New Approach to High Nitrogen Materials with Dual Use Properties via Tetraaza-Nazarov Cyclization

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ABSTRACT: In this report, we describe the application of an electrocyclization toward the synthesis of a high nitrogen heterocycle. It entails the synthesis of a novel, high nitrogen, 2-3-disubstituted tetrazolium via the tetraaza-Nazarov cyclization (4π electrocyclization) of 3-bromo-1,5-bis(3-nitro-1,2,4-triazole-1H-5-yl)-formazan (BDNF). The cyclization takes place under mild conditions using the hypervalent iodine oxidant phenyliodine(III) diacetate (PIDA). The proposed electrocyclic mechanism is supported by DFT calculations and data from previous studies of formazan cyclizations. This is noteworthy because while 4π electrocyclizations with one or two nitrogen atoms have been documented previously, this case represents the first example of generation and cyclization of a conjugated intermediate with four nitrogen atoms. Experimental behavior of electrocyclization is consistent with predictions of DFT.

Functional organic materials are traditionally based around high-carbon backbones where the heteroatoms make up a small percent of the structure. Due to the carbonaceous backbone in all applications of organic chemistry, the development of C-C and C-Heteroatom bond forming reactions compose a vast percentage of all synthetic chemistry. What is vastly underexplored in comparison is new methods of bond forming reactions between heteroatoms, particularly N-N bonds.

Nitrogen heterocycles with varying nitrogen contents are used in a wide variety of applications from energetic materials[1–7] (propellants, explosives, pyrotechnics) to the pharmaceutical industry.[8–15] Nitrogen heterocycles are one of the most frequently appearing structural motifs in pharmaceuticals[16] and 59% of USA FDA approved drugs contain a nitrogen heterocycle.[17]

The multitude of contributions of nitrogen rich materials to the chemical sciences in very diverse ways has a rich history starting from the foundations of modern chemistry where the concept of isomerism was determined by Liebig and Gay-Lussac upon realizing that non-explosive and explosive silver cyanate and silver fulminate had the same chemical formula.[18–20] In the more modern era, the same high-nitrogen azasydnone heterocycle found in energetic materials[21] is also found in antihypertensive drugs.[15] Furthermore, the same hexaazaisowurtzitane backbone found in the powerful explosive CL-20[22] is now also found in a new non-narcotic analgesic drug.[13] Thus, advances in the chemistry of nitrogen-rich heterocycles can have impacts on diverse fields.

Much attention, including that of our research group, has been devoted to unsaturated, high nitrogen heterocycles given the seemingly limitless structural variants that are attainable. They derive much of their energy from possessing high positive heats of formation, and many analogs have the added advantage of possessing high thermal stability due to their aromatic nature and stabilizing substituents. Recently, Piercey et al. reported the synthesis of novel azasydnones from nitrilimine intermediates as precursors to energetic derivatives (general structures in Figure 1). Also identified in low yields during this work was the ammonium salt of a novel tetrazolium species: ammonium 2,3-bis(3-nitro-1,2,4-triazol-1-ide-5-yl)-5-bromo-2H-tetrazole-3-ium (ammonium BTNT) (Scheme 1). It was thought to form through nitrilimine **3,** which would result from the loss of nitrous acid from **1** (Scheme 1). We sought to better understand the synthesis of BTNT because 2,3-disubstituted tetrazolium salts have could lead to new, high nitrogen materials with

enhanced densities, heats of formation, and oxygen balance.[23,24] Furthermore, tetrazolium salts with this 2,3-disubstitution pattern (Figure 1) are used in cellular biology to measure metabolic activity and cytotoxic effects.[25,26] The reduction of the tetrazolium to its corresponding formazan within the cell involves a detectable change in color and often solubility.[26] Additionally, because of their easily detectable color change in the presence of cellular metabolism, tetrazolium salts are used in meat, dairy, and canning industries to detect the presence of bacteria or other organisms.[24] Consequently, research into new substituted tetrazolium compounds could lead to dual-use materials with tunable properties.

