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Investigation on stereoconfiguration of azoxybenzene formed via Grignard reaction and further Consequences on Z & E isomerism of diazeniumdiolates

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Abstract

Nitric oxide's importance in biochemistry was recognized in the mid 1980's. Nitric oxide (NO) is critical for the function of neuronal cells, for blood flow and to defend against tumour cells and microorganisms. Diazeniumdiolates, ions of structure $[RN(O)NO]^-$, are being used as probes to study the biological and pharmacological implications of NO because compounds bearing this functional group have been found to release NO. The conformation about the N=N double bond of diazeniumdiolates has been shown through crystallographic studies to be predominantly Z. To study the stereospecificity of diazeniumdiolates, azoxybenzene was synthesized via a "forgotten" synthetic pathway pioneered by Stevens in 1963 which involved a reaction between an organonitrosohydroxylamine tosylate, RN(O)NOTs, and a Grignard reagent. The product from this preparation was directly compared to azoxybenzene made from a coupling reaction.

Key words

Grignard reaction: *an addition reaction involving and organomagnesium halide*; **stereoisomers**: *compounds with the same molecular formula that differ only in the arrangement of their atoms in space*; **crystallography**: *the experimental science of determining the arrangement of atoms in solids*, **diazeniumdiolate**, **nitric oxide, Azoxybenzene**, **RMgX**.

Introduction

Nitric oxide (NO) was named molecule of the year in 1992 by Science (Koshland D. E. Jr. 1992) and a Nobel Prize was awarded in 1998 for establishing its biological importance. However, its roles in critical physiological pathways have only been fully uncovered since the mid 1980's.

NO is a ubiquitous biochemical agent responsible for many critical biochemical processes and is synthesized in the body by a number of enzymes. This small molecule plays a critical role in regulating blood flow; enzymatically released from L-arginine, NO acts upon enzymes in the smooth muscle cells, which surround blood vessels, to cause their relaxation and consequent vasodilation. Moreover, NO is known to inhibit the adhesion, aggregation and recruitment of platelets to a growing thrombus, the plug necessary in wound healing; NO is essential to regulate platelet hyperactivity by reducing the size of the blood clot (Walford G et al. 2003). Furthermore, the cytotoxicity of macrophages against tumor target cells has been linked to the macrophage's ability to secrete NO. As NO is part of the body's innate immune pathway, it also aids in the protection against parasites (notably *Leishamania major* and *Plasmodium* species) and some bacteria (Butler AR et al. 1993).

When NO is produced acutely, it can lead to large blood pressure drops and destruction of tissue leading to inflammatory disease and degeneration of nerve and brain tissue, whereas chronic overproduction of NO is associated with immune-type diabetes, inflammatory bowel disease, rheumatoid arthritis, carcinogenesis, septic shock, multiple sclerosis, transplant rejection and stroke. Insufficient NO production is linked to hypertension, impotence, arteriosclerosis, and susceptibility to infection (Miessler GL et al. 2004).

Ions of structure $[RN(O)NO]^-$ are called diazeniumdiolates and are used as probes to study the biological and pharmacological implications of NO because many chemical agents bearing this functional group have been found to release bioactive NO when dissolved in physiological fluids either spontaneously or after metabolic transformation (Keefer LK et al. 2001). One of the major problems associated with the current NO-donors is the indiscriminate release of NO. Therefore, the development of donors that can deliver NO at specific times and locations to evoke the desired biological function is of great current interest (Hou Y et al. 2000). Furthermore, some naturally occurring diazeniumdiolates are known to have antitumor, antibiotic, antifungal and even herbicidal properties (Hrabie JA et al. 2002).

Diazeniumdiolates and related azoxy-compounds can be prepared via radically-mediated reactions (Stevens TE 1967, Ogata Y et al 1957, Opolonick N 1935, Bigelow HE et al 1931, Pizzolatti at al 1990, Shemyakin MM et al 1957, Hwu JR et al 1997). Radicals are believed to react non-stereospecifically and to readily attack the closest reactive site. Surprisingly however, most radically-mediated reactions generate the Z-conformer of the diazeniumdiolate; this "discriminate" choice in stereospecificity is seen for compounds containing the R'[N(O)NO]R" unit is almost independent of the identity of R' and R" (Keefer LK et al. 2001).

