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Novel Reagents for N-NO_2 Scission

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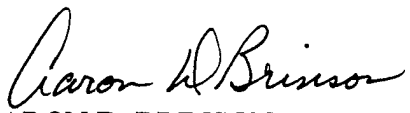

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13. ABSTRACT *(Maximum 200 words)*
Two novel approaches to N-NO_2 bond scission in military nitramines under gentle, environmentally benign conditions were proposed for the Phase I program and have been successfully demonstrated. These approaches to N-denitration were based on mechanisms of: electron transfer hydrogenolysis by certain dihydropyridine derivatives, which was demonstrated on both tetryl and HMX as model aromatic and heterocyclic nitramines, respectively; and catalytic transfer hydrogenolysis, which employed hydrazine as a gentle reagent which denitrated HMX as a model nitramine. In the first system, N-NO_2 bond scisssion in tetryl was demonstrated as the predominant transformation in its reaction with 1-benzyl-1,4-dihydronicotinamide (BNAH), a commercial dihydropyridine derivative, resulting in N-methylpicramide as the major product. In the HMX-BNAH system, HMX was definitively shown to be denitrated, and spectroscopic evidence was obtained for its conversion to hexamethylenetetramine, the expected product of its denitration. Similarly, in palladium-catalyzed reactions between HMX and hydrazine, HMX was unequivocally denitrated. The products produced depended on reaction conditions. The initial intermediate is the reactive species formaldazine; under oxidizing conditions with catalyst, this reacts further to form 4-amino-4*H*-1,2,4-triazole as a final product.

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1. INTRODUCTION

The chemical degradation of nitramines has been of interest to the Department of Defense for years for various practical applications: the disposal of residual product and by-products from the production of nitramine ingredients; treatment of waste streams from the production processes; and now for the demilitarization of nitramine-based ordnance by "denitration" of this energetic component. Of the nitramine treatment procedures developed or studied to date (some at only a research level), none is amenable to bulk-material treatment on a large scale without deleterious effects on the environment or significant (perhaps prohibitive) handling problems generated by the system.

The chemistries of some nitramine disposal processes that have been used on a small scale or considered for development have included:

• Incineration: Though this may be considered a technically valid demilitarization process, destruction methods such as open burning/open detonation and incineration have recently come to be much less favorable options due to environmental and cost restrictions.

• Acid degradation: This approach would entail significant disposal problems for the large amounts of corrosive by-products generated in the process.

• Alkaline degradation: Although such chemical treatment is also technically feasible, the disadvantages are similar to those produced in acidic treatments in that corrosive waste streams are generated, resulting in difficult disposal problems.

• Biodegradation: As described below, the consensus of several studies of this general approach is that only *anaerobic* biotransformation is effective (without a new technological breakthrough) in achieving efficient degradation of nitramines. In these systems, scission of the nitramine bond is *not* achieved; rather, the materials are biochemically reduced to amine derivatives (e.g., nitrosamines and hydrazines) that may be more toxic than the parent compounds. Furthermore, biological approaches tend to be long-term processes (on the order of days to weeks) and efficiencies tend to be more suitable for trace levels (ppm) of nitramines rather than of bulk materials.

• Miscellaneous approaches, such as adsorption-oxidation and/or photochemical processes, have always proved marginally effective in degrading low levels of nitramine contaminants. The known photochemical mechanisms that are known usually effectively result in deoxygenation of nitramines rather than $N–NO_2$ scission.

The opportunity thus existed for the demonstration and development of a new, efficient, and environmentally benign process for denitration of nitramine materials in the DoD demilitarization inventory. Two such processes are described herein.

2. BACKGROUND

Several chemical processes have been studied over the past few decades to achieve conversion and disposal of nitramine by-products and waste as a result of the DoD's ordnance production operations as well as load, assembly, and packing (LAP) operations. These historical approaches are described in the following sections. All of these approaches suffer from technical disadvantages upon consideration for an application of increasing interest, namely demilitarization of bulk nitramine-based materials. Indeed, none of these methods is ideal for any large-scale nitramine denitration process requiring high efficiency based on an environmentally benign process.

2.1 ACID DEGRADATION

The instability and degradation of nitramines under non-nitrating-acid conditions has been known for many years—at least since 1924, when Davis and Allen reported that the acid hydrolysis of tetryl with concentrated sulfuric acid yielded *N*-methylpicramide.[1] By 1952, Holstead and Lamberton reported mechanistic studies showing the generation of nitronium ion upon acidic hydrolysis of secondary aliphatic nitramines.[2] More nitramines of ordnance interest (RDX and HMX) were utilized soon thereafter by Šimeček[3] and by Semel et al.;[4] these nitramines were efficiently degraded by concentrated sulfuric acid. Urbański and Żyłowski also utilized the nitronium species generated upon acidic hydrolysis of nitramines (nitroguanidine and nitrourea) as a nitrating agent for other substrates.[5]

The mechanism thus appears well founded, but among the obvious practical disadvantages to such a process for large-scale demilitarization of ordnance are the handling and disposal of inordinate quantities of corrosive solvents and by-products.

2.2 ALKALINE DEGRADATION

The chemical degradation of nitramines under sufficiently basic conditions has also been long recognized—since the 1890's, as reviewed by Lamberton.[6] The DoD accepted this chemical technique as a possible disposal method for nitramine materials at least as early as 1945, when Clear and Rinkenbach recommended a process for destruction of RDX by boiling it in aqueous sodium hydroxide.[7] Similar alkaline degradations were studied in succeeding years. Epstein and

[1] Davis, T.L.; Allen, C.F.H. *J. Am. Chem. Soc.* **1924**, *46*, 1063-1065.
[2] Holstead, C.; Lamberton, A.H. *J. Chem. Soc.* **1952**, 1886-1894.
[3] (a) Šimeček, J. *Chem. Listy* **1957**, *51*, 1699-1703; *Chem. Abstr.* *52*:4665b. (b) Šimeček, J. *Anal. Chem.* **1961**, *33*, 260-262.
[4] Semel, S.; Laccetti, M.A.; Roth, M. *Anal. Chem.* **1959**, *31*, 1050-1052.
[5] Urbański, T.; Żyłowski, J. *Bull. Acad. Polon. Sci. Ser. Sci. Chim.* **1967**, *15*, 7-9.
[6] Lamberton, A.H. *Quart. Rev.* **1951**, *5*, 75-98.

Winkler[8] used the differential hydrolytic reactivity of HMX and RDX as a means of analyzing HMX content in RDX. Basic research on the global mechanism of alkaline degradation of various nitramines was conducted at Los Alamos Scientific Laboratory[9] and at the Naval Surface Weapons Center (White Oak).[10] The latter researchers described a process for the disposal of small amounts of RDX in large volumes of waste water by chemical degradation on strongly basic ion-exchange resins[11] (a process also not readily amenable to scale-up to bulk quantities of nitramines). An academic study of the kinetics of alkaline hydrolysis of RDX and HMX has also been reported.[12]

2.3 BIOLOGICAL DEGRADATION

Biologically based destruction methods for nitramines have been investigated occasionally since the early 1970s.[13,14] Williams et al. reviewed these methods up to 1988.[15] The only methods that were eventually successful in efficiently degrading low levels of nitramine ingredients required anaerobic reaction conditions. In such systems, scission of the nitramine bond is *not* achieved; rather, the materials are biochemically reduced to amine derivatives (e.g., nitrosamines and hydrazines) that may be more toxic than the parent compounds. McCormick et al. (U.S. Army Natick Laboratories) proposed a global mechanism for the biodegradation of RDX (Scheme 1).[16] Several of the products were found to be mutagenic or carcinogenic or both.

Williams et al. described the reduction by 99.1% and 96.5%, respectively, of solvent-extractable RDX and HMX in explosives-contaminated lagoon sediments by composting for 153 days in a thermophilic (55 °C) compost pile.[15] However, it was acknowledged that the exact fate of the explosive contaminants could not be determined. It was suggested that "a large portion of the observed reduction in contaminant concentration may be attributed to chemical sorption and/or

[7] Clear, A.J.; Rinkenbach, W.H. Dover, NJ, Aug 1945, Picatinny Arsenal TR 1556.

[8] Epstein, S.; Winkler, C.A. *Can. J. Chem.* **1951**, *29*, 731-733.

[9] (a) Jones, W.H. *J. Am. Chem. Soc.* **1954**, *76*, 829-835. (b) Jones, W.H. *J. Am. Chem. Soc.* **1954**, *76*, 928-929.

[10] Hoffsommer, J.C.; Kubose, D.A.; Glover, D.J. *J. Phys. Chem.* **1977**, *81*, 380-385.

[11] Hoffsommer, J.C.; Kubose, D.A. Silver Spring, MD, Jun 1977, NSWC/WOL TR 77-30; AD–A045230; *Chem. Abstr. 88*:125981u.

[12] Croce, M.; Okamoto, Y. *J. Org. Chem.* **1979**, *44*, 2100-2103.

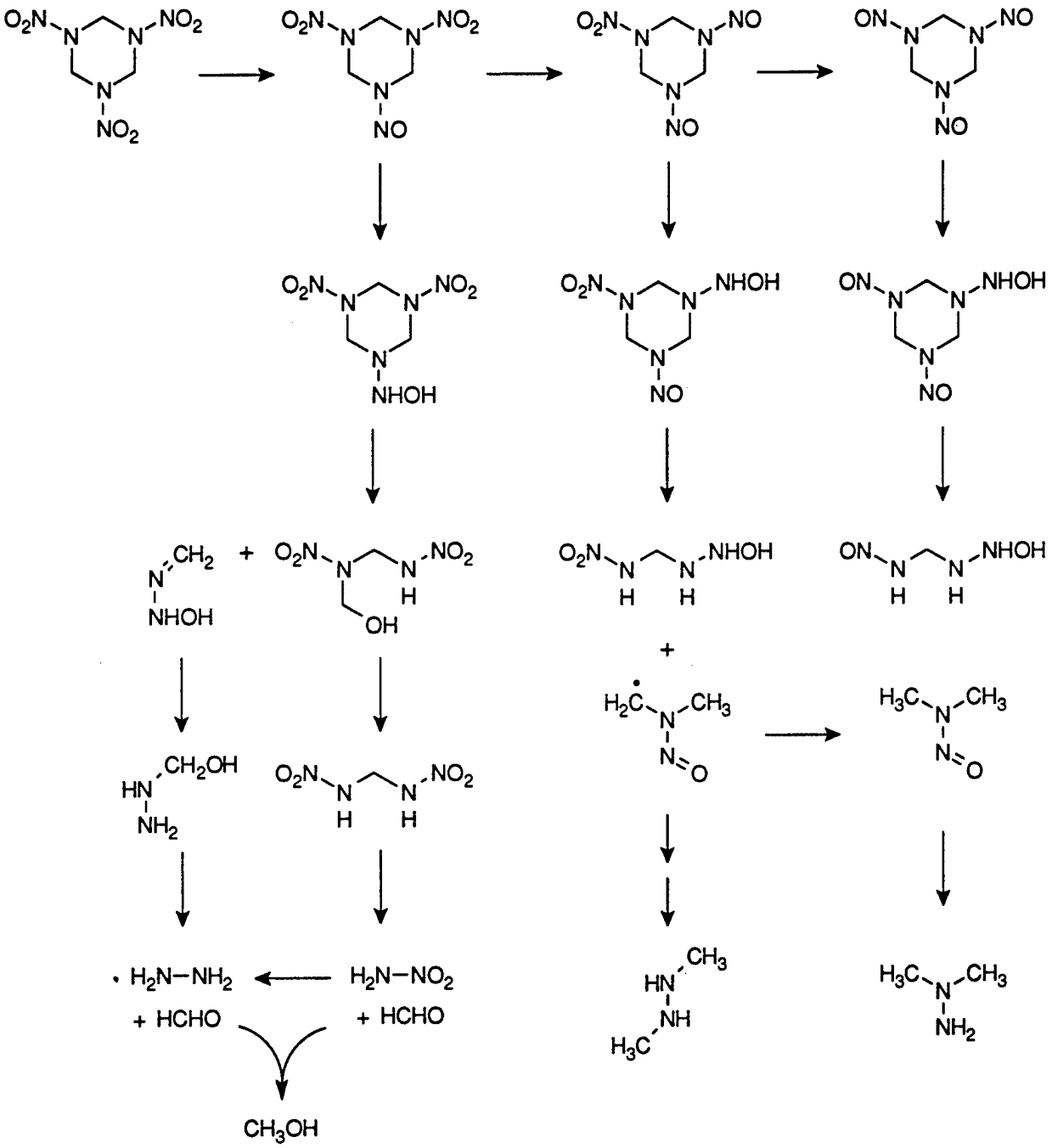
[13] Osmon, J.L.; Klausmeier, R.E. *Dev. Ind. Microbiol.* **1973**, *14*, 247-252; *Chem. Abstr. 82*:47450e.

[14] Soli, G. China Lake, CA, Jun 1973, NWC TP 5525; AD 762751; *Chem. Abstr. 80*:56014b.

[15] Williams, R.T.; Ziegenfuss, P.S.; Marks, P.J. Aberdeen Proving Ground, MD, Sep 1988, USATHAMA Report AMXTH-IR-TE-88242; AD–A202383.

[16] (a) McCormick, N.G.; Cornell, J.H.; Kaplan, A.M. *Appl. Environ. Microbiol.* **1981**, *42*, 817-823. (b) McCormick, N.G.; Cornell, J.H.; Kaplan, A.M. Natick, MA, Jul 1984, U.S. Army Natick Research & Development Center TR-85/007; AD–A149464; *Chem. Abstr. 103*:41939b. (c) McCormick, N.G.; Cornell, J.H.; Kaplan, A.M. Natick, MA, Jul 1984, U.S. Army Natick Research & Development Center TR-85/008; AD–A149462; *Chem. Abstr. 103*:41938a.

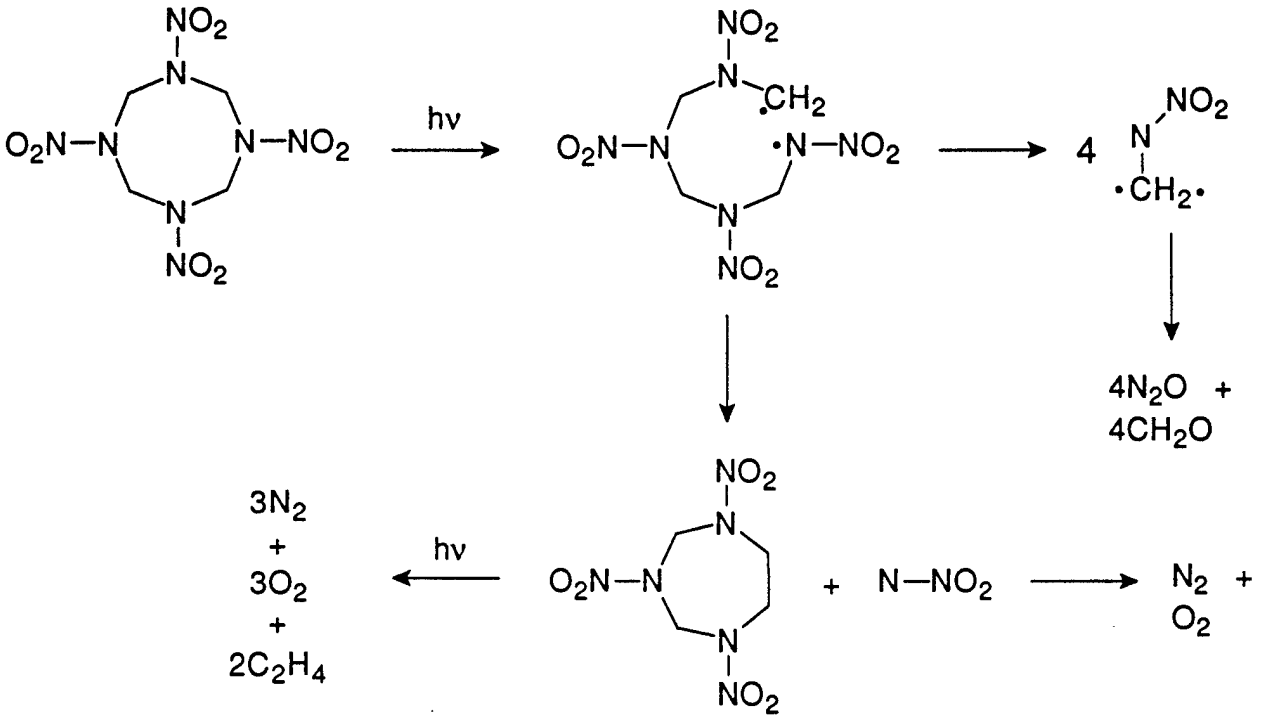
binding of reactive biotransformation products as opposed to complete microbial mineralization of the parent compounds." The process also appears not to be readily amenable to large-scale processing of bulk pure explosives for purposes of demilitarization.



Scheme 1. Chemical processes in microbial degradation of RDX (from reference 16a)

2.4 MISCELLANEOUS DEGRADATION PROCESSES

Over years of research on nitramines, various other chemical degradation mechanisms have been encountered. Stafford reviewed studies of nitramine photochemistry reported up to 1978.[17] Model nitramines have been subjected to UV photolysis by several research groups in government and academic laboratories. Torbit (Naval Postgraduate School) proposed global mechanisms for HMX photodecomposition under various conditions. For the neat compound, the following scheme was suggested:[18]



Scheme 2. Photochemical decomposition mechanism of HMX (from ref. 18 cited in ref. 17)

At Picatinny Arsenal, Bulusu showed that photolysis of neat dimethylnitramine resulted in deoxygenation (N–O bond cleavage) to the corresponding nitrosamine.[19] Hoffsommer and Kubose (NSWC) attempted to develop a photochemical method for treatment of dilute aqueous solutions of RDX,[20] but this did not evolve into a large-scale process. In a study at Simon Fraser

[17] Stafford, S.L. Annapolis, MD, Jun 1978, U.S. Naval Academy Trident Scholar Project Report 96; AD–A058678; *Chem. Abstr. 90*:152141t.

[18] Torbit, J.B. M.A. Thesis, Naval Postgraduate School, 1970; cited in ref. 17.

[19] (a) Suryanarayanan, K.; Bulusu, S. *J. Phys. Chem.* **1972**, *76*, 496-500. (b) Bulusu, S. Compat. Propellants, Explos. Pyrotechnics Plast. Addit., Conf., 1974; Am. Def. Prep. Assoc.: Washington, DC, 1975; p. II-C; *Chem. Abstr. 86*:142410h.

[20] Hoffsommer, J.C.; Kubose, D.A. Silver Spring, MD, Feb 1977, NSWC/WOL TR 77-20.

University, Chow et al. described photolyses of nitramines in organic solvents that resulted in a "plethora of products"; the mechanism could include homolysis of the N–NO_2 bond, generating aminyl radicals in the process.[21] Nitrosamines survive as the final detectable products because of their photostability under the reaction conditions. Nitrogen dioxide free radical formation has also been detected by EPR spectroscopy in UV photolyses of RDX single crystals at liquid nitrogen temperature and in dimethyl sulfoxide solutions (as an electron spin trap).[22]

In studies conducted by Jain (General Electric Co.) for the U.S. Army, "adsorption-oxidation" was attempted as a method for treatment of nitramine-contaminated wastewater.[23] This involves adsorption of nitro-organic contaminants onto activated carbon, followed by regeneration of the carbon by oxidation of the adsorbate with ozone. However, the following was the conclusion of this approach: "Under the experimental conditions investigated in this study, ozonation causes only a small reduction in the concentration of TNT in pure solution and provides no treatment for RDX, HMX and binary mixtures of TNT, RDX, and HMX." By employment of UV irradiation *in addition to* the adsorption-oxidation treatments, nitramine ingredients could be degraded.[23b] This result is, of course, consistent with the known *photochemical* reactivity of the nitramines.