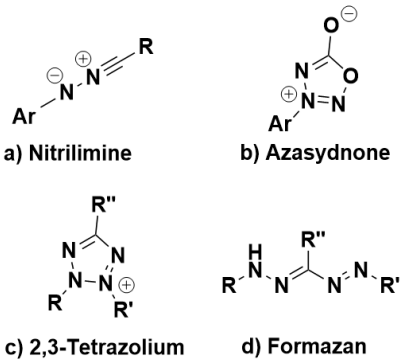
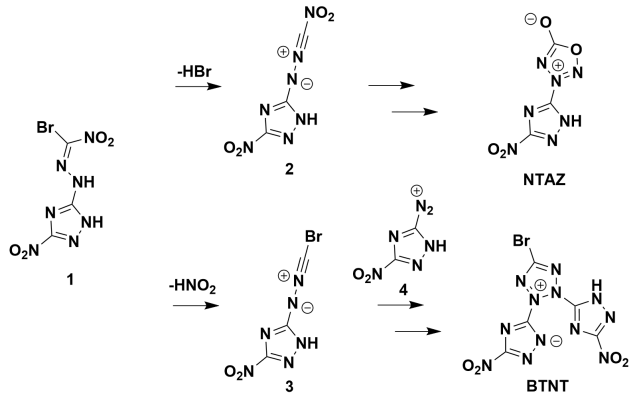


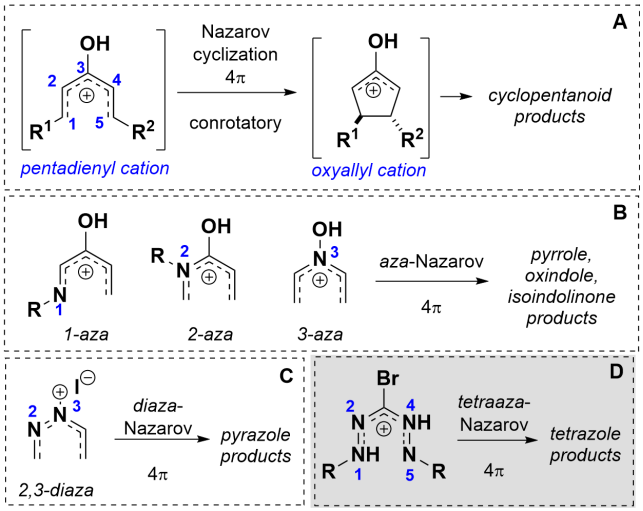
Figure 1. General structure of a) nitrilimine intermediates, b) azasydnones, c) 2,3-tetrazolium salts, and d) formazans.



Scheme 1. Possible nitrilimines and their corresponding final product of either NTAZ or tetrazolium salt BTNT.

In examining the 2,3-tetrazolium core of ammonium BTNT, we noted that it may have formed via a cationic, 4π-electrocyclization pathway generally described as a "Nazarov" cyclization (Scheme 2). We found the literature to be largely devoid of detailed mechanistic investigations pertaining to high nitrogen heterocycles, and importantly, no examples of electrocyclic reactions being purposely used to synthesize them. In 2018 Shreeve et al. reported a few examples of a novel carbon-carbon cleavage process via oxime extrusion, but a mechanistic investigation was not performed.[27] Our research centered on proposing a tetraaa-Nazarov mechanism for this transformation, developing a synthetic process, and then performed DFT calculations that support the electrocyclic pathway hypothesized. While aza-Nazarov cyclizations can deliver heterocycles containing one or two nitrogen atoms, this work represents the first time an electrocyclization has been leveraged to produce a high nitrogen heterocycle. The discovery of this reactivity forges a path into a largely unexplored area, exploring heteroannulative chemistry as it applies to the synthesis of high-nitrogen heterocycles.

