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A Nitric Oxide-Releasing Polydiazeniumdiolate Derived from Acetonitrile

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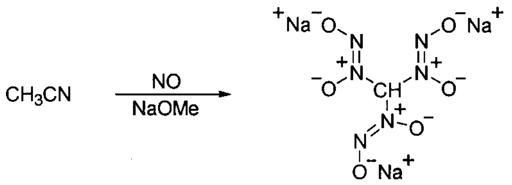
ABSTRACT



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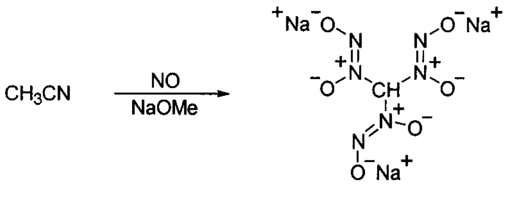
Acetonitrile, frequently used as a solvent in reactions of nitric oxide (NO) with amines and other nucleophiles to introduce the [N(O)NO]$^-$ (diazeniumdiolate) functional group, has itself been shown to react with NO in the presence of strong base to yield methane trisdiazeniumdiolate (1), presumably via an intermediate trisdiazeniumdiolated imidate. Aqueous hydrolysis of 1 does not follow simple first-order kinetics and produces mixtures of NO and nitrous oxide in ratios that vary with solution pH.

Zwitterionic polyamine diazeniumdiolates of the general structure $\mathrm{RN[N(O)NO]^{-}(CH_2)_xNH_2{}^{+}R'}$ have emerged as important nitric oxide (NO) donors for use in biomedical research.[1] Acetonitrile was found to be the solvent of choice for the preparation of these zwitterions, although difficulties were encountered during attempts to prepare pure samples of diazeniumdiolated polyamines containing four or more amino nitrogens.[2] While those results provided no indication that the acetonitrile solvent could itself react with NO gas, the early findings of Traube concerning such reactions involving compounds containing acidic protons,[3] as well as our own investigation of the production of an imidate during similar reactions using benzyl cyanide[4] prompted a study of the reaction of NO with acetonitrile. When conducted in the presence of sodium methoxide, this reaction has now been found to produce methane trisdiazeniumdiolate (**1**) as shown in Scheme 1. This compound has now been isolated, its aqueous solution chemistry has been studied, and a possible mechanism for its formation has been postulated.

Scheme 1



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Although we have described the possible polydiazeniumdiolation of enamines,[5] the well-characterized reactions of

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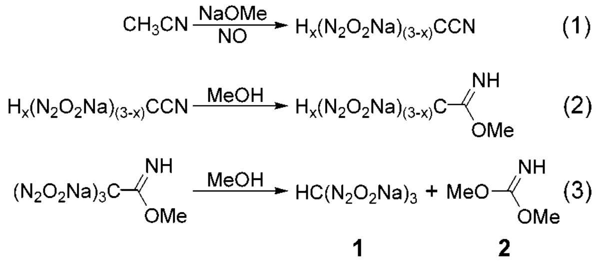
NO with carbanions have generally been limited to either mono-[3,6,7] or bisdiazeniumdiolation[3,4] until the recently reported synthesis of methane trisdiazeniumdiolate.[8] The previously reported[4] yellow solid obtained by reaction of NO with mixtures of acetonitrile and 25% sodium methoxide in methanol solution was thus expected to contain a combination of various diazeniumdiolated nitriles. However, when a mixture of 100 mL of acetonitrile and 10 mL of a 25% sodium methoxide in methanol solution was stirred under NO gas at 40 psig for 24 h, the light yellow precipitate was remarkably clean by NMR spectrometry (exhibiting a single proton signal at 7.6 ppm). Recrystallization of a small sample of this material from 0.01 M NaOH in water/methanol afforded analytically pure trihydrate of methane trisdiazeniumdiolate ($CHN_6O_6Na_3 \cdot 3H_2O$). Arulsamy and Bohle[8] recently reported the isolation and characterization of several crystal forms of the sodium and potassium salts of this trianionic molecular propeller prepared from acetone via the Traube reaction, but none exhibited the exact level of hydration (as indicated by elemental analysis) as this trihydrate, which proved to be rather explosive, detonating violently when heated. Spectroscopic comparison revealed the identity of the trianionic portion of all of these salts, which exhibit identical IR, ^1H NMR, ^{13}C NMR, and UV spectral features.