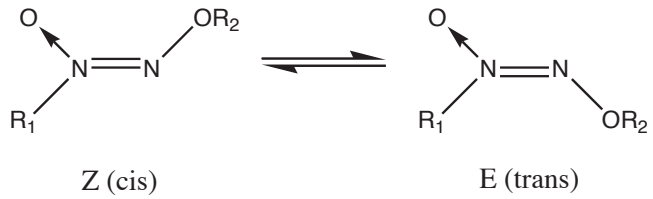

Figure 1. Interconversion of Z/E Isomers of Diazeniumdiolates

This conformational preference of diazeniumdiolates has been under investigation for quite some time. The conformations about the N=N double bond **(Figure 1)** have been studied through ^{13}C and ^{15}N NMR (Schwotzer et al 1977, Simova et al 1983). Crystallographic studies have shown the conformation about the double bond to be Z in all but 5 cases (Bohle DS et al. 2005), where the oxygen atoms are arranged *cis* to each other. If the species with the E stereochemistry could be

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isolated, it could then be compared to its Z analogue to elucidate the relative difference between their respective NO release rates, which greatly affect their pharmacological properties (Wang YN et al. 2005).

Furthermore, an alternate approach to investigate this conformational preference is to probe a related compound, azoxybenzene (III). An alternate method to the synthesis of III was previously examined by Stevens in 1963 (Stevens TE, 1970) (A). An organonitrosohydroxylamine tosylate (II) was prepared from cupferron (I) and followed by a Grignard reaction. The p-toluenesulfonyl derivative of I, an organonitrosohydroxylamine ammonium salt, was prepared in order to have a substituent capable of easy displacement so that the conversion of II to III via a Grignard reaction would take place readily.

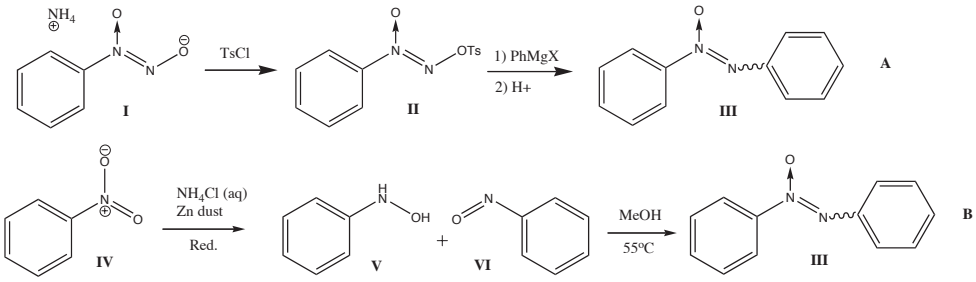

Figure 2. Reaction Pathway A: Formation of N-phenyl-N'-tosyloxydiimide N-oxide **(II)** from cupferron **(I)** and p-toluene sulfonyl chloride followed by the Grignard reaction on the tosylate derivative via phenyl magnesium bromide yielding azoxybenzene **(III)**; Reaction Pathway B: Formation of azoxybenzene **(III)** via the coupling of nitrosobenzene **(VI)** and phenylhydroxylamine **(V)**, synthesized by reducing nitrobenzene **(IV)**

This study focuses on the comparison of both compounds identified as III, the one synthesized from reaction scheme A, a pathway pioneered by Stevens, and the one formed by a conventional radically mediated pathway (B), followed by extensive characterization of all products synthesized. The main focus of this "novel" method of synthesizing diazeniumdiolates precursors is to uncover whether only one configuration (E or Z) is preferred. The method of investigating this resides in proton NMR, IR, UV, and, mainly, crystallographic studies.

Experimental Procedure

Preparation of N-phenyl-N'-tosyloxydiimide N-oxide (Stevens TE, 1970)
A solution of 10.3 g (66.4 mmol) of cupferron in 135 mL of 10% aqueous sodium bicarbonate while 14.2 g (74.5 mmol) of para-toluenesulfonyl chloride was added in one portion without any noticeable heat evolution from the reaction mixture. After 2 hours, an additional 1.5 g (8.0 mmoles) of the para-toluenesulfonyl chloride was added. The mixture was stirred overnight and then extracted with methylene chloride. The dark residue obtained by evaporation of the methylene chloride was treated with 25 mL of methanol to give a colorless precipitate, which was then filtered. The crude white solid obtained was recrystallized by adding chloroform followed by an equal volume of hexane. A total of 11.208 g (38.3 mmoles) of N-phenyl-N'-tosyloxydiimide N-oxide was obtained (58% yield). Crystals suitable for crystallographic characterization **(Figure 3)** were grown from chloroform and hexanes and diffraction data was collected on a Bruker D-8 diffractometer with Mo Kα radiation. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 2.47 (s, 3H), 7.39 (d, J=8.0 Hz, 1H), 7.49 (t, J=8.0 Hz, 2H), 7.59 (t, J=7.2 Hz, 2H), 7.90 (d, J=3.6 Hz, 2H), 7.96 (d, J=8.4 Hz, 2H). IR (KBr, cm^{-1}) 3096 (w, υ_{CH}), 3074 (w, υ_{CH}), 1595 (s, υ_{NO}), 1385 (vs, υ_{SO2}), 1194 (vs, υ_{SO2}), 903 (s, υ_{NOS}), 743.39 (br, υ_{SO}). Raman (cm^{-1}): 1598 (w), 1386 (w), 1318 (w), 1292 (m), 1195 (m), 1178 (m), 1089 (w), 1005 (s), 816 (m), 737 (w), 676 (w), 634 (m), 612 (w), 292 (s).