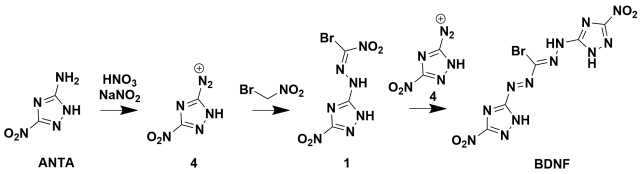
The pericyclic Nazarov cyclization is a cationic pentannulation that occurs stereospecifically, dictated by the rules of orbital symmetry.[28–33] In the usual version of the cyclization, a pentadienyl cation in the ground state cyclizes in a conrotatory fashion, generating an oxyallyl cation enclosed in a five-membered carbocycle (Scheme 2A). Various pathways are available to the oxyallyl cation, such that depending on the reaction design, these reactions can produce different cyclopentanoid products.[34] Pentannulations in which nitrogen atoms are incorporated into the penadienyl system ("aza-Nazarov" cyclizations) have also been reported, but these cases are much less common.[35–37] Examples with one nitrogen atom at position 1,[35,36,38,39] 2,[40–42] and 3[43] of the pentadienyl system have been reported (Scheme 2B), as well as "diaza-Nazarov" cyclizations[44,45] with two nitrogen atoms (Scheme 2C). In this report, we execute oxidation of a formazan to generate a tetrazolium salt, in which the pentadienyl system has nitrogen atoms at positions 1,2 and 3,4 (Scheme 2D).[46] The idea that this transformation is pericyclic, and thus related to the processes in Schemes 1A-C has not been considered previously. In this paper, we examine the energetic profile of the cationic cyclization using density field theory (DFT), to explore the tetra-aza-Nazarov hypothesis shown in Scheme 2D.



Scheme 2. (A) Classical Nazarov cyclization for synthesis of carbocycles, (B) Aza-Nazarov variant, (C) Diaza-Nazarov Variant, (D) Tetraza-Nazarov variant.

In our previous work targeting NTAZ, ammonium BTNT was considered a by-product and removed during purification (Scheme 1). Since it was apparent that 2 equivalents of 3-amino-5-nitro-1H-triazole (ANTA) were required for its formation, the use of a 1:1 ratio of ANTA and bromonitromethane starting materials largely minimized its production. Upon shifting this ratio to 2:1 in this work, we were able to decrease formation of NTAZ in favor of a precipitate which was determined to be 3-bromo-1,5-bis(3-nitro-1,2,4-

triazole-1H-5-yl)-formazan (BDNF, Scheme 3). This precipitate was never previously isolated because BDNF is partially water soluble and did not precipitate under NTAZ conditions.



Scheme 3. Synthesis of BDNF from ANTA.

Thus, treatment of **4** in water at 0-5 ^{0}C with 0.5 equivalents of bromonitromethane afforded BDNF in yields up to 51%. The best yields were obtained from reactions held at colder temperatures for up to 18 h and strict 2:1 stoichiometry. Up to 3 g BDNF were produced in a sing1e run. It was identified first by mass spectrometry with an m/z double peak at 373/375. The solid BDNF was isolated and characterized by NMR giving ^{13}C signals at 162.29, 160.49, and 130.07 ppm in DMSO-d6. The BDNF structure was verified by single crystal X-ray crystallography. Single crystals were obtained by slow evaporation from 2-methoxyethanol. The di-solvated P 21/n crystal had to be stored in the freezer because it would break down at room temperature as the 2-methoxyethanol evaporated (Figure 2). BDNF was determined to be insensitive to both impact (>40 J) and friction (60 N, decomp.). DSC analysis showed that the un-solvated material underwent thermal decomposition at approximately 150 ^{0}C.

