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DISPLACEMENT OF O- VERSUS N-SUBSTITUENTS FROM NITROSAMINE-DERIVED DIAZENIUM IONS BY THREE DIVERGENT MECHANISMS

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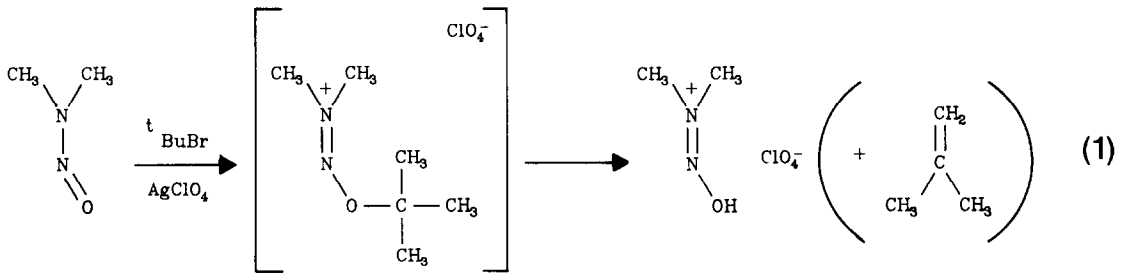
Summary: Cations formed on O-coordination of N-nitrosodimethylamine with different electrophiles decomposed by different routes: dissociation of $Me_2N{=}NOCMe_3^+$ ClO_4^- to $Me_2N{=}NOH^+$ ClO_4^-; regeneration of free nitrosamine by nucleophilic cleavage of the O-Si bond in $Me_2N{=}NOSiMe_3^+$ $CF_3SO_3^-$; and nucleophilic displacement of the N-methyl groups from $Me_2N{=}NOSO_2CF_3^+$ $CF_3SO_3^-$.

CAUTION: Most N-nitroso compounds are potently toxic and carcinogenic.[1] They must be handled, stored, and discarded with due respect for their hazardous properties.

Diazenium ions produced on coordinating nitrosamines ($R_2N{-}N{=}O$) with electrophiles (E^+) have been shown to undergo an interesting variety of reactions,[2-10] certain of which are thought to be implicated in the mechanism of carcinogenesis by N-nitroso compounds.[9-11] Elucidation of the factors that govern which of the numerous available decomposition pathways these $R_2N{=}N{-}OE^+$ ions will follow in their reactions with nucleophiles is a goal of particular urgency if their biological activity is to be adequately understood. Data reported thus far indicate that the identity of the starting nitrosamine and the nature of the attacking nucleophile are both important determinants of reaction course for $R_2N{=}N{-}OE^+$ derivatives in which E is an alkyl group.

To investigate the influence of changes in a third parameter, the identity of the coordinating electrophile, on the reactivity of $R_2N{=}N{-}OE^+$ ions, we have prepared and studied the O-^{t}butylated, O-trimethylsilylated, and O-trifluoromethanesulfonated derivatives of N-nitrosodimethylamine (1). We report below on the unexpected divergence in reactivity among these species.

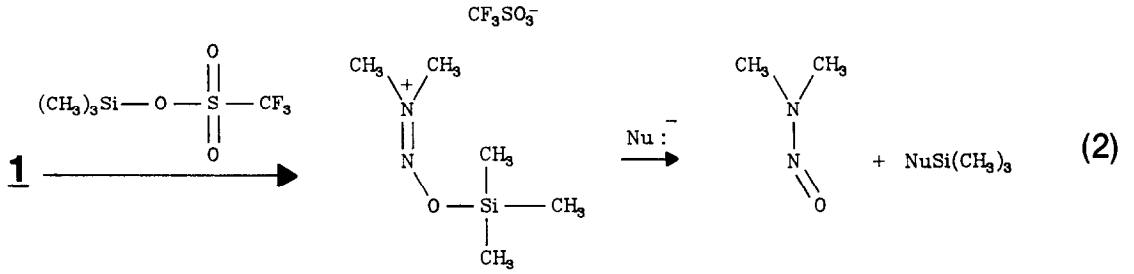
Unlike previously reported O-alkylated nitrosamines, which are normally quite stable in the absence of strong nucleophiles, the ^{t}butyl compound (2)[12] decomposed very rapidly at room temperature.[4] Attempted recrystallization yielded a stable product identified as the perchloric acid salt of N-nitrosodimethylamine, 3, as shown in equation 1.[12] A unimolecular mechanism seems likely for this decomposition, the first step being C-O bond cleavage followed by net proton transfer from the resulting ^{t}butyl cation to the weakly basic nitrosamine leaving group. Net nucleophilic attack can be viewed as occurring at the β-proton of the O-alkyl substituent in this pathway.