3. TECHNICAL APPROACHES

3.1 ELECTRON TRANSFER HYDROGENOLYSIS OF NITRO COMPOUNDS

Our preferred novel approach to an efficient N–NO_2 bond cleavage reagent is based on a general transformation originally described in 1980 by Ono et al. (Kyoto University).[24] A chemical model, 1-benzyl-1,4-dihydronicotinamide (BNAH), for a naturally occurring biochemical, reduced nicotinamide-adenine dinucleotide (NADH), was reported to effect the replacement by hydrogen of nitro groups in certain aliphatic compounds. NADH (**1**) is a chemically reduced (hydrogenated) form of NAD, a coenzyme that is necessary for the fermentation of glucose and is found in fresh baker's yeast. Its phosphate ester, NADP, is widely distributed in living matter.[25] The NAD derivatives act as a hydrogen carrier in biochemical oxidations and fermentations.

---

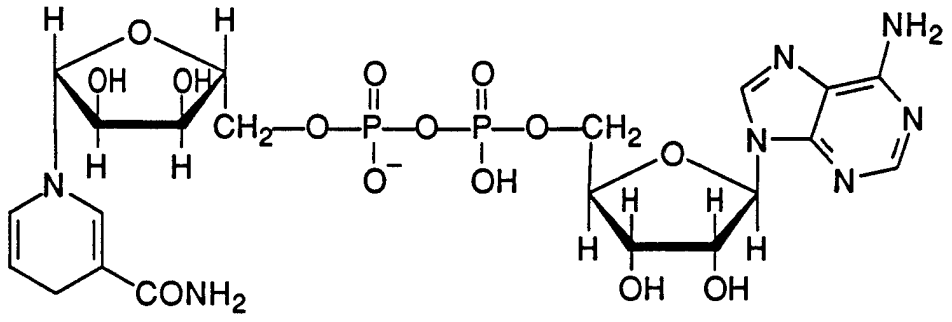
[21] Chow, Y.L.; Richard, H.; Snyder, R.W.; Lockhart, R.W. *Can. J. Chem.* **1979**, *57*, 2936-2943.

[22] (a) Pace, M.D.; Moniz, W.B. *J. Magn. Reson.* **1982**, *47*, 510-514. (b) Pace, M.D.; Holmes, B.S. *J. Magn. Reson.* **1983**, *53*, 143-146.

[23] (a) Jain, K.K. Philadelphia, PA, Jan 1976, General Electric Co. Report, Contract #DAAG53-75-C-0273; AD–A020743; *Chem. Abstr. 85*:130070p. (b) Jain, K.K. Philadelphia, PA, Jan 1976, General Electric Co. Report (Supplement), Contract #DAAG53-75-C-0273; AD–A020744; *Chem. Abstr. 85*:130071q.

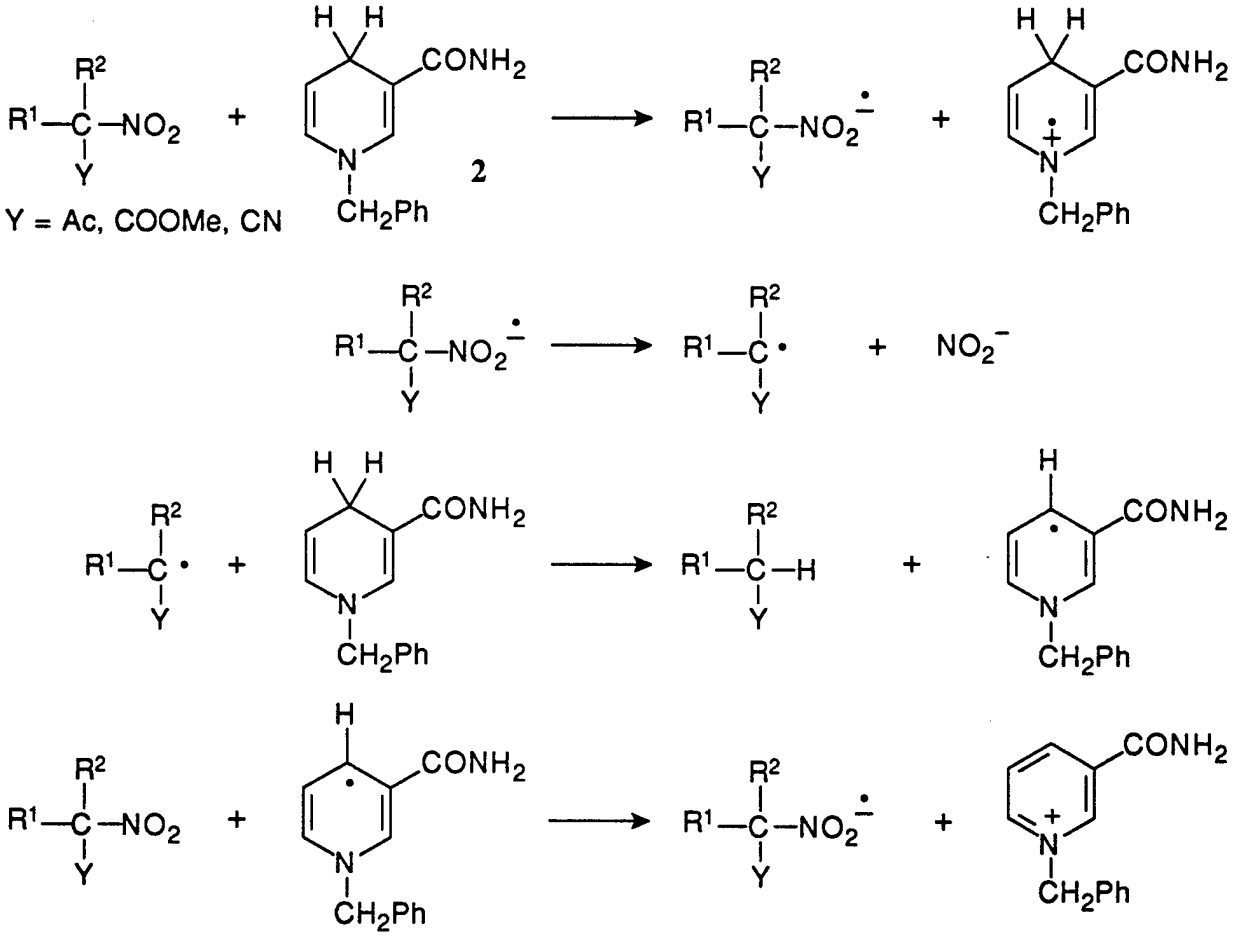
[24] (a) Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* **1980**, *102*, 2851-2852. (b) Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* **1983**, *105*, 4017-4022.

[25] Stecher, P.G., Ed. "The Merck Index", 8th ed.; Merck & Co.: Rahway, NJ, 1968; p. 710.



NADH (1)

The replacement of nitro by hydrogen using BNAH (2) was demonstrated to involve an electron-transfer chain reaction mechanism (Scheme 3).[24]

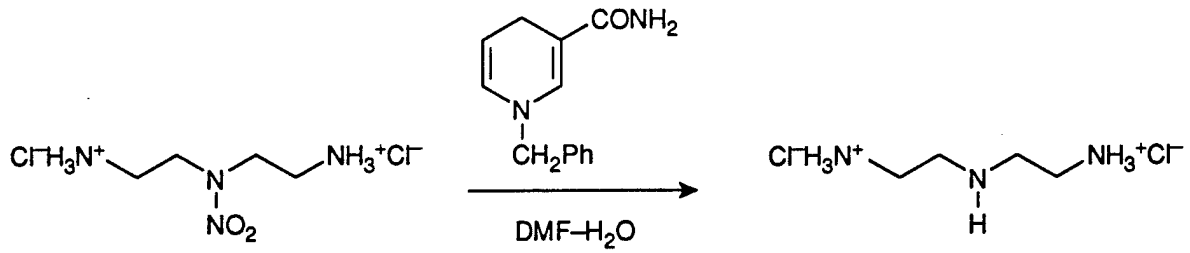


Scheme 3. Electron-transfer hydrogenolysis reaction mechanism (from reference 24)

Soon after the original report of Ono et al., another free-radical chain reaction system was described by Tanner et al. (University of Alberta) in which tributyltin hydride could act as an electron-transfer agent, similarly effecting replacement of nitro groups in nitroaliphatic compounds by hydrogen:[26]

$$R_3CNO_2 + h\nu \rightarrow R_3CNO_2^*$$
$$R_3CNO_2^* + R'_3SnH \rightarrow R_3CNO_2H\cdot + R'_3Sn\cdot$$
$$R_3CNO_2 + R'_3Sn\cdot \rightarrow R_3CNO_2^{-}\cdot + R'_3Sn^+$$
$$R_3CNO_2^{-}\cdot \rightarrow R_3C\cdot + NO_2^-$$
$$R_3C\cdot + R'_3SnH \rightarrow R_3CH + R'_3Sn\cdot$$

Finally, the current Principal Investigator has previously reported that BNAH, at least, *is* a suitable reagent for effecting N–NO_2 bond scission under very mild conditions.[27] In that example, commercially available BNAH (**2**) was reacted with a model nitramine, "XIII-diamine dihydrochloride" (**3**), in aqueous dimethylformamide at ambient temperature. (Compound **3** is known from prior literature.[28]) Photolytic radical-initiation by irradiation with a 275-W tungsten sunlamp overnight showed the expected BNAH oxidation product, 1-benzyl-3-carboxamidopyridinium, as the only nicotinamide derivative present and 74% conversion of **3** to the corresponding unnitrated product, diethylenetriamine dihydrochloride. The apparent complete consumption of BNAH without related by-products suggests that the incomplete conversion of nitramine may be a result of impure BNAH or (more likely) of side reactions such as oxidation by adventitious oxygen during handling. These possible complications were not resolved by this single experiment but could be addressed by a systematic study of this reaction.



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Scheme 4. N-Denitration of a model nitramine by BNAH (from reference 27)

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[26] Tanner, D.D.; Blackburn, E.V.; Diaz, G.E. *J. Am. Chem. Soc.* **1981**, *103*, 1557-1559.

[27] Chapman, R.D.; Archibald, T.G.; Baum, K. "Research in Energetic Compounds", Azusa, CA, Oct 1989, Fluorochem Inc. Report ONR-7-1; AD–A214106.

[28] Frankel, M.B.; Tieman, C.H.; Vanneman, C.R.; Gold, M.H. *J. Org. Chem.* **1960**, *25*, 744-747.

A two-step process for the reduction of aliphatic nitramines using the radical-initiated tributyltin hydride system has been reported; the mechanism proceeds through nitrosamine intermediates.[29] This system offers distinct disadvantages, however, in that the nitrosamine intermediates and all tributyltin derivatives are highly toxic materials, and the optimized yields (≤55%) were lower than that seen in the single BNAH reaction described above. In contrast, a nitramine conversion process based on the hydrogen transfer reaction of dihydroniacinamide derivatives would produce only the desired denitrated amines plus innocuous niacinamide (Vitamin B_3) derivatives as products. The niacinamide product might be recycled back to the dihydroniacinamide reagent for continuous nitramine conversion.

The reactions by dihydronicotinamide (*synonymous with dihydroniacinamide*) were expected to proceed under mild conditions, as reported in the literature for the other nitro-to-hydrogen conversions.[24] The reactions had also been shown to proceed in a great variety of different solvents, including benzene, acetonitrile, dimethyl sulfoxide, hexamethylphosphoramide, and dimethylformamide for the nitro reductions. In addition, reductions of non-polar organics by BNAH have been carried out in *aqueous solutions* by the use of appropriate surfactants. Thus, the photoreduction of (1,2-dibromoethyl)benzene by BNAH was achieved in aqueous borate buffer (containing only 4% acetonitrile) in the presence of sodium dodecylsulfate (20 m*M*) or dodecyltrimethylammonium chloride (30 m*M*) surfactant.[30] That report suggested the prospect of conducting the proposed denitrations in predominantly aqueous systems.

As electron-transfer chain reactions of a radical nature, the proposed conversions must be suitably propagated. Although photochemical activation is convenient in homogeneous, optically transparent systems, alternative *chemical initiation* schemes may ultimately be preferable for some real-world demilitarization operations. The chemical denitration mechanism proposed here is also ideal in being amenable to other, chemical initiations. Thus, Ono et al. also demonstrated that the BNAH reduction of nitroaliphatics could be carried out in high yield *in the dark* by the use of sodium dithionite ($Na_2S_2O_4$) as a one-electron transfer reagent to initiate the BNAH reaction.[24] (They also report that the nitro compounds are *not* reduced by dithionite in the absence of BNAH.) The feasibility of nitramine conversions might also be demonstrated using a chemical electron transfer agent such as sodium dithionite.

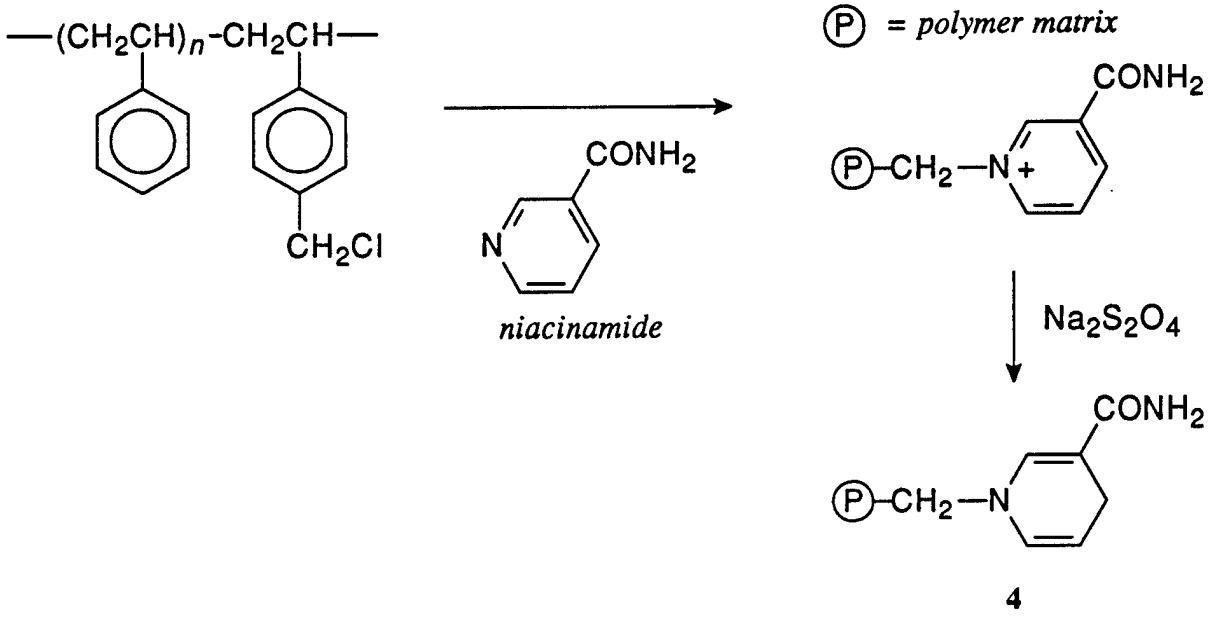
Reports of immobilized NADH models with *polymer-bound* dihydroniacinamides suggested the possible utility of these physicochemical variants as modifications that might be more easily recovered from nitramine conversion procedures, obviating possibly technically difficult separation procedures to recover the niacinamide product. Thus, researchers at the State University of Groningen (The Netherlands) have reported the synthesis and properties of dihydroniacinamide bound to a polystyrene resin (**4**).[31] Later, Bourguignon et al. (Laboratoire de Chimie Organique Fine et Hétérocyclique, Mont Saint Aignan, France) optimized the preparation of this resin, based

[29] de Armos, P.; Francisco, C.G.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1986**, *27*, 3195-3198.

[30] Yamashita, K.; Ishida, H.; Ohkubo, K. *Chem. Lett.* **1991**, 1637-1640.

[31] Eling, B.; Challa, G.; Pandit, U.K. *J. Polym. Sci., Polym. Chem. Ed.* **1983**, *21*, 1125-1137.

on alkylation of niacinamide (Vitamin B_3) with commercial Merrifield resin (chloromethylated polystyrene) followed by reduction of the niacinamide to the dihydroniacinamide with dithionite (Scheme 5):[32]



4

Scheme 5. Synthesis of polymer-bound dihydroniacinamide **4** (from reference 32)

3.2 CATALYTIC TRANSFER HYDROGENOLYSIS OF NITRO COMPOUNDS

It must be clarified that the proposed electron-transfer hydrogenolysis scheme is not equivalent to a chemical reduction process commonly known as "catalytic transfer hydrogenation."[33] In the latter process, a reagent (e.g., cyclohexene or formate ion) capable of supplying hydrogen upon its conversion to a more oxidized form (usually catalyzed by precious metals or their compounds) may act as a "hydrogen transfer reagent" in effecting reduction of other compounds. Thus, the *reduction* of nitro groups to amino groups has been demonstrated using catalytic transfer hydrogenation in several reports over the years: aliphatic and aromatic nitro compounds reduced by cyclohexene–palladium;[34,35] nitroaromatics reduced by palladium-catalyzed formic, hypophosphorous, and phosphorous acids or salts;[36] or palladium-catalyzed reductions of nitroaliphatics by ammonium formate.[37]

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[32] Tréfouel, T.; Tintillier, P.; Dupas, G.; Bourguignon, J.; Quéguiner, G. *Bull. Chem. Soc. Japan* **1987**, *60*, 4492-4494.

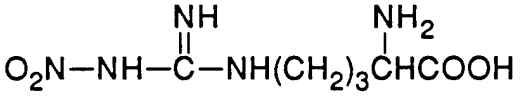
[33] Brieger, G.; Nestrick, T.J. *Chem. Rev.* **1974**, *74*, 567-580.

[34] Braude, E.A.; Linstead, R.P.; Wooldridge, K.R.H. *J. Chem. Soc.* **1954**, 3586-3595.

[35] Entwistle, I.D.; Johnstone, R.A.W.; Povall, T.J. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1300-1301.

[36] Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* **1977**, 443-444.

Nevertheless, this alternative hydrogenolysis mechanism appeared to have prospects in developing a possible technical approach to nitramine denitration because this transformation had been demonstrated in a particularly relevant type of chemical system. Sivanandaiah et al. (Central College, Bangalore, India) reported the deprotection of *N*-nitroarginine (**5**) in protected polypeptides using palladium-catalyzed transfer hydrogenolysis by cyclohexene[38] and by hydrazine.[39] For example, the tetrapeptide BOC–Phe–Arg(NO_2)–Trp–Gly was deprotected to BOC–Phe–Arg–Trp–Gly·HOAc in 88% yield by reaction with cyclohexene and palladium black in acetic acid for 6 hours. Similarly, dipeptides containing Arg(NO_2) were denitrated in 90-95% yields in 0.5–1.0 h with ethanolic hydrazine catalyzed by palladium black. Although these systems collectively constitute little precedence for the general denitration of nitramines, they suggested another technically feasible alternative. One disadvantage of this general approach included an apparent requirement for precious metal catalysts.



5

[37] (a) Ram, S.; Ehrenkaufer, R.E. *Tetrahedron Lett.* **1984**, *25*, 3415-3418. (b) Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1986**, 133-135. (c) Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1988**, 91-95.