Traube-type reactions utilize a base to abstract an acidic proton from the substrate to form a carbanion that then reacts with NO gas. In view of the wide variety of amines that might be considered candidates for diazeniumdiolation in acetonitrile solution in the search for new NO donor molecules,[2] several experiments were conducted in an attempt to correlate the acidity of various nitrile carbon acids with their tendency to undergo reaction with NO. The results demonstrated some correlation with nitrile acidity (as measured in DMSO solutions) and reinforced the previously described solvent dependence of NO reactions. Phenylacetonitrile has a pK_a of 21.9,[9] is thus much more acidic than acetonitrile (p$K_a = 31.3$),[10] and reacts readily with NO under the influence of sodium methoxide in methanol solvent. In contrast, phenoxyacetonitrile (p$K_a = 28.1$)[11] did not react with NO under these conditions to produce an isolable product, although a very slight decrease in gas pressure was observed over 24 h, nor did acetonitrile itself react with NO in dilute methanolic sodium methoxide solutions. These results suggest that acetonitrile is just barely acidic enough to react with NO in the presence of the strong base NaOMe only under the most favorable of conditions (i.e., in acetonitrile solvent, the best that has been found for these reactions) and that this reaction is unlikely to complicate its use as a solvent in the diazeniumdiolation of amines. Examination of the original proton NMR spectra reported in 1993[2] showed no traces of a signal at 7.6 ppm that would indicate that any of the polyamines whose diazeniumdiolates were prepared in acetonitrile solution could cause its conversion to methane trisdiazeniumdiolate.

A possible mechanism for the formation of the methane trisdiazeniumdiolate from acetonitrile consists of the formation of an intermediate imidate. It has been reported that the addition of electron-withdrawing groups to acetonitrile greatly enhances the conversion of the nitrile to the imidate.[12] Also, we have shown that the presence of the diazeniumdiolate group can serve to activate the cyano group of benzyl cyanide to ultimately produce the bisdiazeniumdiolated methyl imidate.[4] As shown in Scheme 2, it is reasonable to suggest that one or more diazeniumdiolate groups initially form on acetonitrile as in eq 1. The multiple diazeniumdiolate groups then activate the nitrile toward conversion to the imidate in the presence of methoxide and methanol (eq 2). Attack of base on the imino carbon center followed by C−C bond cleavage would yield the methane trisdiazeniumdiolate (**1**) and imine **2** (eq 3). Certain imines are known to react with NO,[13] and it was not surprising that no trace of **2** could be found in these reaction mixtures since this further reaction probably leads to a cascade of degradation products.

Scheme 2



The decomposition of the methane trisdiazeniumdiolate in deoxygenated aqueous solution was monitored by chemiluminescence to detect NO,[5] gas chromatography to follow nitrous oxide (N_2O) evolution,[14] and UV spectrophotometry to track the disappearance of the diazeniumdiolate chromophore.[2] The quantities of gases produced are shown in

Table 1. Quantification of Gases Evolved from **1**

	NO release[a]			N_2O release[a]	
compound	pH 7.4	pH 5.0	acid spike	pH 7.4	acid spike
$HC(N_2O_2Na)_3$	0.76	1.05	1.17	1.37	1.50

[a] The amount of NO and N_2O detected from the decomposition of methane trisdiazeniumdiolate at 37 °C in the appropriate solutions. Values are expressed in terms of moles of gas per mole of compound. “Acid spike” refers to the rapid introduction of the sample to be decomposed into a large excess of a pH 2.0 sulfuric acid solution.

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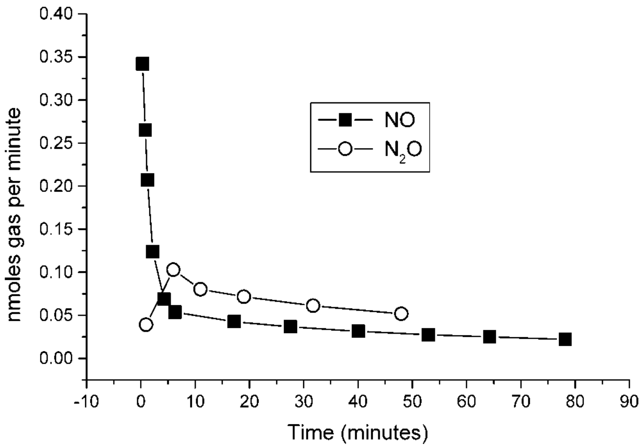

Figure 1. Time Course of NO/N_2O Release From **1**.

Table 1, and a comparison of the NO and N_2O release versus time is shown in Figure 1. The decomposition seems to have two stages. Initial release of NO, with a half-life of 1.6 min in pH 7.4 phosphate buffer, is followed by a second, slower reaction that produces both NO and N_2O with a half-life of 51 min. The spectrophotometric rate of decomposition, as determined by the decay of the peak at 264 nm, was pseudo-first-order, but the above data clearly show that this is a deceptively simple result. The exact nature of the steps involved in the aqueous hydrolysis of **1** still remains to be determined, as does the mechanism of N_2O formation.

These results are noteworthy not only because they present a rare example of a C-diazeniumdiolate which releases NO but also because of the possibilities that they demonstrate for the use of the cyano group as an important tool for the introduction of the diazeniumdiolate functional group into organic compounds of potential medicinal interest. The reported reaction has the effect of replacing the cyano group by the diazeniumdiolate moiety, a reaction of possible future synthetic importance.

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Supporting Information Available: Experimental procedures and characterization data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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