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Unusual Stability and Carbon Acidity of a Dicationic Carbon Species

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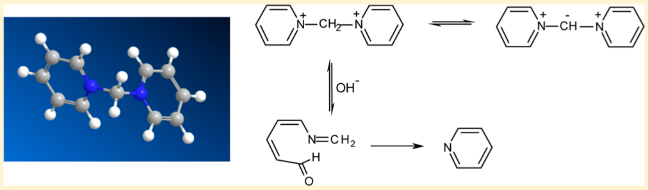
Supporting Information

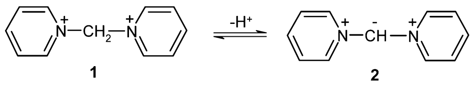
ABSTRACT: 1,1′-Methylenebis(pyridinium) dication (MDP) is an unusual ion with two formal positively charged substituents attached to a central carbon, yet it is remarkably stable to hydrolysis at pH < 8. However, above this pH it undergoes a biphasic reaction liberating two equiv of pyridine sequentially. The rate of the first phase is second order in hydroxide ion, while that of the second is pH-independent. The first phase is also accompanied by the generation of a chromophore at 366 nm, which has been identified as a pyridine-ring-opened unsaturated iminoaldehyde formed by an ANRORC-type mechanism. This intermediate then undergoes ring closure to give the second equiv of pyridine and formaldehyde. Below pD 8 there is a very slow alternative pathway for degradation that is first order in hydroxide ion, liberates only one equiv of pyridine, and forms *N*-(hydroxymethyl)pyridinium ion. Deuterium exchange of the central methylene in D_2O is faster than the breakdown of MDP and is predominantly OD^--catalyzed with a small amount of buffer catalysis. The estimated pK_a of MDP dication in H_2O, 21.2 at 25 °C and $I = 1.0$ M (KCl), is unexpectedly high but is about 9 units lower than that for the monocationic *N*-methylpyridinium ion. Deuterium exchange also occurs at the 2 and 6 positions of the pyridinium rings, but at a lower rate that is first order in deuteroxide ion and competitive with the breakdown of MDP only below pD 11.



■ INTRODUCTION

A central methylene to which is attached two positively charged pyridinium ions, as in 1,1′-methylenebis(pyridinium) dication (MDP, **1**), would appear to be intrinsically reactive and to be a reasonably strong carbon acid, as ionization would produce the ylide **2** (Scheme 1). MDP is surprisingly easy to make from the reaction of pyridine with an excess of methylene chloride.[1] ^1H and ^{13}C NMR spectra show the charged pyridinium ion and the strongly downfield-shifted ^1H NMR CH_2 peak at 7.65 ppm.[2] The crystal structure of MDP dichloride does not show any unusual structural features, with NCN and HCH bond angles of 110° and 108°, respectively, and a H_2C-N bond length of 147 pm, which is not significantly different from the 146−148 pm seen in *N*-methylpyridinium ions.[3]

Scheme 1



The hydrolysis of MDP is expected to yield two equiv of pyridine and 1 equiv of formaldehyde, but although nucleophilic attack on the central carbon is anticipated to be facile, it is known that some activated pyridines and other azines are also susceptible to the ring addition of nucleophiles, giving rise to alternative reaction pathways.

We report here a kinetic study of the hydrolysis and deprotonation of MDP in H_2O and D_2O as a function of pH/pD and buffer type and concentration. The data identify an unusual intermediate during the hydrolysis reaction and the kinetic acidity of MDP.

■ RESULTS AND DISCUSSION

(i). Kinetics and Mechanism of Hydrolysis of MDP.

Despite the anticipated instability of MDP dication **1**, it is remarkably stable in aqueous solution. For example, it remains unchanged in 0.1 M deuterium chloride (DCl) at 25 °C after 4 weeks and at 50 °C after 2 weeks. At higher pH, however, reactions occur that can be monitored by ^1H NMR, UV−vis, and GC−MS.

At pH > 9, a chromophore appears at 366 nm, the absorbance of which increases with time, reaches a maximum, and then decreases (Figure 1), indicative of the formation of an unstable intermediate **I** (Scheme 2). The observed consecutive first-order rate constants associated with this biphasic behavior were determined as a function of pH. The pseudo-first-order rate constant k_1 for the first phase and the appearance of the chromophore **I** (Scheme 2) shows a second-order dependence on the concentration of hydroxide ion (Supporting Information Figure S6), giving a third-order rate constant of 5.47×10^4 M^{-2} s^{-1}, whereas k_2 for the second phase and disappearance of the intermediate is pH-independent with a value of 6.0×10^{-5} s^{-1}.