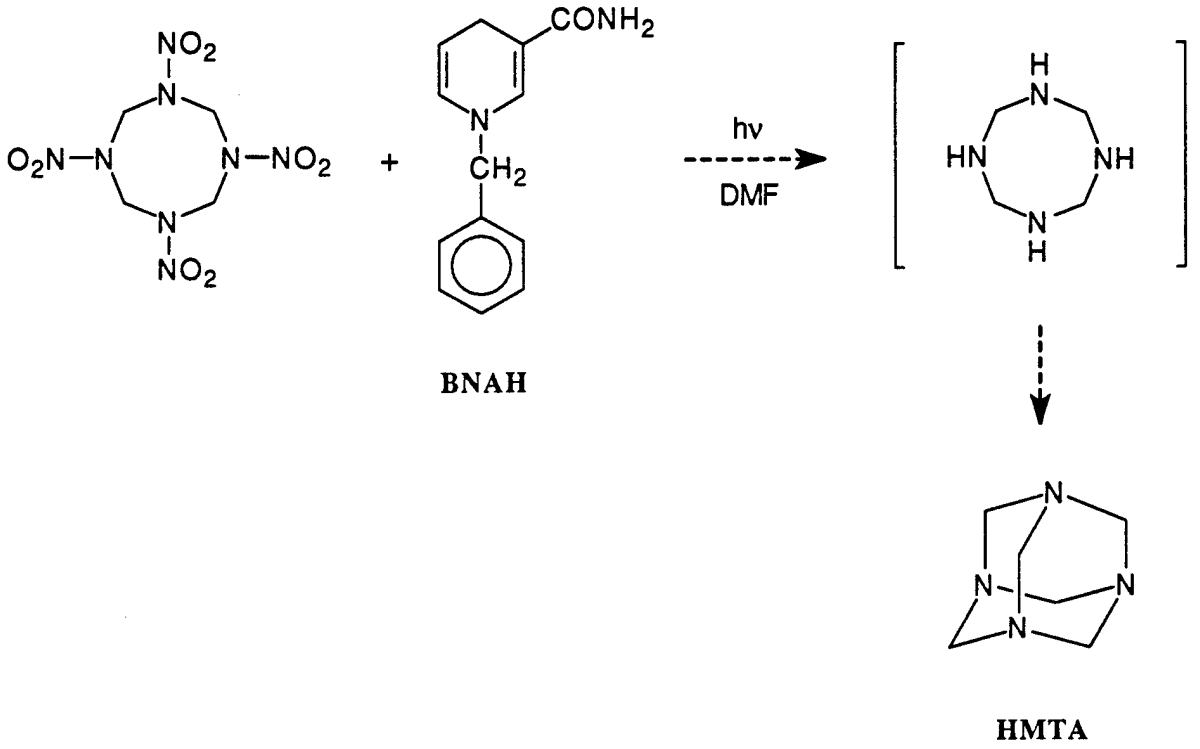
[38] (a) Anantharamaiah, G.M.; Sivanandaiah, K.M. *J. Chem. Soc. Perkin Trans. 1* **1977**, 490-491. (b) Khan, S.A.; Sivanandaiah, K.M. *Synthesis* **1978**, 750-751.

[39] Anwer, M.K.; Khan, S.A.; Sivanandaiah, K.M. *Synthesis* **1978**, 751-752.

4. RESULTS AND DISCUSSION

4.1 HMX–1-BENZYL-1,4-DIHYDRONICOTINAMIDE (BNAH) SYSTEM

Our initial effort was devoted to the demonstration of the denitration of HMX using 1-benzyl-1,4-dihydronicotinamide (BNAH) as a hydrogen transfer agent. By the proposed mechanism (Scheme 6), HMX would be denitrated to the corresponding free amine (octahydro-1,3,5,7-tetrazocine), which would rearrange to the most stable formaldehyde–ammonia adduct, hexamethylenetetramine (HMTA).



BNAH

HMTA

Scheme 6. Proposed N-denitration of HMX by BNAH

4.1.1 Organic Solvent Systems

In the first experiment, the reaction of HMX with BNAH (11.61 equiv per HMX = 2.9 equiv per nitro group) in dimethylformamide (DMF) solvent (nitrogen atmosphere) at ambient temperature, initiated by a 200-W tungsten light bulb, resulted in complete disappearance of the HMX in 24 h, according to ^{1}H NMR analysis. (In the closed cabinet in which this reaction was conducted, the light bulb elevated the ambient temperature of the solution.) A control reaction under the same conditions without BNAH showed no reaction in 5 days. In a modification of the HMX–BNAH–hν reaction, the temperature was controlled with a cooling bath at 5 °C. Under these conditions, an 80% loss of HMX was seen in 24 h; 93% loss in 5 days; and 100%

disappearance in 8 days, according to ^{1}H NMR analysis. Isolation of product from another run under these conditions yielded a D_2O-soluble solute with a single ^{1}H NMR absorption at δ 4.67 which was not residual HOD, being therefore indicative of hexamethylenetetramine.[40] In another modification, the reaction was conducted at ambient temperature outdoors using sunlight as the photolytic initiator. Under these conditions, a 93% loss of HMX was seen in 3 days, and 100% disappearance had occurred after 8 days. Reactions were not monitored on a daily basis, so effectively complete destruction may have occurred within intermediate reaction times.

A proposed alternative initiator of the electron transfer hydrogenolysis is sodium dithionite, which may allow denitrations to be conducted in the dark. In an experiment otherwise similar to the light-initiated reactions, the HMX–BNAH reaction in DMF with $Na_2S_2O_4$ (1 equiv per BNAH = 12 equiv per HMX), at room temperature in the dark, showed only a trace of residual HMX after 65 h reaction. After 4 days, conversion of HMX was complete.

4.1.2 Water Solvent

A preliminary attempt to explore the feasibility of *aqueous* denitration of nitramines (HMX in particular) was made employing conditions that emulated those reported in literature for other aqueous hydrogenolyses by BNAH.[30] HMX (4.5 m*M*) and BNAH (4.9 m*M*) dissolved homogeneously in pH 9 aqueous borate buffer (8% acetonitrile) containing 0.05 *M* dodecyltrimethylammonium bromide as a surfactant. With photolysis by a 200-W tungsten light bulb (under nitrogen atmosphere), the solution under these conditions still contained HMX in aliquots withdrawn after 6 days and 9 days. The preliminary negative result was not surprising, and it might have been reasonably expected that an excess quantity of BNAH reactant could be required or preferable.

A modification of the conditions for aqueous denitration of HMX by BNAH confirmed that the denitration transformation is feasible. HMX (2.6 m*M*) and BNAH (41 m*M*) dissolved homogeneously in pH 9 aqueous borate buffer (5.3% acetonitrile) containing 16 m*M* dodecyltrimethylammonium bromide as a surfactant. With photolysis by a 200-W tungsten light bulb (under nitrogen atmosphere), HMX was consumed in 45 hours. A parallel experiment held outdoors for photolysis by sunlight resulted in consumption of the HMX in 18 days (temperatures ranged from –7 to +13 °C). ^{1}H NMR analyses of the dry product mixtures (after removal of water under vacuum) showed definite absorptions only attributable to the BNAH oxidation product and the surfactant. The product mixture from the sunlight photolysis included an absorption near δ 4.5 in DMSO-d_6, consistent with hexamethylenetetramine.[40]

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[40] Solomon, I.J.; Momil, R.K.; Jarke, F.H.; Kacmarek, A.J.; Raney, J.K.; Adlaf, P.C. *J. Chem. Eng. Data* **1973**, *18*, 335-337.

4.2 HMX–POLYMER-SUPPORTED DIHYDRONICOTINAMIDE SYSTEM

4.2.1 Organic Solvents

Following the synthetic scheme described in Section 3.1 for preparation of this reagent (**4**), chloromethylated polystyrene with a degree of functionalization of 61% was used for alkylation of niacinamide (pyridine-3-carboxamide) in refluxing acetonitrile. By a literature procedure, the reduction by dithionite had been conducted for 6 hours using reactant of a lower degree of functionalization;[32] we continued the reaction for a total of 24 hours.

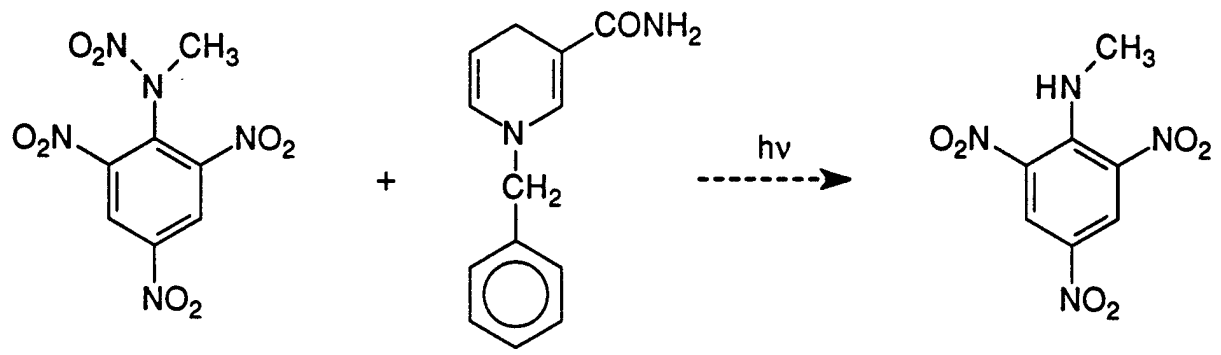
The polymer-supported dihydronicotinamide was first used in a reaction with HMX in DMF solvent catalyzed by a 200-W light bulb at ambient temperature, conditions that were previously successful with BNAH. With a reaction time of only 2 days, HMX was still present. After 14 days of reaction under these conditions, removal of DMF solvent allowed recovery of the majority of HMX starting material. The residue other than crystalline HMX produced a ^{1}H NMR spectrum consistent with a mixture of HMTA and HMX in a mole ratio of 8:92.

4.2.2 Water Solvent

The reaction solvent was changed to water for development of a practical denitration process using this approach. After 11 days of reaction at ambient temperature (catalyzed by a 200-W light bulb), filtration of an aliquot (to remove polymer from the otherwise homogeneous solution) followed by evaporation of water to the air produced a light yellow oily solid that was insoluble in acetonitrile-d_3 but soluble in D_2O. ^{1}H NMR analysis showed no detectable HMX but a predominant peak at δ 4.78 and minor peaks at δ 4.05, 4.42. This major peak's chemical shift coincides with that of residual water, but it is also close to that known for hexamethylenetetramine. The remainder of reaction continued for a total reaction time of 14 days. At that time, the polymer residue was extracted three times with boiling acetone, and the acetone extract showed no sign of HMX according to ^{1}H NMR. Our tentative conclusion was that the polymer-supported dihydronicotinamide denitration of HMX under aqueous conditions is also feasible, although this reagent seems slower in reactivity than the "monomeric" equivalent, BNAH.

4.3 TETRYL–1-BENZYL-1,4-DIHYDRONICOTINAMIDE SYSTEM

By an N-denitration mechanism similar to that observed in other nitramines, tetryl would denitrate straightforwardly to *N*-methylpicramide (**6**); DMF and benzene were expected to be typical technically feasible solvents (Scheme 7).



tetryl **BNAH** **6**

Scheme 7. Proposed N-denitration of tetryl by BNAH

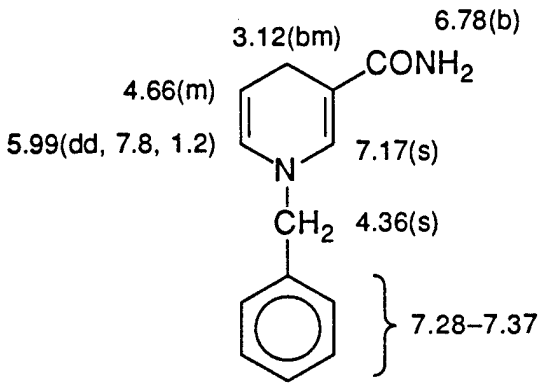
Assessments of the success of the first denitration attempted in DMF were hoped to be based on a comparison of ^{1}H NMR data, which have been reported in the literature for tetryl[41] as well as for **6**.[42] Unfortunately, interferences of overlapping peaks among absorptions of N-methyl protons (from DMF and **6**) precluded a definitive identification of **6** as the product of electron transfer hydrogenolysis under conditions previously successful for HMX. (These conditions included, in all cases with 18–21 equivalents of BNAH per tetryl, unless otherwise indicated: reactions initiated by a 200-W light bulb; reactions initiated by sodium dithionite in the dark; a reaction with 6 equivalents of BNAH per tetryl, initiated by a 200-W light bulb; reactions initiated by sunlight; and a control reaction *without* BNAH, in which no change in spectral properties was observed in 4 days.) However, analysis of the aromatic proton region proved that tetryl is converted in this process.

In the next variations of the BNAH–tetryl reaction, mixtures were prepared with: a tetryl/BNAH ratio of 1:3 in benzene solvent, with the homolytic reaction catalyzed by a 200-W tungsten light bulb; the same reactants in benzene-d_6, also catalyzed by a 200-W tungsten bulb; the same reactants and solvent, catalyzed by sunlight; the same reactants and solvent, catalyzed by sodium dithionite in the dark as a radical initiator. In all of these cases, the original tetryl disappeared according to ^{1}H NMR analysis, but the reaction product could not be definitively assigned as **6**. One reason for uncertainty in assignments of products became apparent upon comparison of the ^{1}H NMR spectrum of pure tetryl in benzene-d_6 to that reported in the literature with dimethyl sulfoxide-d_6 as solvent.[41] In the latter solvent, the two types of protons absorb at δ 9.30 (aromatic) and 3.65 (CH_3). In contrast, the absorptions in benzene-d_6 occurred in our analysis at δ 7.77 (aromatic) and 2.93 (CH_3). This great difference suggested an extrinsic phenomenon other than expected minor solvent effects. The phenomenon responsible for this property appears to be formation of a *charge-transfer complex* (electron donor-acceptor adduct), which has been

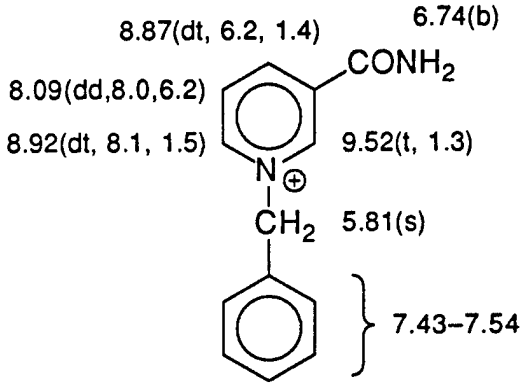
[41] Lamberton, A.H.; Sutherland, I.O.; Thorpe, J.E.; Yusuf, H.M. *J. Chem. Soc. (B)* **1968**, 6-8.
[42] Sekiguchi, S.; Ishikura, H.; Hirosawa, Y.; Ono, N. *Tetrahedron* **1990**, *46*, 5567-5578.

reported to occur between tetryl and benzene or toluene,[43,44] as well as between tetryl and other aromatic hydrocarbons.[45] In none of these reports was an NMR characterization of the effect described. Because *many* trinitrophenyl derivatives exhibit charge-transfer complex formation with aromatic hydrocarbons,[43,44] the definitive assignment of any probable products of the tetryl–BNAH reaction (including **6**) was likely to be complicated by this effect on their NMR chemical shifts.

For these reasons, the solvent of choice was changed to dimethylformamide-d_7 simply for purposes of diagnosis of the course of the reaction. In the first of the reactions in this solvent, a reaction product from a tetryl/BNAH ratio of 1:15, catalyzed by a 200-W light bulb, exhibited an initial NMR absorption for the picryl aromatic protons at δ 9.55. After 48 h reaction under these conditions, the δ 9.55 absorption had disappeared, but definitive identification of the product(s) was still complicated by the excess BNAH. In the next variation of this reaction, a 1:1 ratio of tetryl/BNAH proved more enlightening. In particular, the initial spectrum of this mixture at room temperature prior to photolysis showed that an immediate reaction occurred between these two reactants! For further identification of the products, the reaction was repeated in acetone-d_6 in order to achieve high solubility of the reagents and products. [For comparison, the ^{1}H NMR spectra of pure tetryl in dimethylformamide-d_7 and in acetone-d_6 are typical of those in other inert solvents. DMF-d_7: δ 9.47 (s, aromatic), 3.81 (s, CH_3). Acetone-d_6: δ 9.36 (s, aromatic), 3.77 (s, CH_3). Also for comparison, ^{1}H NMR data for BNAH and its expected oxidation product, 1-benzyl-3-carboxamidopyridinium (**7**), are shown below.] The high concentration allowed an adequate characterization of the reaction products by ^{13}C NMR as well as by ^{1}H NMR.



BNAH



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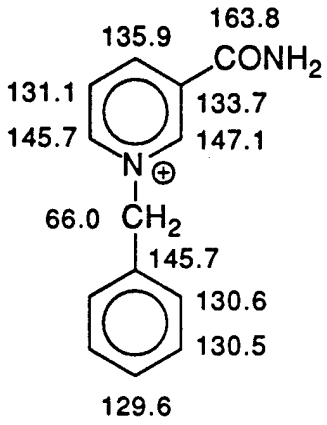
[43] Abe, T. *Bull. Chem. Soc. Japan* **1959**, *32*, 339-344.

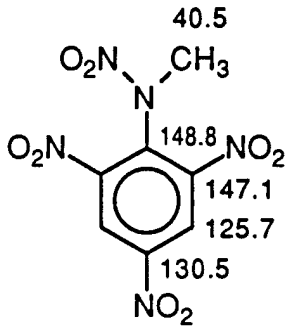
[44] Skulski, L.; Stolarzowa, Z.; Sliwinski, S. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1973**, *21*, 369-380.

[45] Efremov, N.N.; Tikhomirova, A.M. *Ann. Inst. Anal. Phys.-Chim. (Leningrad)* **1928**, *4*, 92-117; *Chem. Abstr. 23*:3214.

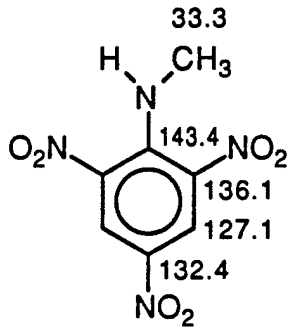
In the ^{13}C spectrum, the aromatic region proved most useful in diagnosing the nature of the reaction. For reference, independent ^{13}C NMR data for the expected oxidation product of BNAH, **7**, and for tetryl and its expected product of denitration, *N*-methylpicramide (**6**), are shown:



7 (CD_3CN)[27]



tetryl (acetone-d_6)



6 (DMSO-d_6)[46]

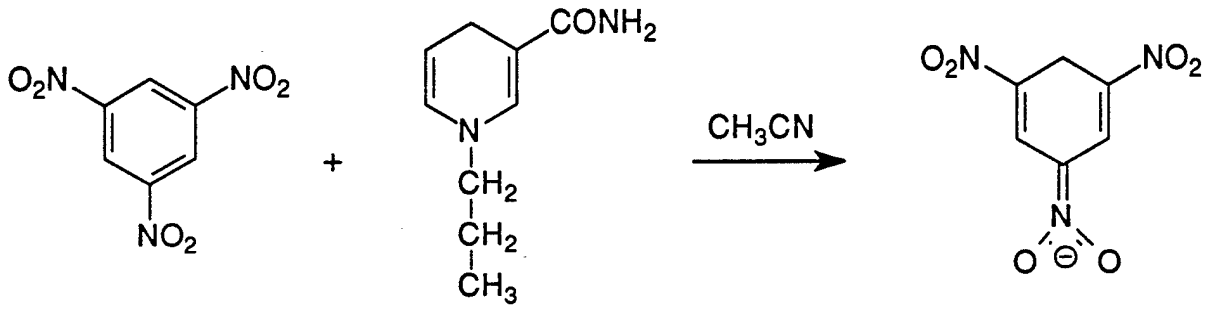
Comparison of the spectral data from the new tetryl–BNAH product allowed definitive assignment of the BNAH-related species as its oxidized form—that expected as the by-product of an electron transfer hydrogenolysis of a nitro species; also, the picryl species was definitively no longer tetryl. However, the spectral data for this immediate hydrogenolysis product were not totally consistent with *N*-methylpicramide (**6**) either. For this reason, the previous conditions were repeated on a larger scale (1.5 g tetryl) in order to take the reaction to completion and to isolate and identify products better.

The simple mixture of acetone solutions of tetryl and of BNAH in stoichiometric proportion produced immediate darkening of the reaction solution and gradual significant precipitation of a brownish solid. After reaction at room temperature for one day, the supernatant soluble portion was purified by preparative thin-layer chromatography (silica gel/ethyl acetate), which produced a major fraction that was confirmed by ^1H and ^{13}C NMR and by elemental analysis to be *N*-methylpicramide. A minor fraction isolated by TLC appeared by NMR to be picric acid, presumably from adventitious hydrolysis. There was no evidence in this reaction of the initial, immediate product seen in the earlier reaction. Re-examination of NMR data from the earlier run then confirmed that the observed intermediate was present only in the early stages of the reaction; the ^{13}C NMR spectrum on which the earlier assignment was based was taken in the period of 60–90 minutes after the reaction commenced, at which time it was realized that tetryl *per se* had been completely consumed. NMR spectra taken of the original reaction solution after 48 hours confirmed *N*-methylpicramide as the predominant product, as was seen in the later reaction. Analysis by ^1H and ^{13}C NMR of the precipitate from this reaction, which was only very sparingly soluble in acetone but soluble in dimethylformamide-d_7, proved it to contain only the 1-benzyl-3-

[46] Lycka, A.; Machacek, V.; Jirman, J. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2946-2952.

carboxamidopyridinium ion (**7**)—the expected oxidation product of BNAH in this conversion—and no trace of picryl-related or other organic species. The salt is presumably the nitrite expected from the N-denitration. The proposed simple N-denitration of tetryl by BNAH (Scheme 7) was therefore successfully demonstrated in acetone solvent.

