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NITRILOTRIACETAMIDE: SYNTHESIS IN CONCENTRATED SULFURIC ACID AND STABILITY IN WATER

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Abstract: Acid hydrolysis of $N(CH_2CN)_3$ leads either nitrilotriacetamide, **1**, and/or 3,5-dioxopiperazineacetamide, **4**, in quantitative yield. **1** slowly and cleanly converts to 3,5-dioxopiperazineacetic acid, **5**, in water, although ammonium salts prevent this reaction.

Nitrilotriacetamide, **1**, is a highly symmetrical open chain neutral ligand or podand.[1] As part of our program to design and study novel amide ligands for metal chelation, we developed several synthetic approaches to **1** and N-substituted derivatives.[2] We reported the crystal structures of the 1:1 complex of **1** with cobalt(II)[3], the 2:1 complex with lead(II)[4] and several 2:2 complexes with mercury(II).[5] In this note we report in detail the synthesis of **1** from nitrilotriacetonitrile[6], **2**, by hydrolysis in concentrated sulfuric acid. The stability

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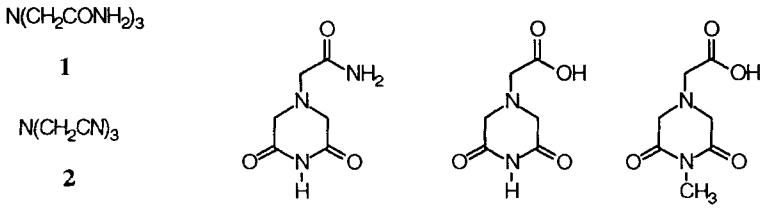
of nitrilotriacetamide in water and various salt solutions is of relevance since **1** has been used to modify the behavior of sodium and potassium chloride solutions; e.g., for the supersaturation of salt solutions during steam-assisted oil drilling[7] and as a crystal habit modifier for sodium and potassium chloride.[8]



Results and Discussion

Amides are often prepared by ammonolysis of carboxylic acid esters with ammonia, primary or secondary amines. The reaction requires water and frequently is slow and low yielding. In 1949, Gordon, et al.[9] described a fast and efficient method for the preparation of amides from esters in the presence of alcohols or glycols. They presented strong kinetic evidence for a mechanism in which hydrogen bonding of ammonia to the solvent causes polarization of a nitrogen-hydrogen bond, followed by attack of the amide ion-like nitrogen at the carbonyl carbon of the ester. A 1974 patent described the application of an improvement in this method to the synthesis of **1**.[10] Esterification of nitrilotriacetic acid, **3**, in neat ethylene glycol followed, without purification, by ammonolysis gave **1** in 90% yield.

A British patent reported a synthesis of **1** that differed significantly from previous routes in that esters were not involved as intermediates. This patent claimed that 3,5-dioxopiperazineacetamide, **4**, formed directly by transamidation of the acid **3** and formamide solvent at 155 - 180 °C.[11] The isolated and purified imide underwent nucleophilic ring opening with aqueous ammonium hydroxide or ammonia to give **1**. A more likely mechanism, based on previous reports of transamidation reactions of **3** by Voronkov and Mikhailova[12] as well as our own work (vide infra) involves the initial formation of **1** followed by cyclization at elevated temperatures to form the piperazine ring. The imide is stable under the reaction conditions, apparently due to the low concentration of ammonia. Further support for this mechanism appears in work by Svedaite, et al., who prepared 3,5-dioxopiperazine derivatives by heating amine diacids in the presence of formamide at 150 - 185 °C.[13] We modified the British procedure to produce a variety of substituted nitrilotriacetamides and 3,5-dioxopiperazineacetamides.[2]