(1)

1 **2** **3**

We then prepared the corresponding silicon derivative, 4, for parallel reactivity studies.[12] Nucleophilic attack of water, fluoride ion, aniline, and iodide ion on 4 rapidly cleaved the Si-O bond and regenerated the nitrosamine (equation 2). This behavior parallels the C-O bond cleavage reactions commonly seen on exposure of otherwise stable O-alkylated nitrosamines to nucleophiles.[2-6]

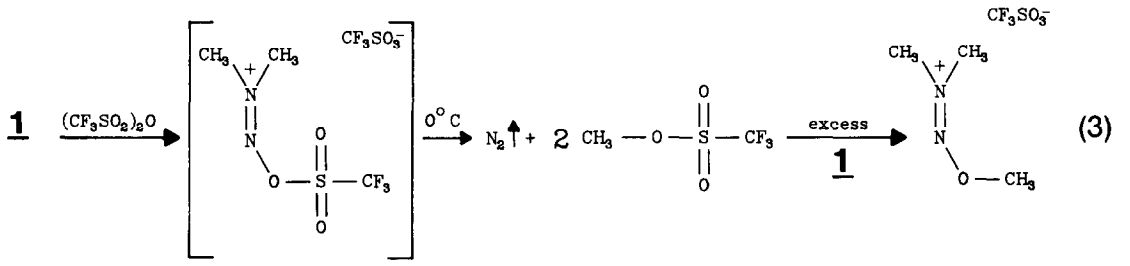


(2)

4 **1**

We next reacted 1 with triflic anhydride. The O-coordinated onium ion, 5, presumably formed initially, but it decomposed with loss of nitrogen on warming to 0 °C. When triflic anhydride was equimolar with the nitrosamine, the major NMR signal of the product was coincident with that of added methyl triflate.[12] When excess nitrosamine was used, however, the spectrum contained three equal-intensity singlets that coincided in both proton and carbon chemical shift with those of the N,N-dimethyl-N'-methoxydiazenium ion, 6.[12]

We rationalize the triflic anhydride reaction in terms of the mechanism shown in equation 3. Apparently, incorporation of the nitrosamino oxygen into an excellent leaving group greatly increases the electrophilicity of the N-alkyl substituent. This behavior is reminiscent of C-N cleavage induced in nitrosamines during certain protolytic reactions[13] and after conversion to the 3-alkyl-4,5-dihydro-1,2,3-oxadiazolium ion.[9] The powerful reactivity of 5 was confirmed by a trapping experiment in which toluene was converted by 5 to a mixture of xylenes.[12] Toluene did not react with triflic anhydride or methyl triflate, however, suggesting that methyl displacement is a process for which 5 is a more powerful electrophile than methyl triflate.



5 6

Nucleophiles have normally been found to react with O-coordinated nitrosamines ($R_2N{=}N{-}OE^+$) to cleave the O-E bond,[2-6] remove an α-proton from R,[5,7] or attack the central (O-bound) nitrogen.[5,6,8] Less frequently, abstraction of a β-proton from R has been observed to initiate decomposition,[6] and nucleophilic displacement of an R group can also occur.[5,9] It is the latter pathway that is thought to be of greatest importance to the genotoxic activity of such species[9,10] though extensive O-E bond cleavage can also be observed with substrates that are susceptible to displacement of the N-substituent.[9] The present results show that these two pathways can be cleanly separated by changing the identity of the coordinating electrophile. Further study of such systems should yield an improved understanding of the role these and other limiting mechanisms of nitrosamine decomposition might play in determining the chemical and biological properties of the cations formed on O-coordination of nitrosamines with electrophiles.

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12. Data supporting the assigned structures include the ^{1}H NMR spectra in CD_2Cl_2: 2 (-40°C) δ 1.56 (9H), 3.89 (3H), 4.16 (3H); 3 (22°C) 3.45 (3H), 3.87 (3H), 13.10 (1H); 4 (22°C) δ 0.52 (9H), 3.72 (3H), 4.14 (3H); methyl triflate (0°C) δ 4.22; 6 (22°C) δ 3.92 (3H), 4.22 (3H), 4.86 (3H). Xylenes were identified by gas chromatography.

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