The aqueous reactions of MDP could also be monitored in deuterium oxide (D_2O) by monitoring changes in the ^1H NMR spectrum. MDP shows the expected proton signals of the pyridinium ring at 9.38 (C2/6), 8.85 (C4), and 8.33 (C3/5)

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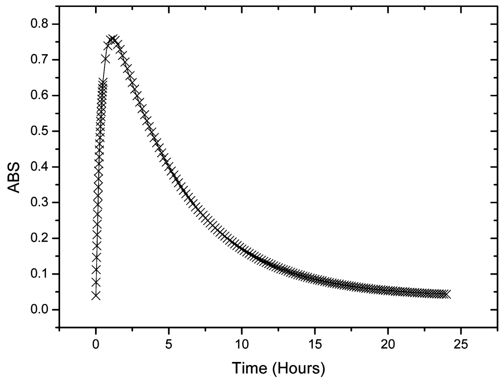


Figure 1. Change in absorbance at 366 nm with time for the hydrolysis of MDP (1.0×10^{-4} M) at pH 10.0 (20 mM CAPS buffer) with $I = 0.1$ M (KCl) at 25 °C. The continuous line shows the fit of the data to the model of Scheme 2.

Scheme 2

$$\mathrm{MDP} \xrightarrow{k_1} \mathrm{I} \xrightarrow{k_2} \mathrm{P}$$

ppm and the bridging CH_2 singlet at 7.47 ppm. The fastest reaction corresponds to deuterium exchange of the central methylene, as shown by the disappearance of the signal at 7.47 ppm. The relevance of this process to the carbon acidity of MDP and the slow deuterium exchange at positions C2 and C6 of the pyridinium rings will be discussed later.

Between pD 7.20 and 10.0 there is also a decrease in the intensity of the pyridinium ring protons of MDP at C2 and C6 due to deuterium exchange. At lower pD, this exchange reaction is competitive with hydrolysis, so some of the pyridine formed had undergone deuterium exchange at C2/6, as indicated by the ratios of the integrated ^{1}H NMR signals at 8.53 (C2/6), 7.90 (C4), and 7.47 (C3/5) ppm. With sodium acetate as an internal standard, the changes in signal intensities with time were used to determine the pseudo-first-order rate constants for the disappearance of MDP and the appearance of pyridine. Those for the latter were biphasic, compatible with a stepwise formation of the expected two equiv of pyridine. This was also confirmed by monitoring the formation of pyridine by GC (Figure 2). The first and higher rate of formation of pyridine at pD 10.0 corresponded to that determined by formation of the UV chromophore described above, indicating that the two analytical techniques were measuring the same reaction.

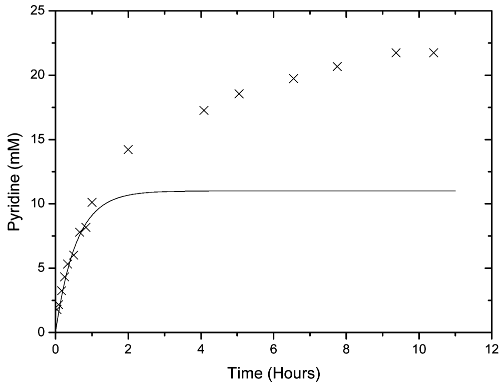
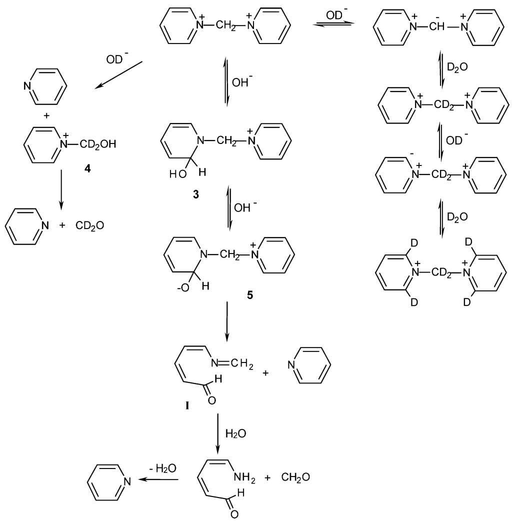


Figure 2. Change in the concentration of pyridine with time for the hydrolysis of MDP (1.01×10^{-2} M) at pH 10.0 (0.3 M CAPS buffer) with $I = 0.1$ M (KCl) at 25 °C. The continuous line represents a first-order fit to 1 molar equivalence of pyridine.

