Reaction of 2-Halo-5-nitropyridines with Hydroxide Ion in Dimethyl Sulfoxide

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Received February 25, 1980

Addition of aqueous base to solutions of 2-halo-5-nitropyridines in dimethyl sulfoxide produces a stable substance which forms 2-hydroxy-5-nitropyridine if the molar ratio of hydroxide to pyridine is greater than 2:1. IR and ^1H and ^{13}C NMR spectra of the intermediate stable substance indicate that the pyridine ring is cleaved to form this material. An S_N(ANRORC) mechanism is proposed for the reaction.

Introduction

The electron-deficient nature of the pyridine ring makes electrophilic substitution reactions on the ring difficult but facilitates attack by nucleophiles. Many examples of attack at the 2 or 4 position of substituted pyridines by nucleophiles in strongly basic solutions are known.[1] When halogen is displaced by a nucleophile, the reaction may proceed by a direct substitution or by a benzyne mechanism.[2] Meisenheimer complexes are possible intermediates in nucleophilic substitution reactions on aromatic systems,[3,4] and the formation of Meisenheimer complexes of suitably substituted pyridines has been described by several investigators.[5-7] Ring-opening reactions have been observed when pyridine rings are treated with a strong base;[8] ring opening during reactions of halopyrimidines with powerful nucleophiles is also common.[9] In these later reactions, halogen is displaced by an amide ion, the nitrogen of which finally becomes one of the ring nitrogens. The mechanism for the process has been dubbed the S_N(ANRORC) mechanism.[9]

Our interest in this field arose when we tried the displacement of halogen from 2-chloro-5-nitropyridine to form 2-hydroxy-5-nitropyridine. Better yields were obtained when the pyridine was treated with strong acid, wherein water is the nucleophile, than when hydroxide in dioxane/water was used.[10] Furthermore, 2-chloro-3-nitropyridine gave no product under basic conditions but readily formed 2-hydroxy-3-nitropyridine with acid. A kinetic study of the reaction of 2-chloro-5-nitropyridine with OH^- showed that the process is not cleanly second order, although the expected product was formed. A reaction process more complicated than a simple bimolecular substitution is thus suggested. The present work was an attempt to investigate more fully these observations.

Experimental Section

NMR spectra were taken with a Varian T-60, CFT-20, or XL-100 instrument, using samples at ambient temperature (30–34 °C). A trace of tetramethylsilane (Me_4Si) was included in samples for ^1H NMR spectroscopy as a reference. A capillary of neat dioxane was used as a reference in the carbon-13 spectra; the signal for dioxane was set at 67.39 ppm relative to Me_4Si. IR spectra were obtained with a Perkin-Elmer Model 283 while UV data were taken on a Cary Model 14 spectrophotometer.

2-Bromo-, 2-chloro-, and 2-iodo-5-nitropyridines were pure samples which have been previously described.[10] 2-Chloro-3-methyl-5-nitropyridine was prepared from 2-hydroxy-3-methyl-5-nitropyridine by the method of Hawkins and Roe[11] to give a product of mp 47–48 °C (lit.[11] mp 47–48 °C).

Sample Preparation. Solid NaOH (Mallinkrodt, reagent grade) was dissolved in deuterium oxide (Stohler Isotope Chemicals, 99.8%) and standardized with HCl. Solutions of the pyridines in dimethyl-d_6 sulfoxide (Aldrich gold label) were prepared. A definite volume (0.500 mL) of the Me_2SO solution was pipetted into an NMR tube, and 0.100-mL portions of the standardized NaOH in D_2O were added. The NMR tubes were inverted and shaken to mix the contents and then the ^1H NMR spectrum was observed. The time elapsed during this process was about 5–6 min. Subsequently, additional portions of base were added until the molar ratio of OH^- to halonitropyridine was 2:1. Finally, more base was added and again the NMR spectrum was observed.

