

Syntheses of Nitroxide Diradicals and Tetraradicals

By

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PREVIEW

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University of Nebraska, 2006

Advisor: Andrzej Rajca

Nitroxides are one of the most widely investigated classes of “stable” free radicals in the chemical, biological and medical sciences owing to their potential applications such as antioxidants, spin-labels, co-oxidants, building blocks for practical organic magnets, controlled free-radical polymerization, EPR and NMR (MRI) based contrast reagents. Central to the progress on these investigations has been the understanding of the effects of orientation (bond torsions), distance, and structure of different coupling units controlling the spin-spin interaction between two and more nitroxide spin moieties. Attachment of nitroxides on a rigid framework, which limits the extent of conformational change, is a necessary step towards addressing these effects on spin-spin exchange qualitatively and quantitatively.

Calix[4]arenes immobilized in a 1,3-alternate conformation are structurally rigid with a cylindrical inner tunnel and possess two cofacial pairs of aromatic rings oriented orthogonal along the cavity axis. From numerous X-ray studies, the distance between the cofacial pair of aromatic rings has been found to be 5 – 6 Å. This arrangement allows one to study the through-bond (spin polarization of the σ - and π -

core) and through-space (overlap of the singly-occupied p-orbitals) mechanism of exchange coupling by attaching two or four nitroxide moieties respectively on the aromatic rings. The design principle, synthetic methods, EPR and magnetic studies for stable nitroxide radicals presented in Chapter 1 were used for the synthesis and characterization of the 1,3-alternate calix[4]arene nitroxide diradical and tetraradical described in Chapter 2.

In order to minimize the effect of bond-torsions as in the above nitroxides and weaken the through-bond exchange coupling, so that the through-space exchange coupling mechanism remains significant, the 1,3-alternate calix[4]arene nitronylnitroxide diradical and tetraradical were synthesized and characterized (Chapter 3).

With the desire of exploring the biological applications of such diradicals and tetraradicals based on rigid scaffolds, a calix[4]arene nitroxide tetraradical with hexa-poly(ethylene)glycol was synthesized (Chapter 4). The observation of good water solubility for the tetraradical (> 50 mM) and the preliminary investigations of EPR properties, provide a foundation for a future synthesis of an octaradical on the same scaffold.

Lastly, our interest in exploring the applications of high-spin nitroxides in biological media led us to synthesize and characterize a glucamine-functionalized nitroxide diradical (Chapter 5).

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First and foremost, I am thankful to my advisor Prof. Andrzej Rajca for giving me the privilege of working under his guidance, and all these years of enriching scientific experience. It is through him, that I learnt how to do careful work and critically think about a problem.

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I am eternally grateful to my parents without whom I would not have made it this far. It is through their sacrifices, inspiration, love and support that I have survived through many of the toughest times during these last 30 years of my life. My parents are my eternal strength.

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To Mom, Dad, Chandrani, Grandpa, and Grandma

Table of Contents

Chapter 1: Nitroxides: Synthesis, Structure, stability and Design of High Spin Nitroxide Diradicals and Triradicals. EPR and Magnetization Studies.....1

1.1 Introduction to Nitroxides.....	1
1.1.2 Structure and Stability of Nitroxides.....	3
1.1.3 Ferromagnetic Spin-Spin Coupling.....	12
1.1.3.1 Predicting the Ground-State Spin (S).....	13
1.1.3.2 Predicted and Experimental Ground States for Nitroxide of Diradicals and Triradicals.....	15
1.1.4 Synthesis of Nitroxides.....	17
1.2 Electron Paramagnetic Resonance (EPR) of Triplet ($S = 1$) State Molecules.....	24
1.2.1 Spin and Magnetic Moments of Electron.....	24
1.2.2 Zeeman Splitting and Resonance Condition.....	25
1.2.3 Spin Multiplicity.....	28
1.2.4 Spin and Magnetic Moment of Nucleus.....	29
1.2.5 Nuclear Hyperfine Interactions.....	29
1.2.5.1 Isotropic or Fermi Contact Interaction.....	29
1.2.5.2 Anisotropic or Dipolar Interaction.....	32
1.2.6 g Anisotropy.....	36
1.2.7 Triplet State ($S = 1$) Molecules.....	37
1.2.7.1 Electron-Exchange Interaction.....	38
1.2.7.2 Electron-Exchange Dipole Interaction.....	39
1.2.7.3 Energies of a Triplet ($S = 1$) System.....	41
1.2.7.4 " $\Delta M_S = \pm 2$ " Transitions.....	45
1.2.7.5 Randomly Oriented Triplet Systems.....	46
1.2.7.6 Curie Law.....	48
1.2.7.7 EPR Spectra of Triplet State Nitroxide Diradicals Illustrated.....	49
1.3 Measurement of Electron Spin Coupling (J) and Determination of Ground State for a Paramagnetic Substance.....	55
1.3.1 Magnetization and Magnetic Susceptibility.....	57
1.3.2 Determination of Ground State Spin (S) and Coupling Constant (J) for Diradicals and Polyradicals with Only Intramolecular Interaction.....	57
1.3.3 Determination of Ground State Spin (S) and Coupling Constant (J) for Diradicals and Polyradicals with Intermolecular Interactions.....	62
1.3.4 Magnetization Data Illustrated.....	63
References.....	66

