CHEMISTRY OF PERSISTENT FREE BI- AND POLYRADICALS

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Abstract- The aim of this paper is to provide an overview of important developments in the chemistry and the use of persistent free bi- and polyradicals to study chemical and biological model systems by electron paramagnetic resonance (epr) or as materials for physical purposes. The paper also discusses the different ways used to synthesize these molecules by structure modifications of carboxylic and heterocyclic nitroxides as well as their diamagnetic precursors. The review tries to sum up our knowledge of these strong paramagnetic species with the aim of drawing the reader's attention to their application in recent fields of physics, chemistry, biochemistry, biology and medical radiology including magnetic resonance imaging (mri) and more recently electron spin resonance imaging (esri).

CONTENTS

I Introduction.

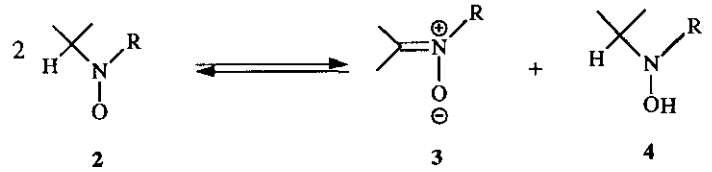
Over almost a century and half has passed since the discovery of the first persistent free radical obtained in the form of potassium nitrodisulfonate ($K_2(SO_3)_2NO$) (**1**) known as Fremy salt. [1] Piloty and Schwerin [2] have reported the preparation of porphyrexide and afterwards Wiland [3] synthesized some diaryl nitroxides. However, the first and original persistent free radical was reported by Lebedev [4] who prepared the first totally aliphatic nitroxide. In essence the great development of esr spectroscopy has largely contributed to substantially study of the growth of new methods of nitroxide synthesis particularly by Rozantsev and Volordarskii in Russia, Rassat in France, Keana and Sosnovsky in the USA. But new horizons in the nitroxide chemistry are being opened up at present with a great of amount of knowledge's attainable in the field. Nitroxide paramagnetism is a unique property in organic compounds, and over the last three decades, an extensive literature has been built up on their synthesis, properties and applications. Firstly introduced by McConnell [5-8] as spin labels to study biological systems, [9-22] they were later exploited as probes in analytical chemistry, the chemistry of ion complexes, [23-24] polymers, [25-30] composites, rubbers [31-32] and hybrid organic-inorganic materials [33] or as spin traps. [34-51] Recently they were used for the determination of oxygen concentration in biological systems [52-57] using esr oximetry. This technique appears to be the method of choice for the measurement of O_2 in small samples. In addition to the possibility of using them as minimum disruptive anti-oxidant additives for bulk polymers, the main interest in these materials is associated with their use as catalysts for the oxidation of organic substrates. [58-75] They are also largely used as contrast enhancing agents for another equally powerful technique called magnetic resonance imaging. Involving nitroxide is a more recent development and makes use of the effect that the paramagnetic nitroxide has on the magnetic relaxation rates of water or aliphatic protons of tissue nmr. In this case the radical shortens the T_1 and T_2 relaxation values of neighboring hydrogen nuclei thus increase contrast differences on nmr images. [76-83] Very recently a great attention has been paid to investigating nitroxyl bi- and polyradicals that are potentially useful for creating new organic ferromagnetic materials. These compounds exhibit a strong exchange interaction that has a ferromagnetic character. [84-98] However, in organic ferromagnetism, several theoretical models have been proposed to study this phenomenon. The spin polarization model of McConnell [87] and the spin multiplicity of the ground state have been used to explain organic ferromagnetism. A spin multiplicity other than 1 is much more difficult to obtain for organic compounds than inorganic compounds, since the former usually possesses low symmetry and orbital orthogonality. In this context many methods of organic synthesis of polyradical molecules presenting unusual magnetic properties have been described. The magnetic susceptibility of them is very unusual. In some cases they show a strong deviation from Curie's law and surprisingly high values at high temperatures. Such properties are unknown for organic compounds and rarely observed for transition-metal complexes.

Using nitroxides as species that is imaged is a new potentially important approaches based on esr technique imaging. Until now many constraints on imaging in biological systems have not been surmounted. Among these problems are the ability to obtain sufficient penetration of the electromagnetic field and the quantity of nitroxide that can be injected without perturbing the biological system. In spite of everything, this spectroscopy (esri) have been very productive the last ten years and poses some formidable challenges. [99-105] However, a number of very interesting reviews dealing with the chemistry of free radicals do not give polynitroxides sufficient consideration and even short review do not supply any knowledge about the few years research. Perhaps this account for duplication in research and for a certain inaccuracy in outlining some polynitroxides properties in organic chemistry courses and reference books.

The object of the present review is to sum up our knowledge on the chemistry of bi- and polynitroxides with the aim of drawing the reader's attention to the application of these paramagnetic species in different fields of physics, chemistry, biochemistry, biology as well as tomography techniques. For those who are interested to mononitroxyls a number of a good books and reviews devoted to different aspects of synthesis and chemistry [106-112] have been written. Biological applications of esr spin labelling and theoretical studies are also discussed. [113-122]

II Nitroxide properties.

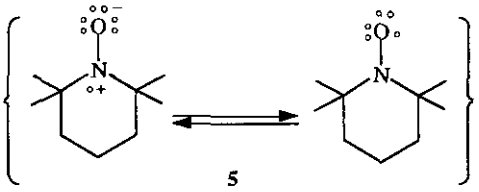
The most important property of nitroxides is the long life time of their paramagnetism character and sensitivity of their esr spectra to environmental factors such as motion and redox potential. Their stability is due to the delocalization of the unpaired electron between oxygen and nitrogen and to the presence of the two alkyl substituents (**2**) which will naturally help to minimize the tendency for dimerization as it shown by Ingold. [123] Or for those which have α hydrogens disproportionate rapidly giving nitrone (**3**) and hydroxylamine (**4**) (Scheme 1) except in extremely hindered nitroxides or where nitrones are destabilized as in bicylic cases. [124]



2 **3** **4**

Scheme 1

The solvatation effects of dipolar radicals can in some cases be observed directly by esr spectroscopy. The 2,2,6,6-tetramethylpiperidine-*N*-oxyl (**5**) like other nitroxyl radicals is dipolar in the sense suggested by the pictured resonance structures (**5**) (Scheme 2).



5

Scheme 2

Solution of **5** in polar solvents show an increase in the ^{15}N hyperfine splitting constant as the hydrogen-bonding interaction increases. The increase of the dipolar resonance contribution, which has the electron spin on nitrogen, induced by specific electrophilic solvatation of negative charge on nitroxyl oxygen, parallels the changes in OH stretching frequencies related to the same interaction. [125] Nitroxides without α hydrogens are probably the more stable free radicals and show no tendency to dimerize or react with air. In epr spectroscopy, a possibility to maximize spectral changes observed with the stable nitroxide labels would be to use specific interaction between two nitroxides which are near to each other (Figure 1). When the nitroxide groups are close enough, electron exchange is fast on the esr scale ($J>>a_N$) and the signal of the odd electrons is split by both nitrogens giving a five line pattern with 1:2:3:2:1 intensities and (a_N) splitting of ($a_N/2$) for the related mononitroxide. However, when the nitroxides are far apart and ($J<<a_N$), a spectrum indistinguishable from that of the mononitroxide is observed. At intermediate values of (**J**), lines 2 and 4 of the five line pattern are broadened more than lines 1 and 5 (Figure 1). The effective range for detection of changes in the spectrum for "Frozen" binitroxide can be as large as 17 Å for dipolar broadening [126-127] but the range for direct electron exchange only extends to about 6 Å.[128] The spectra observed for binitroxides can be very sensitive to conformation and as the nitroxide moieties are brought nearer to one another, the line shapes of the spectra of binitroxides and the monoradical become increasingly different. Then the epr spectra of bi- and polynitroxides imply that the shape of the spectra depends not only on the average distance (**d**) between radicals but also on their relative positions. At room temperature, the epr spectra of dilute solution of binitroxides always exhibit a five line spectrum. The spin exchange will set

as an overlap becomes significant and the 1:1:1 triplet will change to a 1:2:3:2:1 quintet (high exchange).[129] Also the intensities and width lines depend on the temperature and on the distance between nitroxides.[128, 130]

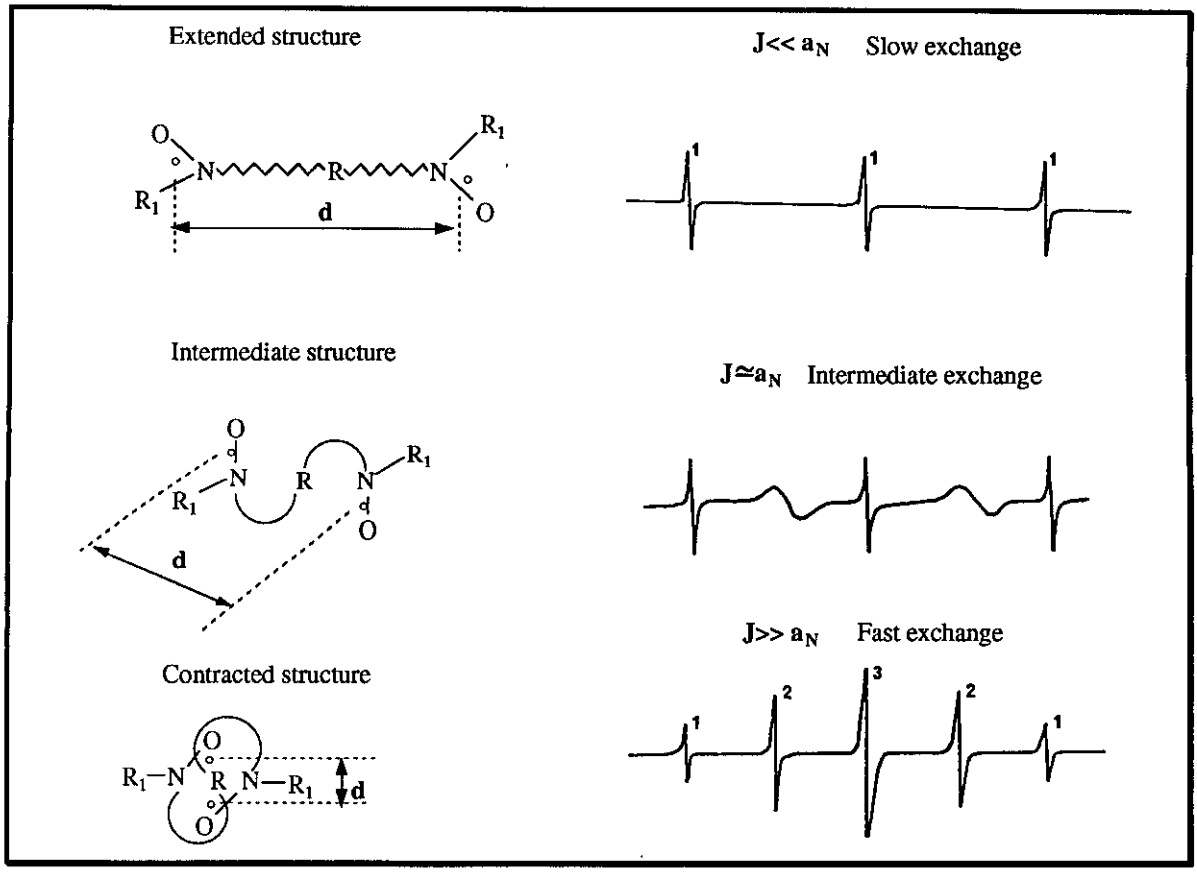
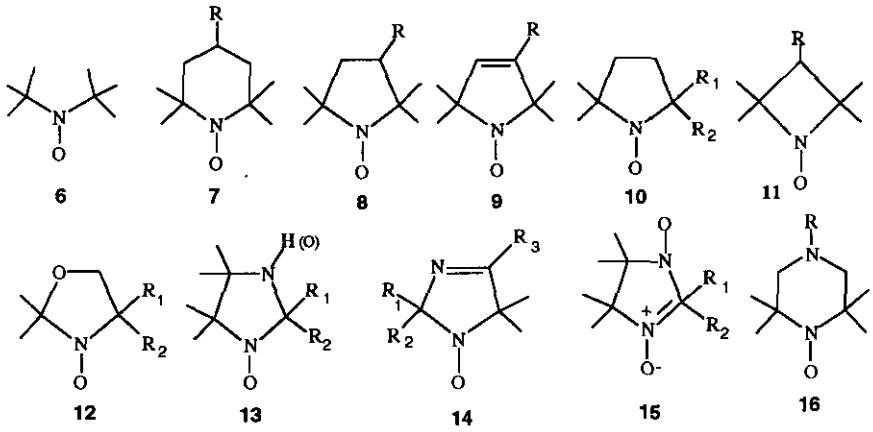


Figure 1

On the other hand, as the electron has a larger magnetic moment than the nuclear magnetic moment, the motion of the paramagnetic component will produce intense fluctuating fields which result in large spin lattice relaxation times of the nuclei and consequently increases the size of lines making the interpretation of high resolution nmr spectrum of spin labelled compounds very difficult. To avoid this problem, nitroxides (**N-O°**) are first reduced to their corresponding hydroxylamine functions (**N-O-H**) and thus information on nitroxides structures are easily obtained. Although nitroxides are extraordinarily stable free radicals, they may be destroyed, with loss of paramagnetism, by components of some biological systems and under some experimental conditions employed in synthetic steps aimed at the non paramagnetic portions of spin label molecule. For example sulfhydryl groups were previously known to affect reduction of nitroxide radicals.[131-132] Also, it has been reported that nitroxides are readily reduced to hydroxylamines by hydrogen and platinum catalyst and further to secondary amines when palladium on carbon is used as a catalyst.[133] However, the best reducing agent of nitroxide is presumably aqueous solutions of ascorbic acid in excess.[134-135] In situ reduction of nitroxide in $CDCl_3$ to hydroxylamine is also obtained when treating them with a solution of phenyl hydrazine.[136] Sodium sulfide was employed to reduce nitroxide to their corresponding secondary amines.[137] Radiolysis processes could also be used for some types of nitroxides structures.[138-139] In addition to these varieties of chemical reducing agents, we have found during our investigation that tetrahydroxy-1,4-quinone, 2,5-dihydroxy-4-benzoquinone, rhodizonic acid are also good reducing agents of nitroxides to hydroxylamines.[140]

III Chemistry of nitroxides.

Generally, a polynitroxide is a paramagnetic molecule containing over two nitroxide groups. The major persistent polyradicals are easily synthesized and are largely exploited in different applications. They can be divided into two main groups: The first one is cyclic analogous of di-*tert*-butyl nitroxide or DTBN (**6**), 2,2,6,6-tetramethylpiperidine-*N*-oxyl (**7**), 2,2,5,5-tetramethylpyrroline-*N*-oxyl (**8**), 2,2,5,5-tetramethylpyrrolidine-*N*-oxyl (**9**), proxyl derived-nitroxide (**10**), 2,2,4,4-tetramethylazetidine derivatives (**11**). The second group is heterocyclic nitroxides containing oxygen or nitrogen in addition to the nitroxyl radical center like 2,2-disubstituted 4,4-dimethyloxazoline-*N*-oxyl or -doxyl nitroxide (**12**), imidazolidine-derived nitroxide (**13**), imidazoline-derived nitroxide (**14**), nitronyl nitroxide (**15**) and nitroxide derivatives of 2,2,6,6-tetramethylhydropyrazine-*N*-oxyl (**16**) (Scheme 3).



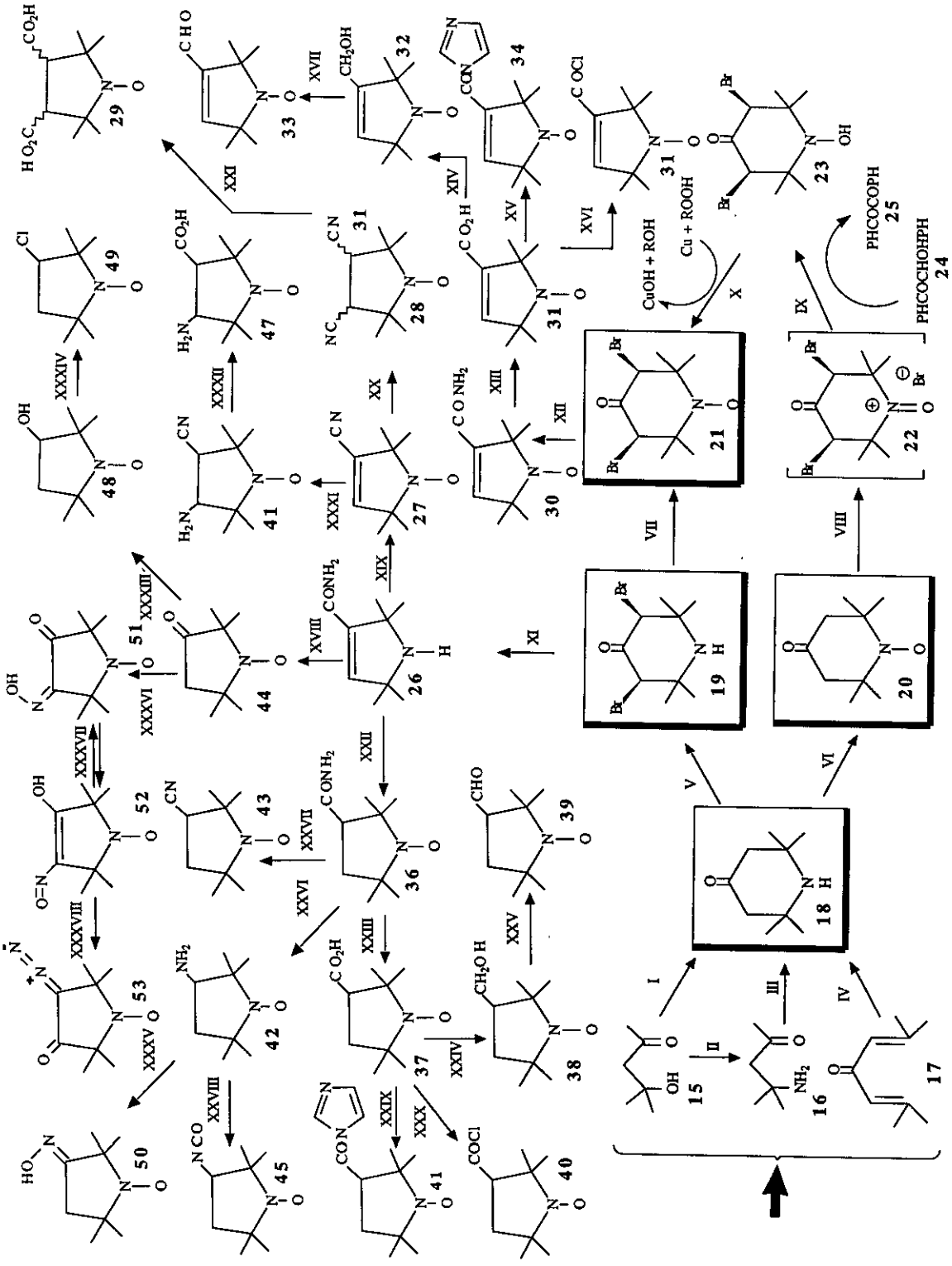
Scheme 3

IV Synthesis of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (**7**).

