1

Triarylmethyl and Related Radicals

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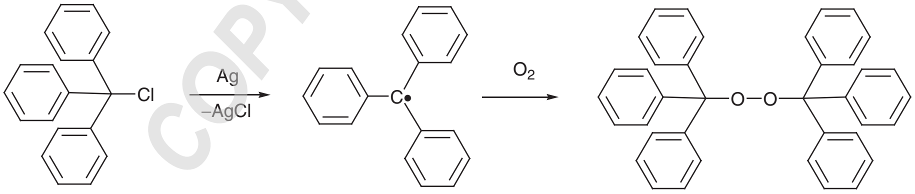
1.1 Introduction

1.1.1 Discovery of the triphenylmethyl radical

During the Nineteenth Century the understanding of the structure of organic compounds was beginning to evolve. The theory of free radicals had risen to prominence, and then fallen into disrepute. This changed abruptly with the bold announcement in 1900 by Moses Gomberg of the formation of the stable and persistent free radical triphenylmethyl **1**, with its radical character shown by its facile reaction with oxygen forming the peroxide **2** (Equation 1.1).[1] This had an immediate impact, and was a major landmark that set the stage for the rapid development of free radical chemistry in the Twentieth Century. Gomberg's work attracted the attention of the world chemical community, and led to careful scrutiny and the ultimate acceptance of this controversial discovery.[2]



1 **2**

(1.1)

Gomberg treated triphenylmethyl chloride with silver or zinc metal and obtained a colored solution, which upon reaction with oxygen yielded peroxide **2**. The species in solution was confidently identified by Gomberg as the triphenylmethyl radical **1**, and he published his discovery in both German and English.[1] Over the next decade there was much dispute as to the identification of **1**, but Wilhelm Schlenk and

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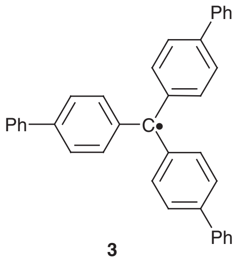
coworkers in 1910 obtained tris(4-biphenylyl)methyl **3** as a deeply colored solid that was almost completely dissociated in solution, which confirmed the existence of **1**.[2i]



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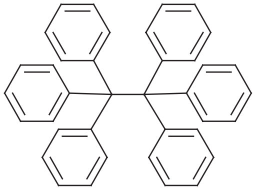
Upon removal of the solvent for the isolation of **1**, a solid dimer was obtained, for which the symmetrical head-to-head structure **4** as well as the unsymmetrical structure **5** (head-to-tail, Jacobson structure)[3a] and **6** (tail-to-tail, Heintschel structure)[3b,c] were given serious consideration. However, as recounted by McBride,[3d] the wrong structure for the dimer, namely the head-to-head structure **4**, became accepted for more than half a century, before this was corrected to the unsymmetrical structure **5** based on spectroscopic data.[3e] In retrospect, not only was the original evidence for the misidentified structure rather flimsy, but techniques, such as NMR, IR, and UV, were also widely available that would have permitted correction of this structure well before 1968. This provides a cautionary tale that skepticism and a critical look at the evidence available for supposed chemical truths is warranted even in the face of conventional wisdom.



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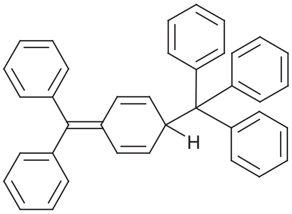

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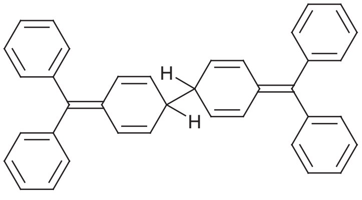