For carbon-13 NMR spectra, longer periods of time were required to obtain spectra and in these cases samples which contained hydroxide and substituted pyridine in the concentration ratio 2:1 were used.

Results

Proton and carbon-13 NMR spectra of the 2-halo-5-nitropyridines and the expected reaction product 2-hydroxy-5-nitropyridine were recorded; some typical results are shown in Figure 1. Solvent effects on the spectra were examined and it was noted that changing the amount of D_2O present in the D_2O/Me_2SO solvent mixtures had only minor effects (0.03–0.06 ppm) on the chemical shifts of the various resonances up to 25% D_2O. Under all conditions it was possible to unambiguously distinguish the resonances of the product from those of the 2-halo-5-nitropyridines.

When hydroxide was added to a Me_2SO solution of 2-chloro-, 2-bromo-, or 2-iodo-5-nitropyridine sufficient to give a concentration ratio of 1:1, the ^1H NMR spectrum showed two sets of signals. One set was identical in

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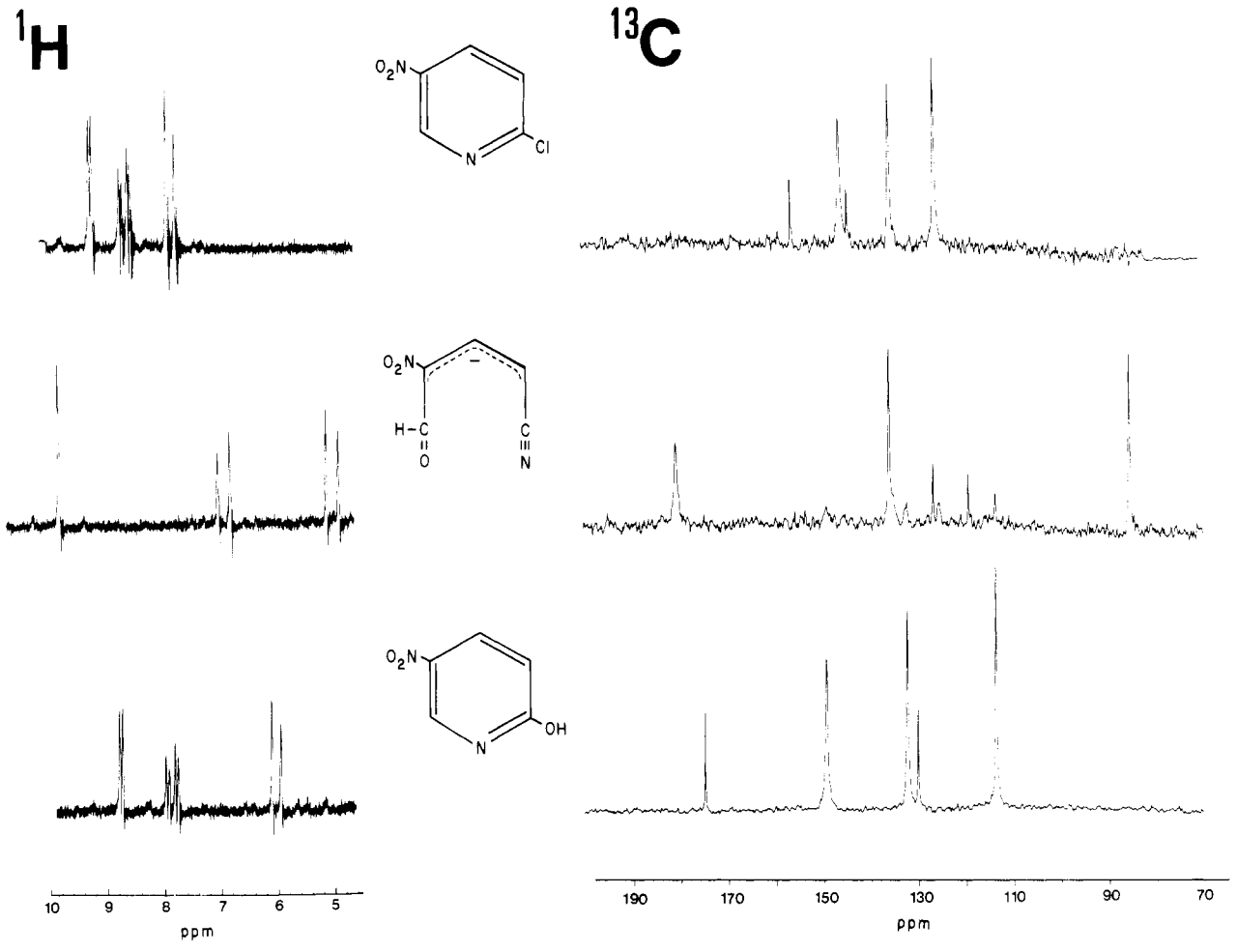


