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A Reversible pH-Dependent Intramolecular Pyridine−Aldehyde Cyclization

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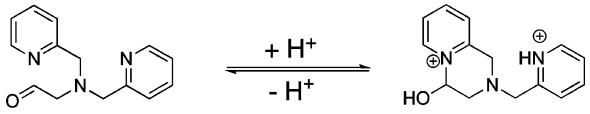
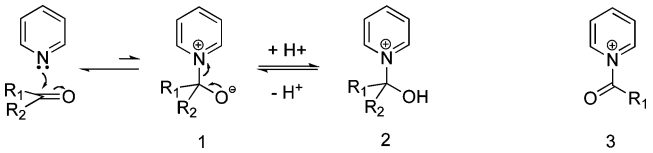


A dipicolylamine (DPA) attached to an aldehyde moiety cyclizes to form a pyridinium-fused heterocycle. This intramolecular reaction between the pyridine and aldehyde moieties is reversible, and the position of the equilibrium is controlled by pH. The fused-ring heterocycle is stabilized under acidic conditions, whereas the ring-opened form is the major species under basic conditions. The ring-closed form can be utilized as a masked aldehyde precursor to access a variety of functional metal chelators containing the DPA unit.

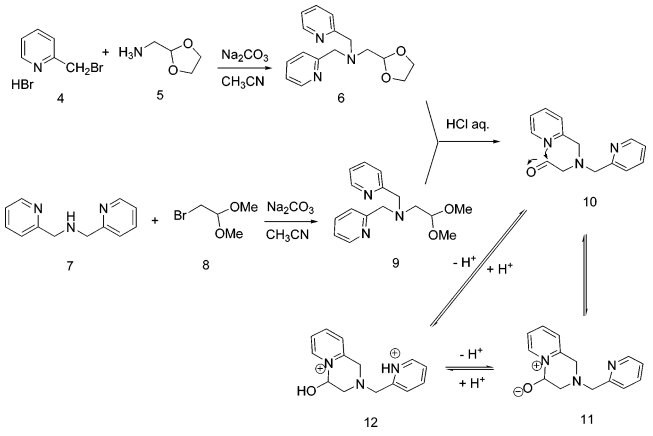
Pyridine and its derivatives have been extensively applied as catalysts or auxiliaries for a variety of organic reactions.[1] A common step in these reactions is the formation of a pyridinium ion intermediate, which results from attack of a pyridyl nitrogen lone pair on an electrophile. One such example is the 4-(dimethylamino)pyridine (DMAP) catalyzed acylation. It is well-established that the transformations proceed via an *N*-acylpyridinium cation.[2] Reactions between pyridine and aldehydes/ketones have been less extensively explored, however.[3] In this report, we describe the synthesis and characterization of a novel pyridinium-fused heterocyclic compound formed by intramolecular nucleophilic attack of a pyridine on an appended aldehyde. We demonstrate that this reaction is reversible and that the equilibrium is controlled by the pH of the reaction mixture. Furthermore, as an aldehyde precursor containing the dipicolylamine (DPA) unit, we further identify this compound as a useful synthon for constructing a variety of metal chelating ligands, including chelators for functional imaging of biological zinc.

SCHEME 1. Reaction of Pyridine with a Carbonyl Group and the Structure of Acylpyridinium 3



Nucleophilic attack of the pyridine lone pair electrons on a ketone or aldehyde is expected to form a zwitterionic product (**1**; Scheme 1). Compound **1** is predicted to be unstable since the close proximity of the two opposing charges favors intramolecular charge recombination and subsequent dissociation to form the starting compounds (Scheme 1). This situation is in contrast to that for the mono-cationic acylpyridinium ion **3**, which is expected to be more stable. We anticipated, however, that protonation of the hydroxyl anion would give rise to the analogue **2**, reducing the charge-recombination propensity. In addition, covalently linking the pyridine and aldehyde/ketone moieties should further stabilize the adduct **2** entropically in the form of a ring structure.