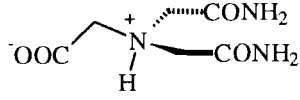
Nitrilotriacetamide was also synthesized from nitrilotriacetonitrile, **2**, by hydrolysis with $Ba(OH)_2$ to obtain the acid, **3**.[14] Subsequent esterification with ethanol and treatment with ammonia effected the transamidation. We reasoned that since nitrile hydrolysis in concentrated sulfuric acid stops at the amide stage[15], **1** could be prepared directly from **2** in a single step.[16] We prepared **1** in this manner utilizing sulfuric acid containing 3 molar equivalents of water. While careful control of the reaction led to quantitative conversion of **2** to **1**, the reaction is exothermic and typically some cyclization of **2** to the imide **4** is

unavoidable. Use of other acids, such as concentrated hydrochloric or 85% phosphoric, gave complicated mixtures of products. Upon complete conversion of **2** to products, the reaction was cooled and poured into methanol to provide a filterable white precipitate, presumably $\mathbf{1}\cdot H_2SO_4$. Dispersion of this solid in methanol followed by treatment with excess anhydrous ammonia both neutralized the acid and opened the piperazinedione ring. We separated the product from the $(NH_4)_2SO_4$ byproduct by washing with DMSO or by crystallization from isopropanol-water.

TLC monitoring of the reaction confirmed that **1** is the initial product. Heating isolated and purified **1** in concentrated H_2SO_4 at 70 °C for 12h gave a mixture from which we isolated **4** in 44% yield. Treatment of **4** under similar conditions did not produce **1**.

The ^1H and ^{13}C NMR spectra of **1**, **2**, and **4** are unremarkable and extremely simple. The chemical shift values are sufficiently unique that ^1H NMR provided routine structure determination. However, we observed that samples of purified **1** in D_2O slowly and cleanly converted into another compound. This new compound exhibited two peaks in a 2:1 ratio, with chemical shift values (δ 3.42, 3.30) similar but not identical to those for **4** (δ 3.60, 3.34). GC/MS indicated a molecular ion at m/z 172 with a major fragment at 127 (loss of CO_2H). We therefore assigned the structure as the hydrolysis product, **5**. Although unable to isolate significant amounts of **5**, we synthesized and characterized, including the single crystal x-ray structure[17], the N-methylated analog, **6**. The ^1H NMR and mass spectrum fragmentation pattern support our assignment of **5**.

Piperazineacetamide **4** did not hydrolyze to **5** under any conditions. Thus, hydrolysis of **1** occurs prior to cyclization. Samples of crude product, that is, **1** mixed with $(NH_4)_2SO_4$ did not convert to **5**. Control experiments involving purifed **1** and various salts showed that ammonium ion completely inhibits this conversion regardless of counterion (Cl^-, SO_4^{-2}, ^-OAc). Whether this is due to a non-specific equilibrium effect, pH, or a specific chelation of ammonium ion by **1** is not clear. Neither is it clear why hydrolysis of one amide functional group to the acid should induce ring closure. Possibly this acid ionizes to the zwitterionic form **7**, as does nitrilotriacetic acid[18], and the concomitant structural changes at the protonated nitrogen facilitate cyclization entropically.



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Experimental Section

All reactions were run in air. Melting points were determined with a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. Infrared (IR) spectra were obtained in dilute solutions in $CDCl_3$ and for crystalline materials as KBr disks on a Nicolet 60SX or 5SX FTIR spectrophotometer. ^1H NMR spectra were obtained at 400 MHz on a Varian VXR-400 spectrophotometer or at 200 MHz on a Gemini VXR-200

spectrometer. ^{13}C NMR spectra were obtained at 50 MHz on a Gemini VXR-200 equipped with a ^{1}H-^{13}C switchable 5mm probe. Chemical shifts are relative to DSS in D_2O or TMS in DMSO and $CHCl_3$. Mass spectra were recorded on a Hewlet Packard 5988A instrument at 70 eV. The samples were introduced into the mass spectrometer as neat solids using the direct inlet probe (DIP), or dissolved in $CDCl_3$ injected through a GC interface equipped with a 12 m methyl silicone capillary column.

Nitrilotriacetamide (1). 10 g (74.6 mmol) of nitrilotriacetonitrile and 4.1 mL (3.1 eq.) of water were added to excess H_2SO_4 (at least 4 eq. of acid are necessary to effect complete hydrolysis) at room temperature. The exothermic reaction began at once and was allowed to warm slowly with mechanical stirring until the temperature reached approximately 40 °C, where it was held using an ice-water bath for 10 min. (WARNING! This reaction is extremely exothermic. Care must be taken to avoid too rapid heating, which can lead to boil-over and violent splattering of acid.) The reaction was allowed to warm further until it reached 60 °C, at which point the exotherm ceased. The reaction was cooled to room temperature after a total reaction time of approximately 30 min to maximize the yield of nitrilotriacetamide and avoid significant formation of the imide. The cooled reaction mixture was poured into 5-10 volumes of anhydrous methanol to give a white precipitate, which was filtered, redispersed in anhydrous methanol, neutralized with anhydrous NH_3 and filtered to give a mixture of **1** and