In a prior report of a similar chemical system, Ohno et al. described the reaction of *N*-propyldihydronicotinamide with 1,3,5-trinitrobenzene.[47] This reaction (Scheme 8) was claimed to reduce the aromatic ring to a 1,4-cyclohexadienylnitronate anion species that readily re-oxidized, upon workup, to 1,3,5-trinitrobenzene. The 1,4-cyclohexadiene product had a ^{1}H NMR absorption at δ 3.85 for the geminal dihydro protons. There is no evidence of such absorptions (or such a product) in our reaction with tetryl.



Scheme 8. Aromatic reduction of trinitrobenzene by 1-propyl-1,4-dihydronicotinamide (ref. 47)

4.4 TETRYL–POLYMER-SUPPORTED DIHYDRONICOTINAMIDE SYSTEM

4.4.1 Tetryl Reactions

Tetryl was subjected to an N-denitration reaction with polymer-supported dihydronicotinamide (**4**) similarly to HMX (Section 4.2). In this tetryl system, acetone was used as a typical good solvent for tetryl. Earlier it was discovered that the N-denitration reaction with BNAH was significantly faster with tetryl than with simpler nitramines like HMX, and it did not require photolysis. With similar conditions (room temperature, no photolysis), the reaction of tetryl with equimolar polymer-supported dihydronicotinamide was found to be significantly slower. ^{1}H NMR analysis of the reaction solution showed only 4–5% conversion (to a mixture of **6** and picric acid) even after 30 days. In the tetryl system, therefore, the polymer-supported reagent appeared to be significantly slower *in comparison to BNAH*. Possible solutions to this lower reactivity appeared to be the use of photolysis (as with other typical nitramines), higher temperature, or a higher dihydronicotinamide/nitramine ratio. In a modification of the reaction, a calculated 9-fold molar excess of reagent **4** relative to tetryl was employed. After 24 days at room temperature in acetone (without photolysis), the yellow polymer **4** had turned brown (indicative of oxidation to pyridinium), but still only 12–13% conversion of the tetryl to a mixture of **6** plus picric acid had occurred.

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[47] Ohno, A.; Yamamoto, H.; Oka, S. *Tetrahedron Lett.* **1979**, 4061-4064.

4.4.2 Polymer-Supported Dihydronicotinamide Analysis

In response to the initial poor performance of the polymer-supported reagent (**4**) compared to the earlier successes with "free" BNAH (**2**), the sample of **4** used in these reactions was analyzed for elemental composition. The discovery of residual sulfur in the sample revealed that incomplete hydrolysis of sulfinate salt intermediate (**8**) had been achieved in the preparation of our polymer-bound dihydronicotinamide (Scheme 9), a potential complication discussed by Endo and Okawara.[48] Residual intermediate **8** appeared to be present to an extent of 11–12 wt% according to elemental analysis. Bourguignon et al. used the absence of chlorine in the final polymer (**4**) as a diagnostic property indicating completion of the reduction.[32,49] Although chlorine was confirmed as absent in our analysis also, this assumption does not account for unhydrolyzed intermediate **8**.

Eling et al.[31] and Bourguignon et al.[32,49] discuss other reasons for possible diminished reactivity of polymer-supported reagents such as **4**. In the latter reports, optimal results were achieved with polystyrene-supported dihydronicotinamide **4** only when a swelling cosolvent such as benzene was used in conjunction with a more polar solvent such as acetonitrile. The latter solvent was desirable for dissolution of some magnesium perchlorate. Magnesium ions have often been incorporated as apparent catalysts for dihydronicotinamide reductions via *hydrogenation*,[50] which those authors used as model reactions. In contrast, magnesium ions have been observed to retard the photo-induced electron transfer *hydrogenolysis* mechanism[51] (Scheme 3) expected to occur in our desired conversions. Of course, metal ion catalysts were not necessary for the denitrations that occur by electron transfer hydrogenolysis.[24,27] Without a swelling cosolvent, slightly crosslinked polymer-supported reagents such as **4** based on microporous polystyrene networks showed diminished kinetic reactivity or even lack of reactivity. The technical improvement offered by Eling et al. was the preparation and use of a highly crosslinked, macroreticular polymeric substrate for functionalization by dihydronicotinamide;[31] this backbone maintained permanent porosity and could be used with both good and poor (non-swelling) solvents. However, note that catalysis originally expected to be required for activation of the electron transfer hydrogenolysis mechanism (e.g., by photolytic or chemical radical initiation) was not utilized in the initial experiments involving polymer-supported reagent **4**; thus, it may be a requirement for *this* system after all.

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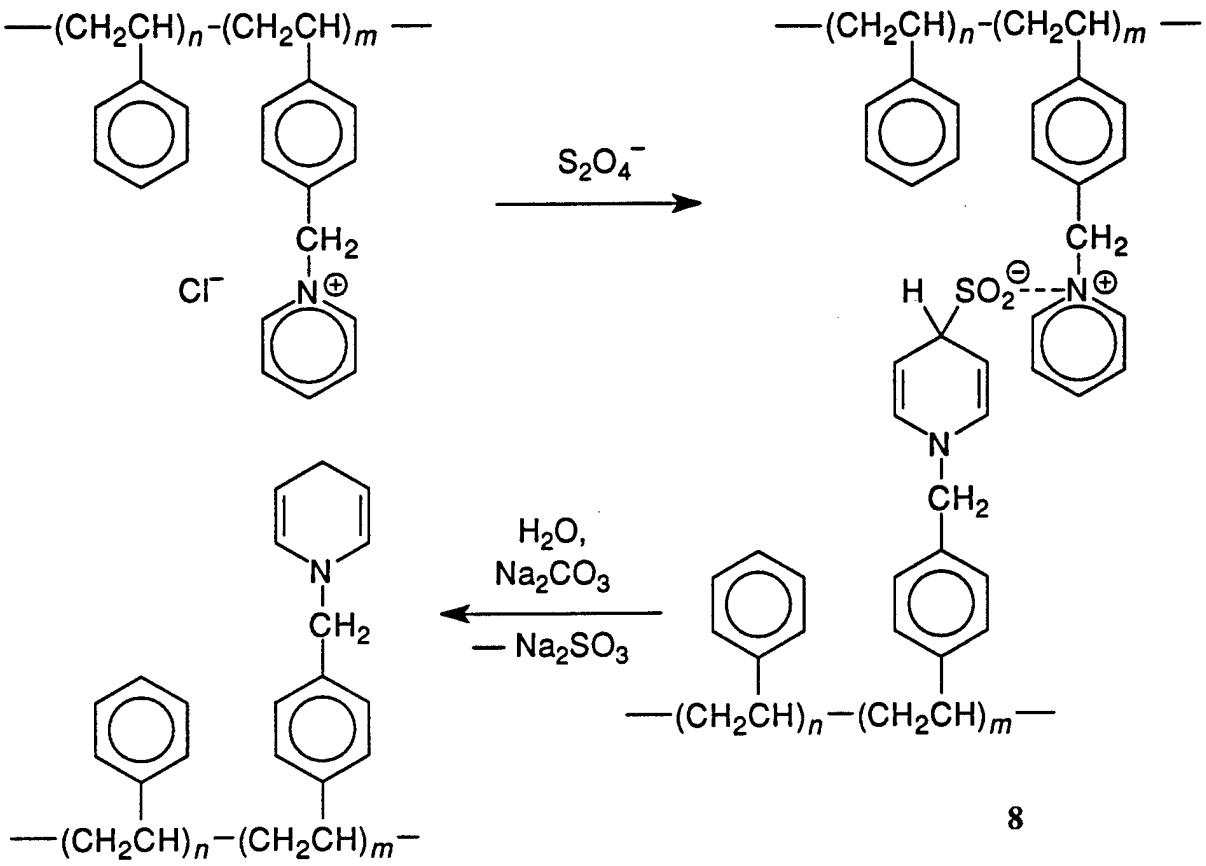
[48] Endo, T.; Okawara, M. *J. Polym. Sci. Polym. Chem. Ed.* **1979**, *17*, 3667-3674.

[49] Dupas, G.; Decormeille, A.; Bourguignon, J.; Quéguiner, G. *Tetrahedron* **1989**, *45*, 2579-2590.

[50] Eling, B.; Challa, G.; Pandit, U.K. *J. Polym. Sci., Polym. Chem. Ed.* **1984**, *22*, 1945-1962.

[51] Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1987**, *109*, 305-316.



Scheme 9. Formation of dihydronicotinamide via sulfinate internal salt (from reference 48)

Another complication in our procedure may be the apparent presence of residual sodium sulfite, the by-product of reduction of niacinamides by sodium dithionite under basic conditions. Although the procedure reported by Bourguignon et al.[32] was followed to the extent that experimental details were given, the overall elemental analysis of product **4** showed that elements other than carbon, hydrogen, nitrogen, and sulfur were present to an excessive degree, indicative of residual sodium sulfite to an extent of ~21 wt%. Although the presence of intermediate **8** should not hinder participation of **4** in the manner desired (Scheme 3), the known susceptibility of sulfite and bisulfite ions to participation in radical redox reactions[52] suggests a *possible* inhibition of the radical-ion mechanism required for the desired N-denitrations, perhaps contributing to the slower reactions and lower yields seen in these experiments. Obvious modifications to alleviate the residual impurities would include longer reaction times to achieve complete reduction and hydrolysis of intermediate **8** (when substrates of higher functionalization are used, as in this case) and thorough and repetitive washing to remove absorbed or adhered sulfite by-product.

[52] Deister, U.; Warneck, P. *J. Phys. Chem.* **1990**, *94*, 2191-2198.

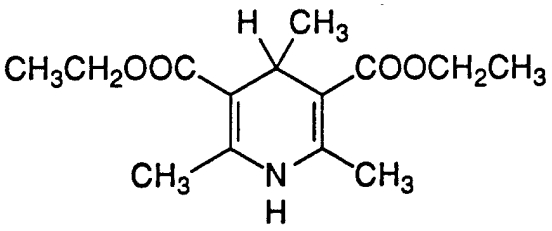
4.4.3 Tetryl Reactions (Modified Procedures)

In response to our discovery of the incompletely hydrolyzed and impure reagent **4**, this material was subjected to further treatment to alleviate the potential complications. It was reacted with sodium dithionite again for a longer period to achieve complete reduction and hydrolysis of the nicotinamide pendant group. The product was washed more thoroughly with water and acetonitrile to assure removal of salts and non-polymer-bound organics. The reaction of the new reagent with tetryl was next conducted in tetrahydrofuran as a superior swelling solvent for polystyrene polymers. The electron transfer radical reaction was also initiated in this run by photolysis (200-W tungsten bulb), as expected to be required for typical nitro compounds. The result of only four days' reaction under these conditions was ~30% conversion of tetryl to a mixture of: *N*-methylpicramide (**6**); the related, picryl-based intermediate seen at short reaction times in the earlier "free" BNAH reactions; and a minor amount of picric acid, presumably from adventitious hydrolysis. The presence of the intermediate (which is not sufficiently well characterized to definitively identify) in this system may be an indication that its formation in this more facile reaction is faster than its conversion to the final product, **6**. In contrast, the slow consumption of tetryl in the first polymer-supported dihydronicotinamide reactions appeared to proceed directly to the final products (**6** and picric acid) with no evidence of the intermediate, which is consistent with conversion of the intermediate being faster than its formation in the inefficient polymer reaction.

The feasibility of N-denitration by the polymer-supported reagent (**4**) under modified conditions was therefore demonstrated. The prospect of regenerating this recoverable reagent conveniently and inexpensively makes this denitration option more attractive.

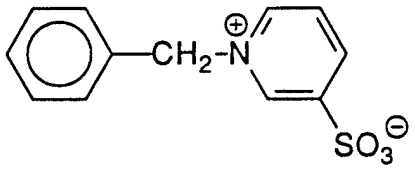
4.5 COMMERCIAL DIHYDROPYRIDINES

Following the success of the BNAH reactions, a search for alternative commercial dihydropyridine derivatives was conducted. (Various dihydropyridines other than dihydronicotinamides have been used as models for NADH reactivity.[51]) This was conducted first as a substructure search in the Registry file of the information service STN International, which revealed 41,985 known compounds that have the *generic* 1,4-dihydropyridine substructure present in BNAH. Of these, only 37 have been listed by "Chem Sources–U.S.A." as commercially available compounds. Of these, several are dihydro-4-pyridones and are thus not suitable hydrogen sources for electron transfer hydrogenolysis. The *technically* viable compounds that are commercially available are listed in the Table below. It is readily apparent that almost all of these are specialty biochemicals far too expensive for practical demilitarization operations. In fact, the only examples that may have a prospect as usable reagents for the demonstrated electron transfer hydrogenolysis of nitramines are the compound initially used as a dihydropyridine model (BNAH) and diethyl 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinecarboxylate (Hantzsch's ester, **9**), the latter costing ~15% of BNAH on a research scale.



9

Although **9** is normally produced by a condensation of ethyl acetoacetate with acetaldehyde-ammonia, pyridine-3,5-dicarboxylates (the expected oxidation products from electron transfer hydrogenolysis by **9**) are known to be amenable to reduction to dihydropyridines by typical hydride reagents.[53] This suggests that **9** (or polymer-bound **9**) may also be regenerated from their oxidized forms by aqueous dithionite, similarly to BNAH and polymer-bound BNAH. An interesting prospective precursor to a water-soluble dihydropyridine, possibly more suitable for conducting denitrations under aqueous conditions without surfactants, has been commercially available as an alkylated pyridinium salt: 1-benzylpyridinium-3-sulfonic acid (inner salt), **10**, available from Janssen Chimica (now Acros Organics) at a price lower than that of **9**. If the reduction to the corresponding dihydropyridine is efficient, this may be an economically attractive variation of BNAH. However, unless **9** or **10** *is* conveniently regenerable (such as by dithionite) and recoverable, polymer-supported BNAH (**4**) may remain the most economical option.



10

[53] Stout, D.M.; Myers, A.I. *Chem. Rev.* **1982**, *82*, 223-243.

Table I. Prices of Commercial 1,4-Dihydropyridine Derivatives					
Name	Source	Price ($/qty)	Quantity (g)	MW	$/mol
R-(+)-Bay K 8644	Research Biochemicals Inc. (RBI)	850.00	0.025	356.3	12,114,200
(±)-Bay K 8644	RBI	1056.00	0.125	356.3	3,010,022
S-(+)-Niguldipine	RBI	180.00	0.05	646.19	2,326,284
3-Acetylpyridine adenine dinucleotide, reduced form	Sigma	320.55	0.1	662.4	2,123,323
Nicotinamide hypoxanthine dinucleotide phosphate, reduced, tetrasodium salt	Sigma	784.95	0.475	834.3	1,378,703
(±)-Niguldipine	RBI	120.00	0.1	646.19	775,428
Nicotinamide hypoxanthine dinucleotide, reduced, sodium salt	Sigma	214.10	0.2375	666.4	600,742
(±)-Isradipine	RBI	150.00	0.1	371.39	557,085
β-Nicotinamide adenine dinucleotide phosphate, reduced, tetrasodium salt	Sigma	2035.00	4.75	833.36	357,029
α-Nicotinamide adenine dinucleotide, reduced	Sigma	332.70	0.9	709.4	262,242
Nitrendipine	RBI	255.00	0.5	360.37	183,789
Nicarpidine·HCl	RBI	20.00	0.5	515.99	20,640
NADH	Calzyme	20.00	0.99	665.45	13,443
Dihydronicotinamide adenine dinucleotide, disodium salt	Sigma	422.75	23.75	709.4	12,627
Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinecarboxylate	Aldrich	19.35	1	253.3	4901
Nifedipine	RBI	30.00	5	346.34	2078
1-Benzyl-1,4-dihydronicotinamide	TCI America	182.00	25	214.27	1560
Diethyl 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinecarboxylate	Aldrich	84.90	100	267.33	227

On the subject of expensive biochemical alternatives, a very recent report of similar chemistry involving tetryl is worthy of note. Shah and Spain (Tyndall Air Force Base, FL) described N-denitration of tetryl using an exotic biochemical system involving ferredoxin-NADP oxidoreductase, an oxygen-sensitive nitroreductase, in the presence of NADPH.[54] The usual biochemical role of ferredoxin-NADP oxidoreductase is to transfer electrons from reduced ferredoxin (an electron source) to oxidized NADP to form NADPH *in situ*:

$$2Fd_{red}^{2+} + 2H^+ + NADP^+ \rightarrow 2Fd_{ox}^{3+} + NADPH + H^+$$

As NADPH, a phosphate ester of NADH (**1**), seemed to be provided as a reagent in the system used there, the participation of oxidoreductase to effect electron transfer should be unnecessary, as we have shown here with other dihydronicotinamides. If NADPH (comparable in cost to NADH) were desired as a reagent, it should be used directly as a starting material. For comparison, commercial ferredoxin as an electron source is an even more expensive biochemical ($225/10 milligrams) than most of the dihydropyridines tabulated above. The oxidoreductase ($144/~4 milligrams) is comparable. However, our current study has shown the same feasibility with industrially practical variations of dihydronicotinamides, and inexpensive sodium dithionite (28¢/mole in bulk) is the initial electron source.

4.6 HMX–HYDRAZINE–PALLADIUM SYSTEM

Hydrazine was chosen as a catalytic transfer hydrogenolysis reagent superior to cyclohexene mainly for environmental and safety considerations, viz., the generation of carcinogenic benzene as the by-product from cyclohexene as the most efficacious hydrogen transfer reagent. A serious consideration in the practical development of a denitration process would be a process for recycle or remediation of any excess reagents involved in the nitramine conversion reactions. Hydrazine is a particularly attractive reagent in this respect because its destruction to non-hazardous products is straightforward and convenient. It is efficiently oxidized specifically to nitrogen and water by hydrogen peroxide in the presence of catalytic cupric or ferric ions:[55]

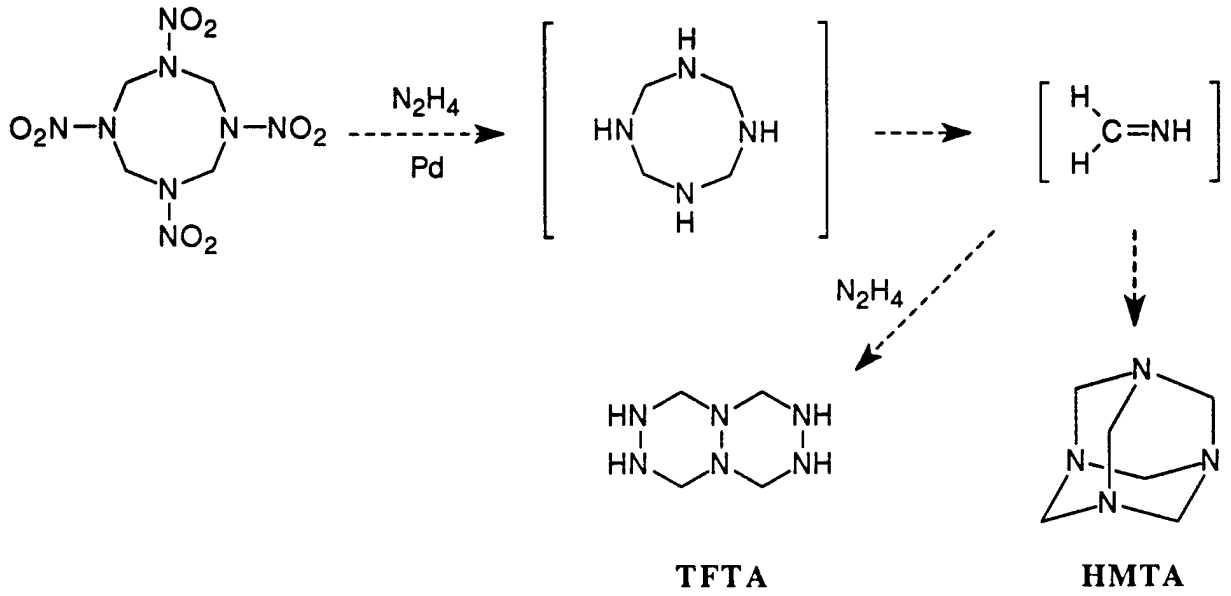
$$N_2H_4 + H_2O_2 \xrightarrow[or\ Cu^{2+}]{cat.\ Fe^{3+}} N_2 + 4H_2O$$

If N-denitration were to proceed cleanly via hydrogenolysis by hydrazine, as in the reported deprotection of *N*-nitroarginine (**5**),[39] HMX would initially convert to the corresponding free amine (Scheme 10), octahydro-1,3,5,7-tetrazocine. This unstable ring system may then

[54] Shah, M.M.; Spain, J.C. "Abstracts of Papers", 209th National Meeting of the American Chemical Society, Anaheim, CA, Apr 1995; American Chemical Society: Washington, DC, 1995; I&EC 121.

