Synthesis and Characterization of High Energy-Density N-Nitramino, Geminal Dinitro and Geminal Difluoramino Propellants

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A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirement for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

Synthesis and Characterization of High Energy-Density N-Nitramino, Geminal Dinitro and Geminal Difluoramino Propellants

by

Lida Qi

Advisor: Professor Theodore Axenrod

Propellants and explosives are composed of energetic materials that produce high temperature and pressure through combustion phenomena. They have both important civilian and military applications. An abbreviated introduction reviews the fundamental properties of the different chemical compounds used for explosives and propellants. Briefly, these include heats of formation of reactants and products, formulation of propellants, oxygen balance, importance of density and specific impulse considerations. A second aspect is devoted to an examination of the many synthetic methods employed to prepare the novel modern high energy-density materials currently being investigated on a world-wide basis. Attention is drawn to the increased energy output of these new materials, their improved environmental attributes as well as their improved insensitive munitions characteristics. Based on predictions of crystal structure and density

considerations a number of target compounds have been identified as having expected physical and performance properties worthy of further investigation.

In a third phase, the cyclodimerization of p-toluenesulfomamide and 3-chloro-2-(chloromethyl)-1-propene to prepare N,N'-bis(4-methylbenzenesulfonyl)-3,7-bis-(methylene)tetrahydro-1,5-diazocine (**47a**) and its ozonation to the corresponding 3,7-dione (**48a**) are described. Unusual transannular cyclizations initiated by lithium aluminum hydride treatment or bromination of **47a** and oxidative coupling of the dioxime derived from **48a** are described. These reactions lead, respectively, to the following derivatives of the little-studied 3,7-diazabicyclo[3.3.0]octane ring system: 1,5-dimethyl-3,7-diazabicyclo[3.3.0]octane (**53**), N,N'-bis(4-methylbenzenesulfonyl)-1,5-bis(bromo-methyl)-3,7-diazabicyclo[3.3.0]octane (**57**), and N,N'-bis(4-methylbenzenesulfonyl)-1,5-dinitro-3,7-diazabicyclo[3.3.0]octane (**61**). Reaction of the dibromide (**57**) with the nucleophiles, sodium sulfide, sodium oxide, and sodium p-toluenesulfonamide conveniently delivers the corresponding novel 3,7,10-triheterocyclic[3.3.3]propellanes.

Finally, the syntheses of new 3,3-dinitro derivatives of the 1,5-diazocine ring system are described. Highly deactivated precursor ketones, 7,7-dinitro-1,5-bis(2- and 4-nitrobenzenesulfonyl)hexahydro-1,5-diazocin-3-ones (**92a** and **92b**), have been difluoraminated to the corresponding gem-bis(difluoramino) diazocines (**93a** and **93b**). The 1,5-bis(4-nitrobenzenesulfonyl)diazocine derivative (**93a**) undergoes N-nitrolysis with the protonitronium reagent formed in the system nitric acid – trifluoromethanesulfonic acid – antimony pentafluoride to produce 3,3-

bis(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-diazocine (**TNFX**), containing nitramine, gem-dinitro and gem-bis(difluoramino) structural components. **TNFX** has been fully characterized by NMR spectroscopy, high resolution mass spectrometry and X-ray crystallography.

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Chapter 1

Introduction

This introductory chapter will examine the fundamental concepts applied to the energetics of chemical compounds used for propellants. Such topics as heat of formation, heat of explosion, oxygen balance, specific impulse and energy-density will be briefly presented. Since numerous types of compounds are used for propellants only some representative energetic crystalline and polymeric materials employed in a few different types of propellants will be discussed. The formulation of different propellants and the characteristics that influence their properties will also be compared and contrasted. This approach is intended to give a somewhat general overview and to provide an understanding of the important considerations that must be addressed in developing new propellants to meet modern requirements. A comprehensive review of the mechanism of combustion processes is beyond the scope of the present treatment.

1.1 Classification of Energetic Materials

Propellants, explosives and pyrotechnics are different classes of energetic materials that share many common features. They are chemical compounds or mixtures which when subjected to combustion undergo complex physicochemical changes accompanied by rapid exothermic reactions. This combustion results in the release of their stored energy and the production of high temperature gaseous products together with a substantial increase in pressure. It is these latter consequences of the combustion process that have

made energetic materials of great practical importance from the time of the discovery of gunpowder to modern day explosives and rocket fuels. History has certainly been profoundly influenced by military utilization of these technologies, but their peaceful uses ranging from the employment of explosives in mining and road building to applications such as missile propulsion systems by far surpass their potential negative destructive power.

Propellants release their energy through relatively slow deflagration processes often requiring several seconds to complete the combustion. Explosives typically undergo detonation, that is, they release their energy at a much faster rate with complete combustion being achieved on the microsecond timescale. When propellants and explosives are burned in a vessel the gaseous products in the vessel generate a high pressure which is converted into a propulsive or a destructive force. Though the energetics of both propellants and explosives are the same the combustion phenomena are different because of the difference in the heat release processes. In typical solid-fuel rocket motors, a propellant is packed around a central air channel. Upon ignition, the propellant burns at the face of the channel that acts as a combustion chamber. The exhaust is expelled through the nozzle at the rear propelling the rocket forward. Propellants with their slow rates of combustion are used to provide propulsive forces over a sustained period while rapidly detonating explosives are used to provide destructive forces.

1.2 Some Important Properties in Propellants

In the past half century of global research and development new more powerful energetic materials have been developed. These advances have been achieved through optimal tradeoffs in power output, cost containment, reduced complexity of syntheses employed, as well as safety considerations. The latter arise from the increasing use of insensitive materials or formulations which are immune to provocative stimuli such as heat, light, impact and shock. In this thesis we shall examine some elementary approaches to predicting the properties of some energetic materials. This information together with molecular modeling techniques can then be helpful in designing new materials as well as assessing the characteristics of synthesized materials.

A list of material name abbreviations for common interesting novel energetic compounds that will be encountered throughout this dissertation is shown in **Table I**. Explicit structures are also provided throughout the text for these novel energetic materials.

Table I. Acronyms and Abbreviations of Some Energetic Materials

ADN	ammonium dinitramide
AN	ammonium nitrate
AP	ammonium perchlorate
CL-20	hexanitrohexaazaisowurtzitane (also abbreviated as HNIW)
DNNC	1,3,5,5-tetranitrohexahydro pyrimidine

DPA	diphenylamine
HHNDZ	octahydro-1,3,3,5,7,7-hexanitro-1,5-diazocine
HHTDD	2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazatricyclo[7.3.0.0]dodecane-5,11-dione
HMX	octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine
HNF	hydrazinium nitroformate
HNFX	3,3,7,7-tetrakis(difluoramino)octahydro-1,5-dinitro-1,5-diazocine
KN	potassium nitrate
NC	nitrocellulose
NG	nitroglycerin
NTO	nitrotriazolone
NQ	nitroguanidine
ONC	octanitrocubane
RDX	1,3,5-trinitro-1,3,5-triazacyclohexane
RNFX	5,5-difluoramino-1,3-dinitro-5-hexahydro pyrimidine
TNAZ	1,3,3-trinitroazetidine
TNCB	1,1,3,3-tetranitrocyclobutane
TNFX	3,3-bis(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-diazocine
TNT	2,4,6-trinitrotoluene

1.2.1 Chemical Energy-Heats of Explosion

When an energetic molecule A reacts to generate product B heat is released (or absorbed). Since the chemical bond energy of A is different from that of B the energy difference between A and B appears as heat. The heat produced by the chemical reaction may be termed the heat of explosion H_{exp} where H_{exp} is determined by the difference between the heat of formation of reactants $H_{f\,(reactant)}$ and the heat of formation of products $\Delta H_{f\,(product)}$ as represented by

$$H_{exp} = \Delta H_{f\,(reactant)} - \Delta H_{f\,(product)}$$

The heat of formation ΔH_f depends on the chemical structure and chemical bond energy of the molecules making up the reactants and products. A higher H_{exp} is favored when $\Delta H_{f\,(reactant)}$ is high and $\Delta H_{f\,(product)}$ is low.

1.2.2 Oxygen Balance

The oxygen balance OB as determined by the number of excess oxygen atoms in the material is an important parameter useful in the measure of the material to serve as an oxidizer. The OB is the number of oxygen molecules remaining after oxidizing hydrogen, carbon, etc. If excess oxygen remains the material is said to have a positive oxygen balance. For example, nitroglycerin NG produces excess oxygen molecules as a combustion product.

$$C_3H_5N_3O_9 \longrightarrow 3CO_2 + 5\ 1/2\ H_2O + 3/2\ N_2 + 1/4\ O_2$$

(MW.: 227.09)

$$OB = 1/4 \times 32/227 \times 100 = 3.52\%$$

1.2.3 Energy Density

Material performance depends strongly on its density. Propellants are generally designed for an energy density that is the energy produced by a unit volume of material, to be as high as possible within the limits imposed by sensitivity, manufacturing, physical properties and combustion characteristics. From simple aerodynamic considerations the drag during flight of a missile in the atmosphere increases as the cross sectional area of the rocket increases. The reduction in cross sectional area is favored by reduction in the size of the combustion chamber and by increase in the density of the propellant used.

Additionally, the high temperature gas resulting from the combustion of an energetic material is not the only condition to generate high pressure. When the product gas has low molecular weight high pressure is generated even at lower temperatures.

1.2.4 Specific Impulse

The specific impulse, I_{sp}, is widely used as the key measure of the propellant performance and is therefore necessarily that of the composite mixture. It is formally defined as the engine thrust (Newtons) divided by propellant mass flow rate (kilograms/sec). Given in

seconds, I_{sp} is how long one kilogram of propellant can produce one Newton of thrust. However, I_{sp} is often expressed in terms of the absolute temperature in the combustion chamber T_c, and the number of moles of gaseous product produced per weight of propellant N according to the following simplified relationship given in equation **(1)**.

$$I_{sp} \sim T_c^{1/2} N^{1/2} \qquad \textbf{(1)}$$

An energetic molecule develops thrust due to the discharge of gaseous products when it undergoes combustion. Depending on the composition of the propellant, the major gaseous products may include CO, CO_2, N_2, H_2O or HF with lesser amounts of H_2, NO and N_2O. Thus, to a first approximation, the thrust generated will depend on the specific small-molecule products formed, the stoichiometry of the combustion process, as well as the combustion temperature.

To illustrate, some typical data discussed in the above sections are given for some representative energetic materials in **Table II**.

Table II. Properties of Some Energetic Materials

Reactant	Heats of Formation $\Delta H_{f,r}$ (Mj /kg)	Heats of Explosion H_{exp} (Mj /kg)	Oxygen Balance OB(%)	Specific Impulse Isp (s)
NG	-1.70	6.32	3.5	247
NC	-2.60	4.13	-28.7	233
HMX	0.25	5.36	-21.6	269
RDX	0.27	5.40	-21.6	269
AP	-2.52	1.11	34.0	160
CL-20	0.96	6.80	-11.0	281
TNT	-0.185	5.07	-73.9	----

1.3 Categories of Materials Used for Propellants

The materials used for propellants may be divided into two categories: (1) energetic materials consisting of chemically bonded oxidizer and fuel components in the same molecule, and (2) a composite mixture consisting of physically mixed oxidizer and fuel components. Stoichiometrically balanced materials are chosen to obtain high heat release and low molecular weight combustion products. Nitrocellulose with O-NO_2 groups attached to a hydrocarbon backbone is an example of the former. It decomposes to produce oxidizer and fuel components and it is an important and widely used nitropolymer propellant. No smoke signature is seen from the rocket nozzle because the combustion products are mainly CO_2, CO, N_2 and H_2O.

An example of a composite mixture of an oxidizer-rich and a fuel-rich component is that of ammonium perchlorate and polymeric hydrocarbon materials, the mainstay of many current missile programs. Unfortunately, neither the energy-density of ammonium perchlorate nor that of the hydrocarbon fuel, for example, hydroxy-terminated polybutadiene, is particularly high. In order to increase the specific impulse, aluminum powders are often added as a fuel component. Other disadvantages of this type of composite mixture is the white smoke signature trail from the nozzle due to the combustion products being mainly HCl, Al_2O_3, CO_2, and H_2O. HCl, when combined with atmospheric moisture, generates a white smoke trail allowing missile launches to be easily detected as well as subjecting the ozone layer to the ravages of chlorine.

1.4 Formulation of Propellants

A typical **single-base propellant** is composed of nitrocellulose **NC** which has been gelatinized with a solvent such as ethyl alcohol and to which diphenylamine is added as a stabilizer. The stabilizer inhibits the autocatalytic decomposition of the nitrocellulose **NC** by absorbing the slowly liberated NO_2. The solvent-softened nitrocellulose can then be formulated into a propellant grain with an adequate size and shape and a smooth surface is insured by finally coating the material with carbon black. The grain shape is important to obtain an optimum pressure versus time relationship during the burning.

Double-base propellants are formed by the use of nitrocellulose **NC** gelatinized with energetic nitrate esters such as nitroglycerin. The nitroglycerin **NG** is absorbed by the nitrocellulose to produce a rigid network of homogenous granular material. This network maintains the desired grain shapes essential for rocket propellants and generates the necessary temperature and combustion products when it burns. To obtain superior characteristics of the grains formed, dibutylphthalate plasticizers and diphenylamine stabilizers are typically used. The physicochemical properties of double-base propellants such as energy-density, mechanical strength, chemical stability and shock sensitivity depend strongly on the NC/NG ratio employed. The energy-density of the propellant is increased by an increase in the fraction of **NG** used while the mechanical properties and shock sensitivities suffer and the chemical stability is likewise decreased.

Incorporation of crystalline nitroguanidine **NQ** into the framework of a double-base propellant produces a **triple-base propellant**. The high mole fraction of hydrogen in **NQ** leads to low molecular weight combustion products even at low flame temperatures.

Instead of using **NQ** to formulate triple-base propellants, crystalline ammonium perchlorate **AP**, **HMX** or **RDX**, can be added to nitrocellulose-nitroglycerin mixtures to form **composite double-base propellants**. The **NC/NG** framework is able to incorporate these particles to give an essentially heterogeneous composition. Such compositions are widely used because of their great potential in producing high specific impulse and a flexible burning rate. The added particles burn as a monopropellant at the surface of the

matrix and the combustion products further react with the combustion products of the base matrix.

With hydrocarbon-based fuels such as polybutadiene and polyurethanes crystalline salts such as ammonium nitrate **AN**, potassium nitrate **KN** and ammonium perchlorate **AP** are frequently employed to give heterogeneous composite propellants. The latter salts, all having abundant oxygen, when thermally decomposed, act as the oxidizing agent and react with the generated gaseous fuel fragments. Thus, the ballistic properties of the propellant such as burning rate and pressure sensitivity depend not only on the chemical ingredients of the oxidizer and the fuel, but also on the shape and size of the oxidizer particles. To produce the optimum stoichiometrically balanced propellant with added aluminum to enhance the specific impulse the mechanical properties of the composite grains must be controlled. The latter are dependent on the complex interplay of the physical and chemical properties of the polymeric materials, as well as additives such as surfactants, bonding agents, cross linkers, curing agents and burn rate catalysts.

A recent review of the fundamental energetics of propellants and explosives[1] and a number of related publications covering the fundamentals of energetic materials[2-8] are listed at the end of this thesis.

Chapter 2

Methodologies Used in Syntheses of Selected Energetic Materials

Organic energetic compounds fall into four structural categories: acyclic compounds, benzenoid aromatics, cycloalkanes and heterocycles. This chapter will briefly survey some recent advances in the design and syntheses of some novel and important classes of saturated cyclic molecules with known or predicted desirable properties for energetic materials.

2.1 Introduction of Common C-Nitro and N-Nitro Energetic Functional Groups

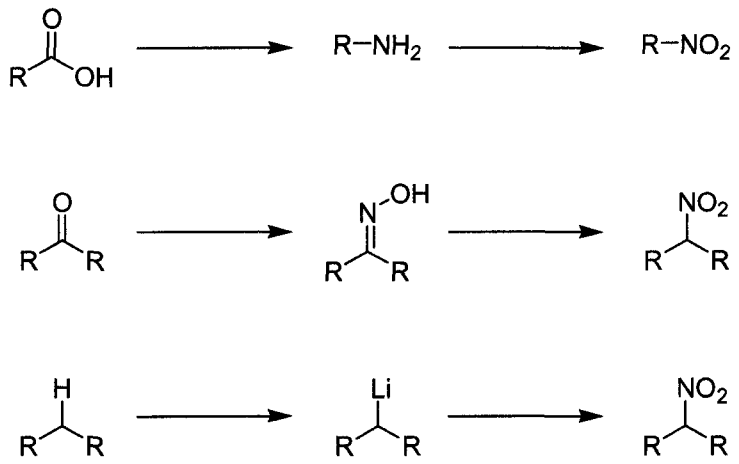
The nitro group is by far the most commonly encountered functional group in energetic materials. Most of the compounds to be discussed subsequently in this chapter contain various forms of nitro-containing functionality, e.g. C-NO_2, C(NO_2)$_2$ and N-NO_2. As such, it will be helpful first to consider some general aspects of the methods employed in introducing these nitro-groups.[9]

2.1.1 Alkyl nitro groups

Nitro groups on saturated systems can be introduced by standard functional group transformations. One of the most frequently adopted protocols involves the sequence of introducing a carboxylic acid substituent (COOH) in place of hydrogen, and subsequent

conversion by some variant of the classic Curtius rearrangement. The amine product can then be oxidized to the desired nitro group using a number of methods.[10-18]

Alternatively, working with starting material at a lower oxidation state, the nitro group can be introduced via a related ketone following the protocol of conversion to oxime followed by oxidation to the nitro functionality.[10,15,16,19-23]

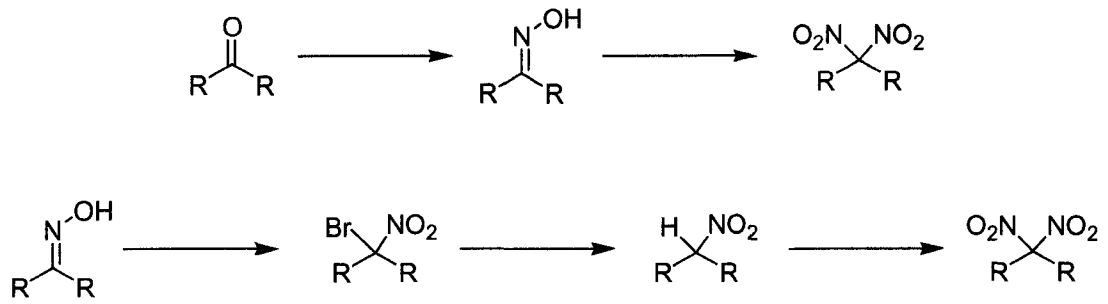


Scheme 1

In other instances, sufficiently acidic protons on certain carbocylces can be removed using a variety of strong bases and the resultant anion reacted with a suitable nitrogen oxide, which results in the direct generation of the nitro-derivative.[24-27]

2.1.2 Geminal dinitro groups

In another class of energetic material the nitro group is encountered as a geminal dinitro derivative. In most cases this moiety is introduced by way of a precursor oxime obtained from the corresponding ketone. Oxidative nitration of the oxime under Scholl[28-35] or Ponzio[36-38] conditions generates the desired dinitro derivative.



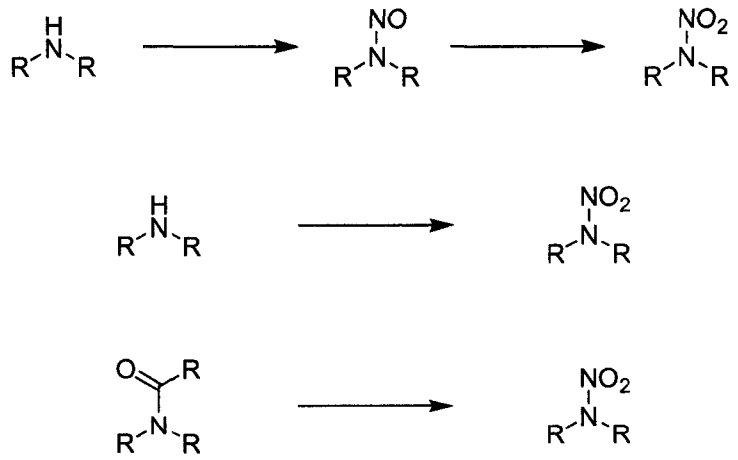
Scheme 2

In other instances, a multi-step but less harsh protocol can be adopted in which the oxime is first converted to an α-halonitro derivative that is subsequently subjected to a redox process that results in the formation of the required gem-dinitro compound.[10,23,29,35,39-50] The chemistry of aliphatic oxidative nitration reactions to produce both mono and geminal dinitro compounds has recently been reviewed.[51]

2.1.3 Nitramines

In addition to nitro derivatized carbons, the nitro group is frequently found attached to a nitrogen atom. The resultant functionality is termed a nitramine. Nitramines are widely used in energetic materials and their chemistry has been extensively reviewed.[52-56]

The introduction of nitramine can often be achieved by oxidation of a nitrosamine precursor. The familiar N-nitroso derivatives can be prepared under acidic conditions by treatment of a starting amine with nitrous acid,[57-60] or under basic conditions using N_2O_3, N_2O_4 [61] or an alkyl nitrite.[62] In cases where the starting materials are insoluble in aqueous media, N-nitrosamines can be accessed in organic solutions by treatment of an amine with $BrCH_2NO_2$.[63] Alternatively, NOCl is often the preferred reagent in instances where the product nitrosamine is highly reactive.[64]



Scheme 3

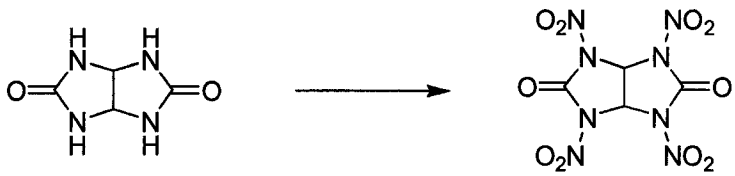
Several conditions have been developed for the subsequent oxidation step which results in the conversion of the nitrosamine to the desired nitramine. The most common involve treatment with concentrated 100% HNO_3,[65-67] HNO_3/H_2SO_4,[68] or 100% HNO_3/N_2O_5.[66] Alternatively, the nitrosamine can be oxidized with peracetic acid.[69]

However, in many cases the preferred methodologies for generation of nitramine are direct N-nitration of amines and amides using nitric acid[70] or a nitronium salt.[71-73] Typically, with a judicious choice of nitronium reagent nitramines can be prepared in good to moderate yield from a wide range of amines with pKa's ranging from 5 to 12.

Other routes to nitramines involve nitrolysis reactions performed on 2° and 3° amides that result in the generation of nitramines in good to moderate yields. A variety of reagents can be used to achieve this transformation, with some of the more common involving the use of 20% N_2O_5/HNO_3,[74] Ac_2O/HNO_3,[75] Ac_2O/NH_4NO_3,[76] HNO_3/H_2SO_4,[77] trifluoroacetic anhydride (TFAA)/100% HNO_3,[78] 100% HNO_3/P_2O_5[75] or $TFAA/NH_4NO_3$.[79] Some more recently developed methods include the nitrolysis of the corresponding N-trialkylsilyl compound using N_2O_5,[80] the reaction of 2° amides with $(CF_3SO)_2O/HNO_3/N_2O_5$ or $TFAA/HNO_3/N_2O_5$,[81] and treatment of 3° amides with nitronium tetrafluoroborate.[82]

2.1.4 N-Nitroureas

The N-nitrourea group is another commonly encountered feature in energetic materials. This functionality is typically introduced in a manner analogous to that described for the preparation of the nitramine group.



Scheme 4

It has been demonstrated that ureas can efficiently be converted to the corresponding N-NO_2 derivative by treatment with HNO_3,[83,84] N_2O_5/HNO_3,[84-86] Ac_2O/HNO_3 or $TFAA/HNO_3$,[84,86-88] or in some difficult cases, with NO_2BF_4.[84]

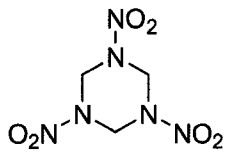
2.2 Synthesis of Some Energetic Materials of Contemporary Interest

2.2.1 Heterocyclic Nitramines

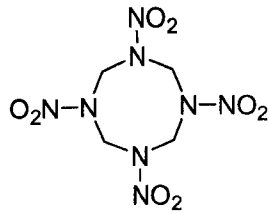
2.2.1.1 RDX and HMX

Perhaps the best known example of this class of energetic material is **RDX**, a compound that achieved great importance during the World War II as a component of many explosive mixtures. Its brisant power is high owing to its high density and high detonation velocity. It is less powerful but also less sensitive than its higher homolog,

HMX. These materials have become the long-standing easily prepared benchmarks against which the performances of newly synthesized target compounds are compared. The tetrazine, **HMX,** is a highly energetic material that has found use in various explosives and propellants for military and non-military applications. It is one of the most powerful nitramine explosives. Both **RDX** and **HMX** can be produced from inexpensive starting materials using standard condensation type reactions. The focus of the most recent research in this area has been on improving the purities, yields, and reducing the costs of productions of these materials rather than developing fundamentally different chemical approaches.[54,89]



RDX

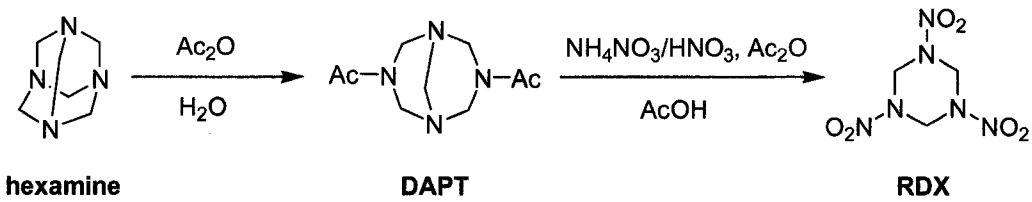


HMX

One of the largest producers of RDX and HMX in Europe, Dyno Nobel, ASA, has developed the improved crystallization techniques that have focused on spheroidizing the crystals. This has made important contributions to the work on explosives for Insensitive Munitions. **RDX** with reduced sensitivity toward shock can now be made in full-scale production.[90]

Discussed below are syntheses of both **RDX** and **HMX** that are representative of the approaches typically adopted for the synthesis of these classes of compound.

RDX is most commonly prepared from the inexpensive starting material, hexamine, as shown in **Scheme 5**.[91]



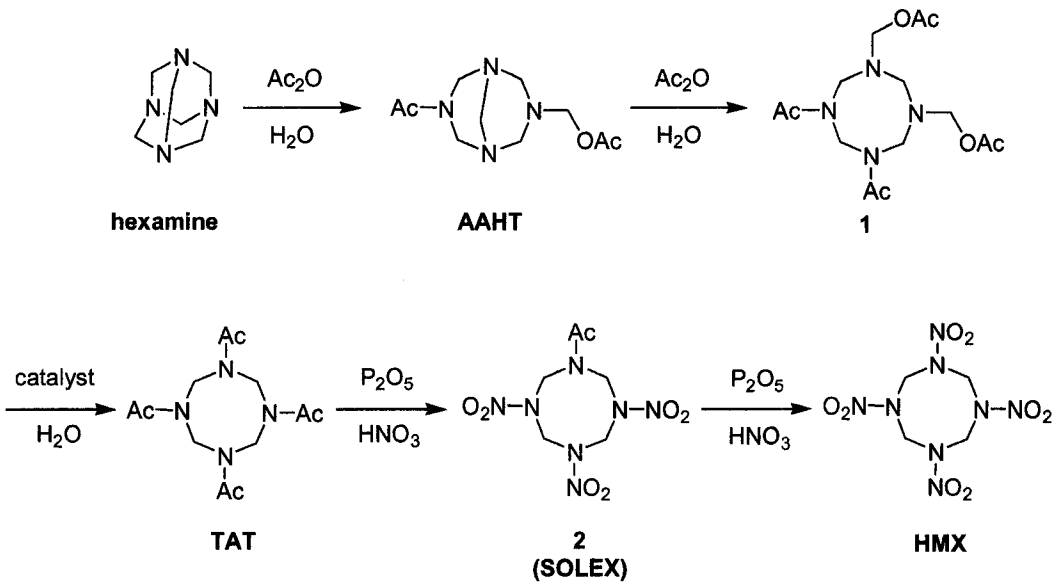
Scheme 5

This process involves the conversion of hexamine to 3,7-diacetyl-1,3,5,7-tetraaza[3.3.1] bicyclononane **DAPT** by treatment of the former with acetic anhydride. Subsequently, repeated sequential addition of NH_4NO_3/HNO_3 and Ac_2O provides near-quantitative yields of **RDX**.