Chapter 2: Calix[4]arene Nitroxide Diradicals and Tetraradicals: Synthesis, Characterization, and Structure.....73

2.1 Introduction.....	74
2.2 Results and Discussion.....	80
2.2.1 Synthesis of 5,11,17,23-tetrakis(N-tert-butylaminoxyl)-25,26,27,28-tetrakis(methoxyethoxy)calix [4]arene 1	80
2.2.2 EPR.....	87
2.2.3 Synthesis of 5,11,-Bis(N-tert-butylaminoxyl)-17,23-dibromo-25,26,27,28-tetrakis(methoxyethoxy)calix[4]arene 2	89
2.2.4 EPR.....	93
2.2.5 Dynamic NMR Experiments for the determination of rotational barrier of the aryl C-N bond in calix[4]arene in tetrahydroxylamine 12 and dihydroxylamine 13	99
2.2.5.1 Results and Discussions.....	100
2.3 Conclusion.....	107
2.4 Experimental Section.....	109
References.....	117

Chapter 3: Synthesis of Nitronyl Nitroxide Tetraradicals and Diradical Based on 1,3-Alternate and Cone Conformation of Calix[4]arene.....121

3.1 Introduction.....	122
3.2 Results and Discussion.....	130
3.3 Conclusions.....	143
3.4 Experimental Section.....	143
References.....	158

Chapter 4: Synthesis and Characterization of a Glucamine-Funtionalized Nitroxide Diradical.....162

4.1 Introduction.....	162
4.2 Results and Discussions.....	167
4.3 Conclusion.....	175
4.4 Experimental Section.....	175
References.....	184

Chapter 5: Synthesis of a Calix[4]arene Based Water-Soluble Nitroxide Tetraradical.....186

5.1 Introduction.....	186
5.2 Results and Discussions.....	190
5.3 Conclusions.....	196
5.4 Experimental Section.....	196
References.....	201
 Appendix A: Electron Paramagnetic Resonance Spectra.....	 204
Appendix B: NMR, IR and Mass Spectra.....	221

PREVIEW

Chapter 1

Nitroxides: Synthesis, Structure, Stability and Design of Nitroxide Diradicals and Triradicals with High-Spin. EPR and Magnetization Studies

The first section of this chapter briefly introduces the synthetic chemistry, structure and stability of nitroxides and design of nitroxide diradicals and triradicals with ferromagnetic coupling. The second section presents a brief background of some of the principles and theory of electron spin resonance with an emphasis on the concepts required to interpret and analyze the EPR spectra of triplet state molecules. The last section discusses magnetization studies with a primary focus on the determination of the intramolecular exchange coupling constant J between two spins.

1.1. Introduction to Nitroxides

In the past two decades, one of the main areas of research in chemistry and biological and medical sciences has been free radicals. Today free radical chemistry and biology are considered as a developed discipline focused on the structure, and physical and chemical properties of free radicals including their useful or harmful role in biological systems.^{1,2,3} One of the most significant events development in this area is the discovery of miscellaneous long-lived radicals, which transformed free radical intermediates only postulated or registered under special conditions into true chemical compounds capable of being isolated in a pure form. Among the stable radicals,⁴ the most interesting and

