JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Bottleable (Amino)(Carboxy) Radicals Derived from Cyclic (Alkyl)(Amino) Carbenes

Janell K. Mahoney,[†] David Martin,[†] Curtis E. Moore,[‡] Arnold L. Rheingold,[‡] and Guy Bertrand*,[†]

[†]UCSD-CNRS Joint Research Laboratory (UMI 3555), Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093-0343, United States

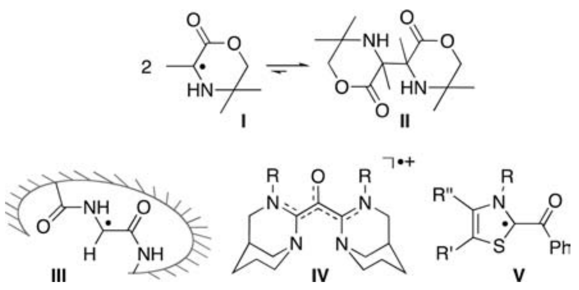
[‡]UCSD Crystallography Facility, San Diego, La Jolla, California 92093-0343, United States

Ⓢ *Supporting Information*

ABSTRACT: Monomeric (amino)(carboxy) radicals were synthesized in two steps: the addition of a stable cyclic (alkyl)(amino) carbene to an acyl chloride, followed by a one-electron reduction. Their stability toward dimerization also allows for the synthesis of related bi- and triradicals.

Persistent organic paramagnetic species have found numerous applications, ranging from synthetic chemistry (radical polymerization, oxidative catalysis) to medicine and material science.[1] Most of the known storable organic radicals are heteroatom-centered. Apart from a few exceptions, such as triarylmethyl radicals or highly π-delocalized phenalenyl systems, carbon-centered radicals are observable, but non-isolable as well-defined monomeric paramagnetic species.[2] The difference in stability is mainly due to the strength of C−C bonds, which is significantly higher (83 kcal·mol^{-1}) than those of O−O, N−N, and S−S bonds (35, 38, 54 kcal·mol^{-1} respectively)[3] and, thus, favors dimerization processes. It is well-known that captodative substitution around a carbon radical center can significantly decrease the strength of the C−C bond,[4−6] but not to the extent of allowing for isolation of well-defined monomers. The 2-oxomorpholin-3-yl radical **I** is a classical example (Scheme 1).[7,8] Although the captodative association of amino and carboxy groups is optimal, only the dimeric form **II** could be isolated. Nonetheless the dimerization is a reversible process; dissolution of **II** in well-degassed solvents yields small, but detectable, amounts of **I** with dissociation constants up to 10^{-9} M. Note that dimerization of glycyl radicals **III** can be prevented when they are sheltered in enzymes.[9,10]

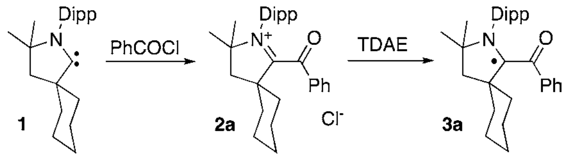
Scheme 1



In recent years, stable carbenes[11] have emerged as efficient tools for the preparation of stable main-group-based radicals and diradicals.[12,13] Recently we made the first foray into the realm of purely organic radicals. Using an anti-Bredt diaminocarbene,[14] we synthesized the air-stable oxyallyl radical cation **IV**,[15] in which the oxygen atom is the principal spin density carrier. On the other hand, Fukuzumi et al. reported the observation of thiazolylidene carbene-based radicals **V** by EPR. These compounds, which were generated *in situ* by electro-oxidation of the corresponding enolate, decomposed within hours at room temperature.[16] Based on these results, we decided to investigate the stability of related radicals built on (alkyl)(amino)carbenes (CAACs).[17] Herein, we report the synthesis and the first structural study of a monomeric (amino)(carboxy) radical. Our synthetic approach is simple and versatile, as demonstrated by the straightforward synthesis and isolation of related bi- and triradicals.

A precursor was readily synthesized by adding benzoyl chloride to a THF solution of CAAC **1** at −78 °C (Scheme 2).

Scheme 2



Dipp: 2,6-iPr$_2$(C$_6$H$_3$)

After workup, iminium salt **2a** was isolated in 81% yield and fully characterized, including a single crystal diffraction study (Figure 1). The cyclic voltammogram of **2a** features two reversible reduction waves (E = −0.93 V and −1.86 V, against Fc$^+$/Fc), for the formation of the radical and the enolate, respectively (see, Supporting Information). Half an equivalent of tetrakis(dimethylamino)ethylene (TDAE) ($E \approx -1.2$ V)[18] was added to a solution of **2a** in dichloromethane at −78 °C, and after workup **3a** was isolated in 94% yield, as deep red crystals.