Scheme 3



A reaction scheme compatible with these observations is shown in Scheme 3. It is known that some substitution reactions of pyridines and azines proceed by initial nucleophilic addition to the ring to form a 1:1 σ-adduct [S_NAr or S_N(AE) mechanism].[4] It also appears that some substitution reactions previously thought to occur by an aryne-type mechanism actually involve ring opening of the 1:1 σ-adduct followed by ring closure [S_N(ANRORC) mechanism].[5] Nucleophilic addition of hydroxide ion on the pyridinium ring of MDP at C2 in basic solution would generate the σ-adduct intermediate **3** (Scheme 3). The second-order dependence on hydroxide ion indicates that this is followed by ionization of the hydroxyl group to give **5** (Scheme 3). It is proposed that this zwitterionic species then undergoes ring opening and expulsion of the first pyridine to generate the conjugated unsaturated iminoaldehyde **I**, which is the chromophore observed at 366 nm. Aminodienone intermediates are well-known in the synthesis of some pyridines[6] and in the ring opening of N-substituted pyridinium ions[7] and show UV absorptions in the 350 nm region.[8] When a solution of MDP at pH 10 was incubated at 25 °C for 30 min, corresponding to the maximum formation of the chromophore (Figure 1), and was then extracted with methylene chloride, the organic layer showed a UV absorption at 330 nm and an $m - 1$ peak in the MS spectrum at m/z 108, corresponding to the mass of **I**. The pH-independent disappearance of the chromophore (Figure 1) corresponds to the hydrolysis of imine **I** followed by rapid ring closure and dehydration to form the second mole of pyridine.

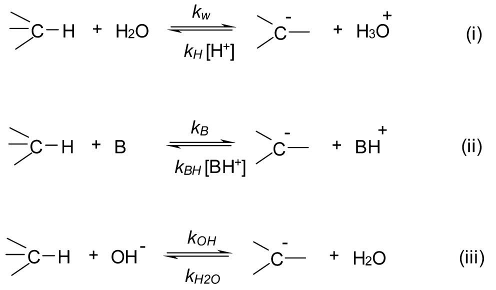
At high pH this S_N(ANRORC) process is the dominant pathway for hydrolysis, but the direct S_N2 displacement of pyridine to generate *N*-(hydroxymethyl)pyridinium ion (**4**) (Scheme 3) becomes competitive at lower pH. At pD 8.0, the ^{1}H NMR spectrum of MDP after 2.4 weeks at 25 °C shows a 20% reduction in the MDP peaks accompanied by the appearance of signals at 9.01 (C2/6), 8.63 (C4), and 8.14 (C3/5) ppm, compatible with the formation of **4**. This slower reaction shows a first-order dependence on the deuteroxide concentration, giving a second-order rate constant of 1.10 M^{-1}

s^{-1}. Because the rate of this reaction is first order in hydroxide ion, at higher pH this reaction is overtaken by the S_N(ANRORC) process, which shows a second-order dependence on hydroxide ion.

The low hydrolysis rates of MDP are presumably a reflection of the stabilization brought about by the attachment of two first-row heteroatoms to the same carbon, as particularly seen in XCH_2Y systems where X and Y are electronegative atoms.[9,10]

(ii). Deuterium Exchange and Carbon Acidity of MDP. In water, carbon acids may undergo deprotonation by the solvent [Scheme 4 (i)], by a buffer base [Scheme 4(ii)], or by hydroxide ion [Scheme 4(iii)].[11] In general, it is expected that the more strongly acidic is the carbon acid, the more likely is deprotonation to occur by solvent and by buffer compared with hydroxide ion at lower pH. Conversely, weak carbon acids, particularly those giving charge-localized carbanions and subject to internal return in the initially formed ion pair, may only show observable deprotonation by strong bases such as hydroxide ion.[12] A simple way to detect deprotonation in carbon acids is to measure the rate of deuterium exchange of the ionizable protons.[13] It was anticipated that the central methylene of MDP would be a moderately strong carbon acid, as ionization would yield what appears to be a fairly stable carbanion ylide (Scheme 1).

