JOC *Note*

Nitric Oxide Reacts with Methoxide

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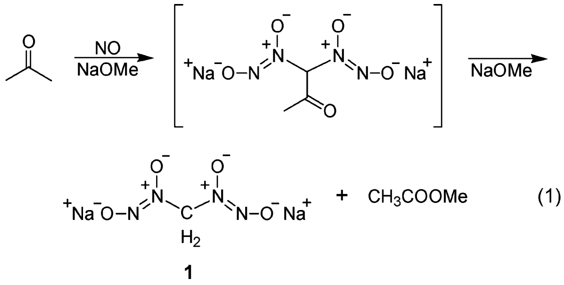
$$CH_3ONa \xrightarrow{NO} HCOONa$$

Despite over a century of reports to the contrary, sodium methoxide has been found to react with nitric oxide (NO). The reaction, whose final organic product is sodium formate, is postulated to occur via an intermediate O-bound diazeniumdiolate [$CH_3O{-}N(O){=}NO^-$] that decomposes to formaldehyde and nitrous oxide. Sodium formate forms from the aldehyde via a Cannizzaro reaction. Carboxylate salts have similarly been obtained by exposing sodium benzylate and sodium neopentoxide to NO in dioxane solution. Accordingly, sodium trimethylsilanoate should be considered as a substitute for sodium methoxide as the base used to accomplish the replacement of active hydrogens by the diazeniumdiolate functional group via the Traube reaction.

The reaction of nitric oxide (NO) with carbanions is one of the most often-used methods for the preparation of carbon-bound diazeniumdiolates (compounds also called nitrosohydroxylamines).[1] Sodium methoxide has remained the preferred base for effecting the deprotonation of a variety of substrates to be subjected to this "Traube reaction" (e.g., that of acetone shown in eq 1) since Wilhelm Traube first introduced the procedure over 100 years ago.[2] Although Weiland and Kerr showed that a variety of other alkoxide anions react with NO, ultimately leading to the production of C-diazeniumdiolated aldehydes, ketones, and carboxylic acid salts, they reported that methoxide does not react "to the slightest degree" (translated from the original German).[3] While carbanion equivalents such as enamines[4] and amidines[5] react with NO as neutral compounds, the addition of NO to carbanions generated in the presence of strongly basic methoxide ion[6−10] is still an attractive route to carbon-bound diazeniumdiolates to be tested as potential NO prodrugs. The continuing use of sodium methoxide in these reactions implies the expectation that it is inert toward NO (a belief that has remained unchallenged for 75 years). However, in contrast to the prior reports, sodium methoxide has now been found to react quite readily with NO to generate intermediates which eventually produce sodium formate as the observable end product. A series of tests using alternative alkoxide bases has led to the recommendation that sodium trimethylsilanoate should be considered the reagent-of-choice for the conduct of the Traube reaction.



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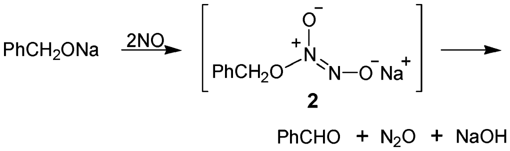
A report of the formation of bisdiazeniumdiolate **1** during the treatment of sodium ethoxide solutions with NO[11] prompted Traube to initially attribute the result to the presence of acetone impurity in the ethanol supply,[12] but eventually led others to the conclusion[3] that the ethoxylate reacted directly with NO to form acetaldehyde, which subsequently underwent the Traube reaction (Scheme 1). In a detailed study of a wide variety of alkoxides, methoxide was reported to be the sole alcoholate that showed no signs of reacting with NO.[3] That study included methanol and benzyl alcohol as the only two representatives of substrates which contain no hydrogens in the β position. β-Hydrogens ultimately become the acidic protons that are replaced by the diazeniumdiolate group after the initial formation of the carbonyl compound. The absence of β-hydrogens in benzyl alcohol prevents the occurrence of the Traube reaction and results in the production of a benzaldehyde/benzoic acid mixture upon treatment of sodium benzylate with NO. These products most likely form in the three-step process illustrated in Scheme 2. The sequence is initiated (eq 2) by the formation of an unstable O-bound diazeniumdiolated intermediate (**2**) that decomposes to generate benzaldehyde, a compound known to undergo the Cannizzaro reaction to create benzoic acid. While several O-alkylated diazeniumdiolated alcohols have been



