Structures of the Intermediates Formed in the Ring-Opening Reaction of 2-Chloro-3-nitropyridine

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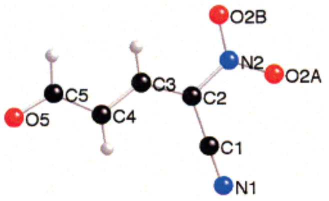

The reaction of 2-chloro-3-nitropyridine with two equivalents of hydroxide ion was studied by NMR and X-ray crystallography. On the basis of NMR coupling constants, the originally formed ring-opened intermediate is the pseudo-cis form, as predicted by the S_N(ANRORC) mechanism. However, the first intermediate is unstable and isomerizes to a second intermediate, which was isolated. The pseudo-trans geometry of the second intermediate [3-pentenenitrile, 2-nitro-5-oxo, ion(−1), sodium] explains why additional base does not lead to the ring-closing reaction as observed with 2-chloro-5-nitropyridine.

During the 1980s Reinheimer and co-workers[1,2] investigated the reaction of 2-chloro-5-nitropyridine **1** and 2-chloro-3-nitropyridine **4** with an excess of hydroxide in dimethyl sulfoxide/water solution between 20 and 60 °C. As shown in Scheme 1a, **1** undergoes a classic S_N(ANRORC) reaction[3] leading to phenoxide **3**. Van der Plas and co-workers studied such ring openings in certain pyrimidine systems and coined the term addition of the nucleophile, ring opening, and ring closure [S_N(ANRORC)] to describe the steps in the reaction.

Proton and carbon-13 NMR spectral studies led Reinheimer et al.[2] to propose structures **2** and **5** for the intermediates. However, they observed that intermediate **5** did not continue on to phenoxide **6** (Scheme 1b). These observations were the first to show that a pyridine ring could open under relatively mild and partially aqueous conditions. Earlier reports[4−7] and one[8] in 1982 had shown that pyridine rings could undergo ring opening when treated with a base, such as lithium diisopropylamide, in a nonaqueous solvent.

The ring opening of **1** has been carried out in the presence of $^{15}NH_3$, which was incorporated into the ring.[9] The ring opening of **1** has also been followed in the gas phase using mass spectrometry.[10] Those studies confirmed the pathway suggested by Reinheimer et al.[1,2] Van der Plas[11] and other scientists[12,13] more recently reviewed the S_N(ANRORC) reaction. The most recent paper[14] concerning substituted pyridines reported a study of solvent effects on the aromatic nucleophilic substitution reaction of 2-chloro-3,5-dinitropyridine via the S_N(ANRORC) mechanism. Interestingly, Al-Lohedan and Kirby[14] observed that the final compound formed in the reaction was the ring-closed product. As best we can determine, the only X-ray structure of an intermediate in a S_N(ANRORC) reaction has been determined by Wermann et al.[15] The intermediate is a triazinium−imidothioate zwitterion.

Reinheimer et al.[2] observed that addition of two more equivalents of hydroxide to the intermediate from **1** yielded the final ring-closed product **3**. However, the intermediate formed from **4** did not yield the corresponding phenoxide **6** but instead underwent slow decomposition. The only decomposition products conclusively identified were the sodium salts of formic acid and isocyanate. Apparently, **4** forms a ring-opened intermediate that does not subsequently undergo ring closure. To resolve this mechanistic puzzle, we determined the crystal structure of the isolated intermediate from reaction of **4** with two equivalents of base.

As shown in Figure 1, the isolated intermediate **7** is a carbanion, crystallized as the sodium salt. When two equivalents of base are added to **4**, the pyridine ring opens and the chlorine substituent leaves as chloride; the result is a carbanion with aldehyde, nitro, and nitrile functional groups. The C−C distances in the backbone range between 1.36 and 1.42 Å, indicating considerable delocalization of the negative charge over the extended π system in the carbanion. In the nitro group the shortened C−N distance (1.38 Å) and lengthened N−O distances (1.25 and 1.26 Å) show that much of the negative charge is concentrated on the nitro group, but the slightly elongated C═O bond (1.25 Å) indicates partial negative charge on the aldehyde oxygen atom as does the interaction of the aldehyde oxygen atom with a cluster of sodium ions in the solid. In the crystal there is a complex set of interactions among the sodium ions, water molecules, aldehyde, and nitro group oxygen atoms that have been analyzed computationally by Gora et al.[16]