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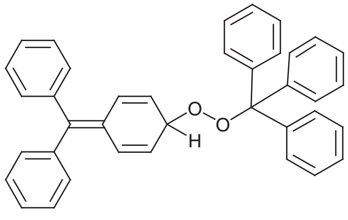
The preparation and identification of the stable triphenylmethyl radical was one of the great chemical discoveries of the Twentieth Century, but surprisingly this was not honored by the award of the Nobel Prize. As revealed by the investigation by Lennart Eberson in the Nobel archives, Gomberg was repeatedly nominated for the award but, due to a series of unfortunate circumstances, the nominations were not accepted.[3f] Despite Gomberg's confident assertion in his first paper that he had proof of the existence of the radical there was later some equivocation, and some contrary opinions, which were enough for the Nobel Committee not to approve the award. With the later preparation of the tris(4-biphenylyl)methyl radical **3** as a stable solid the uncertainty vanished,[2i] but then subsequent nominations were turned down either because both Gomberg and Schlenk were not nominated in the same year, or because too much time had elapsed since the initial discovery. Even in 1940 Gomberg was still being nominated, but without success. Gomberg's discovery was a clearly momentous discovery by a single individual, and although well recognized he did not receive the ultimate accolade he deserved. Paradoxically, Gerhard Herzberg was awarded the 1971 prize in chemistry "for his contributions to the knowledge of electronic structure and geometry of molecules, particularly free radicals", studies which had occupied him for 30 years.

By 1968 the study of stable free radicals had advanced to the stage that the book *Organic Chemistry of Stable Free Radicals* appeared,[4] but in Chapter 2 entitled "Triarylmethyls and Other Carbon Radicals" the introductory paragraph describing the discovery of triphenylmethyl in 1900 ended with the dispiriting words "The behaviour of such radicals was elucidated during the following twenty years, mainly by the work of Gomberg, Schlenk and Wieland, since then little new chemistry has come to light although numerous triarylmethyls have been prepared and more physical data are available." However six pages later, under "Dimerisation" there was the alarming statement "Much of what has been said in this section may require revision in light of the recent communication by Lankamp, Nauta and MacLean", which described the surprising but in retrospect completely predictable finding[3d,e] that the triphenylmethyl dimer had the head-to-tail structure **5**. The rapid development in triarylmethyl radical chemistry since 1968 also belies the tacit assumption of the authors noted above that such studies had become an intellectual backwater. Much of the rather extensive chemistry of triarylmethyl radicals described in this earlier review is not repeated here. The period from 1968 has been a new golden age for free radical chemistry, and this was given great impetus by the widespread use of electron paramagnetic resonance (EPR) spectroscopy, which led to a rapid development of free radical chemistry, and includes many advances in the study of triarylmethyl radicals.

1.1.2 Bis(triphenylmethyl) peroxide

The reaction of the triphenylmethyl radical with oxygen to form the peroxide discovered by Gomberg in 1900 (Equation 1.1) was a strong piece of evidence for the radical structure **1**.[5,6] The affinity of carbon-centered radicals for oxygen remains one of their defining characteristics, and was a striking chemical property that provided strong evidence for the proposed free radical character. The addition of oxygen to **1** had been shown to discharge the color,[5a] and this formation of an initial peroxy radical was later shown to be reversible.[5b]

Just as for the triphenylmethyl radical dimer, there were three conceivable structures for the peroxide corresponding to the dimer structural models, namely head-to-head (**2**), head-to-tail (**7**), and tail-to-tail (**8**). The head-to-head structure **2** proved to be correct, but substituted derivatives of **7** and **8** were later found.[6]



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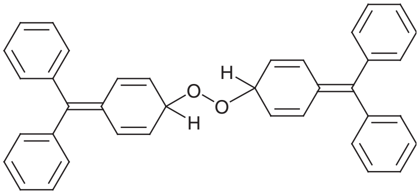

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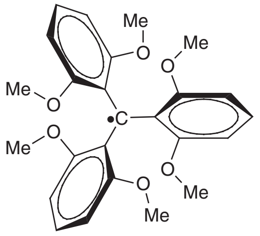
The tris(2,6-dimethoxyphenyl)methyl radical **9** was crystallized and found to have a structure with two of the aryl rings twisted out the plane of the central carbon by 61°, while the third was almost coplanar with an 11° twist angle.[6] Reaction of **9**, and of the bis(2,6-dimethoxyphenyl)phenylmethyl radical **10**, in solution in the presence of air resulted in crystallization of the substituted Heintschel and Jacobson peroxides **11** and **12**, respectively, with the structures proven by NMR, and by X-ray, respectively.[6]



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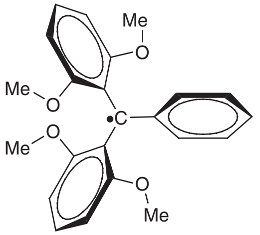