[55] Graham, D.P. *J. Am. Chem. Soc.* **1930**, *52*, 3035-3045.

depolymerize to "methyleneimine," a transient monomer that is the basis for the most stable formaldehyde–ammonia adduct, hexamethylenetetramine (HMTA). HMTA may be formed from the straightforward condensation of "methyleneimine." However, a complicating feature present in the proposed denitrating system is hydrazine as a primary amine reactive with "methyleneimine" as a formaldehyde equivalent. The known product of condensation between excess hydrazine and *formaldehyde* is octahydro[1,2,4,5]tetrazino[1,2-*a*][1,2,4,5]tetrazine (tetraformaltrisazine, TFTA),[56] which was suspected potentially to form competitively with HMTA in the presence of excess hydrazine (Scheme 10).



Scheme 10. Proposed HMX denitration paths utilizing hydrazine

4.6.1 Organic Solvents

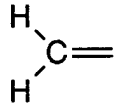
In the first test of this approach for denitration of HMX, conditions simulated those used by Sivanandaiah et al.[39] but with anhydrous hydrazine and with DMF (rather than methanol) as a superior solvent for HMX. The reaction was run with an HMX/hydrazine ratio ranging from 1:21 to 1:42, and with 10 wt% palladium black (based on HMX) at 50–55 °C. In our system, mesitylene was initially incorporated as an inert internal standard to monitor the progress of any HMX disappearance by NMR. Under these conditions, the desired destruction of HMX was indicated by diminution of the HMX peak: the ratio of HMX's to mesitylene's integration in the ^{1}H NMR spectrum, initially 1.89, decreased progressively to 1.05 at 1 h reaction; <0.48 at 14 h reaction; and 0 (HMX absent) at 39 h reaction. Although HMX clearly was converted to another product under these conditions (evidenced by clean disappearance of its NMR absorption), the concomitant appearance of a new pattern of NMR absorptions indicated greater complexity in this process than expected from a concerted denitration with concomitant rearrangement to HMTA (Scheme 10).

[56] Hofmann, K.A.; Storm, D. *Chem. Ber.* **1912**, *45*, 1725-1730.

Upon observation of relatively rapid diminution of HMX content in the 50 °C reaction, the same system was repeated at ambient temperature. In this system, the internal NMR standard was changed to hexamethyldisiloxane because of interference—by one new absorption (δ 6.7) from this reaction's initial product—with mesitylene previously used as an internal standard. In this system, the ratio of HMX/hexamethyldisiloxane NMR integrations, initially at 0.60, also progressively decreased to 0.19 at 16 h reaction; 0.066 at 40 h reaction; and 0.014 at 66 h reaction, indicating ~98% destruction of HMX at this time.

As indicated above, the initial product of catalytic transfer hydrogenolysis under these conditions was not hexamethylenetetramine. Rather, a product with a distinctive ^{1}H NMR absorption pattern appeared concomitantly with disappearance of HMX. Figure 1 shows an excerpt of the NMR spectrum with the new features.

The singlet at δ 6.35 is HMX that is almost gone; this shift matches that given in one report for HMX in DMSO-d_6.[57] The other AB quartet pattern with apparent doublets at δ 6.71 and δ 6.00 is reminiscent of a hindered or constrained 1,3-diaza heterocycle, *like* a hexahydropyrimidine. However, the species' ^{13}C NMR spectrum cast doubt on such an assignment: this chemical shift (DMF-d_7) was δ 127.2. In contrast, cyclic "methylenenitrimine" species (such as HMX) generally exhibit ^{13}C absorptions in the range of δ 50–80, usually δ 60–70. Therefore, the observed downfield shift of the intermediate suggested unsaturation in the molecule. Together, these NMR data very likely indicated a terminal methylene moiety:



The ^{13}C analysis was of a reaction solution consisting of hydrazine–HMX (7:1) in DMF-d_7 held at ~55 °C for 48 h, at which time this product was the major species; HMX was still present to a lesser extent. Formic-*d* hydrazide—formyl-*d*-hydrazine—was observed as an identifiable independent by-product from nucleophilic displacement by hydrazine of the dimethylamino moiety in DMF-d_7, a transformation exhibited by amides in general.[58] That the ^{1}H NMR spectrum from the reaction in DMF-d_7 showed the same multiplet and the ^{13}C absorption for this product was not distinctively coupled to a deuteron proved that it did not result from a reaction involving DMF as a reactant. This reaction was then also conducted—and the same product observed—using acetonitrile solvent. It may be noteworthy that in this solvent the reaction to form the species was significantly slower, requiring 5.8 days at room temperature followed by 3.8 days at 55 °C.

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[57] Bell, J.A.; Dunstan, I. *J. Chem. Soc. (C)* **1966**, 870-872.

[58] (a) Henecka, H.; Kurtz, P. In "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1952; Vol. 8, p. 680. (b) Paulsen, H.; Stoye, D. In "The Chemistry of Amides"; Zabicky, J., Ed.; Interscience: New York, 1970; Chapter 10.

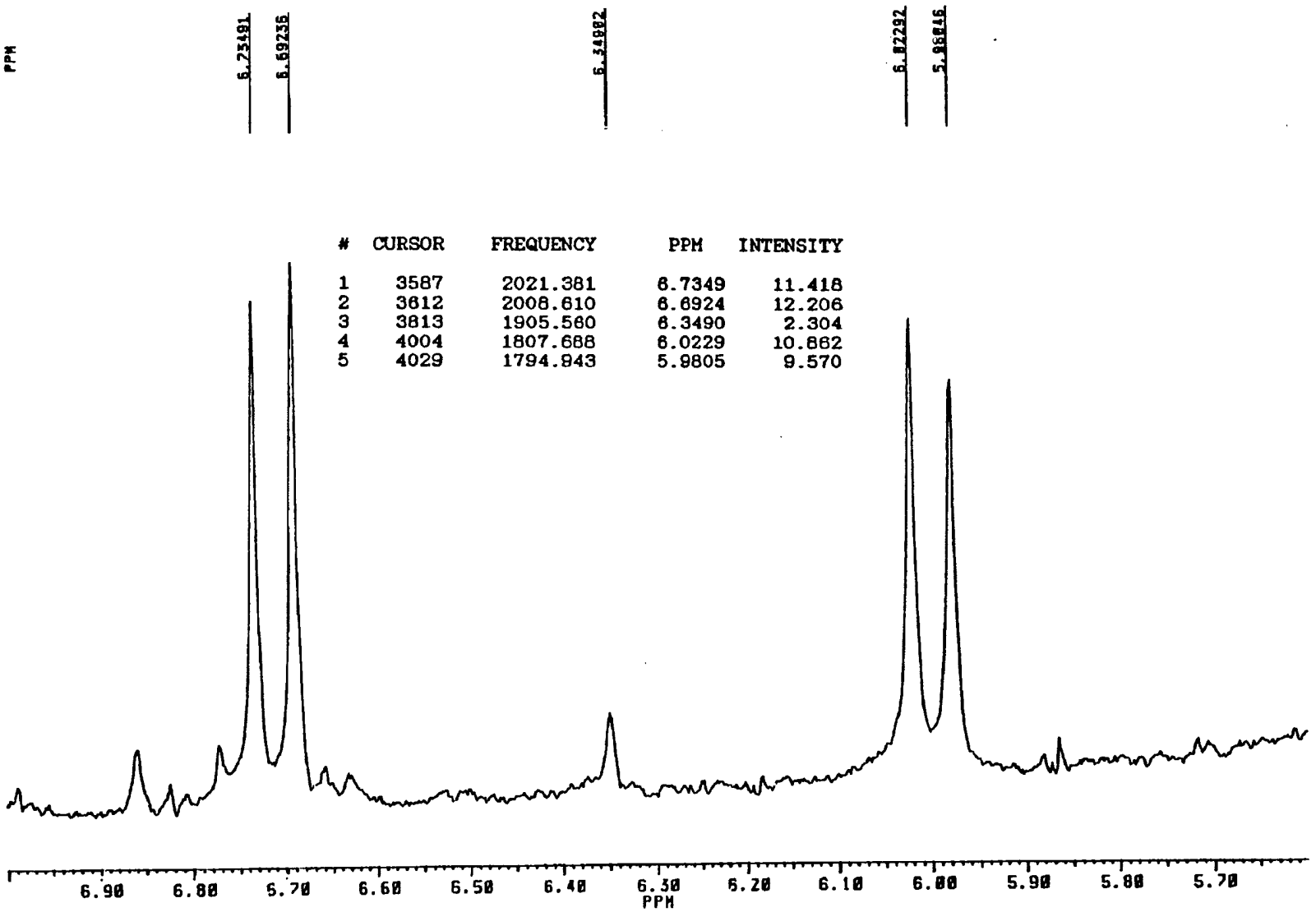
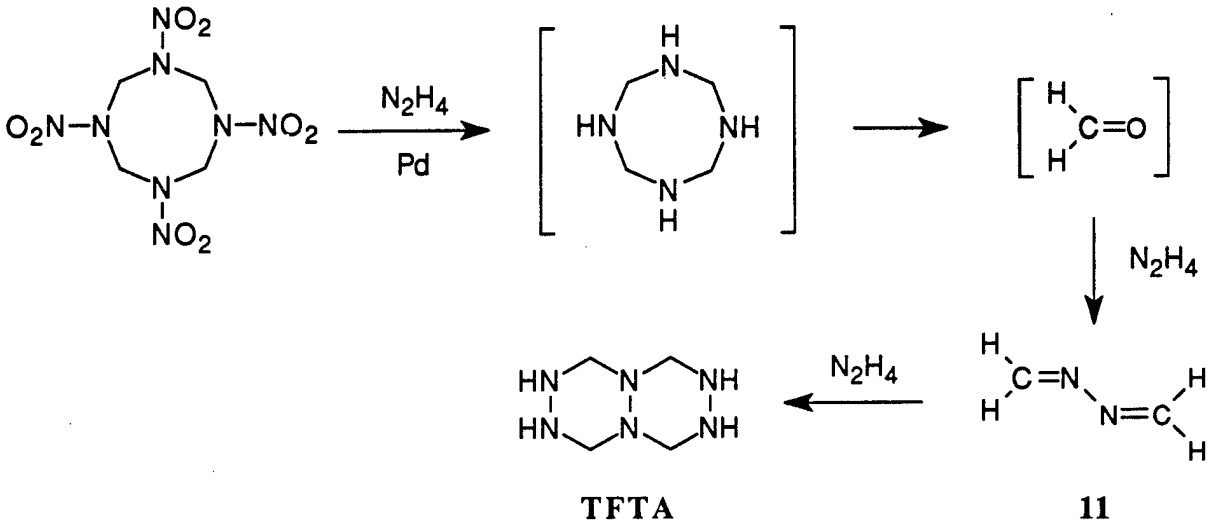


Figure 1. ^{1}H NMR (methylenenitrimine region) of denitrated HMX (hydrazine/DMF, Pd black, room temperature, 66 h)

A structure that appeared consistent with chemical transformations that may reasonably be occurring in this system and with the spectroscopic data was the monomeric condensation product of hydrazine and formaldehyde, formaldazine (**11**), a known compound formed by thermal depolymerization[59] of the insoluble amorphous condensation polymer[60] between hydrazine and formaldehyde or by their condensation below 0 °C.[61] By a variation of the denitration in Scheme 10, octahydrotetrazocine may dissociate into (transient) free formaldehyde, which could be scavenged by a large excess of hydrazine to form the monomeric **11** (Scheme 11).



Scheme 11. Observed denitration of HMX by palladium-catalyzed hydrazine

This logical structural assignment was initially doubted upon referring to literature on this known compound. The following quotes suggested that the stability of **11** was unlikely under the conditions under which the HMX denitration product was formed and observed (48 h at 55 °C, 66 h at room temperature):

• "On warming to room temperature (either neat or in solution) the material polymerized spontaneously, first to a viscous liquid and eventually to a white solid..."[59]

• "The scarcity of studies might be ascribed to the high polymerizability of formaldazine and the resulting difficulty of storage at room temperature."[62]

The direct condensation of aqueous solutions of formaldehyde and hydrazine is reported to produce the amorphous polymer.[60] Furthermore, Kamachi and Murahashi also reported a ^{1}H NMR spectrum of formaldazine (**11**) in THF solution,[63] reproduced as Figure 2. Although the

[59] Neureiter, N.P. *J. Am. Chem. Soc.* **1959**, *81*, 2910.

[60] Mashima, M. *Bull. Chem. Soc. Japan* **1966**, *39*, 504-506.

[61] Moe, H.; Lampert, B.B. *U.S. Patent* 3,329,718 (1967).

[62] Kamachi, M.; Murahashi, S. *Polym. J.* **1974**, *6*, 302-307.

[63] Kamachi, M.; Murahashi, S. *Polym. J.* **1974**, *6*, 295-301.

compound shows an AB quartet at –30 °C and at 50 °C, as any unsymmetrical methylene-terminated molecule should, the chemical shifts at both temperatures are significantly different from those observed in the HMX denitration: **11** shows doublets centered at δ 6.9 and δ 7.3 compared to δ 6.0 and δ 6.7 from the HMX denitration in DMF.

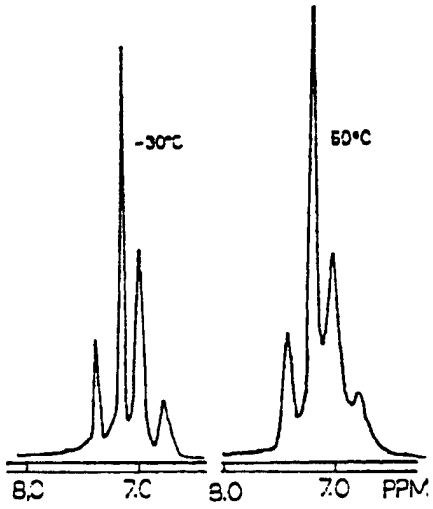


Figure 2. ^{1}H NMR spectra of formaldazine (**11**) in THF solvent (from ref. 63)

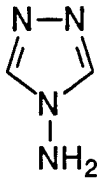
The identity of the HMX denitration's (initial) product was confirmed as **11** fortuitously when a sample of the reaction solution in DMF, separated from palladium catalyst and stored in an airtight bottle, precipitated *TFTA* after several weeks. After observing the expected product of reaction between formaldazine and excess hydrazine—TFTA—the possible stability of **11** and particularly its observability by NMR were confirmed by an independent preparation. Simply mixing aqueous solutions of hydrazine and formaldehyde (with a small amount of D_2O as a lock solvent) immediately produced a distinctive AB quartet of **11** in water: δ 6.38, 6.91 ($^{2}J_{HH}$ = 11.3 Hz). Under the arbitrary conditions used, no precipitate was immediately formed.

Thus, the validity of the proposed clean denitration of HMX by hydrazine (catalyzed by palladium) was successfully demonstrated.

Before the identity of the initial product was confirmed as **11** by its eventual precipitation of TFTA after removal of an aliquot from the initial reaction conditions, the sample in DMF-d_7 left under original reaction conditions took a different course. After 8 days at ~55 °C in DMF-d_7 (hydrazine/HMX ≈ 7:1), the intermediate (**11**) was replaced by a single predominant species (in addition to formic hydrazide) with a ^{13}C NMR chemical shift of δ 144.6. ^{1}H NMR analysis (DMF-d_7) of the product showed (in addition to absorptions expected from the hydrazide and possibly residual hydrazine) a broad absorption at δ 6.47–6.51 and a singlet at δ 8.51–8.56 in different spectra of the sample.

The identity of this later product was finally revealed by an analysis of its ^{13}C NMR spectrum *without* routine decoupling of protons normally used in ^{13}C NMR. The single ^{1}H-

decoupled peak now appeared as a doublet of doublets, centered at δ 144.84, with a large coupling constant of 212 Hz and a small (long-range) coupling constant of 4.2 Hz. C–H coupling constants as large as 212 Hz are rare,[64] and among the classes of compounds that could come about in this reaction, this spectral characteristic clearly indicated the compound to be a 1,2,4-triazole. The ^{1}H spectrum—particularly the narrow and broad peaks with integrals in a ratio of 1:1—in conjunction with the expected chemistry in this system also pointed to 4-amino-4*H*-1,2,4-triazole (**12**) as the likely candidate. The observed ^{13}C NMR spectrum of the product agrees almost exactly with that reported in the literature for **12**:[65] δ 144.8, $^1J_{CH}$ = 212.5 Hz, $^3J_{CH}$ = 4.3 Hz. The ^{1}H NMR spectrum obtained for the reaction product is reasonably close to the literature spectrum of **12**,[66] accounting for the expected solvent dependence of amine protons: δ 6.12(b), 8.32(s). Finally, an authentic sample of **12**, a commercial compound, added to the solution of the reaction product produced no additional peaks in the ^{13}C NMR spectrum, confirming the product as **12**.



12

The discovery of **12** as a final product of denitration of HMX by hydrazine indicates further interesting chemistry in this system. 4-Amino-4*H*-1,2,4-triazole (**12**) is reported to be formed simply by thermal rearrangement of 1,4-dihydrotetrazine upon melting at 125 °C.[67] Tetrazine derivatives may be recognized as reasonable products of condensation of aldehydes and hydrazine. Of course, TFTA, octahydro[1,2,4,5]tetrazino[1,2-*a*][1,2,4,5]tetrazine, is an example that is bicyclic. As related precedent chemistry, Skorianetz and Kováts (l'Ecole Polytechnique Fédérale, Lausanne, Switzerland) reported the condensation of various aldehydes and hydrazines to form, initially, hexahydrotetrazines, which oxidized via platinum(IV) oxide catalysis to dihydrotetrazines.[68] For example, 1,6-dihydro-3,6-dimethyltetrazine (**13**, R = CH_3) is formed from condensation of hydrazine and acetaldehyde followed by PtO_2-catalyzed oxidation by oxygen of the intermediate hexahydrotetrazine (Scheme 12). 1,6-Dihydro-3,6-dimethyltetrazine (**13**) also reportedly decomposes upon melting at 114 °C, but the decomposition product was not

[64] Kalinowski, H.-O.; Berger, S.; Braun, S. "Carbon-13 NMR Spectroscopy"; John Wiley & Sons: New York, 1988.

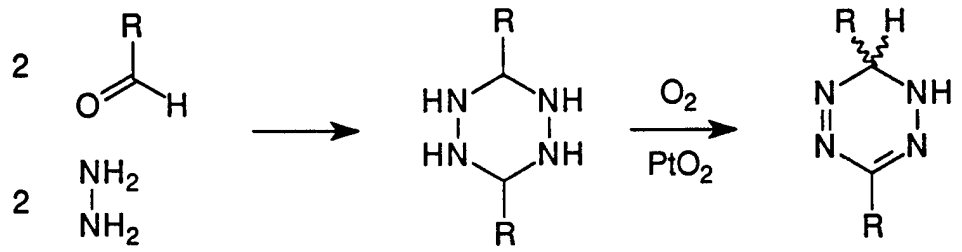
[65] Begtrup, M.; Elguero, J.; Faure, R.; Camps, P.; Estopá, C.; Ilavský, D.; Fruchier, A.; Marzin, C.; de Mendoza, J. *Magn. Reson. Chem.* **1988**, *26*, 134-151.