valuable compounds are nitroxide radicals (nitroxides) – derivatives of nitrogen oxide with a disubstituted nitrogen atom formally containing a one-valent oxygen atom as the third substituent.^{5,6} The presence of this unpaired electron provides for paramagnetic properties and the possibility of detection by electron paramagnetic (spin) resonance spectroscopy (EPR or ESR). The high sensitivity to EPR combined with outstanding stability and synthetic accessibility using everyday preparative methods of organic chemistry,^{7,8} allow nitroxides to be used as reporter molecules, the so-called spin labels and spin probes,^{9,10} with the recent addition of EPR imaging.^{11–13} The unpaired electron allows nitroxides to take part in one-electron transfer processes such as oxidation and reduction; for example 1-oxyl-2,2,6,6-tetramethylpiperidine (TEMPO) is often used as a co-oxidant.¹⁴ However, nitroxides are also considered as potent antioxidants,¹⁵ SOD (Superoxide Dismutase) mimics,¹⁶ and are among the most effective non-thiol radioprotectants.¹⁶ They have been extensively employed industrially as mediators for controlled free-radical polymerization,¹⁷ and thoroughly investigated for the construction of new ferromagnetic organic materials.¹⁸ Nitroxides have also become indispensable tools in bio-analytical chemistry: nitronyl-nitroxides are used to detect nitrogen monoxide¹⁹ and isoindoline nitroxides have proved to be useful in determining oxygen concentration in biological systems.²⁰ Fluorophore linked pyrrolidine (PROXYL) nitroxides were successfully used in determining alkyl and, indirectly, hydroxyl radicals in condensed phase to mention a few examples.²¹ Due to the paramagnetic nature of nitroxides, they are able to influence the relaxation time of neighboring nuclei in nuclear magnetic resonance (NMR), and consequently are applied as contrast-enhancing agents in MRI.^{22–24}

The focus of this section is to present the most common methods of preparation of nitroxides, their structure, factors affecting the stability, and, design of nitroxide diradicals and triradicals with ferromagnetic intramolecular interaction between the spins. This is by no means an exhaustive compendium of the synthesis and chemistry of stable nitroxides neither does it address all the issues in the design of high-spin diradical or triradical. However, concepts and representative examples on each of these topics will be presented, relevant to the understanding of the work presented in this thesis. The chemistry and utilization of nitroxides has been extensively covered in several excellent reviews and monographs.^{5,7,8,25-29}

1.1.2. Structure and Stability of Nitroxides

Under the term “stable nitroxide radicals” are included those nitroxides that can be obtained in pure form and can be handled and stored in the laboratory with no more precautions than would be used for conventional organic compounds. This definition parallels that of Griller and Ingold for carbon centered radicals.³⁰

The nitroxides can be conceived as a superposition of the two resonance structures **1** and **2** or by a structure **3** with a 3-electron bond as in Figure 1. The 3-electron bond structure is supported by determination of oxygen-hydrogen bond dissociation energies for unhindered hydroxylamines (72 – 74 kcal/mol) and unhindered oximes (86 kcal/mol) from calorimetric and equilibrium studies.³¹

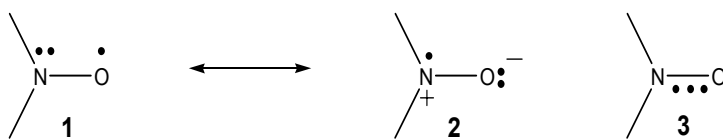


Figure 1

The particularly high delocalization (between the nitrogen and oxygen) energy of this 3-electron bond of about 32 kcal/mol contributes to the thermodynamic stability of the radical center. This is also the reason for the absence of dimerization for most of the known nitroxides, as the formation of a weak O–O bond in a possible dimer cannot compensate for the loss of delocalization energy for two nitroxide groups. However, recently Rajca *et al* reported the observation of non-covalent intramolecular nitroxide dimer (Figure 2) in the solid state of a nitroxide tetraradical based on the cone conformer of a calix[4]arene.³² The dimerization was suggested by short intramolecular N–O contacts of 2.6 – 2.8 Å, well within the N–O Van der Waals contact of 3.07 Å.

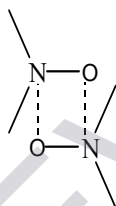
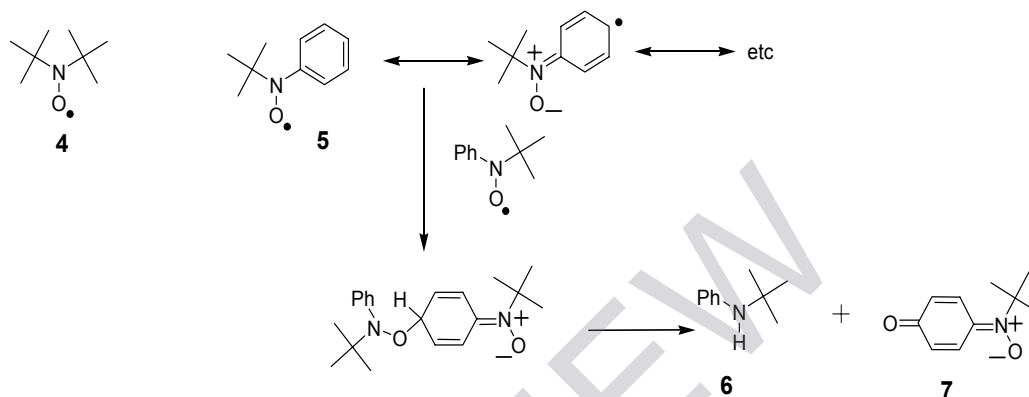