Scheme 4



The rate of deuterium exchange for the methylene of MDP in buffered D_2O (pD 7.20–10) at 25 °C and $I = 1.0$ M (KCl) was followed by ^1H NMR spectroscopy at 500 MHz. Deuterium exchange results in the disappearance of the singlet at 7.47 ppm due to the CH_2 group of the substrate and the appearance of a poorly resolved upfield-shifted triplet at 7.46 ppm due to the CHD group of the first-formed monodeuteriated product. The loss of the methylene signal followed first-order kinetics, and the associated first-order rate constants (k_{obsd}, in s^{-1}) were determined at pD 7.20–10.0 maintained at various phosphate and CAPS buffer concentrations.

There was only a small amount of buffer catalysis of the D-exchange reaction, and the observed pseudo-first-order rate constants k_{obsd} were plotted against the buffer concentration [B] to give the buffer-independent rate constant $k_{int} = k_{OD}[OD^-]$ at zero buffer concentration (eq 1). A plot of k_{int} against the deuteroxide ion concentration $[OD^-]$, calculated from eq 2 with $pK_w = 14.87$,[14] was linear, and its slope gave a value of 297 $dm^3\ mol^{-1}\ s^{-1}$ for k_{OD}, the second-order rate constant for exchange of the methylene proton of MDP catalyzed by DO^-.

$$k_{obsd} = k_{OD}[OD^-] + k_B[B] \qquad (1)$$

$$\log([OD^-]/M) = pD - pK_w \qquad (2)$$

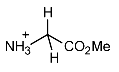
Furthermore, the intercept was indistinguishable from zero, indicating that the pD-independent water-catalyzed D-exchange reaction was insignificant. This was confirmed by the fact that there was no detectable (<2%) D exchange of MDP in 1 and 0.1 M DCl/D_2O at 25 °C after 7.5 weeks, indicating that the rate constant k_w [Scheme 4(i)] for the spontaneous deprotonation of MDP is $<4.38 \times 10^{-9}\ s^{-1}$. The arguments that deuterium exchange in carbon acids usually proceeds through free, solvent-equilibrated carbanion intermediates have been described, and the rate of this process can then be used to estimate the pK_a of the carbon acid.[15] The fact that there was no detectable spontaneous deprotonation of MDP [Scheme 4(i)] indicates that its pK_a must be >17, as the equilibrium constant for ionization is the ratio of the deprotonation rate ($<4.38 \times 10^{-9}\ s^{-1}$) to the protonation rate of the carbanion by D^+, which is expected[16] to be nearly diffusion-controlled ($k_D \approx 10^9\ dm^3\ mol^{-1}\ s^{-1}$). The buffer-catalyzed deprotonation of MDP by DPO_4^{2-} and CAPS in D_2O can also be used to estimate the pK_a of MDP from the rate constants for its deprotonation by a buffer base [Scheme 4(ii)] to give the free carbanion (k_B) and for the reverse protonation of the carbanion by the conjugate acid of this base (k_{BH}) according to eq 3,

$$pK_a = pK_{BH} + \log(k_{BH}/k_B) \qquad (3)$$

where pK_{BH} is the pK_a of the conjugate acid of the buffer base.

The second-order rate constant for the deprotonation of MDP by DPO_4^{2-} in D_2O is $k_B = 4.86 \times 10^{-6}\ dm^3\ mol^{-1}\ s^{-1}$, and it can be assumed that the rate constant for HPO_4^{2-} in H_2O would be very similar because the kinetic solvent isotope effect for this type of reaction is close to unity.[17] Combining this value of k_B with the upper limit[16] of $k_{BH} \approx 10^9\ dm^3\ mol^{-1}\ s^{-1}$ for the diffusion-limited reverse protonation of the carbanion by $H_2PO_4^-$ and the value $pK_{BH} = 6.5$ for $H_2PO_4^-$ in H_2O ($I = 1.0$ M)[18] gives $pK_a = 20.8$ for the methylene ionization of MDP in H_2O. The data using CAPS buffer ($pK_a = 10.15$ in H_2O, $I = 1.0$ M) give $k_B = 3.36 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$, from which a similar calculation yields $pK_a = 21.6$, giving a mean value of 21.2. The maximum value of the rate of reprotonation of the carbanion by water (limited by solvent reorganization[6]) is $10^{11}\ s^{-1}$, which can be combined with the observed second-order rate constant for exchange of the methylene proton of MDP catalyzed by DO^- [$k_{OD} = 297\ dm^3\ mol^{-1}\ s^{-1}$; Scheme 4 (iii)] to give an MDP carbon acid pK_a of ≤22.5, in reasonable agreement with that obtained from the buffer-catalyzed rate constants.