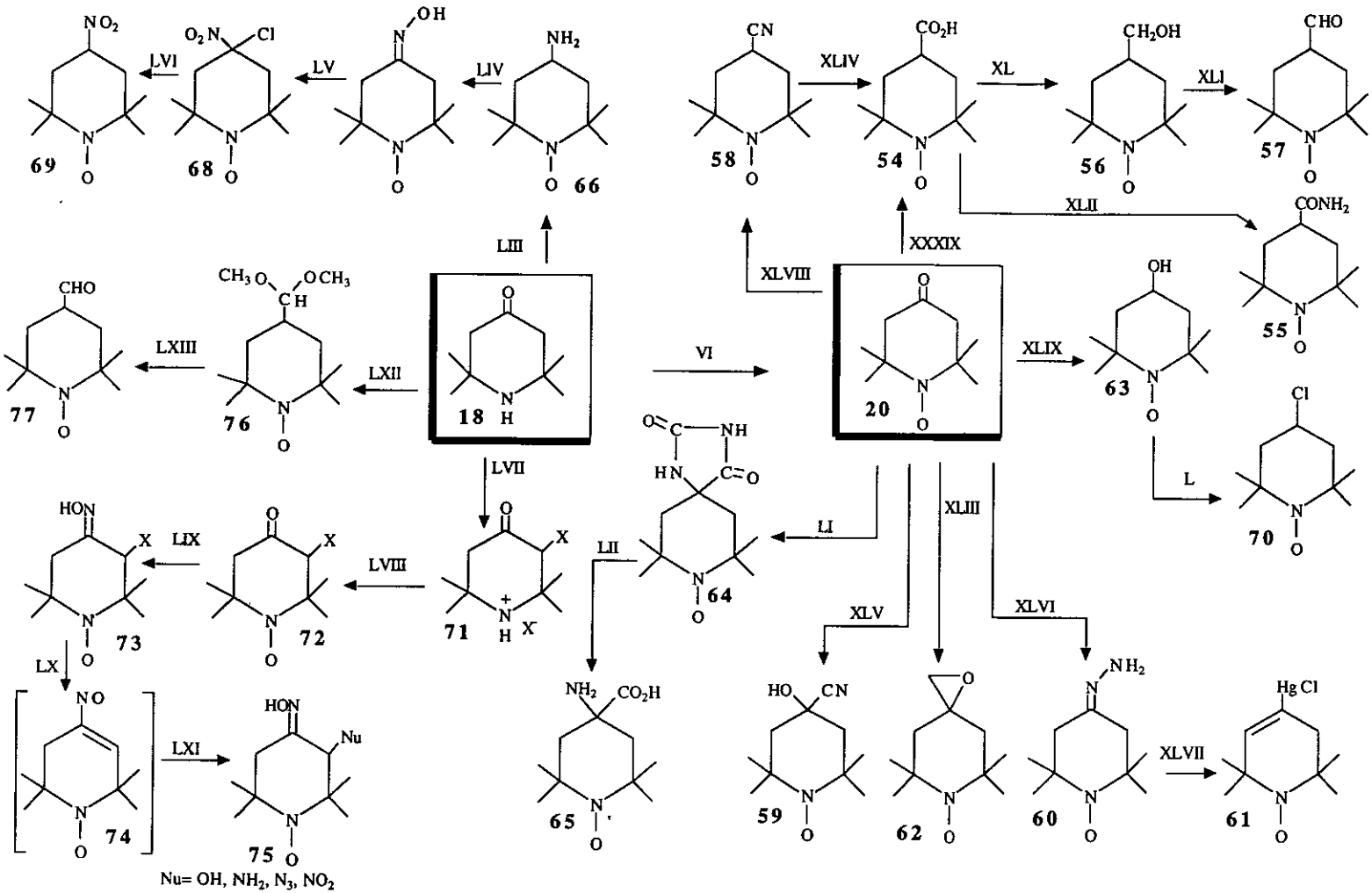
The ring cyclic ditertiary amine-*N*-oxyls (**7**), (**8**) and (**9**) are prepared by oxidation of 4-oxo-2,2,6,6-tetramethylpiperidine or triacetoneamine (**18**) with hydroperoxides, [141] hydrogen peroxide with cerium, [142] alkanes radicals, [143] pertungstate ion, [144] silver oxide, [145] lead(IV) oxide, [146] other tungsten, molybden, vanadium compounds, various peracids, [147-149] dimethyloxiranes [150] and more recently oxone (peroxomonosulfate). [151] However, the design and build of the most polynitroxide compounds are obtained according to (Scheme 4a eq: I, III, IV) in which triacetoneamine (**18**) [152-173] is one of the most used starting materials. Many methods are used to prepare it, but the most practical and useful one is probably the double Michael addition of ammonia on phorone (**17**) giving rise to a reasonable yield of 4-oxo-2,2,6,6-tetramethylpiperidine (**18**) (Scheme 4 eq: IV) meaning that a vast array of nitroxides are available by oxidation of the structure modifications of carboxylic and heterocyclic nitroxides as well as their diamagnetic precursors (Scheme 4b eq: from XXXIX to LXI).

V Synthesis of 2,2,5,5-tetramethylpyrroline-*N*-oxyl (**8**) and 2,2,5,5-tetramethylpyrrolidine-*N*-oxyl (**9**).

The second class of paramagnetic polyradical species is represented by pyrroline-*N*-oxyl (**8**) and pyrrolidine-*N*-oxyl (**9**) compounds. These molecules are obtained by contraction of the ring from six (**19**) and (**21**) respectively to five (**26**) (Scheme 4a eq: XI) and (**30**) (Scheme 4a eq: XII). In general, these compounds serve as precursors used for acylating or alkylating molecules at their reactive functional groups such as alcohols (**36**) and (**32**), amino (**39**), cyano (**27**) and (**38**), aldehyde (**37**) and (**33**), halogen (**42**), diacid (**29**), acids (**35**) and (**31**) etc...) (Scheme 4a from eq: XI to XXXVIII). The (Scheme 4a and 4b) represent the different ways and methods for obtaining these cyclic rings ditertiary amine-*N*-oxyls.



Scheme 4a. **I)** Acetone/NH_3 [155, 171]; **II)** NH_3 [160, 163]; **III)** Acetone [160, 163]; **IV)** NH_3 [154, 157]; **V)** Br_2/AcOH [157]; **VI)** MCPBA or 30% H_2O_2/ Na_2WO_4/H_2O [175]; **VII)** MCPBA/ether [177]; **VIII)** Br_2/AcOH [174]; **IX)** PhCOCHOHPh [174]; **X)** Cu/ROOH/Acetone [174]; **XI)** NH_4OH [175]; **XII)** NH_4OH [175]; **XIII)** NaOH [175]; **XIV)** Sodium bis(2-methoxyethoxyl)aluminium hydride/toluene [176]; **XV)** Imidazole/Carbodiimide/0°C/$CHCl_3$ [126, 178]; **XVI)** $SOCl_2$/Pyridine/0°C [179, 183]; **XVII)** MnO_2/CCl_4 or pyridinium dichromate/CH_2Cl_2 [176]; **XVIII)** 1) 30% H_2O_2/ Na_2WO_4/H_2O, 2) NaOBr/H_2O [180]; **XIX)** 30% H_2O_2/ Na_2WO_4/H_2O, 2) TsCl/KOH [175]; **XX)** KCN/NH_4Cl [181]; **XXI)** NaOH [181]; **XXII)** 1) H_2/Raney Ni/MeOH, 2) MCPBA [175]; **XXIII)** NaOH 10% [175]; **XXIV)** Sodium bis(2-methoxyethoxyl)aluminium hydride/toluene [176]; **XXV)** Pyridinium dichromate/CH_2Cl_2 [176]; **XXVI)** NaOBr/H_2O [180]; **XXVII)** TsCl/pyridine [175]; **XXVIII)** [188]; **XXIX)** Imidazole/Carbodiimide /0°C/$CHCl_3$ [126, 178]; **XXX)** $SOCl_2$/Pyridine/0°C [179, 183]; **XXXI)** NH_4OH [182]; **XXXII)** $Ba(OH)_2/H_2O$/120°C [182]; **XXXIII)** $NaBH_4$/EtOH [107]; **XXXIV)** $SOCl_2$ [183]; **XXXV)** 30% H_2O_2/ Na_2WO_4/H_2O; **XXXVI)** NO^+ [290]; **XXXVIII)** NH_2NH_2 [184].



Scheme 4b. XXXIX) 1) $TosCH_2NC$, 2) $Ba(OH)_2/H_2O/100°C$ [185]; **XL)** Sodium bis(2-methoxyethoxyl)aluminium hydride/toluene [176]; **XLI)** MnO_2/CCl_4 [176]; **XLII)** $CH_2N_2/NH_3/CH_3OH$ [180, 186]; **XLIII)** $CTsCH_2NC/C_4H_9OK$ [185]; **XLIV)** $Ba(OH)_2/NaOH/H_2O$ [185]; **XLV)** HCN [189]; **XLVI)** 1) NH_2NH_2, 2) $K_3Fe(CN)_6$ [161, 190]; **XLVII)** $Hg(OAc)_2/CaCl_2/H_2O$ [191]; **LVIII)** $(CH_3)_3S^+I^-/NaH$ [187]; **XLIX)** $LiAlH_4$; **L)** $SOCl_2$ [183]; **LI)** $KCN/H_2O/(NH_4)_2CO_3$ [182]; **LII)** $Ba(OH)_2/100°C$ [182]; **LIII)** $NH_4OAc/NaBH_3CN/CH_3OH$ [192, 193]; **LIV)** 1)Ac_2O, 2) H_2O_2/Na_2WO_4, 3) NaOH/100°C, 15 h [192-195]; **LV)** NaOCl [196-197]; **LVI)** H_2 [196-197]; **LVII)** $SOCl_2$ or Br_2 [198]; **LVIII)** 30% H_2O_2/ Na_2WO_4/H_2O [198]; **LIX)** NH_3 [199]; **LX** and **LXI)** NuH [199]; **LXII)**1) MCPBA 2) $(C_6H_5)_3P{=}CH\text{-}OCH_3$ 3) CH_3OH [200]; **LXIII)** 1) H_2/Pt, 2) H_2SO_4 3) $(KO_3S)_2NO$ [200].

VI Synthesis of *cis*-3, 5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**21**).

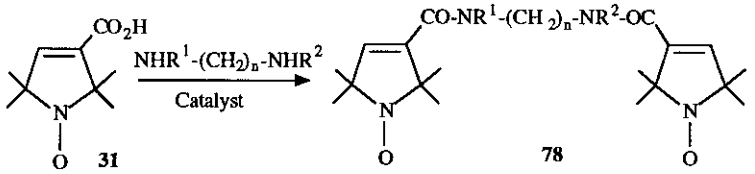
It is well known that the *cis*-3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**21**) is an important precursor that is used in the preparation of functionalized nitroxides such as pyrroline-*N*-oxyls (**8**) and pyrrolidine-*N*-oxyls (**9**). The synthesis method of this nitroxide (**21**), as it has been described in many articles, has always been a bromination in the α and α' positions of the 4-oxo-2,2,6,6-tetramethylpiperidine (triacetoneamine) (**18**) (Scheme 4a eq: V). This bromination gives a mixture of *cis*- and *trans*-3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine hydrobromides (**19**). [157, 201] Only the *cis* isomer is separated from the mixture and afterwards is changed into the nitroxide (**21**) by action of the *m*-chloroperbenzoic acid (MCPBA) in ether as described in Scheme 4a eq: VII. The yield of 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**19**) in the two steps reaction is less than 40 %. [202] As to improve the yield of this precursor (**21**), the 4-oxo-2,2,6,6-tetramethylpiperidine (**18**) is at first changed into nitroxide (**20**) (Scheme 4a eq: VI) followed by the bromination of the α and α' positions of the carbonyl (**20**) in acetic acid. At the end of the reaction, the *cis*-3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-hydroxy (**23**) is obtained in its non paramagnetic form (Scheme 4a eq: IX). This product was washed by ether and was recrystallized in a mixture of ethanol/ether (yield 90%). This selectivity is favoured by the *in-situ* formation of the 4-oxo-2,2,6,6-tetramethylpiperidinium bromide (**22**) that is not isolated (Scheme 4a eq: VIII). The same method is used for the bromination of the triacetoneamine (**18**) in acetic acid but is less efficient as there are two products instead of one, the *cis*- and *trans*- 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidines (**19**) (Scheme 4a eq: V). Also the secondary amine (**19**) when in presence of $CHCl_3$ cannot be oxidized and changed into the nitroxide (**21**) using MCPBA (Scheme 4a eq: VII). This oxidation can only be done in ether. The yield of this reaction is less than 30%. It has also been reported that oxoammonium salt bromide and chloride are good oxidizing agents of primary and secondary alcohols to their corresponding aldehydes and ketones. [202-203]

However, to prove and to explain the *in-situ* presence of 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidinium bromide (**22**) which is not isolated, its oxidizing action is tested by putting it in presence of primary and secondary alcohols that do not contain hydrogens in α position (Scheme 4a eq: IX). These alcohols are chosen so that they do not react with the bromine when the ketone is formed. The solution becomes limpide after three hours and there is release of hydrobromic acid. There is also a white precipitate that corresponds to the *cis*-3,5-dibromo-1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine (**23**) in a good yield (80%). This product is filtered and recrystallized in ether/ethanol. After evaporation of the acetic acid we obtain dibenzyl (**25**) in the benzoine (**24**) case (Scheme 4a eq: IX) which is recrystallized in (50/50) pentane/ether (yield 95%). But the most interesting reaction step is the transformation of the hydroxylamine (**23**) into nitroxide (**21**) by action of peroxide copper catalysis (Scheme 4a eq: X). The metallic copper that has been treated by peroxide in absolute ethanol as solvent will generate R-O° radicals. These R-O° will tear off the proton of the hydroxylamine (**23**). After 30 minutes, a pink precipitate is produced that corresponds to the *cis*-3,5-dibromo-4-oxo-2,2,5,5-tetramethylpiperidine-1-oxyl (**21**). This product is filtered, washed with ether and then recrystallized in ethyl acetate (yield 90%). The *in-situ* production of the bromine oxoammonium (**22**) which is not isolated favours the selective creation of the *cis*-3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**21**) and can also be used as an oxidizing agent of alcohols into aldehydes and ketones. [174]

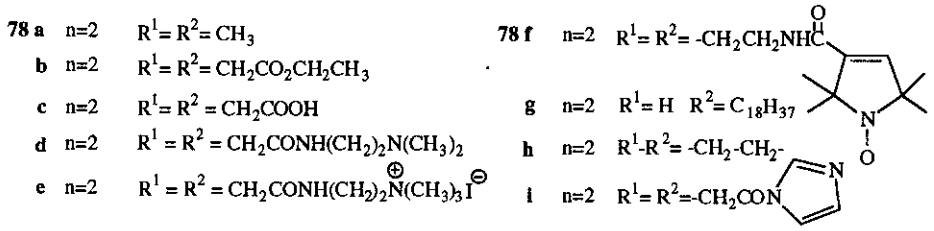
VII Bi- and polyradicals with 2,2,5,5-tetramethylpyrroline-*N*-oxyl (**8**) and 2,2,5,5-tetramethylpyrrolidine-*N*-oxyl (**9**) as radical group.

It has been shown that the Favorsky rearrangement of α-halo ketones react with bases to produce carboxylic acid derivatives. 3,5-Dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**21**) was shown to give 3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (**31**) in two steps: first by treatment **21** with ammonium hydroxide (NH_4OH) (Scheme 4a eq: XII) and second with the sodium hydroxide (NaOH) (Scheme 4a eq: XIII). This precursor (**31**) has been largely exploited by coupling it with the amino or hydroxyl group. In this context, Ferruti and collaborators [126] have prepared a number of biradicals (**78a-h**) and a tetraradical (**78i**) deriving from substituted

3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (**31**) and diamines (Scheme 6). They have used 1-ethyl-3-(3-*N*, *N'*-dimethylaminopropyl)carbodiimide hydrochloride as a coupling agent. This catalyst seems better than *N*, *N'*-carbonyldiimidazole (Scheme 5).

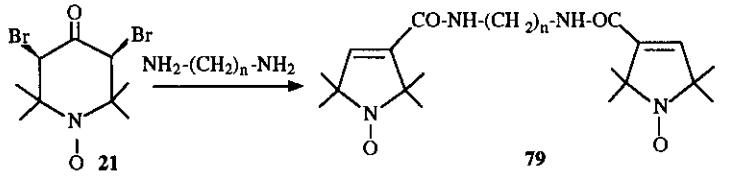


Scheme 5

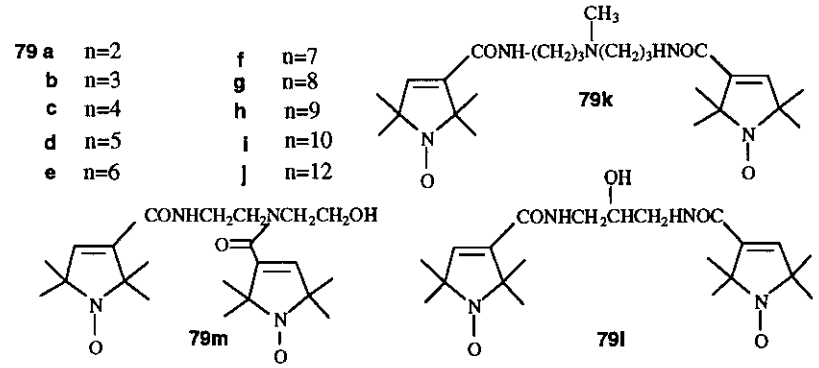


Scheme 6

However, it was found out during our investigation that the reaction of **21** is a highly acylating reaction not only for primary and secondary amines as it has been reported [201] but also more an acylating reaction for bi- and polyamines. [204] This method provides an easy, convenient and short way to prepare directly polynitroxides in one step with a better yield than those reported elsewhere. [126] Incorporation of diamines on 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**21**) was found to be suitable for synthesizing a large number of binitroxides of varying physical and chemical properties. Biradicals obtained by this method are generally derived from diamines and are listed above (**79a-m**) (Scheme 8). This reaction needs two equivalents of 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**21**) for three equivalents of diamine or one equivalent of diamine and four equivalents of triethylamine (Scheme 7).

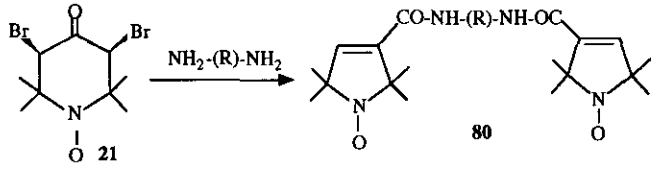


Scheme 7

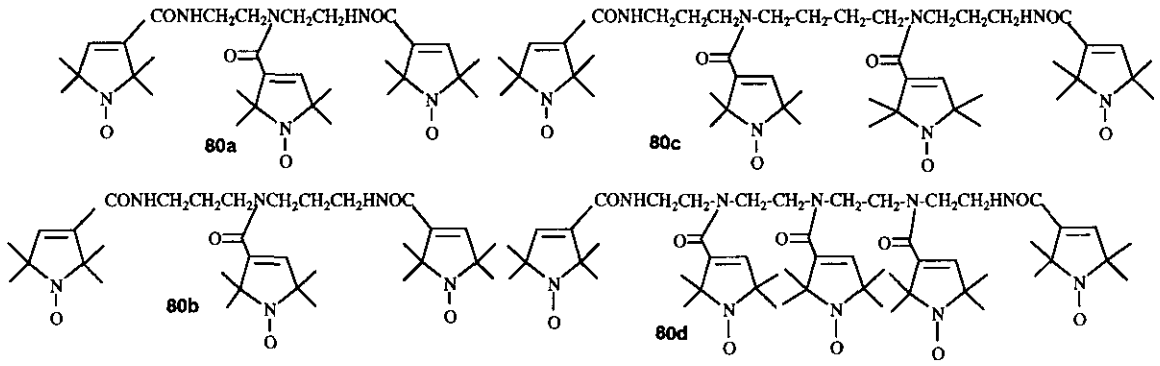


Scheme 8

Tri- (**80a**) and (**80b**), tetra- (**80c**) and pentanitroxide (**80d**) (Scheme 10) have been synthesized by the same method [204] in which polyamines like diethylenetriamine, spermine or tetraethylenepentamine are incorporated on 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**21**) (Scheme 9).