[66] "Standard NMR Spectra", Sadtler Research Laboratories, Inc. (Philadelphia, PA), spectrum 16053M.

[67] Curtius, T.; Darapsky, A.; Müller, E. *Chem. Ber.* **1907**, *40*, 815-837.

[68] (a) Skorianetz, W.; Kováts, E. sz. *Helv. Chim. Acta* **1970**, *53*, 251-262; (b) *ibid.* **1971**, *54*, 1922-1939; (c) *ibid.* **1972**, *55*, 1404-1414.

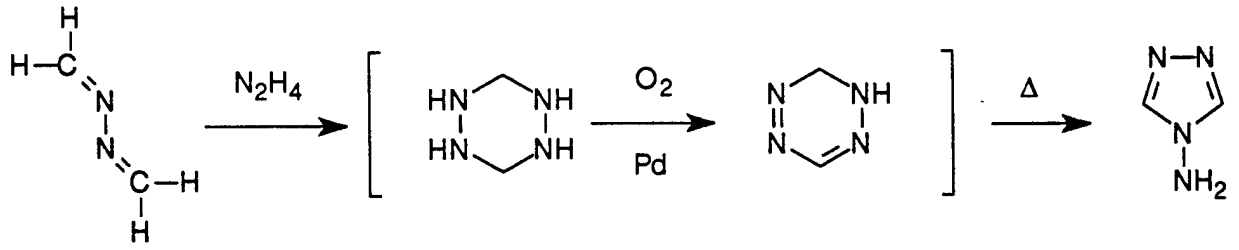
characterized. 4-Amino-3,5-dimethyl-4*H*-1,2,4-triazole formed by thermal rearrangement of 1,4-dihydro-3,6-dimethyltetrazine upon melting,[68c] analogous to the behavior of 3,6-unsubstituted 1,4-dihydrotetrazine, which was not mentioned in these reports.



13

Scheme 12. Formation of dihydrotetrazines from aldehyde–hydrazine condensations (from ref. 68)

It may be surmised, therefore, that the 4-amino-4*H*-1,2,4-triazole (**12**) observed in HMX denitration by hydrazine results from a similar mechanism (Scheme 13), although intermediate tetrazines are not observed. This may mean either that they are transient because the subsequent thermal rearrangement of 3,6-*unsubstituted* dihydrotetrazine is faster than its formation or that the cyclization of *formaldazine* (**11**) under oxidizing conditions (oxygen in the presence of palladium) takes a somewhat different path directly to triazole **12**. Also because it does not accumulate enough to observe, the particular regioisomer of dihydrotetrazine (1,4- or 1,6-) intermediate is not certain.



11 **12**

Scheme 13. Formation of 4-amino-4*H*-1,2,4-triazole (**12**) observed in HMX denitration by N_2H_4

The requirement for oxygen explains discrepant behavior that had been seen in two examples of this reaction. In the initial observation of this product, it had formed in 8 days at ~55 °C in DMF-d_7 (hydrazine/HMX ≈ 7:1); no special precautions had been taken toward excluding air in the preparation of this NMR sample. However, when the reaction was scaled up in order to produce an isolated sample of it, the reaction was conducted with a static atmosphere of

nitrogen, and it was exposed to air only in the course of taking aliquots for analysis. In the latter run, prolonged reaction on the order of 60 days at 55 °C (hydrazine/HMX ratio ranging from 5:1 to 17:1) was required for complete conversion of **11** → **12**. In hindsight, it is recognized that oxygen is required for the oxidation of intermediate hexahydrotetrazine.

Product **12** is less volatile than other constituents of the reaction, and it could be concentrated by removal of DMF solvent at reduced pressure. This property allowed the discovery of a successful isolation procedure. After removal of DMF under reduced pressure at room temperature, addition of dichloromethane produced a tan-white precipitate. ^{1}H NMR analysis of the dichloromethane-soluble portion showed none of the desired product. Analysis of the precipitate by thin-layer chromatography showed three spots by elution with acetonitrile. Similar purification of a sample by preparative TLC produced three fractions, whose analysis by ^{1}H NMR confirmed **12** as one of the isolated fractions. The others are presumed to be formic hydrazide and *N,N'*-diformylhydrazine formed in this long-term reaction in DMF.

4.6.2 Water Solvent

A test of possible N-denitration of HMX by hydrazine in *aqueous* solution (palladium catalyst, 50 °C, dodecyltrimethylammonium bromide surfactant to dissolve HMX) was carried out by reaction for 8 days. The product solution was worked up by concentration through evaporation. Analysis of the concentrated residue was conducted by ^{1}H NMR spectroscopy in dimethyl sulfoxide-d_6, which completely redissolved the residue. This analysis confirmed the complete disappearance of HMX in this reaction and its conversion to the same intermediate (**11**) previously seen in the reactions in DMF and in acetonitrile, evidenced by a distinctive pair of doublets centered at δ 5.95 and δ 6.62. The AB quartet was a trace but distinct spectral component in the presence of a much larger, very broad absorption centered about δ 5.4 (perhaps indicative of the amorphous condensation polymer from spontaneous polymerization of **11**).

In another test of water as solvent, the reaction between HMX and hydrazine (palladium catalyst, dodecyltrimethylammonium bromide surfactant to dissolve HMX at elevated temperature) held at 50 °C for only 5 days left some unreacted HMX, which reprecipitated upon cooling of the solution. However, when a similar reaction mixture without surfactant was held at reflux temperature for only 21 h, the HMX totally dissolved and did not reprecipitate upon cooling.

We assess, therefore, that the denitration of HMX by hydrazine (catalyzed by palladium) works successfully as proposed in water solvent also.

4.6.3 Neat Hydrazine Solvent

In a variation of conditions attempted early on in the course of the HMX–hydrazine reactions, neat hydrazine was attempted as both reagent and solvent in order to avoid complications of isolation from less-volatile DMF. HMX was added gradually to anhydrous hydrazine in the presence of palladium black at 5 °C. (*Warning:* Hydrazine added to solid HMX in a septum-capped flask caused the HMX to combust.) After 94 hours at 40–42 °C, HMX was totally con-

sumed (according to ^{1}H NMR), and fractional distillation of the product mixture was conducted at reduced pressure to remove excess hydrazine. According to ^{1}H NMR data, the product of the HMX–hydrazine–palladium reaction under these conditions was different from that previously observed in DMF solvent.

A single peak at δ 4.92 (vs. external sodium trimethylsilylpropionate-d_4 in D_2O) appeared greatly predominant; small peaks were also present at δ 3.63 and δ 4.77 but were initially presumed to be minor by-products. In addition, ^{13}C NMR showed two major peaks at δ 72.2 and δ 75.0 (vs. external sodium trimethylsilylpropionate-d_4 as δ 1.7)[64] in a ratio of 1:1.58, respectively. It was initially difficult to reconcile either: two structures with a single type of carbon in each, or a single structure with two types of carbons in a ratio of 2:3, in either case exhibiting very similar protons absorbing only at δ 4.92. This mystery was resolved by a heteronuclear correlation 2D-NMR analysis of this sample in D_2O. The contour plot (Figure 3) clearly shows that the carbon peaks are actually associated with (i.e., strongly coupled to) the *minor peaks* seen in the ^{1}H NMR spectrum at δ 3.63 and δ 4.77, suggesting that the major peak was residual hydrazine (exchanged with D_2O). The combination of a ^{1}H absorption at δ 4.77 and ^{13}C absorption at δ 72.2 is reasonably close to that reported in the literature for hexamethylenetetramine (HMTA): δ 4.75 and δ 74.5.[69] (Note, however, that a figure in this reference showing the ^{13}C spectrum of HMTA seems clearly to show that shift as closer to δ 72 rather than a tabulated value of δ 74.5.) Although the ^{1}H chemical shift of δ 3.6 is close to that reported for TFTA,[70] the lack of the distinctive AB quartet required for it rule it out as the identity of this by-product. Also, an authentic sample of TFTA was prepared and purified according to literature procedures.[56,60] The AB quartet pattern is clearly apparent, centered at δ 3.59 (two doublets, $^2J_{HH}$ = 12 Hz, at δ 3.44, δ 3.73). Its ^{13}C chemical shift is δ 70.9 in D_2O vs. sodium trimethylsilylpropionate-d_4 as δ 1.7. Therefore, neither reaction product's ^{13}C chemical shift corresponds exactly to that of TFTA, either.

Another NMR analysis that was hoped to provide further insight into the identity of these components is the ^{14}N NMR. The ^{14}N NMR spectrum of this aqueous hydrazine solution (Figure 4) shows that the predominant (~94%) constituency of nitrogen species is as amine-type structures, i.e., the δ –320 to δ –340 region. This would include hydrazines (N_2H_4 as well as heterocyclic organics) and amines such as heterocyclic methyleneimines. A relatively sharp peak is present at δ –25. This range corresponds to either oximes or the nitro group of nitramines. In either case, it is relatively small (<5%) and does not account for the major nitrogenous species in this solution. (The corresponding amine nitrogen expected of an organic nitramine is not clearly apparent around δ –200.) Another interesting feature is the absorption at δ 230. Although it is also relatively small (<2%), this chemical shift is characteristic for nitrite (NO_2^-) ion, perhaps confirmatory evidence that the mechanism obtaining in these conversions involves direct denitration of the nitramine group, as previously reported for the palladium-catalyzed deprotection by hydrazine of a nitramine-containing oligopeptide,[39] the observation upon which the current approach was based.

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[69] Nielsen, A.T.; Moore, D.W.; Ogan, M.D.; Atkins, R.L. *J. Org. Chem.* **1979**, *44*, 1678-1684.

[70] Kintzinger, J.P.; Lehn, J.M.; Wagner, J. *Chem. Commun.* **1967**, 206-207.

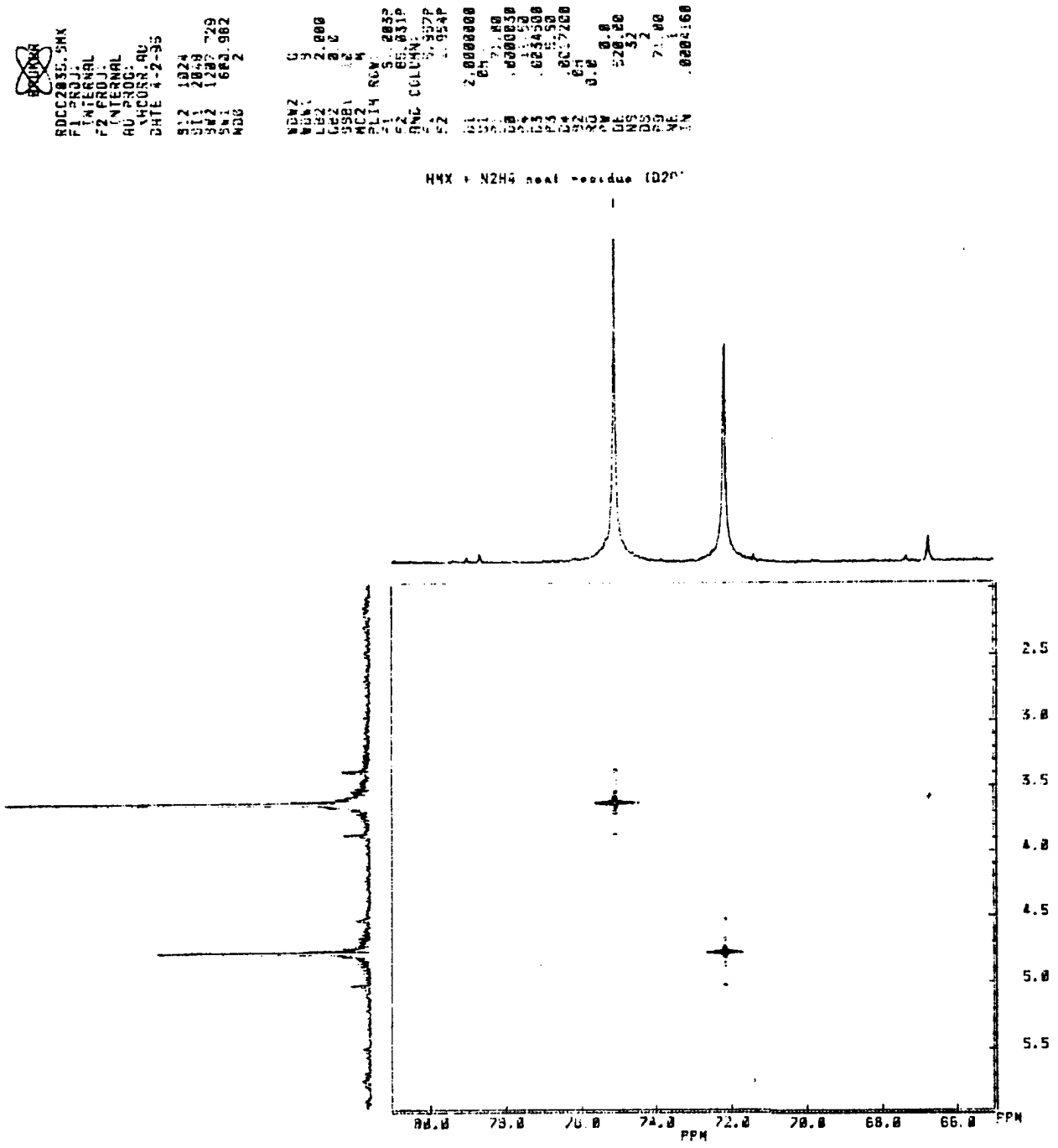


Figure 3. 2D heteronuclear correlation (^{13}C–^{1}H) NMR spectrum of products of HMX denitration by neat hydrazine (D_2O containing hydrazine as solvent for NMR)

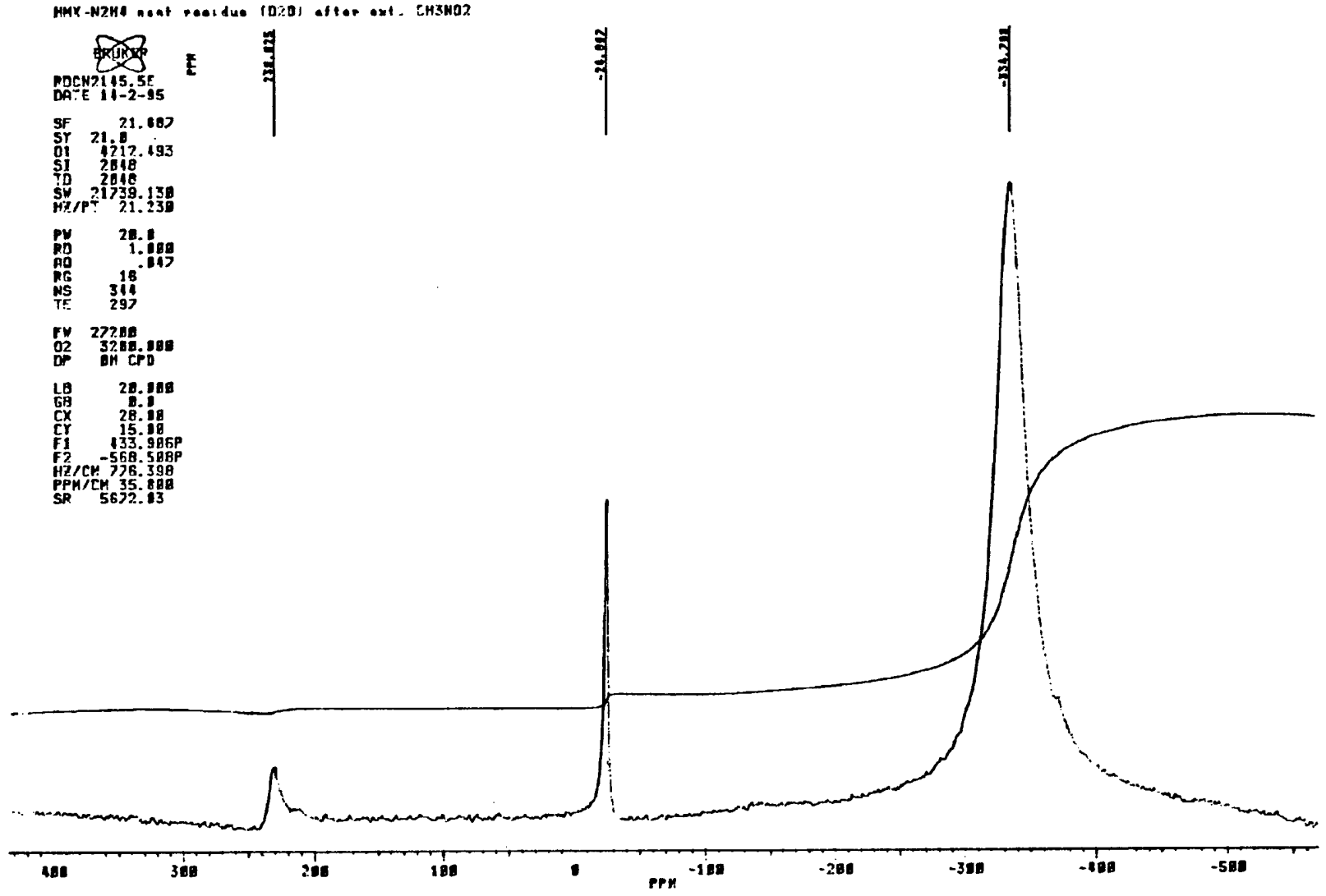


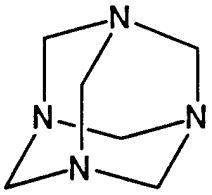
Figure 4. ^{14}N NMR spectrum of products of HMX denitration by neat hydrazine (D_2O containing hydrazine as solvent for NMR)

Gas chromatography–mass spectrometry (GC-MS) analysis of the aqueous hydrazine solution of this product mixture was attempted next for identification of the unknown component. The GC analysis showed three volatile components, with retention times of 2.3–2.7 min, 3.7–4.4 min, and 4.7–5.1 min. The first fraction had a base peak and apparent molecular ion peak at *m/e* 73; a second major peak is at *m/e* 44. The second fraction had a base peak at *m/e* 93 and an apparent molecular ion peak at *m/e* 94 or 95, which are both present; the *m/e* 95 peak is minor but significant, and M–1 peaks are common in electron impact mass spectrometry; a major *m/e* 28 peak is also present. The third volatile fraction had a predominant base peak at *m/e* 32, which corresponds expectedly to hydrazine, N_2H_4.

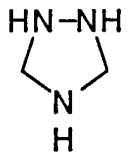
For further analysis of the solute in this product solution, the volatile solvent components (aqueous hydrazine based on the ^1H NMR spectrum) were removed under high vacuum. Redissolution of the solid residue in D_2O showed a significantly different ^{13}C NMR spectrum from that exhibited by the crude product solution without reaction solvent completely removed! Although the spectrum taken immediately after redissolution of the residue had relatively poor signal-to-noise ratio from a small number of transient acquisitions, there was only *one* predominant peak, at δ 71.2 (vs. sodium trimethylsilylpropionate-d_4 as δ 1.7). Furthermore, after standing at room temperature for 3 days, a new analysis showed still different ^{13}C peaks at δ 66.8, δ 72.0 (ratio ~2:1), with a δ 70.9 peak now minor!

The collective evidence of these analyses strongly suggests that the crude product(s) from this reaction, as previously analyzed by NMR in its aqueous hydrazine solution, consisted of *intermediates* that were not ultimately stable in isolation. The following behavior is now suggested as occurring in the course of this product analysis.