HMX on the other hand, is known to exist in four different crystal structures or polymorphic forms: α, β, γ and δ. Recently, it was discovered that α-**HMX** exhibits less sensitivity to impact than the alternate polymorphs and a method for its' synthesis has recently been reported, as shown in **Scheme 6**.[92,93]

In this method, hexamine is treated with acetic anhydride under conditions which result in acylation of one of nitrogen atoms and subsequent attack by the acetate anion at the

methylene carbon α to the same nitrogen. This process results in rupture of the ring system and the generation of the intermediate **AAHT**.

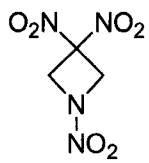


Scheme 6

These steps are then repeated to provide the monocyclic intermediate **1**, which was subsequently converted to the tetra-acetyl derivative **TAT** using transition metal oxide mediated catalysis. Nitrolysis of the tetra-amide (**TAT**) using phosphorous pentoxide and nitric acid resulted in the generation of the tri-amide, 1-(N)-acetyl-3,5,7-trinitro-cyclotetramethylenetetramine **2**, also known as **SOLEX™**. This material was then converted to **α–HMX** via a novel solid-state nitration reaction employing a mixture of phosphorous pentoxide and nitric acid.

2.2.1.2 TNAZ (1,3,3-Trinitroazetidine)

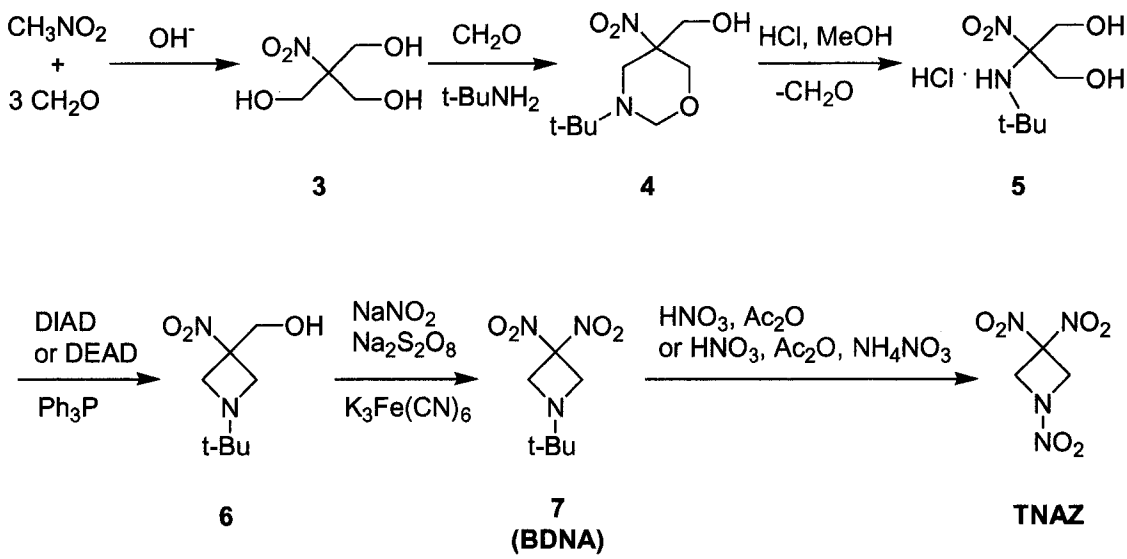
Highly nitrated small ring heterocycles and carbocycles are of interest as energetic materials as it can be predicted that the increased bond strain energy present in these analogs will result in improved explosive performance. The most widely studied energetic small-ring compound is 1,3,3-trinitroazetidine (TNAZ), a potentially insensitive melt-castable explosive that has been investigated as a possible replacement for TNT.[94] This compound has a melting point of 103–104 °C, a crystal density of 1.84 g/ml and a thermal stability of >240 °C.[95]



TNAZ

Numerous synthetic approaches to this ring system have been reviewed[96] with one of the more recent examples shown in **Scheme 7**.[97-100] This method involved a base catalyzed condensation of nitromethane with three equivalents of formaldehyde to produce tris(hydroxymethyl)nitromethane **3**. This was then condensed with *tert*-butylamine and another equivalent of formaldehyde to yield 3-tert-butyl-5-hydroxymethyl-5-nitrotetrahydro-1,3-oxazine **4**. This heterocycle was then heated in methanolic HCl to yield the linear product, 2-*tert*-butylaminomethyl-2-nitro-1,3- propanediol hydrochloride **5** which was subsequently cyclized under Mitsunobo conditions to yield 1-*tert*-butyl-3-hydroxymethyl-3-nitroazetidine hydrochloride **6**. This intermediate was treated with

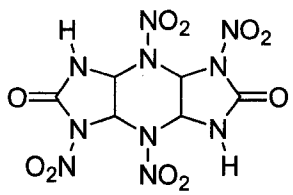
NaOH and oxidatively nitrated using a mixture of sodium nitrite, potassium ferricyanide and sodium persulfate to yield 1-tert-butyl-3,3-dinitroazetidine **7**, also known as (**BDNA**). Subsequent nitrolysis of **BDNA** with a mixture of nitric acid and acetic anhydride, or a mixture of nitric acid, acetic anhydride, and ammonium nitrate yielded TNAZ in 57% overall yield.[94]



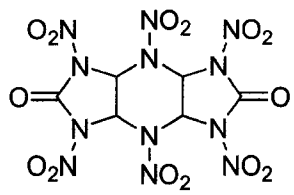
Scheme 7

2.2.1.3 Mono- and dinitroureas

Many examples of mono and dinitroureas have been investigated as energetic materials based largely on their attractive densities, high oxygen content and predicted explosive performance characteristics. In general, both the mono- and dinitroureas (see **Scheme 8**) have very high densities due to the inherently high density of the urea scaffold. However, their use has been impaired by an intrinsic hydrolytic liability, although this problem is less severe in the case of the mono-nitrated analogs.[94]



10a



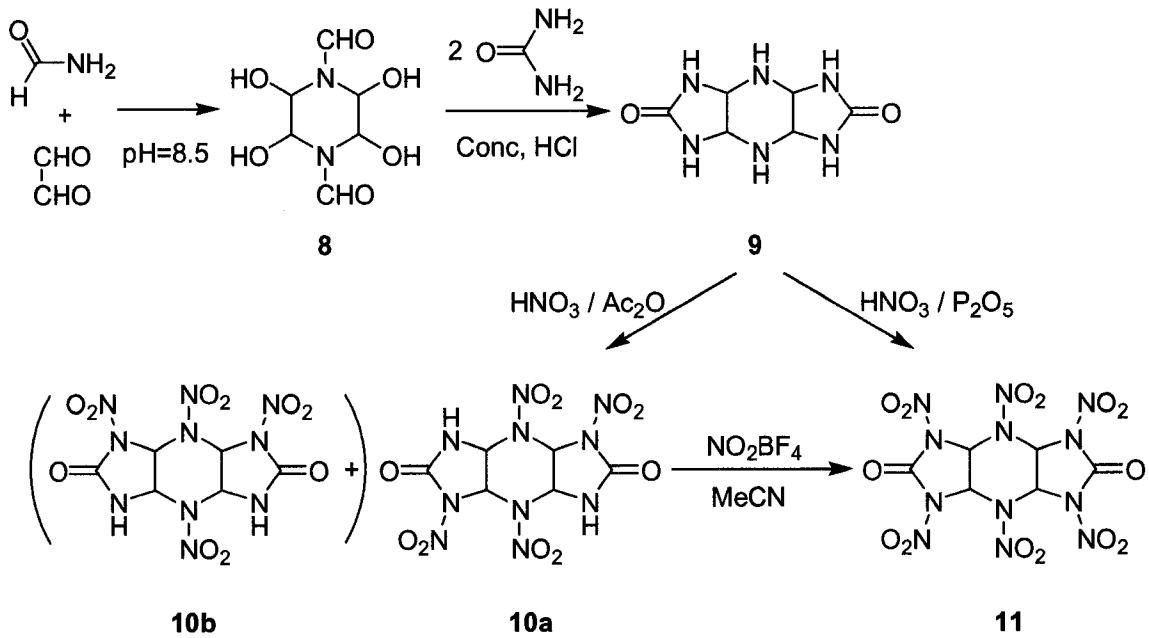
11

Scheme 8

Cis-syn-cis-2,6-dioxo-1,3,4,5,7,8-hexanitrodecahydro-1*H*,5*H*-diimidazo[4,5-*b*:4',5'-*e*]pyrazine (**11**) has an estimated detonation velocity of 9700 m/sec and a crystal density of 2.07 g/ml which is the highest yet recorded for a simple C, H, N and O containing explosive, and is probably the most powerful such explosive synthesized to date. However, this material decomposes explosively above 210 °C and is readily decomposed in water,[101] two features that severely limit its utility. These issues are addressed in the related mono-nitrourea analog, *cis-syn-cis*-2,6-dioxo-1,4,7,8-tetranitrodecahydro-1*H*,5*H*diimidazo[4,5-*b*:4',5'-*e*]pyrazine (**10a**), a compound with a density of 1.970 g/cm^3, a melting point of 225 °C and that is stable to water and decomposes only very slowly in boiling MeOH. However, these characteristics are achieved at the expense of reduced explosive performance.

The syntheses of these materials are shown in **Scheme 9** below.[86] 1,4-Diformyl-2,3,5,6-tetrahydroxypiperazine **8** was obtained by cyclization of formamide and aqueous glyoxal under basic conditions. Compound **8** was then condensed with urea in concentrated HCl to provide the tricycle **9** as a monohydrochloride salt. Nitration of this intermediate using

a solution of HNO_3 and Ac_2O produced a mixture of tetranitro-derivatives **10b** and **10a**, with the later being the minor product. Using the more forcing conditions of NO_2BF_4 in acetonitrile afforded the hexanitro compound **11**. It has also been reported that **11** can be prepared in one step in 74% yield from the monohydrochloride **9** by nitration with nitric acid in combination with phosphorous pentoxide. In this reaction, an initial partial nitration at low temperature was followed by more forcing conditions to complete the nitration process.



Scheme 9

Other mono- and dinitroureas with improved hydrolytic stability and insensitivity to impact and friction are the subject of ongoing studies.

2.2.2 Highly Nitrated Cage Compounds

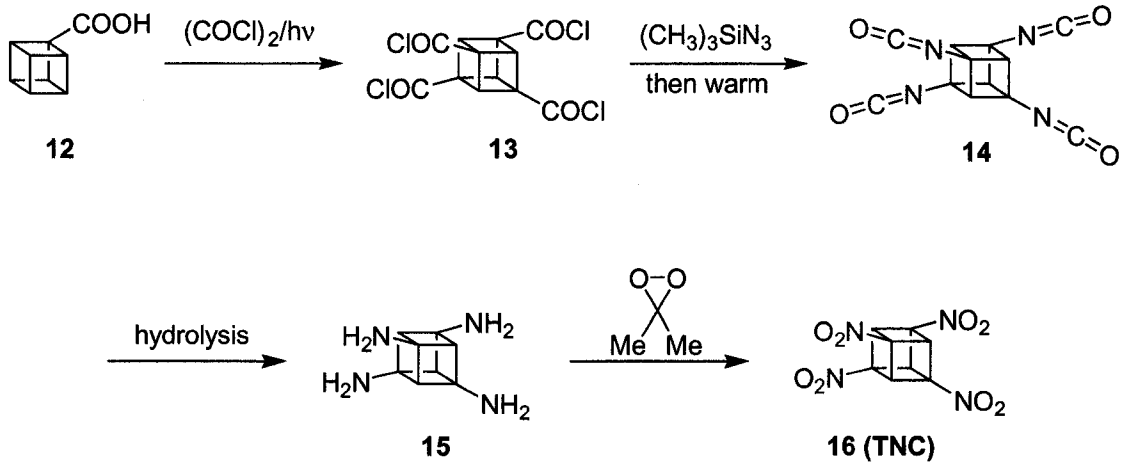
2.2.2.1 Nitrocubanes

Caged polycyclic hydrocarbons are of interest in the field of energetic materials as they exhibit substantially increased densities over their acyclic analogs. This, together with the inherent bond angle strain present in many of these systems results in large positive heats of formation. The prototypical example of this class of compound is cubane. This ring system has been studied extensively in the area of energetic materials both as high energy jet fuels and most commonly polynitrated derivatives.[102]

In-silico calculations predict that nitrated cubanes should be high density, shock-resistant energetic matierals with significant potential as explosives and propellants.[103-105] In the case of **octanitrocubane** (**ONC**), the use of the Kamlett-Jacobs equations[106-108] using calculated values for density (1.9-2.2 g/cm^3)[109-117] and heats of formation (81-144 kcal/mol)[89,118-121] predicts detonation velocities and pressures much higher than those observed for **TNT**, and 15–30% greater than that of the N-nitro compound **HMX**, presently a standard used for military explosives.

The synthesis of **octanitrocubane** (**ONC**) has been reported[27] using the cubane mono acid **12** as starting material.[102] This compound was subjected to the photochlorocarbonylation[25,122-124] process shown in **Scheme 10**. The resultant tetraacylchloride **13** was converted to the corresponding polyacylazide which underwent a Curtius rearrangement to provide the polyamine **15** in good yield. This polybasic

imtermediate was then oxidized to provide 1,3,5,7-tetranitrocubane[125] (**TNC**) using dimethyldioxirane as oxidant. An interesting feature of **TNC** is the acidity of the protons β to the nitro groups, with a measured pKa ≈ 21.[24,25] This material can therefore be used as an intermediate in the synthesis of more highly nitrated analogs via deprotonation and condensation with a suitable oxide of nitrogen.



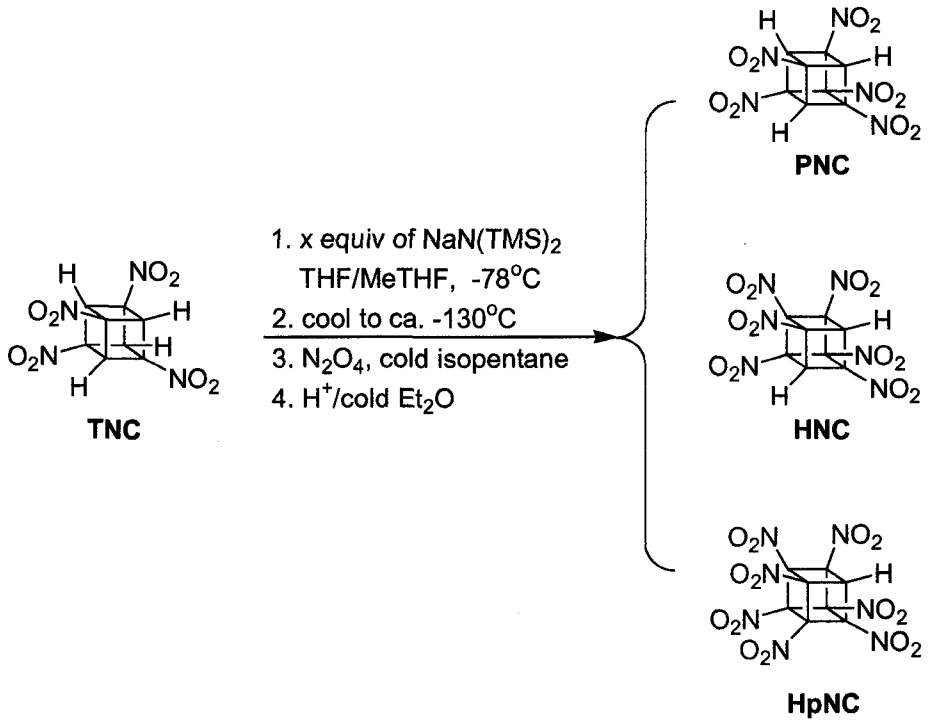
Scheme 10

It should be noted at this point that the more highly nitrated cubanes cannot be prepared directly from the corresponding polycarboxylated derivatives as the required conversions would proceed through intermediates that contain electron donating groups vicinal to groups that are electron withhdrawing, a situation that results in cleavage of the strained cubane ring system.[25]

The nitration reaction noted above is unusual and occurs under conditions described in a process termed *Interfacial Nitration*.[26] In this technique, solid N_2O_4 is deposited on the

surface of the sodium salt of **TNC** in frozen THF (-105°C), nitration then occurs upon melting at the interface resulting in the generation of 1,2,3,5,7-pentanitrocubane (**PNC**). This process could be repeated on the pentanitrated analog, resulting in the generation of the hexanitrated analog, 1,2,3,4,5,7- hexanitrocubane (**HNC**).

Unfortunately, it was found that this process could not be efficiently extended further and the alternative methodology shown in **Scheme 11** had to be developed in order to access heptanitrocubane (**HpNC**).

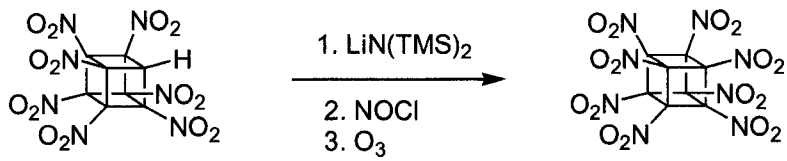


Scheme 11

In this approach, **TNC** was treated with 4.0 equivalents of sodium hexamethyldisilazide and subsequently exposed to N_2O_4. This resulted in the clean and reproducible conversion

of starting material into heptanitrocubane, which was isolated as a crystalline material. Using fewer equivalents of sodium hexamethyldisilazide, this method can be applied to the preparation of **PNC** and **HNC**. It was reported that this reaction probably proceeds by a series of sequential conversions involving mono-anion generation followed by nitration. It was found that this sequence ends with formation of the anion of heptanitrocubane as was shown by the high-yield production of methylheptanitrocubane on quenching with methyl triflate rather than acid. It was also noted that even on addition of excess N_2O_4 to this anion, no octanitrocubane was formed.

Subsequently, it was reported that treatment of a solution of the lithium salt of heptanitrocubane with excess nitrosyl chloride (NOCl) in CH_2Cl_2 at -78 °C followed by ozonation at the same termperature gave after standard workup, octanitrocubane (**ONC**) in 45% to 55% yield when run on a millimole scale.[27] This is outlined in **Scheme 12**. The intermediate product prior to oxidation was suspected of being unstable and was speculated to be the related nitrosoheptanitrocubane.

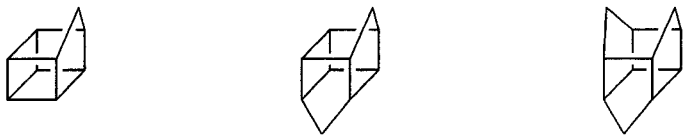


HpNC **ONC**

Scheme 12

2.2.2.2 Nitrohomocubanes

An interesting class of energetic materials related to the nitrocubanes is the nitrohomocubanes, in which the symmetry of the cubane ring system has been reduced by the introduction of methylene moieties. One, two or three methylenes can be introduced giving rise to the ring systems shown in **Scheme 13**. Many of the nitrated analogs of these ring systems are predicted to have similar physicochemical properties to the nitrated-cubanes and the synthetic difficulties are much less formidable.



Monohomocubane **Bishomocubane** **Trishomocubane**

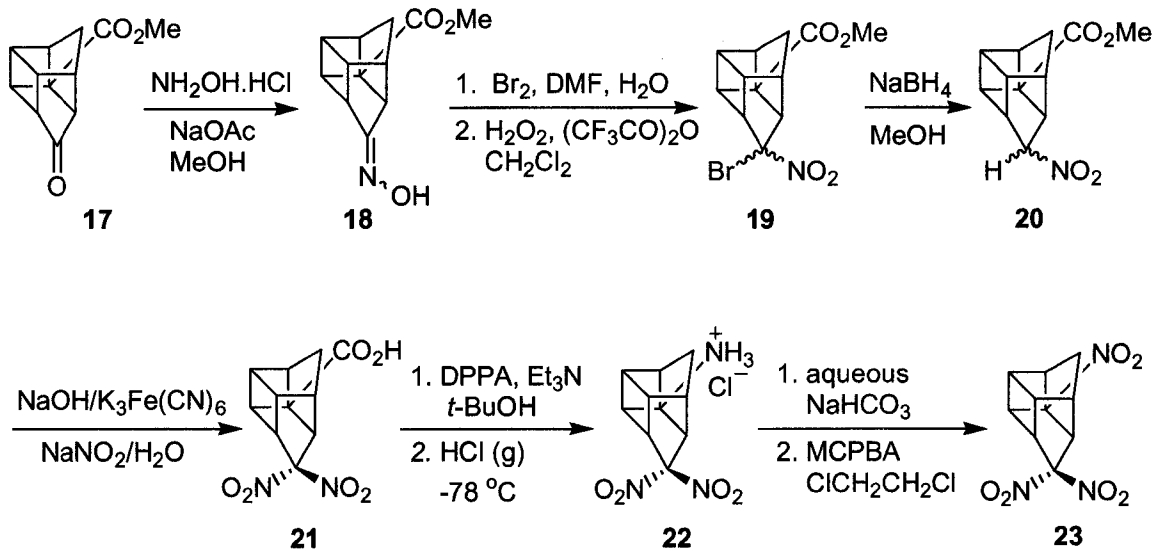
Scheme 13

The chemistry of this class of compounds has been extensively reviewed.[44,126] This section is limited to describing an illustrative example, **trinitrobishomocubane**, which involves both the construction of the ring system as well as the introduction of the pendant nitro functionality.

The synthesis of **trinitrobishomocubane**[127] as shown in **Scheme 14** was designed around the introduction of a latent carboxylate and ketone functionality that could

subsequently be converted to the required mono and geminal-dinitro moieties as outlined in the introduction to this chapter.

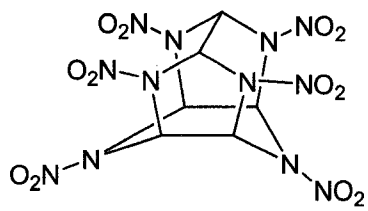
The necessary transformations starting from the easily accessible keto-ester **17**, prepared from readily available cyclopentadiene and p-benzoquinone in 4 steps,[127] were achieved by successive oximation followed by oxidation to obtain the bromo-nitro derivative **19**. Reduction of the latter with $NaBH_4$ yielded the mono nitro compound which under Kornblum oxidation conditions gave rise to the geminal-dinitro acid **21**. Using the Curtius rearrangement-oxidation methodology described earlier, the intermediate amine **22,** obtained with diphenylphosphorylazide (DPPA) from acid **21**, was oxidized to afford the desired trinitrobishomocubane derivative **23**.



Scheme 14

2.2.2.3 Polyazaheterocycles

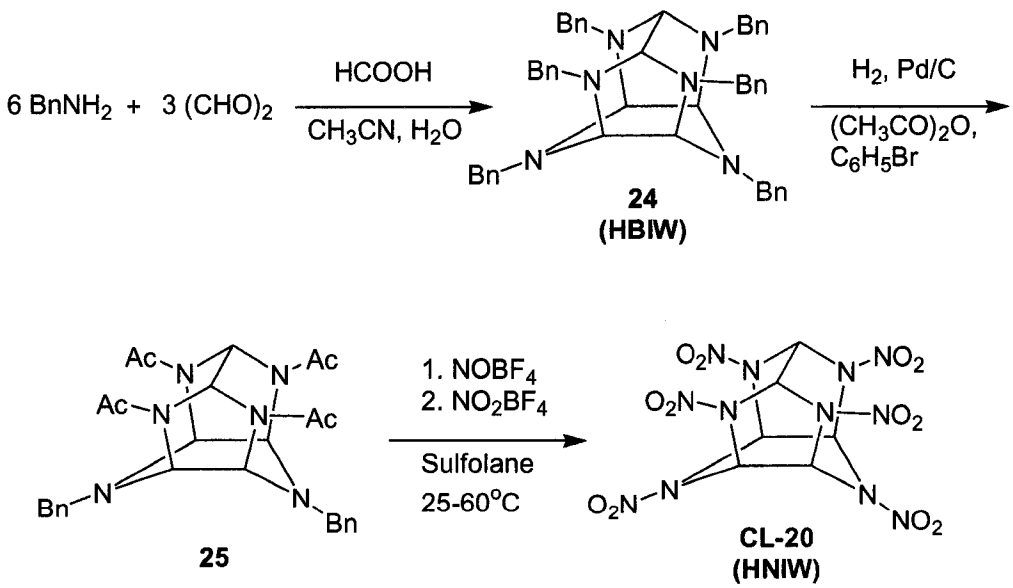
A class of compounds closely related to the caged structures described above is the polyazaheterocycles, typified by the high density high performance explosive hexanitrohexaazaisowurtzitane (**HNIW**, commonly known as **CL-20**).



CL-20

These compounds constitute a new class of energetic materials that are known to have properties superior to those of the compounds previously discussed. These heterocyclic ring systems have intrinsic strain energies similar to the previously discussed carbocyclic systems, but they have higher densities and are thus found to have superior energetic characteristics. **CL-20** is the most powerful explosive currently being investigated at the pilot plant or larger scale.[128] Although the sensitivity properties of **CL-20** are not good, it has been satisfactorily desensitized by incorporating it into various formulations making it safe to handle in large quantities. It exists in multiple polymorphric forms with the ε-form being the most suitable as a high-performance explosive. This polymorph has a density of 2.04 g/ml, and a velocity of detonation of 9380 m/sec.[94,95]

However, a major impediment to the study of this class of compound has been the increased complexity of their synthesis, making it difficult to access members of this group. The most extensively studied member of the polyazaheterocyclic class to date has been **CL-20**. This compound was first synthesized as shown in **Scheme 15**.[129] The synthesis involves condensing stoichiometric quantities of benzylamine and glyoxal in aqueous acetonitrile at 25 °C in the presence of formic acid as catalyst[130] to generate 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.$0^{5,9}$.$0^{3,11}$]dodecane (hexabenzyl-hexaazaisowurtzitane **24**, also known by the abbreviation **HBIW**). Subsequent reductive acetylation of this stable caged polyamine in acetic anhydride with an acid catalyst gave the intermediate 4,10-dibenzyl-2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazainsowurtzitane **25**. Sequential treatment of this material with $NOBF_4$ and NO_2BF_4 in sulfolane gave the desired **CL-20** in greater than 90% overall yield.



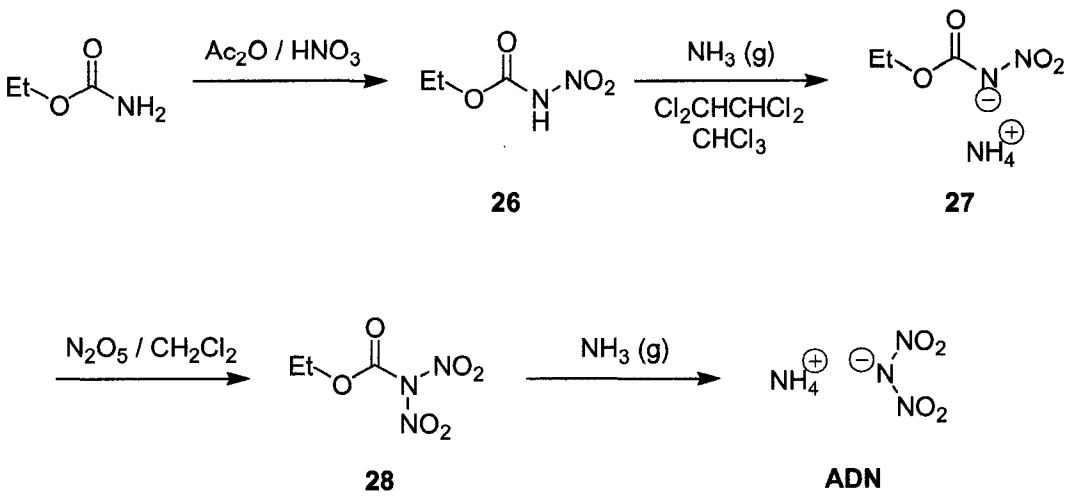
Scheme 15

2.3 Other High Nitrogen-Containing and Potential Novel Polynitrogen Compounds

The evolution of new rocket propellants is primarily driven by the need for greater performance, although a combination of other desirable properties including insensitivity, thermal stability, high density and economy of synthesis have become important corollary requirements. Additional new materials that are under serious developmental consideration are such oxidizers as ammonium dinitramide (**ADN**) and hydrazinium nitroformate (**HNF**) and such other polynitrogen compounds as tetraazatetrahedrane and octaazacubane

2.3.1 Ammonium dinitramide (ADN)

Ammonium dinitramide shows promise as a replacement oxidizer for ammonium perchlorate (**AP**). The latter contains environmentally undesirable chlorine giving rise to an unfavorable signature as well as causing acid rain and ozone depletion. **ADN** has an excess of oxygen content and its high combustion rate can be used for high specific impulse propellant applications. As outlined below, it can be synthesized from rather inexpensive starting materials.[131,132]



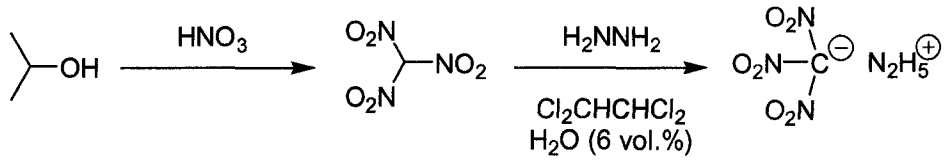
Scheme 16

The density of **ADN** is 1.81g/cm^3 and it is less sensitive than **RDX**, **HMX** and **CL-20** to impact, friction and electrostatic discharge. However, it is rather light sensitive and hygroscopic. The latter can be improved by encapsulation in a polymeric binder.

