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Release of Nitrosating Species in the Course of Reduction of Benzo-1,2,3,4-tetrazine 1,3-Dioxides

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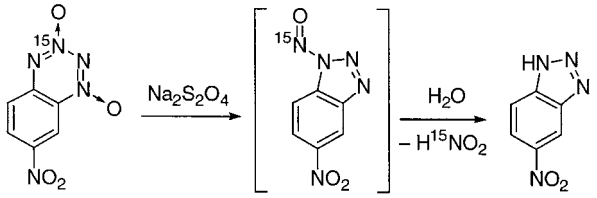
ABSTRACT



1c' **3c'** **2c**

The reduction of benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) 1 with $Na_2S_2O_4$ or $SnCl_2$ is suggested to proceed via intermediate *N*-nitrosobenzotriazoles 3 to afford benzotriazoles 2. The ^{15}N-labeling experiments exhibit that the N-3 atom of the tetrazine ring is incorporated into the nitroso group of 3 that is ultimately released into solution. It is possible that the biological activity of BTDOs is due to their ability to release nitrosating species, i.e., *N*-nitrosotriazol 3 or HNO_2, in the course of reduction.

Benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) represent a fairly new class of heterocycles,[1] and their chemistry is hitherto insufficiently studied. Interest in these compounds has increased sharply since they were found to exhibit a broad spectrum of biological activities.[2] In particular, they proved to be the effective thiol-dependent activators of soluble guanylate cyclase and inhibitors of ADP-induced aggregation of human platelets.[3] It was suggested that the biological activity of BTDOs (5-NO_2-BTDO among them) was due to their ability to release NO (nitric oxide) or its redox forms,[3] and BTDOs were considered as a new class of NO-donors.[4] At the same time, the pathway of NO/NO^+ generation has remained unclear. This fact stimulated us to examine this question in terms of the chemistry of BTDOs. It is possible that NO/NO^+ species could arise in the course of reduction of BTDOs. Herein we have confirmed this assumption.

BTDOs **1a**−**c** were selected as model compounds for studies.[5] It has been found that these compounds are readily reduced with the same reagents that are usually used for reduction of the nitro group[6] ($Na_2S_2O_4$, $SnCl_2$, Fe/HCl) with the difference that the investigated reaction takes place in milder conditions. The reduction reached completion within 2−3 min at room temperature to afford the appropriate benzotriazoles **2a**−**c** (Scheme 1). The reduction of BTDO **1c** afforded 5-nitrobenzotriazole (**2c**); hence the 1,2,3,4-tetrazine 1,3-dioxide ring (TDO-ring) was reduced faster than

(1) (a) Churakov, A. M.; Ioffe, S. L.; Tartakovsky, V. A. *Mendeleev Commun.* **1991**, 101. (b) Churakov, A. M.; Smirnov, O. Yu.; Ioffe, S. L.; Strelenko, Yu. A.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **2002**, 2342−2349.

(2) This work is in progress.

(3) (a) Pyatakova, N. V.; Khropov, Yu. V.; Churakov, A. M.; Tarasova, N. I.; Serezhenkov, V. A.; Vanin, A. F.; Tartakovsky, V. A.; Severina, I. S. *Biokhimia* **2002**, *67*, 396 [*Biochemistry (Moscow)* **2002**, *67*, 329]. (b) Rus. Pat. 2123526, 1997; *Chem. Abstr.* **2000**, *133*, 55324d.

(4) For a review on the major classes of NO-donors and the pathways of NO generation in course of oxidation, reduction, or hydrolysis, see: Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev.* **2002**, *102*, 1091.

(5) For synthesis of BTDOs **1a**−**c** and **1c′**, see ref 1b.

(6) Hudlicky, M. *Reduction in Organic Chemistry*; Wiley: New York, 1984.