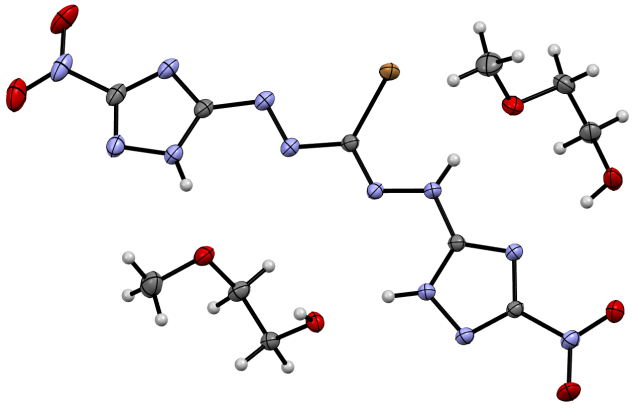
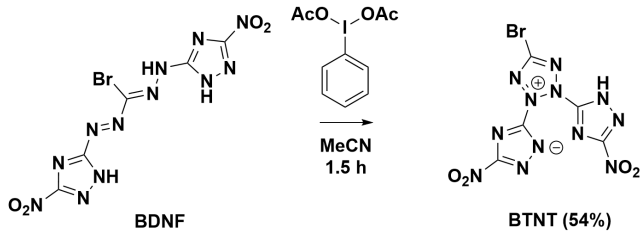


Figure 2. Crystal structure of BDNF after slow evaporation from 2-methoxyethanol.

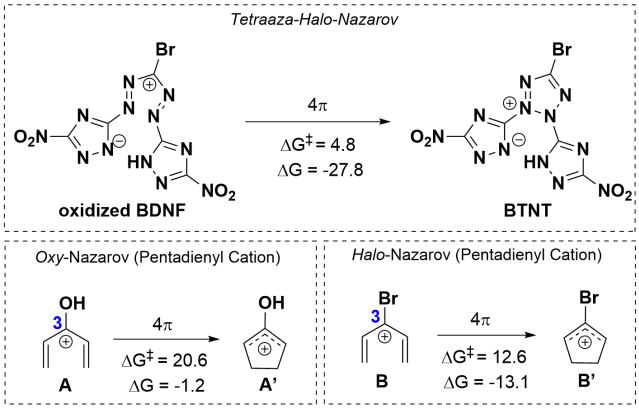
Because BDNF was never isolated during the production of NTAZ, we decided to carefully study its cyclization to BTNT. Initially, we attempted the same conditions used to form NTAZ (18h in ammonium nitrate/acetonitrile or ammonium nitrate/1,4-dioxane). These methods, however, resulted in a complex mixture of products.[47] The use of elemental bromine in water showed product by MS, but the strong oxidizing nature of bromine led to extensive decomposition. Ultimately, we were able to achieve the successful cyclization of BDNF to give BTNT by using the hypervalent iodine reagent phenyliodine(III) diacetate (PIDA) (Scheme 4). PIDA was chosen as the oxidizer for this reaction because it is generally mild and it has been used to cyclize a number of different heterocyclic systems, including hydrazones to form annulated 1,2,3-triazoles.[48–50]



Scheme 4. Oxidation of BDNF and cyclization of BTNT.

Mass spectrometry, taken at 30 minute intervals, was used to monitor the disappearance of BDNF. Complete cyclization was typically seen at 1.5 h. The volatile by-products iodobenzene and acetic acid were initially removed by heating the mixture to reflux for 1 hr, but the NMR indicated extensive decomposition of BTNT. Fortunately, BTNT precipitated upon addition of benzene to the reaction mixture dissolved in a minimum amount of ethyl acetate. This method afforded reasonably pure BTNT in 54% yield upon filtration and drying *in vacuo*. Despite extensive attempts, we were unable to grow a single crystal of this material. Treatment of BTNT with NH_4HCO_3 (aq) followed by evaporation, however, led to the isolation of the known ammonium salt from our previous work as confirmed by powder X-ray crystallography.[47]

DFT calculations were carried out on the cyclization of oxidized BDNF to give BTNT (Scheme 5). A transition state was located connecting the oxidized BDNF formazan to the BTNT product, with a $\Delta G^{\ddagger}$ of 4.8 kcal/mol, while the overall process is calculated to have a ΔG of -27.8 kcal/mol, indicating that this process is very facile.