2.3.2 Hydrazinium nitroformate (HNF)

Hydrazinium nitroformate (**HNF**) is similarly a powerful solid oxidizer with a density greater than that of **ADN** (~1.9g/cm^3). The ballistic properties of **HNF** are about 4% better than **AP**. There are, however, a number of problems which further development of this material require to be improved. In particular, its thermal stability is unfavorable and incorporation of a binder has a negligible effect. It is also highly reactive and it is incompatible with isocyanates resulting in problems in curing polymer composites. **HNF**

can be prepared from readily available nitroform and hydrazine starting materials as shown in the following Scheme.[133,134]



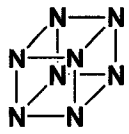
Nitroform **HNF**

Scheme 17

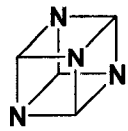
2.3.3 Tetraazatetrahedrane and Octaazacubane

Polynitrogen compounds such as tetraazatetrahedrane **29** and octaazacubane **30** are intriguing polymeric forms of nitrogen which offer considerable potential as high energy-density materials.[135] In principle, these compact strained cage structures could be derived from abundant diatomic nitrogen, if pathways could be found. On disruption of the ring systems there would be considerable energy released without any detriment to the environment. To a lesser extent these considerations would also be true for other high nitrogen-containing structures. An illustrative example might be the tetraazacubane **31**.

29



30



31

Scheme 18

In **29** and **30** an attractive structural feature of these systems is that one nitrogen atom is connected to another by single or double bonds instead of the conventional triple bond. Quantum mechanical calculations[136-139] suggest that both $\mathbf{N_4}$ and $\mathbf{N_8}$ polyhedra are metastable species. The predicted high heats of formation of both these compounds are considered not to result from excessive bond strain energy, but rather from the weakness of the N-N single bond. Calculations also suggest that these materials may have sufficiently long lifetimes to allow their study using matrix isolation techniques. Although neither of these materials has been synthesized to date, their realization is encouraged by the recent success of the synthesis of the linear cation $N_5^+AsF_6^-$.[140] Intense efforts are currently in progress in many laboratories to synthesize and stabilize such new materials.

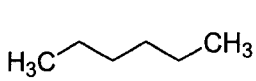
Chapter 3

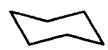
Identification of Potential High Energy-Density Propellant Candidates

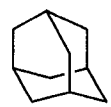
3.1 Structure-Density considerations

The design and synthesis of new insensitive energetic compounds with high density and improved energetic properties have been the focus of recent studies in our laboratory and elsewhere around the globe. The need exists for innovative and optimally designed high energy-density oxidizers/fuels for future advanced rocket propulsion requirements. From simple structure relationships it can be seen, for example, that there is a significant progressive increase in density in going from n-hexane (0.66 g/cm^3) to cyclohexane (0.78 g/cm^3) to adamantane (1.07 g/cm^3). In other words, densities increase significantly in going from acyclic to monocyclic to polycyclic compounds.

Figure 1. Densities Increase from Linear to Cyclic Molecules







Density (g/cm^3)	0.66	0.78	1.07

Within a given type of molecular structure replacement of hydrogens or methylene groups by energetic functional groups similarly produces a marked increase in density. Thus, replacement of the three alternate methylene groups in cyclohexane by nitramino

functions produces **RDX** which has a substantially increased density of 1.8 g/cm^3 compared with cyclohexane. In fact, the corresponding eight-membered nitramine analog, **HMX**, is unrivaled among other long-established and widely employed explosives for its ease of synthesis and other important characteristics which include power, density (1.894 g/cm^3) and thermal stability. Thus, with appropriate functionalization the basic nitramino function incorporated in the **HMX** and related skeletons was adopted in the present work as the model for the design and synthesis of new energetic propellants with high density, increased power and reduced sensitivity. Functional groups that contain nitrogen, oxygen and fluorine are inherently dense. Consequently, fluorine and oxygen rich energetic crystals provide a potentially new approach to increasing the composite propellant and explosive energy density and energy release rates. Oxidizers derived from these materials, unlike the widely used **AP** (ammonium perchlorate) are expected to be low signature propellants and the absence of chlorine makes them desirable from an environmental point of view. It is also known that, in general, heterocycles have a higher heat of formation, density, and oxygen balance than their carbocyclic analogs.

Incorporation of difluoramino groups in energetic materials has long been recognized to improve propellant thrust because in addition to the usual combustion products --- CO_2, N_2, CO and H_2O -- as compared to oxygen the NF_2 group produces low molecular weight HF making efficient use of the hydrogen atoms in the propellant.[141]

A procedure for crystal structure density prediction for an unknown energetic compound has been developed by Professor Herman Ammon (University of Maryland). This method takes into account factors such as the structure and conformation of the molecule, probable crystal packing arrangements and packing efficiency. The so-called "model-MOLPAK-refinement" procedure consists of three steps: (1) construction of a reasonable three-dimensional model (the search probe) for the compound of interest followed by *ab initio* geometry optimization; (2) determination of a number of possible crystal structures for the search probe (MOLPAK program[115]); and (3) refinement of the unit cell parameters, search probe orientation and position by lattice energy minimization for the best of the hypothetical structures obtained in step 2 (WMIN program[142]). The information on molecular coordination environments used in MOLPAK was determined by examining more than a thousand known crystal structures with the MOLCON/MOLPAN (MOLecular CONnectivity/MOLecular Packing ANalysis) programs.

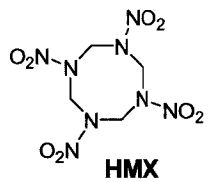
From computational chemistry, based upon energetic considerations, heats of formation, oxidizer balance (oxygen plus fluorine) and MOLPAK predictions of crystal densities, Ammon has identified a number of compact 4 to 8-membered cyclic nitramines containing geminal NF_2 groups as possible high performance rocket propellant candidates. **Table III** presents the structure density relationship of some cyclic geminal difluoramino / nitramino molecules[143] using the combination of experimental X-ray data and MOLPAK predicted values. Available experimental X-ray data are listed for all the

known compounds except for **HNFX** and **TNFX** that will be discussed in later chapters. (^{X}: Experimental X-ray data; ^{M}: MOLPAK calculation.).

It is interesting to note that these calculations lead to the expectation that the N-NO_2 function enhances molecular density over $C(NO_2)_2$, and the replacement of geminal NO_2 groups with the geminal NF_2 groups could potentially improve the energetic properties of these materials.

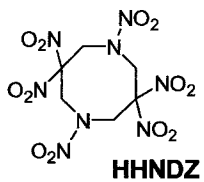
Table III.

Calculated and Experimental Densities (g/cm^3) of Some Representative Cyclic Geminal Difluoramino / Nitramino Moleclues



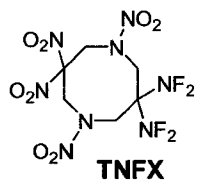
HMX

1.90^X



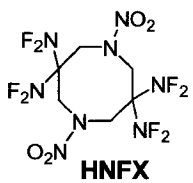
HHNDZ

1.86^X



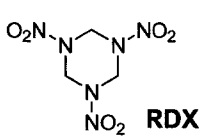
TNFX

1.90^M



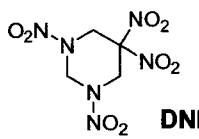
HNFX

2.00^M



RDX

1.81^X

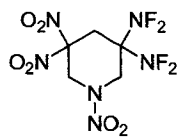


DNNC

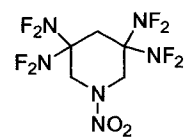
1.80^X

RNFX

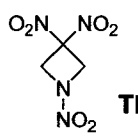
1.97^M, 1.88^X



1.93^M

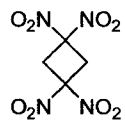


2.03^M



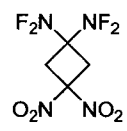
TNAZ

1.84^X

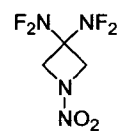


TNCB

1.83^X



1.94^M



1.95^M

3.2 Current Research Directions in Energetic Materials

The study and design of new energetic materials span many disciplines. Worldwide research programs to meet requirements for modern propellants and explosives are driven by the need to develop new high-energy high-density materials with densities greater than 2.0g /cm^3, with detonation velocities (D) approaching 10 mm /μsec and detonation pressures (P_{CJ}) greater than 400 Kbar. Since the detonation pressures at the shockwave front are proportional to the square of the density of the material,[144] a small increase in density can significantly increase the energy of an explosive. In volume-limited propellant applications crystal density considerations are particularly important to maximize the net volumetric heat of combustion.

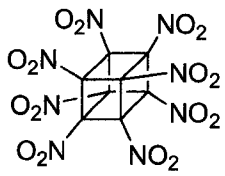
Thus, major efforts in recent years have been aimed at the development of new energetic materials with higher performance characteristics and enhanced insensitivity to thermal or shock insults. Several significant considerations form the basis of much of this on-going research and development. The first is the continuing important necessity to discover higher performance materials to defeat increasingly hardened targets. The goals here are new crystalline high-energy-density materials with enhanced specific impulses exceeding those of familiar materials in current use. A second objective is discovery of new nitramines capable of replacing ammonium perchlorate as the mainstay oxidant of many current missile propellants. Chlorine-free oxidizers avoid the white contrail signature formed by chlorinated oxidants allowing missile launches to be less easily

detected as well as protecting the ozone layer from the ravages of chlorine. In addition to higher performance, an increasingly important requirement is for the development of insensitive munitions (IM). Combat vulnerability of weapons systems has attracted increasing concern. The basis of this concern is straightforward. Violent reactions of munitions subject to initiation, accidental or intended, can destroy not only the weapon but also the platform (ship, aircraft and rockets) and their respective crews. Due to the number of accidents involving initiation of munitions by impact and the many worldwide catastrophic consequences, there is now agreement among Western countries that IM are required to give acceptable responses to unplanned hazardous initiation from such stimuli as fire, fragment impact, static charge and shock. Furthermore, it is desirable that IM have long-term chemical stability. Current generation of munitions particularly those derived from melt cast formulations based on **TNT** often respond violently up to detonation. In fact, achievement of the IM requirements for which the Western countries have policies for phased introduction represents a considerable challenge to the research community. Complete success remains some ways off. Reducing ordnance vulnerability is therefore an important goal in increasing operational effectiveness. While new high performance fillers are being sought for IM applications, considerable effort is also placed on dispersing energetic materials such as **HMX** in a rubbery polymer matrix, as are analogous low vulnerability ammunition (LOVA) propellants.

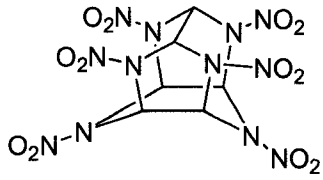
Synthetic organic chemistry is the branch of science that has increasingly employed structure to function relationships to design high performance propellants and explosives. This has resulted in an ever-extending array of advanced materials with tailored

properties. Among the more prominent new generation of energetic materials that have come to the forefront in recent years are, as shown in **Figure 2**, the highly nitrated cage compounds, octanitrocubane (**ONC**), hexanitrohexaazaisowurtzitane(**CL-20**), the melt-castable explosive 1,3,3-trinitroazetidine (**TNAZ**), the insensitive nitrotriazolone (**NTO**), a number of energetic binders for LOVA propellants and the environmentally friendly rocket propellant ammonium dinitramide (**ADN**).

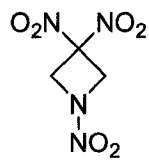
Figure 2. Some New Energetic Materials Developed in Recent Years



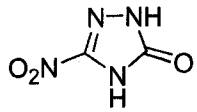
ONC



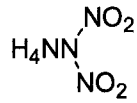
CL-20



TNAZ



NTO



ADN

Thus, the objectives of this investigation are:

A. To develop synthetic strategies to prepare new energetic 1,5-diazocines indicated in **Table III**.

B. To exploit the ring contraction reactions that often accompanied our attempts to construct and functionalize 1,5-diazocines

C. To functionalize these ring systems leading to **TNFX** and **HNFX** including the development of the required fluoramination and nitration procedures

D. To characterize the energetic properties of these precursors and target molecules

Chapter 4

1,5-Diazacyclooctane-3,7-Derivatives as Precursors of the 3,7-Diazabicyclo [3.3.0] octane and 3,7,10-Polyheterocyclic [3.3.3] propellane Ring Systems

Introduction

The chemistry of 1,5-diazacyclooctanes has been the subject of ongoing investigations in this laboratory as part of programs aimed at the synthesis of functionalized, high density, thermally-stable small[145] and medium-ring nitrogen heterocycles containing poly nitro groups. The latter are expected to produce novel high performance energetic materials. As a class of compounds, 1,5-diazacyclooctanes[146] provide a number of versatile intermediates having important pharmaceutical applications as well as materials useful as polymerization accelerators, antiknock agents in motor fuels and energetic materials.[145,147] Several 1,5-diazacyclooctane intermediates have been found to undergo unexpected transannular reactions. These reactions have been exploited to provide direct and facile entry into the little-studied 3,7-diazabicyclo[3.3.0]octane ring system and various polyheteroatom-containing tricyclic compounds conjoined in a carbon-carbon single bond (propellanes). [148,149] In this chapter, the synthetic strategies applicable to the preparation of various 3,7-functionalized-1,5-diazacyclooctanes are discussed. This presentation will be supplemented by a description of the often accompanying unanticipated ring-contraction reactions. The latter contractions provide convenient

synthetic routes to the 3,7-diazabicyclo[3.3.0]octane and several 3,7,10-polyheterocyclic [3.3.3] propellane ring systems.

Results and Discussion

1,5-Diazacyclooctanes. Conspicuously absent from the many known 1,5-diazocyclooctanes are the 3,7-diketo and 3,7-dimethylene derivatives. The latter compounds were initially targeted as simple intermediates useful for the facile functionalization of the 3,7-ring positions.

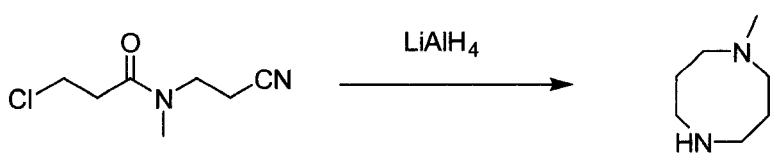
In beginning this discussion it is instructive to examine the more useful synthetic methodologies that maybe applicable to the construction of the 1,5-diazocine ring system, particularly when functionalization of the 3,7-ring positions is of paramount importance. There are several literature reaction types that lend themselves to straightforward 1,5-diazocine ring formation with easily introduced and manageable substituents at the 3,7 positions. These general procedures include: (**a**) intramolecular ring closures involving alkylation and / or acylation, (**b**) ring expansion strategies, and (**c**) cyclization-condensation reactions. Each of these reaction types was considered essential to developing the chemistry needed in this study. An illustration of these procedures in the synthesis of the desired 1,5-diazocines follows.

4.1 Formation of 1,5-Diazocine Rings

4.1.1 Intramolecular Ring Closure Involving Alkylation and Acylation Procedures

Several methodologies have been developed that employ intramolecular ring closure reactions to construct the diazocine ring system. These essentially involve either alkylative or acylative processes. In reviewing this chemistry, it was noted that in all of these reactions there is a degree of unsaturation in the acyclic substrates or putative intermediates. This clearly facilitates these reactions by limiting the degree of flexibility of the reagents, a feature that might otherwise compromise the formation of the eight-membered ring.

An early example of such an intramolecular alkylative process is shown in **Scheme 19**. Treatment of halocyanamide **32** with lithium aluminum hydride produces the 1,5-diazocine **33** in moderate yield.[150,151] It is to be noted that the LAH reduction not only results in the cyclization, but also concomitantly effects the reduction of the amide linkage while preserving the eight-membered ring. The latter process is rather uncommon.

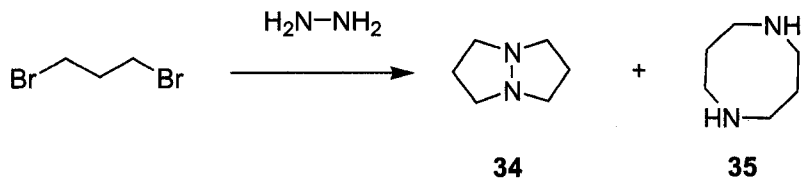


32 **33**

Scheme 19

4.1.2 Ring Expansion Strategies

An entirely different approach to the 1,5-diazocine ring system involves various methods to effect ring expansion of suitably functionalized smaller rings. Some of the more interesting methods involve either two atom ring expansions performed on 6-membered rings,[152] or various bond cleavage approaches performed on fused [3.3.0]bicyclic rings. Reductive nitrogen-nitrogen bond scission of N,N'-trimethylenepyrazolidines is one of the more frequently reported routes to 1,5-diazocines. For example, when 1,3-dibromopropane was allowed to react with hydrazine, in addition to **34**, the corresponding ring-opened compound **35** was obtained.[153]



34 **35**

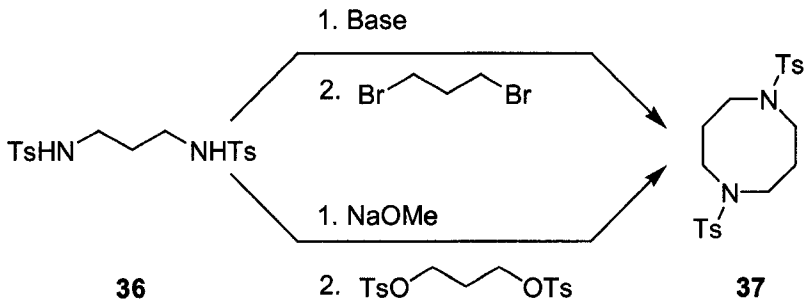
Scheme 20

Numerous studies on related substrates using various reducing agents have also been subsequently reported.[154]

4.1.3 Cyclization-Condensation Reactions

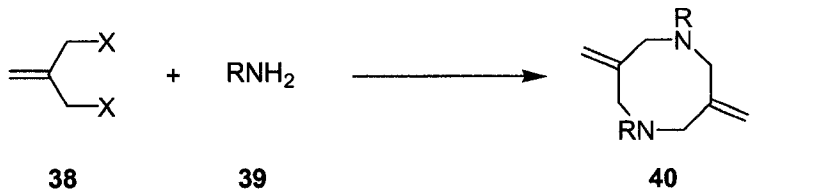
More adaptable in the current investigation are condensations of amines or sulfonamides with saturated electrophilic carbons. The latter readily undergo displacement of halogen

or other leaving group by the basic amino functionality and have been extensively employed for the construction of 1,5-diazocines. The first reported example using this approach is shown in **Scheme 21**.[155] When bis-tosylamide **36** was treated with alkali followed by 1,3-dibromopropane, diazocine **37** was obtained. Alternatively, the same diazocine **37** can be formed using 1,3-propanediol ditosylate as demonstrated in a recent diazacyclooctane type ligand synthesis.[156]



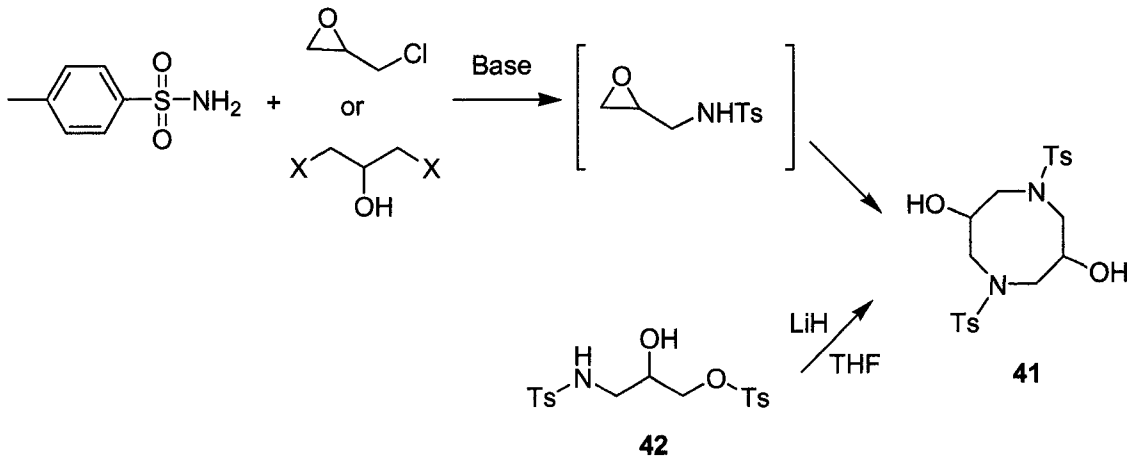
Scheme 21

More highly functionalized versions of the diazocine ring have been prepared using related methodology. In particular, bismethylenediazocines have been prepared by treating methallyl dihalides with alkyl and aryl primary amines.[147]



Scheme 22

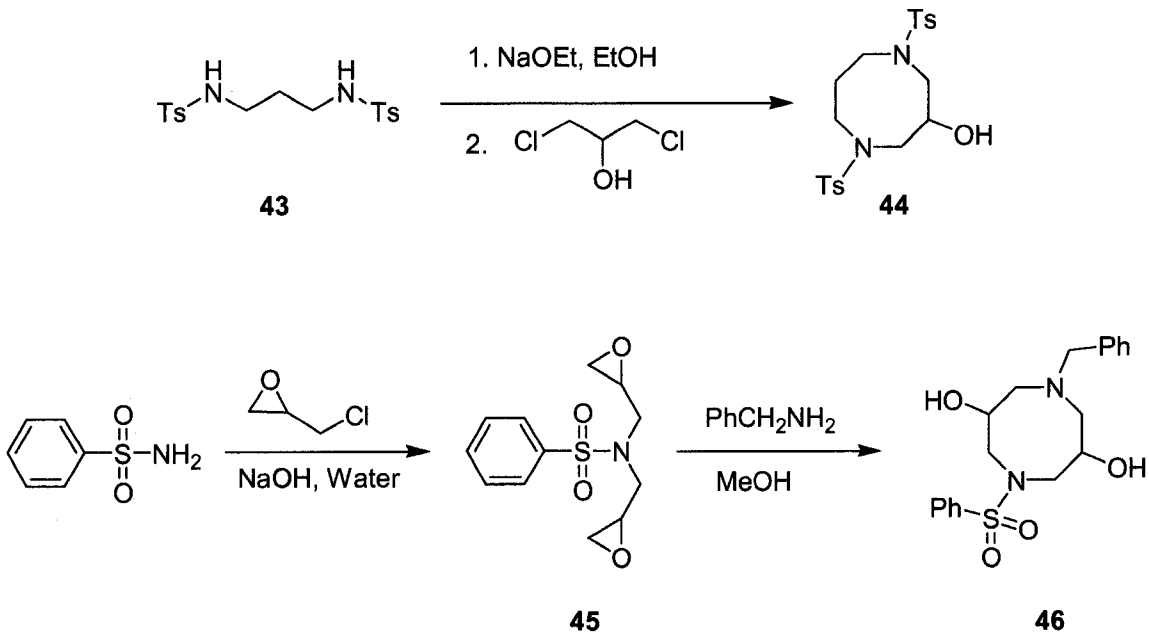
Using similar methodology, a number of diazocines with identical substitution patterns have been synthesized by condensation of amines with epoxides or haloalcohols. Earlier reports in this area appeared in the 1960's[157,158] and different variations and applications of the methodology have been published subsequently. For example, as outlined in **Scheme 23**, the base-mediated reaction of *p*-toluenesulfonamide with either epichlorohydrin or 1,3-dihalo-2-propanols provided the cyclodimerization product **41** as a mixture of *cis*- and *trans*-1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocines. The same diol compounds can also be prepared from the cyclodimerization of compound **42** in the presence of LiH.[159]



Scheme 23

This strategy has been extended to the synthesis of a series of unsymmetrically substituted 1,5-diazocine derivatives. Two recent illustrative examples are shown in **Scheme 24**. Cyclization of N,N'-trimethylenebis(*p*-toluenesulfonamide) dianion with

1,3-dichloro-2-propanol yielded diazocinol **44**,[160] whereas mixed condensation of diglycidylbenzenesulfonamide **45**, generated from the reation between benzenesulfonamide and epichlorohydrin, with benzylamine afforded diols **46** as a *cis*- and *trans*- mixture.[161]



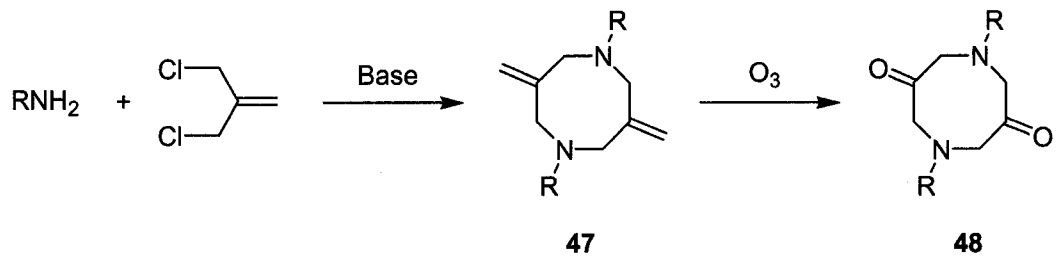
Scheme 24

4.2 Synthesis of Symmetrical 3,7-Functionalized-1,5-Diazocines

An important objective in this synthetic effort is the development of methods to prepare 3,7-functionalized-1,5-diazacyclooctanes, where both symmetrical and unsymmetrical intermediates are needed as precursors to future planned materials. The present chapter will concentrate on those methods required to prepare the symmetrical intermediates

whereas the preparation of the more unsymmetrical derivatives will be discussed in **Chapter 5**.

The formation of the required symmetrical 3,7-substituted 1,5-diazocine ring system was achieved by employing the chemistry shown in **Scheme 25**. This involved a base-induced cyclodimerization reaction of either p-toluenesulfonamide or methanesulfonamide with 3-chloro-2-chloromethyl-1-propene to give the bis-exomethylene derivatives **47** in moderate to good yields (~50%).



47 **48**

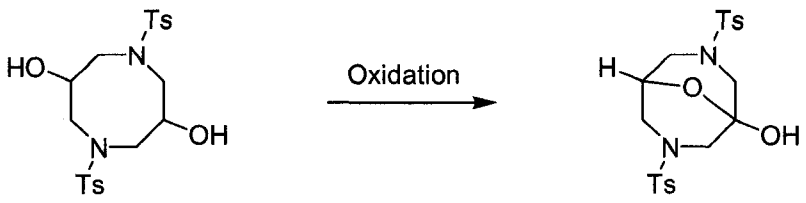
R = (a) p-$CH_3C_6H_4SO_2$; (b) CH_3SO_2

Scheme 25

It was readily apparent that the use of sulfonamides in this procedure was superior to the previously described reactions of amines with 3-halo-2-(halomethyl)-1-propenes[147,162] or other bifunctional allylic compounds. In the latter cases the reaction products were frequently complex mixtures consisting of the 3-methylene-1-azetidines, 3,7-bis(methylene)-1,5-diazacyclooctanes, and higher cyclic oligomers as well as noncyclic materials.[163,164]

Analysis of the respective ^{1}H and ^{13}C NMR spectra together with their mass spectra confirms that the cyclodimerization products of the reaction of *p*-toluenesulfonamide or methanesulfonamide with 3-chloro-2-(chloromethyl)-1-propene are the 3,7-bis(methylene)-1,5-diazacyclooctane derivatives **47** and not azetidines or some higher cyclic oligomers that are possible. Ozonation of the exocyclic double bonds in the 3,7-bis(methylene)-1,5-diazacyclooctanes **47** produced the corresponding symmetrically substituted 1,5-diazacyclooctane-3,7-diones **48** in excellent yields.