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SCHEME 1. The Reaction of Sodium Ethoxide with NO

$$CH_3CH_2ONa + 2NO \longrightarrow CH_3CHO + N_2O + NaOH$$

$$CH_3CHO + 2NaOEt + 4NO \longrightarrow (NaO_2N_2)_2CHCHO + 2EtOH$$

$$(NaO_2N_2)_2CHCHO + NaOH \longrightarrow \mathbf{1} + HCOONa$$

SCHEME 2. The Reaction of Sodium Benzylate with NO

$$PhCH_2ONa \xrightarrow{2NO} PhCHO + N_2O + NaOH$$

$$2\,PhCHO + NaOH \xrightarrow[\text{Rxn.}]{\text{Cannizzaro}} PhCH_2OH + PhCOONa$$

$$PhCH_2OH + NaOH \longrightarrow PhCH_2ONa + H_2O$$

reported,[1] these were not prepared directly from the parent alcohols and no alkylating agents are present in this reaction. Among the O-bound diazeniumdiolates, the only frequently studied example remains the inorganic compound known as Angeli's salt $[Na^+O^- - N(O){=}NO^-Na^+]$. Interestingly, Angeli's salt has been shown to convert 1-naphthaldehyde to 1-naphthoic acid under aqueous conditions,[13] so the Cannizzaro reaction may not be the only source of the benzoic acid observed above. While **2** must undergo an isomerization from the cis diazeniumdiolate shown here to the trans isomer to enable its fragmentation to the aldehyde via a cyclic transition state, formation of these types of ring systems is well-known.[1] The previous studies of NO/alkoxide reactions seem to indicate that, although the final products vary, some type of reaction occurs in every instance. They also suggest no apparent reason for the reported and heavily relied upon stability of methanol under these reaction conditions.

We have on many occasions been troubled by the appearance of a seemingly unexplainable singlet at 8.46 ppm in the proton NMR spectra of both carbon- and nitrogen-bound diazeniumdiolate preparations that employed the assistance of sodium methoxide. After realizing that this impurity was sodium formate, the product of the Cannizzaro reaction of formaldehyde[14] produced in a side reaction of the methoxide, we sought reaction conditions that would finally prove the existence of this reaction.

Although a solution of methoxide in methanol forms sodium formate crystals slowly on stirring under a blanket of NO at 4 atm (15% yield after 48 h), the use of a dioxane/methanol solution (5:1) affords a nearly complete reaction in that same amount of time. Assuming that the processes described above are the only ones occurring in this solution (the present work does not prove this!) then the overall reaction of methanol with NO under the influence of strong base may be written as shown in eq 3. Dioxane has not been used previously as a solvent for

$$CH_3ONa \xrightarrow{4NO} HCOONa + 2N_2O + H_2O \qquad (3)$$

NO reactions but seems to provide the ideal combination of NO solubility and product insolubility often required to drive these reactions to completion. Sodium benzylate also reacts rapidly with NO in dioxane to afford sodium benzoate in reasonable yield. Neopentyl alcohol, a third example containing no β-hydrogens, is converted to sodium pivalate by this process.

The intermediate formation of benzaldehyde in the conversion of sodium benzylate to sodium benzoate was verified by conducting the reaction using only the parent alcohol as the solvent. The 2,4-dinitrophenylhydrazone of benzaldehyde could be isolated in 20% yield (based on sodium benzylate) when this reaction was interrupted after 4 h. Attempts to trap the intermediate O-bound diazeniumdiolate in both the methoxide/NO and benzylate/NO reactions via alkylation with either dimethyl sulfate or methyl iodide proved unsuccessful. However, support for the first step in Scheme 2 comes from the fact that, under the anhydrous conditions employed in this study, the use of alkoxide bases in these reactions would lead to the formation of esters in the Cannizzaro reaction (since there would be no hydroxide ion to attack the aldehydic carbonyl in the first step) rather than the acid salts which are isolated were it not for the generation of sodium hydroxide in this step. Benzaldehyde has previously been shown to be a stable end product of the reaction of Schiff bases with NO.[15] No further oxidation to benzoic acid was observed in those reactions. We were unable to verify the formation of nitrous oxide gas as a byproduct due to the construction of our NO reactor, which does not allow for convenient testing of the gases produced. The pressure decrease during the course of these reactions does correspond roughly to a net uptake of 2 mol of gas as shown in eq 3. Elemental analysis as well as traditional wet analytical testing (see the Experimental Section) revealed the presence of small yields of sodium nitrite (1.25%) and sodium nitrate (0.39%) in one sample of sodium formate removed directly from the reaction conducted in dioxane/methanol. Since further testing revealed considerable variation in these numbers, it is assumed that these impurities arise from the presence of traces of oxygen in the reactions upon addition of NO. It should be noted that these inorganic salts are not present in quantities that could be attributable to any significant alternate mechanistic pathway for the reaction.