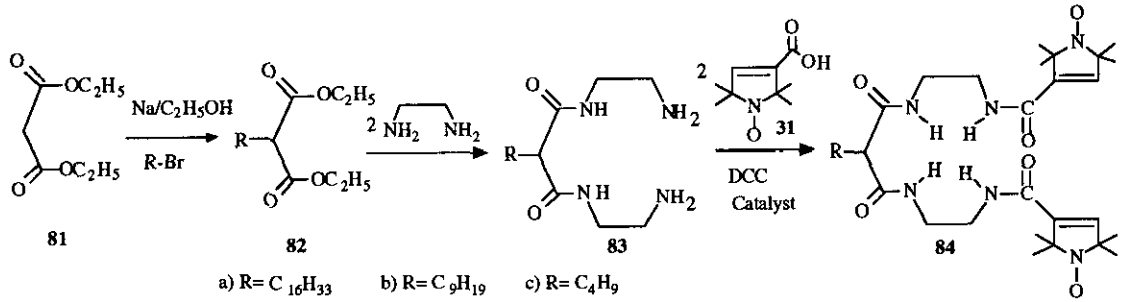
Scheme 9



Scheme 10

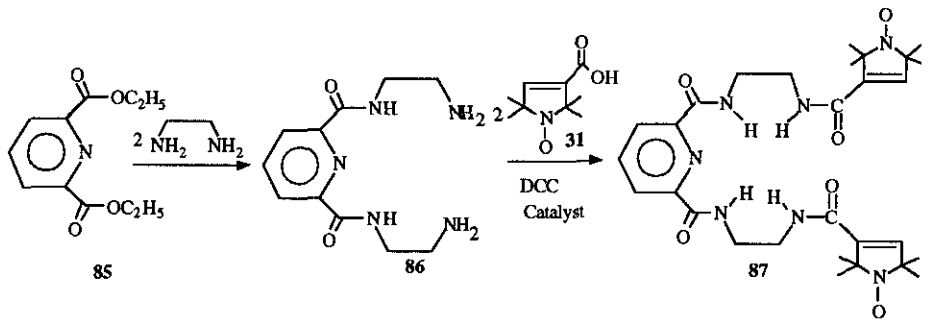
The preparation of these persistent bi- and polyradicals is dictated by their interest of potential use as contrast agents in magnetic resonance imaging (mri). Indeed, in order to reduce the injected dose of radical, molecules containing 2, 3 and 4 nitroxyl moieties can be more effective proton relaxers than compounds containing only one nitroxyl moiety and hence, the polyradical could be used in smaller quantities than the monoradical and the use of smaller quantities would result in diminished osmolality and toxicity effects. [80] These characteristics include a relatively strong electron paramagnetism and chemical stability in biological systems.

Looking for new paramagnetic molecules with a specific biodistribution and biospecificity to some target organs, various substituted alkyl groups of ranging polarity were introduced in the labelled molecule. [205] Five-membered cyclic nitroxides (pyrroline) were preferred to six membered ones (piperidine derivatives) because of their higher resistance to *in vivo* reduction as demonstrated elsewhere. [180, 206] Synthesis of a such binitroxides involved three subsequent steps. (Scheme 11). The reaction of diethyl malonate (**81**) with bromoalkane in ethanol led to the formation of diethyl 2-alkylmalonate (**82**) which was coupled to ethylenediamine to give 6-alkyl-1,4,8,11-tetraazaundecane-5,7-dione (**83**) in yields ranging from 50 to 70%. Finally the biradicals (**84**) were obtained by coupling of 3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (**31**) with **83** at room temperature using *N,N'-dicyclohexylcarbodiimide* (DCC) and 4-pyrrolidinopyridine as a catalyst.



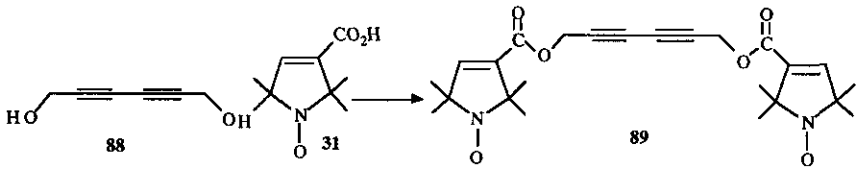
Scheme 11

The same sequence has been used to synthesize the biradical (**87**) [205] in which the alkyl group in the α position is replaced by the pyridine group (Scheme 12). This increases its solubility in water by converting the tertiary aromatic amine function into the hydrochloride salt group and consequently *in vitro* esr biodistribution together with spin clearance of these biradicals and their imaging in the whole body of animals could be easily undertaken.



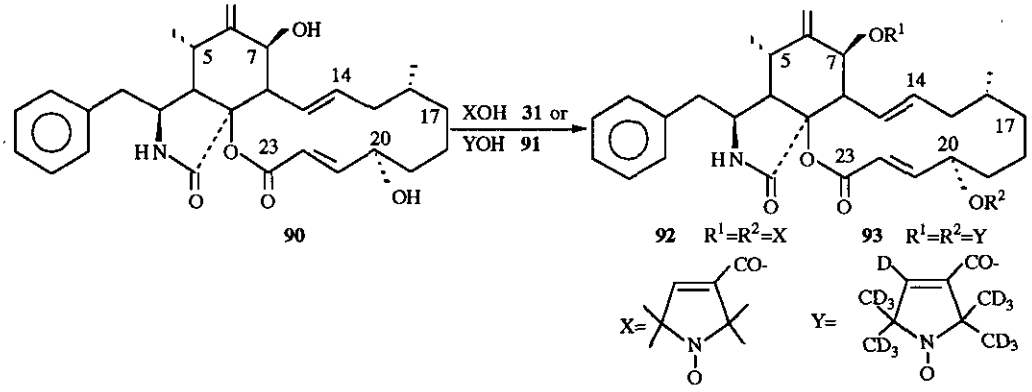
Scheme 12

Cao and co-workers reported that the biradical 2,4-hexadiyne-1,6-diyl bis-(3-carboxylate-2,2,5,5-tetramethylpyrroline-1-oxyl) (**89**) exhibits a spontaneous magnetization of 88.5 emuG/mol and a coercive field of 455 G. [207] This biradical was synthesized by the condensation of 2,4-hexadiyne-1,6-diol (**88**) with 3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (**31**) in the presence of DCC and 4-dimethylpyridine as a catalyst according to (Scheme 13). [208]



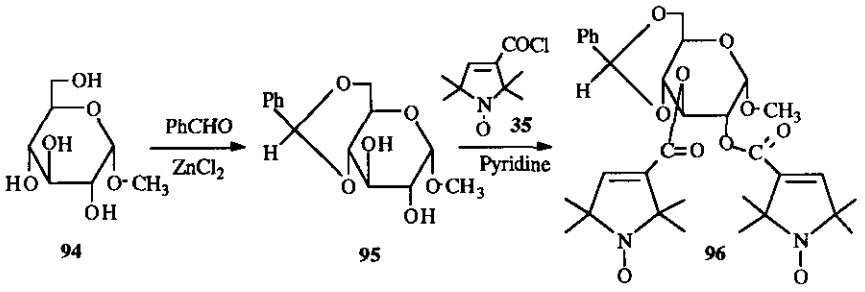
Scheme 13

Recently, in order to study the motional characteristics of the cytochalasin B (CB) (**90**) binding on the glucose transporter protein in erythrocytes, the CB (**90**) was labelled in two sites 20 and 7 by esterification with different nitroxide carboxylic acid such as 3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (XOH) (**31**) and the entirely deuterated 3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (YOH) (**91**). This reaction gives a mixture of monoester radical and diester biradicals of **92** and **93** which are separated by hplc (Scheme 14). [209]



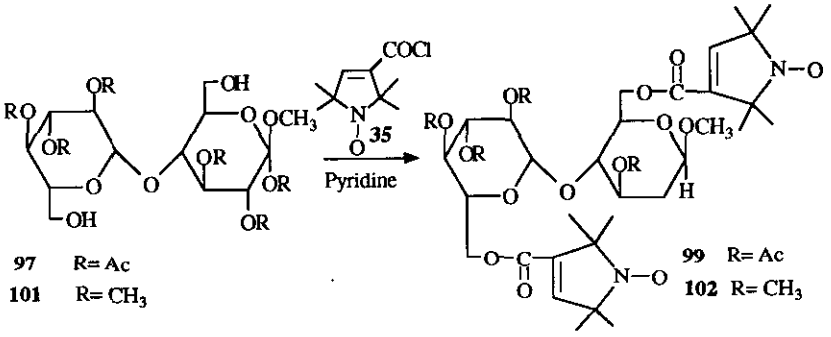
Scheme 14

Activation of 3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl (**31**) to nitroxyl carboxylic chloride (**35**) by the action of thionyl chloride ($SOCl_2$) (Scheme 4a eq: XVI) seems to be the easiest and a general way to prepare polyradicals. This method is illustrated in the chemistry of carbohydrate where a monosaccharide (**94**) is spin labelled at the C_2 and C_3 positions as shown in Scheme 15. [210] Thus methyl-4-*O*-benzylidene-α–D-glucopyranoside (**95**) prepared from methyl-α–D-glucoside (**94**) was reacted with 2 mole equivalents of **35** yielding the analogue (**96**).

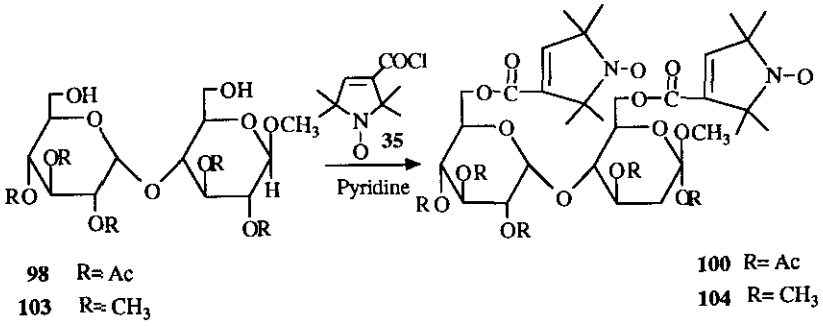


Scheme 15

The same reaction has been used for labelling a variety of cellulose compounds with nitroxyl groups (**35**). As an example the acylation of disaccharides (**97**) and (**98**) with the spin label **35** in pyridine yielding respectively 6, 6'-labelled cellulobioside (**99**) and maltoside (**100**). [210] The methyl ether analogues of cellobiosides (**102**) and (**104**) were prepared similarly respectively from **101** and **103** compounds (Schemes 16 and 17).



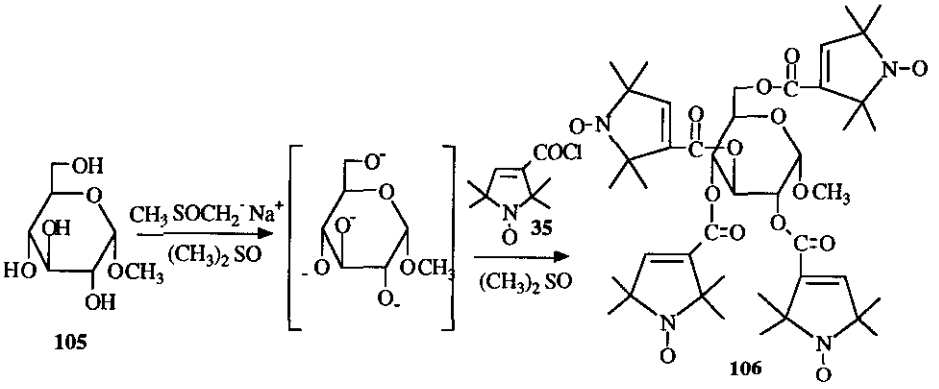
Scheme 16



Scheme 17

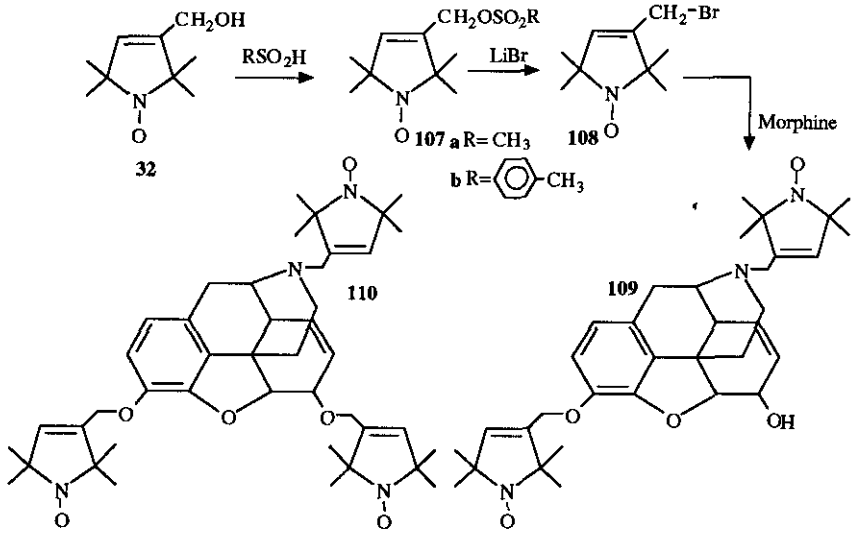
A method for non-specific acylation of all the hydroxyl groups in mono- or polysaccharides was reported. [211-212] For example, the reaction of methyl-α–D-glucoside (**105**) with sodium dimethyl sulfoxide, followed by the

reaction with nitroxyl carboxylic chloride (**35**) gave **106** (Scheme 18). However, no molar ratio of reactants or yields of product were given. The microanalysis of the isolated spin labelled product agreed with a monosubstitution of the hydroxyl groups. [211] It appears that the product is random mixture of 2-, 3-, 4- and 6-labelled positional isomers. This method has the advantage of simplicity without tedious chemical modification of the sugar. It has the disadvantage of a complete lack of specificity of covalent binding.



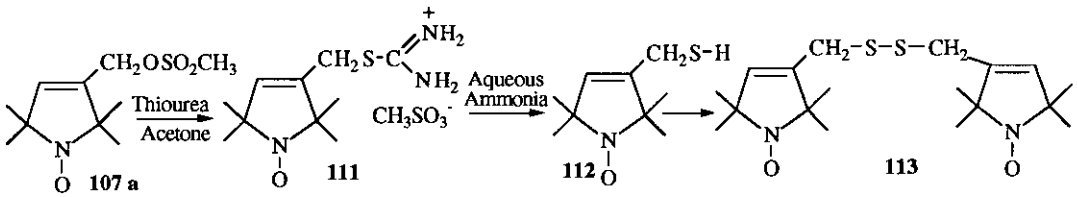
Scheme 18

To prepare a labelled morphine with two and three nitroxyl groups, Hideg prepared sulfonic ester (**107**) by the reaction of sulfonic chloride or 3-methoxy-2,2,5,5-tetramethylpyrroline-1-oxyl (**32**) (Scheme 4a eq: XIV) which was expected to enhance reactivity towards several nucleophiles in acetone or alcohol solution. The bromoethyl compound (**108**) was then formed by the reaction of lithium bromide (LiBr) with nitroxide (**107**). [213] When morphine was reacted with excess of reagent (**108**), the biradical (**109**) [213] and triradical (**110**) [214] were obtained (Scheme 19).



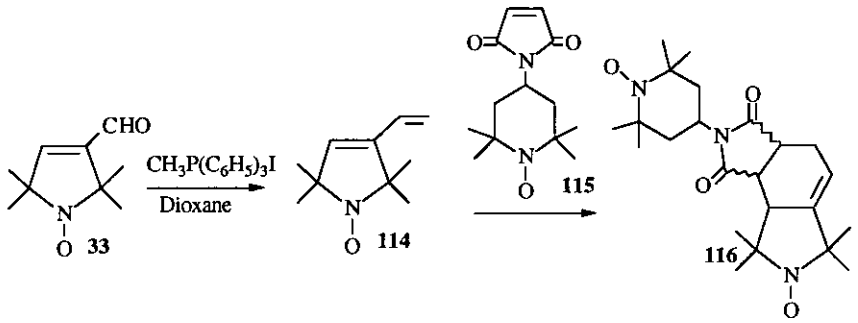
Scheme 19

The 3-thiomethyl-2,2,5,5-tetramethylpyrroline-1-oxyl (**112**) [213] is an interesting paramagnetic thiol prepared from thiuronium methanesulfonate (**111**) and then oxidized to biradical disulfide (**113**). [214] This biradical constitutes an interesting intermediate which could react with protein SH group [214] (Scheme 20).



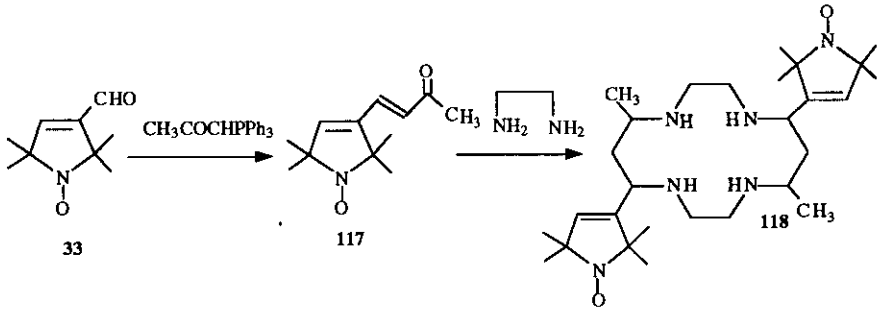
Scheme 20

The unsaturated 3-formyl-2,2,5,5-tetramethylpyrroline-1-oxyl (**33**) is used as a convenient synthon for the preparation of poluenes. The precursor diene or 3-vinyl-2,2,5,5-tetramethylpyrroline-1-oxyl (**114**) (Scheme 4a eq: XVII) obtained by phase transfer Wittig reaction of aldehyde (**33**) with methyltriphenyphosphonium iodide in dioxane, reacted with the spin labelled maleimide (**115**) giving rise to a biradical (**116**) (Scheme 21). [215]



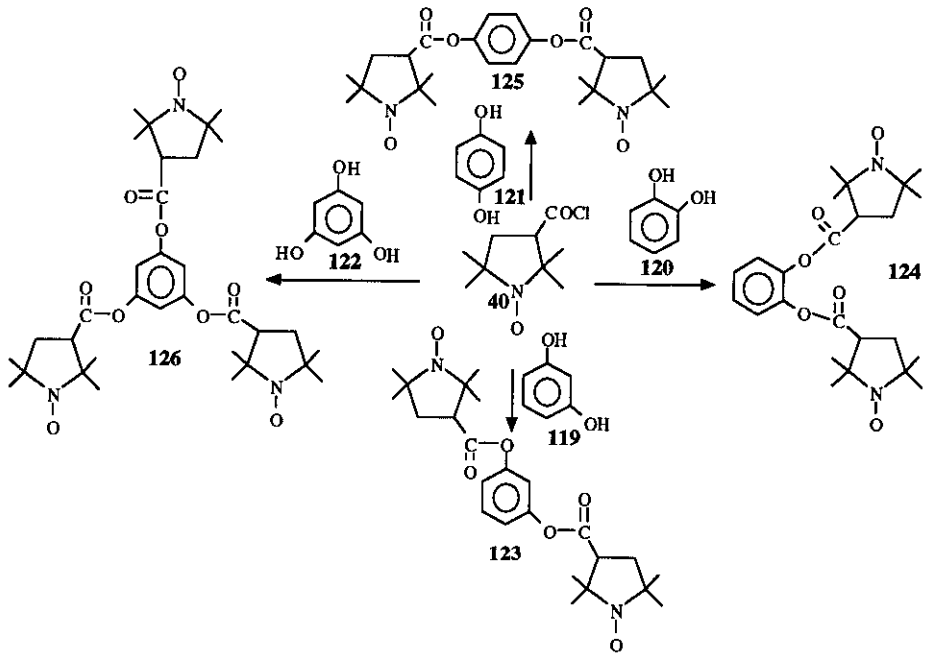
Scheme 21

Hankovszky and co-workers [216] have prepared a more reactive dienones (**117**) suitable for nucleophilic addition of thiol or amine groups. The methyl dienone (**117**) is obtained by a Wittig reaction of 3-formyl-2,2,5,5-tetramethylpyrroline-1-oxyl (**33**) with acetylmethylene-triphenylphosphorane. The 14 membered more stable structural macrocycle binitroxide (**118**) is obtained from the reaction of **117** with ethylenediamine and sodium borohydride (Scheme 22). This product is a useful spin labelled tetradendale ligand in complex formation reactions.