$(NH_4)_2SO_4$. The organic product was extracted into DMSO that was then removed by vacuum distillation. Recrystallization from isopropanol and water provided 13.75 g (98%) of nitrilotriacetamide, **1**, mp 210-213 °C. ^1H NMR (deuterium oxide): δ 3.44 (s, 6H); ^1H NMR (dimethyl sulfoxide-d_6): δ 7.64 (s, 3H), 7.15 (s, 3H) 3.11 (s, 6H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 172.8 (s, 3C), 58.5 (t, 3C). IR (deuteriochloroform) 2255, 1642, 1588, 1564, 1479, 1094, 0989, 908, 735, 652; MS: m/z 188 (M+), 171, 144, 87, 42. *Anal.* Calcd for $C_6H_{12}N_4O_3$: C, 38.30; H, 6.43; N, 29.77. Found: C, 38.04; H, 6.34; N, 29.99.

Nitrilotriacetonitrile (2).[6] Nitrilotriacetonitrile was obtained from Hampshire and used without further purification, mp 126-8 °C. ^1H NMR (deuterium oxide): δ 4.07 (s, 6H); ^1H NMR (dimethyl sulfoxide-d_6): δ 3.97 (s, 6H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 115.6 (s, 3C), 41.8 (t, 3C). IR (deuteriochloroform) 3157, 2852, 2256, 1382, 1120, 1098, 753, 718, 650.

3,5-Dioxo-1-piperazineacetamide (4). This compound was obtained by prolonged heating of the acid hydrolysis reaction of nitrilotriacetonitrile, **2**, or by treating nitrilotracetamide, **1**, in H_2SO_4. mp 215-216.5 °C. ^1H NMR (deuterium oxide): δ 3.60 (s, 4H), 3.34 (s, 2H); ^1H NMR (dimethyl sulfoxide-d_6): δ 11.14 (bs, 1H), 7.40 (bs, 1H), 7.12 (bs, 1H), 3.31 (s, 4H), 3.05 (s, 2H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 171.6 (s, 2C), 171.1 (s, 1C), 58.1 (t, 1C), 55.4 (t, 2C). IR (deuteriochloroform) 2361, 2255, 1750, 1717, 1699, 1684, 1670, 1663, 1559,

1541, 1522, 1506, 1474, 1395, 1258, 1207, 1007, 908, 735, 727, 652; MS: m/z 171 (M+), 144, 127, 99, 71, 59, 44, 24. *Anal.* Calcd for $C_6H_9N_3O_3$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.61; H, 5.28; N, 24.56.

1-methyl-2,6-dioxopiperazineacetic acid, (5). This material was isolated in 10-28% yield from the reaction of nitrilotriacetic acid, **3**, with N-methylformamide[2], purified by flash column chromatography and recrystallized from 2:1 isopropyl alcohol: toluene. The crystals were filtered and dried on a water aspirator. mp 150-155 °C; IR ($CDCl_3$) 3442, 2251, 1682, 1653, 1055, 1028, 1009, 823, 762, 679, 667; MS (m/e) 186, 141, 113, 42; ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H), 3.60 (s, 4H), 3.37 (s, 2H), 2.99 (s, 3H); ^{1}H NMR (DMSO-d_6) δ 3.7 (bs, 1H), 3.58 (s, 4H), 3.34 (s, 2H), 2.96 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.5, 170.8, 55.3, 25.5. *Anal.* Calcd for $C_7H_{10}N_3O_4$: C, 45.13; H, 5.43; N, 15.04; Found C, 45.51; H, 5.55; N, 14.94.

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16 Direct, single step conversion of nitriles to amides can also be accomplished using 30% H_2O_2 and 6N NaOH; see Org. Synth. Coll. Vol. II, 586. All attempts to convert **2** to **1** under these conditions proceeded vigorously but failed to produce any clean or identifiable products.

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