Other mechanisms for the oxidation of the alcoholates in the first step of this reaction are possible and the data at hand do not allow exclusion of these pathways. In these pressurized systems NO may be reacting either as the monomer or dimer. Alkoxides are capable of acting as single electron donors[16] so the formation of the aldehydes via the corresponding alkyl nitrites and/or alkoxide radicals cannot be excluded.[17] It is likely that different pathways prevail for each alkoxide and the present study was not designed to resolve all these issues.

This newly observed reaction of NO with methoxide represents a potential complication to be overcome in the preparation of any diazeniumdiolate requiring the use of added base. In addition to the carbon-bound materials described above, sodium methoxide has been enlisted to assist in the formation of some of the less readily prepared nitrogen-bound diazeniumdiolates. It has been used in the preparation of diazeniumdiolates of amino acids such as proline[18] and a variety of other obstinate nucleophiles,[19] and in the treatment of polymeric materials with

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NO.[20] Generation of sodium formate might be expected to compete with the formation of the desired products in any or all of these reactions, where diazeniumdiolate formation is either slow or readily reversible. Thus, in addition to avoiding the presence of β-hydrogens to prevent the Traube reaction, it is the avoidance of α-hydrogens that should be paramount in the selection of alcohols as solvents for these reactions.

One possible solution to this problem is the use of sodium trimethylsilanoate as a replacement for sodium methoxide in sluggish diazeniumdiolation reactions. This material offers a higher solubility in organic solvents than sodium *tert*-butoxide and it is somewhat less basic than the standard alkoxides.[21] The lower basicity is advantageous in those cases requiring the presence of methanol cosolvent because it prevents the deprotonation (and subsequent involvement) of the solvent in the reaction. In fact, we have found that a solution of sodium trimethylsilanoate in methanol only very slowly develops a cloudy appearance due to the possible precipitation of sodium formate after being stirred under NO for several days, and no isolable quantity is produced.

The presence of an extra salt such as sodium formate may significantly influence the release of NO from diazeniumdiolated materials, and we have previously noted the detrimental consequences of the presence of even carbonate salts.[22] Since many diazeniumdiolates are not sufficiently stable to be purified by recrystallization,[22] the present results favor the use of sodium trimethylsilanoate as an alternative to sodium methoxide in the Traube reaction and in the diazeniumdiolation of other nucleophiles.

Experimental Section

General Information. NO was purchased in UHP grade and allowed to stand in a ballast tank at about 5 atm pressure over potassium hydroxide pellets for several hours before use. The NO pressure apparatus employed has been described previously.[22] The glass bottles employed should be pressure tested and used behind a shield with caution. NMR spectra were recorded at 400 MHz for proton and 100 MHz for carbon.

Sodium Formate from Reaction of Sodium Methoxide with NO (in Methanol). A 25% NaOMe/MeOH solution (60 mL, 0.26 mol) was placed in a 250-mL glass Parr hydrogenation bottle and purged with argon. The solution was then placed under approximately 80 psi of NO gas and stirred at ambient temperature for 48 h. After approximately 24 h, a white precipitate formed. After 48 h, the pressure was released and the solution was purged with argon. The precipitate was filtered, rinsed with methanol followed by diethyl ether, and dried in vacuo resulting in a white powder. Yield: 1.37 g (7.7%). ^{1}H NMR (D_2O) δ 8.46 (s); ^{13}C NMR (D_2O) δ 173.9.

Sodium Formate from Reaction of Sodium Methoxide with NO (in Dioxane/Methanol). A mixture (containing some suspended solid NaOMe as evidenced by its cloudy appearance) of dioxane (250 mL) and 25% NaOMe/MeOH solution (10.0 g, 46.3 mmol) was prepared in a 500-mL glass Parr hydrogenation bottle and treated in an analogous manner as above. The formation of additional white solid became apparent within approximately 1 h. During the course of 2 d, the pressure dropped substantially and additional NO was added to the apparatus occasionally as required to maintain a pressure of 50−80 psig. After 47 h, copious amounts of precipitate had formed. The pressure was released and the solution was purged with argon. The precipitate was filtered, rinsed with dioxane followed by diethyl ether, and dried in vacuo resulting in a white powder. Yield: 3.10 g (98%). ^{1}H NMR (D_2O) δ 8.46 (s); ^{13}C NMR (D_2O) δ 173.9. Addition of a small quantity of a standard sodium formate sample to either of these NMR solutions did not result in the appearance of any new signals. Anal. Calcd for $C_1H_1O_2Na_1$: C, 17.66; H, 1.48. Found: C, 17.29; H, 1.63; N, 3.08.

A sample of this product was analyzed for nitrite using the standard Griess assay, and then for total nitrite/nitrate via the chemiluminescence signal generated on complete reduction with vanadium(III) chloride followed by reaction of the NO produced with ozone in a Sievers 280i NO Analyzer. In an average of two determinations, it was found to contain 1.79% total nitrite/nitrate and 1.29% nitrite. These represent yields (based on NaOMe) of 1.25% for $NaNO_2$ and 0.39% for $NaNO_3$.