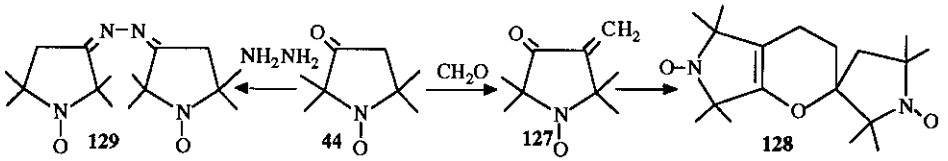
Scheme 22

The carboxylic acid function of 3-carboxy-2,2,5,5-tetramethylpyrrolidine-1-oxyl (**37**) has been changed into acid chloride (**40**) (Scheme 4a eq: XXX) and used for the preparation of several binitroxides (**123**), (**124**), (**125**) as well as the trinitroxide (**126**) respectively from pyridine solutions of resorcinol (**119**), pyrocatecol (**120**), hydroquinone (**121**) and phloroglucinol (**122**) (Scheme 23). [179]



Scheme 23

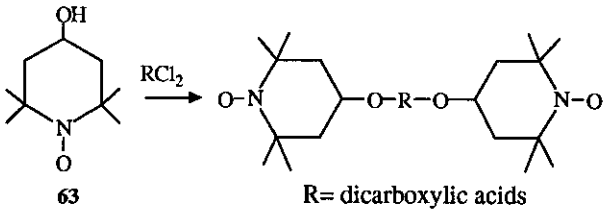
Using the keto radical (**44**) (Scheme 4a, eq:XVIII), Rassat and co-workers [217] have prepared a biradical (**129**) by condensation of 2 moles of radical (**44**) with one mole of hydrazine in diethylene glycol. However the yield of this reaction is very low (14%). In other reaction the keto nitroxide (**44**) has been methylated to give **127** which is not isolated and condensed slowly to give the biradical (**128**) [218] (Scheme 24). These molecules are of a great interest in epr studies owing to the short separation between the two nitroxyl functions.



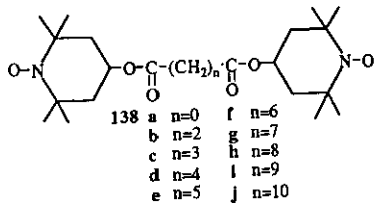
Scheme 24

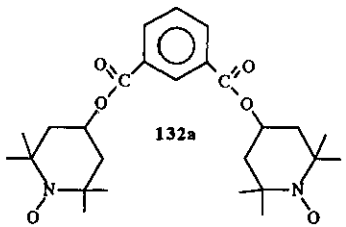
VIII Bi- and polyradicals with 2,2,6,6-tetramethylpiperidine-*N*-oxyl (**7**) as radical group.

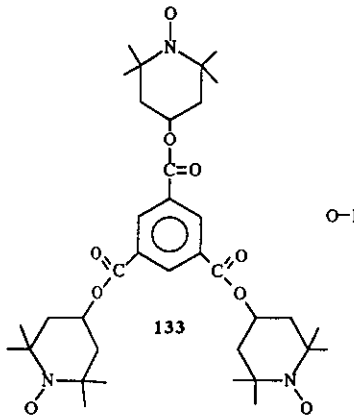
The tempol or 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**63**) (Scheme 4b eq: XLIX) was largely used to prepare polyradicals by esterification with dicarboxylic acids using DCC as a condensing agent [219-220] or simply with dicarboxylic acid dichloride (Scheme 25a). These reactions represent a general method for obtaining a large variety of bi- and polyradicals (Scheme 25b). [118, 221-225]



Scheme 25a


138 a n=0
b n=2
c n=3
d n=4
e n=5
f n=6
g n=7
h n=8
i n=9
j n=10


132a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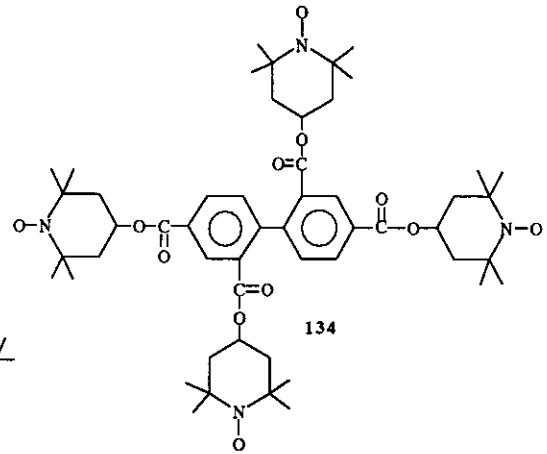
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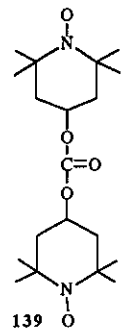
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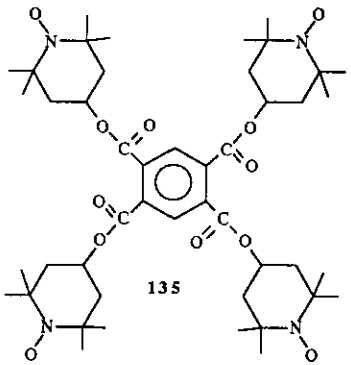
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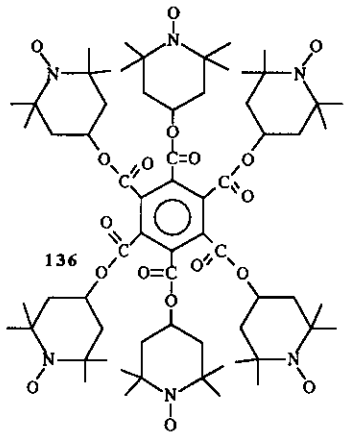
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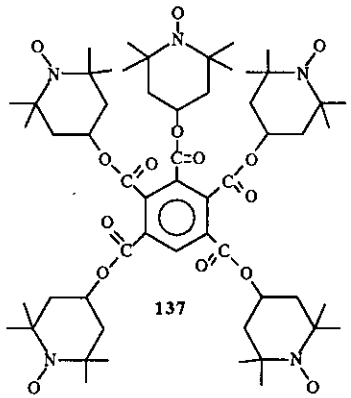
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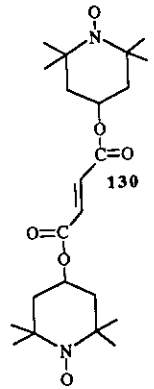
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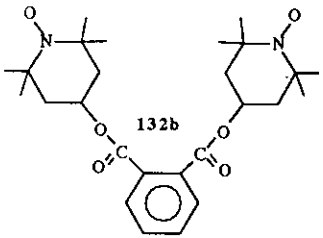
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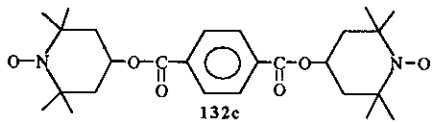
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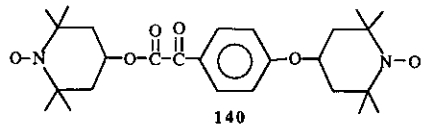
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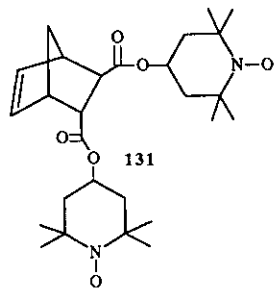
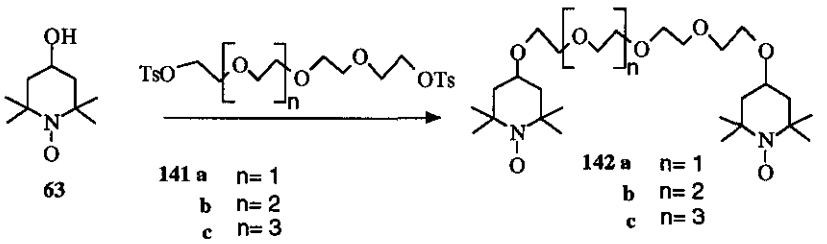

131

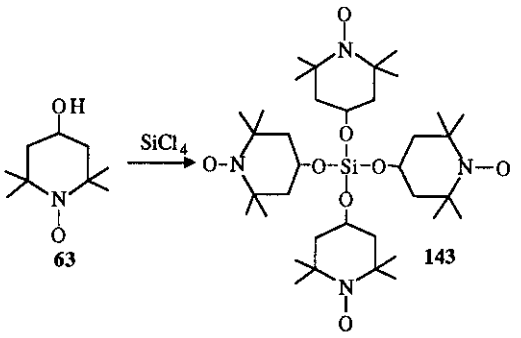
Scheme 25b

To study the regulation of dipolar splitting in a biradical compound by a neutral molecular substrate, the synthesis of biradicals (**142a-c**) has been reported. [226-228] These molecules were obtained by treatment of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**63**) and hexaethylene glycolditosylate (**141a-c**) with sodium hydride in refluxing tetrahydrofuran (Scheme 26). This method constitutes an interesting way to prepare biradicals separated by a long chain and with the possibility of complexing some metals for many chemical and physical purpose studies.

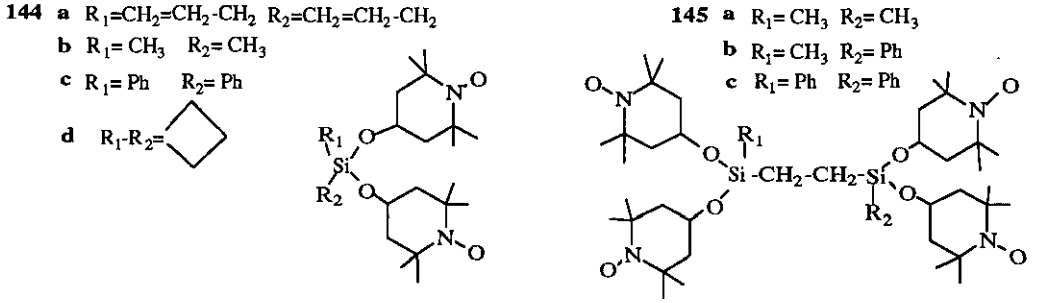


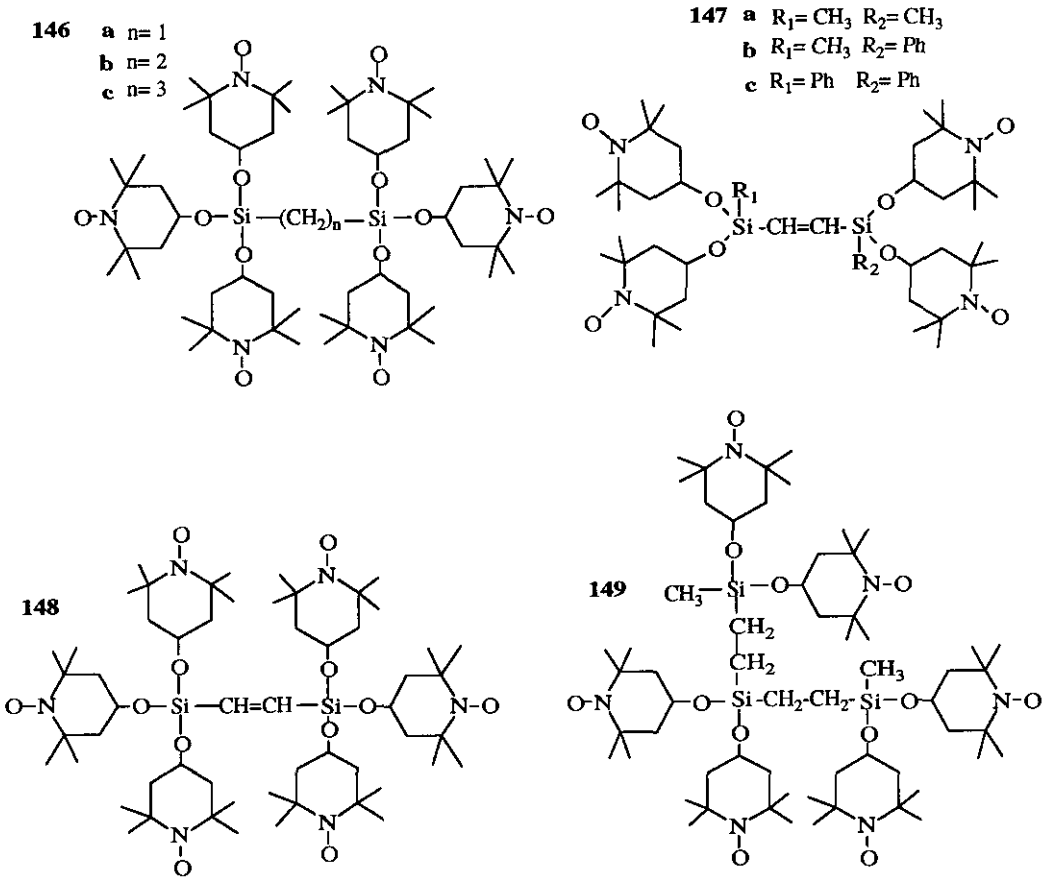
Scheme 26

The silicon tetraradical (**143**) [225] has been prepared by the reaction of silicon tetrachloride with tempol (**63**) (Scheme 27). Similarly, this synthetic method has been largely exploited to prepare many polyradicals (Scheme 28). [229-230]



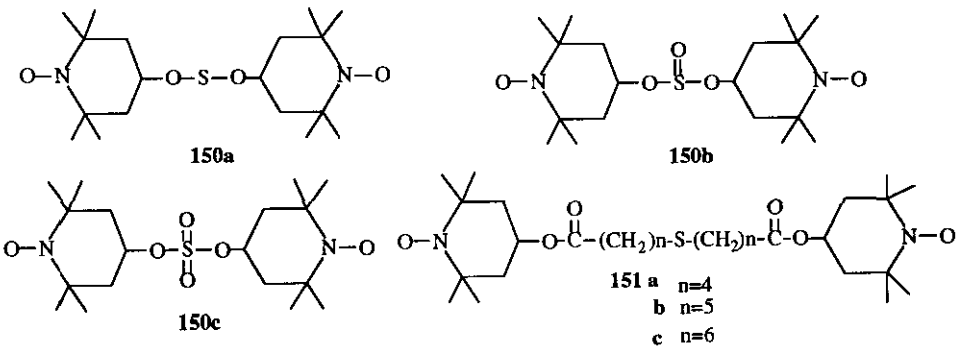
Scheme 27





Scheme 28

Tempol (**63**) also reacts readily with isocyanates and sulfur chloride to give some biradicals such as **150a, b, c** [225] and **151a, b, c** [118, 231] (Scheme 29).



Scheme 29

The method of preparation of spin-labelled phosphorus compounds containing many paramagnetic centres has been reported and described by the pioneers chemists Sosnovsky and Koniecny. In this paper we summarized only the methods leading to the preparation of bi- and polyradicals. In fact, the first well defined spin labelled

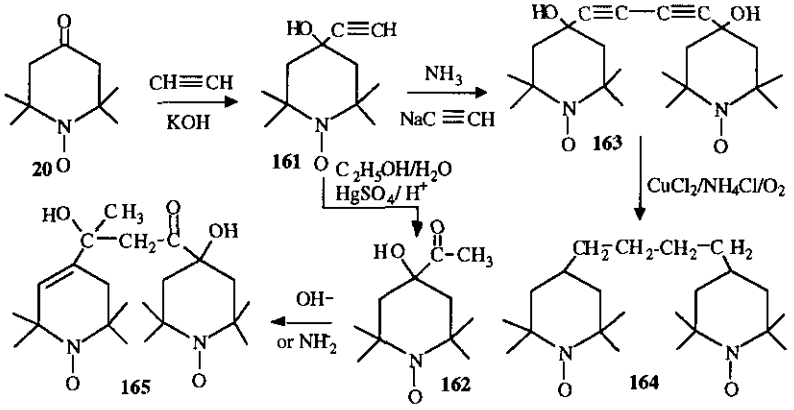
phosphorus compound tri-(2,2,6,6-tetramethylpiperidine-1-oxyl) phosphate (**152**) was prepared by the interaction of phosphorus (III) chloride with tempol (**63**) in the presence of triethylamine. [225]

Also, some biradical phosphonates (**153a-f**) have been prepared by the condensation of phosphonic dichloride ($RPOCl_2$) with tempol (**63**) in the presence of triethylamine. [232-237] These compounds could be used as possible probes for biological studies. [242] Phosphoramidates (**154a-b**) has been also prepared by the reaction of biradical (**153g**) with diethylamine (R=alkyl, aryl...). These products are of interest from a spectroscopic and biological point of view. [243] For example, biradical phosphorofluoridate (**153h**), prepared from phosphonic dichloride fluoride and tempol (**63**) is used to label α-chymotrypsine, [238-241] thrypsine, [238, 240] cholineesterase, [238, 240] elastase, [240] subtilisine [240] and erothrycite. [240]

However, preparation of bis(2,2,6,6-tetramethylpiperidine-1-oxyl)phosphoradates (**155a-c**) involves the reaction of phosphorus(III) chloride with the appropriate amino compounds followed by reaction with radical tempol (**63**). The aziridinophosphoramidothioate (**157**) was synthesized in two steps, by reaction of the thiophosphoryl chloride with an excess of tempol (**63**). The intermediate chloridate (**156**) is not isolated and reacted with the aziridine group to give the diradical aziridinophosphoramidothioate (**157**) in a yield of 45%. In the other case, the reaction of $S{=}PCl_3$ with three equivalents of tempol (**63**) gives triradical phosphoramidothioate (**158**).