Preparation of Azoxybenzene via Grignard reaction (Stevens TE, 1970)
A solution of 2.20 g (7.526 mmoles) of N-phenyl-N'-tosyloxydiimide N-oxide in 40 mL of dry tetrahydrofuran was stirred at ambient temperature while 11.0 mL of 1.0 M phenylmagnesium bromide (in THF) was added dropwise. The mixture was stirred at 50-60°C for 2 hours, then cooled to room temperature and poured into an ice-dilute hydrochloric acid mixture. The organic product was isolated by extraction with methylene chloride. After concentration of the organic layer, the residue was chromatographed on silica gel. Elution of the column with 100% hexanes was performed to remove impurities and was followed by further elution with a 3:1 and 2:1 hexanes-methylene chloride solution to recover azoxybenzene in a 64% yield. UV ($CHCl_3$) λmax (ε) 323.0 nm (br). 1H NMR (400 MHz, CDCl3, δ) 7.40 (m, 1H), 7.49 (m, 2H), 7.52 (m, 2H), 7.54 (m, 1H), 8.16 (d, J=7.6 Hz, 2H), 8.31 (d, J=7.2 Hz, 2H). IR (KBr, cm^{-1}) 3066 (w), 1483 (m), 1473 (m), 1451 (m), 1328 (w), 1299 (w), 1093 (br), 1022 (br), 926 (w), 906 (w), 763 (s), 683 (s), 579 (w).

Preparation of Azoxybenzene via coupling reaction (Ogata Y et al. 1957)
A vigorously stirred mixture of 4.2 ml nitrobenzene (0.04 mol), 2.50 g NH4Cl (0.05 mol) and 80 mL water was maintained below 60°C while 5.90 g of zinc dust (0.09 mol) was slowly added (highly exothermic process). After the addition of all the zinc, the mixture was stirred for an additional 20 minutes and filtered. The filter cake was washed with hot water. The filtrate and washings were combined and saturated with 25.0 g of KCl and cooled to 0°C for 30 minutes. The resultinglong, yellow, needle-like crystals of phenylhydroxylamine (3.7 g, 33.91 mmoles) were filtered, dried and stirred in 20.0 mL of methanol. A methanolic solution (15 mL) of 3.5 g of nitrosobenzene (32.67 mmoles) was added and stirred at room temperature. The greenish color of the solution gradually darkened but remained green even after warming to 60°C. A small amount of water (2 mL) was added and the solution mixture was then chilled to 0°C for 10 minutes until a precipitate formed. The solid material was filtered and the mother liquor was evaporated under vacuum yielding 1.072 g of azoxybenzene (15%). UV ($CHCl_3$) λmax (ε) 324.0 nm (br). 1H NMR (400 MHz, $CDCl_3$, δ): 7.46 (m, 1H), 7.48 (m, 2H), 7.49 (m, 2H), 7.50 (m, 1H), 8.16 (d, J=8.4 Hz, 2H), 8.29 (d, J=5.2 Hz, 2H). IR (KBr, cm^{-1}): 3066 (s), 1572 (w), 1483 (m), 1473 (m), 1451 (m), 1438 (s), 1300 (w), 1275 (w), 1165 (w), 1097 (w-br), 1069 (w), 763 (s), 684 (s), 612 (w), 580 (w).

