Didgan, A. F., Dickelson, T. J., Janda, K. D. Angew.} Chem., Int. Ed. 2006, 45, 8100.
(20) Alder, R. W.; Goode, N. C.; Miller, N.; Hibbert, F.; Hunte, K. P. P.; Robbins, H. J. J. Chem. Soc. Chem. Comm. 1978, 89.
(21) Cheney, J.; Lehn, J. M. J. Chem. Soc. Chem. Comm. 1972, 487.

⁽²²⁾ Krishtalik, L. I. Biochem. Biophys. Acta 2000, 1458, 6.

⁽²³⁾ Williams, A. L.; Johnston, J. N. J. Am. Chem. Soc. 2004, 126, 1612. Nugent, B. M.; Yoder, R. A.; Johnston, J. N. J. Am. Chem. Soc. 2004, 126, 3418.

⁽²⁴⁾ Water catalysis of hydrogen exchange: Gregory, R. B.; Crabo, L.; Percy,

 ⁽A) J.; Rosenberg, A. Biochemistry 1983, 22, 910.
 (25) Batts, B. D.; Gold, V. J. Chem. Soc. Inorg. 1969, 984. Gopalakrishnan, G.; Hogg, J. L. J. Org. Chem. 1989, 54, 768. SlebockaTilk, H.; Rescorla, C. G.; Shirin, S.; Bennet, A. J.; Brown, R. S. J. Am. Chem. Soc. 1997, 119, 10969. Smith, I. Science 2007, 313, 470. Venkatasubban, K. S.; Bush, M.; Ross, E.; Schultz, M.; Garza, O. J. Org. Chem. 1998, 63, 6115. Venkatasubban, K. S.; Davis, K. R.; Hogg, J. L. J. Am. Chem. Soc. 1978, 100, 6125

⁽²⁶⁾ Barbosa, L.; van Santen, R. A. THEOCHEM 2000, 497, 173. Pitarch, J.; Ruiz-Lopez, M. F.; Silla, E.; Pascual-Ahuir, J. L.; Tunon, I. J. Am. Chem. Soc. 1998, 120, 2146.

stration of the interplay between Brønsted acid and water on both cycloaddition and triazoline fragmentation steps.

Conclusion

In summary, we have identified the intervening steps in the Brønsted acid-catalyzed conversion of olefin 1 to oxazolidine dione 2. Significant rate acceleration is provided by triflic acid to the azide-olefin addition step, leading to an intermediate triazoline under anhydrous conditions that has been characterized by *in situ* IR spectroscopy.²⁹ Triazoline•HOTf (**5a/b**) is, at a minimum, a resting state along this pathway, and its stability is significantly altered by the presence of water. Our current hypothesis is that the isomerization of triazoline to oxazolidine dione requires protonation of N1, and that bidentate complex **5b** is favored under anhydrous conditions at low temperature (-20 °C).

We have further characterized the effect of water on the triazolinium stability in which it works in concert with triflic acid at low temperature to promote triazoline fragmentation in a nonhydrolytic step. There is a balance to be observed, however, in the overall conversion: triazoline formation is most rapid with conditions of high Lewis acidity and anhydrous TfOH, whereas triazoline fragmentation is most rapid with a single equivalent of TfOH and water. Furthermore, excess triflic acid retards triazoline fragmentation, and excess water can lead to hydrolysis of the imide. A conclusion from this study is a cautionary one in that the feasibility of a proton-catalyzed process cannot be established (or studied) by protonation state alone but must also include charged ligands (the counterion) and perhaps neutral ligands such as water.

This work provides an experimental basis for the discovery and characterization of other organic reactions in which water might play the role of a secondary catalyst in the condensed phase,⁷ and may help to explain similar phenomena involving hydrogen bond acceptors. Regardless, these findings complement the classic examples of Alder²⁰ and Lehn²¹ in which unique ligands were developed to immobilize the proton by tight binding.

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Supporting Information Available: Preparation, analytical data, and spectra for all new compounds; full data sets for the experiments described; movies corresponding to experiments in Figures 1-3 at the point of nitrogen evolution.

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⁽²⁹⁾ Azide-olefin cycloaddition solvent effects: Kadaba, P. K. Tetrahedron 1969, 25, 3053. Kadaba, P. K. Tetrahedron 1966, 22, 2453.