Figure 2. Intramolecular nitroxide dimer (the dotted lines indicate the short N–O contacts)

The stability of molecules with nitroxide moieties depends mostly upon the surroundings of the radical center, which determine the possible degradation reaction pathways. Adjacent groups, even those that increase the thermodynamic stability of the molecule can result in decreased persistency if they enable new degradation reactions. For example, conjugation of the radical center with the benzene ring in nitroxide **5**, increases the thermodynamic stability compared to **4** (Scheme 1), however, at the same time, it delivers a higher unpaired electron density to the ring carbon atoms setting up new centers for dimerization. In fact **4** is indefinitely stable in pure form while **5**³³ is able to

persist only for a limited time in the solution and rapidly disproportionates through dimerization by C–O coupling in the *para*-position and subsequent decomposition yielding products **6** and **7**.

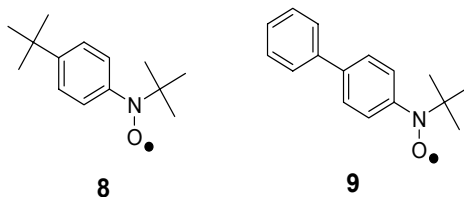
Scheme 1.



However stable isolable aryl-*tert*-butyl nitroxides were obtained when: i) the *para*-position was blocked by a *tert*-butyl or phenyl group; ii) the *para*-position was sterically hindered by two *meta*-methyl substituents (with one *meta*-methyl group the rate of disproportionation merely decreased); and iii) the aryl group was twisted out of conjugation with the nitrogen atom to some extent by one or two *ortho*-methyl substituents, reduced unpaired electron density at the *para*-position. All the above mentioned factors prevent dimerization and subsequent decomposition through C–O coupling in the *para*-position shown in Scheme 1.

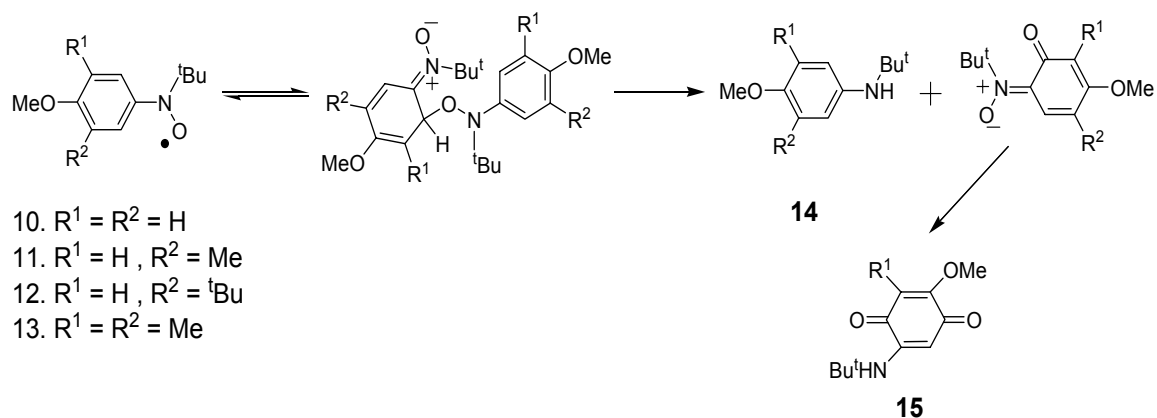
The red crystalline solids *p*-biphenylyl-*t*-butyl nitroxide **8** and *p*-*t*-butyl-phenyl-*t*-butyl nitroxides **9** were stable for months in the solid state and for several days in hot concentrated (temperature and concentration not specified) solution.³³ They were also resistant to dilute hydrochloric acid and to dilute sodium hydroxide solution.

Dimerization at the *para*-position was blocked and dimerization via the *ortho*-position is not favored because of steric hindrance by the adjacent bulky group.