A single crystal X-ray diffraction study revealed that the N1, C1, C2, and O1 atoms are coplanar, as expected from the captodative stabilization (Figure 1). Note that this conjugated

Received: October 18, 2013
Published: December 4, 2013

dx.doi.org/10.1021/ja4104765 | *J. Am. Chem. Soc.* 2013, 135, 18766−18769

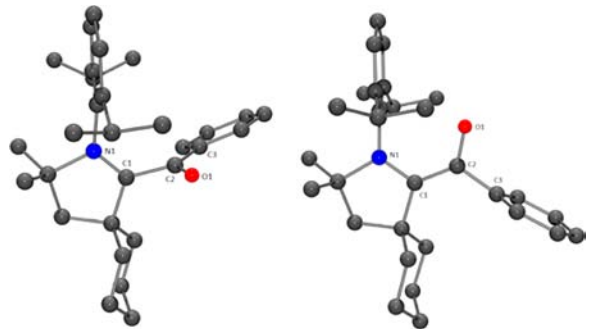


Figure 1. X-ray structure of **2a** (left) and **3a** (right). Hydrogen atoms, solvent molecules, and the chloride anion (for **2a**) were omitted for clarity.

π-system is orthogonal to the phenyl group, in contrast with the precursor **2a**, in which the iminium moiety is orthogonal to the planar benzoyl group. In addition, there is a significant shortening of the C1−C2 bond [**2a**: 1.521(2), **3a**: 1.429(2) Å] and a lengthening of the N1−C1 [**2a**: 1.292(2), **3a**: 1.3601(19) Å], C2−O1 [**2a**: 1.217(2), **3a**: 1.2587(18) Å], and C2−C3 bonds [**2a**: 1.465(2), **3a**: 1.507(2) Å].

The SOMO of **3a** (B3LYP/6-311g** level of theory) is a bonding combination of the π*(CO) molecular orbital and the LUMO of the carbene, with significant electronic density on all conjugated atoms (Figure 2).[19] The delocalization of the spin density across the iminium and carbonyl moieties, which is a consequence of the captodative stabilization, was confirmed by calculations (see Supporting Information for a detailed discussion). About 40% of the spin density is localized on the C1 carbon atom, which is the principal spin carrier, whereas about 28% is localized on O1, 24% on N1, 6% on C2, and less than 2% on the phenyl group.

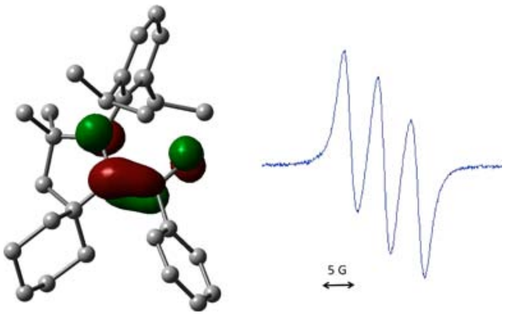
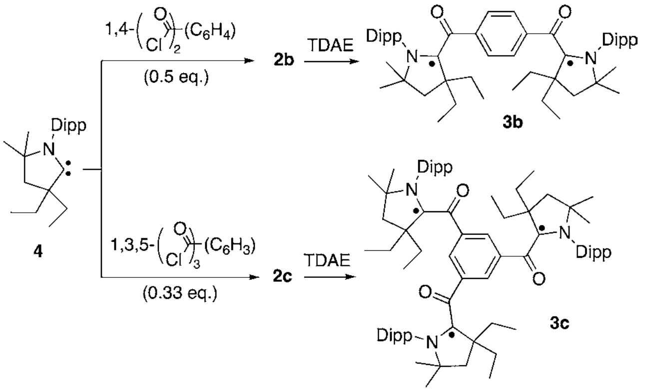


Figure 2. Left: Representation of the SOMO of **3a** (isosurfaces at 0.05 au). Right: X-band EPR spectra of **3a** in benzene at room temperature.