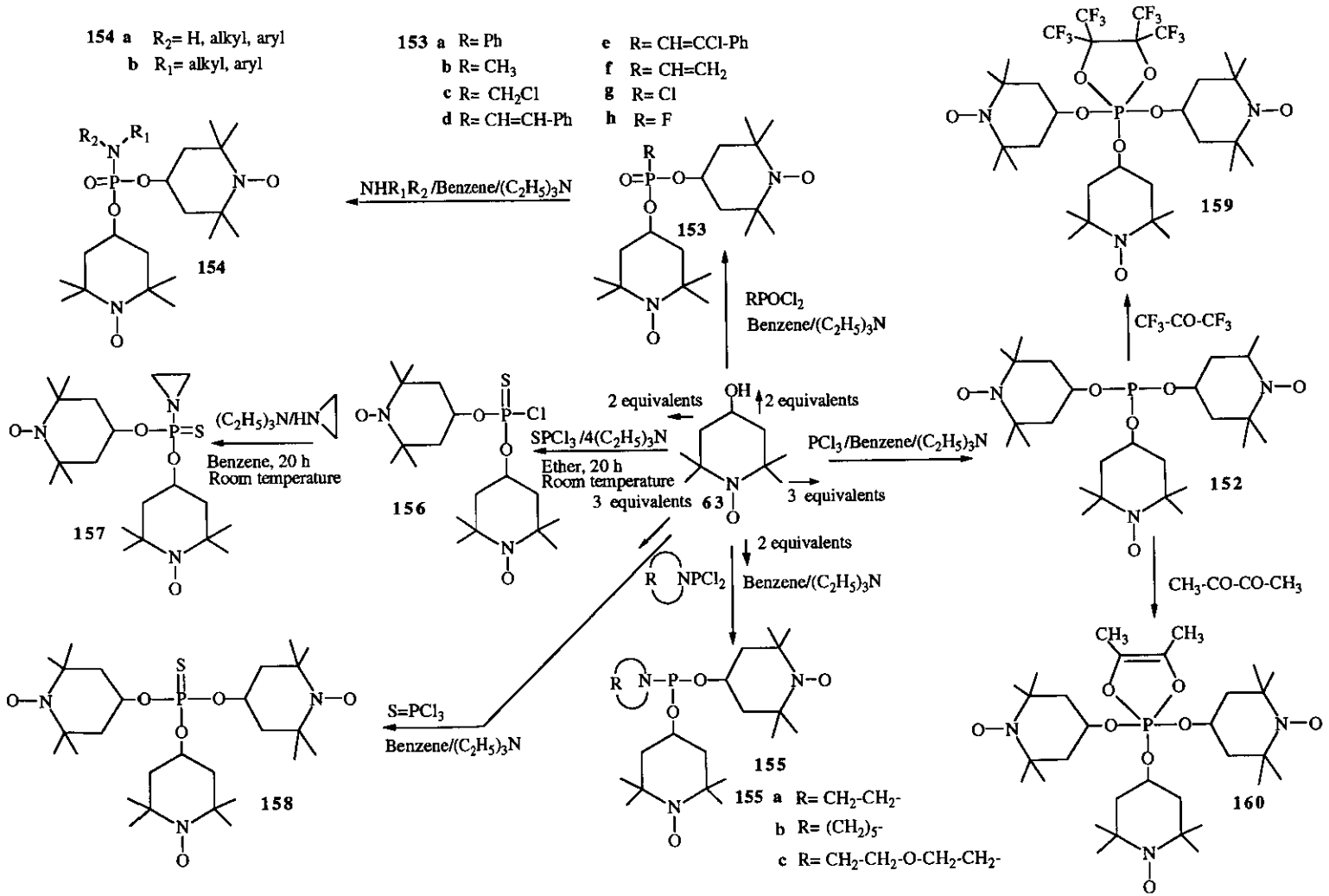
The phospholenes (**159**) and (**160**) were obtained (31% and 98 % yields) respectively from the reaction of the phosphate radical (**152**) with the appropriate carbonyl. The Scheme 30 summarises the different polyradical phosphorus compounds reported elsewhere and for those interested to the phosphorus spin labelled, a good review dealing with this chemistry is reported by Sosnovsky and Konieczny. [110]

Tertiary alcohol (**161**) was obtained at a high yield by the reaction of the acetylene with tempone (**20**) [243] (Scheme 4 eq: VI) in the presence of potassium hydroxide and used to produce nitroxide (**162**) (Scheme 31). These two radicals are good precursors for the preparation of alkylated spin probes and analytical reagents [244] or to synthesize a variety of binitroxides (**163**), (**164**) and (**165**). However the biradical 4,4'-(butadiyne-1,4-diyl)-bis(2, 2, 6, 6-tetramethylpiperidine-1-oxyl) (**163**) was found to form a black polymer of which some samples exhibits field depend magnetization corresponding to an insignificant amount (0.1%) of ferromagnet.[245]

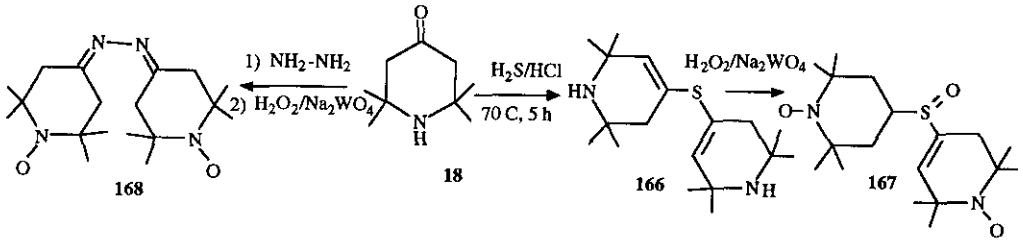


Scheme 31

To protect some polymers against oxidative degradation, [246] binitroxide (**167**) has been prepared in two steps by reaction of 4-oxo-2,2,6,6-tetramethylpiperidine (**18**) with hydrogen sulfide in the presence of hydrogen chloride to yield sulfide (**166**), followed by oxidation of the two secondary amines into biradical (**167**) using H_2O_2 / Na_2WO_4 (Scheme 32). The two radical synthons are separated only by one atom (sulfur). Another biradical in which the two paramagnetic groups are separated by two atoms (nitrogen) (**168**) is also obtained in two steps by the reaction of two moles of **18** with one mole of hydrazine followed by the oxidation of secondary amino functions into nitroxides. [217]

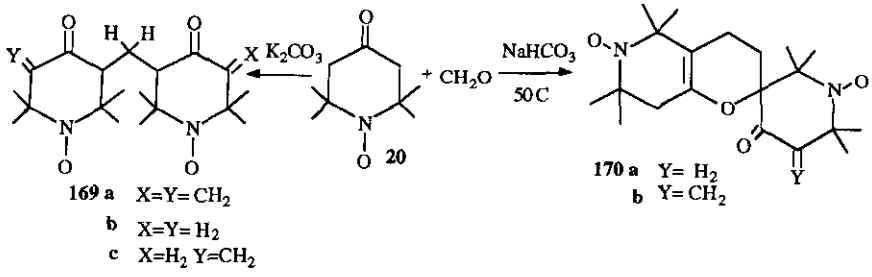

154 a R2= H, alkyl, aryl
b R1= alkyl, aryl
153 a R= Ph
b R= CH3
c R= CH2Cl
d R= CH=CH-Ph
e R= CH=CCl-Ph
f R= CH=CH2
g R= Cl
h R= F
NHR1R2 /Benzene/(C2H5)3N
RPOCl2
Benzene/(C2H5)3N
2 equivalents
2 equivalents
3 equivalents
3 equivalents
63
SPCl3 /4(C2H5)3N
Ether, 20 h
Room temperature
(C2H5)3N/HN
Benzene, 20 h
Room temperature
PCl3/Benzene/(C2H5)3N
CF3-CO-CF3
CH3-CO-CO-CH3
2 equivalents
NPCl2
Benzene/(C2H5)3N
S=PCl3
Benzene/(C2H5)3N
154
153
156
157
158
159
152
160
155
155 a R= CH2-CH2-
b R= (CH2)5-
c R= CH2-CH2-O-CH2-CH2-

Scheme 30



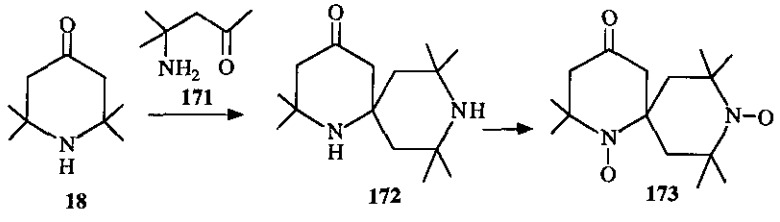
Scheme 32

Hydroxymethylation of tempone (**20**) proceeds in an unusual manner. The first formed hydroxymethylated derivative is dehydrated under conditions of the reaction and the biradicals (**169a-c**) and (**170a-b**) corresponding to the α, β-unsaturated ketones are isolated. [247-250] Owing to the presence of some interesting functions (carbonyls and double bonds), these compounds are good precursors to be functionalized and to be applied in many physical studies (Scheme 33).



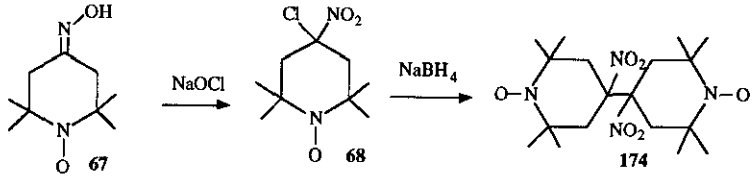
Scheme 33

The pentacetonediamine (**172**) was prepared by the reaction of 4-amino-4-methylpentane-2-one (**171**) with 4-oxo-2,2,6,6-tetramethylpiperidine (**18**) and then submitted to peracid oxidation to give 1,9-diaza-2,2,8,8,10,10-hexamethyl-4-oxo-spiro [5,5]-undecane-1,9-dioxyl (**173**) according to Scheme 34. [251]



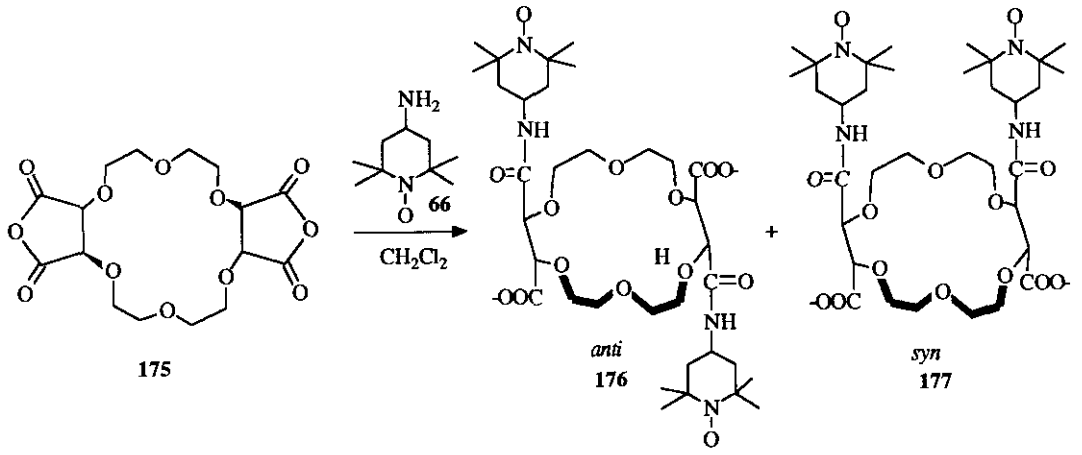
Scheme 34

In other cases, the treatment of 4-hydroxyimino-2,2,6,6-tetramethylpiperidine-1-oxyl (**67**) (Scheme 4b eq: LIV) with sodium hypochlorite gave the 4-nitro-4-chloro-2,2,6,6-tetramethylpiperidine-1-oxyl (**68**) which is converted into binitroxide (**174**) using sodium borohydride (Scheme 35). [252-253]



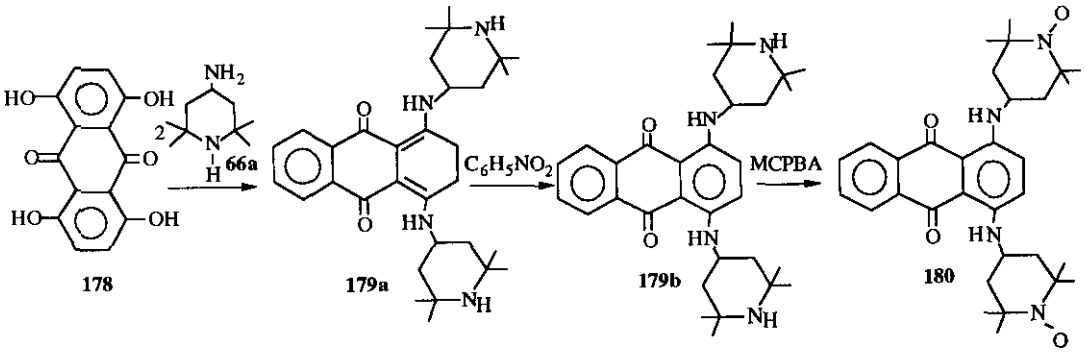
Scheme 35

Spin labelling of crown ethers containing two chiral binitroxides (**176**) and (**177**) has been synthesized to study their intrinsic structural properties as well as their cation complexing and possible cation transporting behaviour. [254] The two isomers compounds were obtained according to the Behr's procedure [255-256] in which 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (**66**) (Scheme 4b eq: LIII) reacted with crown ether (**175**) at room temperature in methylene chloride (Scheme 36). A mixture of 85% of about equal amounts of the *syn* (**176**) and *anti* (**177**) isomers were obtained as an orange oil. However in the presence of an excess of triethylamine the *syn*-isomer (**177**) was formed almost exclusively (90%) (Scheme 36).



Scheme 36

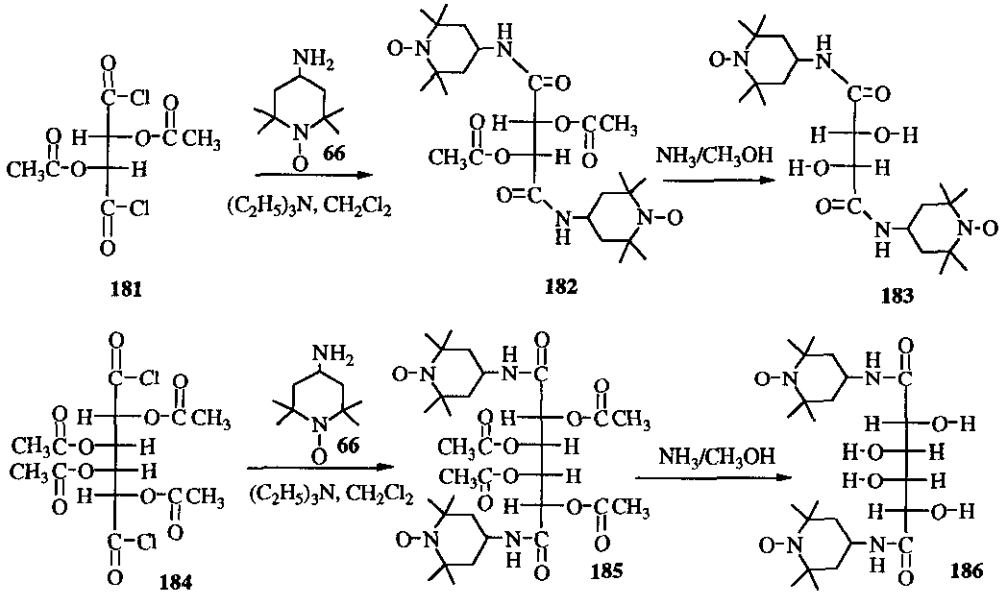
To examine whether the nitroxyl moiety [257] would improve the activity of alkylaminoanthraquinone and for investigating the binding interaction of this class of compounds with various biological systems, Mathew and Cheng [258] prepared a spin label (**180**). This biradical (**180**) is obtained in three steps as shown in Scheme 37. Reaction of leuco-1,4,4,8-tetrahydroxyanthracene-9,10-dione (**178**) with 4-amino-2,2,6,6-tetramethylpiperidine (**66a**) in *N,N,N,N*-tetramethylenediamine gave the dihydroxyalkylaminoanthracenedione (**179a**) which is firstly aromatized to produce **179b** in the presence of nitrobenzene and secondly oxidized to binitroxide (**180**) using MCPBA in ether.



Scheme 37

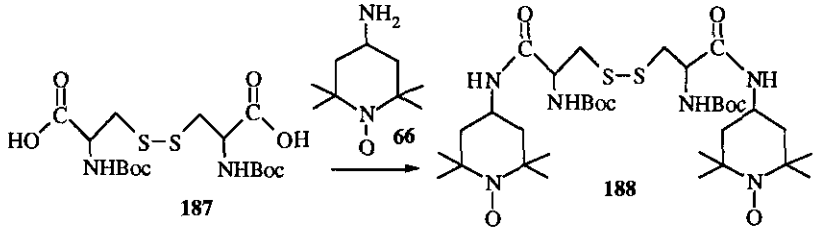
In the magnetic resonance imaging contrast agents Sosnovsky and collaborators [259] have reported the preparation of two original biradicals derived from tartaric and galactaric diamides (**181**) and (**184**). The synthesis of diacetoxy derivatives (**182**) and (**185**) was obtained by reaction of the readily available *O,O*-diacetyltartaric dichloride (**181**) and *O,O*-diacetylgalactaric dichloride (**184**) with the 4-amino-2,2,6,6-

tetramethylpiperidine-1-oxyl (**66**) (Scheme 4b eq: LIII) in methylene chloride and triethylamine. The removal of the acetoxy groups from **182** and **185** was conveniently achieved at low temperature by the use of methanolic ammonia (Schemes 38). These two biradical compounds (**183**) and (**186**) elicited excellent spin-lattice T_1 and spin-spin T_2 relaxation of protons in water and plasma.