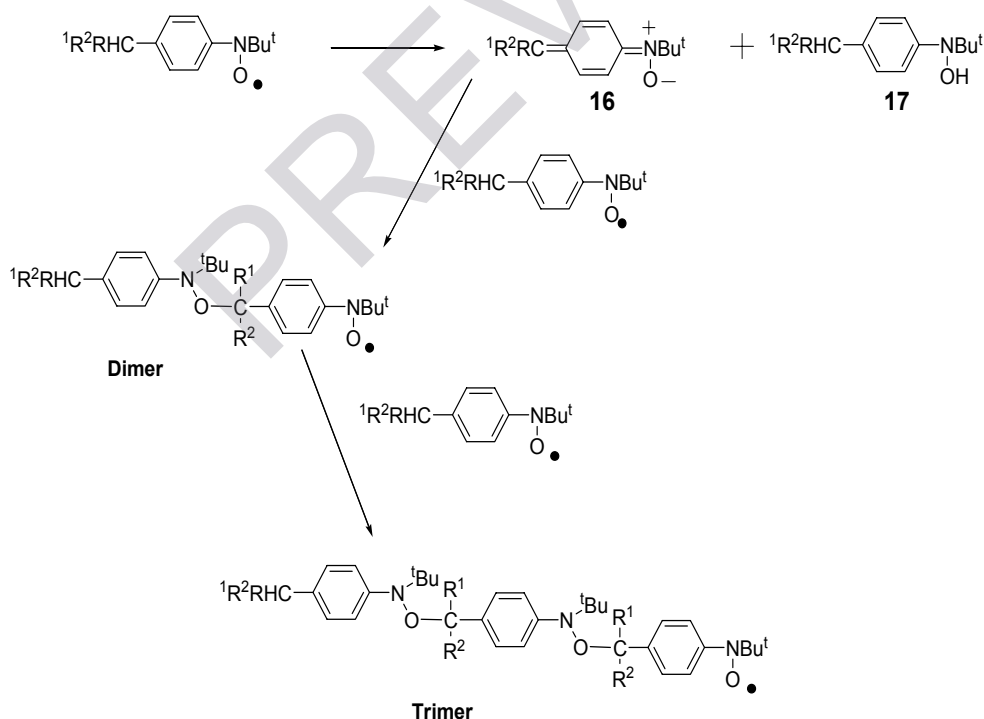
4-Methoxyphenyl-*t*-butyl nitroxide **10**, 4-methoxy-3-methylphenyl nitroxide **11**, 4-methoxy-3-*t*-butylphenyl nitroxide **12**, were sufficiently stable to be crystallized and analysed.³⁴ Their decomposition in concentrated solutions of benzene was slow and required several months for completion. The decomposition proceeds through a slow O-to-*ortho*-C coupling (Scheme 2) and the principal product was the corresponding amine **14** and the amino-quinone **15**. Oxidative displacement of the methyl for **11**, *t*-butyl for **12** to give the corresponding **15** is believed to be catalysed by the starting nitroxide in each case.

Scheme 2.



The 4-methoxy-3,5-dimethylphenyl-*t*-butyl nitroxide **13** was stable in the solid state and relatively more stable than **10**, **11**, and **12** in solution, deteriorating very little during 5 months in benzene.³⁴ Even, 3,5-dimethylphenyl-*t*-butyl nitroxide has been reported to be stable enough for isolation and analysis, although the stability in solution is not described. However, aryl-*t*-butyl nitroxides with primary or secondary alkyl *para*-substituents behaved differently.³³ 4-Ethylphenyl-*t*-butyl nitroxide ($R^1 = \text{CH}_3$, $R^2 = \text{H}$) and *p*-benzylphenyl nitroxide ($R^1 = \text{Ph}$, $R^2 = \text{H}$) are not sufficiently stable to be isolated and in concentrated solution decomposed to mixtures of the parent hydroxylamines and the dimer and trimers, whereas, *p*-isopropylphenyl-*t*-butyl nitroxide ($R^1 = \text{Me}$, $R^2 = \text{Me}$) gave the parent hydroxylamine and the dimer as shown in Scheme 3.³³

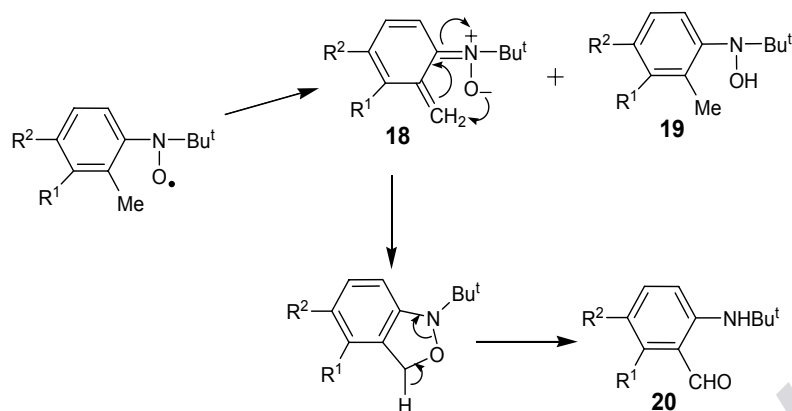
Scheme 3.



