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Modulating spin delocalization in conjugated nitroxides: 2-(*N*-aminoxyl-*N*-*tert*-butyl)-benzothiazole

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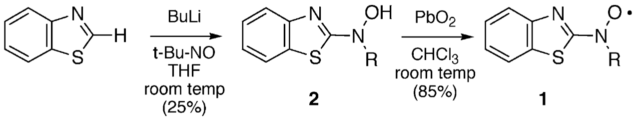
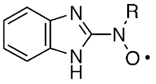
Abstract—The first controlled synthesis of the title radical, **1**, was achieved by oxidation of a hydroxylamine precursor; the radical itself can thus readily be isolated, studied by ESR and UV–vis, and compared to results of computational modeling. The benzothiazole ring induces substantial delocalization of the nitroxide spin density (a(NO) = 9.2 G, a(ring N) = 2.7 G, about 10% more than is seen in the benzimidazole nitroxide analog.

Spin density distribution is a key factor in controlling or understanding the reactivity of organic radicals.[1] Also, control of spin density distributions is important in the design of radical-based molecular materials.[2] Spin density modulation by structural variation allows some control over molecular reactivity and electronic exchange interaction, for instance by use of second row atoms with larger orbital extents than first row elements. Some of the highest magnetic ordering temperatures for purely organic molecules have been observed for a dithiadiazolyl-based radicals, for example.[3,4] In this article, we report a convenient synthesis of 2-(*N*-aminoxyl-*N*-*tert*-butyl)-benzothiazole, **1**, a nitroxide radical with substantial nitroxide π-delocalization. Radical **1** has previously been generated by trapping radical chemistry, and its solution electron spin resonance (ESR) spectrum analyzed,[5] but there has been no general synthetic method to make it. Our computational and experimental hyperfine coupling analyses of **1** show how the thiazole ring induces increased spin delocalization by comparison to closely related[6] nitroxides, making this a class of molecules worth pursuing as building blocks for molecular magnetic materials.





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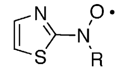

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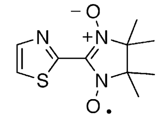

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In order to make **1**, we deprotonated benzothiazole at the 2-position with *n*-butyl lithium in the presence of 2-methyl-2-nitrosopropane to give colorless solid hydroxylamine **2**. This precursor molecule was stable and easily characterized by spectroscopy and X-ray crystallography, although it readily turns pink upon exposure to air. Lead dioxide treatment in dichloromethane solution converted **2** to nitroxide **1** within 15–30 min. After column chromatography, nitroxide **1** can be isolated as an elementally pure, thick red oil that completely lacks an –OH stretching band at 3000–3600 cm^{-1} in the IR spectrum. Radical **1** exhibits UV–vis absorbances at 476, 512, and 558 nm, and solution electron spin resonance (ESR) hyperfine coupling constants (hfc) of $a_N = 9.16$, 2.67 G, $a_H = 1.05$, 1.31, 0.33, 0.43 G. The experimental and simulated spectra are shown in Figure 1, and are similar to (though slightly better resolved than) those previously assigned[5] to radical **1** by trapping

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Keywords: Radicals; Nitroxides; Spin delocalization; Spin density.

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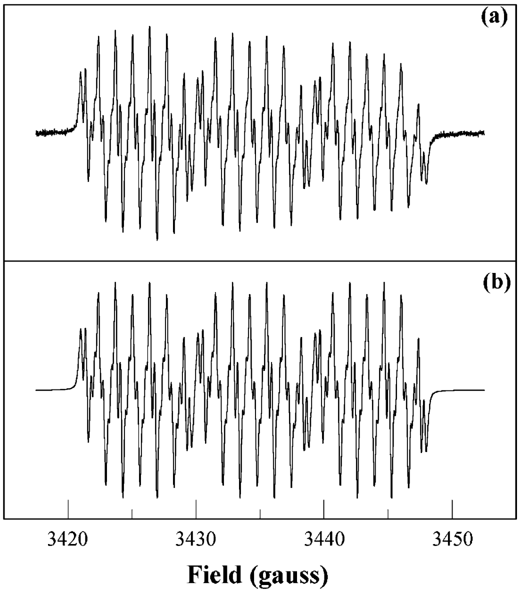