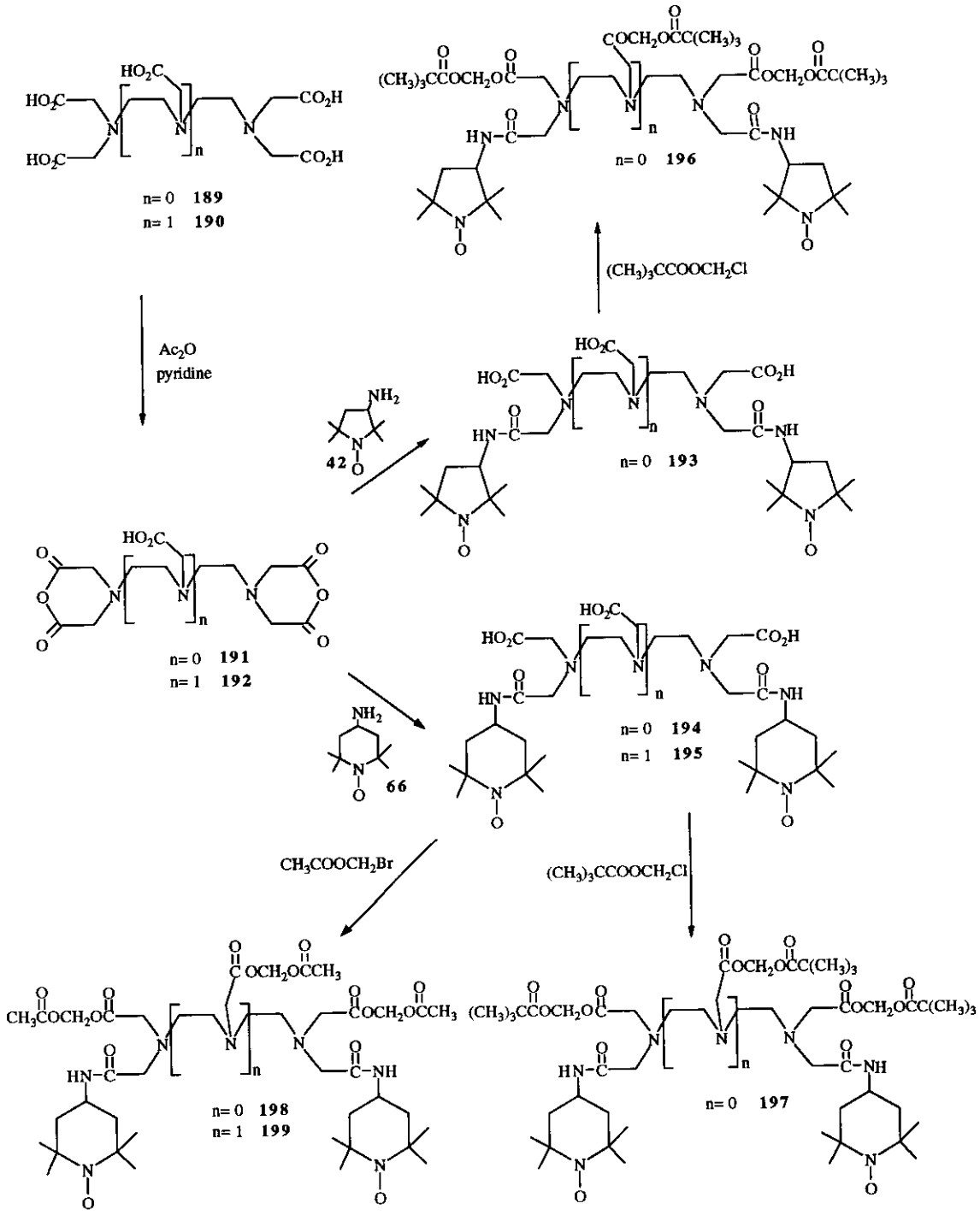
Scheme 38

As a consequence of extensive work on promotes of protein electrochemistry and of examination of the nature of the protein-electrode interface both in the presence and the absence of a redox protein, a spin label (**188**) has been prepared in a good yield from di-*N,N'-tert*-butoxycarbonyl-L-cystein (**187**) and 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (**66**) using DCC (Scheme 39). [260]



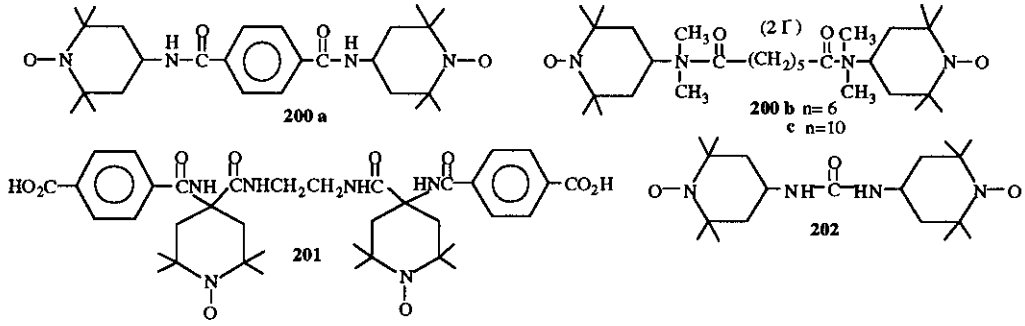
Scheme 39

To study intracellular environments by esr spectroscopy and mri, Sosnovsky and co-workers have reported the synthesis of spin labelled chelating agents using different synthetic methods. The starting materials are EDTA (n=0) and DTPA (n=1) anhydrides (**191**) and (**192**). The condensation of **66** (Scheme 4b eq: LIII) and (**42**) (Scheme 4b eq: XXVI) with **191** and **192** yielded compounds (**193**), (**194**) and (**195**). The esterification of these compounds with either bromomethyl acetate or chloropropylmethyl acetate in the presence of *N,N'*-diisopropylethylamine resulted in active esters of EDTA and DTPA analogues (**196**), (**197**), (**198**) and (**199**) (Scheme 40). [261]


n= 0 189
n= 1 190
Ac2O
pyridine
42
n= 0 193
(CH3)3CCOOCH2Cl
n= 0 196
n= 0 191
n= 1 192
66
n= 0 194
n= 1 195
CH3COOCH2Br
(CH3)3CCOOCH2Cl
n= 0 198
n= 1 199
n= 0 197

Scheme 40

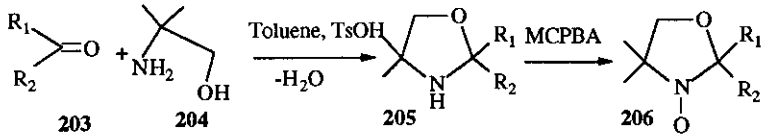
Selective acylation of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (**66**) with dicarboxylic acid functions has also given rise to a variety of biradicals such: **200a**, [126] **200b**, [262] **201** [126] and **202** [264] (Scheme 41).



Scheme 41

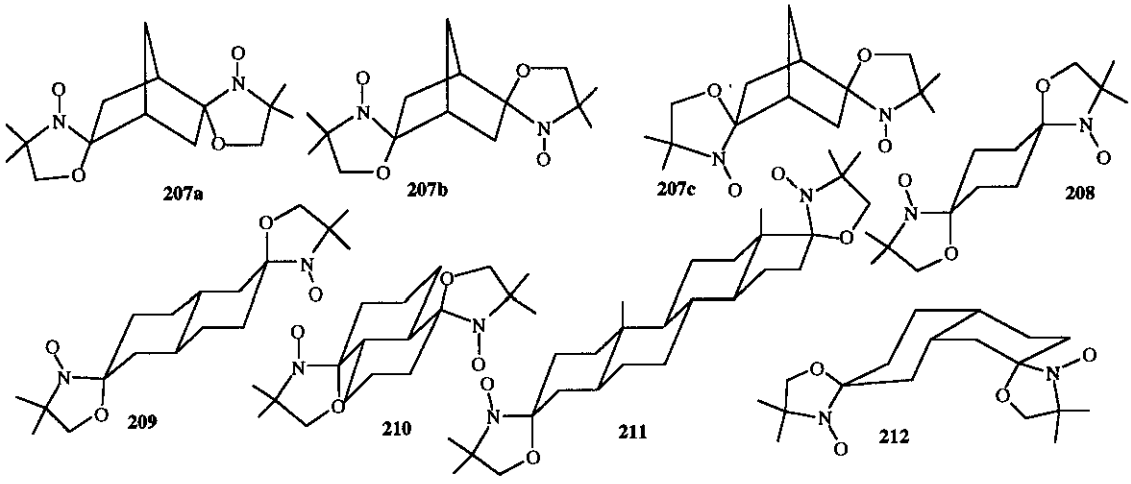
IX Bi- and polyradicals with 2, 2-disubstituted 4, 4-dimethyloxazoline-*N*-oxyl or -doxyl (**10**) as radical group.

Keana demonstrated that most ketones (**203**) react with 2-amino-2-methylpropanol (**204**) to give the corresponding oxazolidine or 2,2-disubstituted 4,4-dimethyloxazolidine (**205**) which can be converted into nitroxide (**206**) by MCPBA as shown in Scheme 42. [263]



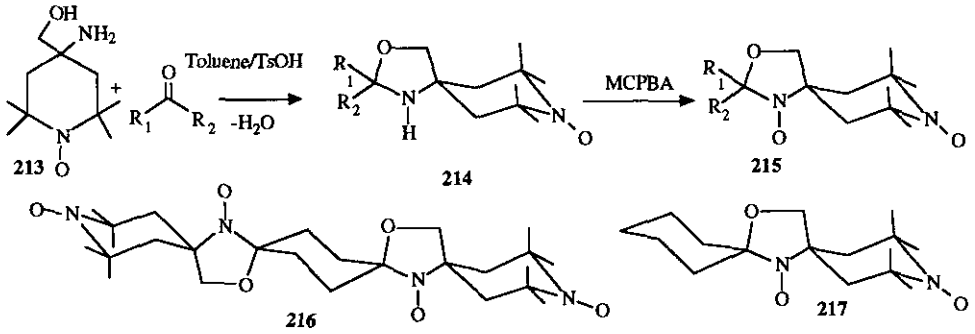
Scheme 42

Despite the low yield of this reaction, almost 30% based on the starting compound (**205**) used, this method has been exploited successfully for the preparation of many nitroxide multiradicals particularly when the condensed molecules possess more than one function (eg. diketones) **207a-c**, [93] **208**, [266] **209**, [265] **210** [265], **211** [115] and **212** [265] (Scheme 43). These multiradicals with more than two unpaired electrons present in some cases a large dipolar interaction. Structural formula of these binitroxides are relatively rigid and correspond to isomers with equatorial N-O groups.



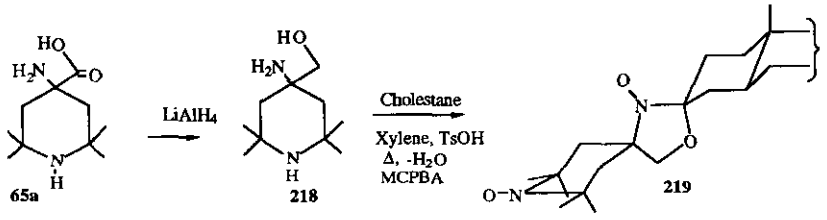
Scheme 43

Another method also permits the preparation of polyradicals in which the main paramagnetic molecule is a combination of oxazolidine-*N*-oxyl (**12**) and 2,2,6,6-tetramethylpiperidine-1-oxyl (**7**). Indeed, the polyradicals **216** [93] and (**217**) [267], have been obtained by condensing 4-amino-4-hydroxymethyl-2,2,6,6-tetramethylpiperidine-1-oxyl (**213**) with ketone followed by oxidation as shown in Scheme 44. For example, detailed analysis of the esr spectrum of frozen solution of the dispiro[(2,2,6,6-tetramethylpiperidine-1-oxyl)-4,4'-(oxazolidine-3'-oxyl)-2',1"-cyclohexane] (**217**) [268] and calculation of Lande (g), dipolar (D) and hyperfine (A) tensors show that C-N bond of oxazolidine ring being equatorial position relative to the chair cyclohexane ring.



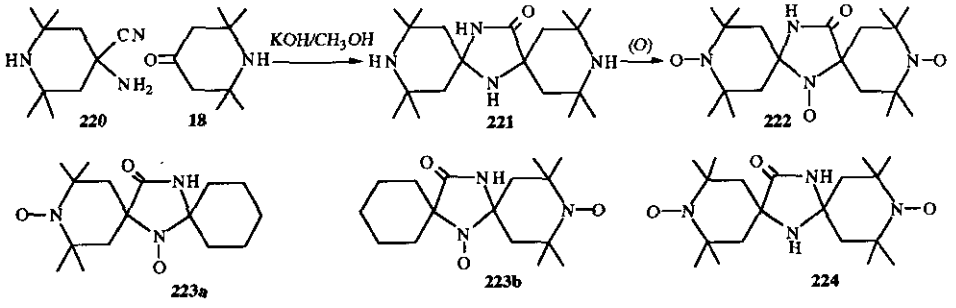
Scheme 44

To show that binitroxide has a potential use as new sensitive probes for membrane structures, Keana and co-workers have prepared biradical (**219**) [269] using as starting material 4-amino-4-carboxy-2,2,6,6-teramethylpiperidine (**65a**) prepared by the Rassat's method. [182] This later was firstly reduced with LiAlH4 in refluxing ether to produce 4-amino-4-hydroxymethyl-2,2,6,6-tetramethylpiperidine (**218**) and then condensed on cholestane to give secondary amines which are oxidized with MCPBA into binitroxide (**219**) (Scheme 45).



Scheme 45

Murayama and co-workers [270] have described a new method in which two and three nitroxyl functions are present in the same molecule. The reaction of the 4-amino-4-cyano-2,2,6,6-tetramethylpiperidine (**220**) with 4-oxo-2,2,6,6-tetramethylpiperidine (**18**) gave in the presence of a basic catalyst the substituted compound (**221**) which is oxidized to trinitroxide (**222**). Using the same method, other biradicals were also prepared **223a-b** and **224** (Scheme 46).

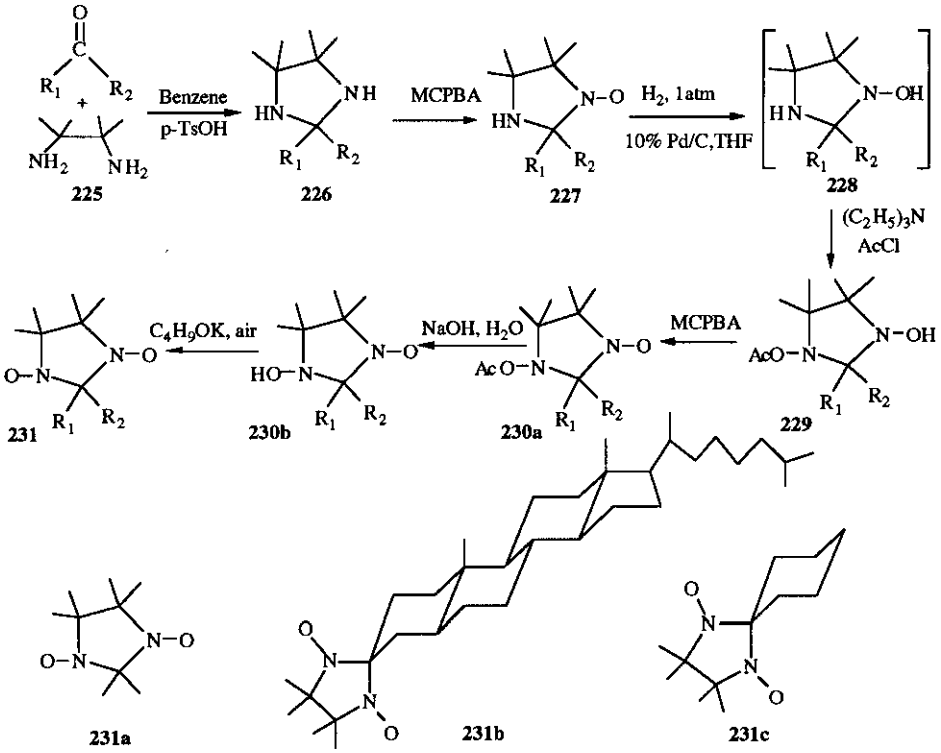


Scheme 46

The esr spectrum of the triplet state of the biradicals cyclohexane-1-spiro-2'-(4'-oxoimidazolidine)-5'-spiro-4"-(2",2",6",6"-tetramethylpiperidine)-1',1"-dioxyl (**223a**) and cyclohexane-1-spiro-2'-(3'-oxoimidazolidine)-5'-spiro-4"-(2",2",6",6"-tetramethylpiperidine)-1',1"-dioxyl (**223b**) have been observed in a frozen 2-methyltetrahydrofuran glass. The distance (d=5 Å) between the two radical sites in these biradicals indicates that one piperidine ring can exist in chair form and the other in twisted form. On the other hand, the biradical 2,2,6,6-tetramethylpiperidine-4-spiro-2'-(4'-oxoimidazolidine)-5'-spiro-4"-(2",2",6",6"-tetramethylpiperidine)-1,1"-dioxyl (**224**) in a frozen 2-methyltetrahydrofuran glass shows no spectra corresponding to a triplet state. [270]

X Bi- and polyradicals with imidazolidine-*N*-oxyl (**11**) as radical group.

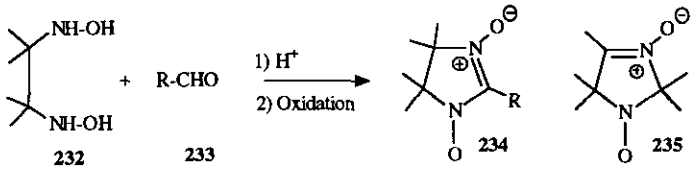
Keana has described the synthesis of a new binitroxide ketone spin label (**231a-c**) [271-272] in which the nitroxyl groups are separated from each other by only one carbon atom. Condensation of 1 equivalent of 2,3-diamino-2,3-dimethylbutane (**225**) with a ketone (**224**) in refluxing benzene led to the corresponding imidazolidine (**226**). Oxidation with 1.5 equivalents of MCPBA in ether gave the corresponding mononitroxide (**227**). This nitroxide was reduced to hydroxylamine (**228**) with catalytic hydrogen (10% Pd/C, THF) and without isolation, it was acetylated to give **229**. Oxidation of **229** with MCPBA gave *N*-acetoxy nitroxide (**230a**). Hydrolysis of the *N*-acetoxy group with NaOH in H_2O produces *N*-hydroxy nitroxide (**230b**). Finally, (**230b**) was treated with O_2 gas at 25 C affording binitroxide (**231**). The rigid attachment of these spin labels to the molecule of interest together with the relatively small size of the radical group and the large dipolar splitting makes these structures (**231a-c**) of considerable interest in both theoretical and spin labelling studies where extreme sensitivity to orientation is important (Scheme 47).



Scheme 47

XI Bi- and polyradicals with nitronyl nitroxide (**15**) as radical group.

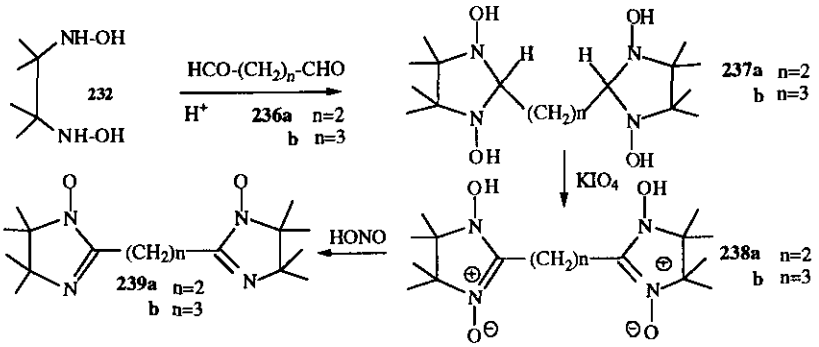
The condensation of 1 equivalent of 2,3-dihydroxyamino-2,3-dimethylbutane (**232**) with aldehyde (**233**) led to the formation of nitronyl nitroxide (**234**) and the isomeric class of nitronyl nitroxide (**235**) (Scheme 48). [273-277]



Scheme 48

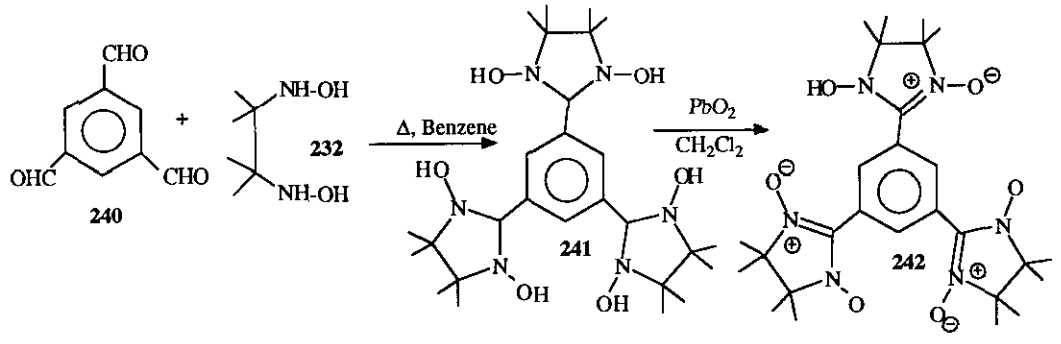
The stability of the nitroxyl function is so great that many chemical reactions can be carried out leaving this functional group intact, including ring expansions and most of the usual ketone reactions. [278]

Reaction of the bishydroxylamine (**232**) with succinic dialdehyde (**236a**) or glutaric dialdehyde (**236b**) in aqueous solution yields the corresponding anhydro adducts (**237a**) n=2 and (**237b**) n=3. After oxidation with potassium periodate (KIO_4) the radicals (**238a**) n=2 and (**238b**) n=3 are obtained. Treatment of these biradicals with nitrous acid led to the sequential removal of the oxygen atoms and the formation of bis-imino nitroxides (**239a**) and (**239b**) [279] (Scheme 49).