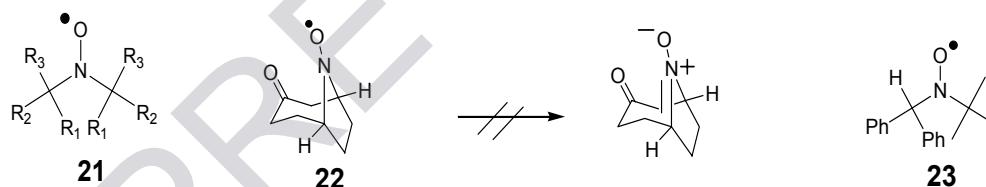
The instability of **16** and **17** could be attributed to the ease of disproportionation by hydrogen abstraction from the carbons attached to the ring. Anomalous results were obtained for the stability of diaryl nitroxides. Bis-*p*-methoxyphenyl nitroxide, although stable in solid state, rapidly decomposes in solution to the bis-*p*-methoxyphenyl amine and the corresponding *p*-quinoneimine *N*-oxide.³⁴ Bis-*p*-nitrophenyl nitroxide behaves in the same way in solution.³⁴

Among the *ortho*-alkylphenyl nitroxides, 2,6-xylyl and mesityl *t*-butyl nitroxides have been reported to be exceptionally stable, with the latter showing no sign of decomposition after several months at 45 °C.³⁵ In the former, the two *ortho*-methyl groups sterically force the N–O group out of conjugation with the phenyl ring, decreasing the unpaired electron density at the *para*-position ($a_{p-H} = -0.15$ for 2,6-xylyl-*t*-butyl nitroxide compared to $a_{p-H} = 3.07$ for phenyl nitroxide³⁶), preventing O-to-*para*-C coupling. In both of them, the *meta*-positions are sterically protected, and, hydrogen abstraction to form the *ortho*-methylene-imine *N*-oxides like **18** (Scheme 4) is prevented because of non-planarity of the N–O group with the phenyl ring. However, *o*-tolyl ($R^1 = \text{Me}$, $R^2 = \text{H}$) and 2,3-xylyl ($R^1 = \text{Me}$, $R^2 = \text{Me}$) *t*-butyl nitroxides having only one methyl at the *ortho*-position partially decomposed even as a solid at room temperature during 8 weeks, giving mainly the parent hydroxylamines **19** and aldehydes **20** arising from rearrangement on a *ortho*-methylene-imine *N*-oxide intermediate (Scheme 4). The N–O group is perhaps not as severely twisted out of conjugation in these cases as with the two methyls in the *ortho*-position for 2,6-xylyl and mesityl *t*-butyl nitroxides.³⁵

Scheme 4.



In general, the most important prerequisite for stability for dialkyl nitroxides is the absence of α -hydrogen atoms. The vast majority of stable dialkyl nitroxides are of the general structure **21**. However, a few unusual nitroxides containing an α -hydrogen atom are relatively stable and even isolable.

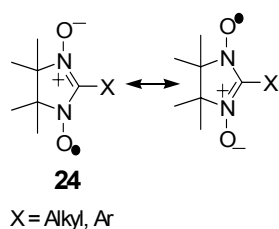


The unusual stability of **22**³⁷ towards disproportionation is attributed to the violation of Bredt's rule if the resulting nitronium were to form. Another example is **23**,³⁸ where, hindered rotation maintains the α -C-H bond approximately in the nodal plane of the N-O π -system, thus inhibiting disproportionation.

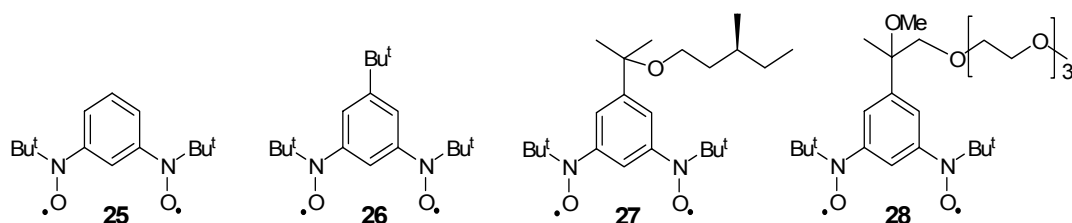
Significantly greater stability of the nitronyl-nitroxides **24** is attributed to the spin density dissipation to the two N-O centers through two equivalent resonance structures shown in Scheme 5. As a consequence there is much less unpaired electron density dissipation to the alkyl or aryl substituent X on the α -carbon, compared to the nitroxides. In fact,

nitronyl nitroxides with $X = \text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, Ph, CH_2Cl , CH_2Ph etc. are all indefinitely stable as a solid and in solution.³⁹