Figure 1. ESR spectrum of **1**. Curve a is experimental, room temperature in CH_2Cl_2, 9.645 GHz, room temp; curve b simulated[8] with a(NO) = 9.16 (1), a(N) = 2.67, a(H) = 1.31, 1.05, 0.43, 0.33 G, corr coef = 0.991.

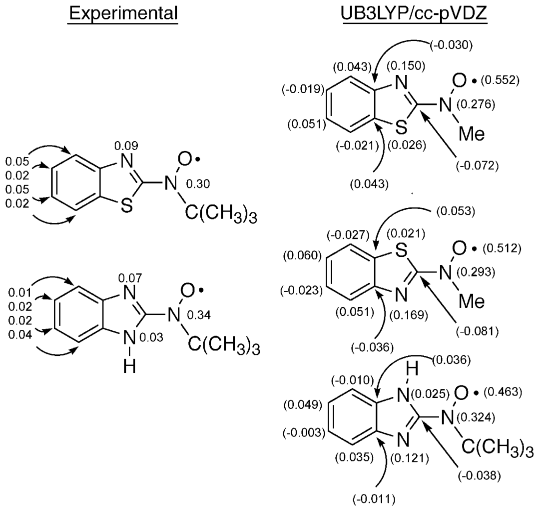


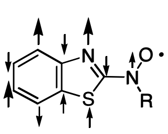
Figure 2. Comparison of experimental and computed spin densities for **1** and **3**. Computed spin densities are for C/N/O/S atoms. Experimental spin densities were estimated[8] from ESR hyperfine coupling (a) using the formulae $a(\text{H–}[\pi\text{-C}]) = (-22\,\text{G})\cdot\rho(\pi\text{-[C]})$ and $a(\text{N}) = (30\,\text{G})\cdot(\rho[\text{N}])$, where ρ are the estimated spin densities for π-carbons and nitrogens. Only the absolute values are given for the experimental spin density estimates. The sp^3 carbons attached to the nitroxide nitrogen had ⩽1–2% spin in the computed spin density results. See the text for further details.

of benzothiazol-2-yl radical with 2-methyl-2-nitrosopropane. The hyperfine constants show that there is significant spin density throughout the benzothiazole ring. In particular, the nitroxide hfc in **1** is appreciably smaller than the values of 10.0–10.2 G observed for isoelectronic 2-(*N*-aminoxyl-*N*-*tert*-butyl)-benzimidazole, **3**, and analogs that our group has described[6] in earlier work. It is, however, fairly close to the nitroxide hfc values of about 9 G observed for **1** and 2-(*N*-aminoxyl-*N*-*tert*-butyl)-thiazole **4** generated in the earlier[5a] radical trapping studies. Clearly, the thiazole ring enhances delocalization of the nitroxide spin density into the heteroatomatic ring system.

We carried out UB3LYP/cc-pVDZ//UB3LYP/6-31G* computations[7] on a model for **1** using a methylnitroxide rather than *tert*-butylnitroxide (Fig. 2). The optimized structure with the N–O group *syn* to the thiazole nitrogen was lower in energy than the *anti* conformer by 7.5 kcal/mol. The computations for both conformers show significant spin density delocalization onto all of the π-atoms of the benzothiazole system. Figure 2 compares the observed hfc of **1** with computationally estimated hfc and with results[6b] for analog **3** based on similar computations.

