The reactivity of aminoxyls towards peroxyl radicals: an *ab initio* thermochemical study †

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A thermochemical study has been carried out in order to gain deeper insight into the mechanism with which aminoxyls and peroxyl radicals react together. CBS-QB3 has been chosen from the *ab initio* high accuracy energy methods available. Different mechanisms are discussed and the thermodynamic quantities computed for each species involved in the different reaction steps. The results from this study suggest a mechanism involving a radical–radical coupling between aminoxyl and peroxyl with formation of an unstable amino trioxide that may decompose yielding dioxygen and the corresponding alkoxyamine. The latter derivative can undergo C–O bond cleavage forming the starting aminoxyl, which along with dioxygen represents the main reaction product.

Introduction

The fast reactivity of aminoxyls with carbon-centered radicals has been extensively studied as well as the thermal behaviour of the corresponding radical–radical coupling products (alkoxyamines).[1,2] However, the reactivity of aminoxyls towards oxygen-centered radicals still remains not well determined: studies based on the identification of the reaction products have been possible only when the aminoxyls employed were able to delocalize their free valency in an aromatic π system.[3] Nevertheless this subject remains of interest because of the use of aminoxyls as spin probes,[4] contrast agents[5] and antioxidants in polymers[6] as well as in biological systems.[7] Recently the reaction between 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and *tert*-butylperoxyl radicals has been reported[8] and the proposed mechanism is reproduced in Scheme 1.

The aminotrioxide intermediate TEMPO-OOBu^t, which is the key intermediate, has not been isolated, but its structure was established by its chromatographic behaviour, its ^{1}H-NMR spectrum and by analogy with di-*tert*-butyl trioxide, which has previously been studied only at low temperatures.[9] The proposed mechanism explains the fact that as expected the reaction products are mainly TEMPO and dioxygen, along with *tert*-butyl alcohol and di-*tert*-butyl peroxide; in addition some of the alkoxyamine TEMPO-CH_3, probably arising from the coupling between TEMPO and methyl radicals produced by the β-scission of some *tert*-butoxyl radicals, has been detected.

In order to gain deeper insight into this mechanism, we carried out a thermochemical study by means of *ab initio* high accuracy energy methods.

Method

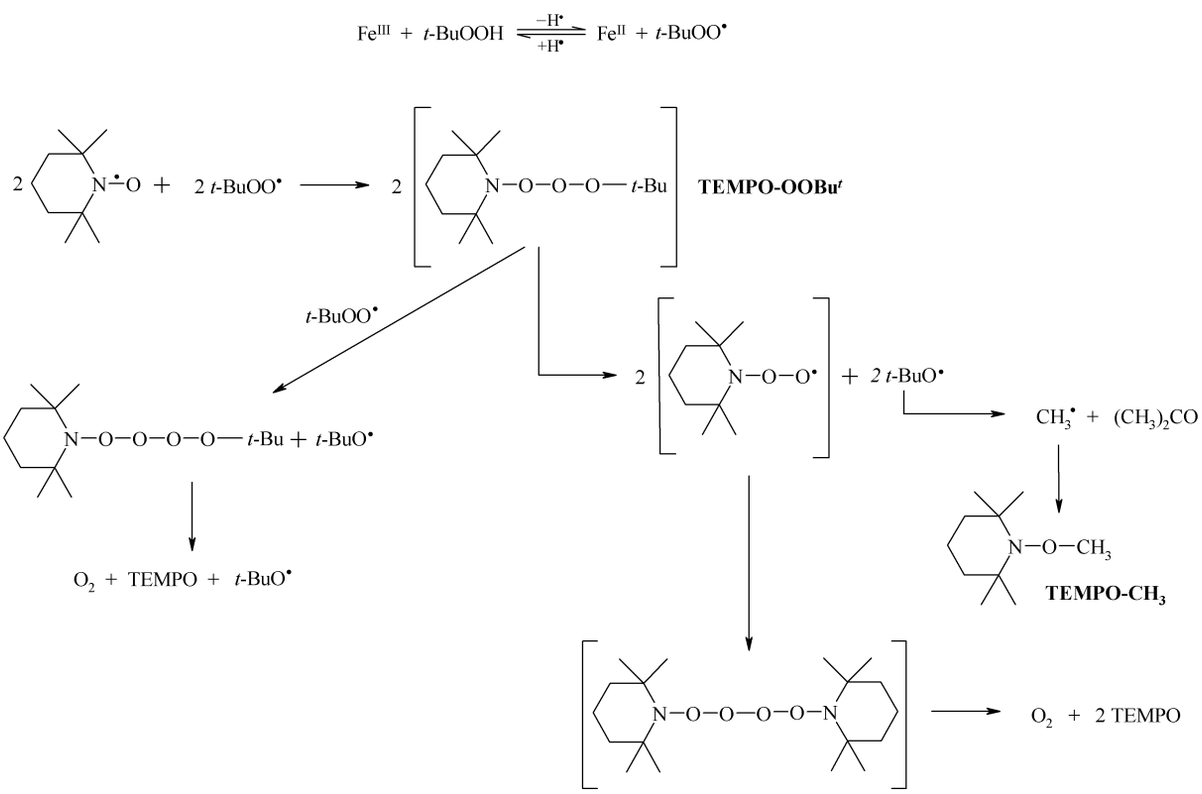
Among the complete basis set (CBS) family of methods[10] we have chosen the CBS-QB3 method available in Gaussian 98;[11] for our purposes these calculations represent a good compromise between accuracy and computational cost. In fact we obtained results in very good agreement with the experimental heat of formation of the free radicals (see Table 1). Considering that such calculations become practical only for species