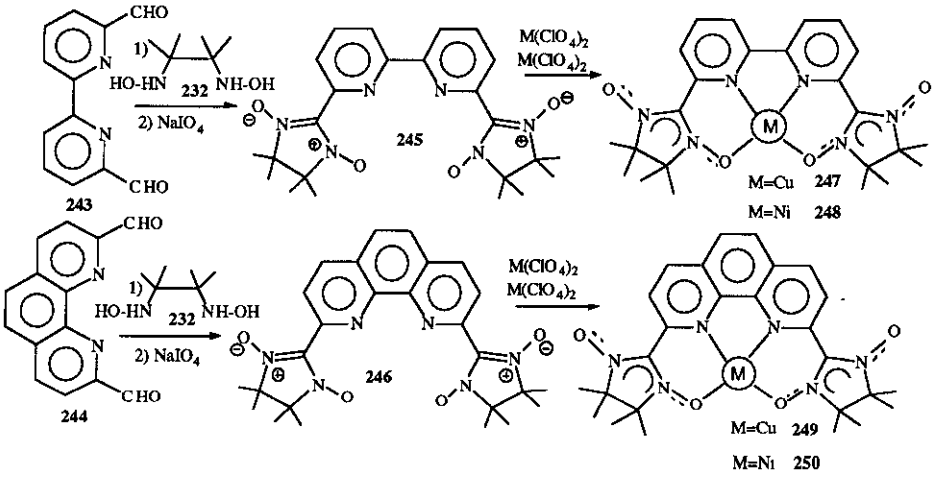
Scheme 49

An extensive literature has been built on the synthesis, properties and applications of nitronyl nitroxides and pure organic radicals [96, 280, 281-282] or metal-organic magnets are prepared. [283-285] Indeed, Dulong and Kim [94] have reported the synthesis of a new stable triradical (**242**) which presents ferromagnetic properties. This compound contains three stable nitronyl nitroxide rings in a single molecule. To generate the triradical (**242**), they used a condensation reaction between an aldehyde (**240**) and a dihydroxylamine (**232**) followed by oxidation with lead dioxide PbO_2 in methylene chloride as shown below (Scheme 50).



Scheme 50

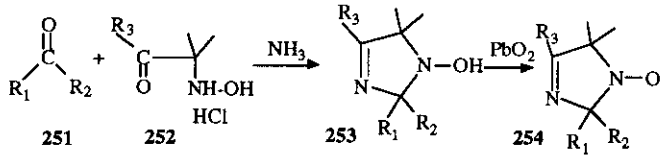
Gatteschi and Rey have reported a novel family of stable chelate based biradicals. [285-286] These molecules are obtained by multiple condensation followed by mild oxidation to give the chelating *N*-oxide-*N*-oxyl biradicals (**245**) and (**246**) (Scheme 51). Both ligands gave mononuclear copper (II) and nickel (II) complexes (**247**), (**248**), (**249**) and (**250**) which are coordinate the two radicals and display a strong anti ferromagnetic coupling at low temperature. [286]



Scheme 51

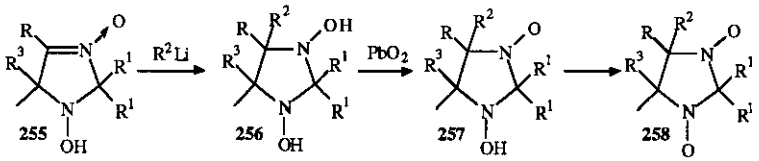
XII Bi- and polyradicals with imidazoline-*N*-oxyl (**12**) as radical group.

The first imidazoline-derived nitroxide has been reported by Volodarskii. [287] The condensation of 1 equivalent of 2-hydroxyamino-2-methylbutanone hydrochloride (**252**) with a ketone (**251**) in the presence of ammonia gave the *N*-hydroxyimidazoline (**253**) which is oxidized to nitroxide (**254**) with lead dioxide (PbO_2) or air (Scheme 52).



Scheme 52

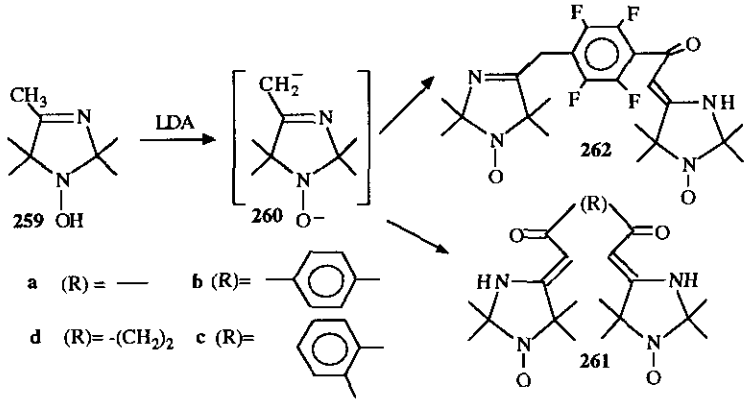
Functionalisation of 3-oxide-*N*-hydroxyimidazoline (**255**) with alkyllithium followed by oxidation (PbO_2) gave the biradicals (**258a-h**) with two nitroxyl groups of imidazolidine (Scheme53). [288] These compounds present an interesting particularity to contain two nitroxyl groups on one heterocycle and exhibit strong exchange interaction with a ferromagnetic character.



a: $R = R^2 = Ph$, $R^1 = R^3 = CH_3$
b: $R = Ph$, $R^1 = R^2 = R^3 = CH_3$
c: $R = R^2 = Ph$, $2\ R^1 = (CH_2)_5$, $R^3 = CH_3$
d: $R = R^2 = Ph$, $R^1 = OC_2H_5$, $R^3 = CH_3$
e: $R = R^2 = Ph$, Ph, $2\ R^1 = OCH_2CH_2O$, $R^3 = CH_3$
f: $R + R^3 = (CH_2)_4$, $R^1 = CH_3$
g: $R = R^1 = R^2 = Ph$, $R^3 = CH_3$
h: $R = Ph$, $R^2 = C_4H_9$, $R^1 = R^3 = CH_3$

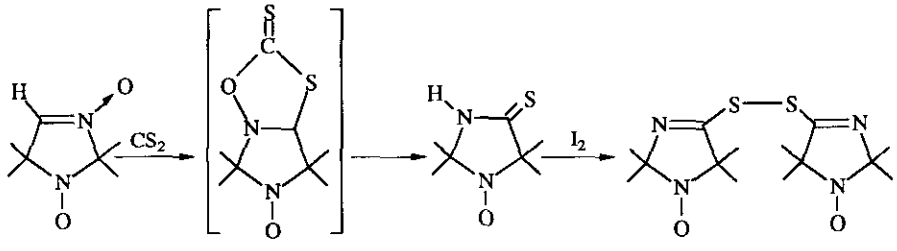
Scheme 53

Similarly the reaction of metalled 2,2,4,5,5-pentamethyl-3-imidazoline-1-hydroxy (**259**) with electrophilic reagents followed by oxidation produces mono- and bifunctional substituted nitroxides of 3-imidazoline and imidazolidine. [289] Indeed, biradicals (**261**) are prepared using the metalled derivative (**260**) formed by the reaction of lithium diisopropylamide (LDA) on imidazoline (**259**), with diesters of oxalate (**a**), phthalic (**b**), terephthalic (**c**) and succinic acids (**d**) (Scheme 54). These compounds contain an enamino ketone unit as tetradental ligands and their complexes were found to undergo low temperature phase transitions to the ferromagnetic state. Besides these molecules, the compound (**262**) presenting only one enaminoketone was obtained by the reaction of **260** with methyl pentafluorophenylbenzoate (Scheme 54). [288]



Scheme 54

The reaction of aldonitrone (**263**) with carbon sulfur gives sulfur derivatives (**265**) which in presence of I_2 affords binitroxide (**266**). [290]

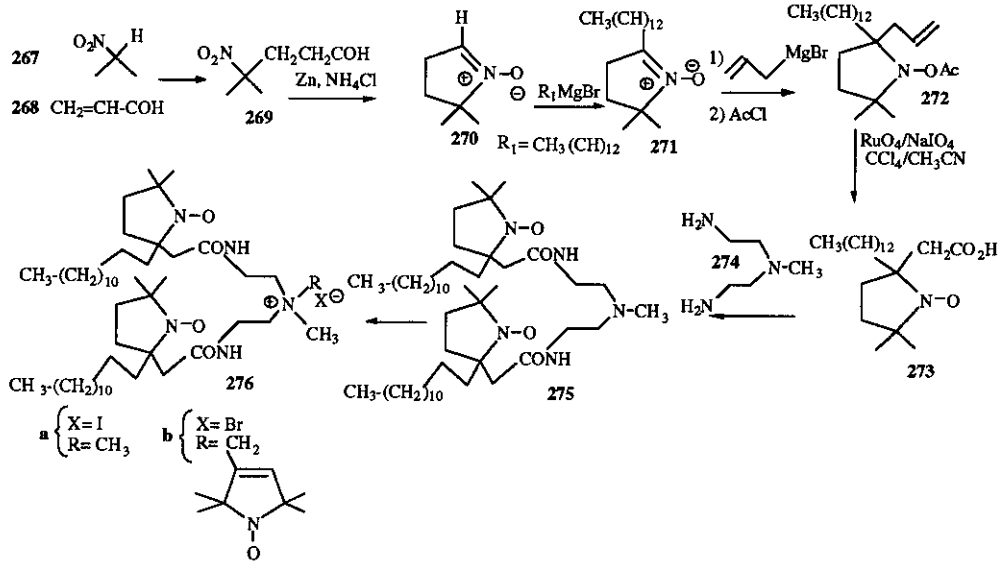


Scheme 55

XIII Bi- and polyradicals with nitrone-*N*-oxyl or -proxyl (**10**) as radical group.

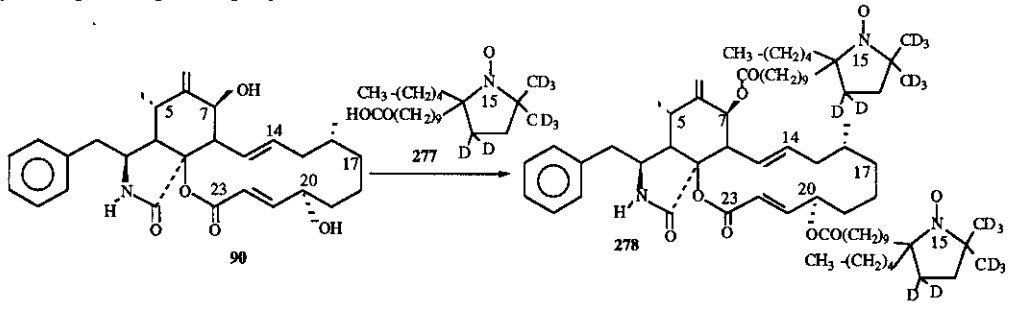
Nitrones could also be used for coupling functionalized carbon chains. [108, 291] The best advantage of this reaction is the possibility of introducing on the α of nitroxyl function a group other than methyl. The commercially available nitrone (**270**) is treated with organometallic reagent (tridecylmagnesium bromide) affording after Cu^{2+}-air oxidation of the intermediate a new nitrone (**271**). Reaction of **271** with a second organometallic reagent (allylmagnesium bromide) followed by Cu^{2+}-air oxidation gives the proxyl nitroxide which was quenched with acetyl chloride to give *N*-acetoxypyrrolidine (**272**). After selective oxidation of the terminal double bond and basic hydrolysis under air followed by acidification, the acid (**273**) is obtained in a good yield (Scheme 56). This reaction described by Keana [209] has been used to prepare a new aliphatic binitroxides in which the ethoxycarbonyl mixed anhydride of acid (**273**) was used to dialkylate the two primary amino groups of *N,N*-bis(2-aminoethyl)methylamine (**274**) giving the diamide (**275**) (Scheme 56). Quaternization

with MeI gave the binitroxide salt (**276a**) while quaternization with 5-bromoethyl-2,2,5,5-tetramethylpyrroline-*N*-oxyl gave a trinitroxide salt (**276b**).

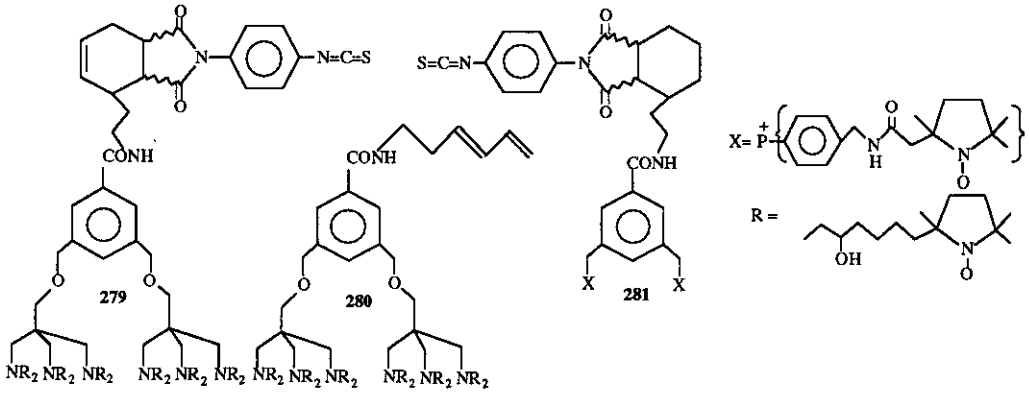


Scheme 56

The same method has been used to prepare the ^{15}N-nonadeutero-11-proxylpalmitic acid (**277**) which was then used to label the cytochalasin B (CB) (**90**) into (CB) ester (**278**) (Scheme 57) or to prepare a new series of paramagnetic molecular amplifiers (**279**), (**280**), (**281**) (Scheme 58). These molecules contain many paramagnetic centers (proxyls **R** and **X**) which have been used to a targeting device such as a monoclonal antibody through a single uniquely functionalized reaction arms. [209]



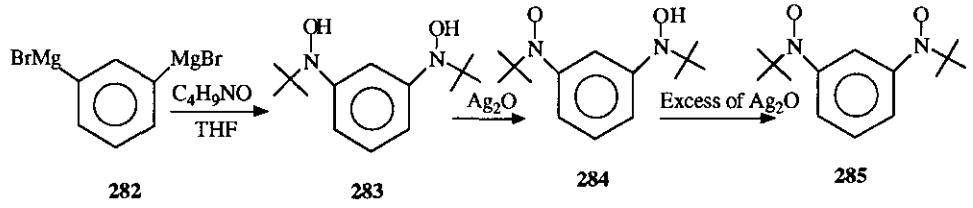
Scheme 57



Scheme 58

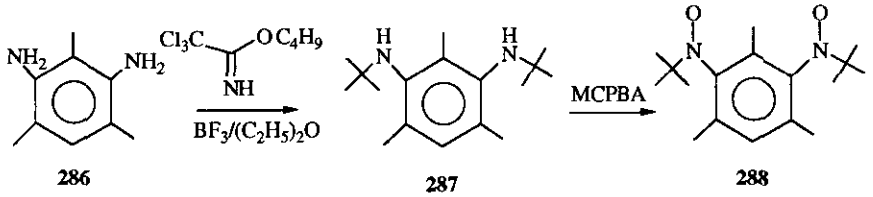
XIV Bi- and polyradicals using *N, N'*-di-*tert*-butylnitroxide (**6**) as radical group.

The first epr study of biradical based on *tert*-butyl nitroxide as a paramagnetic group has been reported by. Lukhurst and collaborators. [292] The biradical (**285**) was prepared by treatment of the bis-Grignard reagent (**282**) obtained from 1,2-dibromobenzene with 2-methyl-2-nitrosopropane followed by hydrolysis yielding the dihydroxylamine (**283**). Oxidation of **283** with silver oxide afford hydroxlamine (**284**) which was treated again with excess of silver oxide to give the biradical (**285**) (Scheme 59).



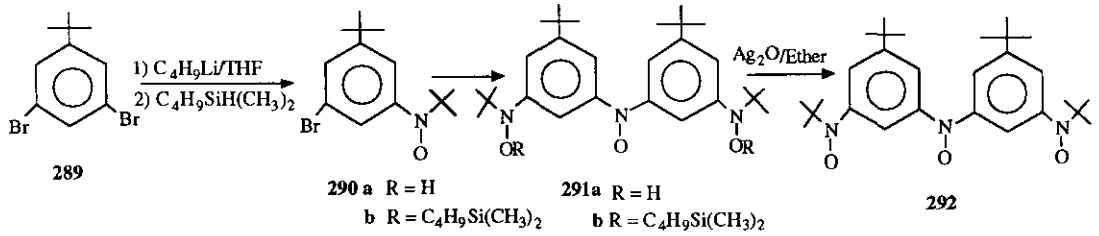
Scheme 59

However, this biradical was shown to be a ground-state triplet but unfortunately it is not fully persistent and undergoes spontaneous decomposition into an isomeric aminoquinone-imine-*N*-oxide after a few hours.
In order to obtain persistent radical, Rassat and collaborators [293] have reported the synthesis of 2,4,6-trimethyl-*m*-phenylene binitroxide (**288**) obtained in a three steps as a form of two isomers in a very low yield. In contrast, both isomers were found to have a singlet ground state (Scheme 60).



Scheme 60

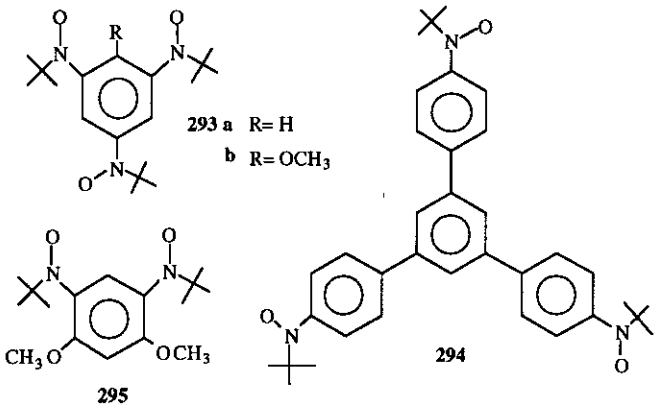
On the other hand and looking for a persistent polyradical based on *tert*-butyl nitroxide, Iwawara [294] has reported the synthesis of a triradical (**292**). This molecule was prepared as shown in Scheme 61. The 3,5-dibromo-*tert*-butylbenzene (**289**) was lithiated with t-BuLi in THF and coupled with 2-methyl-2-nitrosopropane to give **290a**. After protection of hydroxyimino group with *tert*-butyldimethylsillyl group in quantitative yield, **290a** was lithiated with t-BuLi in THF and coupled with *n*-pentyl nitrite to give diacyl nitroxide (**291a**). Finally the trinitroxide (**292**) was obtained at 80% yield by means of the desilylation of **291b** with tetrabutylammonium fluoride trihydrate in THF followed by oxidation with lead oxide in ether.