SCHEME 2. Synthesis and Equilibrium of 10 with Its Ring-Closed Form 12



We tested these ideas in a model system (Scheme 2). The target molecule was conveniently prepared by either of two synthetic pathways. The reaction of 2 equiv of picolylbromide (**4**) with 1,3-dioxolane-2-methylamine (**5**) under basic conditions readily afforded the precursor **6**, the aldehyde group of which was protected as an acetal with ethylene glycol. Alternatively, the carbonyl group could be protected as the dimethoxyacetal, compound **9**, by coupling DPA (**7**) with 2-bromo-1,1-dimethoxyethane (**8**) under a modified condition.[4] Deprotection of both **6** and **9** was performed under acidic conditions (1 M aq HCl) at

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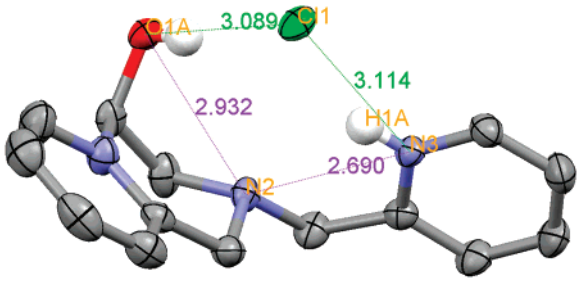
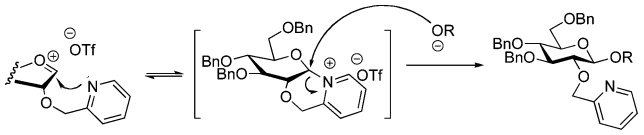


FIGURE 1. X-ray structure of (**12**)Cl_2, displaying only one of the two orientations of the six-membered ring (see Supporting Information). Close intramolecular contacts are marked with dotted lines. One chloride anion and all other hydrogen atoms are omitted for clarity.

room temperature. Although the proposed intermediate **11** should be readily protonated in acid, we could still detect the presence of **10** during the course of the deprotection. An aliquot early in the time course, 3 h after deprotection was initiated, of the acidification of **6** was analyzed by LC-MS. In addition to a major peak for the starting material (retention time 3.7 min; MS: 286.1551 observed; 286.1550 calculated for **6**), two new peaks were detected by HPLC (Supporting Information Figure S1). A high-resolution ESI-MS spectrum of these two peaks, which have retention times of 0.8 and 1.0 min, showed identical *m*/*z* values of 242.1293 and 242.1295, respectively. This observation suggests the presence of both **10** and **12**, for which the calculated (M + H)/*z* = 242.1293.

Deprotection of **6** was complete after 3 days, whereas **9**, being more acid labile, required only 5 h. A similar workup procedure was applied in both cases. After the reaction mixture was evaporated, **12** was determined to be the major product and was sufficiently pure to be characterized by ^{1}H and ^{13}C NMR spectroscopy and by mass spectrometry. Compound **12** was further purified by recrystallization from MeOH/Et_2O, which afforded single crystals of the dichloride salt, suitable for X-ray diffraction (Figure 1).

SCHEME 3. A Mechanism for the "Arming Participating Group" Strategy for Stereoselective Glycosylation[5]



In the solid state, the chloride counterions are involved in hydrogen bonding interactions with the hydroxyl and the pyridinium hydrogen atoms (Figure 1). The newly formed six-membered ring adopts a flattened boat conformation, with the non-aromatic nitrogen atom (N2) in an endo position with respect to the hydroxyl group and protonated pyridine nitrogen atom, resulting a weak hydrogen bonding interaction with H1A (Figure 1). The structure is the first X-ray report of this kind of heterocyclic compound. Recently, a strategy termed the "arming participating group" was described as a means of controlling the stereoselectivity of glycosylation by introducing pyridine as a neighboring group.[5] The proposed mechanism involved formation of a similar six-membered ring pyridinium ion as the key intermediate (Scheme 3).[5] The crystal structure of **12** may