The experimental results show about a 10% decrease in of spin density on the nitroxide nitrogen in **1** relative to **3**,[8] consistent with the computational modeling results. Also, the benzothiazole ring in **1** bears more computed spin density than the analogous benzimidazole ring in **3**, consistent with the experimentally larger hyperfine of the ring nitrogen in **1**. Although the computations overestimate the experimentally observed spin densities of the ring nitrogen for both **1** and **3**, both computation and experiment qualitatively show more delocalization in the benzothiazole-containing system. Since ^{32}S does not have a nuclear spin moment, we could not experimentally test the computed spin density prediction for the sulfur atom of **1**. However, the computations estimate it to be as large as the spin density on the NH group of **3**, a radical that exhibits[6d] 2-D antiferromagnetic ordering with a Neél temperature of 1.5 K. While the ordering behavior of **3** depends critically on its crystal packing,[6a] we note that even a small spin density on the sulfur atom of **1** as a component of a solid-state molecular magnetic material could have a substantial exchange overlap effect, due to its larger orbital extent by comparison to nitrogen.

The qualitative effect of the change in spin density from **1** to **3** is shown below, with the large arrows indicating positions of experimentally increased spin density in **1**. The UB3LYP/cc-pVDZ//UB3LYP/6-31G* computations are a useful guide for the spin density distribution, and properly reflect both the qualitatively increased spin densities on the ring system in **1** versus **3**, and the magnitude of the shift (about 10–15% shift from the nitroxide to the rings in **1**). In both computations, the exocyclic nitroxide spin population is computational underestimated, and the thiazole nitrogen spin density overestimated.



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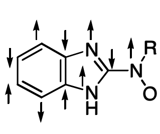

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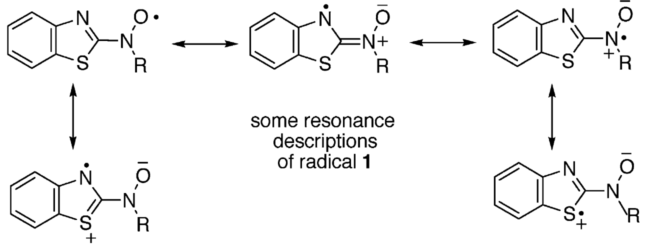
The larger spin delocalization in **1** versus **3** is consistent with the tendency of sulfur-containing heterocycles and sulfur substituents to stabilize nearby unpaired spin density, as seen in dithiadiazolyl and thioaminyl radicals.[4c,9] In system **1**, the benzothiazole ring can support resonance structures that enhance spin delocalization. Despite its greater spin delocalization and noncrystallinity, radical **1** is persistent once purified—with eventual decomposition—and is made more readily than previously studied analog **3**.



There is a dearth of thiazole-based *tert*-butylnitroxides for comparison to **1** (other than **4**). But, 2-(2-thiazolyl)-4,4,5,5-tetramethyl-4,5-dihydro-*1H*-imidazole-3-oxide-1-oxyl (nitronylnitroxide **5**) based coordination complexes with paramagnetic ions have recently been made,[10] and serve as other examples of the continuing interest in using stabilized radical building blocks that incorporate sulfur-containing heterocycles.

Radical **1** is an example of using heteroatom effects to modulate the spin delocalization of a nitroxide group into a conjugated π-system. The present work shows a convenient synthetic route to make **1** in preparative quantities, rather than by previously used spin trapping methods. We hope to continue to improve the ability of organic radicals—and molecular solids that incorporate them—to have strong exchange interactions through space by use of atoms with larger orbital extents, including sulfur. This will assist in their use as building blocks for molecular electronic materials.