Reaction of Potassium Tert-butoxide and N-phenyl-N'-tosyloxydiimide N-oxide
A solution of 0.32 g (1.095 mmoles) of N-phenyl-N'-tosyloxydiimide N-oxide in 5 mL of methanol was stirred at ambient temperature while 1.64 mL of 1.0 M potassium tert-butoxide (in tert-butanol) was added. The mixture was stirred at ambient temperature overnight. The organic product was filtered from solution. A mixture of tert-butyl 4-methylbenzenesulfonate and cupferron was collected as a white powder (0.3216 g). 1H NMR (400 MHz, $CDCl_3$,δ): 2.48 (s, 3H, t-Bu-SO_3PhCH_3), 3.31, (s, 9H, t -Bu-SO_3PhCH_3), 7.09 (d, J=7.6 Hz, 2H, PhN_2O_2-), 7.17 (t, J=7.2 Hz, 1H, PhN_2O_2-), 7.31 (t, J=7.8 Hz, 2H, PhN_2O_2-), 7.45 (d, J=8.0 Hz, 2H, t-Bu-SO_3PhCH_3), 7.84 (d, J=7.6 Hz, 2H, t -Bu-SO_3PhCH_3).

Discussion

To date, all diazeniumdiolates and closely related analogues such as azoxy-compounds have been found to exist in the Z (*cis*) conformation; however, only 5 examples of the E (*trans*) configuration analogue have been observed. These involve cyclic ring systems forcing the specific conformation (Bohle DS et al. 2005).

There are various known methods for synthesizing azoxybenzene; the main and most frequently used approaches are the oxidation of amines and azo compounds, reduction of nitro (Opolonick N 1935, Bigelow HE et al 1931) and nitroso compounds, acid-catalyzed or base-catalyzed coupling of nitroso compounds with hydroxylamines (Ogata Y et al 1957, Pizzolatti MG et al 1990, Shemyakin MM et al 1957) and by thermal- and photo-induced transformations of N-aryl-N-nitrosohydroxylamine ammonium salts (Hwu JR et al. 1997). Most of these preparations will proceed, in some form or another, as radicals to form azoxybenzene which, when produced by this particular pathway, always generates the Z (*cis*) conformer.

Therefore, a method that deviated from the conventional radical pathway was of interest. The reaction of Grignard reagents with O2-alkyl diazeniumdiolates producing azoxy-compounds was pioneered by Stevens even before the true structures of the starting materials were known. Stevens was also able to perfect reaction pathway A, the preparation of azoxy-compounds from the O2-tosylated acyl diazeniumdiolates (Stevens TE, 1970).

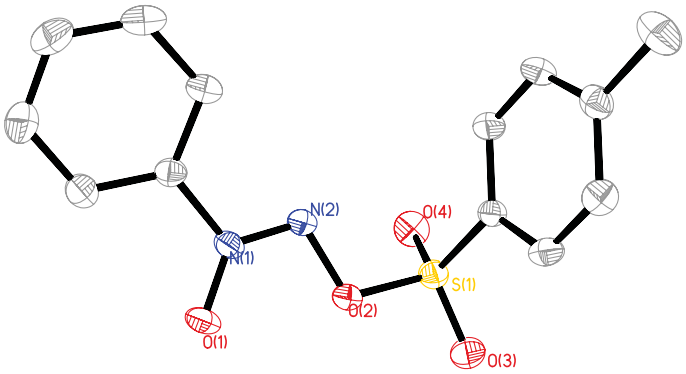

Figure 3. Stereoscopic view of N-phenyl-N'-tosyloxydiimide N-oxide reflects its Z (*cis*) stereoconfiguration

The structure of II was determined by X-ray diffraction techniques and solved by direct methods. The structure obtained clearly reflects the Z configuration about the O(1) atom of II **(Figure 3)**. This structure had also been previously determined but reported only in outline by White and coworkers (White EH et al.), who also synthesized the molecule by tosylating I.

Since II is in the Z configuration, one possible mechanism of this particular Grignard reaction for the generation of azoxybenzene is a back-side attack with respect to the tosyl group by the phenyl anion, leading to an inversion of configuration yielding an E (*trans*) isomer.

To examine this hypothesis, azoxybenzene generated by reaction pathway A was directly compared to azoxybenzene synthesized from B (Ogata Y et al. 1957) (III is formed either when two phenyl nitroxide radicals react or after the formation of the arylnitroxide radical). Radical coupling reactions such as the latter have been previously shown through X-ray crystallography to yield azoxy-compounds in the Z (trans) configuration (Yamamoto J et al. 1987). Proton NMR and IR indicate that azoxybenzene produced via each reaction is relatively similar. Webb and Jaffé have previously published UV-visible values for the E (trans) and Z (cis) conformers of azoxybenzene, 327 nm and 323 nm respectively (Webb DL et al. 1964). Therefore, this points towards the fact that azoxybenzene made from both A and B are in the Z (cis) configuration; however, this would need to be confirmed through crystallographic studies.