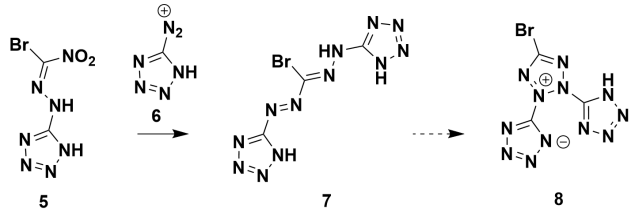
Scheme 5. DFT results of the tetraaza-halo-Nazarov cyclization in comparison to the *oxy*- and *halo*-Nazarov.

It is known that replacing oxygen for bromine at the 3-position of a pentadienyl cation enhances the reactivity of the pentadienyl cation, and these systems undergo thermal conrotatory ring closure (Scheme 5). We reason that this process proceeds through a typical electrocyclization mechanism, because computational analysis of the system gives results consistent with previous calculations performed on electocyclizations of similar reactants. Based on these closely analogous DFT results, we propose that this oxidized BDNF may also proceed through an electrocyclic mechanism.

A radical path was also considered, but it is considered unlikely based on relevant literature. Although 4π electrocylization was not explicitly proposed for the reactions, Hegarty et al. suggested that a cationic path was operative in their 1975 study on the oxidative cyclization of formazans

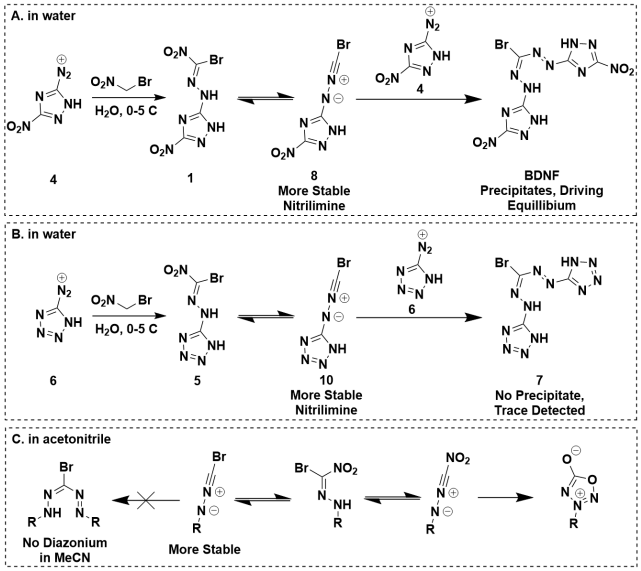
using bromine.[46] These researchers found that neither irradiation nor performing the reaction in the dark affected rate constants, which led them to rule out the radical pathway. In 2012, Semanta and co-workers demonstrated that I(III) mediated cyclizations of aryl acetamides were consistent with a 4π electrocyclization process, based on Hammett plot data.[50] In this study, radical scavengers had no effect on reaction outcomes, which enabled the investigators to rule out a radical cyclization mechanism. The C-H insertion pathway for cyclization was also eliminated, based on results obtained from KIE experiments, indicating to us that the analogous N-H insertion process (to form the N-N bond in BTNT) is also unlikely.

The synthesis of the bis-tetrazole-tetrazolium salt derivative **8**, an alternative high nitrogen target, was attempted (Scheme 6). Reaction of compound **5** with diazonium salt **6** in 1:1 stoichiometric ratio did not give the desired formazan **7**. Using increased equivalents of **6** and lowering the reaction temperature also did not lead to precipitation of **7**. Formazan **7** was detected in trace amounts by mass spectrometry, but was unable to be isolated.