1. Experimental section

1.1. General

Benzothiazole and *n*-butyl lithium were used as purchased. THF was dried over sodium/benzophenone and distilled immediately prior to use. 2-Methyl-2-nitrosopropane was prepared according to literature methods.[11]

1.1.1. 2-(*N-tert*-Butyl-*N*-hydroxylamino)benzothiazole (2). To a solution of benzothiazole (0.62 g, 4.6 mmol) and 2-methyl-2-nitrosopropane (0.8 g, 9.12 mmol) in THF (50 mL), under argon, was added *n*-BuLi (3.1 mL, 4.65 mmol) slowly at room temperature with vigorous stirring (dark red color), following which the solution was allowed to stir for 15 min. The reaction was quenched with a saturated solution of NH_4Cl. The phases were separated and the aqueous phase extracted with 3×15 mL of ether. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield an orange oil. Hexanes were added to the oil and the two-phase mixture kept at $-30\,°C$ for 24 h to give crystals of **2** (0.26 g, 25%) as pale yellow plates with mp 157–159 °C (darkens ~145 °C). The product gradually turns pink if exposed to air. The structure was confirmed by single crystal X-ray diffraction analysis, which was submitted to the Cambridge Crystallographic Databank (CCDC Ref #232908). Anal. Calcd for $C_{11}H_{14}N_2SO$: C, 59.43; H, 6.39; N, 12.60. Found: C, 59.50; H, 6.35; N, 12.43. ^1H NMR (200 MHz, DMSO-d_6): δ 10.51 (1H, s), 7.82 (1H, m), 7.58 (1H, m), 7.31 (1H, m), 7.13 (1H, m), 1.43 (9H, s).

1.1.2. 2-(*N*-Aminoxyl-*N-tert*-butyl)benzothiazole (1). To a solution of **1** (0.026 g, 0.117 mmol) in $CHCl_3$ (15 mL), PbO_2 (0.168 g, 0.468 mmol) was added and the resulting suspension stirred at RT for 15 min under argon. The final dark red mixture was filtered through Celite, the filtrate evaporated under vacuum, and the residue purified using column chromatography (silica gel 9:1 hexanes/ethyl acetate) to give **1** (0.022 g, 85%) as a red, very thick oil. Sometimes the TLC of the crude product showed a fluorescent spot at slightly higher R_f than the red product spot. In this situation, the product should be separated from the unidentified fluorescent material by chromatography through alumina (same solvent system as above) prior to silica gel chromatography. The purified product **2** appears stable for a few days in air at ambient temperatures, based on HPLC analysis, but longer storage results in decomposition according to TLC, HPLC, and elemental analysis. Anal. Calcd for $C_{11}H_{13}N_2SO$: C, 59.70; H, 5.92; N, 12.66. Found: C, 59.94; H, 6.00; N, 12.43. UV–vis (MeOH, λ_{max}/nm[ϵ]): 482[3180], 512[3540], 557[3090].

Acknowledgements

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Supplementary material

Supplementary data includes crystallographic and structural parameters for compound **2**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.06.084.

References and notes

1. For a relatively recent example of appying this long-used relationship, see: Griesbeck, A. G.; Gudipati, M. S.; Hirt, J.; Lex, J.; Oelgemoeller, M.; Schmickler, H.; Schouren, F. *J. Org. Chem.* **2000**, *65*, 7151.