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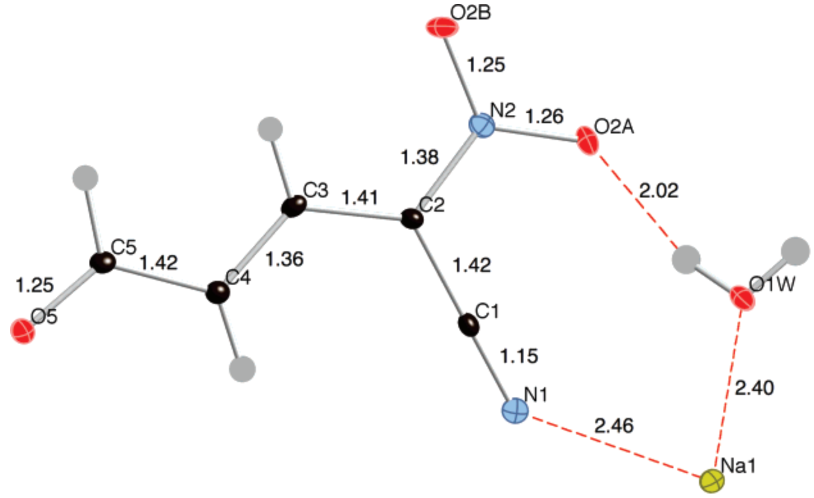
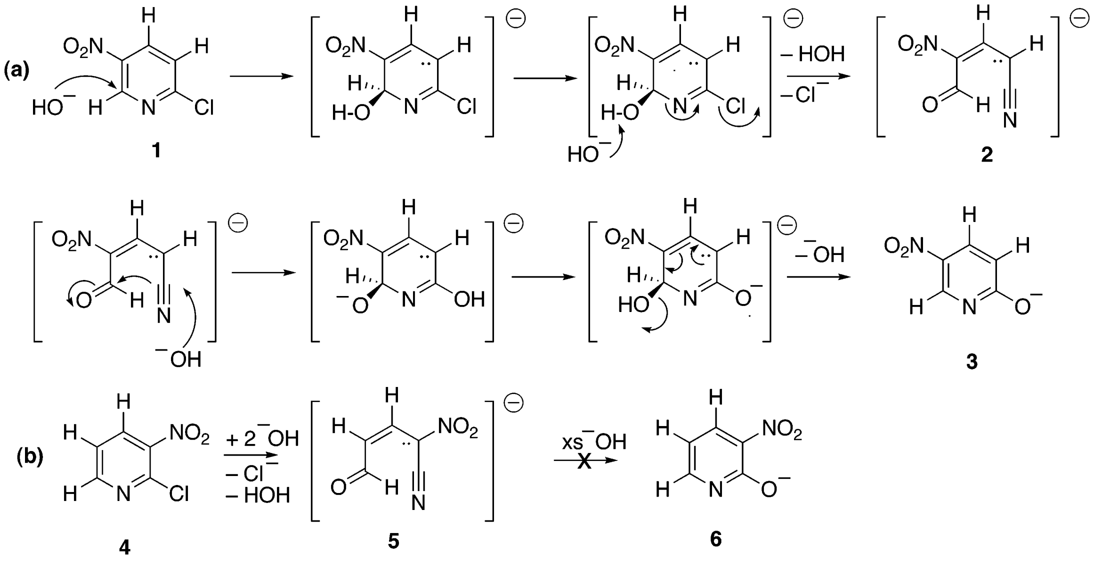


FIGURE 1. Crystal structure of the ring-opened intermediate from **4**, the pseudo-trans carbanion 3-pentenenitrile, 2-nitro-5-oxo, ion(−1), sodium **7**. Interatomic distances are shown in Ångstoms. The non-hydrogen atoms are drawn as thermal ellipsoids (95%).[17] Hydrogen-atom positions were refined but not the isotropic temperature factors. Diffraction data were obtained at 93 K.