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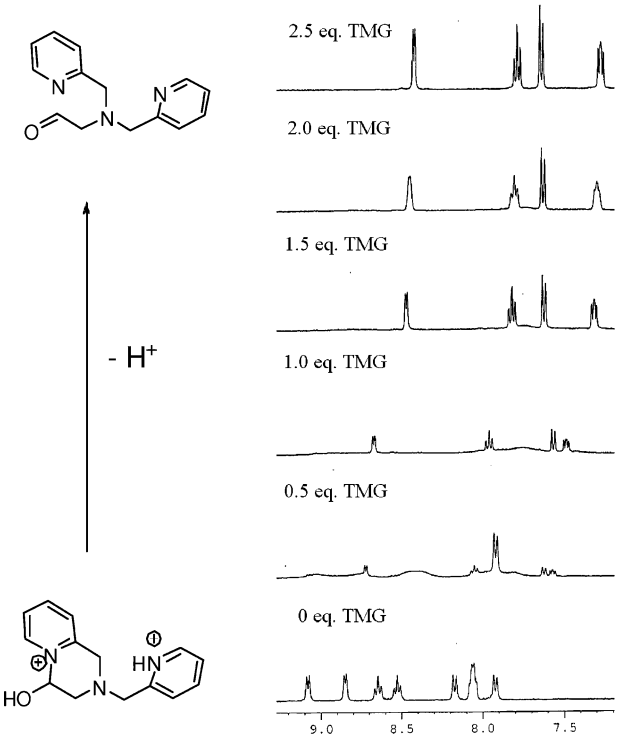


FIGURE 2. Partial 400 MHz ^{1}H NMR spectra of 10 mM (**12**)Cl_2 in MeOH-d_4 in the absence (bottom) and presence of increasing amount of TMG. Only the aromatic signals are shown for clarity.

mimic structural features required to achieve this type of chemical transformation.

If ring formation is indeed stabilized by protonation of the hydroxyl group of **11**, deprotonation should drive the equilibrium in the reverse direction and eventually lead to formation of aldehyde **10**. This hypothesis was confirmed by ^{1}H NMR spectroscopy, which was used to follow the stepwise addition of strong base to a solution of **12** in MeOH-d_4. The compound *N*,*N*′-tetramethylguanidine (TMG) was chosen as the base for this study because of its high pK_{BH}, 13.6, and very simple ^{1}H NMR spectrum, which minimizes overlap with other signals of interest. As the partial ^{1}H NMR spectra in Figure 2 indicate, compound **12** exhibits eight aromatic proton resonances (two of which overlap at 8.06 ppm) because the two pyridine rings are chemically distinct. Adding TMG directly to the NMR sample led to dramatic changes in the spectrum. Upon addition of 0.5 equiv of TMG, the original proton signals became significantly broader, while a new set of signals appeared that are consistent with the structure of compound **10**. The new species exhibits four signals in the aromatic region instead of the eight of compound **12** since the two pyridines of **10** are chemically identical. Increasing the amount of TMG led to further broadening and a decrease of signals from **12** with an increase in the intensity of signals from **10**. Finally, after more than 2 equiv of TMG were added, all signals of **12** disappeared and the signal intensity of **10** reached its maximum. No further changes were observed upon introduction of additional equivalents of TMG. This experiment clearly demonstrates that **12** converts to **10** under basic conditions.

The pH-dependent interconversion between **12** and **10** was also followed by UV−vis spectroscopy. The pH of an aqueous solution of **12** was adjusted to the desired value by adding small aliquots of HCl or NaOH stock solutions, and the spectra were recorded at different pH values between 1.5 and 11.5. Since