† Electronic supplementary information (ESI) available: Gaussian 98 archives for all calculations performed. For direct electronic access see http://www.rsc.org/suppdata/p2/b1/b103763n

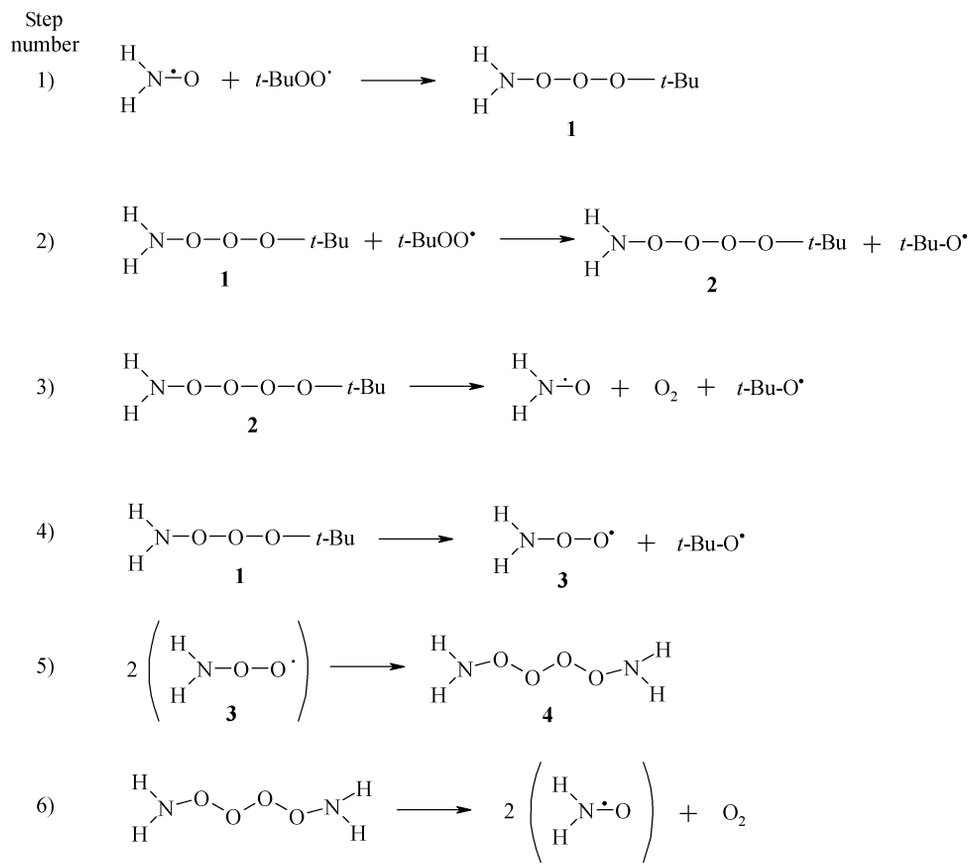
Table 1 Thermodynamic parameters for all species involved in reaction steps 1–22 of Schemes 2–5