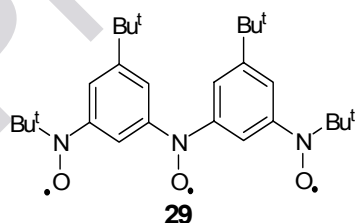
Scheme 5.



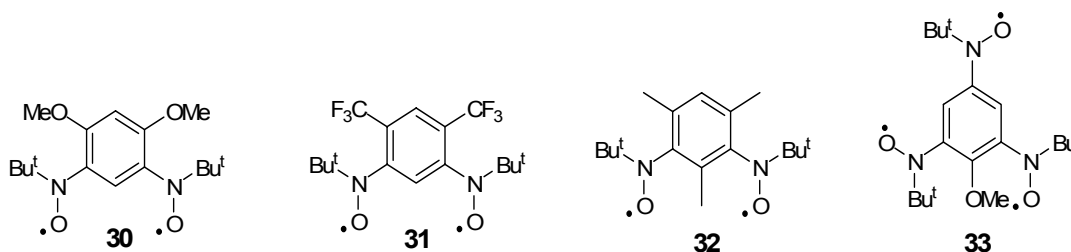
To obtain strong ferromagnetic exchange coupling (Section 1.1.3) in nitroxide diradicals and triradicals, the nitroxide moieties were connected through the *m*-phenylene unit. However, this should in principle increase the unpaired electron density in the phenyl ring by approximately twice at the free *ortho* and *para*-positions and hence, there is a significantly increased possibility of C–O coupling at these positions as shown in Scheme 1 and 2. The nitroxide diradical **25** has a relatively strong ($J/k > 300$ K) intramolecular ferromagnetic coupling between the nitroxide moieties, however, it spontaneously decomposes in solution to an isomeric aminoquinone imine *N*-oxide by an intermolecular process.⁴⁰



The problem of instability of such metaphenylene bisnitroxides have been circumvented by putting a bulky substituent at the *meta*-position. This also ensures that the nitroxide moieties are not twisted out of conjugation with the phenyl ring by steric interaction with the substituent, so that a strong intramolecular interaction is maintained. The diradical **26** is reported to be stable in solid and solution (single crystals were grown in solution) and has a strong ferromagnetic coupling ($J/k = 420$ K) between the nitroxides.^{41,42} No original reference discussing the stability and the nature and magnitude of the intramolecular coupling could be found. The diradical **27** was stable to column chromatography on silica gel purification, however the stability in solution and solid for the diradical and the nature and magnitude of the intramolecular coupling has not been discussed.⁴³ The water soluble diradical **28** has been found to be stable only for few hours. It shows a relatively strong intramolecular ferromagnetic coupling ($J/k = 325$ K).⁴⁴ Nitroxide triradical **29** was also found to be stable as a solid and in solution with a relatively strong intramolecular ferromagnetic coupling ($J/k = 240 \text{ K} \pm 20 \text{ K}$).⁴⁵



Stable nitroxide diradicals and triradicals were also obtained when one or two *ortho*-substituents were attached to the ring. However, the nitroxide moieties were severely twisted out of conjugation with the phenyl ring, reducing unpaired electron density in the ring. As a result, and very weak intramolecular ferromagnetic or antiferromagnetic coupling was observed for such systems.



The nitroxide diradicals **30**⁴⁶ and **32**⁴⁷ are very stable and show very weak antiferromagnetic coupling ($J/k = -3.5$ K in solution and $J/k = -37$ K for crystalline samples of **30**; $J/k = -66$ K and -81 K for *syn* and *anti* conformation of **32**) whereas, diradical **31**⁴⁸ (at low temperatures) and triradical **33**⁴¹ shows weak ferromagnetic coupling ($2J/k < 100$ K for **31** and $J/k = 5$ K between nitroxides at 1 and 3 and $J/k = 68.4$ K between 1 and 5 and 3 and 5 of **33**). The presence in **33** of a methoxy group *ortho* to the two nitroxide moieties forces the nitroxides out of planarity and weakened the through-ring exchange coupling by an order of magnitude.