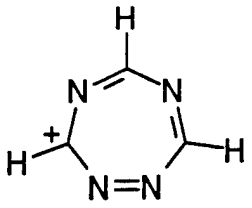
In the 2D-NMR spectrum (Figure 3), the combination of a ^1H absorption at δ 4.77 and ^{13}C absorption at δ 72.2 still corresponds reasonably well to that reported in the literature for hexamethylenetetramine. (A control reaction showed that HMTA does not react spontaneously with hydrazine.) HMTA is also relatively involatile (subl. 263 °C) and may not readily be detected by gas chromatography under the conditions used here. There are relatively few empirical formulas that correspond to a mass of 73, as seen by mass spectrometry of the first GC fraction. Based on the expected chemistry occurring in this system, the likely structure is 1,2,4-triazolidine (**14**). The significant *m/e* 44 peak should correspond to $HN\dot{N}–NH^+=CH_2$. In the second GC fraction, the identity of the mass 95 peak is not as clearly apparent. A conceivable structure arising from recombinations of formaldehyde, ammonia, and hydrazine, followed by eliminations and ionization expected under mass spectrometer conditions may be a tetrazepine structure, $C_3H_3N_4$ (**15**).



hexamethylenetetramine



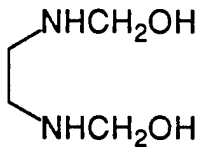
14



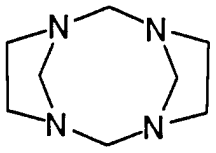
15

The significant *m/e* 28 peak is clearly N_2, consistent with elimination from **15**. 1,2,4-Triazolidine (**14**) is interesting in not having been reported in prior literature as a discrete compound. It is not surprising that it has not been and cannot be isolated, as it may be expected to rearrange to the most stable forms of the corresponding aldehyde–amine condensation products, hexamethylenetetramine and TFTA (or the amorphous condensation polymer). Nevertheless, this structure is also consistent with the observed 2D-NMR data, having a ^1H chemical shift similar to that of TFTA but occurring as a singlet (not being a constrained binuclear ring system like TFTA) rather than an AB quartet, and a ^{13}C chemical shift in the typical range for methyleneimine carbons, δ 70–75. Although ^{13}C NMR data are scarce for 2-unsubstituted generic α,γ-diazacyclopentanes (**14** being an example), a relevant report is the chemical shift of 1,3-bis(2-hydroxyphenyl)imidazolidine as δ 74.5,[71] compared to δ 75.0 observed from the second component (**14**) in Figure 3. Upon removal of the solvent that allows its existence *in situ*, the components rearrange into more-stable forms; the unstable **14** may also volatilize during this process.

The complex chemical behavior suggested here is very similar to that described for a different amine–aldehyde condensation system. Zheng et al. (Beijing Institute of Technology) reported their re-investigation of the ethylenediamine–formaldehyde condensation system as follows:[72] "The condensation product of 1,2-ethylenediamine with formaldehyde was thought to be compound [**16**] while it was present in condensation solution, but to be compound [**17**] or [**18**] after it was separated out as a solid by evaporating the reaction solution immediately after the condensation had completed. It seems to us that the...key point of knowing the reaction mechanism is to understand whether [**16**] is the correct condensation product or not. In order to do this the condensation liquor was examined by following techniques: (a) Gas Chromatography... (b) Mass Spectroscopy... (c) N.M.R. Spectroscopy... It may be inferred from these data that the correct condensation product is compound [**19**], 1,3-diazacyclopentane, not compound [**16**]."



16



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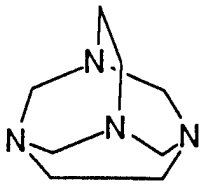

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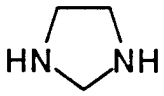

19

Thus, it was seen that imidazolidine (**19**) is another small saturated heterocycle, similar to **14**, that is unstable in an isolated state but can exist in a solution of its condensation reactants.

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[71] Rivera, A.; Gallo, G.I.; Gayón, M.E.; Joseph-Nathan, P. *Synth. Commun.* **1993**, *23*, 2921-2929.

[72] Zheng, M.; Shao, X.; Wang, H. In "Proceedings of the International Symposium on Pyrotechnics and Explosives"; Ding, J., Ed.; China Academic Publishers, Beijing, 1987; pp. 220-227.

Because the reaction conditions resulting in the sequence of transformations described above (i.e., neat hydrazine) are not likely to be used in a scaled-up demilitarization process, the further elucidation of this behavior was not pursued in the Phase I contract.

4.7 RDX–HYDRAZINE–PALLADIUM SYSTEM

The reactivity of RDX, the six-membered-ring congener of HMX, in the same conversion scheme was also tested by a reaction with hydrazine in DMF solvent at 55 °C. In 18 h, the RDX was all consumed, and the same characteristic intermediate (**11**) was observed. This result is evidence that this pathway does *not* depend on the instability of tetrazocine intermediates or on undesirable intermediates such as nitrosamines. The nitrosamine analogue of RDX, hexahydro-1,3,5-trinitroso-1,3,5-triazine (R-salt) is a well-known, stable compound; it was not formed in this process. Mixed nitro-nitroso triazine derivatives are also known and characterized, and there was no evidence for such species either.

4.8 TETRYL–HYDRAZINE SYSTEM

Tetryl was subjected only to the electron transfer hydrogenolysis conditions with BNAH. Tetryl upon reaction with hydrazine would otherwise undergo facile displacement reactions that would remove the N-methylnitramino substituent from the trinitrophenyl ring rather than effecting hydrogenolytic N-denitration. Similar examples are the displacement of N-methylnitramino by ammonia and by even less nucleophilic amines like aniline (Scheme 14).[73] A similarly reactive picryl derivative, 2,4,6-trinitroanisole (methyl picrate), undergoes substitution by hydrazine to make picrylhydrazine.[74] Even less activated polynitroaromatics are susceptible to substitution by hydrazine, a strong nucleophile: 2,4-dinitroanisole also forms (2,4-dinitrophenyl)hydrazine quantitatively with hydrazine.[75]

Other competing reactions would be reduction of the aromatic nitro substituents to amino groups via catalytic hydrogenation, a well known phenomenon produced by hydrazine in the presence of certain metal catalysts.[76] These catalytic transfer hydrogenolysis conditions would therefore also achieve demilitarization of tetryl, but not via simple N–NO_2 bond scission.

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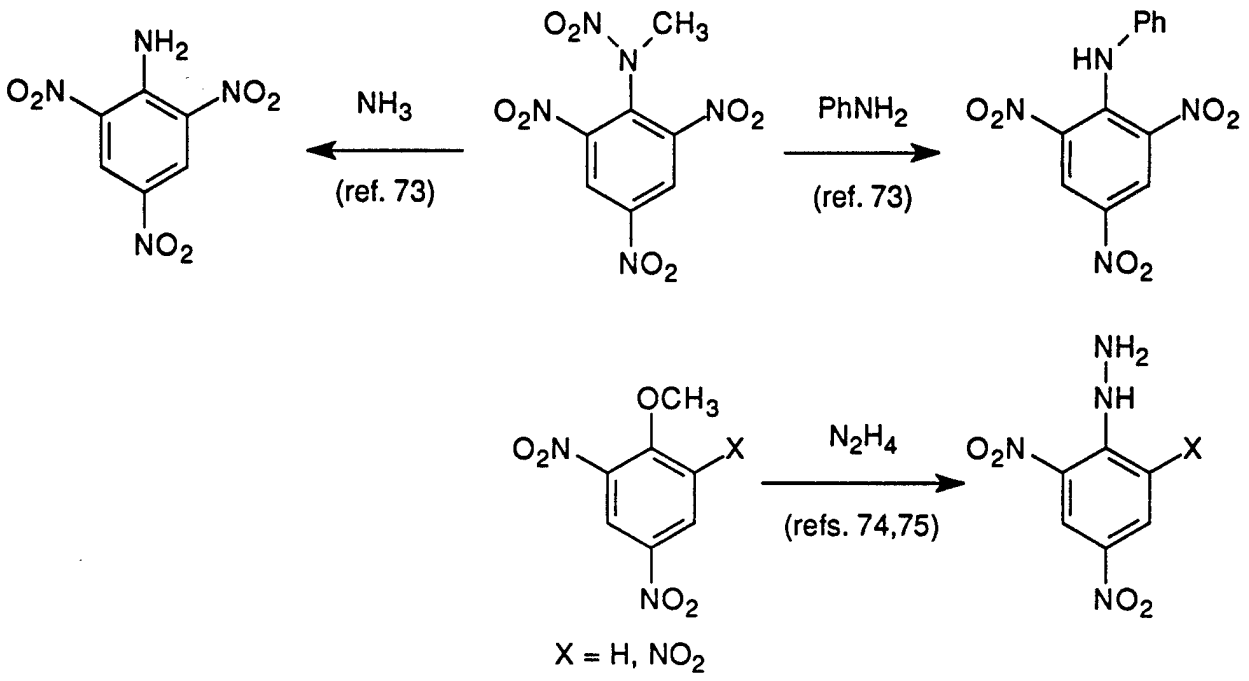
[73] Urbański, T. "Chemistry and Technology of Explosives"; Pergamon Press: New York, 1964; Vol. III, page 51.

[74] Giua, M.; Cherchi, F. *Gazz. Chim. Ital.* **1919**, *49*(II), 155-157; *Chem. Abstr.* **1920**, *14*, 1530.

[75] Ayyangar, N.R.; Kalkote, U.R.; Lugade, A.G.; Nikrad, P.V.; Sharma, V.K. *Bull. Chem. Soc. Japan* **1983**, *56*, 3159-3164.

[76] Furst, A.; Berlo, R.C.; Hooton, S. *Chem. Rev.* **1965**, *65*, 51-68.



Scheme 14. Nucleophilic substitutions of picryl derivatives, including tetryl

5. CONCLUSIONS AND RECOMMENDATIONS

Success achieved in applying *two* novel synthetic transformations to the conversion of designated nitramines to the corresponding free amines (i.e., achievement of the desired N–NO_2 bond scission) clearly technically warrants further development of these systems. The long-term viability of dihydronicotinamides as electron transfer hydrogenolysis reagents would depend on the technical feasibility of regenerating them economically, as they are otherwise expensive specialty chemicals. Fortunately, methodology has been developed and published for such regeneration. The preparation of a polymer-bound variation of BNAH has been reported, offering the prospect for easy use and recovery of the reagent from reaction solutions. Consistent with the long-term goal of any program for demilitarization of energetic formulations, the development of improved chemical conversion processes for this purpose should take advantage of the new methods demonstrated in this Phase I contract.

The success of homogeneous aqueous systems for denitration of HMX (Section 4.1.2) suggests the prospect of nitramine degradation/demilitarization under conditions in which the material may not be amenable to conventional means of removal, reclamation, or destruction—e.g., material entrapped in hardware components permeable to homogeneous aqueous solutions under mild conditions but not otherwise conveniently accessible.

Included in any further development of nitramine denitration by hydrazine should be an investigation of alternative, more economical catalysts for the catalytic transfer hydrogenation by hydrazine. In particular, our speculation about such feasibility is based on precedence for the

efficacy of *nickel* catalyst (in the form of Raney nickel), rather than precious metals such as palladium or platinum, in many of the catalytic transfer hydrogenations effected by hydrazine.[75] Although the apparent precedent for N-denitration of nitramines with hydrazine hydrate used palladium black as an effective catalyst,[39] other relevant hydrogenations by hydrazine have been achieved with Raney nickel, a much cheaper potential catalyst, including reductions of polynitroaromatics to corresponding anilines.[75,77]

Finally, improvements in the preparation of the polymer-supported dihydronicotinamide (**4**) should be developed. At the higher degree of functionalization (61%) used in the current study, the literature preparation[32] of **4** required modification to alleviate the incomplete hydrolysis reaction evidenced by the diminished reactivity and residual contamination discovered in the current studies using this reagent. Additionally, particular solvents may play a critical role in the reactivity of the polystyrene-supported reagent if swelling of the matrix is desired for optimal reactivity.[49] Here, tetrahydrofuran was found to be a superior solvent to acetone. Appropriate modifications of the nature of the polymer matrix[31] may improve the performance even in water solvent.

6. EXPERIMENTAL SECTION

General. HMX, RDX, and tetryl were purified production-grade materials obtained from Pacific Scientific—Energy Dynamics Division (Goodyear, AZ and Chandler, AZ). The NMR spectrometer used for all analyses was a Bruker AC-300 (IBM NR-300) multinuclear spectrometer using 5-mm samples. All chemicals were reagent grade or better, unless specified by source.

HMX denitration by BNAH (dimethylformamide). The following example is representative of the reagent scale. BNAH **2** (1.4936 g, 6.97 mmol, TCI America) was added to a dried 25-mL 3-necked round-bottom flask equipped with a Teflon stirring bar and rubber septum cap. The flask was evacuated and then refilled with nitrogen. Dimethylformamide (3.50 mL) and mesitylene internal standard (71.5 mg, 0.59 mmol) were added via syringe. This solution was transferred via cannula (nitrogen pressure) to a 10-mL single-necked round-bottom flask, equipped with a Teflon stirring bar and rubber septum cap, containing HMX (0.1779 g, 0.60 mmol) in 1.0 mL DMF. The mixture produced a clear orange solution. This reaction was placed in a photochemical reactor cabinet and purged with nitrogen for 1 h. The electron transfer hydrogenolysis reaction was initiated by a 200-W tungsten light bulb, and the reaction mixture was maintained at a slightly elevated ambient temperature in the cabinet. After 4 h of light exposure, the reaction turned red in color. After 20 h, it had turned very dark; after 24 h, the reaction was terminated. ^{1}H NMR analysis of an aliquot in acetone-d_6 confirmed the disappearance of the HMX absorption peak.

In variations of this procedure, the reaction flask was held in a water cooling bath at 5 °C, and photolysis was conducted as above in the photochemical reactor cabinet. A solution of BNAH **2** (2.3100 g, 10.81 mmol) in 15 mL DMF was transferred via cannula (nitrogen pressure) into a

[77] (a) Balcom, D.; Furst, A. *J. Am. Chem. Soc.* **1953**, *75*, 4334. (b) Furst, A.; Moore, R.E. *J. Am. Chem. Soc.* **1957**, *79*, 5492-5493.

50-mL round-bottom flask, equipped with a Teflon stirring bar and reflux condenser, containing a solution of HMX (0.5336 g, 1.80 mmol) in 15 mL DMF. Photolysis of the reaction was conducted with a 200-W tungsten light bulb. After 1 h of exposure, the solution turned red in color; after 16 h, it turned very dark. Some of the solution (4 mL) was concentrated under reduced pressure by rotary evaporation to remove DMF, yielding a red-brown viscous oil. Water (10 mL) was added and a precipitate formed. The aqueous filtrate was again concentrated by rotary evaporation, yielding a solute with a single ^{1}H NMR absorption at δ 4.67 (D_2O).

Alternatively, the reaction proceeded outdoors via photolysis by direct sunlight.

In a variation initiated by sodium dithionite, HMX (0.1728 g, 0.58 mmol), BNAH **2** (1.5021 g, 7.01 mmol), mesitylene internal standard (88.7 mg, 0.74 mmol), and sodium dithionite (1.2245 g, 5.98 mmol, Aldrich 85% sodium hydrosulfite) were mixed in 4.43 mL DMF. The reaction flask was equipped with a Teflon stirring bar, condenser, and nitrogen bubbler. The reaction was covered with aluminum foil, purged with nitrogen, and stirred at ambient temperature in the dark. After 18 h, distilled water (0.50 mL) was added to the yellow slurry. Aliquots were analyzed by ^{1}H NMR in acetone-d_6. After 4 days, consumption of HMX was complete.

HMX denitration by BNAH (water). HMX (0.1463 g, 0.493 mmol) was dissolved in acetonitrile (10.0 mL). BNAH **2** (0.8310 g, 3.88 mmol) and dodecyltrimethylammonium bromide (0.9484 g, 3.08 mmol, Aldrich) were dissolved in 180 mL of pH 9 borate buffer solution. Both solutions were transferred into a 250-mL single-necked round-bottom flask equipped with a Teflon stirring bar and rubber septum. A portion (25 mL) of this solution was subjected to photolysis, under nitrogen atmosphere, by a 200-W tungsten light bulb in a photochemical cabinet. After 45 h, an aliquot was removed; analysis by ^{1}H NMR (DMSO-d_6) confirmed the disappearance of HMX.

In a modification, 15 mL of the HMX–BNAH solution in a septum-capped 25-mL round-bottom flask was placed outside for sunlight photolysis (temperatures ranged from –7 to +13 °C). The complete consumption of HMX was achieved in 18 days, according to NMR analysis.

Polystyrene-supported dihydronicotinamide (4).[32] Chloromethylated polystyrene (25.19 g, 0.1146 mol Cl) with a degree of functionalization of 61% (Fluka, 16.09% Cl) was stirred in acetonitrile (200 mL) for 20 min in a 1-L round-bottom flask before adding a slurry of nicotinamide (32.85 g, 0.2690 mol) in acetonitrile (100 mL). After reaction for 7 days at reflux temperature, the polymer was filtered (glass frit) and washed with acetonitrile (300 mL) and warm water (300 mL), yielding 157 g of wet, golden-colored polymer. FTIR analysis (diffuse reflectance with KBr) confirmed the disappearance of CH_2Cl (1268 cm^{-1}) in the polymer. To the wet resin in 300 mL water in a 1-L round-bottom flask was added sodium carbonate (38.00 g, 0.358 mol) in 100 mL H_2O and, slowly, solid sodium dithionite (175.50 g, 0.857 mol, Aldrich 85%). More H_2O (450 mL) was added, and the flask was fitted with a rubber septum cap and a syringe needle vent. The mixture was stirred at ambient temperature; after 5 min, the reaction turned red-orange and eventually yellow. After 24 h, the polymer was filtered (glass frit) and washed with H_2O (300 mL) and acetonitrile (100 mL). The yellow polymer was dried under vacuum at 40 °C for 48 h, yielding 41.22 g of yellow powder that was stored under argon in a refrigerator. Elemental analysis: C, 61.00%; H, 5.61; N, 6.94; S, 5.98; Cl, <0.05; residue, 12.65; (Na + O), 20.47 by difference. Calcd. for 66.75 wt% **4** + 11.87 wt% **8** + 21.38 wt% Na_2SO_3: C, 61.07%;

H, 5.34; N, 7.05; S 6.00; Na + O, 20.53.

HMX denitration by polystyrene-supported dihydronicotinamide (DMF). Polymer **4** (1.9992 g) was stirred in 100 mL DMF under a nitrogen atmosphere for 24 h prior to use. HMX (0.4250 g, 1.44 mmol) in 15 mL DMF was added to the polymer suspension. The mixture was purged with nitrogen for 1 h before initiation of photolysis by a 200-W tungsten light bulb in a photochemical cabinet, which maintained a slightly elevated ambient temperature. After 14 days, the polymer was filtered off, leaving a yellow filtrate. Evaporation of the DMF at ambient pressure and temperature left colorless crystals (0.42 g), confirmed to be HMX by ^{1}H NMR, and a yellow oil, with NMR absorptions (^{1}H δ 4.66, 6.07; ^{13}C δ 72.52, 63.18 in DMSO-d_6) consistent with an 8:92 mole ratio of hexamethylenetetramine and HMX.

HMX denitration by polystyrene-supported dihydronicotinamide (water). Polymer **4** (1.9652 g) was stirred in 200 mL H_2O under a nitrogen atmosphere for 2 days prior to use. HMX (0.4253, 1.44 mmol) was added to the polymer suspension. The mixture was purged with nitrogen before initiation of photolysis by a 200-W tungsten light bulb in a photochemical cabinet, which maintained a slightly elevated ambient temperature. After 11 days, the polymer was filtered off of an aliquot of the reaction mixture. Evaporation of water at ambient pressure and temperature left a light yellow oily solid, which was insoluble in CD_3CN but soluble in D_2O. ^{1}H NMR analysis (predominant δ 4.78, minor peaks at δ 4.05, 4.42) was consistent with hexamethylenetetramine as the major soluble product. After 14 days, the polymer residue was extracted three times with hot acetone, yielding only 10 mg of a yellow oil; ^{1}H NMR analysis confirmed the absence of HMX.