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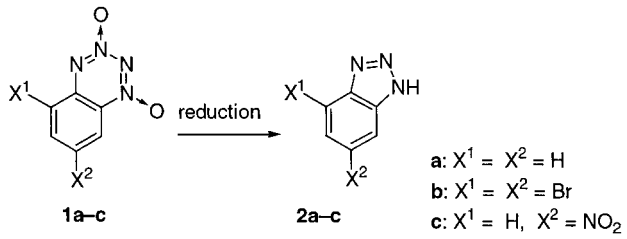
Scheme 1[a]

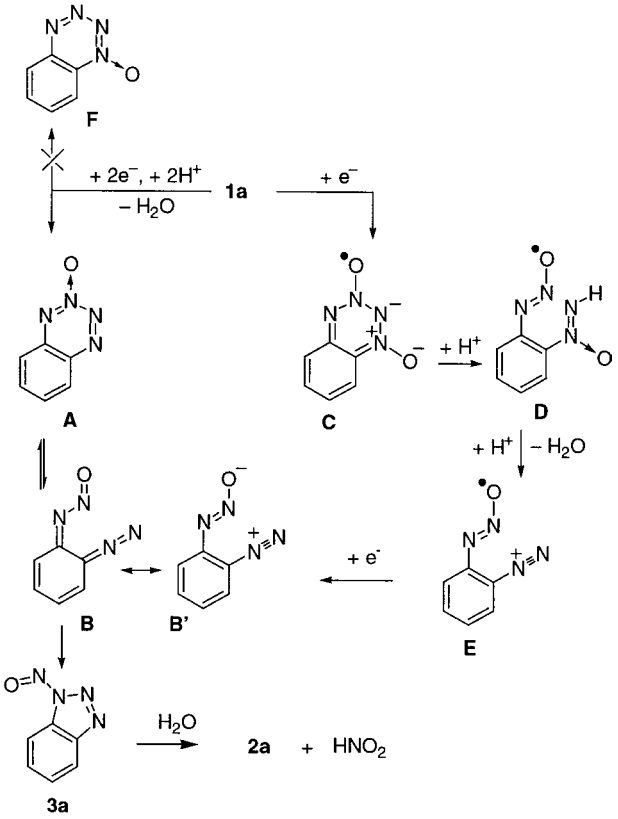


[a] Reagents and conditions: $Na_2S_2O_4$ (4 equiv), EtOAc/H_2O, 24 °C, 3 min, **1a**→**2a** (90%); **1b**→**2b** (84%), **1c**→**2c** (66%); $SnCl_2 \cdot 2H_2O$ (4 equiv), EtOAc/EtOH, **1a**→**2a** (97%); **1b**→**2b** (95%), **1c**→**2c** (98%).

the nitro group. The structures of benzotriazoles **2a**−**c** were confirmed by comparison with those of authentic samples.[7]

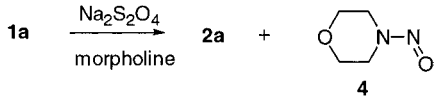
The plausible pathway of the transformation of the TDO-ring into the triazole ring is shown in Scheme 2.

Scheme 2



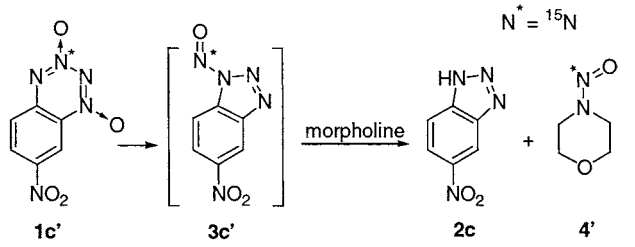
This pathway involves two-electron reduction of **1a** accompanied by elimination of H_2O resulting in benzo-1,2,3,4-tetrazine 2-oxide **A** (pathway 1). The latter could provide the open-chain tautomer, depicted by two resonance structures **B** and **B′**. The calculations at the RHF/6-31G* level of theory show that molecules **A** and **B** could exist in equilibrium with each other (structure **A** is 1.7 kcal/mol more favorable than structure **B**[8]). Then, compound **B** could irreversibly cyclize into *N*-nitrosotriazole **3a** (more favorable by 21.3 kcal/mol) followed by hydrolysis to give benzotriazole **2a**.