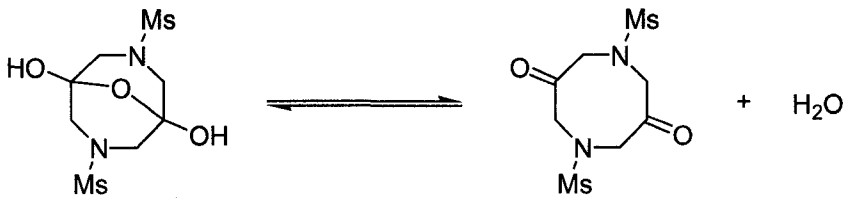
In addition to this ozonation strategy just outlined, an alternative procedure was carried out for the preparation of N,N'-diprotected diazacyclooctanediones. This involved the oxidation of intermediate 1,5-diazacyclooctane-3,7-diols of the type **41** shown in **Scheme 26.** While the diol **41** could be readily prepared from the reaction of *p*-toluenesulfonamide anion with epichlorohydrin, or alternatively from the condensation of tosylsulfonamide with 1,3-dihalo-2-propanols, as previously shown in **Scheme 23**, the route was found to be unsatisfactory due to the failure of the diols to undergo complete oxidation. In our hands, oxidation under Swern conditions gave the transannular hemiketal **49,** consistent with prior literature reports that utilized chromic anhydride as oxidant. [157] More recently, Chapman et al[165] reported the successful conversion of diol **41** to the corresponding dione **48** using the Swern oxidation method.



41 **49**

Scheme 26

This strong tendency of substituted 1,5-diazacyclooctane ring systems to undergo transannular reactions was repeatedly encountered in our investigation. In the course of characterizing compounds **48a** and **48b** the latter was found to form a rather stable hydrate **50** which could only be dehydrated by prolonged azeotropic distillation with benzene (**Scheme 27**).

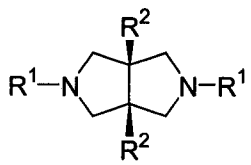


50 **48b**

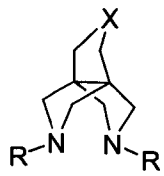
Scheme 27

The marked propensity of these eight-membered ring systems to undergo transannular reactions was anticipated to be a major hurdle for the further derivatization of these symmetrical intermediates. Unsymmetrical 3,7-substituted-1,5-diazacyclooctanes were considered to be less likely to participate in these types of reactions and the syntheses of these intermediates will be amplified in **Chapter 5**.

The tendency towards 3,7-transannular reactions has been exploited to access the bicyclic [3.3.0]octanes **51** and tricyclic [3.3.3]propellanes **52** as elaborated more fully in the subsequent section.



51



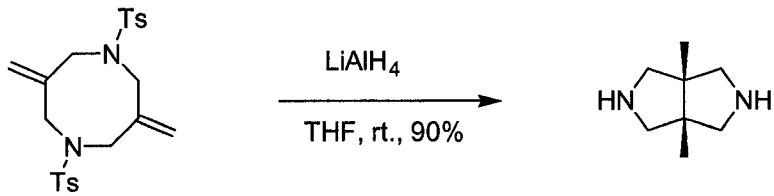
52

4.3 Syntheses of 3,7-diazabicyclo[3.3.0]octanes

During the course of the current work, we sought to prepare a variety of N,N'-disubstituted-3,7-bis(methylene)-1,5-diazacyclooctanes and their corresponding diketones. This required the removal of the sulfonamide protecting groups and subsequent derivatization. Precedents for the hydrolysis of sulfonamides[166] or their smooth reductive cleavage by hydride reagents[167] are available in the literature.

However, when **47a** was treated with lithium aluminum hydride, in an attempted reductive detosylation to prepare the parent 3,7-bis(methylene)-1,5-diazacyclooctane, the first indication of the pronounced tendency toward transannular cyclization to form a 0-bridged bicyclic compound was detected. This normally predictable hydride reduction was found to follow an unexpected course. The reductive cleavage of the tosyl group proceeded smoothly as evidenced by the disappearance of the tosyl signals in the NMR spectrum of the product. However, surprisingly, this was accompanied by the

simultaneous disappearance of the vinyl proton resonances at δ 5.19 and the emergence of a singlet at δ 0.99 in the methyl region along with an AB pattern centered at δ 2.71 and δ 2.92 (J =11.2 Hz). The complete structure of this product was deduced by analysis of its ^{1}H and ^{13}C NMR spectra including recording the DEPT and HETCORR spectra. From these determinations it was concluded that the transannular bond formation shown in **Scheme 28** had occurred to afford 1,5-dimethyl-3,7-diazabicyclo[3.3.0]octane **53** in 90% yield. This conclusion is also supported by the measured mass spectrum of **53**.



47a **53**

Scheme 28

To probe further the nature of this rather unexpected reductive cyclization, a series of experiments with lithium aluminum hydride and lithium aluminum deuteride was carried out, where the reaction mixtures were quenched with either H_2O or D_2O. The deuterium content of the several labeled reaction products was determined from the *m/z* value of the prominent $(M + 1)^+$ ion in the chemical ionization (NH_3) mass spectra of the 1,5-dimethyl-3,7-diazabicyclo[3.3.0]octanes. Before mass measurement, azeotropic distillation of the reduction products with benzene containing added H_2O was employed to exchange any N-D species and convert them to the corresponding N-H compounds. The position of deuterium incorporation was determined by analysis of the carbon

chemical shifts and multiplicities in the $^{13}C\{^1H\}$ spectra. These results are summarized in **Table IV**.

Table IV. Deuterium Content of 1,5-Dimethyl-3,7-diazabicyclo[3.3.0]octanes-d_x 53 Obtained in Hydride Reduction of 47a

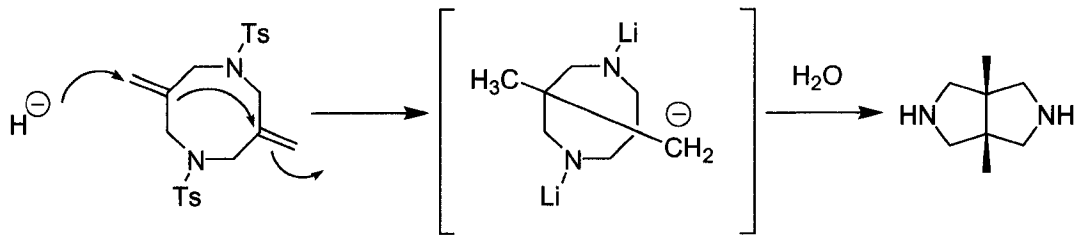
	Products, 53				
	LRMS[b]		**δ ^{13}C $\{^1H\}$, ppm**		
Reactant[a]					
Hydride/Quench	**m/z**[c]	**$(m+1)^+$**	**methyl**	**CH_2**	**Cq**
LAH/H_2O	141	$C_8H_{17}N_2$	20.4, -	51.7	62.6
LAH/D_2O	142	$C_8H_{16}DN_2$	20.4, 20.0[d]	51.5	62.3
LAD/H_2O	142	$C_8H_{16}DN_2$	20.4, 20.0[d]	51.5	62.3
LAD/D_2O	143	$C_8H_{15}D_2N_2$	-, 20.0[d]	51.5	62.1

[a] Compound **47a** in THF treated with indicated reagents. [b] Low resolution chemical ionization (NH_3) mass spectrum. [c] Base peak (100%); other isotopomeric $(M+1)^+$ ions less than 10%. [d] Triplet, $^1J(^{13}C\text{-}^2H) = 19.0$ Hz.

Analysis of the $(M + 1)^+$ ions in the mass spectra of the various reaction products indicated that either one or two deuterium atoms were quantitatively introduced. Thus, reduction of **47a** with LAH and quenching with D_2O or reduction with LAD and quenching with H_2O afforded material having an *m/z* value equal to 142 corresponding to

$C_8H_{15}DN_2$. Similarly, reduction with LAD followed by D_2O resulted in material having the composition $C_8H_{14}D_2N_2$. The isotope shifts and multiplicities in the $^{13}C\{^1H\}$ spectra establish unequivocally that the deuterium atoms appear, as the case may be, in either one or both of the methyls and then only as isotopically labeled CH_2D groups.

While there appears to be no precedent for this reaction, the formation of this bicyclic system can be rationalized mechanistically in terms of a hydride attack at one of the exocyclic methylene carbons followed by carbanion addition to the proximal transannular double bond. The ring closure process is then completed by transfer of a proton to the newly generated intermediate methyl carbanion as shown in **Scheme 29**. This proposed interpretation is consistent with the results of the deuterium labeling experiments. An alternative free radical interpretation cannot be excluded but seems less likely.



47a — Hydride attack

presumed intermediate

53

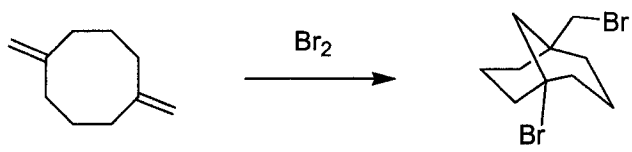
Scheme 29

On the other hand, the smooth reduction of alkenes by $LiAlH_4$ in combination with catalytic quantities of such first-row transition metal salts as $CoCl_2$, $NiCl_2$, and $TiCl_3$ is well-known. However, the low deuterium incorporation found when the product mixtures

were quenched with D_2O suggests that the reactive intermediates arise from the homolytic dissociation of a transition metalalkyl which subsequently abstracts hydrogen from the solvent.[168] This pathway is quite different from the present case where good yields and essentially quantitative deuterium incorporation are obtained in the absence of any added transition metal salts.

In addition to the transannular reactions initiated by nucleophilic reagents, the transannular reactions induced by electrophilies were also examined.

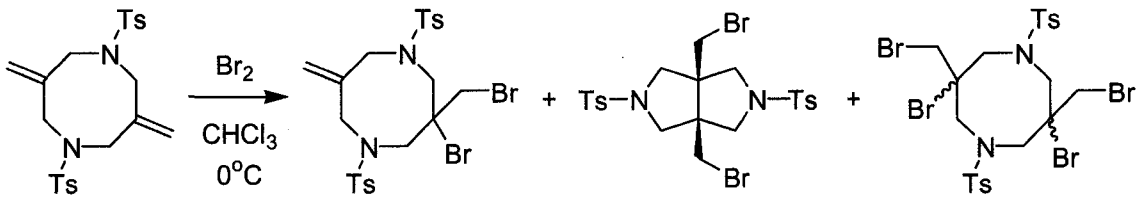
The 3,7-diazabicyclo[3.3.0]octane ring system has scarcely been investigated. The one reported example in the literature was prepared by a lengthy multistep synthesis.[148,149] While ring contractions to diazepines and piperidines have previously been observed in diazocine chemistry,[166] transannular cyclizations to bicyclic systems appear to be unknown. Thus, a significant contrast in behavior is observed in the electrophilic addition of bromine to the carbocycle, 1,5-bis-(methylene) cyclooctane **54**, and its diaza analog **47a**.



54 **55**

Scheme 30

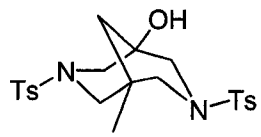
Both systems are disposed to undergo transannular cyclizations, but quite dissimilar ring skeletons are obtained. For example, carbocycle **54** is transformed by bromine into bridgehead substituted bicyclo[3.3.1]nonan derivative **55**,[169] (**Scheme 30**) whereas, as outlined in **Scheme 31**, **47a** gives an unexpected mixture of the 1,2- and 1,4-dibromo addition products, *N,N'*-bis(*p*-toluenesulfonyl)-3-bromo-3-(bromomethyl)-7-methylene-1,5-diazacyclooctane (**56**) and *N,N'*-bis(*p*-toluenesulfonyl)-1,5-bis(bromomethyl)-3,7-diazabicyclo[3.3.0]octane (**67**) together with very small quantities of the tetrabromide, *N,N'*-bis(*p*-toluenesulfonyl)-3,7-dibromo-3,7-bis(bromomethyl)-1,5-diazacyclooctane (**58**). The relative amounts of **56** and **57** formed are sensitive to the reaction conditions. Rapid addition of a solution of bromine to **47a** in CH_2Cl_2 at 0°C affords mainly **56**, whereas slow addition of the bromine reverses the situation leading to **57** as the major product. Attempts to convert **56** to **57** by heating in DMSO at 110°C for 16h were unsuccessful, and the starting material was recovered.



Scheme 31

The structures assigned to compounds **56--58** are confirmed by their ^1H and ^{13}C NMR properties and their mass spectra.

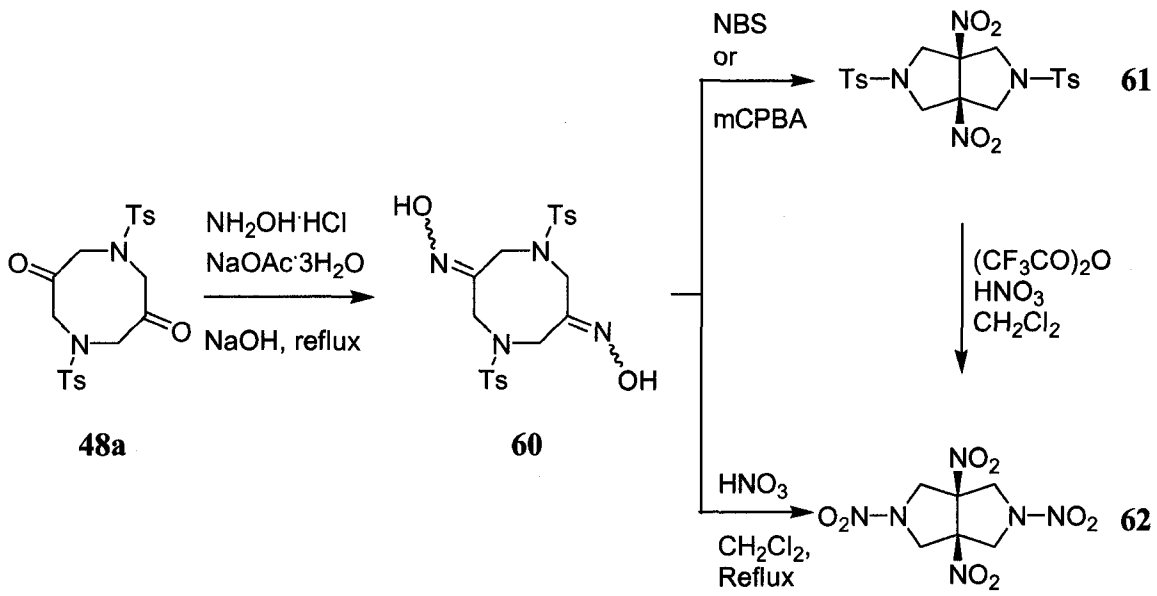
From carbonium ion considerations, the reaction of **47a** with bromine to give **56** and **57** is exceptional and clearly at variance with the anticipated and more readily rationalized formation of the 3,7-diazabicyclo[3.3.1]-nonane skeleton. In this connection, it is interesting to note that **47a** reacts with H_2SO_4 in a manner that parallels the behavior exhibited by carbocycle **54** toward electrophilic reagents. Thus, by treatment with acid, **47a** is quantitatively converted to the expected 5-methyl-3,7-diazabicyclo[3.3.1]nonan-1-ol **59**.



59

The structure of **59** has been deduced from its ^1H and ^{13}C NMR properties as well as analysis of its mass spectrum. The reaction path that leads to the formation of **59** highlights the apparent disparity in the behavior of **47a** toward acid-catalyzed hydration compared with the product of what is presumed to be electrophilic addition of bromine.

Transannular cyclizations in the diazacyclooctane system offer an attractive and viable synthetic route to the inaccessible 3,7-diazabicyclo[3.3.0]octane ring system. This property was utilized in the synthesis of 1,3,5,7-tetranitro-3,7-diazabicyclo[3.3.0]octane (**62**) shown in **Scheme 32**.



Scheme 32

Compound **48a** was converted to the corresponding dioxime **60** by standard method. NMR analysis showed the dioxime product so obtained to be a mixture of the *syn* (minor) **60a** and *anti* (major) **60b** stereoisomers, from which the latter could be isolated in pure form by recrystallization from 95% ethanol. Employing the methods previously discussed in **Chapter 2.1.2**, treatment of the stereoisomeric mixture of the dioximes **60** with *N*-bromosuccinimide in aqueous dioxane or with *m*-chloroperbenzoic acid in a buffered medium leads in both instances to ring-closure giving *N,N'*-bis(*p*-toluenesulfonyl)-1,5-dinitro-3,7-diazabicyclo[3.3.0]octane **61.** NMR and mass spectroscopic data provide evidence for the structure of compound **61**.

In a recent parallel report 3,7-dinitrotricyclo[3.3.1.$0^{3,7}$]-nonane has been prepared[170,171] from the dioxime of the corresponding bridgehead bicyclic diketone by oxidative

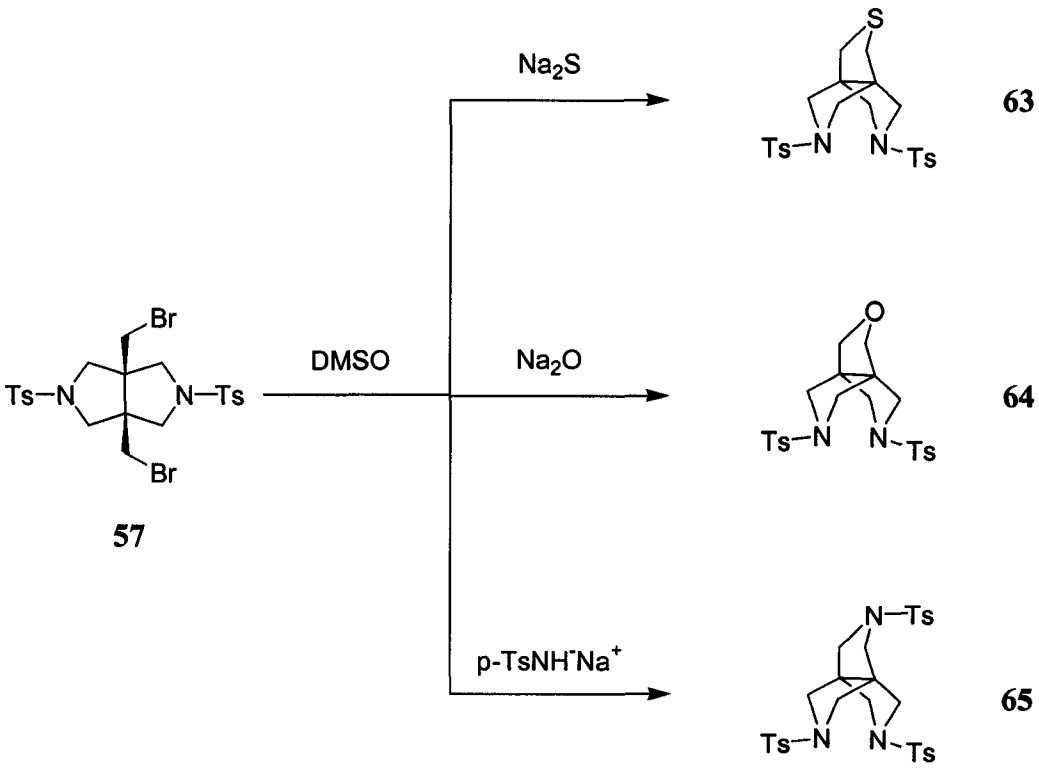
coupling with *m*-chloroperbenzoic acid. Similar transannular reactions of bisoximes have also been described by Paquette[47] and Camps et al.[172,173]

Adopting the methodologies shown in **Chapter 2.1.3**, treatment of **61** with trifluoroacetyl nitrate in CH_2Cl_2, results in the nitrolysis of the tosyl groups affording the tetranitro compound **62**. The structure of **60** is supported by the presence of the expected AB system centered at δ 4.99 and δ 5.14 (J = 13.9 Hz) in the ^1H spectrum. Alternatively, compound **62** could be prepared directly from **60** by nitrolysis with 100% HNO_3. In this case considerable nitration of the tosyl groups was observed, but it proved possible to isolate pure **62** in 25% yield by preparative scale thin-layer chromatography. These assignments and the structure of **62** were further substantiated by X-ray crystallographic analysis.[174]

4.4 Syntheses of 3,7,10-Triheterocyclic [3.3.3]Propellanes

It has previously been observed that heterocyclic propellanes are difficult to prepare. In particular, it has been reported that angular halomethyl groups which form part of substituted neopentyl systems fail to undergo cyclization to the corresponding heterocyclic propellanes. [148,149] The ready availability of appropriate precursors in the present work prompted us to examine anew these ring-closures, which, if successful, would open a facile route to these desired heterocyclic propellanes. Although the reaction of **57** with nucleophiles was sluggish, this difficulty was surmounted by heating the reactants in dimethyl sulfoxide. Thus, as shown in **Scheme 33**, when **57** was heated with

either Na_2S, Na_2O, or the preformed sodium salt of *p*-toluensulfonamide, cyclization could be induced to give the corresponding triheterocyclic propellanes. In this manner, propellanes **63**, **64**, and **65** were conveniently prepared in 80%, 75%, and 78% yield, respectively.



Scheme 33

The ^1H and ^{13}C NMR spectral properties of these propellanes were consistent with the expected structures. The chemical shifts observed for the different carbons attached to nitrogen, oxygen, and sulfur in these propellanes also compare favorably with the trends reported for other related heteropolycycloalkanes.[175]

In conclusion, procedures for convenient preparation of 3,7-functionalized N,N'-protected-1,5-diazacyclooctanes have been developed. Unusual transannular cyclizations in these systems leading to the little known 3,7-diazabicyclo[3.3.0]octane system have been examined. Efficient routes were developed that permit the ready conversion of the latter ring system to novel 3,7,10-triheterocyclic[3.3.3]propellanes. The methods described constitute simple and efficient syntheses of otherwise inaccessible 3,7-diazabicyclo[3.3.0]octanes and various 3,7,10-triheterocyclic [3.3.3]propellanes.

Chapter 5

Synthesis and Characterization of Difluoramino Energetic Materials

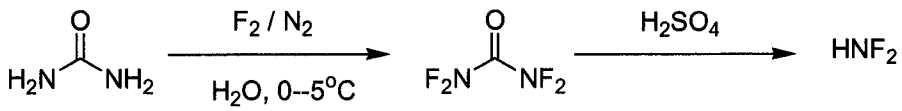
5.1 Introduction

During the 1960's extensive research was carried out on the synthesis of difluoramino compounds where the primary emphasis was to develop propellants rather than explosives. Only a rather incidental effort was expended in the study of mixed nitro-difluoramino compounds, despite the strong oxidizing potential towards organic compounds of both the difluoramino and nitro groups. Recently, there has been renewed interest in this class of compounds.[176,177]Solid nitramines containing difluoroamino groups could be especially useful as high-energy oxidizers in solid rocket propellants. With the basic **HMX** skeleton as the model, recent advances in the synthesis of dense cyclic energetic compounds prompted attempts to prepare a new class of solid diazocine propellants by combining appropriately structured gem-dinitro, nitramino and gem-difluoramino groups. Our attempts to prepare **HNFX** as well as the successful chemistry leading to **TNFX**, two important members of this group, will be presented here.

5.1.1. Generation of Difluoramine

Since the incorporation of difluoramino funtionalities is a crucial step in these synthetic sequences, it is pertinent at the outset to discuss the mechanism of the reaction and use of difluoramine, HNF_2. Difluoramine, a rather treacherous gaseous reagent, is generated by

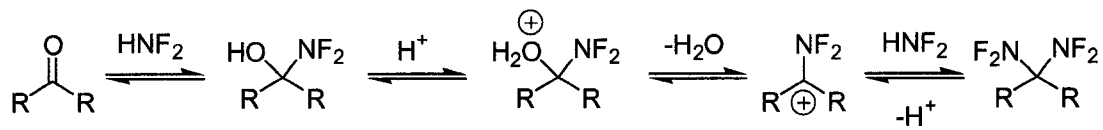
the hydrolysis of N,N-difluorourea, prepared by the direct aqueous fluorination of urea.[178-181] This process is shown in **Scheme 34**.



Scheme 34

5.1.2 Mechanism of Difluoramination

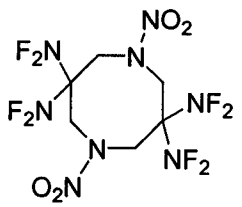
Geminal-difluoramino groups have been introduced into complex organic molecules by the reaction of carbonyl compounds[178,182] or their functional equivalents, such as gem-halonitro derivatives,[183] with difluoramine in fuming sulfuric acid (difluorosulfamic acid). Strong acid conditions are essential to drive the difluoramination equilibrium forward and any diazocine ring substituents present must be able to survive the harsh environment which is experimentally necessary.



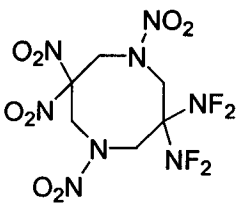
Scheme 35

5.2 Synthesis and Characterization of HNFX and TNFX: Results and Discussion

Since first proposed by Zheng et al.[184] and by Baum and coworkers,[171,185] the synthesis of gem-bis(difluoramino)-substituted heterocyclic nitramines, such as 3,3,7,7-tetrakis(difluoramino)octahydro-1,5-dinitro-1,5-diazocine **HNFX** and 3,3-bis(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-diazocine **TNFX** has been a challenging research goal because of their potentially high density and superior properties as solid propellant oxidizers. The effort to design and develop these new solid propellant oxidizers has largely been concentrated in our laboratories as well as at the Naval Laboratory at China Lake and the U.S. Army's Picatinny Arsenal.



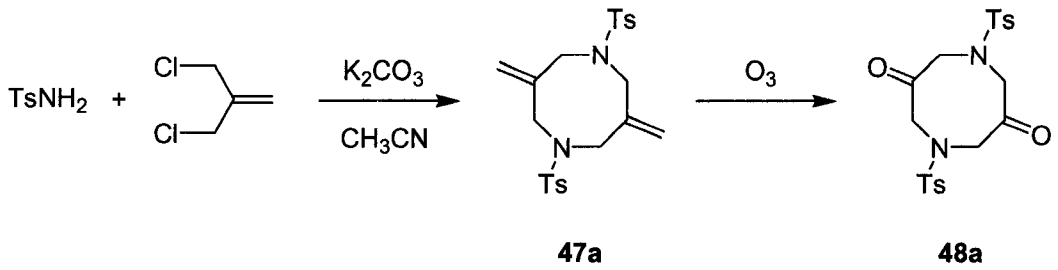
HNFX



TNFX

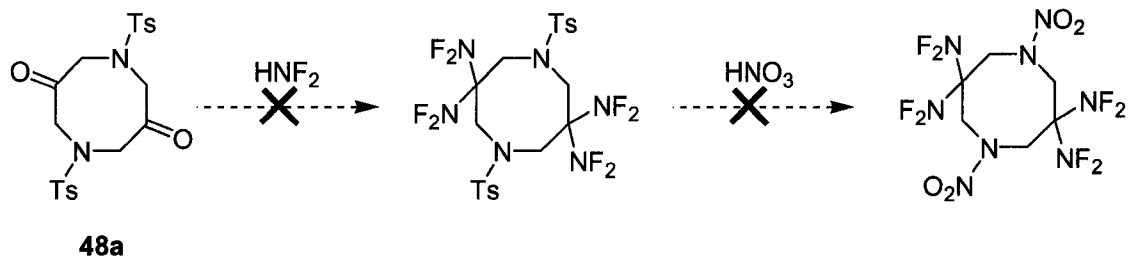
5.2.1 Attempts to synthesize HNFX

Our approach to the synthesis of the symmetric diazocine analog **HNFX** involved the development of a simple cyclo-condensation reaction of p-toluenesulfonamide with 3-chloro-2-chloromethypropene-1 to give the 3,7-bis(exo-methylene)-1,5-diazacyclooctane. Ozonation of this bis(exo-methylene) product readily afforded the diketone.[186]



Scheme 36

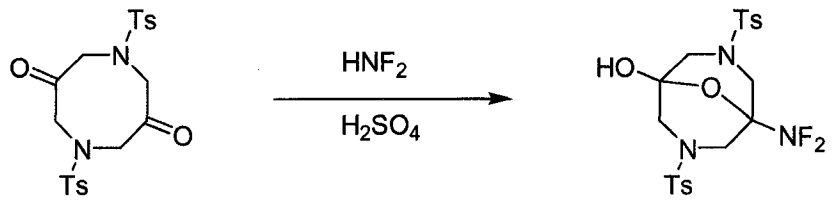
Thus, a convenient preparation of 3,7-diketo-N,N'-ditosyl-1,5-diazacyclooctane was developed. With the desired ring skeleton in place, this precursor could by appropriate functionalization lead to the desired **HNFX**. To convert this precursor to **HNFX** the following subsequent steps were contemplated.