Tetryl denitration by BNAH (acetone). A solution of tetryl (1.5064 g, 5.25 mmol) in 3 mL of acetone was added to a solution of BNAH (1.1161 g, 5.21 mmol, TCI America) in 9 mL of acetone in a 50-mL round-bottom flask equipped with a Teflon stirring bar. The solution immediately turned very dark, and gradual significant precipitation of a brownish solid occurred. The reaction mixture was stirred for 3 h. After 1 day at room temperature, the supernatant soluble portion was purified by preparative thin-layer chromatography (silica gel/ethyl acetate), which produced a major fraction that was confirmed by ^{1}H and ^{13}C NMR and by elemental analysis to be *N*-methylpicramide (**6**): ^{1}H NMR (DMF-d_7) δ 2.99 (s, CH_3), 9.02 (s, CH); ^{13}C NMR (DMF-d_7) δ 32.96, 127.29, 133.43, 136.73, 144.19. Elemental analysis (mean of two): C, 34.55%; H, 2.41; N, 22.30. Calcd. for $C_7H_6N_4O_6$: C, 34.72; H, 2.50; N, 23.14. A minor fraction isolated by TLC appeared by NMR to be picric acid: ^{1}H NMR (DMF-d_7) δ 8.71 (s, CH); ^{13}C NMR (DMF-d_7) δ 126.18, 156.0. The insoluble precipitate from the reaction appeared by NMR to be only 1-benzyl-3-carboxamidopyridinium ion (**7**), the oxidized form of BNAH: ^{1}H NMR (DMF-d_7) δ 6.16 (s), 7.46 (t), 7.74 (t), 8.18 (b), 8.39 (t), 9.23 (d), 9.37 (b), 9.60 (d), 10.08 (s); ^{13}C NMR (DMF-d_7) δ 64.74, 129.14, 129.92, 130.02, 130.18, 134.85, 135.40, 145.25, 145.82, 147.42, 163.11.

Tetryl denitration by polystyrene-supported dihydronicotinamide (acetone). Polystyrene-supported dihydronicotinamide **4** (1.1439 g) was stirred in 100 mL of acetone—which had been purged with nitrogen for 30 min—for 24 h prior to use. A solution of tetryl (1.4114 g, 4.92 mmol) in acetone (10 mL) was added; the mixture was stirred at ambient temperature under a

nitrogen atmosphere. The reaction mixture, initially yellow in color, gradually turned brown over 6 days. Analysis by NMR of a sample of the solution after 30 days confirmed the conversion of 4–5% of the tetryl to a mixture of **6** and picric acid.

Purification of polystyrene-supported dihydronicotinamide (4). To a suspension of impure polymer **4** (27.98 g) in 200 mL deionized water were added solutions of Na_2CO_3 (10.25 g, 96 mmol) in 100 mL H_2O and then $Na_2S_2O_4$ (44.15 g, 216 mmol, Aldrich 85%) in 200 mL H_2O, all solutions being purged with nitrogen. This aqueous mixture was stirred under nitrogen for 56 h at room temperature. The yellow polymer was filtered off and then washed with deionized H_2O (1 L), reagent-grade CH_3CN (800 mL), warm H_2O (500 mL), HPLC-grade H_2O (200 mL), and then reagent-grade CH_3CN. The solid was suction-dried for 10 min and then dried under vacuum (0.35 torr) for 12 h at room temperature and then for 48 h at 40–50 °C (0.35 torr). The product (27.93 g) was stored under nitrogen in a refrigerator.

Tetryl denitration by polystyrene-supported dihydronicotinamide (tetrahydrofuran). Repurified polystyrene-supported dihydronicotinamide **4** (2.11 g) was stirred in 100 mL of THF, which had been purged with nitrogen, for 16 h prior to use. A solution of tetryl (0.260 g, 0.906 mmol) in THF (5 mL), which had been purged with nitrogen, was added via syringe. The reaction flask was fitted with a reflux condenser, and a nitrogen atmosphere was maintained. The reaction, while stirring, was photolyzed by a 200-W tungsten light bulb in a photochemical reaction cabinet. The reaction mixture, initially yellow in color, turned orange within 4 days. At that time, analysis by ^1H NMR (acetone-d_6) of a sample of the solution—from which THF had been removed under reduced pressure—confirmed the conversion of 30% of the tetryl (δ 9.37 for aromatic CH) to a mixture of: *N*-methylpicramide (the major product, δ 9.02 for aromatic CH); a presumed intermediate (δ 8.88) which appeared in the course of the reaction but diminished in later stages as **6** built up; and a minor amount of picric acid (δ 8.71).

HMX denitration by hydrazine (dimethylformamide)—formation of formaldazine (11). A mixture of HMX (0.3484 g, 1.18 mmol) and palladium black (0.0340 g) in DMF (7.7098 g) was warmed with an oil bath to 50–55 °C in a 25-mL 3-necked round-bottom flask equipped with a Teflon stirring bar and a rubber septum cap. Mesitylene (0.1789 g, 1.49 mmol) was added as an internal NMR standard, and anhydrous hydrazine (0.8050 g, 25.12 mmol) was added via syringe. After 24 h at 50–55 °C, more hydrazine (0.8033 g, 25.06 mmol), palladium black (0.1040 g), and DMF (5.0 mL) were added to the reaction mixture. Analysis by NMR of the reaction solution after 39 h confirmed the complete disappearance of HMX and the formation of the characteristic AB quartet of formaldazine (**11**).

In a modification of this reaction, HMX (0.3473 g, 1.17 mmol), palladium black (0.0816 g), hexamethyldisiloxane (0.1907 g, 1.17 mmol) internal standard, DMF (10.2067 g), and hydrazine (1.8206 g, 56.79 mmol) were mixed in a 25-mL round-bottom flask equipped with a Teflon stirring bar and then a rubber septum cap vented with a syringe needle. The reaction was stirred at room temperature for 66 h, at which time the NMR spectrum shown in Figure 1 (Section 4.6.1) was obtained, indicating >98% consumption of HMX, with concomitant formation of **11**.

HMX denitration by hydrazine (dimethylformamide)—formation of 4-amino-4*H*-1,2,4-triazole (12). A mixture of HMX (0.0938 g, 0.317 mmol) and palladium black (9.0 mg) in

DMF-d_7 (0.7453 g) was warmed with an oil bath to 55 °C in a 5-mL glass vial equipped with a rubber septum cap. Hexamethyldisiloxane (0.0573 g, 0.353 mmol) was added as an internal NMR standard, and anhydrous hydrazine (0.0749 g, 2.33 mmol) was added via syringe. After 48 h at 55 °C, ^{1}H and ^{13}C NMR analysis showed intermediate **11** as the major component. At this time, more hydrazine (0.2061 g, 6.43 mmol) was added to the reaction mixture, which was heated at 55 °C for another 6 days (8 days total). ^{1}H and ^{13}C NMR analysis (see text) showed product **12** as the predominant component at this time.

In a separate reaction for isolation of **12**, a solution of HMX (5.03 g, 17.0 mmol) in DMF (70 mL) was warmed with an oil bath to 55 °C in a 100-mL 3-necked round-bottom flask equipped with a Teflon stirring bar and a rubber septum cap. Palladium black (0.5205 g) was added, and the system was purged with nitrogen for 30 min at 55 °C. Hydrazine (3.2272 g, 0.1007 mol) was added via syringe, and the reaction flask was fitted with a nitrogen bubbler providing static N_2 pressure. After 40 h at 55 °C, HMX and intermediate **11** were still present. After 86 h at 55 °C, more hydrazine (1.7508 g, 54.63 mmol) was added. After 175 h at 55 °C, half of the reaction solution was removed for characterization of the intermediate (**11**). Additional portions of hydrazine were added to the continuing remainder of the reaction at the following times until complete conversion of **11** to product **12** was observed: 20 days (1.96 g, 61.1 mmol); 35 days (2.61 g, 81.4 mmol); 45 days (3.18 g, 99.1 mmol); 55 days (2.75 g, 85.7 mmol). The reaction was terminated after 60 days at 55 °C. DMF solvent was removed under high vacuum. The addition of dichloromethane formed a solid precipitate, which was removed by filtration. This product was purified by preparative thin-layer chromatography: 50 mg was dissolved in acetonitrile–ethyl acetate (1:1) and applied to a 500-μm silica gel plate; acetonitrile was used as the mobile phase. Three major bands were produced at R_f values of 0–0.15, 0.15–0.30, and 0.30–0.35. All of the fractions were extracted from the silica gel with methanol. The last of these fractions was confirmed as product **12** by NMR.

HMX denitration by hydrazine (acetonitrile). A mixture of HMX (0.3272 g, 1.10 mmol), hydrazine (1.1817 g, 36.87 mmol), and palladium black (48.0 mg) in acetonitrile (25 mL) was stirred at room temperature for 5.8 days. At this time, NMR analysis showed that conversion to **11** was progressing slower than in DMF; the reaction was then warmed with an oil bath to 55 °C for another 3.8 days. At this time, NMR analysis showed **11** as the major component, though **12** was already apparent. **11**: ^{1}H NMR (CD_3CN) δ 6.05, 6.68 (AB quartet). **12**: ^{1}H NMR (CD_3CN) δ 5.75 (b, NH_2), 8.28 (s, CH).

HMX denitration by hydrazine (water). HMX (0.0747 g, 0.25 mmol) and dodecyltrimethylammonium bromide (0.5521 g, 1.79 mmol, Aldrich) were added to deionized water (100 mL) in a 250-mL round-bottom flask equipped with a Teflon stirring bar and then a rubber septum cap. Palladium black (8.5 mg) was added; the mixture was purged with nitrogen; and hydrazine (0.2950 g, 9.20 mmol) was added via syringe. The reaction was warmed to 50 °C. After 8 days, evaporation of the water yielded 0.8424 g of a white solid, which was vacuum-dried for 16 h at room temperature. ^{1}H NMR analysis of the residue (DMSO-d_6) confirmed the disappearance of HMX.

In a variation of these conditions, HMX (0.5031 g, 1.70 mmol) and palladium black (0.0654 g) were added to HPLC-grade water (500 mL) in a 1-L 2-necked round-bottom flask equipped with a Teflon stirring bar, a reflux condenser, and a rubber septum cap. Hydrazine (2.5123 g, 78.39 mmol) was added via syringe. The reaction was heated to reflux. After 21 h, the reaction mixture was clear and homogeneous. ^1H NMR analysis (D_2O) of an aliquot from 35 mL of the solution concentrated to 15 mL confirmed the absence of HMX.

HMX denitration by hydrazine (neat hydrazine). A mixture of hydrazine (13 mL) and palladium black (0.0595 g) was purged with nitrogen and cooled to 5 °C in a 50-mL 3-necked round-bottom flask equipped with a Teflon stirring bar, a condenser, and a powder addition funnel containing HMX (0.4965 g, 1.68 mmol). The HMX solid was added slowly to the hydrazine over the course of 85 min at 5 °C. (*Warning:* Hydrazine added to solid HMX in a septum-capped flask caused the HMX to combust.) The mixture was then gradually warmed to 40–42 °C over the course of 3 h and then maintained for 94 h. The supernatant solution was transferred away from the palladium. Short-path distillation of the solution at 3.0 torr removed most of the hydrazine at 22 °C. The pot residue was analyzed as described in the text (Section 4.6.3). GC-MS data were acquired at Los Alamos National Laboratory on a Hewlett-Packard 5890-A GC interfaced with a Hewlett-Packard 5971 Mass Selective Detector. The column was a Quadrex Corp. MPS 5 (SE-54 equivalent) capillary column, 0.25 mm × 25 m with 0.1 μm film thickness. The temperature program started at 40 °C, ramping up at 20 °C/min to a final temperature of 240 °C. Raw MS data for fractions showing proposed products **14** and **15** (the latter generated *in situ* in the mass spectrometer) follow as Figures 5–6.

RDX denitration by hydrazine (dimethylformamide)—formation of formaldazine (11). A mixture of RDX (0.7037 g, 3.17 mmol) and palladium black (0.0810 g) in DMF (10 mL) was made up in a 100-mL 2-necked round-bottom flask equipped with a Teflon stirring bar, a condenser, and a rubber septum cap. The solution was purged with nitrogen for 30 min, and then anhydrous hydrazine (2.8123 g, 87.75 mmol) was added via syringe. The mixture was warmed with an oil bath to 55 °C for 18 h. Analysis by NMR of the reaction solution confirmed the complete disappearance of RDX (δ 6.22) and the formation of the characteristic AB quartet of formaldazine (**11**).

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Date Acquired: 6 Feb 95 4:23 pm
Method File: MFWA2.M
Sample Name: ob3-241-hm
Misc Info: sample 3 from ROB dilute w/ MeOH
ALS vial: 1

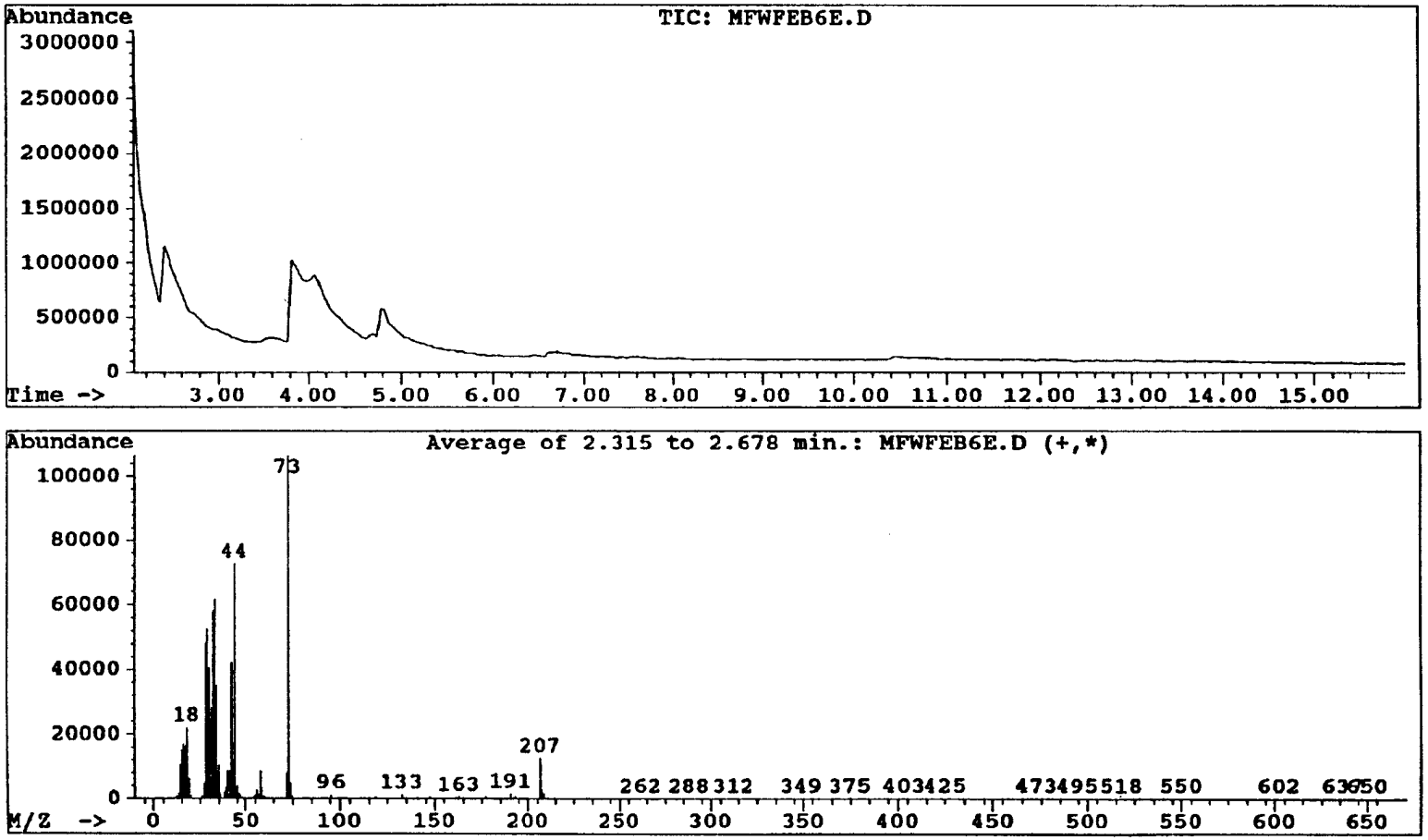

Figure 5. GC of products of HMX denitration by neat hydrazine; mass spectrum of early fraction (tentative product 14)

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Method File: MFWA2.M
Sample Name: ob3-241-hm
Misc Info: sample 3 from ROB dilute w/ MeOH
ALS vial: 1

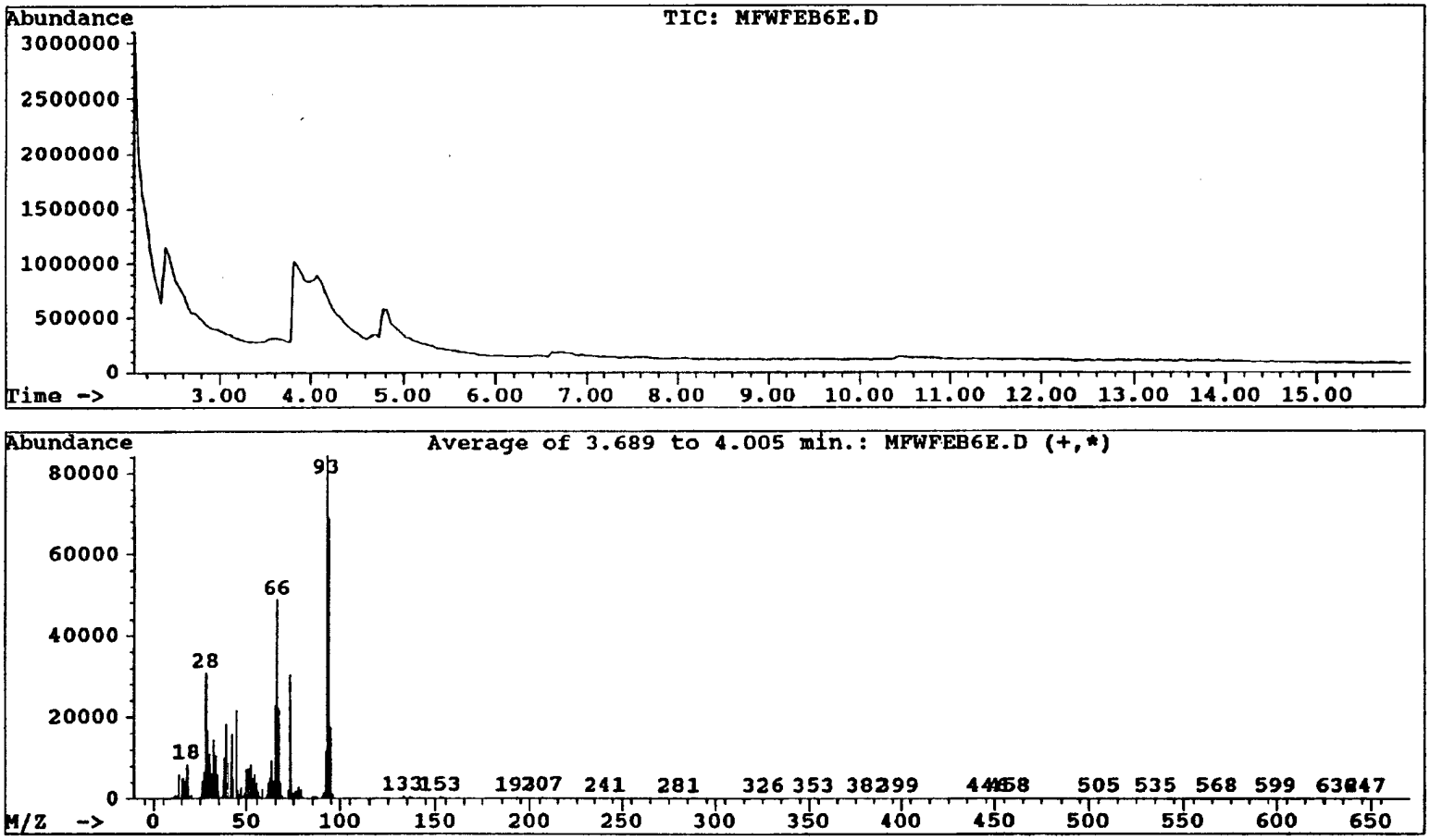

Figure 6. GC of products of HMX denitration by neat hydrazine; mass spectrum of middle fraction (tentative product **15**)

7. ACKNOWLEDGEMENTS

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