Our synthetic strategy affords in principle an easy entry to a plethora of (amino)(carboxy) radicals from the corresponding acyl chlorides. In order to showcase the versatility of the method, we reacted CAAC **4** with terephthaloyl and trimesoyl chlorides, respectively. The resulting di- and trichloride salts **2b** and **2c** were obtained in 67% and 58% yield, respectively (Scheme 3). Reduction with TDAE afforded the corresponding bi- and triradicals **3b** and **3c**. X-ray diffraction studies revealed structures similar to that of **3a**, the phenyl linker being orthogonal to the (amino)(carboxy) radical units (Figure 3).

The X-band EPR spectra of **3a−c** in solution at room temperature are similar. They feature a triplet with close *g* values (2.0039, 2.0040, and 2.0040, respectively) and isotropic hyperfine coupling constants with nitrogen (a_N = 15.4, 16.8, and 16.8 MHz, respectively). These preliminary data are in line with the expected weak electron exchange couplings in polyradicals **3b−c**, which feature nonconjugating spacers, and radical units far away from each other (C1−C1′ distances range from 6.60 to 7.40 Å).[20]

Scheme 3



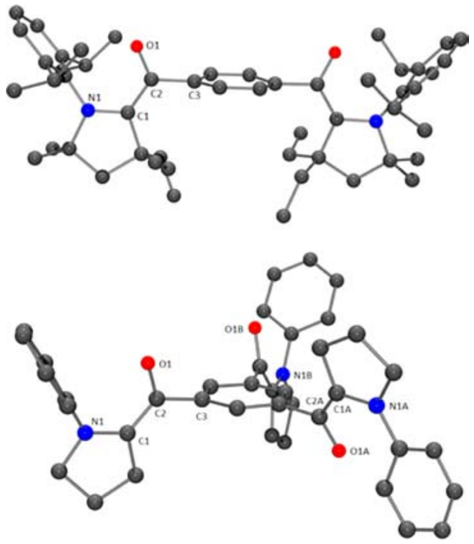


Figure 3. X-ray structure of **3b** (top) and **3c** (bottom). Hydrogen atoms and solvent molecules, as well as isopropyl and ethyl substituents in the case of **3c**, are omitted for clarity.

To summarize, cyclic (alkyl)(amino)carbenes afford in two simple steps (amino)(carboxy)radicals, which do not dimerize and could be characterized for the first time by X-ray diffractometry as monomeric species. Radicals **3a−c** have been stored at room temperature, in solution, and as a solid, for weeks under an inert atmosphere without any apparent decomposition. These results as a whole demonstrate that (amino)(carboxy) radicals have now to be considered as stable monomeric paramagnetic building blocks, similarly to verdazyl and nitroxyl radicals.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and X-ray crystallographic data for **2a−b** and **3a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

guybertrand@ucsd.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Thanks are due to the NSF (CHE-1316956) for financial support and M. Melaimi, M. Angelella, and M. Tauber for assistance with EPR experiments. D.M. acknowledges the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the NSF (OCI-1053575).

REFERENCES

(1) For reviews, see: (a) Rajca, A. *Chem. Rev.* **1994**, *94*, 871. (b) *Magnetic Properties of Organic Materials*; Lahti, P. M., Ed.; Marcel Dekker: New York, 1999. (c) Berliner, L. J. *Spin Labelling: Theory and Applications*; Academic Press: New York, 1979. (d) *Stable Radicals: Fundamental and Applied Aspects of Odd-Electron Compounds*; Hicks, R. G., Ed.; Wiley: Chichester, 2010. (e) Sugawara, T.; Komatsua, H.; Suzukia, K. *Chem. Soc. Rev.* **2011**, *40*, 3105. (f) Ratera, I.; Veciana, J. *Chem. Soc. Rev.* **2012**, *41*, 303.

(2) Hicks, R. G. *Org. Biomol. Chem.* **2007**, *5*, 1321.

(3) Sanderson, R. T. *Chemical Bonds and Bond Energy*; Academic Press: New York, 1976.

(4) For the captodative stabilization of radicals (also known as push−pull or merostabilization), see: (a) Baldock, R. W.; Hudson, P.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1422. (b) Balaban, A. T.; Caproiu, M. T.; Negoita, N.; Baican, R. *Tetrahedron* **1977**, *33*, 2249. (c) Viehe, H. G.; Mértnyi, E.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917. (d) Viehe, H. G.; Janousek, Z.; Mértnyi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148. (e) Zipse, H. *Top. Curr. Chem.* **2006**, *263*, 163.