1.1.3. Ferromagnetic Spin-Spin Coupling

A pair of electrons can interact either ferromagnetically ($S = 1$) or antiferromagnetically ($S = 0$). Because electrons are fermions, the total electronic wavefunction must be antisymmetric. The electronic wave function is a product of two parts, spin and space.

$$[\text{Electronic Wave Function}] = [\text{Space}] \times [\text{Spin}]$$

A = antisymmetric

$$A \times S$$



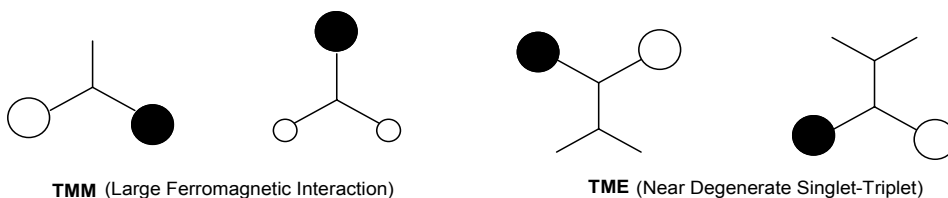
S = symmetric

$$S \times A$$



When the spatial part is symmetric, there is a large probability of finding an electron between the nuclei. Thus the preference for “parallel” vs “antiparallel” alignment of a pair of spins is associated with their distribution with respect to nuclei. Thus a pair of electrons with two available orbitals will interact antiferromagnetically, if the orbitals overlap in phase. In this case the spatial part of the two-orbital wave function is symmetric; e.g. H_2 molecule (two $1s$ orbitals). When the orbitals are restricted to be orthogonal, they will overlap out-of-phase; the spatial part of the two-orbital wave function will have a node and the electrons will interact ferromagnetically; e.g. CH_2 (two $2p$ orbitals). In molecules with a pair of half-occupied degenerate or near-degenerate nonbonding molecular orbitals (NBMO's), if the lobes of these orbitals coincide significantly (non-disjoint MO's), very strong ferromagnetic interaction is observed (Scheme 6); e.g. trimethylene methane (TMM). If the NBMO's coincide to very small extent (disjoint MO's) then the interaction is small (Scheme 6) and, consequently, the spin coupling is small (the $S = 0$ and $S = 1$ state are near degenerate); e.g. tetramethylenethane (TME).⁴⁹

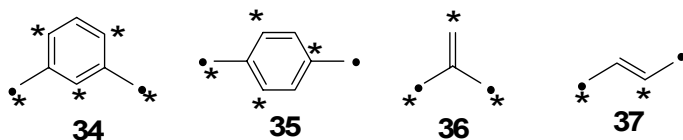
Scheme 6.



1.1.3.1. Predicting the Ground-State Spin (S)

There are two simple models for predicting the ground-state spin S of alternant hydrocarbons. The model developed by Longuet-Higgins⁵⁰ predicts that an alternant

hydrocarbon contains $x = (N - 2T)$ NBMO's in which N is the number of carbon atoms and T is the maximum number of double bonds.



The *meta*-benzoquinodimethane **34** can be drawn with three double bonds and *para*-benzoquinodimethane **35** can be drawn with four double bonds. As a consequence **34** will have $(8 - 2 \times 3 = 2)$ NBMO's and **35** will have $(8 - 2 \times 4 = 0)$ NBMO's. So the *meta*-isomer with two NBMO's, will each be occupied with one unpaired electron according to Hund's rule, thus, resulting in a triplet ($S = 1$) ground-state and the *para*-isomer **35** will have a singlet ($S = 0$) ground state. Similarly trimethylene methane (TMM) **36** will have a $S = 1$ ground-state and butadiene **37** will have a $S = 0$ ground-state.

In a second model, developed by Ovchinnikov,⁵¹ the carbon atoms of an alternant hydrocarbon are starred (n^*) and unstarred (n) in alternating fashion so that every starred atom has only unstarred atoms as nearest neighbors. If $n^* > n$, the spin state S is given by: $S = (n^* - n)/2$. Application of this to the isomeric benzoquinodimethane results in $S = (5 - 3)/2 = 1$ or triplet state for the *meta*-isomer **34** and $S = (4 - 4)/2 = 0$ or singlet state for the *para*-isomer **35**. Similarly, a triplet ground-state is predicted for **36** and a singlet ground-state for **37**. The theoretical basis for this model relies on MO calculation of the spin densities (including their sign) at the carbon atoms. The results of such calculations show that the starred atoms have a large positive spin density and the unstarred atoms have a small negative spin density. This is called the spin polarization mechanism, where