Figure 1. Proton and proton-decoupled ^{13}C NMR spectra of reactant, product, and intermediate in the conversion of 2-chloro-5-nitropyridine to 2-hydroxy-5-nitropyridine. The solvent was Me_2SO-d_6 (2 mL) and DOD (0.5 mL). Proton spectra were obtained at 60 MHz while the operating frequency for the carbon spectra was 25.2 MHz. Sample temperature was 30–34 °C. Proton decoupling was not complete for the carbon spectra so that carbons having directly attached hydrogen nuclei appear as slightly broadened singlets in the spectrum.

chemical shifts with those of the starting pyridine. The second set of lines was not, however, lines of the product, 2-hydroxy-5-nitropyridine, but rather an intermediate in the reaction. Integration showed that the signals of the remaining starting material and the intermediate were in the intensity ratio 1:1. Upon addition of a second mole of base, the resonances of the starting material disappeared and only the signals for the intermediate remained (Figure 1). It was only upon addition of still more base that the spectrum of the product could be observed. Formation of the intermediate is rapid on the time scale used to prepare the samples (~5–6 min) and, as long as the ratio $[OH^-]/[\text{pyridine}]$ is less than or equal to 2:1, the intermediate is stable for days under the reaction conditions. When more base is present, the disappearance of the intermediate and formation of the product takes about 1 h at NMR probe temperatures.

Carbon-13 spectra of this process were also obtained (Figure 1) and confirm that an intermediate which is structurally distinct from the reactants or product is formed. In the ^1H NMR spectrum, the intermediate displays three sets of peaks, δ 9.7 (a pair of doublets, J = 1.0 and J = 0.5 Hz), 6.8 (a pair of doublets, J = 12.6 and J = 1.0 Hz), and 5.0 (a pair of doublets, J = 12.6 and J = 0.5 Hz). The ^{13}C NMR spectrum of the sample showed 5 major signals at δ 182.7, 137.0, 127.9, 120.4, and 86.5 (external dioxane reference). Smaller peaks in the ^{13}C spectrum could be assigned to reagent or product, when these same substances appeared in the ^1H spectrum.

The UV–visible spectrum of the intermediate from the reaction of 2-halo-5-nitropyridines with hydroxide in Me_2SO was observed by diluting the NMR samples with Me_2SO/D_2O of the same composition. Regardless of the halogen present in the starting compound, essentially the same UV spectrum was obtained. Two peaks were found with λ_{max} 375.0 nm (ϵ ~1.44 × 10^4) and λ_{max} 315 nm (ϵ ~1.40 × 10^4). Small differences in the extinction coefficients were observed for the three halopyridines, but the differences are likely due to small amounts of unreacted starting material since the added base may not have been present in exactly stoichiometric amounts. The extinction coefficients reported are the average of determinations with the three halopyridines.