Scheme 61

Using the same method, the 1,3,5-benzenetriyltris(*N*-*tert*-butylnitroxide) (**293a**), its 2-methoxy derivative (**293b**) and 1,3,5-tris(p-(*N*-oxyl-*N*-*tert*-butylamino)phenyl)benzene (**294**) have been prepared. [295] Indeed, the epr study, the magnetic susceptibility and magnetisation measurement revealed a quartet ground state and an

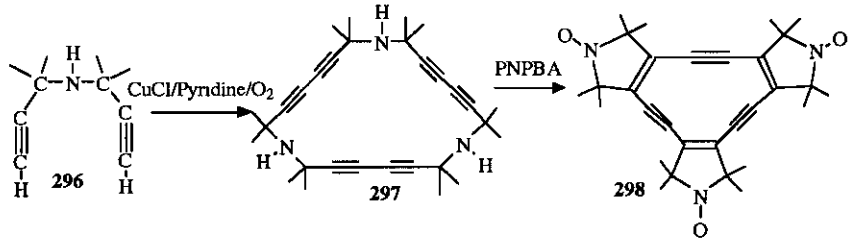
intramolecular triangular exchange coupling among nitroxide radical centers. In contrast, the 4,6 dimethoxy-1,3-phenylene bis(*N-tert*-butyl)nitroxide (**295**) [296] prepared similarly present a singlet ground state (Scheme 62). For many details, the molecular magnetism properties of some excellent reports are available. [84, 297]



Scheme 62

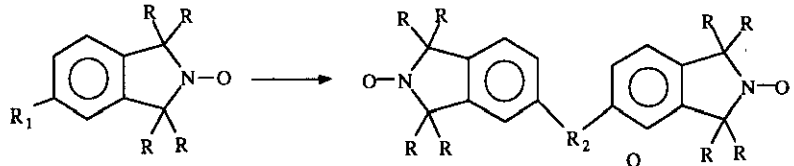
XV Cyclic bi- and polyradicals.

In addition to the classical ring nitroxides, Van Roosmalen and collaborators [298] have reported the synthesis of a novel polycyclic compound tri-(2,2,5,5-tetramethylpyrrolo)-3,7,11-tridehydro(12) anulene (**298**) formed by valence isomerisation from the intermediate cyclic hexaacetylenic triamine (**297**). [299] The cyclisation is obtained using a CuCl/pyridine/O_2 complex in a good yield. Oxidation of this cyclic form is obtained by putting excess of paranitroperbenzoic acid (PNPBA) in toluene to afford a trinitroxide (**298**) (Scheme 63). This interesting structure presenting a cyclic conjugation has not been yet exploited for any application.



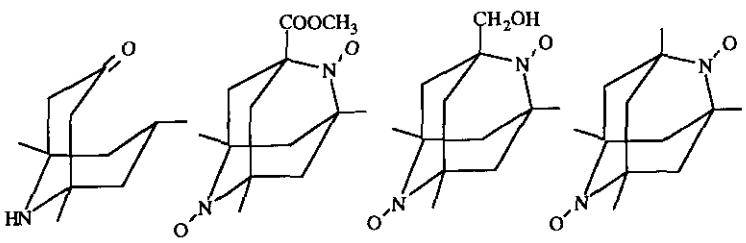
Scheme 63

Based on the precursors (**299**) and (**300**), [300-301] a class of biradicals (**301**) and (**302**) derived from isoindoline have been reported [129, 302] (Scheme 64). These molecules seem to possess a rod-like structure which permits them to be used as a probe to study liquid crystal phases. [303]



Scheme 64

Another variety of cyclic binitroxides has been described by Rassat and collaborators. Starting from compound (**303**) they obtained different cyclic biradicals (**304**), (**305**) and (**306**) [93] (Scheme 65). In particular the biradical (**306**) [97] presents an interesting intramolecular ferromagnetic interaction between the two orthogonal N-O groups and shows the existence of a ferromagnetic transition at 1.48 K. As yet this is the highest transition temperature found for a purely organic non ionic material.

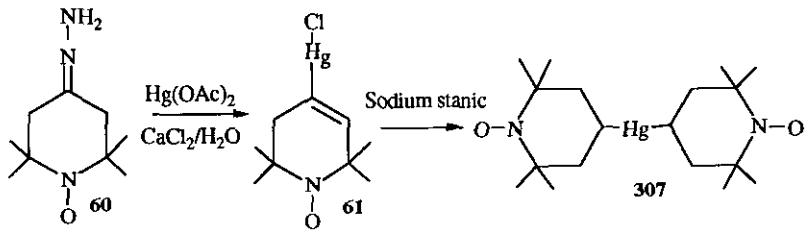


303 **304** **305** **306**

Scheme 65

XVI Bi- and polyradicals as ligands for metallic ions.

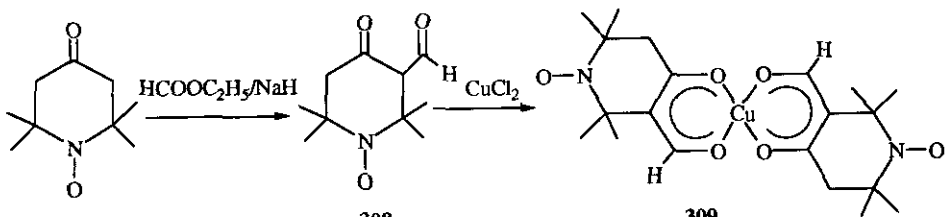
Hydrazone radical (**60**) has been used as a ligand and as a starting product [190, 304] for the synthesis of organometallic compounds. Treatment of this radical with mercury (II) acetate and calcium chloride in water gives the organomercuric radical (**61**) which reacts with sodium stannic to give organomercuric biradical (**307**) [191] (Scheme 66).



60 **61** **307**

Scheme 66

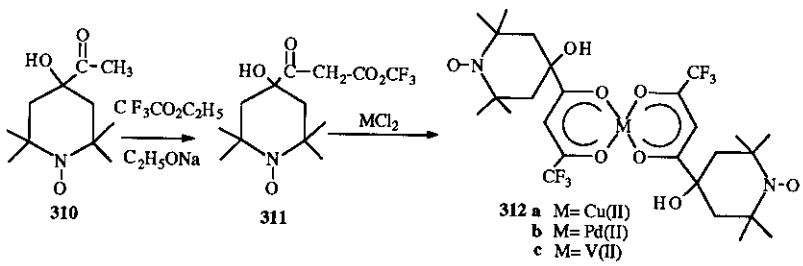
3-Formyl-4-oxo-2,2,6,6-tetramethylpiperidine-1-oxyl (**308**) is prepared by reaction of tempone (**20**) with ethyl formate in the presence of sodium hydride. The compound obtained forms a complex with copper ions (**309**) [305-307] (Scheme 67).



20 **308** **309**

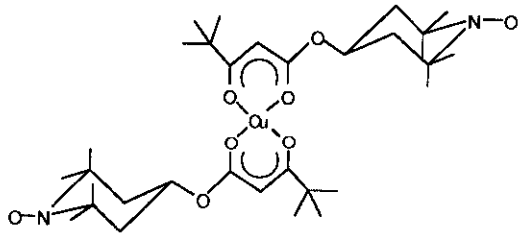
Scheme 67

Also, the reaction of nitroxide (**310**) [244] with trifluoroethyl formate in the presence of sodium hydride, gives the β–cetoaldehyde (**311**) which is used to prepare metallic complexe nitroxide (**312**) (Scheme 68).



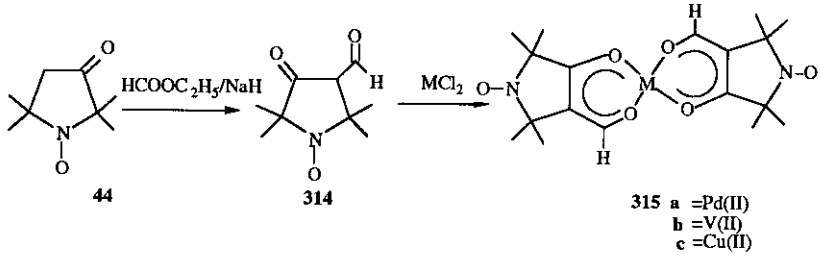
Scheme 68

The copper(II) binitroxide complex (**313**) is the first example of a strong electron exchange six spin system reported in the literature (Scheme 69). [308]



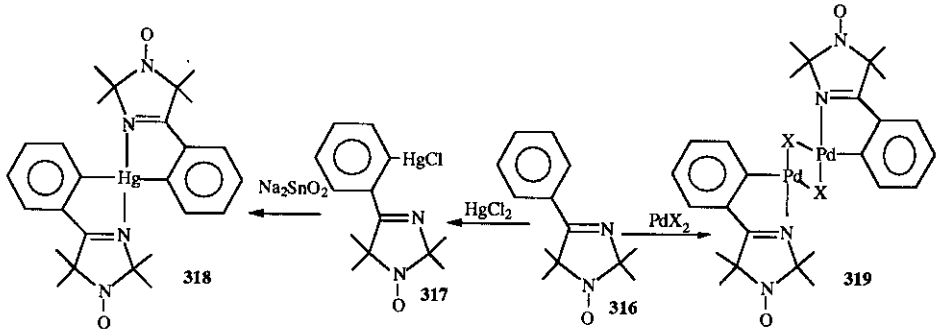
Scheme 69

Based on the keto nitroxide precursor (**44**) (Scheme 4a eq: XVIII), the β-ketoaldehyde nitroxide (**314**) is prepared and used as chelating agent of copper, palladium and vanadyl (Scheme 70). [305-307]



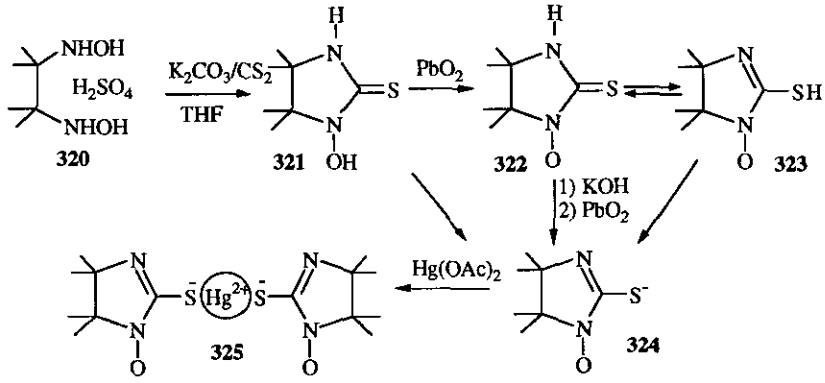
Scheme 70

In the other case, complexation of imidazoline nitroxide (**316**) with metals by cyclometallation has been described by Volodarskii for Pd and Hg (Scheme 71). This reaction gives the possibility to introduce functional groups *via* cycloadducts.[184]



Scheme 71

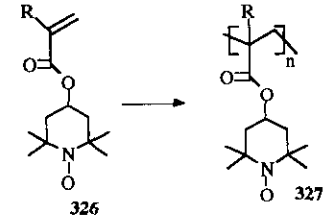
In order to prepare the mercuric biradical complex (**325**), [309] the precursor (**321**) has been used as starting material. The later was prepared by the reaction of 2,3-bis(hydroxyamino)-2,3-dimethylbutane sulfate (**320**) with carbon disulfide and anhydrous potassium carbonate in THF. The oxidation of **321** in DMSO with lead dioxide gives a purple solution of radical (**322**). Its oxidation in benzene produces a yellow solution of tautomer (**323**) which in the presence of KOH followed by treatment with lead oxide gave **324**. Finally in the presence of aqueous solution of Hg(II) acetate, the compound (**324**) is converted into mercuric complex (**325**) (Scheme 72). This complex is of interest to study some epr interactions. [309]



Scheme 72

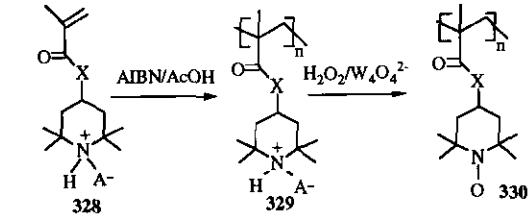
XVII Persistent polymeric radicals.

Due to their potential use as antioxidants and as catalysts for single electron transfer reactions, polymeric nitroxides have been given significant attention and development. [310] The first paramagnetic polymer has been described by Keana in 1967. [311] The poly(tempoacrylates) (**327**) have been made by anionic polymerization of monomers (**326**) prepared from tempol (**63**) and a substituted acrylic acid chloride (Scheme 73)



Scheme 73

The treatment of the analogous hydrochloride or hydrogen sulfate salts (**328**) with AIBN as initiator and acetic acid as solvent gave good yield of polymers (**329**). These compounds were then converted into polymeric nitroxide (**330**) by the action of hydrogen peroxide (Scheme 74).

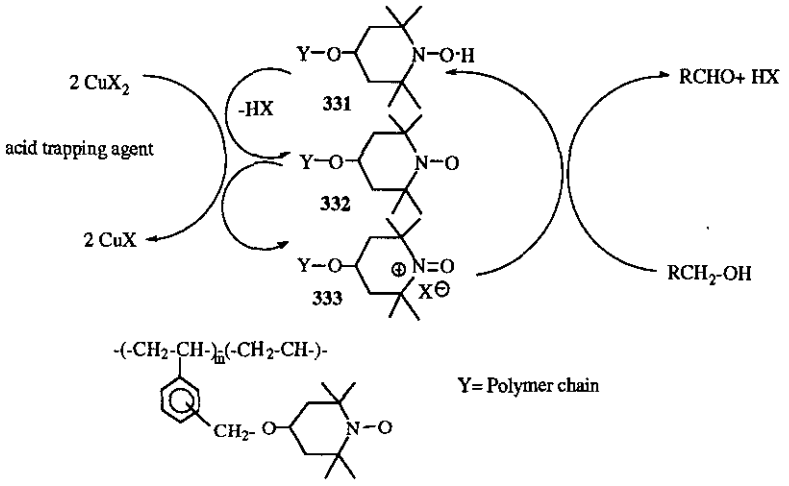


a: X= O, NH
b: A= Cl, HSO_4

a: X= O, NH
b: A= Cl, HSO_4

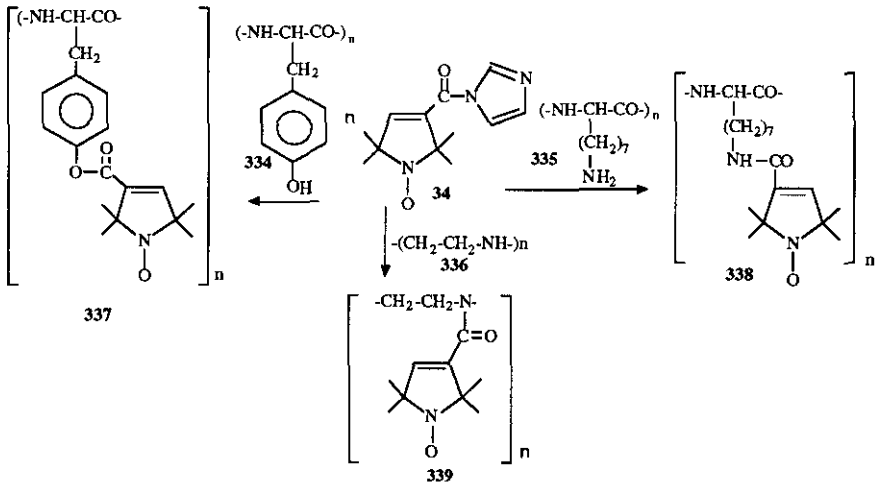
Scheme 74

Endo and collaborators [312] have reported a method of oxidation in which the polymeric nitroxide chain (**332**) is used as mediator of the redox system in a catalytic cyclic reaction (Scheme 75). This study revealed that the polymeric oxoammonium salt as mediator is superior to the monomeric one particularly in the oxidation of benzyl alcohol.



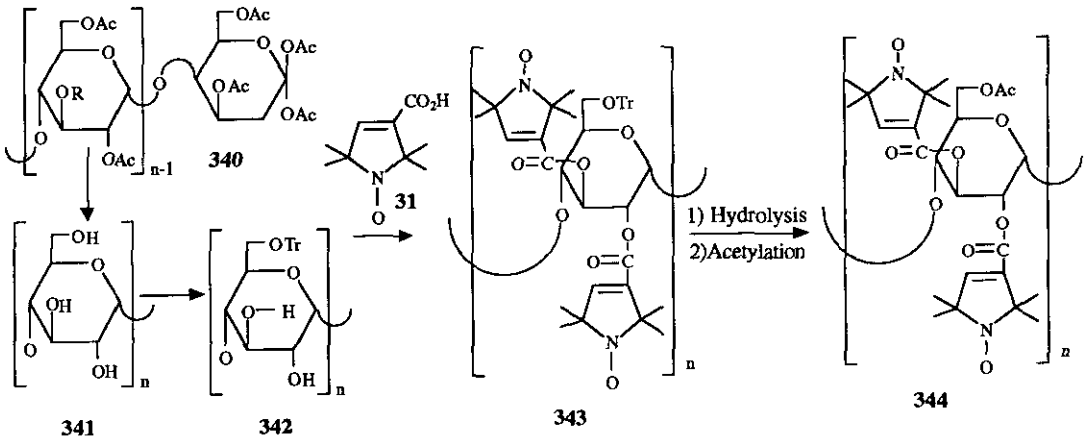
Scheme 75

In order to synthesize radical polymers, [126] the precursor (**34**) has been used as an acylating radical. [178] In fact, treatment of suitable macromolecular compound containing acylated functions with **34** in excess results in almost complete acylation without side reactions. This method has allowed the preparation of poly-*N*-(3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl)ethylenimine (**339**), poly-*O*-(3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl)-L-tyrosine (**337**) and poly-*N*-(3-carboxy-2,2,5,5-tetramethylpyrroline-1-oxyl)-L-lysine (**338**) (Scheme 76).



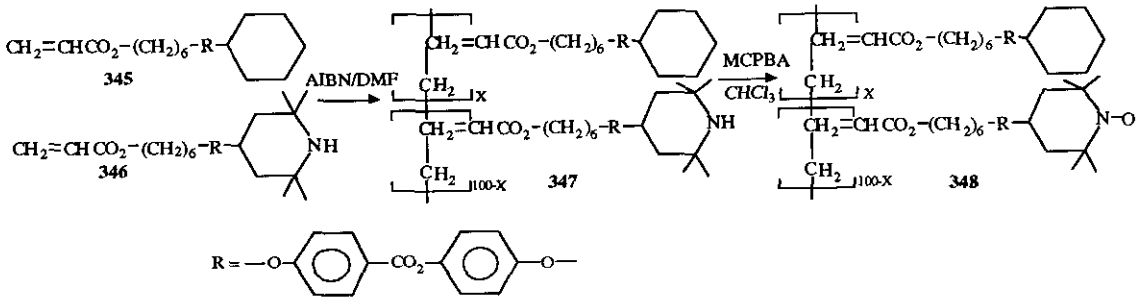
Scheme 76

In chemistry of cellulose field, the acetate (**340**) was completely deacylated (**341**). The 6-position was tritylated **342** and the remaining free hydroxyls at C_2 and C_3 were esterified with spin label **31** to give **343** Acid hydrolysis of the triethyl **343** followed by the acetylation gives the final product (**344**). This product was shown to be a mixture of 3-mono- and 2,3-disubstituted derivatives (Scheme 77). [210]



Scheme 77

Recently Morishima and co-workers [313] reported the synthesis and copolymerization of a mesogenic acrylate having 4-(2,2,6,6-tetramethylpiperidine-1-oxyl)phenyl benzoate as a precursor for nitroxide-containing liquid crystalline side-chain-polymers (**348**). The preparation of this copolymer is carried out by copolymerization of monomer (**345**) with 1% mol of monomer (**346**) in the presence of AIBN in DMF at 60°C. The copolymer (**347**) was then oxidized to copolymer (**248**) by MCPBA in $CHCl_3$ at room temperature (Scheme 78).



Scheme 78

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