48a

Scheme 37

However, it soon became apparent that this selected route to the desired target compound had a number of flaws. From work in Chapman's laboratory the 1,5-ditosyldiazocinedione system undergoes protonation at the diazocinedione site deactivating and preventing carbocation formation two carbons away. The result is that the intermediate N,N-difluorohemiaminal **66** does not proceed further.[165]



48a **66**

Scheme 38

Additionally, the nitrolysis is likely to be problematic since the tosyl nucleus readily undergoes ring nitration complicating its cleavage to generate the required N-NO_2 group.

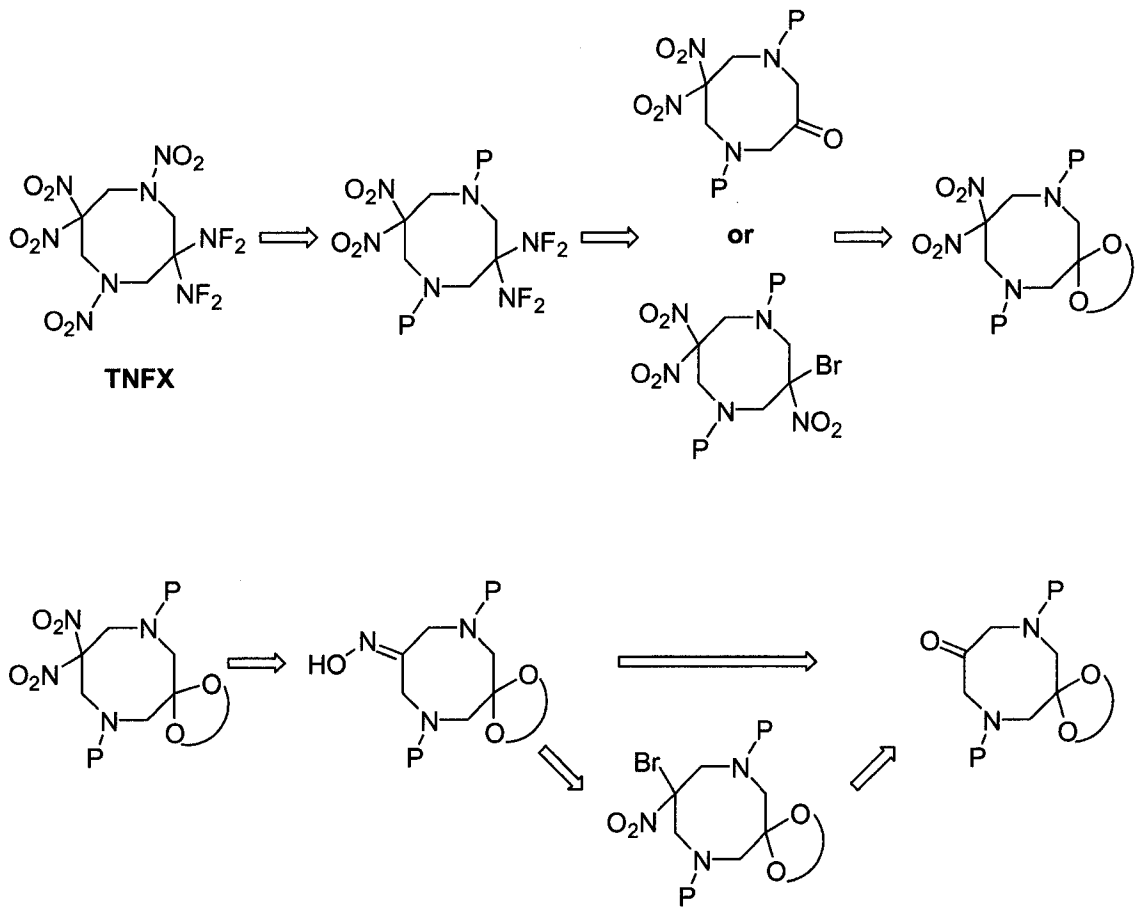
In view of the superior synthesis of **HNFX** that has recently been reported,[165,187] our efforts along these lines were halted. In this connection it is worth noting that the prepared sample of **HNFX** was found to have a density of 1.807 g/cm^3,[187] which is considerably less than predicted. This was attributed to channels of solvent in the crystal lattice.

5.2.2 Synthesis of TNFX

In this section, we discuss our work that has resulted in the successful synthesis of the less symmetric derivative **TNFX**. Incorporating both difluoramino and C-nitro substituents in addition to the nitramine functionality, **TNFX** may offer potentially superior propellant performance in certain formulations, based either on arguments involving qualitative chemical features of the ingredient,[171,185] or on computational

estimates of its thermodynamic properties.[188] Presented below is our synthetic approach which required development of a judicious protection strategy.

A retro synthetic analysis of **TNFX** is outlined in **Scheme 39**. The introduction of the geminal-difluoramino or geminal-dinitro functionality typically involves the derivatization of a ketone precursor or its surrogate, gem-bromonitro intermediate[189,190] under strongly acidic conditions (e.g. anhydrous H_2SO_4). This severe synthetic constraint limits the types of functional groups that will survive this treatment. A suitably N,N'-diprotected diazacyclooctane ketone is the precursor of choice for the introduction of difluoramino groups. As repeatedly demonstrated in **Chapter 4**, this ring system has a strong propensity to undergo numerous transannular reactions. Thus, satisfactory methodologies that circumvent bridging are needed for the preparation of asymmetric saturated gem-dinitro-1,5-diazocine precursors that will undergo difluoramination reactions. An obvious approach is to introduce the carbonyl functionalities sequentially and mask one of them as an inert ketal, while derivatizing the opposed ketone, as shown in **Scheme 39**.



Scheme 39

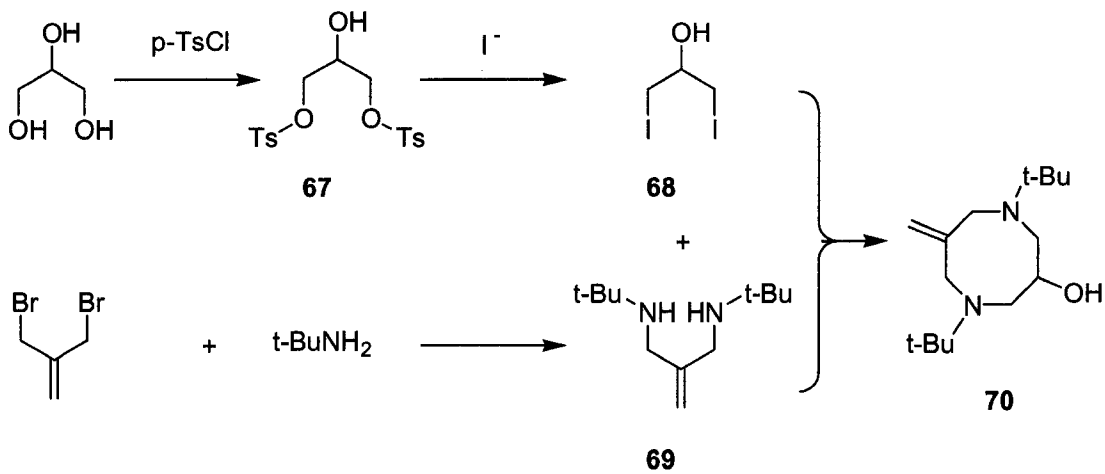
Detailed below are two approaches that can accommodate these conditions, and afford important new *gem*-dinitro-1,5-diazocine derivatives that have been successfully developed as difluoramination precursors to **TNFX**.

5.2.2.1 Acylative Dealkylation Route

To construct the 1,5-diazocine skeleton essential to the synthesis of unsymmetrical **TFNX** a strategy of sequential functionalization and protective blockage was developed.

This approach should avoid the risk of transannular reactions leading to a collapse of the desired eight-membered ring.

The synthesis[191] of the key intermediate, 3-hydroxy-1,5-(di-t-butyl)-7-exo-methylene-1,5-diazacyclooctane **70**, was undertaken by constructing the ring system from the constituent components as outlined in **Scheme 40**.



Scheme 40

In parallel fashion, tosylation of glycerol readily afforded the 1,3-ditosyl derivative which reacted with iodide ion to give 1,3-diiodo-2-hydroxypropane, while 1-bromo-2-(bromomethyl)-2-propene[192] was converted by t-butyl amine to the corresponding diamine. Cyclization resulting from combination of the latter prepared materials produced the desired unsymmetrical diazocine **70** in 85% yield. Groups less bulky than t-butyl are found to be ineffective in bringing about the cyclization to diazocine ring. Evidence that the diazocine ring is formed in this reaction stems from the x-ray

crystallographic analysis of the initially formed mono-hydrogen iodide salt that was isolated. The ORTEP diagram of this compound is shown **Figure 3**. It is interesting to note that the NH^+ associates with the transannular nitrogen and not directly with the iodide anion. The iodide ion associates in the crystal with the hydroxyl group.

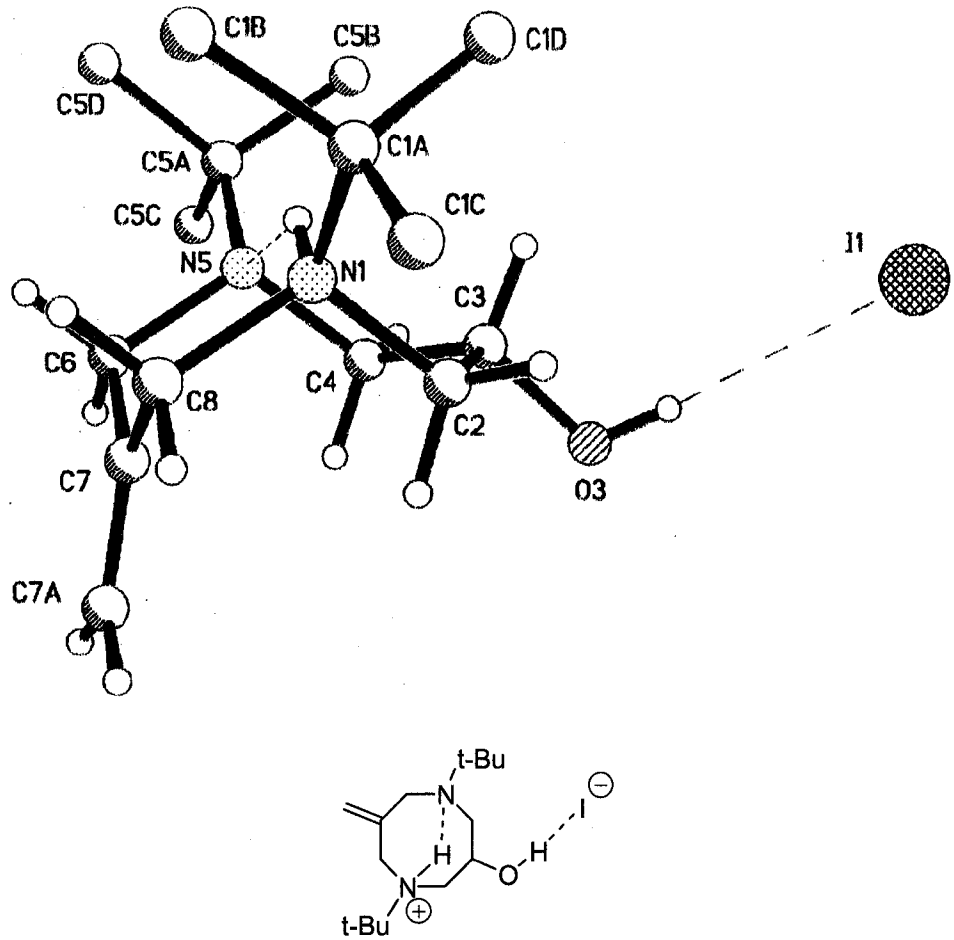
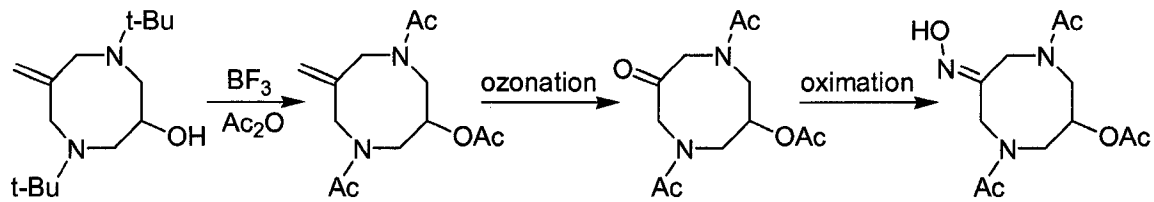


Figure 3. ORTEP diagram of the mono-HI salt of compound 70

Scheme 41 shows some of the functionalization studies that were carried out with diazocine **70**. Acylative dealkylation[193] can be effected when **70** is treated with acetic

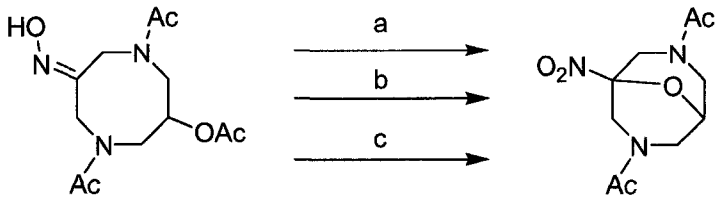
anhydride in the presence of catalytic amounts of boron trifluoride etherate and the triacetyl derivative **71** is readily obtained. Ozonation of **71** produces ketone **72** which is then converted to its oxime **73**.



70 **71** **72** **73**

Scheme 41

The strong tendency towards undesired transannular reactions in this ring system became apparent again when standard methodologies[51] were used in attempts to convert oxime, **73** to the corresponding geminal bromo / nitro and gem-dinitro compounds **74a** and **74b**. As outlined in **Scheme 42**, the oxidation conditions investigated included N-bromosuccinimide, m-chloroperbenzoic acid and ~100% HNO_3. In each case transannular bridging intervened and only the 9-oxa-3,7-diazabicyclo[3.3.1]nonane **75** could be isolated. Consequently, our functionalization sequence was modified.



73 **75**

Reagents and conditions (yield): (**a**) NBS, $NaHCO_3$, dioxane-H_2O, rt (40%);

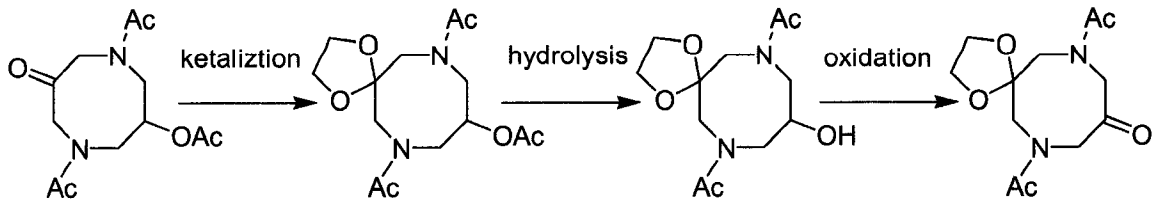
(**b**) m-CPBA, Na_2HPO_4, urea, MeCN, reflux (49%);

(**c**) HNO_3, NH_4NO_3, urea, CH_2Cl_2, reflux (29%);

Scheme 42

74a **(Not obtained)** **74b**

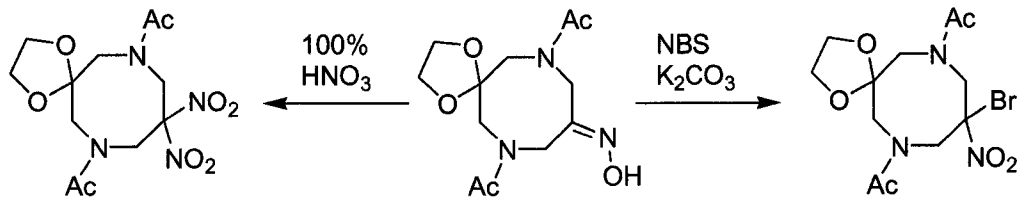
The modified approach shown in **Scheme 43** involves protective ketalization of **72** followed by hydrolysis of the O-acetate **76** and subsequent oxidation (PCC or Jones) of the alcohol **77** to the protected ketone **78**. The 1,3-dioxolane protection of the keto function was employed to avoid transannular reactions.



72 **76** **77** **78**

Scheme 43

Oxime **79** derived from ketone **78** can be converted to the geminal dinitro compound **80** by treatment with nitric acid or to the corresponding Br / Nitro compound **81** by treatment with N-bromosuccinimide, as shown in **Scheme 44.**

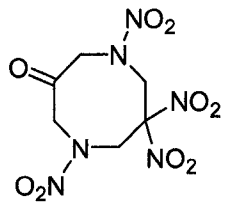


80 **79** **81**

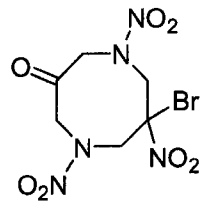
Scheme 44

Our objective in this multi-step route is to prepare the key carbonyl **82** or **83** precursors that will undergo fluoramination to the desired product **TNFX**. Toward this end it will necessary to convert **80** to **82** and **81** to **83** by hydrolysis and / or nitrolysis, respectively. The sequence of these steps to accomplish this has been

investigated. However, the conversion of the ketal back to the ketone has proved to be a major hurdle.



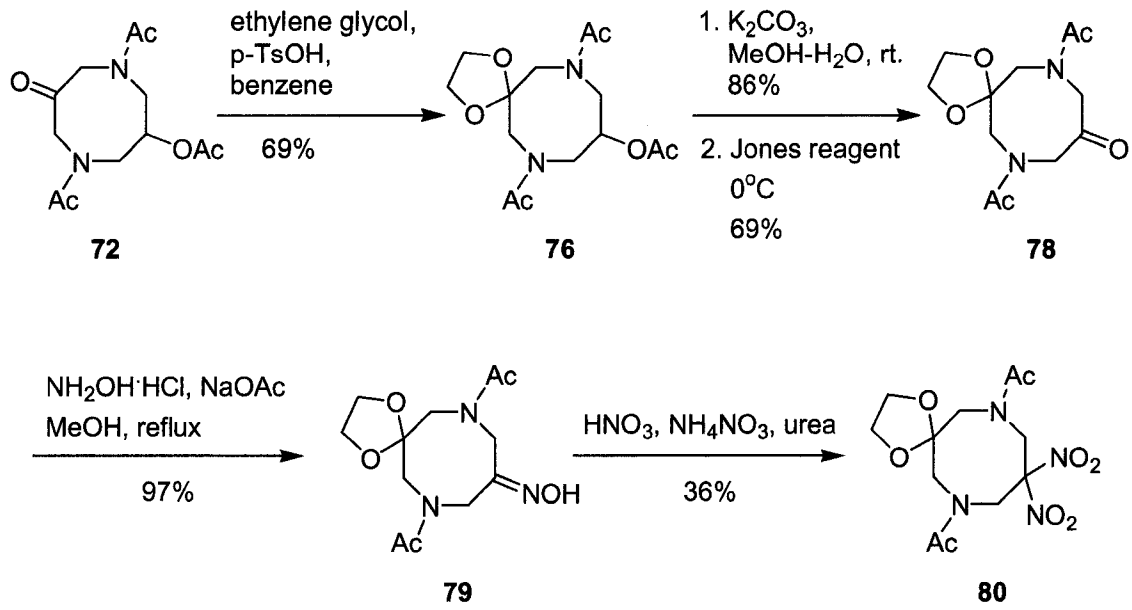
82



83

Scheme 45

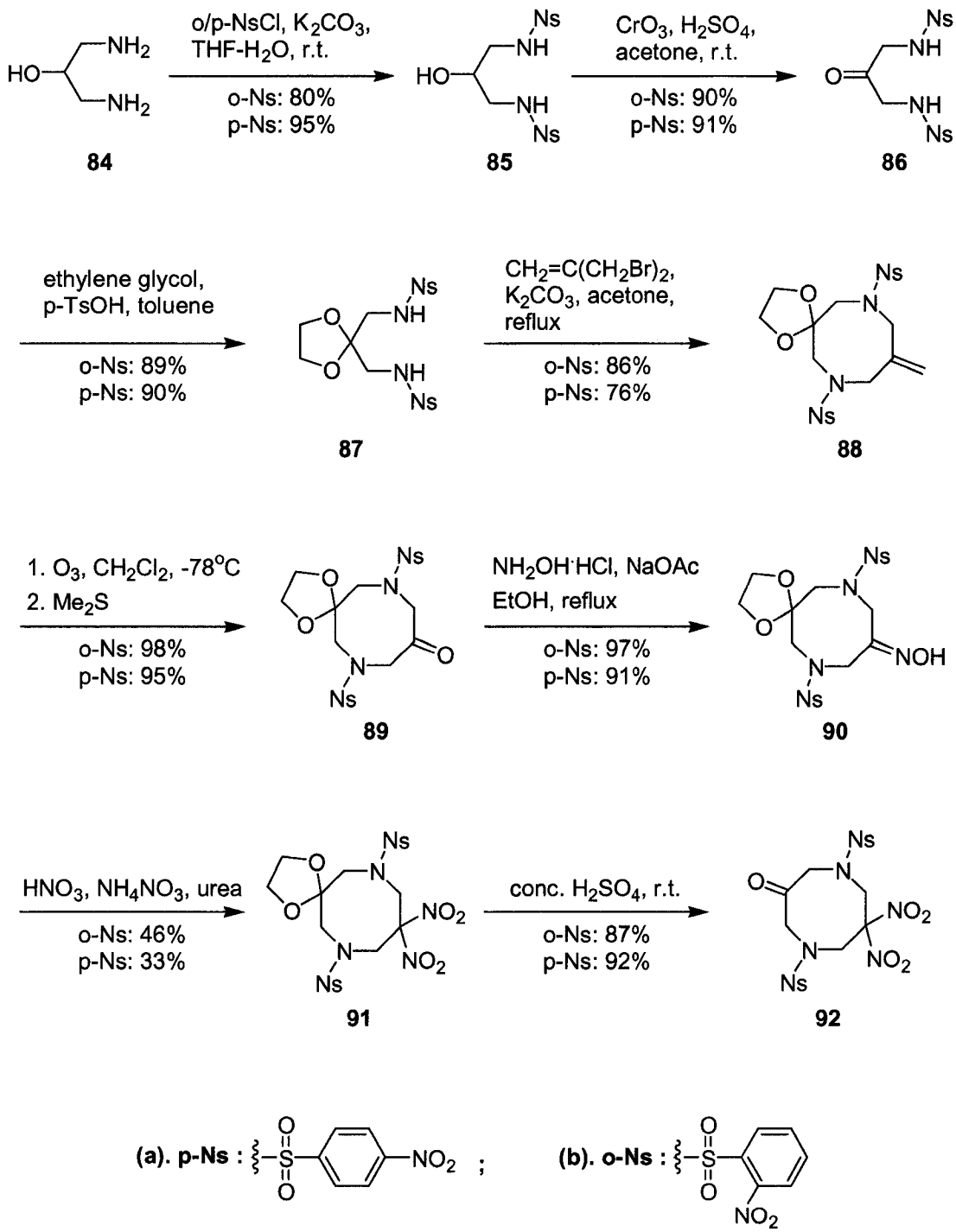
In the first approach, the ketone (**72**) was subjected to the sequence of transformations shown in **Scheme 46.** This led to the synthesis of the intermediate oxime (**79**). It should be noted that the choice of the 1,3-dioxolane protection of the keto function in this compound was employed to avoid the transannular reactions that were previously encountered. With this protecting group in place, the conversion of the oxime **79** to the corresponding *gem*-dinitro compound **80** took place in a highly efficient manner. However, under a variety of conditions, deprotection of **80** to the corresponding ketone **82** proved impossible in our hands. Attempts to convert **80** to the corresponding ketone by acid hydrolysis led to the recovery of starting material with dilute acid and to the destruction of **80** under more vigorous conditions. An alternate route was therefore necessary.



Scheme 46

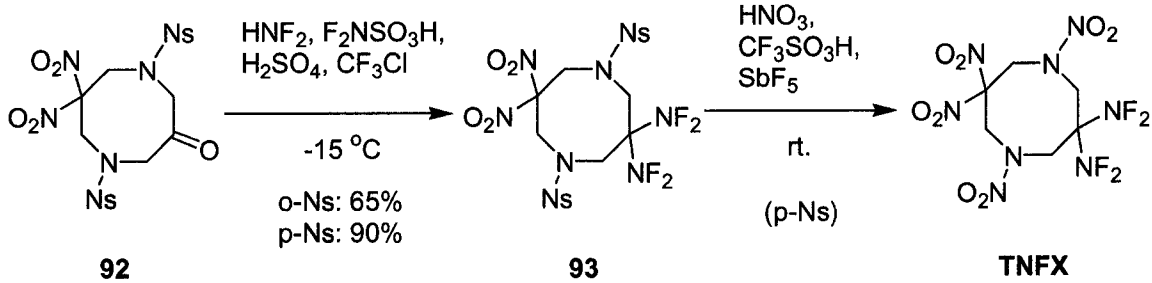
5.2.2.2 Nosyl Deprotection-Ozonation Route

In an alternate strategy outlined in **Scheme 47**, a commercially available starting material, 1,3-diaminopropan-2-ol (**84**),[194] was N-protected in separate synthetic routes by both *o*-nosyl and *p*-nosyl groups. This was followed by chromic acid oxidation to ketones **86**, and the latter carbonyl function was protected through reaction with ethylene glycol to form their 1,3-dioxolane derivatives **87**. Cycloalkylation of **87** with methallyl dibromide[192] followed by ozonolysis of the readily formed *exo*-methylene-1,5-diazocine intermediates **88** afforded the monoprotected 1,5-diazocin-3(2*H*)-ones **89**. Oximation followed by HNO_3 oxidation of **90** afforded the *gem*-dinitro derivatives **91**. Hydrolysis of the latter produced the desired hexahydro-7,7-dinitro-1,5- diazocin-3(2*H*)-one derivatives **92**.



Scheme 47

As shown in **Scheme 48**, the *gem*-bis(difluoramino) derivative **93** was obtained by a modified difluoramination[165] of ketone **92** with difluoramine-difluorosulfamic acid in sulfuric acid. N-Nitrolysis of dinosyldiazocine **93** proved remarkably difficult. This could be anticipated for reasons elaborated in the previous report on the synthesis of **HNFX** by N-nitrolysis of a dinosyldiazocine precursor.[187]



(a). p-Ns; (b). o-Ns

Scheme 48

Sterically hindered and electronegatively substituted protected amines are especially resistant to N-nitrolysis, and diazocine **93** incorporates both of these features. A β,β-bis-(difluoramino)alkyl plus a β,β-dinitroalkyl substituent impart even more electron-withdrawing character than the two bis(difluoramino)alkyl substituents of the **HNFX** precursor; for example, Taft's $\sigma^*(NO_2) = 4{,}72$[195,196] vs. $\sigma^*(NF_2) \approx 4{,}13$.[197] Thus, even extended nitrolysis (14 days) of **93** with the system nitric acid–trifluoromethanesulfonic acid, a source of strongly nitrating species protonitronium (NO_2H^{2+}),[198,199] at elevated temperature (55°C) produced predominantly only the corresponding mononitramine. Only by addition of a strong Lewis acid, SbF_5, to the nitrating system—in order to

generate a higher concentration of protonitronium[200]— followed by further nitrolysis (2 days) was **TNFX** formed by a clean conversion as the major product, though so far in unquantified yield. Therefore, the second nitrolysis step of **Scheme 48** may well be the most difficult N-nitrolysis ever successfully achieved, since the second nitrolysis step producing **HNFX** was complete in HNO_3–HOTf (without Lewis acid) in only ~40 h.[187] Also, only the *p*-nosyl isomer of **93** was useful for formation of **TNFX** because the *o*-nosyl derivative underwent para-C-nitration, and the resulting 2,4-dinitrobenzenesulfonyl derivative was not effectively nitrolyzed. The product was identified by multinuclear NMR spectroscopy as well as X-ray crystallography.