Stevens observed that reactions of II with Grignard reagents conducted in THF led to the formation of significant quantities of undesirable side-products (VIII) and thus indicated that the Grignard reaction proceeded via a radical intermediate (VII). He postulated that both III and VIII arise from radical coupling or radical displacement reactions. Although we have found many side products in the Stevens' reaction, none have been identified as compound VIII (Stevens, T. E., 1967). However, the fact that the Grignard reaction of II also proceeds via a radical reaction indicates that the E (trans) isomer would not get generated via this type of reaction.

Furthermore, the synthesis of the diazeniumdiolate, N-phenyl-N'-tert-butyloxydiimide N-oxide, was attempted from II and potassium tert-butoxide. The O-alkylation of I has been well documented (Hou Y et al. 2000) and leads to the Z (cis) isomer therefore, the O-alkylation of II could potentially lead to a single isomeric product. This would occur through simple nucleophilic attack at nitrogen and displace the tosylate group (N-attack) and generate IX, a diazeniumdiolate. However, an alternate mechanism (S-attack) exists and involves initial nucleophilic attack at sulfur to produce I and an intermediate tosyl ester X. This S-attack mechanism has been known to proceed exclusively and has been confirmed through ^{18}O labeling and incorporation studies (D'Sa RA et al. 2003).

Therefore, to bypass the nucleophilic attack at the sulphur atom, a different leaving group such as a diphenylphosphinoyl (Vankayalapati H et al. 2001) or a triflate (Netscher T et al 2002, Olah GA et al 1986) should be fashioned and coupled to I to allow easy displacement and to prevent the aforementioned S-attack. These reactions with various sodium alkoxides will be examined to determine whether O-alkylation of the new derivative will proceed and yield an isomeric diazeniumdiolate, which could then be characterized by X-ray analysis.

An essential question is whether these reactions are thermodynamically controlled (both E and Z products are formed and the E to Z isomerization ensues) or kinetically controlled (one isomer, Z, is exclusively formed from the mechanism of the reaction). Insight into this is best gained by computational density function calculations. The rotation barriers for even the simplest diazeniumdiolates are very high (approximately 40 kcal/mol). Therefore, the absence of the E (trans) isomer is not likely due to

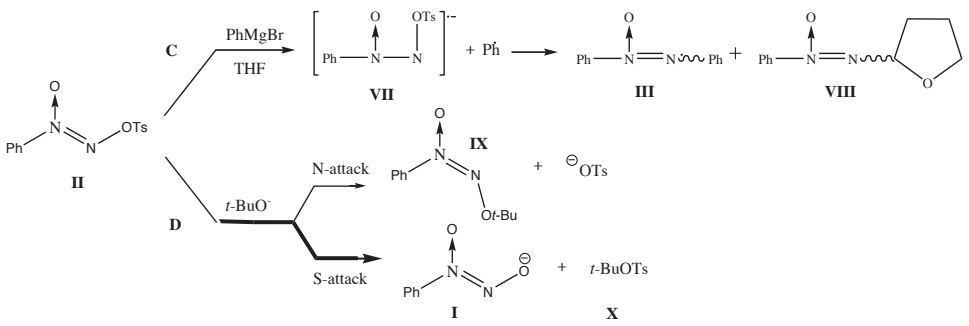

Figure 4. Reaction pathway C: Formation via radical intermediate (VII) of azoxybenzene **(III)** and of side-product **(VIII)** when reaction pathway A is performed in THF as postulated by Stevens; Reaction Pathway D: N-phenyl-N'-tosyloxydiimide N-oxide **(II)** is reacted with tert-butoxide and yields compounds X and I via an S-attack mechanism

isomerization from a product under thermodynamic control, but rather due to product distribution that is Z (*cis*)-preferential and is thus kinetically controlled (Bohle DS et al. 2005). Therefore, the observed products correspond to the isomers initially formed and reflect their mechanism of formation.

Conclusion

X-ray diffraction will be the only way to confirm the stereo-configuration of the azoxybenzene made with the Grignard reaction and from the coupling reaction; it will also verify that that both adopt the Z (*cis*) conformation. Moreover, to produce diazeniumdiolates from O-alkylation, diphenylphosphinoyl chloride ($P(O)Ph_2Cl$) as well as triflic anhydride ($((CF_3SO_2)_2O$) and I will need to be coupled. Finally, to confirm whether the mechanistic pathway of A truly occurs via VII, the reaction can be performed with a radical quencher, such as TEMPO or DMPO. This would allow us to capture and examine the radical intermediate and determine whether azoxybenzene is still formed (and in the same yield) and whether our hypothesized mechanism would occur.

Acknowledgements

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