SCHEME 1. Reaction of 2-Chloro-5-nitropyridine with Four Equivalents of Sodium Hydroxide Proceeds to the Phenoxide Product As Predicted by the S_N(ANRORC) Mechanism (a), but Reaction of 2-Chloro-3-nitropyridine Does Not Go To Completion (b)



An important aspect of the reaction of **4** with hydroxide was investigated. Might the pseudo-cis intermediate predicted by the S_N(ANRORC) mechanism form initially and then isomerize to the isolated pseudo-trans intermediate? Our NMR time/temperature studies revealed that the initially formed intermediate isomerizes over a period of 48 h at ~21 °C to predominantly (91%) the pseudo-trans intermediate **7** that was isolated for X-ray diffraction. (See Table 1 for additional data.) The NMR coupling constants for the adjacent vinyl hydrogens are 11.9 Hz for the initial intermediate and 15.2 Hz for the second intermediate; therefore, we can reasonably conclude that the first intermediate has the predicted[2] pseudo-cis structure **5**. All of our attempts to isolate a pure sample of **5** failed, even though the various isolation steps to remove solvent and inorganic salts were carried out at room temperature or below. The proton spectra of material that was isolated at each step of the

TABLE 1. Time Study of the Conversion of Intermediate 5 to Intermediate 7 Formed in the Reaction of 4 with Two Equivalents of NaOD at ~21 °C[a]

hours after mixing at 21 °C	percentage of intermediate **5**	percentage of intermediate **7**
0.17	89.3	10.7
1.02	83.3	16.7
2.00	77.5	22.5
4.18	66.2	33.8
7.25	54.1	45.9
10.9	41.3	58.7
23.8	20.1	79.9
48.0	9.19	90.8
104	0	100

[a] Percentages of **5** and **7** were determined by integration of the aldehydic signals: intermediate **5**, 10.1 ppm; intermediate **7**, 9.2 ppm.

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(17) Image generated using CrystalMaker from CrystalMaker Software Ltd. (www.crystalmaker.com).