Scheme 3



However, one can suggest the alternative pathway (pathway 2) for **1a**→**3a** transformation. The anion−radical **C**, which is formed as a result of one-electron transfer, could open the tetrazine ring after protonation to give radical **D**. The diazene oxide moiety of the latter could easily turn into the diazonium group[9] with formation of **E**. The following one-electron reduction of **E** could afford the open-chain structure **B**.

Scheme 4



Interestingly, the reduction of BTDOs does not involve the intermediate formation of benzo-1,2,3,4-tetrazine 1-oxides (compound **F** in Scheme 2). The decomposition of the latter compounds is known to proceed via ring-opening to afford *ortho*-azido-nitroso-benzenes followed by evolution of the

(7) Compounds **2a**,**c** are commercially available. The authentic triazole **2b** was prepared by diazotization of 3,5-dibromo-1,2-benzenediamine (see Supporting Information).

(8) (a) Absolute energies calculated[8b] using RHF/6-31G*: **A**, −522.014345 au; **B**, −522.0116344 au; **3a**, −522.0455798 au. We thank Dr. V. Solkan (N. D. Zelinsky Institute) for performing the calculations. (b) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.3; Gaussian, Inc.: Pittsburgh, PA, 1998.

(9) For transformation of the diazene oxide moiety into the diazonium moiety, see: Tyurin, A. Yu.; Churakov, A. M.; Ioffe, S. L.; Strelenko, Yu. A.; Tartakovsky, V. A. *Izv. Akad. Nauk, Ser. Khim.* **1997**, 613 (*Russ. Chem. Bull.* **1997**, *46*, 592) and references therein.

N_2 molecule to finally give benzofurazans,[10] which were not observed in the reactions under investigation. These observations enable pathway 2 to be considered the most probable.

Both pathways involve the formation of the intermediate *N*-nitrosotriazole **3a**. However, we failed to isolate this compound due to its easy hydrolysis.[11] Nevertheless, the formation of a nitrosating species was confirmed when reduction of BTDO **1a** with $Na_2S_2O_4$ was carried out in the presence of excess morpholine to afford *N*-nitrosomorpholine **4** in 20% yield.[12]

The following confirmation of the mechanism was gained by the labeling experiments. The reduction of BTDO **1c′** incorporating ^{15}N-labeled nitrogen (96 at. % ^{15}N) at the 3-position resulted in triazole **2c** (68% yield), which does not include the labeled nitrogen at all as judged from the MS data. At the same time, reduction in the presence of excess morpholine afforded *N*-nitrosomorpholine **4′** (29% yield), the ^{15}N-labeled nitrogen being entirely transferred into the *N*-nitroso group as judged from MS (*m*/*z* 117 $[M]^+$) and ^{15}N NMR spectrum ($\delta_N = -154.0$; lit.[13] -153.6).

In conclusion, the reduction of BTDOs is accompanied by the formation of a nitrosating species. It is possible that the biological activities of BTDOs are due to these species and/or products of their transformation. Alternatively, these activities might be caused by the intermediate radicals of the **C** type or related ones.

Acknowledgment. We thank Dr. Yu. V. Khropov, Moscow State University, for helpful discussions.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Lipilin, D. L.; Smirnov, O. Yu.; Churakov, A. M.; Strelenko, Yu. A.; Ioffe, S. L.; Tartakovsky, V. A. *Eur. J. Org. Chem*., in press.

(11) Treatment of the yellow solution of **3a** in Et_2O (obtained by a literature procedure) with a few drops of water resulted in immediate decoloration of solution, suggesting the hydrolysis. For synthesis of **3a**, see: Cadogan, J. I. J.; Thomson, J. B. *J. Chem. Soc. D* **1969**, 770.

(12) *N*-Nitrosomorpholine remained unchanged when treated with $Na_2S_2O_4$ under similar reaction conditions.

(13) (a) Bandmann, H.; Heymanns, P.; Siem, C.; Radenmacher, P. *Angew. Chem*. **1984**, *96*, 354. (b) From external $MeNO_2$, upfield shifts are negative.