Compound	CBS-H [a,b]	CBS-G [a,c]	CBS-E [a,d]	D_0^0 [e]	$\Delta_f H_{298}^0$ [f]	Exp [g]
$H_2NO^{\bullet}$	−130.916358	−130.943257	−130.920564	259.006	13.720	—
t-BuOO$^{\bullet}$	−307.648920	−307.688878	−307.657496	1281.5978	−26.4086	−25.217[15]
H_2NO_3–*t*-Bu	−438.567183	−438.613644	−438.578593	1540.938	−13.2905	—
H_2NO_4–*t*-Bu	−513.635395	−513.686425	−513.648244	1592.409	−5.9084	—
t-BuO$^{\bullet}$	−232.559957	−232.597180	−232.567529	1217.378	−20.770	−21.82[16]
$H_2NOO^{\bullet}$	−205.962779	−205.993390	−205.967617	296.296	34.777	—
H_2N–O_4–NH_2	−411.974155	−412.013598	−411.982446	622.218	39.652	—
O_2 [h]	−150.161335	−150.184608	−150.164642	118.842	0	—
$HOO^{\bullet}$	−150.737263	−150.763244	−150.741067	166.914	1.400	2.51[17]
H_2NO_3H	−281.659627	−281.692764	−281.665594	428.41	11.944	—
H_2NOH	−131.537424	−131.564063	−131.541587	335.063	−11.743	—
H_2O_2	−151.374580	−151.401134	−151.378795	253.454	−34.262	−32.58[17]
H_2NO–*t*-Bu	−288.440496	−288.480528	−288.449540	1444.428	−34.165	—
t-Bu$^{\bullet}$	−157.425488	−157.462383	−157.425488	1125.106	13.425	12.380[18]
$H_2N^{\bullet}$	−55.787394	−55.810157	−55.791175	170.049	44.461	44.192[17]

[a] In hartrees (E_h) as obtained from the CBS calculation. [b] CBS enthalpy at 298.15 K. [c] CBS Gibbs free energy at 298.15 K. [d] CBS energy at 0 K. [e] Atomization energy in kcal mol^{-1} at 0 K. [f] Heat of formation at 298.15 K in kcal mol^{-1} obtained following the method described in ref. 14. [g] Gas phase experimental heat of formation in kcal mol^{-1}. [h] Referred to the triplet state.



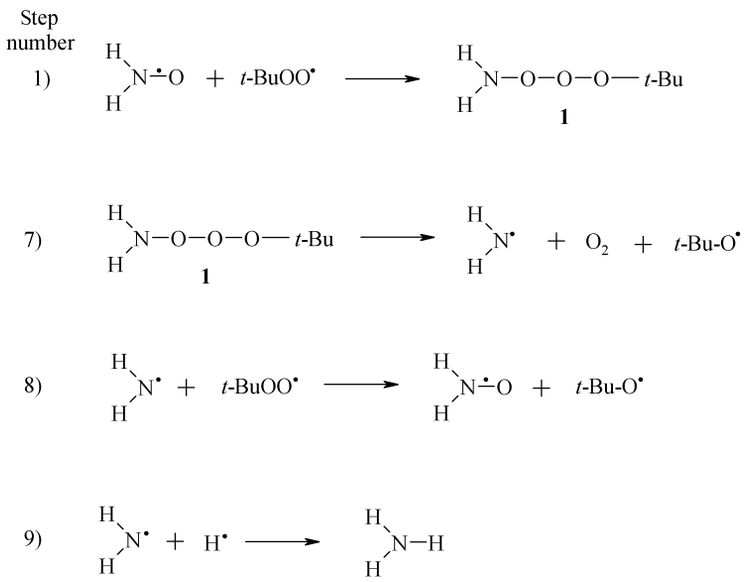
Scheme 1



Scheme 2

containing few non hydrogen atoms,[10,12] we replaced TEMPO with the simplest aminoxyl $H_2NO^{\bullet}$ (dihydro nitroxide) in our runs as previously reported.[13] For the same reason Scheme 1 has to be replaced by Scheme 2.