A reaction mixture which had only NMR lines of the intermediate from 2-bromo-5-nitropyridine was lyophylized over several days to remove the solvent. Some crystals embedded in a viscous dark oil were obtained. Part of this residue was dissolved in Me_2SO-d_6; the ^1H NMR spectrum of this solution showed only lines of the intermediate. A second portion was dissolved in D_2O and again the intermediate lines were observed. Addition of alcoholic $AgNO_3$ solution to this solution gave a copious white precipitate but no change in the downfield ^1H NMR spectrum. A third portion was placed on NaCl plates and the IR spectrum recorded. A fourth portion was placed on polyethylene plates and the IR spectrum in the 600–200-cm^{-1} region observed. Infrared bands were observed at 2200 (C≡N), 1640 (C=O), and 1590 cm^{-1} (C=C), but no

peak was observed in the 500–400 cm^{-1} region. Infrared spectra of the 2-halo-5-nitropyridine (KBr pellets) showed carbon–halogen stretching vibrations at 530 (chloro), 470 (bromo), and 450 cm^{-1} (iodo), while 2-bromo-3-methylpyridine exhibited a C–Br vibration at 480 cm^{-1}. Thus, the intermediate compound formed in the reaction of base with the 2-halo-5-nitropyridines likely does *not* contain halogen.

Attempts to observe the intermediate in other solvent systems gave different results. In dioxane/DOD, when the molar ratio of OH^-–2-chloro-5-nitropyridine was less than 2:1, the downfield intermediate and reagent ^1H NMR lines were seen. However, the product lines began to appear and the spectrum became that of the 2-hydroxy-5-nitropyridine (product) in about 1 h. A qualitative attempt to use CH_3CN as a solvent also showed some new lines, but these disappeared before a second ^1H NMR scan (250 s) could be completed.

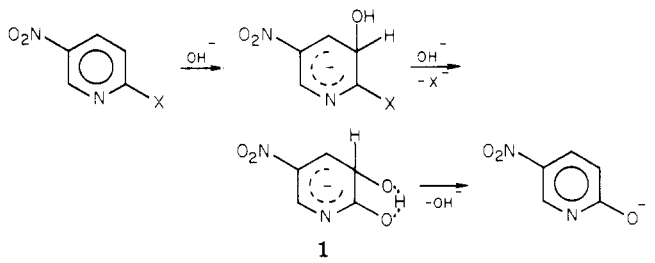
The ^1H NMR spectrum of 2-chloro-3-methyl-5-nitropyridine was also observed under the same experimental conditions as above. New intermediate lines, three sets, appeared as follows: the CH_3 at δ 1.8 (d, J = 1.2 Hz), the other at 9.7 (d, J = 0.6–0.8 Hz), and 6.7 (br m).

Attempts to better resolve this spectrum were not successful; the coupling constants were not very precise, but the methyl group was clearly broadened when compared to the reagent at the same sweep width. The chemical shifts of the downfield resonance were similar to those of the intermediate from the nonmethylated compounds. The rate of decomposition of the methylated intermediate to products was much slower than observed with the nonmethylated cases; under comparable conditions (3:1 molar ratio of OH^-–reagent) the intermediate lines disappeared in 1 day rather than 1 h.

Discussion

The replacement of the halogen on 2-halo-5-nitropyridines by OH^- was initially thought to be a straightforward process. The product was isolated and identified as 2-hydroxy-5-nitropyridine and the reaction was quantitative in terms of the amount of halide released. However, the kinetic expression for a simple bimolecular process was not quite obeyed and a reaction scheme involving one or more intermediate forms was a possible explanation of the results.

A number of observations including (1) the ^1H NMR spectrum of a species different from that of reactant or product when up to 2 mol of hydroxide are present per mole of 2-halo-5-nitropyridine, (2) the UV–vis spectra, (3) the stability of the intermediate, (4) the stoichiometry for formation of the intermediate, and (5) the absence of halogen in the intermediate suggested the presence of a Meisenheimer complex (1).[3-7] While the timing of the