(5) (a) Leroy, G.; Peeters, D.; Sana, M.; Wilante, C. *Substituent Effects in Radical Chemistry*; Viehe, V. H., Janousek, Z., Mértnyi, R., Eds.; Reidel: Boston, 1986; pp 1−48. (b) Katritzky, A. R.; Zerner, M. C.; Karelson, M. M. *J. Am. Chem. Soc.* **1986**, *108*, 7213. (c) Pasto, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 8164. (d) Bordwell, F. G.; Lynch, T.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558. (e) Wright, J. S.; Shadnia, H.; Chepelev, L. L. *J. Comput. Chem.* **2009**, *30*, 1016.

(6) Captodative C-centered radicals are also pivotal intermediates in radical organic chemistry; see: (a) *Radicals in organic chemistry*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (b) Easton, C. J. *Chem. Rev.* **1997**, *97*, 53.

(7) (a) Koch, T. H.; Olesen, J. A.; DeNiro, J. *J. Am. Chem. Soc.* **1975**, 97, 7285. (b) Himmelsbach, R. J.; Barone, A. D.; Kleyer, D. L.; Koch, T. H. *J. Org. Chem.* **1983**, *48*, 2989. (c) Gaudiano, G.; Sweeney, K.; Haltiwanger, R. C.; Koch, T. H. *J. Am. Chem. Soc.* **1984**, *106*, 7628. (d) Benson, O., Jr.; Demirdji, S. H.; Haltiwanger, R. C.; Koch, T. H. *J. Am. Chem. Soc.* **1991**, *113*, 8879. (e) Benson, O., Jr.; Gaudiano, G.; Haltiwanger, R. C.; Koch, T. H. *J. Org. Chem.* **1988**, *53*, 3036.

(8) For other related isolated dimers, see also: (a) Kleyer, D. L.; Haltiwanger, R. C.; Koch, T. H. *J. Org. Chem.* **1983**, *48*, 147. (b) Welle, F.; Verevkin, S. P.; Keller, M.; Beckhaus, H.-D.; Rüchardt, C. *Chem. Ber.* **1994**, *127*, 697. (c) Frenette, M.; Aliaga, C.; Font-Sanchis, E.; Scaiano, J. C. *Org. Lett.* **2004**, *6*, 2579 and references cited herein.

(9) For reviews on radical based proteins, see: (a) Stubbe, J.; van der Donk, W. A. *Chem. Rev.* **1998**, *98*, 705. (b) Buckel, W.; Golding, B. T. *Annu. Rev. Microbiol.* **2006**, *60*, 27.

(10) (a) Frey, M.; Rothe, M.; Wagner, A. F.; Knappe, J. *J. Biol. Chem.* **1994**, *269*, 12432. (b) Mulliez, E.; Fontecave, M.; Gaillard, J.; Reichard, P. *J. Biol. Chem.* **1993**, *268*, 2296. (c) Leuthner, B.; Leutwein, C.; Schulz, H.; Horth, P.; Haehnel, W.; Schiltz, E.; Schägger, H.; Heider, J. *Mol. Microbiol.* **1998**, *28*, 615. (d) O'Brien, J. R.; Raynaud, C.; Croux, C.; Girbal, L.; Soucaille, P.; Lanzilotta, W. N. *Biochemistry* **2004**, *43*, 4635. (e) Martins, B. M.; Blaser, M.; Feliks, M.; Ullmann, G. M.; Buckel, W.; Selmer, T. *J. Am. Chem. Soc.* **2011**, *133*, 14666. (f) Jarling, R.; Sadegh, M.; Drozdowska, M.; Lahme, S.; Buckel, W.; Rabus, R.; Widdel, F.; Golding, B. T.; Wilkes, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1334.

(11) For reviews, see: (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Vignolle, J.; Cattoën, X.; Bourissou, D. *Chem. Rev.* **2009**, *109*, 3333. (c) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8810. (d) Droege, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940. (e) Martin, D.; Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Organometallics* **2011**, *30*, 5304. (f) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122. (g) *N-Heterocyclic carbenes, from laboratory curiosities to efficient synthetic tools*; Díez-González, S., Ed.; Royal Society of Chemistry Publishing: Cambridge, 2011.