5.2.2.3 Confirmation of the Structure of TNFX

The first successful synthesis of 3,3-bis-(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-dazocine (**TNFX**) has been realized. All compounds and intermediates described here have been fully characterized (^1H, ^{13}C NMR, HRMS and /or X-ray crystallography). The identity of **TNFX** is confirmed by its X-ray crystallographic analysis as well as the ^1H and ^{19}F NMR spectra shown in **Figures 4**, **5** and **6**. The X-ray crystallographic analysis reveals the presence of two polymorphs one with density 1.712 g/ml and the other with density 1.904 g/ml. The latter finding agrees with the MOLPAK density prediction. The ^1H spectrum shows δ 5.14 (br, 4H) and δ 5.50 (s, 4H) while the ^{19}F spectrum shows δ 29.7 (s).

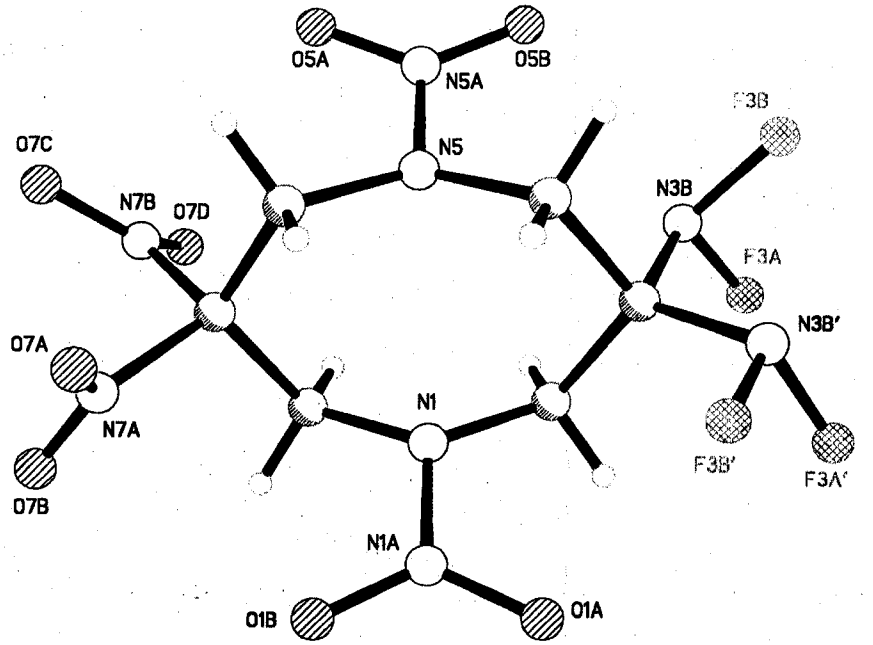


Figure 4. ORTEP Diagram of High-Density Polymorph of TNFX

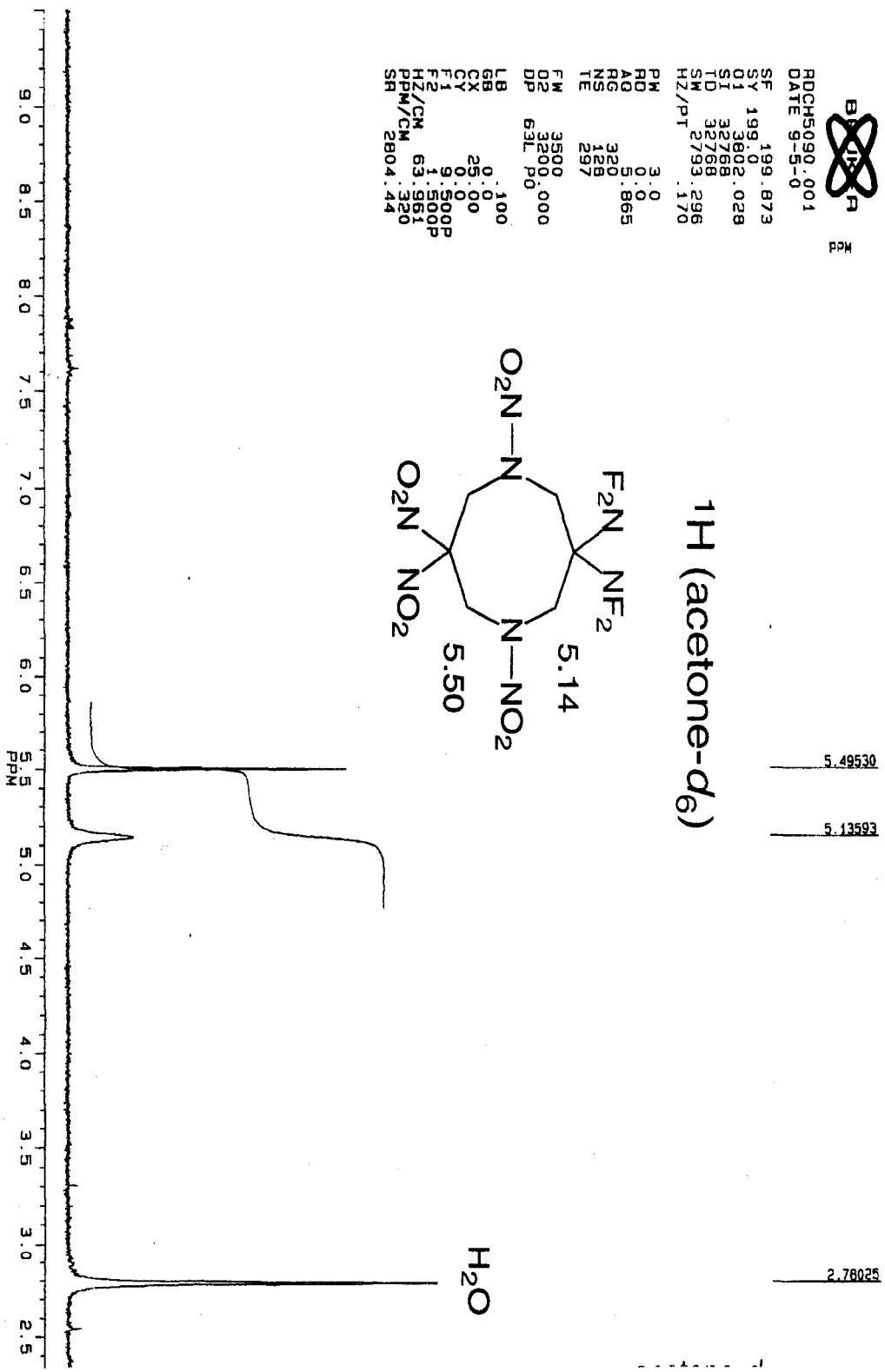


Figure 5. ^{1}H NMR of TNFX

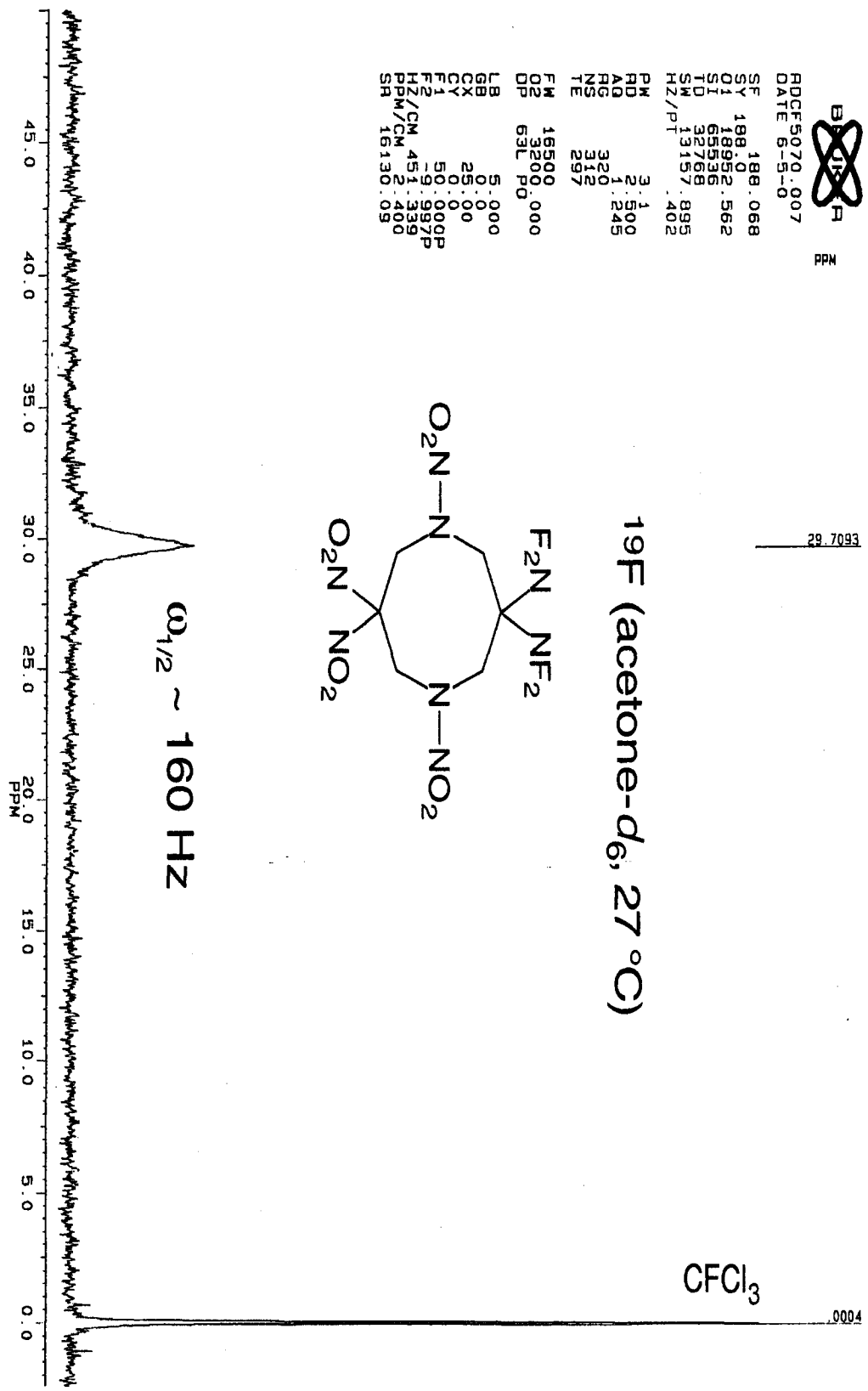


Figure 6. ^{19}F NMR of TNFX

Chapter 6

Experimental

The chemical shifts in $CDCl_3$, DMSO-d_6, and acetone-d_6 are reported in δ (ppm) relative to TMS and were measured against the solvent as an internal standard. Melting points are uncorrected. THF was distilled from Na/benzophenone immediately prior to use. Other solvents and reagents were obtained from commercial sources and used without further purification.

N,N'-Bis(4-methylbenzenesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (47a). To a suspension of *p*-toluenesulfonamide (27.5 g, 160 mmol) and anhydrous K_2CO_3 (45.0 g) in anhydrous acetonitrile (250 mL) was added 3-chloro-2-(chloromethyl)-1-propene (20.0 g, 160 mmol) in acetonitrile (25.0 mL) over a 15-min period. After stirring the mixture at reflux for 4 h, the solvent was evaporated in vacuo, and the solid residue was extracted with hot ethyl acetate. Cooling the extract gave 21.5 g (60%) of colorless crystalline N,N'-bis(4-methylbenzenesulfonyl)-3,7-bis(methylene)-tetrahydro-1,5-diazocine (**47a**): mp 194-197 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 6H), 3.82 (s, 8H), 5.19 (s, 4H), 7.67 (d, J = 8.3 Hz, 4H), 7.31 (d, J = 8.3 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.5, 53.0, 118.1, 127.1, 129.7, 135.8, 141.8, 143.5. HRMS (FAB) calcd for $C_{22}H_{27}N_2O_4S_2$ $(MH)^+$ 447.1412; found *m/z*, 447.1402. Anal. Calcd for $C_{22}H_{26}N_2O_4S_2$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.21; H, 5.98, N, 6.54.

N,N'-Bis(methanesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (47b). To a well-stirred refluxing suspension of methanesulfonamide (15.2 g, 160 mmol) and anhydrous K_2CO_3 (48.5 g) in acetonitrile (150 mL) was added 3-chloro-2-(chloromethyl)-1-propene (20.0 g, 160 mmol). The mixture was heated at reflux for 4 h and then cooled and filtered, and the filtrate was concentrated to give a solid residue, which was extracted with CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was washed with 5% NaOH (50 mL) and water, dried ($MgSO_4$), and evaporated to give 4.96 g (22%) of crude N,N'-bis(methanesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (**47b**). Recrystallization from ethyl acetate afforded a colorless crystalline solid: mp 136-137 °C; ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 6H), 3.99 (s, 8H), 5.28 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 38.1, 52.8, 119.3, 141.2. HRMS (FAB) calcd for $C_{10}H_{19}N_2O_4S_2$ $(MH)^+$ 295.0786; found *m/z*, 295.0781. Anal. Calcd for $C_{10}H_{18}N_2O_4S_2$: C, 40.80; H, 6.16; N, 9.52. Found: C, 41.11; H, 5.87; N, 9.32.

N,N'-Bis(4-methylbenzenesulfonyl)tetrahydro-1,5-diazocine-3,7-dione (48a). A mixture of ozone in oxygen was bubbled through a solution of N,N'-bis(4-methylbenzenesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (**47a**) (1.0 g, 2.24 mmol) in CH_2Cl_2 (20 mL) at -78 °C until the blue color persisted. The mixture was stirred for 1 h and then allowed to warm to 0 °C. Oxygen was bubbled through the mixture to remove excess ozone, and then excess dimethyl sulfide was added. After stirring at rt for 1 h the mixture was concentrated, and the residue was dissolved in CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was recrystallized from acetone/hexanes to give pure N,N'-bis(4-methylbenzenesulfonyl)-

tetrahydro-1,5-diazocine-3,7-dione (**48a**) (0.86 g, 85%): mp 275 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H), 4.08 (s, 8H), 7.72 (d, J = 8.3 Hz, 4H), 7.36 (d, J = 8.3 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 59.9, 127.1, 130.3, 133.9, 145.1, 204.3; HRMS (FAB) calcd for $C_{20}H_{23}N_2O_6S_2$ $(MH)^+$ 451.0998; found *m/z* 451.0990. Anal. Calcd for $C_{20}H_{22}N_2O_6S_2$: C, 53.32; H, 4.92; N, 5.93. Found: C, 53.61; H, 5.09, N, 5.93. If the reaction mixture was not worked up until the next day, a sticky white substance was obtained; addition of CH_2Cl_2 or ether resulted in the formation of a white precipitate in 6% yield, that was identified as the cyclic hydrate of the diketone: ^{1}H NMR (acetone-d_6) δ 2.42 (s, 6H), 2.30 (d, J = 11 Hz, 4H), 3.66 (d, J = 11 Hz, 4H), 7.45 (d, J = 7.3 Hz, 4H), 7.65 (d, J = 7.3 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 21.4, 52.0, 93.7, 128.6, 130.4, 133.1, 145.5. Heating the hydrate with benzene with azeotropic removal of water resulted in smooth dehydration to **48a**.

N,N'-Bis(methanesulfonyl)tetrahydro-1,5-diazocine-3,7-dione (48b). A mixture of ozone in oxygen was bubbled through a suspension of N,N'-bis(methanesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (**47b**) (1.0 g, 3.34 mmol) in CH_2Cl_2 (50 mL) at –78 °C until the blue color of ozone persisted. The mixture was stirred for 1 h and then allowed to warm to 0 °C. Oxygen was then bubbled through the reaction mixture to remove excess ozone. Excess dimethyl sulfide was then added, and the mixture was stirred at rt for 1 h to decompose the ozonide. The mixture was then filtered, and the collected solid was washed with a small amount of CH_2Cl_2 to give 0.94 g of N,N'-bis(methanesulfonyl)tetrahydro-1,5-diazocine-3,7-dione (**48b**) (93%): mp 305 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.36 (s, 6H), 4.18 (s, 8H); ^{13}C NMR (DMSO-d_6) δ 38.7, 59.1, 206.5.

HRMS (FAB) calcd for $C_8H_{15}N_2O_6S_2$ $(MH)^+$299.0372; found *m/z*, 299.0379. Anal. Calcd for $C_8H_{14}N_2O_6S_2$: C, 32.21; H, 4.73; N, 9.39. Found: C, 32.47; H, 4.48, N, 9.81.

Oxidation of Stereoisomeric N,N'-Bis(4-methylbenzenesulfonyl)octahydro-1,5-diazocine-3,7-diols (41). A solution of pyridine sulfur trioxide complex (0.88 g, 5.54 mmol), triethylamine (0.82 g, 8.72 mmol), and a stereoisomeric mixture of the N,N'-bis(*p*-toluenesulfonyl)-1,5-diazacyclooctane-3,7-diols (0.20 g, 0.44 mmol) in DMSO (6.91 g, 88.5 mmol) stirred at rt for 1 h and then poured over ice and extracted with ethyl acetate (4 x 10 mL). The combined extracts were washed with water (5 x 10 mL), dried (MgSO4), and concentrated to give an oil which solidified on standing. Recrystallization from ethanol/hexane gave 0.41g (41%) of **49** as a colorless solid: mp 215-217 °C (lit. mp[157] 217 °C); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6H), 2.53 (d, 2H), 2.88 (m, 2H), 3.51 (d, J = 11 Hz, 2H), 3.71 (d, J = 11 Hz, 2H), 4.21 (m, 1H), 7.69 (d, J = 8.2 Hz, 4H), 7.33 (d, J = 8.2 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 46.1, 52.3, 68.8, 90.4, 128.1, 129.9, 132.1, 144.2. LRMS (CI-NH_3) 453 (M + 1), 470 (M + 18).

1,5-Dimethyl-3,7-diazabicyclo[3.3.0]octane (53). A slurry of N,N'-bis(4-methyl-benzenesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (**47a**) (2.22 g, 4.98 mmol), in THF (75 mL) containing $LiAlH_4$ (1.90 g, 50 mmol), was stirred under N_2 for 42 h. The reaction mixture was quenched with 20% NaOH (4.5 mL) with external cooling. Stirring was continued at rt for 3 h, and the white granular precipitate that formed was removed by filtration and washed with anhydrous ether (3 x 50 mL). The combined organic extracts were concentrated to give 0.574 g (82%) of **53** as a colorless oil which slowly

solidified: mp ~ 30 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 6H), 2.71 (d, J = 11.2 Hz, 4H), 2.92 (d, J = 11.2 Hz, 4H), 2.61 (s, 2H, br); ^{13}C NMR ($CDCl_3$) δ 20.4, 51.7, 62.6. HRMS (FAB) calcd for $C_8H_{17}N_2$ $(MH)^+$ 141.1392; found *m/z*, 141.1388. Treatment of an ethanolic solution of **53** with picric acid afforded the picrate as a yellow solid, mp 258 °C.

1,5-Dimethyl-3,7-diazabicyclo[3.3.0]octane-d_1. The procedure used to prepare **5** was modified by the use of deuterated reagents in two separate experiments.

A. N,N'-Bis(4-methylbenzenesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (**47a**) (0.223 g, 0.50 mmol) in THF (50 mL) was treated with $LiAlH_4$ (0.25 g, 6.6 mmol). Quenching of the reaction mixture with D_2O (1.0 mL) followed by 40% NaOD (0.5 mL) gave, after workup, 0.52 g (82%) of **53**-d_1 as a colorless oil.

B. Procedure (**A**) was repeated using $LiAlD_4$ and H_2O followed by 40% NaOH to give 0.57 g of **53**-d_1 (82%).

Prior to mass spectral measurement, the crude products were dissolved in benzene (25 mL) to which was added H_2O (3 x 1 mL), and the mixtures were independently subjected to azeotropic distillation using a Dean-Stark trap. Analysis of these samples by a DEPT experiment and their respective mass spectra confirmed the presence of only one deuterium atom and a CH_2D group. LRMS (EI) 141 (M).

1,5-Dimethyl-3,7-diazabicyclo(3.3.0)octane-d_2. A suspension of N,N'-bis(4-methyl-benzenesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (**47a**) (0.446 g, 1.00 mmol) in THF (50 mL) and $LiAlD_4$ (0.427 g, 10.2 mmol, 99% ^{2}H atom-enrichment) in THF (50 mL) afforded 0.152 g of crude product after quenching with D_2O, followed by NaOD,

and workup as described for the preparation of **53**. Prior to mass spectral measurement, the crude product was azeotropically distilled with benzene and water as described above.

N,N'-Bis(4-methylbenzenesulfonyl)-3-bromo-3-(bromomethyl)-7-(methylene)-hexahydro-1,5-diazocine (56), N,N'-Bis(4-methylbenzenesulfonyl)-1,5-bis-(bromomethyl)-3,7-diazabicyclo[3.3.0]octane (57), and N,N'-Bis(4-methyl-benzenesulfonyl)-3,7-dibromo-3,7-bis(bromomethyl)octahydro-1,5-diazocine (58). A solution of bromine (3.2 g, 20 mmol) in CH_2Cl_2 (50 mL) was added dropwise over a 4 h period to a stirred solution of **47a** (8.92 g, 20 mmol) in CH_2Cl_2 (250 mL) at 0 °C. The reaction mixture was then stirred for an additional 6 h and then it was washed successively with 5% $Na_2S_2O_3$ (100 mL), saturated $NaHCO_3$ (100 mL), and water. The organic phase was dried ($MgSO_4$) and concentrated at reduced pressure to give a residue which was treated with ice-cold acetone (15 mL). Pure **57** (8.2 g, 68%) was isolated as crystalline material which remained insoluble in the acetone: mp 228-231 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H), 3.16 (d, J = 10.5 Hz, 4H), 3.31 (d, J = 10.5 Hz, 4H), δ 7.33 (d, J = 8.4 Hz, 4H), δ 7.64 (d, J = 8.3 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 34.0, 56.0, 57.3, 127.7, 130.0, 131.9, 144.5; HRMS (FAB) calcd for $C_{22}H_{27}N_2O_4S_2Br_2$ $(MH)^+$ 604.9778, found *m/z*, 604.9768. Anal. Calcd for $C_{22}H_{26}N_2O_4S_2Br_2$: C, 43.58; H, 4.32; N, 4.62. Found: C, 43.66; H, 4.73, N, 4.96. Concentration of the acetone mother liquor deposited the tetrabromide **58** (0.30 g, 2%) as colorless crystals: mp 210 – 212 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 6H), 3.33 (d, J = 15.6 Hz, 4H), 4.18 (s, 4H), 4.35 (d, J = 15.6 Hz, 4H), 7.38, 7.40, 7.75, 7.77; ^{13}C NMR ($CDCl_3$) δ 21.61, 39.85, 61.13, 67.07, 127.93, 130.22, 133.96,144.89; LRMS (EI) 762 (M).

After separating the undissolved **58**, column chromatography of the mother liquor on silica gel using hexane-ethyl acetate (4:1) as the elution solvent afforded the dibromide **56** (3.6 g, 30%): mp 192-197 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H), 3.45 (d, J = 12.6 Hz, 2H), 3.88 (d, J = 12.6 Hz, 2H), 3.56 (d, J = 15.7 Hz, 2H), 3.85 (d, J = 15.7 Hz, 2H), 4.11 (s, 2H), 5.24 (s, 2H), 7.33, 7.35, 7.69, 7.72; ^{13}C NMR ($CDCl_3$) δ 21.55, 42.61, 55.28, 55.58, 67.29, 124.23, 127.66, 130.03, 134.04, 139.33, 144.27; HRMS (FAB) calcd for $C_{22}H_{27}N_2O_4S_2Br_2$ $(MH)^+$ 604.9779; found *m/z*, 604.9779. Anal. Calcd for $C_{22}H_{26}N_2O_4S_2Br_2$: C, 43.58; H, 4.32; N, 4.62. Found: C, 43.25; H, 4.95, N, 4.90.

Attempts to convert **56** to its isomer **57** by heating at 110 °C for 16 h in anhydrous DMSO lead to the recovery of the starting material.

Rapid Addition of Bromine to 47a. To an ice-cooled (-5 to 0 °C) solution of N,N'-bis(4-methylbenzenesulfonyl)-3,7-bis(methylene)tetrahydro-1,5-diazocine (**47a**) (2.68 g, 6.0 mmol) in CH_2Cl_2 (80 mL) was added a solution of bromine (0.96 g, 6.0 mmol) in CH_2Cl_2 (15 mL) over a 30-min period. The reaction mixture was stirred at 0 °C for an additional 5 h and then was washed successively with 5% sodium bicarbonate (30 mL), 5% sodium bisulfite (30 mL), brine, and water. The organic layer was dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to give 2.07 g of a crude mixture of **56** and **57**. NMR analysis showed this material to be an 88:12 mixture of **56** and **57**.

5-Methyl-3,7-diazabicyclo[3.3.1]nonan-1-ol (59). A solution of **47a** (112 mg, 0.25 mmol) in chloroform (2.0 mL) was stirred at rt for 24 h with concd H_2SO_4 (4.0 mL). The reaction mixture was poured into ice-water (60 mL) and extracted with chloroform (3 x

25 mL). The chloroform layer was washed with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated to leave 115 mg of crude product which was essentially pure **59**. Recrystallization from alcohol afforded needle-shaped crystals: mp 238-240 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.33 (s, 2H), 1.62 (s, br, 1H), 2.32 (d, 2H, J = 11.2 Hz), 2.41 (s, 6H), 2.48 (d, 2H, J = 10.7 Hz), 3.43 (d, 2H, J = 11.2 Hz), 3.66 (d, 2H, J = 10.7 Hz), 7.30, 7.33, 7.67, 7.69; ^{13}C NMR ($CDCl_3$) δ 21.54, 24.76, 33.19, 45.38, 54.08, 54.35, 66.57, 127.91, 129.78, 133.03, 143.67. HRMS (FAB) calcd for $C_{22}H_{29}N_2O_5S_2$ $(MH)^+$ 465.1518; found *m/z*, 465.1510. Anal. Calcd for $C_{22}H_{28}N_2O_5S_2$: C, 56.88; H, 6.07; N, 6.03. Found: C, 56.68; H, 5.78, N, 5.72.

Stereoisomeric Mixture of N,N'-Bis(4-methylbenzenesulfonyl)-tetrahydro-1,5-diazocine-3,7-dione Dioximes (60). A suspension of N,N'-Bis(4-methyl-benzenesulfonyl)tetrahydro-1,5-diazocine-3,7-dione **(48a)** (0.900 g, 2.00 mmol), hydroxylamine hydrochloride (0.556 g, 8.00 mmol), and sodium acetate trihydrate (2.18 g, 16.0 mmol) in ethanol (70 mL) was stirred under reflux for 5 d. The ethanol was removed, and the residue was washed with water and dried over P_2O_5 in vacuo to give 0.710 g (74%) of **60** as a colorless solid comprised of two geometric isomers (syn, minor, **60a** and anti, major, **60b**).

A sample of crude **60** was recrystallized from ethanol to give the pure anti isomer **60b**: mp 239 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 6H), 3.84 (s, 4H), 4.09 (s, 4H), 7.46 (d, J = 7.9 Hz, 4H), 7.69 (d, J = 7.9 Hz, 4H), 11.3 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 21.0, 47.0, 52.3, 126.6, 130.0, 134.6, 143.9, 152.9. HRMS (FAB) calcd for $C_{20}H_{25}N_4O_6S_2$ $(MH)^+$ 481.1216; found *m/z*, 481.1198.