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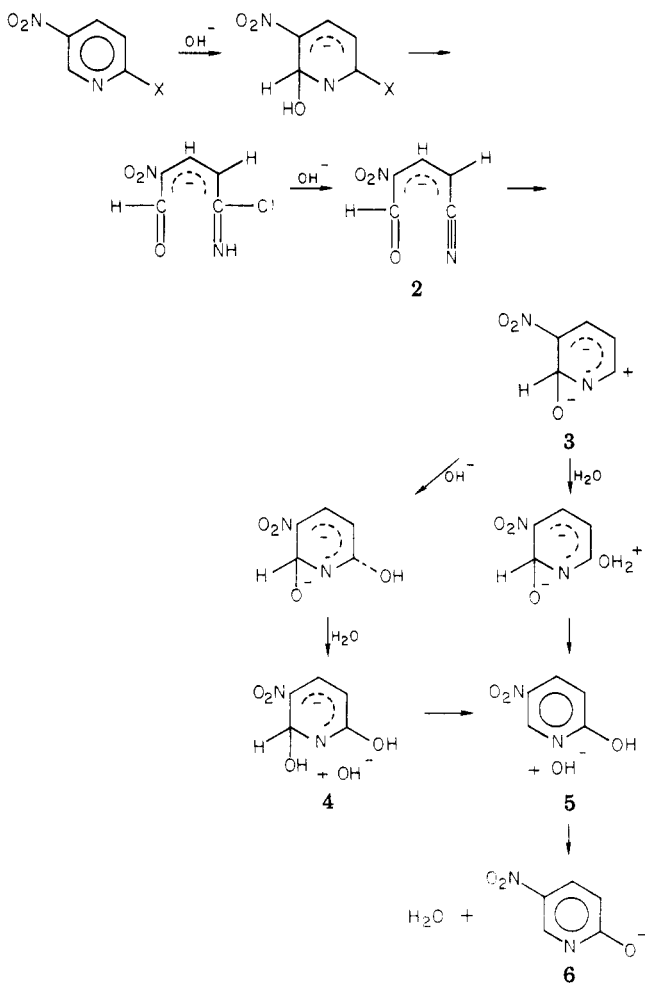
steps leading to 1 is unclear, this structure requires two OH^- to form, has no halogen, two aryl-like protons, and one aliphatic proton, and may well be stabilized by electron delocalization and hydrogen bonding.

However, several difficulties exist with this structure. First, it was hard to understand why one aryl H was shifted downfield relative to starting material, when the expectation was that it should go the opposite way.[3,4] The large coupling constant, J = 12.6 Hz, was not unreasonable, but the smaller coupling constants (J = 1.0, 0.5 Hz) are considerably smaller than similar coupling constants that are reported for Meisenheimer complexes.[7,12] A further objection to this model was the placement of the OH^- on carbon 3, or meta to the nitro and the ring nitrogen. While there was precedent for the rearrangement of groups within a Meisenheimer complex,[3] this seemed to be a strange requirement. Placing a methyl group at position 3 had little effect on the ability of the substituted pyridine to form the intermediate although we would expect the formation of a structure analogous to 1 to be inhibited by the electronic and steric effect of a methyl group at position 3.

Scheme I



Acquisition of ^{13}C NMR and IR data indicated the presence of new groups in the intermediate. A ^{13}C signal with a chemical shift at 182 ppm, the ^1H NMR chemical shift at δ 9.7, and an IR peak at 1640 cm^{-1} pointed to the presence of an aldehyde function in the intermediate while the IR band at 2200 cm^{-1} was indicative of a nitrile group in this structure. Scheme I, reminiscent of the S_N(ANRORC) mechanism proposed by Van der Plas[9] for reactions in the pyrimidine series, accounts for all of our observations. The properties of intermediate 2 are in accord with the data already discussed but are also consistent with the ^{13}C NMR and IR observations. The ^{13}C spectrum of the intermediate exhibits signals for three proton-bearing