This compound method, based upon optimized geometries at the B3LYP level of theory, gave for all open shell species $\langle S^2 \rangle = 0.7500 \pm 0.0002$ for spin contamination; in addition, we never found imaginary frequencies, confirming that the



Scheme 3

Table 2 Thermodynamic parameters for reaction steps 1–22 in Schemes 2–5

Step[a]	CBS-ΔH[b]	CBS-ΔG[b]	CBS-ΔS[c]	$\Delta_r H^0_{298}$[d]
1	−1.195	11.603	−42.925	−1.794
2	13.021	11.87	3.860	10.779
3	−1.4150	−24.234	76.535	−2.1916
4	27.891	14.479	44.984	26.2475
5	−30.495	−16.828	−45.839	−29.902
6	−12.485	−36.097	79.195	−12.212
7	36.707	13.616	77.448	35.663
8	−25.101	−25.980	2.948	−27.075
9	−107.32	−98.889	−30.866	−107.802
10	−3.769	8.620	−41.553	−4.286
11	−24.556	−35.0825	35.306	−23.687
12	−10.198	−10.720	1.751	−9.627
13	−21.742	−32.312	35.452	−20.874
14	61.904	46.993	50.012	60.265
18	58.449	45.928	41.996	56.537
19	−8.817	0.863	−32.467	−9.415
20	−51.797	−52.063	0.892	−51.529
21	−42.980	−52.925	33.356	−42.114
22	33.348	19.948	49.057	29.462

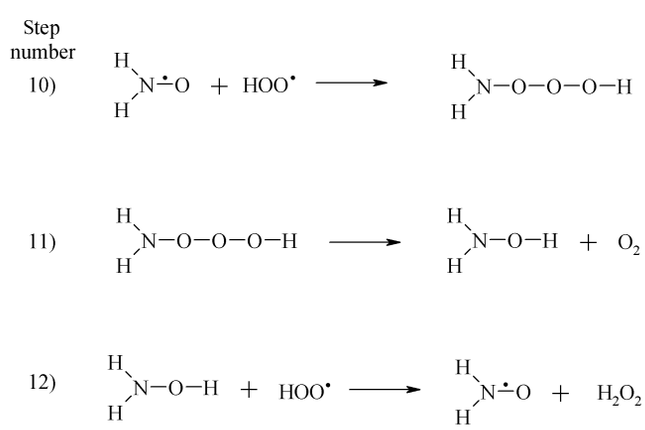
[a] Steps as numbered in Schemes 2–5. [b] In kcal mol^{-1} from the corresponding CBS–*H* and CBS–*G* values in Table 1. [c] ($\Delta H - \Delta G$)/298.15 in cal mol^{-1} K^{-1}. [d] In kcal mol^{-1} computed from the corresponding heat of formation at 298.15 K and using experimental values when available (see Table 1).

computed geometries always referred to a minimum. Moreover, using the procedure described in the literature,[14] we calculated the heat of formation in the gas phase for all species involved. These data, together with other quantities arising from our calculations, are collected in Table 1. In Table 2 the data for each reaction step are reported.

Results and discussion

According to Scheme 2, the first reaction which takes place is represented by a coupling between two radicals, the aminoxyl and the *tert*-butylperoxyl, with the formation of the amino trioxide intermediate **1**. Intermediate **1** is believed to react, as described in step 2, with *t*-BuOO$^{\bullet}$ to form the corresponding tetraoxide **2** and producing *tert*-butoxyl radicals, or to decompose giving the aminoperoxyl **3** and *tert*-butoxyls (step 4). On the other hand, tetraoxide **2** can decompose as described in step 3 producing the starting $H_2NO^{\bullet}$, dioxygen and *tert*-butoxyls. Moreover intermediate **3** can undergo self-reaction (step 5) forming **4** which after decomposition yields the starting aminoxyl and dioxygen (step 6). In addition to the fact that the data reported in Table 2 refer to the gas phase while the reaction takes place in pyridine solution,[8] if the formation of intermediate **1** is considered as thermoneutral, then the reaction of step 2 should be disfavoured as well as the formation of the aminoperoxyl **3** from step 4. This last step can be viewed as the computing of the H_2NOO-OBu-*t* bond dissociation energy (BDE) in **1** to form the aminoperoxyl **3**, the TEMPO analogue of which has been previously detected at low temperatures[19] by EPR. On the other hand step 3 shows favourable parameters as well as steps 5 and 6, these latter have already been proposed in the mechanism of HALS (hindered amines light stabilizers).[20] In Scheme 3 is shown an alternate mechanism reported in the same paper[8] as the "McKee proposal" in which steps 2–6 are replaced with steps 7–9: in this case the decomposition of the key intermediate **1** as described in step 7 should be disfavoured as well.