2. For general references, see: (a) Kahn, O. *Molecular Magnetism*; VCH: New York, NY, 1993; *Magnetic Properties of Organic Materials*; Lahti, P. M., Ed.; Marcel Dekker: New York, NY, 2000; *Molecular Magnetism: New Magnetic Materials*; Itoh, K., Kinoshita, M., Eds.; Gordon & Breach: Newark, NJ, 2000; (b) Shultz, D. A. In *Magnetic Properties of Organic Materials*; Lati, P. M., Ed.; Marcel Dekker: New York, NY, 1999, pp 103–125; (c) Shultz, D. A.; Fico, R. M., Jr.; Bodnar, S. H.; Kumar, R. K.; Vostrikova, K. E.; Kampf, J. W.; Boyle, P. D. *J. Am. Chem. Soc.* **2003**, *125*, 11761; (d) Shultz, D. A.; Fico, R. M., Jr.; Lee, H.; Kampf, J. W.; Kirschbaum, K.; Pinkerton, A. A.; Boyle, P. D. *J. Am. Chem. Soc.* **2003**, *125*, 15426.
3. Antorrena, G.; Palacio, F.; Rawson, J. M.; Smith, J. N. B. *NATO ASI Series, Series C: Mathematical and Physical Sciences* **1999**, *518*, 217.
4. (a) Palacio, F; Antorrena, G.; Castro, M.; Burriel, R.; Rawson, J.; Smith, J. N. B.; Bricklebank, N.; Novoa, J.; Ritter, C. *Phys. Rev. Lett.* **1997**, *79*, 2336–2339; (b) Alberola, A.; Less, R. J.; Pask, C. M.; Rawson, J. M.; Palacio, F.; Oliete, P.; Paulsen, C.; Yamaguchi, A.; Farley, R. D.; Murphy, D. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4782; (c) McManus, G. D.; Rawson, J. M.; Feeder, N.; van Duijn, J.; McInnes, E. J. L.; Novoa, J. J.; Burriel, R.; Palacio, F.; Oliete, P. *J. Mater. Chem.* **2001**, *11*, 1992; (d) Fujita, W.; Awaga, K. *Science* **1999**, *286*, 261.
5. (a) Torssell, K. *Tetrahedron* **1970**, *26*, 2759; (b) Bentley, T. W.; Jennifer, A. J.; Johnstone, R. A. W.; Russell, P. J.; Sutcliffe, L. H. *J. Chem. Phys., Perkin* **1973**, *2*, 1039.
6. (a) Ferrer, J. R.; Lahti, P. M.; George, C.; Antorrena, G.; Palacio, F. *Chem. Mater.* **1999**, *11*, 2205; (b) Ferrer, J. R.; Lahti, P. M.; George, C.; Oliete, P.; Julier, M.; Palacio, F. *Chem. Mater.* **2001**, *13*, 2447; (c) Lahti, P. M.; Ferrer, J. R.; George, C.; Oliete, P.; Julier, M.; Palacio, F. *Polyhedron* **2001**, *20*, 1465; (d) Miyazaki, Y.; Sakakibara, T.; Ferrer, J. R.; Lahti, P. M.; Antorrena, G.; Palacio, F.; Sorai, M. *J. Phys. Chem. B* **2002**, *106*, 8615.
7. Computations were carried using Gaussian03, Revision B03 on an SGI computer, by Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. J.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian: Pittsburgh, PA, 2003. The hybrid UB3LYP density functional (Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652) was used with the cc-pVDZ basis set for the final spin density computations (Woon, D. E.; Dunning, T. H., Jr. *J. Chem. Phys.* **1993**, *98*, 1358).
8. Experimental spin densities were estimated using the formula $\mathbf{a}_{\mathrm{X}} = Q\cdot\rho$ where the hyperfine constant ($\mathbf{a}_{\mathrm{X}}$) is equal to a constant (Q) times the spin density (ρ) on the atom in question (or, for aryl hydrogens, the spin density on the attached π-carbon atom). For X = N, we used $Q = 30$ G, for X = aryl H we used $Q = -22$ G. Simulation of experimental spectra were carried out using WINSIM (Duling, D. R. *J. Magn. Res.* 1994, *B104*, 105).
9. (a) Miura, Y.; Momoki, M.; Nakatsuji, M.; Teki, Y. *J. Org. Chem.* **1998**, *63*, 1555; (b) Miura, Y.; Kurokawa, S.; Nakatsuji, M.; Teki, Y. *Mol. Cryst. Liq. Cryst. Sci. Technol., Sect. A* **1999**, *334*, 195–204; (c) Zhang, J.; Lahti, P. M.; Wang, R. S. *J. Phys. Org. Chem.* **1999**, *12*, 53; (d) Miura, Y.; Tomimura, T.; Teki, Y. *J. Org. Chem.* **2000**, *65*, 7889.
10. Lin, H.-H.; Mohanta, S.; Lee, C.-J.; Wei, H.-H. *Inorg. Chem.* **2003**, *42*, 1584.
11. Stowell, J. C. *J. Org. Chem.* **1971**, *36*, 3055.