The value $k_B = 4.86 \times 10^{-6}\ dm^3\ mol^{-1}\ s^{-1}$ for deprotonation of MDP by DPO_4^{2-} is ca. 10-fold larger than the value $k_B = 5.6 \times 10^{-7}\ dm^3\ mol^{-1}\ s^{-1}$ for carbon deprotonation of N-protonated glycine methyl ester (**6**) by the same base; for **6**, the carbon acid pK_a in water is 21.0.[19] The second-order rate constant $k_{OD} = 297\ dm^3\ mol^{-1}\ s^{-1}$ for deprotonation of MDP by deuteroxide ion can be compared with those for some monocationic carbon acids. The k_{OD} values for deprotonation of **6** and the quaternary cation **7** are 6.0 and 570 $dm^3\ mol^{-1}\ s^{-1}$, respectively.[15] The kinetic acidities for the carbon ionization of **6** and **7** in water are $pK_a = 18.0$ and 21.0, respectively.[15]



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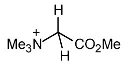

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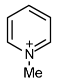


8

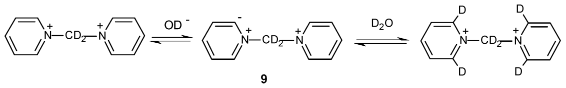
The second-order rate constant for deprotonation of *N*-methylpyridinium ion (**8**) by deuteroxide ion at 25 °C (k_{OD} =

4.74×10^{-7} dm^3 mol^{-1} s^{-1}) is much smaller than that for MDP. The calculation of the pK_a of **8** from this value requires knowledge of the rate constant k_{H_2O} for the reverse reaction, the protonation of the carbanion by solvent water [Scheme 4(iii)]. If the pK_a of **8** is >25, it is likely[11] that $k_{H_2O} \approx 10^{10}$ s^{-1}, giving an estimated pK_a of 30.3 for **8** in water, again assuming no significant isotope effect and using pK_w = 14.0.[14] Deuterium exchange of the methyl hydrogens of tetramethylammonium ion is not observed in 1 M deuteroxide solution over several weeks,[20] which may indicate that the zwitterionic ylidic conjugate base of **8** is relatively stabilized by the aromatic pyridinium ring compared with that of Me_4N^+ or that Me_4N^+ is additionally stabilized.

In summary, the kinetic data for the deprotonation of MDP are consistent with pK_a = 21.2 in water, which may appear surprisingly high for a dicationic species, but the second pyridinium ion lowers the pK_a by about 9 units compared with *N*-methylpyridinium ion (**8**).

A slower H/D exchange occurs at the 2 and 6 positions of the pyridinium rings of MDP in basic solutions of D_2O, the rate of which was determined in buffered D_2O (pD 7.20−10) at 25 °C and *I* = 1.0 M (KCl) by following the reaction with ^{1}H NMR spectroscopy at 500 MHz. There was negligible buffer catalysis of the D-exchange reaction (eq 1), and a plot of the logarithm of the observed first-order rate constant against pD was linear with a slope of 1.0, indicative of a rate that is first order in deuteroxide ion concentration with a second-order rate constant of k_{OD} = 2.84 dm^3 mol^{-1} s^{-1}. This value at 25 °C is about 2 orders of magnitude greater than that for the similar reaction of *N*-phenylpyridinium ion ($k_{OD} = 5.4 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} at 50 °C[21]) and about 10-fold greater than that for *N*-methylpyridinium ion at 75 °C.[12] The exchange of the pyridinium ion ring protons probably occurs through the intermediate formation of zwitterion **9** (Scheme 5).

Scheme 5



■ CONCLUSIONS

Although 1,1′-methylenebis(pyridinium) dication (MDP) has two formal positively charged substituents attached to a central carbon, it is remarkably stable to hydrolysis at low pH (<7). It undergoes a complex series of reactions that vary with pH. Below pH 7 there is a very slow degradation (e.g., at pH 7 and 25 °C it has a half-life of about 10 weeks) that is first order in hydroxide ion, liberates only one equiv of pyridine, and forms *N*-(hydroxymethyl)pyridinium ion. Above pH 9 there is a change in the reaction pathway, with expulsion of one of the pyridines and the formation of an unsaturated iminoaldehyde intermediate by an ANRORC-type mechanism that involves opening the other pyridine ring. This intermediate subsequently undergoes ring closure back to pyridine with formation of formaldehyde. The rate of the first phase is second order in hydroxide ion, while the second is pH-independent. Deuterium exchange of the central methylene in D_2O is faster than the breakdown of MDP and is predominantly OD^--catalyzed with a small amount of buffer catalysis. The estimated pK_a of MDP dication in H_2O is unexpectedly high at 21.2 at 25 °C and *I* = 1.0 M (KCl), compared with an estimated value of 30.3 for the monocationic *N*-methylpyridinium ion (**8**). Deuterium exchange also occurs at the 2 and 6 positions of the pyridinium rings, but at a lower rate that is first order in deuteroxide ion and only competitive with the breakdown of MDP below pD 11.