N,N'-Bis(4-methylbenzenesulfonyl)-1,5-dinitro-3,7-diazabicyclo[3.3.0]octane (61) by N-Bromosuccinimide Oxidation of 60. A mixture of sodium bicarbonate (7.4 g, 88.1 mmol), NBS (6.6 g, 37.1 mmol), and a stereoisomeric mixture of the dioximes **60** (3.5 g, 7.3 mmol) in 5% aqueous dioxane (200 mL) was stirred at rt for 4 d. The reaction mixture was partitioned between CH_2Cl_2 (150 mL) and 5% sodium hydroxide (150 mL), and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layers were successively treated with 5% NaOH (2 x 50 mL), water (2 x 100 mL), and brine, dried (Na_2SO_4), and concentrated in vacuo to give 2.06 g of a slightly yellow solid, most of which dissolved on treatment with acetone (70 mL). The acetone solution was concentrated in vacuo to give 1.89 g of **61** as a slightly yellow solid (48%). Recrystallization from acetone/water gave crystalline needles of **61**: mp 154-156 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 6H), 3.89 (d, J = 11.5 Hz, 4H), 4.00 (d, J = 11.5 Hz, 4H), 7.40 (d, J = 8.3 Hz, 4H), 7.70 (d, J = 8.3 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.7, 55.1, 94.0, 127.5, 130.4, 131.8, 145.5. HRMS (FAB) calcd for $C_{20}H_{23}N_4S_2O_8$ (MH)+ 511.0957; found *m/z*, 511.0955.

N,N'-Bis(4-methylbenzenesulfonyl)-1,5-dinitro-3,7-diazabicyclo[3.3.0]octane (61) by *m*-CPBA Oxidation of 60. A mixture of urea (0.02 g, 0.3 mmol), disodium hydrogen phosphate (0.8 g, 5.6 mmol), and the dioxime **60** (0.240 g, 0.5 mmol) in anhydrous acetonitrile (5.0 mL) was stirred at reflux for 10 min, and then *m*-chloroperbenzoic acid (0.3 g, 1.8 mmol) was slowly added over 1 h. The suspension was heated under reflux for 2 h and concentrated at reduced pressure, and the residue was extracted with CH_2Cl_2 (3 x

20 mL). The combined extracts were washed with a saturated sodium bicarbonate solution (4 x 15 mL), water (4 x 15 mL), and brine (2 x 30 mL), dried (Na_2SO_4), and concentrated to give compound **61** (0.064 g, 24%). The properties of **61** obtained in this experiment were identical with those exhibited by compound **61** isolated from the NBS oxidation of **60**.

1,3,5,7-Tetranitro-3,7-diazabicyclo[3.3.0]octane (62) by Nitrolysis of 61. Over a 2-min period 100% nitric acid (0.9 g, 14.2 mmol) was added to a stirred solution of trifluoroacetic anhydride (2.9 g, 14.1 mmol) in CH_2Cl_2 (10 mL) at -10 °C. To this mixture, maintained at -10 °C, was added a solution of **61** (0.36 g, 0.7 mmol) in CH_2Cl_2 (4 mL) was added over 0.5 h, and stirring was continued for 2.5 h. The reaction mixture was poured into ice-water (35 g) and extracted with CH_2Cl_2 (35 mL). The combined organic layers were washed successively with 5% sodium carbonate (50 mL) and water (50 mL), dried (Na_2SO_4), and evaporated to give a crude yellowish product (0.26 g) which was chromatographed on silica gel and eluted with acetone-hexane to give 0.06 g of **62** (36%), as colorless crystals: mp 222-224 °C; ^{1}H NMR (acetone-d_6) δ 5.14 (d, J = 13.9 Hz, 4H), 4.99 (d, J = 13.9 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 56.6, 94.0.

1,3,5,7-Tetranitro-3,7-diazabicyclo[3.3.0]octane (62) from the Nitrolysis of N,N'-Bis(4-methylbenzenesulfonyl)tetrahydro-1,5-diazocine-3,7-dione Dioxime (60). A solution of 98% nitric acid (5 mL) in CH_2Cl_2 (10 mL) containing catalytic quantities of urea and ammonium nitrate was added to a refluxing solution of dioxime **60** (0.3 g, 0.6 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was heated under reflux for 1 h, initially

developing a blue-green color which changed to dark brown as the reaction progressed. The reaction mixture was cooled to rt and poured over ice, and the organic layer was washed with water (50 mL), saturated sodium bicarbonate solution (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel and eluted with acetone-hexane. The appropriate fractions were combined and recrystallized from acetone-hexane to give **62** (0.045 g, 25%) which was identical in all respects with the material isolated from the reaction of **61** with trifluoroacetyl nitrate. Although no other pure material was isolated, NMR evidence indicated by-products arising from nitration of the aromatic rings.

N,N'-Bis(4-methylbenzenesulfonyl)-3-thia-7,10-diaza[3.3.3]propellane (63). To a solution of **57** (150 mg, 0.25 mmol) in DMSO (15 mL) was added sodium sulfide (100 mg, 0.42 mmol). After heating at 125 °C for 1.5 h, the mixture was cooled to rt and poured into water (45 mL). The aqueous medium was extracted with ethyl acetate (2 x 20 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo, and the resulting residue was recrystallized from acetone/hexanes to give **77** (0.95 g, 80%): mp 195-6 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H), 2.96 (d, J = 9.5 Hz, 4H), 3.01 (d, J = 9.5 Hz, 4H), 2.73 (s, 4H), 7.33 (d, J = 8.0 Hz, 4H), 7.58 (d, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.61, 42.22, 57.15, 65.88, 127.93, 129.93, 131.10, 144.34; HRMS (FAB) calcd for $C_{22}H_{27}N_2O_4S_3$ $(MH)^+$ 479.1133; found *m/z*, 479.1119. Anal. Calcd for $C_{22}H_{26}N_2O_4S_3$: C, 55.21; H, 5.47; N, 5.85. Found: C, 55.37; H, 5.29, N, 6.14.

N,N'-Bis(4-methylbenzenesulfonyl)-3-oxa-7,10-diaza[3.3.3]propellane (64). To a solution of **57** (0.20 g, 0.33 mmol) in anhydrous DMSO (15 mL) was added anhydrous sodium oxide (0.021 g, 3.3 mmol). The reaction mixture was heated for 20 h at 120 °C under N_2. The solvent was removed under vacuum and the residue taken up in water (30 mL) which was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with water (2 x 25 mL) and dried (Na_2SO_4), and the solvent was removed under vacuum. After triturating the residue with cold ethyl acetate, **64** was obtained as a colorless solid (0.114 g, 75%): mp 212-216 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H), 2.95 (d, J = 9.5 Hz, 4H), 3.01 (d, 9.5 Hz, 4H), 3.62 (2H), 7.33 (d, J = 8.0 Hz, 4H), 7.59 (d, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.62, 56.03, 63.53, 76.19, 127.95, 129.99, 131.05, 144.45; HRMS (FAB) calcd for $C_{22}H_{27}N_2O_5S_2$ $(MH)^+$ 463.1361, found *m/z*, 463.1349. Anal. Calcd for $C_{22}H_{26}N_2O_5S_2$: C, 57.12; H, 5.67; N, 6.06. Found: C, 56.93; H, 5.89, N, 6.41.

N,N,'N''-Tris(4-methylbenzenesulfonyl)-3,7,10-triaza[3.3.3]propellane (65). *p*-Toluenesulfonamide (0.865 g, 5.05 mmol) was added to a solution of metallic sodium (115 mg, 5.05 mmol) in anhydrous methanol (50 mL), the solvent was removed under vacuum, and the residue was dissolved in DMSO (50 mL). The freshly prepared sodium salt solution was added dropwise to a heated solution of dibromide **57** (1.0 g, 1.65 mmol) in anhydrous DMSO (25 mL) under N_2. After heating the solution for 16 h at 110 °C the solvent was removed and the residue taken up in chloroform (50 mL), washed with water (3 x 50 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo gave pure **65** (0.79 g, 78%): mp 208-210 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 9H), 2.99 (s, 12H), 7.29 (d, J = 8.3

Hz, 6H), 7.51 (d, J = 8.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 21.47, 56.08, 60.73, 127.70, 129.92, 130.85, 144.44; HRMS (FAB) calcd for $C_{29}H_{34}N_3O_6S_3$ $(MH)^+$ 616.1610; found *m/z*, 616.1606. Anal. Calcd for $C_{29}H_{33}N_3O_6S_3$: C, 56.57; H, 5.40; N, 6.82. Found: C, 56.73; H, 5.56, N, 7.05.

Glycerol-1,3-ditosylate (67).

(1). To a stirred heterogeneous mixture of *p*-toluenesulfonyl chloride (2.0 mol) and anhydrous pyridine (1.0 mol) at rt under nitrogen atmosphere was added anhydrous CH_2Cl_2 (350 mL) until a homogeneous mixture was obtained.

(2). To a 2L 3-necked round bottom flask containing glycerol (1.0 mol) was added anhydrous pyridine (1.25 mol) under nitrogen atmosphere. The mixture was stirred until a homogenous viscous mixture was obtained (~1.5 hours). Anhydrous CH_2Cl_2 (500 mL) was added to facilitate stirring. After the mixture was cooled in an ice-salt bath for 1.5 h, the above *p*-toluenesulfonyl chloride solution from (1) was added with a pressure equilibrated dropping funnel at a rate so that that the temperature of the reaction mixture was under 10 °C. The reaction mixture was stirred at 0 °C for 4 h then transferred to a separatory funnel with CH_2Cl_2 (1 L), washed with ice-cold 1.0 M HCl. The organic layer was further washed with water followed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford pure **67** as a gum which on long standing solidified in nearly quantitative yield.

1,3-Diiodo-2-propanol (68). In a 5L 3-necked round bottom flask equipped with a mechanical stirrer, a reflux condenser and an addition funnel was introduced glycerol-

1,3-ditosylate (**67**) (1.0 mol). A solution of NaI (2.1 mol) in anhydrous acetone (600 mL) was added to the flask with stirring via the addition funnel. The reaction mixture was heated at reflux for 2 h. The deep red solution was cooled then filtered. The residue was washed with acetone. The combined acetone solution was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and a saturated solution of sodium thiosulphate. The organic layer was washed with water followed by brine, dried over $MgSO_4$ and concentrated in vacuo to give the light yellow diiodo compound **68** in 60% yield. Compound **68** was stored in the dark at –20 °C to avoid decomposition.

N,N'-Di(tert-butyl)-2-methylene-1,3-diaminopropane (69). To a stirred excess of t-butyl amine (40 mol) maintained at –5°C was added dropwise methallyl dibromide(1 mol). When the reaction was complete the mixture was stirred with a solution of 10% NaOH and the excess unreacted t-butyl amine was removed by distillation. The residue was transferred to a separatory funnel and extracted with ether. The organic layer was washed with water, brine, dried and after removal of the volatile solvent, the light greenish yellow colored diamine (**69**) was obtained in quantitative yield and essentially pure form sufficient for the subsequent steps.

N,N'-Di(tert-butyl)-3-hydroxy-7-methylene-hexahydro-1,5-diazocine (70). By a procedure similar to that of **47a**, compound **71** was obtained as an HI salt. The free amine was obtained after the following basic work-up.

To a stirred mixture of hydrogen iodide salt of diazocine **70** and a 50% (w/v) solution of sodium hydroxide (100 mL) was added ethanol (300 mL) in small portions until the

mixture became homogeneous. The mixture was stirred overnight and the methanol was removed on a rotary evaporator. The slurry was extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, filtered. Removal of the solvent in vacuo provided compound **70** as a gum.^{1}H NMR ($CDCl_3$) δ 1.08(s, 18H), 1.40(s, 1H), 2.70(dd, J_{AB} = 14.3Hz, J = 5.8Hz, 2H), 2.78(dd, J_{AB} = 14.3Hz, J = 3.5Hz, 2H),), 3.35, 3.07(ABq, J_{AB} = 12.5Hz, 4H), 3.44-3.54(m, 1H), 4.95(s, 2H). ^{13}C NMR ($CDCl_3$) δ 27.3, 52.5, 54.9, 56.1, 69.4, 115.5, 151.3. MS (CI/NH_3): *m/z* 255(M+1, 100). HRMS (FAB) calcd for $C_{15}H_{31}N_2O$ $(MH)^+$ 255.2436, found *m/z* 255.2434. The structure of the hydrogen iodide salt of **70** was further confirmed by X-ray crystallographic analysis.

1,5-Diacetyl-3-acetoxy-7-methylene-hexahydro-1,5-diazocine (71). To a solution of **70** (5.00 g, 19.7 mmol) in acetic anhydride (25mL) was added boron trifluoride etherate (5 mL). The resulting solution was refluxed for 2 days, then additional boron trifluoride etherate (1 mL) was added and the reaction mixture was refluxed for another day. The reaction mixture was cooled to room temperature and vacuum distilled. The dark residue was dissolved in 300 mL chloroform, washed with $NaHCO_3$ (aqueous) and dried over $MgSO_4$. Removal of the solvent in vacuo gave a dark tar, which was chromatographed through a short column of silica gel, and eluted successively with chloroform, ethyl acetate and acetone to give the crude product as a brown oil. Then the brown oil was extracted with hot ethyl acetate/hexane (1:3) to give a straw yellow oil (1.02 g, 19.3%) that solidified on standing at room temperature. Recrystallization from ethyl acetate/hexane gave the pure product **71** as colorless crystals: mp 100.8 - 101.2 °C. ^{1}H NMR ($CDCl_3$) δ 2.01(s, 3H), 2.05(s, 3H), 2.15(s, 3H), 3.02(dd, J_{AB} = 13.3Hz, J =

10.1Hz, 1H), 3.10(dd, J_{AB} = 14.7Hz, J = 10.1Hz, 1H), 3.49(d, J_{AB} = 14.7Hz, 1H), 3.75(dd, J_{AB} = 14.7Hz, J = 3.7Hz, 1H), 3.76(d, J_{AB} = 13.7Hz, 1H), 3.89(dd, J_{AB} = 13.3Hz, J = 4.5Hz, 1H), 4.22(d, J_{AB} = 13.7Hz, 1H), 4.88(d, J_{AB} = 14.7Hz, 1H), 5.26(m, 1H), 5.28(s, 1H), 5.32(s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 21.8, 47.1, 49.4, 51.7, 55.7, 66.4, 122.0, 141.3, 169.7, 170.8, 171.5. MS (CI/NH_3): *m/z* 269(M+1, 100). HRMS (FAB) *m/z* 269.1490(M+1), Calcd for $C_{13}H_{21}N_2O_4$ 269.1501. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.89; H, 7.44; N, 10.35. The structure of compound **71** was further confirmed by X-ray crystallographic analysis.

1,5-Diacetyl-3-acetoxy-7-oxo-hexahydro-1,5-diazocine (72). A mixture of O_3 in O_2 was bubbled through a stirred solution of **71** (3.98 g, 14.9 mmol) in CH_2Cl_2 (100 mL) at –78°C until a blue color persisted. The mixture was stirred for another half an hour. Then O_2 was bubbled through to remove the excess O_3. Excess Me_2S was added and the mixture was allowed to warm to room temperature. After stirring overnight, the mixture was washed with brine, dried over $MgSO_4$ and concentrated. The residue was extracted with hot ethyl acetate/hexane (1:3) to give a light yellow oil **72** (2.34 g, 58.4%). ^{1}H NMR ($CDCl_3$) δ 2.08(s, 1H), 2.09(s, 1H), 2.24(s, 1H), 3.37(dd, J_{AB} = 14.3Hz, J = 8.0Hz, 1H), 3.56(dd, J_{AB} = 14.3Hz, J = 5.6Hz, 1H), 3.6~4.3(m, 6H), 5.40(m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.7, 21.2, 21.7, 50.1, 52.7, 57.0, 59.4, 68.8, 169.4, 171.3, 172.0, 203.7. MS (CI/NH_3): *m/z* 271(M+1, 8%), 288(M+NH_4^+, 100). HRMS (FAB) *m/z* 271.1288(M+1), Calcd for $C_{12}H_{19}N_2O_5$ 271.1294.

1,5-Diacetyl-3-acetoxy-7-hydroxyimino-hexahydro-1,5-diazocine (73). A suspension of **72** (311 mg, 1.15 mmol), hydroxylamine hydrochloride (160 mg, 2.30 mmol) and NaOAc (378 mg, 4.61 mmol) in MeOH (20 mL) was heated under reflux with stirring overnight. The solvent was removed on a rotary evaporator and the residue was extracted with hot CH_2Cl_2 (5×10 mL). The combined CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a colorless semi-solid (304 mg, 92.6%) comprised of geometric isomers. Recrystallization from EtOAc/EtOH gave colorless crystals (**73**): mp 119.6~121.5 °C. ^{1}H NMR ($CDCl_3$) δ 1.95~2.20(m, 9H), 3.0~4.6(m, 9H), 4.96, 5.15, 5.24(m, 1H). ^{13}C NMR (DMSO) δ 20.7, 21.1, 21.3, 21.4, 21.6, 21.7, 43.9, 45.8, 46.5, 47.9, 48.3, 48.6, 49.7, 50.3, 51.1, 52.0, 52.6, 67.2, 68.3, 152.0, 153.0, 153.2, 153.5, 169.2, 169.3, 169.5, 170.6, 170.7, 170.9. MS (CI/NH_3): *m/z* 286(M+1, 20%), 303($M+NH_4^+$, 100). HRMS (FAB) *m/z* 286.1405(M+1), Calcd for $C_{12}H_{20}N_3O_5$ 286.1403.

3,7-Diacetyl-5-nitro-9-oxa-3,7-diazabicyclo[3.3.1]nonane (75).

Method A: A mixture of **73**. (55 mg, 0.19 mmol), NBS (178 mg, 1.00 mmol) and $NaHCO_3$ (191 mg, 2.27 mmol) in 5% aqueous dioxane (10 mL) was stirred at room temperature for 3 days. NaOH (10 mg) was added and the mixture was stirred at room temperature for half an hour. The reaction mixture was extracted with CH_2Cl_2 (4×5 mL), and the combined organic layer was washed with 10% NaOH (2×2 mL), water and dried over $MgSO_4$. Removal of the solvent in vacuo gave a light yellow oil, which was chromatographed through a short column of silica gel which was eluted successively with chloroform, ethyl acetate and acetone. Concentration in vacuo gave a colorless oil (20 mg, 40%) which solidified on standing. Recrystallization from EtOAc/Cyclohexane gave

colorless crystals (**75**): mp 156.5 - 157.1 °C. ^{1}H NMR ($CDCl_3$) δ 2.03(s, 1H), 2.07(s, 1H), 2.97(dd, J_{AB} = 13.3Hz, J = 2.8Hz, 1H), 3.08(ddd, J_{AB} = 14.2Hz, J = 3.9Hz, J = 2.2Hz, 1H), 3.51(dd, J_{AB} = 12.8Hz, J = 2.8Hz, 1H), 3.64(ddd, J_{AB} = 13.7Hz, J = 3.7Hz, J = 2.3Hz, 1H), 3.80(d, J_{AB} = 13.7Hz, 1H), 4.36(t, J = 3.7Hz), 4.44(dd, J_{AB} = 12.8Hz, J = 0.9Hz, 1H), 4.70(d, J_{AB} = 14.2Hz, 1H), 5.31(dd, J_{AB} = 13.3Hz, J = 0.9Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 20.0, 41.6, 45.6, 46.8, 50.5, 69.8, 98.7, 168.9. MS (CI/NH_3): *m/z* 275($M+NH_4^+$, 100%). HRMS (FAB) *m/z* 258.1089(M+1), Calcd for $C_{10}H_{16}N_3O_5$ 258.1090.

Method B: To a refluxing mixture of **73**. (30 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) was added a solution of 100% nitric acid (1 mL), NH_4NO_3 (10 mg, 0.13 mmol) and urea (10 mg, 0.17 mmol) in CH_2Cl_2 (3 mL). After refluxing for 2 h, the reaction mixture was cooled and washed with ice-water, $NaHCO_3$ (aqueous) and dried over $MgSO_4$. Removal of the solvent gave a yellow oil (8 mg) which contains the product **75.**

Method C: To a magnetically stirred suspension of **73**. (30 mg, 0.11 mmol), urea (50 mg, 0.85 mmol) and Na_2HPO_4 (200 mg, 1.40 mmol) in refluxing acetonitrile (10 mL) was added *m*-CPBA (110 mg, 0.3 mmol). The reaction mixture was allowed to reflux overnight and freed of solvent in vacuo. The residue was taken up in CH_2Cl_2 (6×10 mL), and the combined organic phase were washed successively with $NaHSO_3$ (aqueous), $NaHCO_3$ (aqueous), water and dried over $MgSO_4$. Removal of the solvent on a rotary evaporator gave a light yellow oil (19 mg) which NMR analysis showed to contain the product **75**.

1,5-Diacetyl-3-acetoxy-7-(1,3-dioxolan-2-yl)octahydro-1,5-diazocine (76). A mixture of **72** (2.67 g, 9.89 mmol), ethylene glycol (1.65 mL, 29.6 mmol), *p*-toluenesulfonic acid monohydrate (~90 mg) in benzene (100 mL) was heated under reflux using a Dean-Stark apparatus for 2 days. After cooling to room temperature, the reaction mixture was washed with $NaHCO_3$ (aqueous), H_2O and dried over $MgSO_4$. Removal of benzene in vacuo gave the product **76** as a light yellow oil (2.15 g, 69.2 %) which solidified on standing. ^1H NMR ($CDCl_3$) δ 2.09(s, 3H), 2.15(s, 3H), 2.20(s, 3H), 3.3~3.5(m, 4H), 3.6~3.8(m, 2H), 3.9~4.0(m, 4H), 4.1~4.2(m, 2H), 5.26(m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 21.7, 22.0, 49.4, 52.2, 52.4, 58.1, 65.0, 65.6, 69.1, 107.1, 169.9, 172.1, 172.4. MS (CI/NH_3): *m/z* 315(M+1, 49%), 332($M+NH_4^+$, 100%). HRMS (CI/CH_4) *m/z* 315.1554(M+1), Calcd for $C_{14}H_{23}N_2O_6$ 315.1556.

1,5-Diacetyl-3-hydroxy-7-(1,3-dioxolan-2-yl)octahydro-1,5-diazocine (77).

Method A: A mixture of **76** (1.98 g, 6.31 mmol), K_2CO_3 (1.75 g, 12.7 mmol) and H_2O (10 mL) in MeOH (60 mL) was stirred at room temperature for 2 days. After removal of most of the solvent, the residue was extracted with $CHCl_3$. The combined organic phase was washed with water and dried over $MgSO_4$. Concentration in vacuo gave a colorless oil (1.47 g, 85.6%) which solidified on standing. The ^1H and ^{13}C spectra indicate the product to be a mixture of two isomers. Recrystallization from EtOAc/Cyclohexane gave colorless crystals of **77**: mp 130.3~131.5 °C. ^1H NMR ($CDCl_3$) δ 2.09, 2.12, 2.14(s, 6H), 2.8~4.3(m, 13H), 5.43, 5.20(d, J = 8.2Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 21.6, 21.8, 51.8, 52.4, 53.0, 54.3, 57.4, 58.6, 64.5, 64.7, 65.0, 66.0, 67.0, 68.4, 107.1, 108.4, 172.0, 173.4,

174.5. MS (CI/NH_3): *m/z* 273(M+1, 100%), 290(M+NH_4^+). HRMS (FAB) *m/z* 273.1441 (M+1), Calcd for $C_{12}H_{21}N_2O_5$ 273.1450.

Method B: A mixture of **76** (50 mg, 0.16 mmol), NaOH (15 mg, 0.38 mmol) and H_2O (1 mL) in MeOH (9 mL) was stirred at room temperature for 1 day. After removal of most of the solvent, the residue was extracted with $CHCl_3$. The combined organic phase was washed with water and dried over $MgSO_4$. Concentration in vacuo gave **77** (41 mg, 95%) as a colorless oil which solidified on standing.

1,5-Diacetyl-3-oxo-7-(1,3-dioxolan-2-yl)hexahydro-1,5-diazocine (78).

Method A: A solution of **77**. (1.19 g, 4.38 mmol) in acetone (60 mL) was cooled to ~0°C. To this magnetically stirred solution was added dropwise the standard Jones Reagent (7.5 mL). After stirring for 4 hrs, excess isopropyl alcohol was added dropwise to destroy excess Jones Reagent. The reaction mixture was then extracted with $CHCl_3$, and the combined organic phase was washed successively with H_2O, $NaHCO_3$ (aqueous) and dried over $MgSO_4$. Removal of the solvent on a rotary evaporator gave **78** (810 mg, 68.6%) as a colorless oil which solidified on standing. ^1H NMR ($CDCl_3$) δ 2.11(s, 3H), 2.23(s, 3H), 3.65(s, 2H), 3.72(s, 2H), 3.94(s, 2H), 4.15(s, 2H), 3.9~4.2(m, 4H). ^{13}C NMR ($CDCl_3$) δ 21.6, 22.0, 51.9, 54.6, 56.9, 57.7, 65.4, 107.0, 171.7, 171.9, 203.9. MS (CI/NH_3): *m/z* 271(M+1, 100%). HRMS (FAB) *m/z* 271.1323(M+1), Calcd for $C_{12}H_{19}N_2O_5$ 271.1294.

Method B: A solution of **77** (49 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added to a suspension of pyridinium chlorochromate (78 mg, 0.36 mmol) in CH_2Cl_2 (5 mL). The mixture was heated under reflux with stirring for 12 hrs. After cooling to room temperature, ether was added and the supernatant liquid was decanted from a black gum. The black gum was extracted with hot ether. The combined organic solution was then passed through a short column of Florisil. Removal of the solvent in vacuo gave the product **78** as a colorless oil (35 mg, 72%).

Method C: A solution of **77** (49 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added to a suspension of pyridinium dichromate (300 mg, 0.80 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 2 days. Then ether was added and the supernatant liquid was decanted from a black gum. The black gum was extracted with hot ether. The combined organic solution was then passed through a short column of Florisil. Removal of the solvent in vacuo gave the product **78** (22 mg, 46%) as a colorless oil.

1,5-Diacetyl-3-(1,3-dioxolan-2-yl)-7-hydroxyimino-hexahydro-1,5-diazocine (79). A suspension of **78** (859 mg, 3.18 mmol), hydroxylamine hydrochloride (442 mg, 6.35 mmol) and $NaHCO_3$ (535 mg, 6.37 mmol) in MeOH (40 mL) was heated under reflux with stirring for 3 days. The solvent was removed on a rotary evaporator and the residue was extracted with hot $CHCl_3$. The combined $CHCl_3$ layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a colorless solid (875 mg, 96.5%) comprised of geometric isomers. Recrystallization from EtOAc/EtOH gave colorless crystals of oxime **79**, mp 166.8~168.3°C. ^1H NMR (DMSO-d_6) δ 1.90, 2.01, 2.07, 2.10,

2.13(s, 6H), 3.43~3.58(m, 4H), 3.72~4.33(m, 8H), 11.01, 11.16, 11.35(s, 1H). ^{13}C NMR (DMSO-d_6) δ 21.1, 21.5, 21.6, 21.8, 21.9, 22.0, 43.7, 44.2, 44.6, 44.7, 48.0, 49.9, 50.1, 50.3, 50.9, 51.9, 54.2, 55.1, 55.5, 56.8, 64.5, 64.7, 107.0, 107.2, 107.6, 152.8, 153.7, 154.3, 154.8, 170.6, 170.8, 170.9, 171.0, 171.1. MS (Negative CI/NH_3): *m/z* 284[(M-1)$^-$, 100%].

1,5-Diacetyl-3-(1,3-dioxolan-2-yl)-7,7-dinitro-octaahydro-1,5-diazocine (80). To a refluxing suspension of oxime **79** (558 mg, 1.96 mmol) in CH_2Cl_2 (25 mL) was added a solution of 100% HNO_3 (7.5 mL), NH_4NO_3 (50 mg, 0.63 mmol) and urea (50 mg, 0.83 mmol) in CH_2Cl_2 (25 mL). A transient deep green color faded quickly. After refluxing for 1 h, the reaction mixture was cooled and washed successively with ice-water, $NaHCO_3$ (aqueous) and dried over $MgSO_4$. Removal of the solvent in vacuo gave the crude product as colorless crystals (245 mg, 36.2%). Recrystallization from $CHCl_3$ gave colorless crystals of the gem dinitro dioxolane **80**, mp 200.0~200.9 °C (dec.). ^{1}H NMR ($CDCl_3$) δ 2.17(s, 6H), 3.57(s, 4H), 4.06(s, 4H), 4.55(s, 4H). ^{13}C NMR (acetone-d_6) δ 22.0, 51.5, 57.7, 65.8, 109.1, 118.4, 174.4. MS (CI/CH_4): *m/z* 347(M+1, 37%), 284(100). HRMS (FAB) *m/z* 347.1197(M+1), calcd for $C_{12}H_{19}N_4O_8$ 347.1203. The structure of compound **80** was further confirmed by X-ray crystallographic analysis.