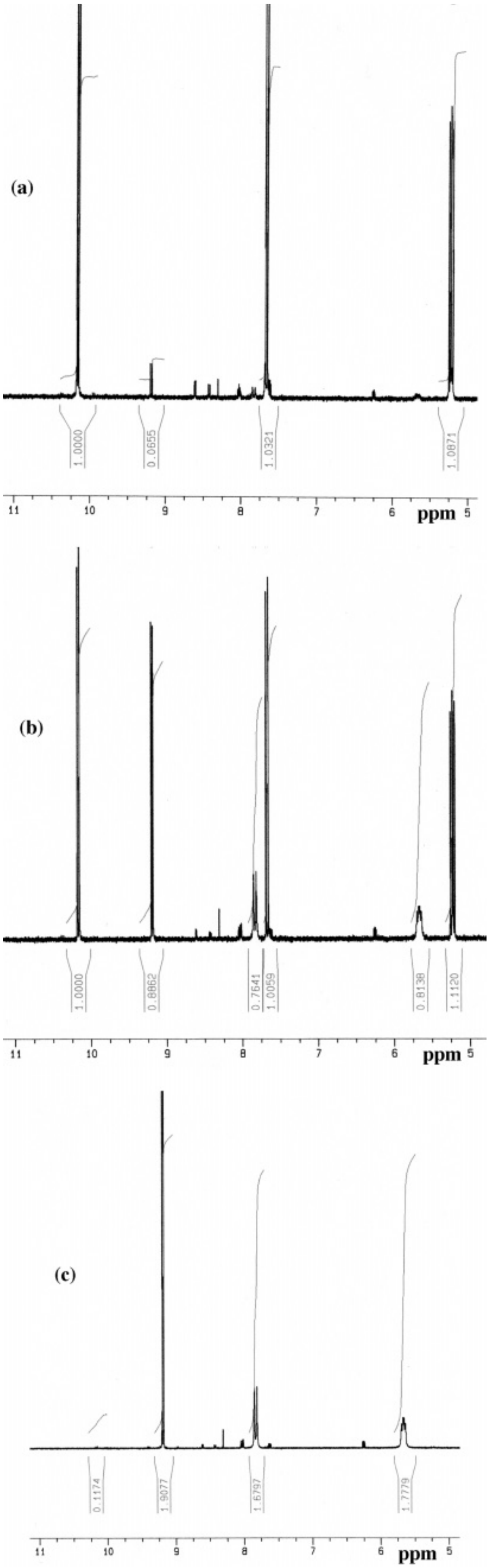

FIGURE 2. Proton NMR spectra of intermediates **5** and **7** after mixing **4** and 2 equiv of NaOD/D_2O (a) 0.45 h after mixing, **5** $\gg$ **7**; (b) 7.36 h after mixing, **5** $\approx$ **7**; (c) 72.8 h after mixing, **5** $\ll$ **7**. Intermediate **5**: 10.1 (d), 7.7 (d), 5.2 (dd). Intermediate **7**: 9.2 (d), 7.8 (d), 5.7 (dd).

purification procedures revealed only the presence of second intermediate **7**. The experimental evidence supports our conclusion that the crystal structure shown in Figure 1 is the second intermediate formed in the ring-opening reaction.

Thus, in our experimental study of the ring-opening reaction of **4** we found evidence for two intermediates. We verified by NMR coupling constants the pseudo-cis geometry predicted by the S_N(ANRORC) mechanism for the first intermediate **5**. By determining the crystal structure of the intermediate isolated by Reinheimer et al.,[2] we showed that this second intermediate **7** possesses a pseudo-trans geometry. The extended, pseudo-trans geometry of **7** prevents the ring-closing reaction, which explains why it does not react to give phenoxide **6** analogous to **3** in the presence of excess hydroxide.

Experimental Section

Crystallization of Intermediate 3-Pentenenitrile, 2-Nitro-5-oxo, Ion(−1), Sodium 7. A sample prepared by Reinheimer et al.[2] was dissolved in acetone. Yellow crystals appeared after 10 days of vapor diffusion with petroleum ether. A twinned crystal was cut with a razor blade to yield the diffraction sample, 0.24 × 0.12 × 0.01 mm. (See Supporting Information for further details of the crystallographic determination.)

NMR Evidence for Two Intermediates. The reaction between **4** in d_6-DMSO and 2 equiv of NaOD/D_2O was carried out in an NMR tube at probe temperature (∼21 °C). Dioxane (3.5 ppm) was set as the internal reference. The aldehydic hydrogen in the initial spectrum had a chemical shift of 10.1 ppm; in subsequent spectra the signal at 10.1 ppm decreased as a second aldehydic signal at 9.2 ppm increased (see Table 1). The proton NMR spectra between 5 and 11 ppm as recorded over time are shown in Figure 2. The relative amounts of **5** and **7** are indicated by the integration values.

Additional time/temperature studies were carried out at higher temperatures. After 6.60 h at 38 °C (NMR probe temperature of the instrument used by Reinheimer et al.[2]) the percentage of **5** was 12.3% and that of **7** was 87.7%. After 30 min at 56 °C (temperature at which **4** was converted preparatively to an intermediate by Reinheimer et al.[2]) 80.8% of the sample was **7**, and after 60 min only **7** was present.

To make sure that the sample from which the crystals for the X-ray crystallographic study were isolated had the same spectrum as intermediate **7**, a sample of the partially purified intermediate was prepared at the same concentration and in the same solvent system, d_6-DMSO and D_2O. The spectra were identical except for very small signals, indicating the presence of trace impurities, none of which had chemical shifts identical to those of **5**.

Acknowledgment. This report is dedicated to the memory of John D. Reinheimer, who was accidentally killed in December 2003 when struck by a vehicle near his home. Diffraction data were obtained by V.B.P. during sabbatical leave in the Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC.

Supporting Information Available: Crystallographic details (Tables S1−S8), complete NMR spectra, and crystallographic information file (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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