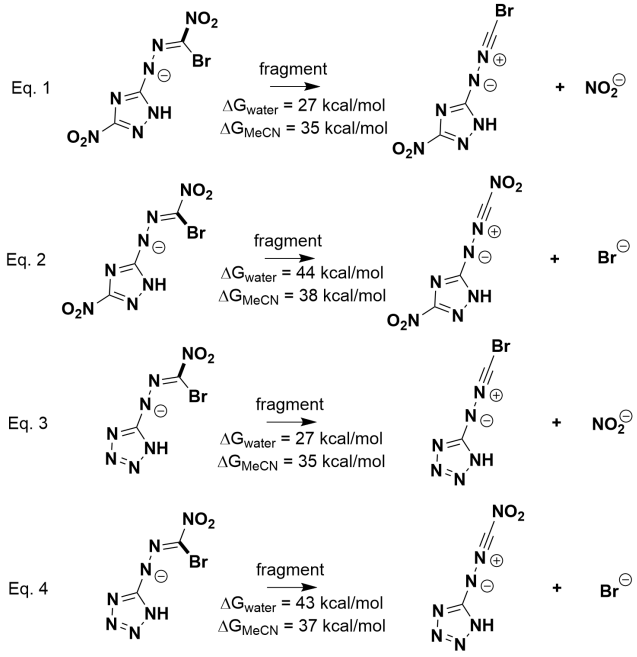
Scheme 6. General scheme of the failed formation of bis-tetrazole-formazan following the reaction conditions for BDNF.

Scheme 7 outlines a comparison between the similar syntheses of NTAZ and 5-azasydnone-1H-tetrazole (TAZ)[21], reactions that initially vary only in starting material. In water, the bromo-nitrilimines **9** and **10** react with diazonium intermediates in solution to form the corresponding formazans (BDNF and **7**). In the case of ANTA, BDNF precipitates, which may drive the equilibrium towards further BDNF formation. In both the NTAZ and TAZ reactions, the hydrazones (**1** and **5)** are extracted from water into ethyl acetate and isolated. They are then stirred in acetonitrile (MeCN) over ammonium nitrate, yielding the cyclized azasydnones in low yield. Since tetrazole bromonitrilimine **10** did not form to any appreciable extent and additional diazonium **6** is not available in MeCN, tetrazole formazan **7** was not produced.



Scheme 7. Comparison of A) **4** in water forming BDNF, B) **6** in water forming **7**, and C) the generalized reaction of both hydrazones in MeCN.

To elucidate the observed selectivity for formation of the BDNF product in the nitrotriazole case and not the tetrazole, DFT calculations were carried out to examine the thermodynamics for bromo-nitrilimine and nitro-nitrilimine formation (Scheme 8). These calculations were performed at the M06-2X/Def2TZVP level of theory with SMD=water and MeCN (see supporting information for more detail). The calculations reveal that formation of the bromo-nitrilimine ion is more favorable thermodynamically than the nitro-nitrilimine ion for both the nitrotriazole and the tetrazole ring in both water and MeCN solvents. The stable nitrotriazole bromonitrilimine then reacts with another equivalent of diazonium in water to give an insoluble formazan, which may help drive the reaction forward. However, the aforementioned discussion regarding solubility could explain why the formazan did not form for the tetrazole substrate despite the calculations suggesting it is thermodynamically feasible.[51] Furthermore, prior to extraction, the tetrazole bromonitrilimine may have a low equilibrium concentration because there is a high kinetic barrier for its formation.



Scheme 8. Equations showing possible nitrilimine products and with their corresponding thermodynamic data for formation.

In conclusion, a new high nitrogen formazan was synthesized and then cyclized to give a novel 2,3 disubstituted tetrazolium salt. Experimental data, supported by DFT calculations, suggest that a tetraaza-Nazarov mechanism is operative. To address why the cyclization occurred with nitrotriazole substitution but failed with tetrazoles at terminal formazan positions, additional DFT calculations were performed. These calculations indicate that bromo nitrilimine intermediates are thermodynamically favored over nitronitrilimines in both water and MeCN, which supports cyclization of the ANTA-based formazan. In the 5AT-substituted case, a potentially high kinetic barrier to the corresponding bromo nitrilimine in conjunction with its aqueous solubility could explain why cyclized product was not generated.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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