1,5-Diacetyl-3-(1,3-dioxolan-2-yl)-7-bromo-7-nitro-octaahydro-1,5-diazocine (81). A mixture of oxime **79** (37 mg, 0.13 mmol), NBS (180 mg, 1.02 mmol) and $NaHCO_3$ (180 mg, 2.14 mmol) in 5% aqueous dioxane (6 mL) was stirred at room temperature for 3 days. NaOH (10 mg) was added and the mixture was stirred at room temperature for half

an hour. The reaction mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with 10% NaOH (2×2 mL), water and dried over $MgSO_4$. Concentration in vacuo gave **81** (10 mg, 20%) as a light yellow oil. MS (CI/NH_3): *m/z* 397, 399($M+NH_4^+$, 48), 332(66), 319(100), 288(74), 273(82).

N,N'-Bis(4-nitrobenezenesulfonyl)-1,3-diaminopropan-2-ol (85a). To a stirred solution of 1,3-diamino-2-propanol (**84**) (5.30 g, 58.8 mmol) and potassium carbonate (21.54 g, 155.8 mmol) in water (100 mL) maintained at 0 °C was added *p*-nosyl chloride (29.27 g, 132.1 mmol) in THF (60 mL) dropwise. Upon completion of the addition, the reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure to remove THF. The solid was filtered. After washing with water, methylene chloride and drying, compound **85a** was obtained as a pale yellow solid (25.57 g, 95%); **85a** was chromatographed on silica gel and eluted with ethyl acetate/hexanes (1:1). Removal of the solvent and recrystallization from acetone and hexanes gave the product (**85a**) as colorless crystalline material: mp 210-212 °C (sub.). ^{1}H NMR (acetone-d_6) δ 2.96 (m, 2H), 3.11 (m, 2H), 3.78 (m, 1H), 4.40 (d, J = 5.49Hz, 1H), 6.89 (t, 2H), 8.11 (d, J = 9.16Hz, 4H), 8.42 (d, J = 9.15, 4H). ^{13}C NMR (acetone-d_6) δ 47.4, 69.8, 125.2, 129.2, 147.5, 151.0. MS (CI/NH_3): *m/z* 478 ($M+1+NH_3$,100). Anal. Calcd for $C_{15}H_{16}N_4O_9S_2$: C, 39.13; H, 3.50; N, 12.17. Found: C, 39.46; H, 3.55; N, 11.86.

N,N'-Bis(2-nitrobenezenesulfonyl)-1,3-diaminopropan-2-ol (85b). To a stirred solution of 1,3-diamino-2-propanol (**84**) (2.38 g, 26.4 mmol) and potassium carbonate (9.35 g, 67.7 mmol) in water (100 mL) maintained at 0 °C was added *o*-nosyl chloride

(11.71 g, 52.8 mmol) in THF (50 mL) dropwise. Upon completion of the addition, the reaction mixture was stirred at room temperature overnight. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x50 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$. Removal of the solvent gave **85b** as a pale yellow solid (9.67 g, 80%). Recrystallization from ethyl acetate and hexanes afforded a colorless solid: mp 134-136 °C. ^{1}H NMR (acetone-d_6) δ 3.08 (m, 2H), 3.26 (m, 2H), 3.89 (m, 1H), 4.56 (d, J = 5.49Hz, 1H), 6.56 (t, 2H), 7.92 (m, 6H), 8.09 (m, 2H). ^{13}C NMR (acetone-d_6) δ 47.6, 69.6, 125.9, 131.5, 133.6, 134.2, 134.9, 149.2. MS (CI/NH_3): *m/z* 478 (M+1+NH_3, 100). Anal. Calcd for $C_{15}H_{16}N_4O_9S_2$: C, 39.13; H, 3.50; N, 12.17. Found: C, 38.99; H, 3.49; N, 11.80.

N,N'-Bis(4-nitrobenezenesulfonyl)-1,3-diaminopropan-2-one (86a). To a stirred solution of **85a** (10.28 g, 22.35 mmol) in acetone (300 mL) maintained at 0 °C was added dropwise a mixture of CrO_3 (5.82 g, 58.2 mmol) in water (15 mL) containing concentrated sulfuric acid (6 mL). After the addition was complete, the reaction mixture was stirred vigorously at room temperature overnight and poured into ice-water. The resulting solid was filtered, washed with water and dried. Compound **86a** was obtained as a colorless solid (9.31 g, 91%), which was recrystallized from acetone and hexanes to give a colorless crystalline product: mp 212 °C (dec.). ^{1}H NMR (acetone-d_6) δ 4.12 (d, J = 5.50Hz, 4H), 7.19(t, 2H), 8.09 (d, J = 9.16Hz, 4H), 8.39 (d, J = 9.15Hz, 4H). ^{13}C NMR (DMSO-d_6) δ 49.1, 124.3, 127.9, 146.1, 149.4, 199.9. MS (CI/NH_3): *m/z* 476 (M+1+NH_3,100). Anal. Calcd for $C_{15}H_{14}N_4O_9S_2$: C, 39.30; H, 3.08; N, 12.22. Found: C, 39.23; H, 3.03; N, 11.79.

N,N'-Bis(2-nitrobenezenesulfonyl)-1,3-diaminopropan-2-one (86b). To a stirred solution of **85b** (0.48 g, 1.04 mmol) in acetone (20 mL) maintained at 0 °C was added dropwise a mixture of CrO_3 (0.30 g, 3.0 mmol) in water (0.63 g) containing concentrated sulfuric acid (0.63 g). After the addition was complete, the reaction mixture was stirred vigorously at room temperature overnight and poured into ice-water. The resulting solid was filtered, washed with water and dried. Compound **86b** was obtained as a colorless solid (0.43g, 90%), which was recrystallized from acetone and water to give a colorless crystalline product: mp 165 °C (dec.). ^{1}H NMR (acetone-d_6) δ 4.23 (d, J = 4.58Hz, 4H), 6.90(t, 2H), 7.82-8.05 (m, 8H). ^{13}C NMR (DMSO-d_6) δ 49.3, 124.3, 129.5, 132.5, 133.0, 133.9, 147.2, 200.1. MS (CI/NH_3): *m/z* 476 (M+1+NH_3, 100). Anal. Calcd for $C_{15}H_{14}N_4O_9S_2$: C, 39.30; H, 3.08; N, 12.22. Found: C, 39.25; H, 3.30; N, 12.14.

N,N'-Bis(4-nitrobenezenesulfonyl)-2-(1,3-dioxolan-2-yl)-1,3-diaminopropane (87a). A mixture of ketone **86a** (12.29 g, 26.83 mmol), ethylene glycol (6.06 g, 97.63 mmol), and *p*-toluenesulfonic acid monohydrate (~0.5 g) in toluene (200 mL) was heated under reflux for 3 days using a Dean-Stark apparatus to remove water. After cooling, the solid was filtered, washed with water and methylene chloride. Compound **87a** was obtained as a light gray solid (12.12 g, 90%) that was recrystallized from DMF and water to give a colorless crystalline product: mp 237 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 2.99 (d, J = 6.41Hz, 4H), 3.59 (s, 4H), 7.99 (d, J = 9.15Hz, 4H), 8.13 (t, 2H), 8.37 (d, J = 8.84Hz, 4H). ^{13}C NMR (DMSO-d_6) δ 45.9, 65.0, 106.7, 124.2, 127.8, 146.7, 149.3. MS (CI/NH_3):

m/z 520 (M+1+NH_3,100). Anal. Calcd for $C_{17}H_{18}N_4O_{10}S_2$: C, 40.64; H, 3.61; N, 11.15. Found: C, 40.63; H, 3.44; N, 11.11.

N,N'-Bis(2-nitrobenezenesulfonyl)-2-(1,3-dioxolan-2-yl)-1,3-diaminopropane (87b). A mixture of ketone **86b** (3.30 g, 7.21 mmol), ethylene glycol (1.50g, 24.17 mmol) and *p*-toluenesulfonic acid monohydrate (~0.5 g) in benzene (150 mL) was heated under reflux for 3 days using a Dean-Stark apparatus to remove water. After cooling, the solvent was removed and the residue was recrystallized from DMF and water. Compound **87b** was obtained as colorless crystals (3.20 g, 89%): mp 195-197 °C. ^{1}H NMR (acetone-d_6) δ 3.35 (d, J = 6.41Hz, 4H), 3.69 (s, 4H), 6.56 (t, 2H), 7.90 (m, 6H), 8.05 (m, 2H). ^{13}C NMR (acetone-d_6) δ 47.2, 66.2, 108.3, 125.7, 131.5, 133.5, 134.7, 135.1. HRMS (FAB): Calc for $C_{17}H_{19}N_4O_{10}S_2$ (MH^+) 503.0543, Found *m/z* 503.0546. Anal. Calcd for: $C_{17}H_{18}N_4O_{10}S_2$ C, 40.64; H, 3.61; N, 11.15. Found: C, 40.67; H, 3. 63; N, 11.00.

N,N'-Bis(4-nitrobenezenesulfonyl)-3-methylene-7-(1,3-dioxolan-2-yl)hexahydro-1,5-diazocine (88a). To a refluxing solution of **87a** (1.01 g, 2.01 mmol), potassium carbonate (0.72 g, 5.21 mmol) in acetone (50 mL) was added dropwise a solution of 3-bromo-2-bromomethyl-propene (0.46 g, 2.15 mmol) in acetone (20 mL) in 1 h. The resulting mixture was heated with stirring under reflux overnight and the acetone was evaporated. After the residue was washed with water and dried, a yellow solid was obtained which was recrystallized from acetone and hexanes to give **88a** as colorless crystals (0.85 g, 76%): mp 199-201 °C. ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 4H), 3.81 (s, 4H), 4.06 (s, 4H), 5.22 (s, 2H), 8.04 (d, J = 9.16Hz, 4H), 8.38 (d, J = 9.16Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 53.1,

54.0, 65.3, 106.6, 120.9, 124.4, 128.8, 140.0, 144.3, 150.3. MS (CI/NH_3): *m/z* 572 (M+1+NH_3,100). Anal. Calcd for $C_{21}H_{22}N_4O_{10}S_2$: C, 45.48; H, 4.00; N, 10.10; S, 11.56. Found: C, 45.57; H, 4.02; N, 9.65; S, 11.31.

N,N'-Bis(2-nitrobenezenesulfonyl)-3-methylene-7-(1,3-dioxolan-2-yl)hexahydro-1,5-diazocine (88b). To a refluxing solution of **87b** (0.54 g, 1.08 mmol), potassium carbonate (0.43 g, 3.11 mmol) in acetone (50 mL) was added dropwise a solution of 3-bromo-2-bromomethyl-1-propene (0.23 g, 1.07 mmol) in acetone (30 mL) in 1 h. The resulting mixture was heated with stirring under reflux overnight and the acetone was evaporated. The residue was dissolved in methylene chloride, washed with water and dried over $MgSO_4$. Removal of the solvent gave a pale yellow solid (0.51 g, 86%). The crude product was purified by passing through silica gel and eluting with ethyl acetate and hexanes. The resulting solid was recrystallized from ethyl acetate and hexanes affording colorless crystalline **88b**: mp 150-151 °C. ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 4H), 4.01 (s, 8H), 5.26 (s, 2H), 7.70 (m, 6H), 8.02 (m, 2H). ^{13}C NMR (acetone-d_6) δ 53.7, 55.0, 65.9, 107.9, 119.2, 125.1, 131.8, 132.6, 133.0, 135.3, 142.4, 149.5. HRMS (FAB): Calc for $C_{21}H_{23}N_4O_{10}S_2$ (MH^+) 555.0856, Found *m/z* 555.0860.

N,N'-Bis(4-nitrobenezenesulfonyl)-3-oxo-7-(1,3-dioxolan-2-yl)hexahydro-1,5-diazocine (89a). A mixture of ozone in oxygen was bubbled into a stirred solution of **88a** (0.98 g, 1.77 mmol) in methylene chloride (100 mL) at –78 °C until the solution turned blue, then oxygen was continued to bubble into it to remove excess ozone. To the solution was added excess of methyl sulfide. Upon completion of the addition, the

mixture was slowly warmed up to room temperature. After stirring for 1 h, solvent was removed under reduced pressure. The residue was washed with water, filtered, washed with water, acetone and dried to afford **89a** as a colorless solid (0.94 g, 95 %): mp 244 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 3.58 (s, 4H), 3.92 (d, J = 2.74Hz, 8H), 8.10 (d, J = 8.24Hz, 4H), 8.39 (d, J = 9.16Hz, 4H). ^{13}C NMR (DMSO-d_6) δ 55.1, 64.8, 106.5, 124.7, 128.7, 142.9, 150.1, 202.3. MS (CI/NH_3): *m/z* 574 (M+1+NH_3,100). Anal. Calcd for $C_{20}H_{20}N_4O_{11}S_2$: C, 43.16; H, 3.62; N, 10.07; S, 11.52. Found: C, 42.95; H, 3.60; N, 9.83; S, 11.43.

N,N'-Bis(2-nitrobenezenesulfonyl)-3-oxo-7-(1,3-dioxolan-2-yl)hexahydro-1,5-diazocine (89b). A mixture of ozone in oxygen was bubbled into a stirred solution of **88b** (3.26 g, 5.88 mmol) in methylene chloride (250 mL) at –78 °C until the solution turned blue, then oxygen was continued to bubble into it to remove excess ozone. To the solution was added excess of methyl sulfide. Upon completion of the addition, the mixture was slowly warmed up to room temperature. After stirring for 1 h, solvent was removed under reduced pressure and **89b** was obtained as a colorless solid (3.20 g, 98%). Recrystallization from methylene chloride and hexanes gave a colorless crystalline solid: mp 219 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 3.67 (s, 4H), 3.94 (s, 4H), 4.06 (s, 4H), 7.90 (m, 4H), 8.04 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 55.0, 55.3, 65.0, 106.2, 124.7, 130.0, 132.8, 135.0, 147.7, 201.9. HRMS (FAB): Calc for $C_{20}H_{21}N_4O_{11}S_2$. (MH^+) 557.0648, Found *m/z* 557.0652.

N,N'-Bis(4-nitrobenezenesulfonyl)-3-hydroxyimino-7-(1,3-dioxolan-2-yl)hexahydro-1,5-diazocine (90a). A mixture of **89a** (4.00 g, 7.19 mmol), sodium acetate (2.75 g, 33.52 mmol) and hydroxylamine hydrochloride (1.02 g, 14.68 mmol) in ethanol (200 mL) was heated with stirring under reflux for 24 h, then cooled to room temperature and poured into ice-water. The precipitate was collected by filtration and dried. A colorless solid was obtained (3.76 g, 91%) which was recrystallized from acetone and hexanes to give **90a** as a colorless crystalline solid: mp 213 °C. ^{1}H NMR (DMSO-d_6) δ 3.30 (s, 2H), 3.58 (s, 2H), 3.83 (s, 2H), 3.84 (s, 2H), 4.01 (s, 2H), 4.07 (s, 2H), 8.08 (dd, J = 9.16Hz, 2.75Hz, 4H), 8.38 (m, 4H),11.3 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 45.0, 50.2, 54.0, 54.3, 64.5, 106.3, 124.3, 124.7, 128.5, 142.8, 144.8, 149.7, 150.0, 152.1. MS (CI/NH_3): *m/z* 589 (M+1+NH_3,100). Anal. Calcd for $C_{20}H_{21}N_5O_{11}S_2$: C, 42.03; H, 3.70; N, 12.25; S, 11.22. Found: C, 41.97; H, 3.75; N, 12.12; S, 11.35.

N,N'-Bis(2-nitrobenezenesulfonyl)-3-hydroxyimino-7-(1,3-dioxolan-2-yl)hexahydro-1,5-diazocine (90b). A mixture of **89b** (2.14 g, 3.85 mmol), sodium acetate (1.97 g, 24.00 mmol) and hydroxylamine hydrochloride (0.54 g, 7.77 mmol) in ethanol (200 mL) was heated with stirring under reflux for 48 h, then cooled to room temperature and poured into ice-water. The precipitate was collected by filtration and dried. A colorless solid was obtained (2.13 g, 97%) which was recrystallized from acetone and hexanes to give **90b** as a colorless crystalline solid: mp 220 °C (dec.). ^{1}H NMR (acetone-d_6) δ 3.56 (s, 2H), 3.70 (s, 2H), 3.97 (s, 4H), 4.19 (s, 2H), 4.45 (s, 2H), 7.92 (m, 6H), 8.11 (m, 2H), 10.51 (s, 1H). ^{13}C NMR (acetone-d_6) δ 46.1, 51.2, 55.7, 56.7, 66.0, 107.6, 125.2, 125.5, 131.4, 131.6, 132.0, 133.0, 133.2, 135.1, 135.7, 149.4, 154.3. HRMS (FAB): Calc for

$C_{20}H_{22}N_5O_{11}S_2$. (MH^+) 572.0757, Found *m/z* 572.0749. Anal. Calcd for $C_{20}H_{21}N_5O_{11}S_2$: C, 42.03; H, 3.70; N, 12.25; S, 11.22. Found: C, 42.12; H, 3.91; N, 12.17; S, 11.03.

N,N'-Bis(4-nitrobenezenesulfonyl)-3,3-dinitro-7-(1,3-dioxolan-2-yl)octahydro-1,5-diazocine (91a). A suspension of **90a** (1.75 g, 3.06 mmol) in methylene chloride (100 mL) was heated with stirring under reflux and a solution of 100% nitric acid (15 mL), ammonium nitrate (0.32 g, 4.00 mmol) and urea (0.23 g, 3.83 mmol) in methylene chloride (50 mL) was added dropwise in 1 h. Upon completion of the addition, the reaction mixture was heated under reflux for 1.5 h, cooled to 0 °C, and then ice-water (150 mL) was added followed by removal of methylene chloride in a vacuum. The resulting mixture was filtered and a pale yellow solid was obtained. The dried solid was stirred in acetone for 20 min and filtered to give a colorless solid which was identical with compound **89a** (0.83 g, 49%). The filtrate was evaporated and the residue was washed with methylene chloride to give **91a** as a colorless solid (0.64 g, 33%). Recrystallization from acetone and hexanes gave a colorless crystalline solid: mp 258 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 3.45 (s, 4H), 3.93 (s, 4H), 4.58 (s, 4H), 8.09 (d, J = 8.24Hz, 4H), 8.44 (d, J = 9.15Hz, 4H). ^{13}C NMR (DMSO-d_6) δ 50.2, 55.5, 64.9, 105.7, 118.2, 124.8, 129.1, 141.2, 150.5. MS (CI/NH_3): *m/z* 650 (M+1+NH_3,100). Anal. Calcd for $C_{20}H_{20}N_6O_{14}S_2$: C, 37.98; H, 3.19; N, 13.29. Found: C, 38.19; H, 3.15; N, 12.93.

N,N'-Bis(2-nitrobenezenesulfonyl)-3,3-dinitro-7-(1,3-dioxolan-2-yl)octahydro-1,5-diazocine (91b). A suspension of **90b** (0.39 g, 0.68 mmol) in methylene chloride (30 mL) was heated under reflux with stirring and a solution of 100% nitric acid (5 mL),

ammonium nitrate (81 mg, 0.96 mmol) and urea (82 mg, 1.37 mmol) in methylene chloride (15 mL) was added dropwise in 1 h. Upon completion of the addition, the reaction mixture was heated under reflux for 2 h, cooled to room temperature, washed with water, aqueous sodium bicarbonate, brine and dried over $MgSO_4$. Removal of the solvent afforded a colorless solid. The dried solid was stirred in methylene chloride for 20 min and filtered to give **91b** as a colorless solid (0.20 g, 46%). Recrystallization from DMF and water afforded a colorless crystalline solid: mp 245 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 4H), 3.90 (s, 4H), 4.83 (s, 4H), 7.87-8.10 (m, 8H). ^{13}C NMR (DMSO-d_6) δ 50.3, 55.3, 64.9, 105.4, 118.2, 124.8, 128.7, 130.0, 132.9, 135.5, 147.9. MS (CI/NH_3): *m/z* 632 (M+1+NH_3, 15). Anal. Calcd for $C_{20}H_{20}N_6O_{14}S_2$: C, 37.98; H, 3.19; N, 13.29; S, 10.14. Found: C, 37.98; H, 3.11; N, 13.05; S, 10.25. Concentration of the filtrate afforded a colorless solid which was identical with **89b** (0.16 g, 42%).

7,7-Dinitro-1,5-bis(4-nitrobenzenesulfonyl)hexahydro-1,5-diazocine-3-one (92a). A mixture of **91a** (0.64 g, 1.01 mmol) and concentrated sulfuric acid (1 mL) in methylene chloride (20 mL) was stirred at room temperature for 3 days followed by addition of ice-water (50 mL). The resulting mixture was filtered and the solid obtained was washed with water, acetone and dried to afford compound **92a** as a colorless solid (0.55 g, 92%): mp 230 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 4.29 (s, br, 4H), 4.92 (s, br, 4H), 8.14 (d, J = 8.24Hz, 4H), 8.48 (d, J = 8.24Hz, 4H). ^{13}C NMR (DMSO-d_6) δ 54.2, 60.2, 120.3, 125.1, 129.3, 140.4, 150.7, 202.7. MS (CI/NH_3): *m/z* 606 (M+1+NH_3, 25). Anal. Calcd for $C_{18}H_{16}N_6O_{13}S_2$: C, 36.74; H, 2.74; N, 14.28. Found: C, 36.80; H, 2.80; N, 13.80.

7,7-Dinitro-1,5-bis(2-nitrobenzenesulfonyl)hexahydro-1,5-diazocine-3-one (92b). A mixture of **91b** (0.80 g, 1.27 mmol) and concentrated sulfuric acid (1 mL) in methylene chloride (20 mL) was stirred at room temperature for 3 days followed by addition of ice-water (50 mL). The resulting mixture was filtered and the solid obtained was washed with water and dried to afford compound **92b** as a colorless solid (0.65 g, 87%): mp 247 °C (dec.). ^{1}H NMR (acetone-d_6) δ 4.47 (s, 4H), 5.24 (s, 4H), 8.06 (m, 8H). ^{13}C NMR (DMSO-d_6) δ 54.9, 60.2, 120.5, 125.7, 128.1, 129.7, 133.6, 136.1, 148.0, 202.6. MS (CI/NH_3): *m/z* 542 (M^+-NO_2, 100). Anal. Calcd for $C_{18}H_{16}N_6O_{13}S_2$: C, 36.74; H, 2.74; N, 14.28; S, 10.90. Found: C, 37.06; H, 2.62; N, 13.97; S, 10.77.

3,3-Bis(difluoramino)octahydro-7,7-dinitro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine (93a). In a jacketed tube reactor, 2.0 mL of 30% fuming sulfuric acid plus 10 mL of trichlorofluoromethane were cooled to -25 °C, and 2.0 g of difluoramine was condensed into the mixture, which was then warmed to +10 °C. (to melt the acid layer) and recooled to -15 °C. Solid 7,7-dinitro-1,5-bis(4-nitrobenzenesulfonyl)hexahydro-1,5-diazocine-3-one (**92a**, 0.21 g, 0.36 mmol) was added via a solid addition funnel and then washed in with 10 mL trichlorofluoromethane. The mixture was stirred, sealed, at -15 °C for 3 hours and then poured onto ice; the reactor was washed with dichloromethane and then water. The quenched mixture was made alkaline with saturated aqueous sodium bicarbonate to reach a pH of 2, and then extracted with dichloromethane (4x100 mL). The solute was redissolved in hot dichloromethane; chloroform was added; and the mixture was concentrated by rotary evaporation. The precipitate from the dichloromethane-chloroform mixture was removed by filtration and then redissolved in

acetone. The remaining glassware was washed off with acetone, which solution was filtered through a 5 medium-porosity glass frit. Acetone solutions were collected and evaporated to dryness. To the solute was added 25 mL chloroform, 10 mL dichloromethane, and 5 mL acetone, and the mixture was boiled. Dichloromethane was removed by rotary evaporation, and the precipitate was removed by filtration. The collected solid as well as the solid residue stuck to the recrystallization flask were dried in a vacuum desiccator. The product was analyzed by NMR to be an acetone adduct of 3,3-bis(difluoramino)octahydro-7,7-dinitro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine **93a** (0.2358 g); m.p. 208 °C (explodes). ^{1}H NMR (acetone-d_6) δ 2.09 (s), 4.58 (s, br, 4H), 4.76 (s, 4H), 8.31 (d, J = 9.1 Hz, 4H), 8.57 (d, J = 9.1 Hz, 4H). ^{1}H NMR (DMSO-d_6) δ 2.09 (s), 4.47 (s, 4H), 4.59 (s, br, 4H), 8.19 (d, J = 9.0 Hz, 4H), 8.51 (d, J = 9.0 Hz, 4H). ^{13}C NMR (DMSO-d_6) δ (30.7, 49.4, 52.9, 07.8, 118.3. 125.2, 129.9, 140.3, 150.9). ^{19}F NMR (acetone-d_6) δ 29.9.

The acetone solvent adduct was dried in a vacuum oven at 50--55°C for 3 days, producing pure 3,3-bis(difluoramino)octahydro-7,7-dinitro-1,5-bis(4-nitrobenzene-sulfonyl)-1,5-diazocine **93a** (90% yield)). ^{1}H NMR (DMSO-d_6) δ 4.47 (s, 4H), 4.59 (s, br, 4H), 8.18 (d, J = 8.8 Hz, 4H), 8.51 (d, J = 8.9 Hz, 4H). ^{1}H NMR ($CDCl_3$) δ 4.18 (s, br, 4H), 4.54 (s, 4H), 8.01 (d, J = 9.0 Hz, 4H), 8.48 (d, J = 8.9 Hz, 4H). ^{19}F NMR ($CDCl_3$) δ 29.3.

3,3-Bis(difluoramino)octahydro-7,7-dinitro-1,5-bis(2-nitrobenzenesulfonyl)-1,5-diazocine (93b). By a procedure similar to that of **93a**, difluoramination of 0.20 g of 7,7-

dinitro-1,5-bis(2-nitrobenzenesulfonyl)hexahydro-1,5-diazocine-3(2H)-one (**92b**) produced 0.1495 g (65% yield) of pure 3,3-bis(difluoramino)octahydro-7,7-dinitro-1,5-bis(2-nitrobenzenesulfonyl)-1,5-diazocine **93b** after recrystallization from acetone-chloroform, m.p. 225-228 °C (dec.). ^{1}H NMR (acetone-d_6) δ 4.67 (s, br, 4H), 5.02 (s, 4H), 8.01-8.21 (m, 8H). ^{13}C NMR (acetone-d_6) δ 50.6 (quintet, J = 7.0Hz), 53.7, 98.0 (m), 118.9, 126.3, 129.5, 132.4, 134.0, 137.3, 149.6. ^{19}F NMR (acetone-d_6) δ 29.3.

3,3-Bis(difluoramino)octahydro-1,5,7,7-tetranitro-1,5-diazocine (TNFX). To 10 mL of triflic acid was added 1.0 mL of 98-100% nitric acid at ambient temperature, and the mixture was stirred for 1 hour. To this mixture cooled in an ice-water bath was slowly added solid 3,3-bis(difluoramino)octahydro-7,7-dinitro-1,5-bis(4-nitrobenzenesulfonyl)-1,5-diazocine (**93a**, 49.6 mg) via a solid addition funnel. The resulting suspension was warmed to 55 °C in an oil bath. After re-cooling in an ice-water bath, another 1.0 mL portion of nitric acid was added, and the mixture was re-warmed to 55 °C. Another 10 portion of triflic acid was added dropwise, and the mixture was stirred at 55 °C overnight. Additional triflic acid was added dropwise to make a total of 40 mL of solution, and the solution was stored in an oven at 55 °C. After 14 days, one-fourth of the reaction solution was separated, and to this portion was added ~10% by volume of antimony pentafluoride. After two days of storage of this solution at room temperature, most of the triflic acid was vacuum-distilled at 55 °C; the residue was quenched onto ice-water, neutralized to pH 7 with aqueous sodium carbonate and extracted with dichloromethane. Chromatography of the solute (silica gel / chloroform-dichloromethane) separated 3,3-bis(difluoramino)-octahydro-1,5,7,7-tetranitro-1,5-diazocine (**TNFX**) from by-products, and its identity was

confirmed by X-ray crystallography. ^{1}H NMR (acetone-d_6) δ 5.14 (s, br, 4H), 5.50 (s, 4H). ^{19}F NMR (acetone-d_6) δ 29.7.

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