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carbons (as indicated by NOE and line-width data) and two nonprotonated carbons. The resonance at 182 ppm is assigned to the carbonyl group while the nonprotonated ^{13}C signals at 127 and 120 ppm are assigned to carbon 5 and the C≡N function, respectively.[13] The ^1H NMR spectra are also consistent with **2**; the chemical shift at 9.7 ppm arises from the aldehyde while δ 6.8 is assigned to the proton at C_4, with δ 5.0 for the proton at C_3. The large coupling constant between H_3 and H_4 (J_{cis} = 12.6 Hz) and longer range couplings to the aldehyde proton have ample literature precedent.[14] The IR frequencies for the C≡N and CHO groups are a bit low compared to standard values.[15] Bellamy suggests that conjugation lowers the C≡N and CHO stretching frequencies and our assignment of 1640 cm^{-1} to the CHO stretch and 2200 cm^{-1} to the C≡N stretch are in reasonable agreement with Bellamy's values of 1664 and 2218 cm^{-1} for conjugated molecules.[15]

Intermediate **2** should be extensively stabilized by electron delocalization and the presence of the nitro group in the conjugated system accounts for the strong yellow color of the reaction mixtures. The driving force for decomposition of **2** to product presumably is the formation of the anion of the product, 2-hydroxy-5-nitropyridine.[16]

Scheme I is also consistent with our observations regarding attack of hydroxide on 2-chloro-3-methyl-5-nitropyridine. Formation of an intermediate analogous to **2** in this reaction should not be particularly affected by the presence of the methyl group. The methyl group at position 3 does influence the reclosure of the intermediate to the pyridine nucleus, possibly by a conformation biasing effect at the C_3–C_4 bond.

We have therefore shown that a stable intermediate intervenes in the process which converts 2-halo-5-nitropyridines and hydroxide to 2-hydroxy-5-nitropyridine, at least in mixed organic solvent/water systems. A substantial body of evidence points to **2** as the structure of this intermediate.

Acknowledgment. We gratefully acknowledge the support of E.I. du Pont de Nemours and Company and the support of generous alumni of the College of Wooster. Work at the University of California, Santa Barbara, was supported by Grant GM-25975 from the U.S. Public Health Service.

Registry No. 2-Chloro-3-methyl-5-nitropyridine, 22280-56-4; 2-chloro-5-nitropyridine, 4548-45-2; 2-hydroxy-5-nitropyridine, 6191-11-3.

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Effect of Charged Substituents on Rates of the Thiol–Disulfide Interchange Reaction

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Received January 16, 1980

Rate constants in aqueous solution at 25 °C are reported for the production of *p*-nitrothiophenol from the mixed disulfides $RSSC_6H_4NO_2$ upon reaction with the thiol anions $R'S^-$. The R′ groups used varied in charge and include $^-O_2CCH_2CH_2$, $^+H_3NCH_2CH_2$, and $HOCH_2CH_2$. The R groups used were these same three in addition to $^-O_2CCH_2CH_2CH_2$. The solutions of $RSSC_6H_4NO_2$ were prepared by allowing $O_2NC_6H_4S^-$ to react with an excess of RSSR, followed by rapidly mixing $R'S^-$ and measuring the return of the absorption due to $O_2NC_6H_4S^-$. The rates for reactions involving charged R and R′ groups differ from those with uncharged groups of identical pK_a by factors of up to 2.5. Negatively charged groups, especially on the central thiol, slow the reaction and positively charged groups speed the reaction to a greater extent than that predicted by the calibrating ionization reaction. Ramifications of these observations are considered for the prediction of rate constants of thiol–disulfide interchange reactions and for the interpretation of β values when reactants of various charge types are used.

Introduction

We have demonstrated recently a simple method whereby the rates of reaction of disulfides with protein thiol groups may be measured.[1] Comparison of the rates of these reactions with the predicted rates based on structure–reactivity correlations[2-5] provides useful information about the site wherein the thiol group resides. The thiol–disulfide interchange reaction is important in cellular redox chemistry, as in the mechanism of glutathione reductase[6] or dihydrolipoamide dehydrogenase,[7] and is also important in the generation of protein tertiary structure.[8]

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