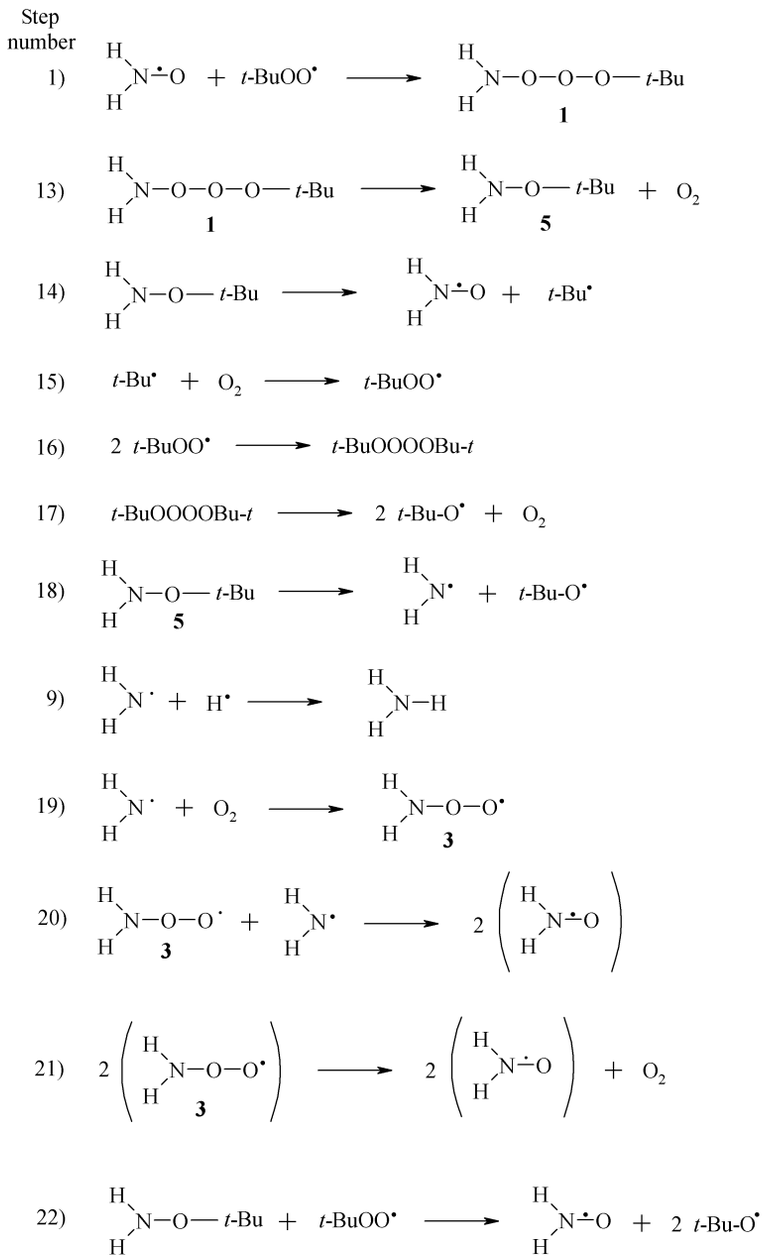
Indeed, an intermediate similar to **1** has been previously postulated in the mechanism reported in Scheme 4, which was



Scheme 4

proposed to explain how some aminoxyls act as superoxide dismutase (SOD) mimics.[21,22] Also in this case we run the same calculations using $H_2NO^{\bullet}$ as the model aminoxyl but replacing *t*-BuOO$^{\bullet}$ with HOO$^{\bullet}$: the results show that all steps in Scheme 4 are likely, substantiating that hypothesis.

Upon this basis, assuming that amino trioxide **1** still represents the key intermediate, we propose in Scheme 5 an alternative mechanism to that reported in Scheme 2.