(12) For isolated carbene main-group-element-centered radicals: (a) Back, O.; Donnadieu, B.; Parameswaran, P.; Frenking, G.; Bertrand, G. *Nat. Chem.* **2010**, *2*, 369. (b) Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 5930. (c) Back, O.; Celik, M. A.; Frenking, G.; Melaimi, M.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2010**, *132*, 10262. (d) Back, O.; Donnadieu, B.; von Hopffgarten, M.; Klein, S.; Tonner, R.; Frenking, G.; Bertrand, G. *Chem. Sci* **2011**, *2*, 858. (e) Kinjo, R.; Donnadieu, B.; Celik, M. A.; Frenking, G.; Bertrand, G. *Science* **2011**, *333*, 610. (f) Percival, P. W.; McCollum, B. M.; Brodovitch, J.-C.; Driess, M.; Mitra, A.; Mozafari, M.; West, R.; Xiong, Y.; Yao, S. *Organometallics* **2012**, *31*, 2709. (g) Mondal, K. C.; Roesky, H. W.; Schwarzer, M. C.; Frenking, G.; Tkach, I.; Wolf, H.; Kratzert, D.; Herbst-Irmer, R.; Niepötter, B.; Stalke, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 1801. (h) Abraham, M. Y.; Wang, Y.; Xie, Y.; Gilliard, R. J., Jr.; Wei, P.; Vaccaro, B. J.; Johnson, M. K.; Schaefer, H. F., III; Schleyer, P. v. R.; Robinson, G. H. *J. Am. Chem. Soc.* **2013**, *135*, 2486. (i) Mondal, K. C.; Roesky, H. W.; Schwarzer, M. C.; Frenking, G.; Niepötter, B.; Wolf, H.; Herbst-Irmer, R.; Stalke, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 2963. (j) Mondal, K. C.; Samuel, P. P.; Tretiakov, M.; Singh, A. P.; Roesky, H. W.; Stückl, A. C.; Niepötter, B.; Carl, E.; Wolf, H.; Herbst-Irmer, R.; Stalke, D. *Inorg. Chem.* **2013**, *52*, 4736. (k) Martin, C. D.; Soleilhavoup, M.; Bertrand, G. *Chem. Sci.* **2013**, *4*, 3020. (l) Abraham, M. Y.; Wang, Y.; Xie, Y.; Gilliard, R. J., Jr.; Wei, P.; Vaccaro, B. J.; Johnson, M. K.; Schaefer, H. F., III; Schleyer, P. v. R.; Robinson, G. H. *J. Am. Chem. Soc.* **2013**, *135*, 2486. (m) Mondal, K. C.; Roesky, H. W.; Stueckl, A. C.; Ehret, F.; Kaim, W.; Dittrich, B.; Maity, B.; Koley, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 11804.

(13) For transient and persistent diaminocarbene-$BR_2^\bullet$ adducts, see: (a) Matsumoto, T.; Gabbaï, F. P. *Organometallics* **2009**, *28*, 4252. (b) Ueng, S.-H.; Solovyev, A.; Yuan, X.; Geib, S. J.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Newcomb, M.; Walton, J. C.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 11256. (c) Walton, J. C.; Brahmi, M. M.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Chu, Q.; Ueng, S.-H.; Solovyev, A.; Curran, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 2350. (d) Curran, D. P.; Solovyev, A.; Brahmi, M. M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 10294.

(14) Martin, D.; Lassauque, N.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6172.

(15) Martin, D.; Moore, C. E.; Rheingold, A. L.; Bertrand, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 7014.

(16) (a) Nakanishi, I.; Otoh, S.; Suenobu, T.; Fukuzumi, S. *Chem. Commun.* **1997**, 1927. (b) Nakanishi, I.; Otoh, S.; Fukuzumi, S. *Chem.—Eur. J.* **1999**, *5*, 2810.

(17) (a) Lavallo, V.; Canac, Y.; Prasang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705. (b) Jazzar, R.; Dewhurst, R. D.; Bourg, J.-B.; Donnadieu, B.; Canac, Y.; Bertrand, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2899. (c) Jazzar, R.; Bourg, J.-B.; Dewhurst, R. D.; Donnadieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492. (d) Back, O.; Henry-Ellinger, M.; Martin, C. D.; Martin, D.; Bertrand, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 2939.

(18) Burkholder, C.; Dolbier, W. R., Jr. *J. Org. Chem.* **1998**, *63*, 5385.

(19) Calculations were performed on the Gaussian suite of programs: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.;

Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision 4.2.0; Gaussian, Inc.: Wallingford, CT, 2009.

(20) Triradical **3c** is reminiscent of some well known hindered 1,3,6-trinitroxylbenzenes: Fujita, J.; Tanaka, M.; Suemune, H.; Koga, N.; Matsuda, K.; Iwamura, H. *J. Am. Chem. Soc.* **1996**, *118*, 9347.