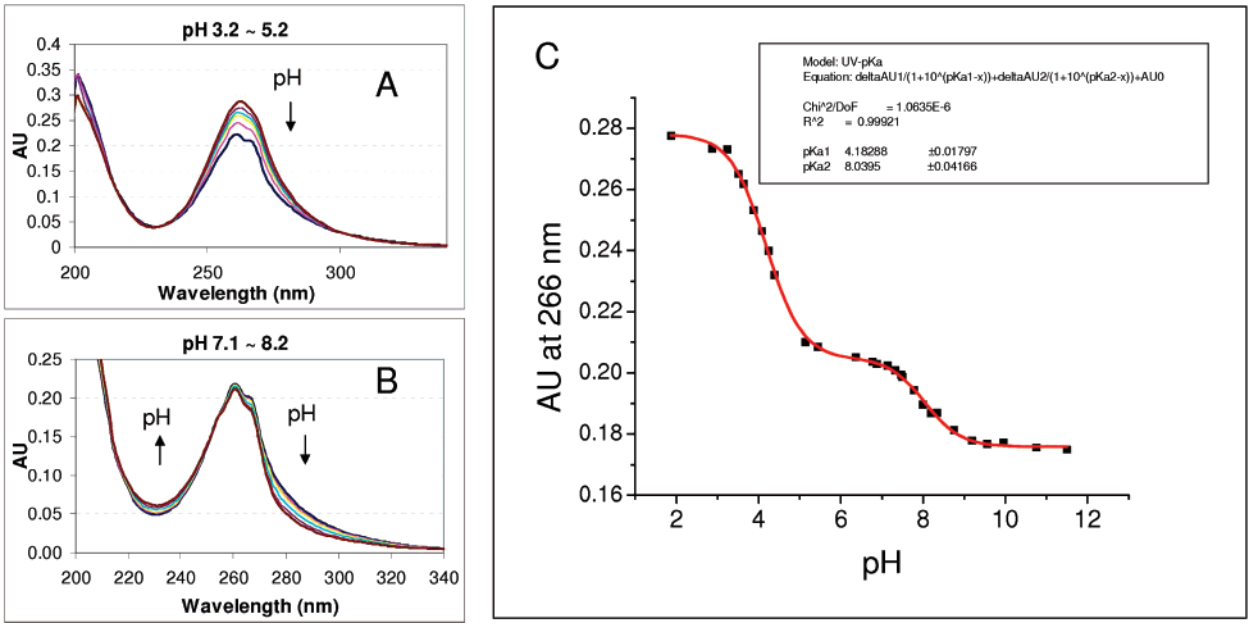
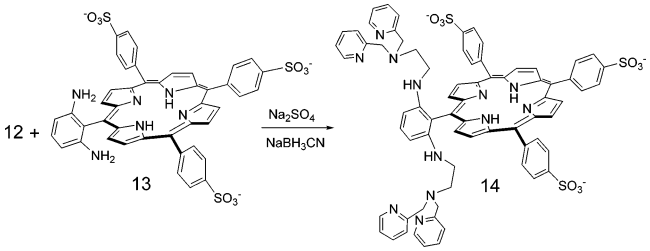


FIGURE 3. UV responds to the pH change of the aqueous solution of **12** from pH 3.2 to 5.2 (A), and from 7.1 to 8.2 (B), and fitting of the UV−pH titration data to a two-protonation-step model from **10** to **12** (C).

two deprotonation steps are required to convert dicationic **12** to neutral **10**, two plateau regions were observed, as expected. Increasing the pH from 3.2 to 5.2 caused a decrease of signal intensity at 261 nm (Figure 3A); at another UV-sensitive region between pH 7.1 and 8.2, an increase in pH led to increased absorption at around 230 nm and a decrease at 280 nm (Figure 3B). The pH-dependent UV change is reversible. The same UV spectrum at any pH point examined could be reproduced either by adding acid or base to a given solution. This observation confirms that **10** and **12** are interconvertible and that the equilibrium is controlled by pH. The pH dependence of the UV absorption data is well fit by a two-site protonation model, yielding pK_a values of 8.0(4) and 4.2(2) (Figure 3C).

The chemical properties of **12** facilitate its use as a precursor of aldehyde **10** for organic synthesis. Compound **12** reacts with different primary amines under reductive amination conditions to produce the DPA unit, which is an excellent ligand for binding transition metal ions. For example, we have developed a series of fluorescent sensors for imaging mobile Zn^{2+} ions using DPA as the metal-binding moiety.[6] Recently, we described a molecular platform (compound **14**, Scheme 4) for dual-function (MRI/fluorescence) zinc sensing. A key step in the synthesis involved linkage of **12** to a water-soluble porphyrin template, $2NH_2$-$TPPS_3$ (**13**) by reductive amination (Scheme 4).[7] A series of cell membrane-impermeable functional zinc chelators were prepared in a similar manner, the detailed description of which will be published elsewhere.[8]

SCHEME 4. Synthetic Application of 12 as Precursor for Functional Zinc Chelator[6]



By rational design of derivatives of **12** or **10**, it should be possible to investigate the effects of nucleophilic and electrophilic substitution on the pyridine−carbonyl interaction. Moreover, we envision that **12** will be applied as a synthetic precursor to construct many new functional metal chelators. Finally, the pH-dependent reversible interconversion of **12** and **10** should facilitate the design of novel pH-responsive materials.