Scheme 5

We believe that step 2 can be replaced by the more likely step 13 with the formation of alkoxyamine **5**. Despite the fact that the cleavage of the C–O bond in such molecules requires energy, it is known that in similar compounds step 14 is a reversible process.[1] In fact the rate constant and activation parameters for the decomposition of the TEMPO-Bu^t alkoxyamine have beeen measured,[2] and this behaviour represents the basis of the aminoxyl-mediated living radical polymerization controlled by the persistent radical effect.[23] In addition, the presence of dioxygen could shift this equilibrium to the right side[1] for the very high rate constant of step 15 which, together with 16 and 17, participate in the accepted mechanism for autooxidation. Moreover, the key role played by alkoxyamine **5** could be strengthened by step 22 which foresees its reaction with another molecule of *tert*-butoxylperoxyl to give back the starting aminoxyl along with two molecules of *tert*-butoxyl. On the other hand, if **5** should undergo N–O bond cleavage as in step 18 requiring less energy than in 14, the aminyl radical formed may abstract a hydrogen to give the corresponding amine (step 9), react with dioxygen or with **3** as already described[24] according to the exoenergetic steps 19–21.

Conclusions

The reactivity of aminoxyls towards oxygen-centered radicals is still not well established. In a recent work[8] the reaction between 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and *tert*-butylperoxyl radicals, in pyridine at room temperature, has been studied and the main products were the starting aminoxyl and dioxygen. To explain this behaviour a mechanism has been proposed in which the first step is represented by a coupling of the two free radicals with the formation of an amino trioxide intermediate. In order to verify if alternate mechanisms have to be considered, we carried out a thermochemical study. The availability of *ab initio* high accuracy energy compound methods allowed us to perform this investigation but, to make possible these very computationally demanding calculations, we had to replace TEMPO with the model aminoxyl $H_2NO^{\bullet}$. Taking into account that another limitation could be the fact that these calculations refer to the gas phase, the alternate mechanism that we propose foresees that an analogous amino trioxide intermediate decomposes to form dioxygen and the corresponding alkoxyamine. The known C–O bond cleavage of

these latter derivatives, along with their reaction with additional peroxyls, could then give back the starting aminoxyl.

Acknowledgements

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References

1 J. A. Howard and J. C. Tait, *J. Org. Chem.*, 1978, **43**, 4279; D. W. Grattan, D. J. Carlsson, J. A. Howard and D. M. Wiles, *Can. J. Chem.*, 1979, **57**, 2834; J. Chateauneuf, J. Lusztyk and K. U. Ingold, *J. Org. Chem.*, 1988, **53**, 1629; A. L. J. Beckwith and V. W. Bowry, *J. Org. Chem.*, 1988, **53**, 1632; T. Khote, S. Marque, R. Martschke, M. Popov and H. Fisher, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1553.

2 P. Stipa, L. Greci, P. Carloni and E. Damiani, *Polym. Degrad. Stab.*, 1997, **55**, 323.

3 J. A. Howard, *Adv. Free Radical Chem.*, 1971, **4**, 161; M. A. Khloplyankina, A. L. Buchachenko, M. B. Neiman and A. G. Vasil'eva, *Kinet. Katal.*, 1965, **6**, 465; C. Berti, M. Colonna, L. Greci and L. Marchetti, *Tetrahedron*, 1977, **33**, 2321; C. Berti, M. Colonna, L. Greci and L. Marchetti, *Tetrahedron*, 1977, **33**, 3149; L. Greci, *Tetrahedron*, 1982, **38**, 2435; L. Cardellini, P. Carloni, L. Greci and P. Stipa, *Gazz. Chim. Ital.*, 1989, **119**, 621; E. Damiani, P. Carloni, P. Stipa and L. Greci, *Free. Radical Res.*, 1999, **31**, 113; P. Carloni, E. Damiani, M. Scattolini, P. Stipa and L. Greci, *J. Chem. Soc., Perkin Trans. 2*, 2000, 447.

4 B. Ranby and J. F. Rabek, *ESR Spectroscopy in Polymer Research*, Springer Verlag, Berlin, 1971.

5 R. C. Brash, D. A. London, G. E. Wesbey, T. N. Tozer, D. E. Nirecki, R. D. Williams, J. Doemeny, L. D. Tuck and D. P. Lallemand, *Radiology (Easton, Pa.)*, 1983, **147**, 773.

6 P. P. Klemchuk and M. E. Gande, *Polym. Degrad. Stab.*, 1988, **22**, 241 and references cited therein; N. Kocherginsky and H. M. Swartz, *Nitroxide Spin Labels, Reactions in Biology and Chemistry*, CRC Press, Boca Raton, 1995.