Sodium *tert*-Pentanoate (Sodium Pivalate) from Reaction of Sodium Neopentoxide with NO. A stirring solution of neopentyl alcohol (7.0 g, 79 mmol) in anhydrous dioxane (50 mL) was treated with sodium hydride (0.80 g, 33 mmol) in small portions under an inert atmosphere. As the solution became foamy, aliquots of anhydrous dioxane were added bringing the total volume to approximately 300 mL. Upon completion, the solution was gently heated for 15 min. The resulting light yellow solution was filtered, poured into a 500-mL glass Parr hydrogenation bottle, and purged with argon. The solution was then placed under approximately 80 psi of NO gas and stirred at ambient temperature for 24 h. After approximately 3 h, a white precipitate formed. After 24 h, the pressure was released and the solution was purged with argon. The precipitate was filtered, rinsed with dioxane followed by diethyl ether, and dried in vacuo resulting in a white powder. Yield: 1.08 g (26%). ^{1}H NMR (D_2O) δ 1.11(s); ^{13}C NMR (D_2O) δ 30.3 (3C), 42.6, 191.7. A sample of sodium pivalate was prepared from the free acid using sodium hydroxide; a portion was added to each of these NMR solutions, and no additional signals were observed.

Sodium Benzoate from Reaction of Sodium Benzylate with NO. A stirring solution of benzyl alcohol (4.0 g, 37.0 mmol) in anhydrous dioxane (50 mL) was treated with sodium hydride (0.445 g, 18.5 mmol) in small portions under an inert atmosphere. As the solution became foamy, aliquots of anhydrous dioxane were added bringing the total volume to approximately 150 mL. Upon completion, the solution was gently heated for 30 min. The resulting light yellow solution was filtered, poured into a 250-mL glass Parr hydrogenation bottle, and purged with argon. The solution was then placed under approximately 80 psi of NO gas and stirred at ambient temperature for 24 h. After approximately 10 min, a white precipitate formed. After 24 h, the pressure was released and the solution was purged with argon. The precipitate was filtered, rinsed with dioxane followed by diethyl ether, and dried in vacuo resulting in a white powder. Yield: 1.15 g (43%). ^{1}H NMR (CD_3OD) δ 7.33−7.39 (m, 3H), 7.86−7.89 (m, 2H); ^{13}C NMR (CD_3OD) δ 128.3 (2C), 129.8 (2C), 130.4, 139.5, 172.0. These NMR signals were identical with those observed using a solution of commercial sodium benzoate.

Benzaldehyde 2,4-Dinitrophenylhydrazone. A solution of 2,4-dinitrophenylhydrazine (0.37 g, 1.9 mmol) in methanol (40 mL) was treated with 6 M HCl (1.0 mL) and warmed to ensure dissolution. Separately, the reaction of sodium benzylate with nitric oxide (described above) was performed with slight variation. Benzyl alcohol (1.0 g, 9.25 mmol) was directly treated in a vial with sodium hydride (47 mg, 1.88 mmol), placed into a 250-mL glass Parr hydrogenation bottle, and purged with argon. The solution was then placed under approximately 70 psi of NO gas and stirred at ambient temperature. The reaction was quenched after 4 h via addition of 6 M HCl (0.5 mL). At this time, the previously prepared 2,4-dinitrophenylhydrazine solution was brought to a gentle boil.

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The biphasic mixture that resulted upon quenching of the reaction was then added to the boiling solution. A bright orange precipitate formed immediately and the hot solution was stirred for approximately 1 min. Upon cooling to room temperature, the mixture was filtered, rinsed with the minimum amount of cold water, and dried in vacuo resulting in a bright orange fluffy precipitate. Yield: 0.11 g (20%). ^{1}H NMR (DMSO-d_6) δ 7.48−7.50 (m, 3H), 7.77−7.81 (m, 2H), 8.10 (d, $J = 9.6$ Hz, 1H), 8.37 (dd, $J = 9.6$ Hz, $J = 2.7$ Hz, 1H), 8.70 (s, 1H), 8.86 (d, $J = 2.7$ Hz, 1H), 11.67 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 116.8, 123.0, 127.3 (2C), 128.9 (2C), 129.5, 129.7, 130.5, 133.8, 137.0, 144.5, 149.4; UV (CH_3CN): λ_{max} (ϵ) 380 nm (27.0 mM^{-1} cm^{-1}) [lit.[23] UV (95% EtOH): λ_{max} (ϵ) 378 nm (29.2 mM^{-1} cm^{-1})]. Mp 247−248 °C (lit.[23] mp 238−239 °C).

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Supporting Information Available: Copies of the NMR spectra for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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