Experimental Section

Synthesis of (1,3)-Dioxolan-2-ylmethylbispyridin-2-ylmethylamine (6). A mixture of 2-picolylbromide HBr salt (2.02 g, 8 mmol), 2-aminomethyldioxolane (470 μL, 5 mmol), and sodium carbonate (4.50 g, 40 mmol) in 40 mL of acetonitrile was heated to reflux for 14 h. The reaction was cooled to room temperature and filtered. The inorganic salts were washed with fresh acetonitrile, and the combined eluents were evaporated to dryness. The residue was purified by silica gel column chromatography, eluting with a CH_2Cl_2/MeOH gradient from 12:1 to 5:1 with 1% ammonia. The product (868.4 mg, 60.9%) was obtained as a brown solid. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 2.78 (2H, d), 3.80−3.90 (4H, m), 5.03 (1H, t), 7.13 (2H, m), 7.55 (2H, d), 7.65 (2H, td), 8.48 (2H, d). ^{13}C NMR (CD_2Cl_2, 100.6 MHz): δ 56.9, 61.0, 64.9, 104.0, 122.0, 123.0, 136.4, 149.1, 160.1. HRMS calcd $(M + H)^+$ 286.1556; found 286.1551

Synthesis of 2,2-Dimethoxy-*N*,*N*-bis(pyridin-2-ylmethyl)-ethanamine (9). A mixture of DPA (1.80 mL, 10 mmol), 2-bromo-1,1-dimethoxyethane (4.8 mL, 40 mmol), Na_2CO_3 (10 g), KF/Celite

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(50%, 0.78 g), and 40 mL of CH_3CN was refluxed for 3 days. Decolorizing charcoal (3 g) was added, and the system was refluxed for another 0.5 h. The reaction mixture was cooled and filtered, and the solid was washed with fresh CH_3CN. The filtrate was evaporated, and the residue was purified by silica gel column chromatography using hexane/ethyl acetate (1:1) to yield 1.27 g of product (44.3%) as a light yellow oil. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 2.72 (2H, d, J = 5.2 Hz), 3.26 (6H, s), 3.86 (4H, s), 4.49 (4H, t, J = 5.2 Hz), 7.14 (m, 2H), 7.54 (2H, d, J = 7.8 Hz), 7.66 (2H, td, J_1 = 1.8 Hz, J_2 = 7.6 Hz), 8.48 (2H, m). ^{13}C NMR (CD_2Cl_2, 100.6 MHz): δ 53.9, 56.3, 61.4, 104.2, 122.3, 123.4, 136.7, 149.4, 160.4. ESI-MS calcd $(M + H)^+$ 288.2, $(M + Na)^+$ 310.2; found 288.2, 310.2.

Synthesis of 4-Hydroxy-2-pyridin-2-ylmethyl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrazin-5-ylium chloride (12). Compound **6** (109.9 mg, 0.385 mmol) was dissolved in 8 mL of 1 M aq HCl and stirred at room temperature for 72 h. The reaction mixture was evaporated to remove solvent. The 157.5 mg of crude product, a yellow oil, was dissolved in 0.5 mL of MeOH and crystallized by vapor diffusion of Et_2O into the solution. The pure product was obtained as white crystals (119.1 mg), which are very hydroscopic. Compound **12** can be obtained from **9** by deprotection in 1 M aq HCl for 5 h, followed by the same workup procedure. ^{1}H NMR (MeOH-d_4, 400 MHz): δ 3.37 (1H, dd), 3.53 (1H, dd), 4.46 (2H, m), 6.26 (2H, dd), 7.95 (1H, d), 8.08 (2H, m), 8.21 (1H, D), 8.53 (1H, td), 8.67 (1H, td), 8.86 (1H, d), 9.13 (1H, d). ^{13}C NMR (MeOH-d_4, 100.6 MHz): δ 54.6, 56.0, 57.8, 64.4, 87.6, 127.5, 127.7, 128.1, 128.5, 143.0, 143.7, 146.9, 148.6, 153.6, 153.9. HRMS calcd $(M + H)^+$ 242.1293; found 242.1293.

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Supporting Information Available: Experimental procedures for preparation of **6**, **9**, and **12** including characterization data, UV titration, ^{1}H NMR titration, and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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