7 L. Greci, E. Damiani, P. Carloni and P. Stipa, *Free Radicals in Biology and Environment*, ed. F. Minisci, Kluwer Academic Publishers, The Netherlands, 1997, p. 223; A. Samuni and M. C. Krishna, *Handbook of Synthetic Antioxidants*, ed. L. Packer and E. Cadenas, Marcel Dekker Inc., New York, 1997, p. 351; M. C. Krishna and A. Samuni, *Methods Enzymol.*, 1994, **234**, 580.

8 D. H. R. Barton, V. N. Le Gloahec and J. Smith, *Tetrahedron Lett.*, 1998, **39**, 7483.

9 S. L. Khursan, A. F. Khalizov and V. V. Shereshovets, *Russ. Chem. Bull.*, 1997, **46**, 884.

10 M. R. Nyden and G. A. Petersson, *J. Chem. Phys.*, 1981, **75**, 1843; G. A. Petersson and M. A. Al-Laham, *J. Chem. Phys.*, 1991, **94**, 6081; G. A. Petersson, T. Tensfeldt and J. A. Montgomery, *J. Chem. Phys.*, 1991, **94**, 6091; J. A. Montgomery, J. W. Ochterski and G. A. Petersson, *J. Chem. Phys.*, 1994, **101**, 5900; J. W. Ochterski, G. A. Petersson and J. A. Montgomery, Jr., *J. Chem. Phys.*, 1996, **104**, 2598; J. A. Montgomery, Jr., M. J. Frisch, J. W. Ochterski and G. A. Petersson, *J. Chem. Phys.*, 1999, **110**, 2822.

11 Gaussian 98, Revision A.9, M. J. Frisch, G. W. Trucks, H. Schlegel, G. E. BScuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, B. Cammi, C. Mennucci, C. Pomelli, S. Adamo, J. Clifford, G. A. Ochterski, P. Y. Petersson, Q. Ayala, K. Cui, R. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. P. Challacombe, M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.

12 J. W. Ochterski, G. A. Petersson and K. B. Wiberg, *J. Am Chem. Soc.*, 1995, **117**, 11299.

13 V. Barone, A. Grand, C. Minichino and R. Subra, *J. Phys. Chem.*, 1993, **97**, 6355; N. Rega, M. Cossi and V. Barone, *J. Chem. Phys.*, 1996, **105**, 11060; V. Barone, A. Bencini, M. Cossi, A. Di Matteo, M. Mattesini and F. Totti, *J. Am. Chem. Soc.*, 1998, **120**, 7069; V. Barone and A. Di Matteo, *J. Phys. Chem. A*, 1999, **103**, 7676.

14 L. A. Curtiss, K. Raghavachari, P. C. Redfern and J. A. Pople, *J. Chem. Phys.*, 1997, **106**, 1063.

15 J. L. Holmes, F. P. Lossing and P. M. Mayer, *J. Am. Chem. Soc.*, 1991, **113**, 9723.

16 H. P. Diogo, M. E. Minas da Piedade, J. A. M. Simoes and Y. Nagano, *J. Chem. Thermodyn.*, 1995, **27**, 597.

17 CRC Handbook of Chemistry and Physics, 80th edn., ed. D. R. Lide, CRC Press, New York, 1999–2000.

18 J. A. Seetula and I. R. Slagle, *J. Chem. Soc., Faraday Trans.*, 1997, **93**, 1709.

19 A. Faucitano, A. Buttafava and F. Martinotti, *J. Phys. Chem.*, 1984, **88**, 1187; H. A. Gottinger, V. E. Zubarev and O. Brede, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2167.

20 J. Pospisil, *Advances in Polymer Science*, ed. K. Dusek, Springer Verlag, Berlin, 1995, vol. 124.

21 P. Carloni, E. Damiani, L. Greci, P. Stipa, G. Marrosu, R. Petruccu and A. Trazza, *Tetrahedron*, 1996, **52**, 11257.

22 The accepted mechanism for the SOD mimic behaviour of aminoxyls foresees their oxidation to the corresponding oxo-ammonium cations by superoxide anion. Since the redox potential of some aminoxyls is sufficiently negative to make this step very unlikely, in ref. 21 an alternate mechanism has been proposed, here reported in Scheme 4, as a possible explanation.

23 H. Fisher, *J. Am. Chem. Soc.*, 1986, **108**, 3925; B. E. Daikh and R. G. Finke, *J. Am. Chem. Soc.*, 1992, **114**, 2938.

24 K. U. Ingold and J. R. Roberts, *J. Am. Chem. Soc.*, 1973, **95**, 3228.