■ EXPERIMENTAL SECTION

Materials. MDP (**1**) was prepared by adding 130 mL of methylene chloride to 30 mL pyridine and refluxing the mixture at 60 °C until a solid precipitate was formed. The precipitate was filtered, and any pyridine was washed off with excess methylene chloride. ^{1}H NMR (500 MHz, D_2O) for **1**: δ 9.38 (m, 4H), 8.85 (tt, *J* = 7.90 Hz, *J* = 1.28 Hz, 2H), 8.33 (m, 4H), 7.47 (s, 2H).

Sodium deuteroxide (30 wt %, 99+% D), deuterium chloride (37 wt %, 99+% D), and deuterium oxide (99.9% D) were obtained from Aldrich. All other organic and inorganic chemicals were AnalaR grade and were used without further purification.

General Methods. Phosphate, CAPS, and borate buffers were prepared by dissolving the acid form and KCl in D_2O and then adding NaOD to give the desired acid/base ratio at *I* = 1.0 M (KCl). The solution pH was determined at 25 °C using a pH meter equipped with an ultramicroelectrode. Values of pD were obtained by adding 0.40 to the observed reading of the pH meter.[13] The concentration of deuteroxide ion at any pD was calculated using eq 2, where $K_w = 10^{-14.87}$ is the ion-product constant of D_2O at 25 °C.[14]

^{1}H NMR spectra at 500 MHz were recorded in D_2O at 25 °C using a 500 Hz NMR spectrometer. Chemical shifts are reported relative to TSP at 0.00 ppm, and sodium acetate was used as an internal standard. UV−vis spectra were acquired using a spectrometer equipped with a 12-compartment cell block thermostatically maintained by using a Peltier system. A gas chromatograph equipped with flame ionization or MS-QQQ detection was used. An HP-5 column with dimensions 30 m × 0.25 mm × 0.25 μm was used. The inlet temperature was set at 250 °C, with an injection volume of 1 μL and a split ratio of 50:1. The carrier gas was helium at a constant pressure of 16.1 psi and a flow rate of 1.5 mL/min. The oven temperature was initially held at 45 °C for 2 min and then increased at a ramping rate of 20 °C/min. The final oven temperature was 320 °C, which was held for 2 min.

Kinetic Measurements. All of the reactions were carried out in H_2O or D_2O at 25 °C. The rate of hydrolysis of MDP was studied by injecting a stock solution of MDP (10 mM in H_2O) into a buffered solution (*I* = 0.1 M) to give 1×10^{-4} M MDP and measuring the change in UV absorbance at 366 nm as a function of time. The biphasic change in absorbance was dissected into pseudo-first-order rate constants for the formation and breakdown of the intermediate using Origin Laboratories software. The deuterium exchange reactions of MDP were initiated by mixing MDP into 1.0 or 0.1 M DCl or buffered D_2O solutions at an ionic strength (*I*) of 1.0 M (KCl) to give final substrate concentrations ranging from 19.85 to 21.22 mM. The pD of the reaction mixture was closely monitored and was found to be constant to within 0.05 pD units during the time the isotope exchange reaction was followed by ^{1}H NMR analysis at 25 °C.

To monitor the formation of pyridine, 10.1 mM MDP was added to a 300 mM CAPS buffer at pH 10.0, *I* = 0.1 M, 25 °C with methoxybenzene at 5 mM as an internal standard. At intervals, 1 mL of this solution was added to 2 mL of methylene chloride, and the layers were shaken to ensure maximum transfer of organic materials into the methylene chloride layer. The layers were left to separate, and the methylene chloride layer was analyzed using GC.

The exchange of the methylene proton of MDP for deuterium in D_2O buffered at pD 7.20 and 10.0 was followed by ^{1}H NMR monitoring of the disappearance of the singlet at 7.47 ± 0.03 ppm and the appearance of a poorly resolved triplet at 7.46 ± 0.03 ppm due to the α-CHD group of the product. Reactions were monitored during the exchange for deuterium of a minimum of 60−20% of the methylene proton of MDP.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of kinetic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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