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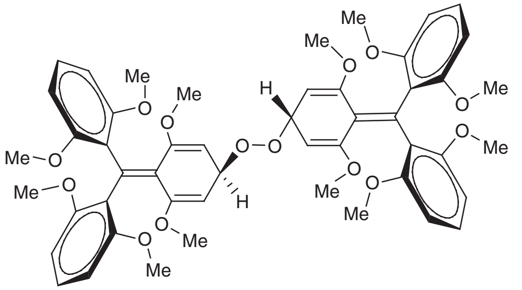

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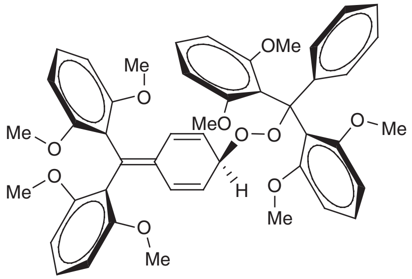

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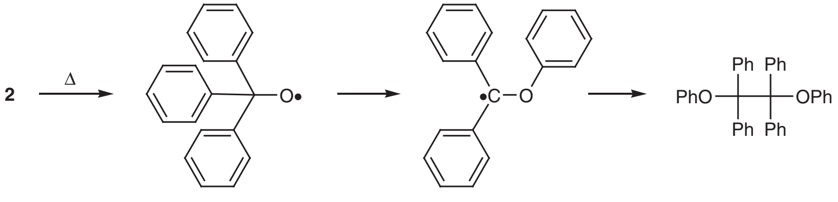
1.2 Free radical rearrangements

Substrates containing the triphenylmethyl group have been important in the discovery and elucidation of the first free radical rearrangements.[7] Wieland observed in 1911 that the Gomberg peroxide **2** rearranged upon heating to the pinacol ether **15** and attributed this to initial dissociation forming an intermediate oxyl radical **13**, and this rearranged forming the radical **14** which dimerized to give **15** (Equation 1.2).[7a] Recent experimental and computational studies indicate this reaction occurs via a phenyl-bridged intermediate.[7g]

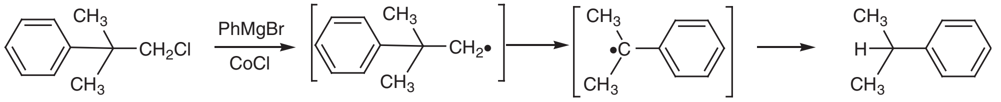


13 **14** **15**

(1.2)

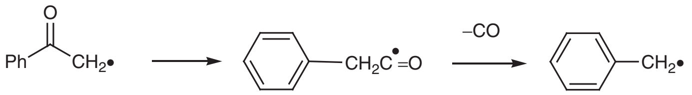
There was a long delay from this observation by Wieland of a radical rearrangement of Gomberg's peroxide until the generality of radical rearrangements was recognized. A key discovery by Urry and Kharasch in 1944 of the neophyl rearrangement (Equation 1.3)[7d] included the proposal for the neophyl radical intermediate **16** and radical **17** forming **18** and other products after work-up (Equation 1.3).[7c]

The McBay rearrangement of acyl radical **19** forming **20** leading to the benzyl radical by decarbonylation is a more recent example (Equation 1.4).[7e,f]



(1.3)

16 **17** **18**



(1.4)

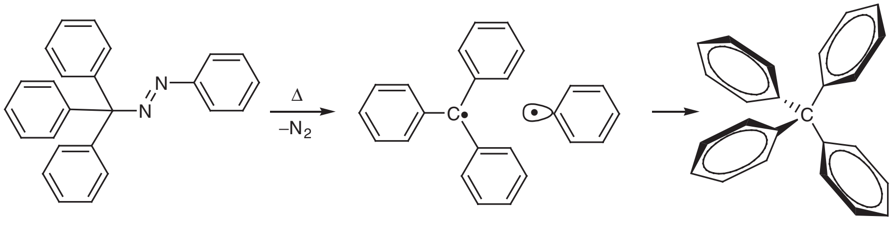
19 **20**

Thermolysis of bis(triphenylmethyl) peroxide **2** in the presence of triphenylmethyl radical resulted in the observation of luminescence from both benzophenone and triphenylmethyl radical.[8] The reaction was interpreted as involving chemiluminescent activation of the triphenylmethyl radical by triplet benzophenone, and was claimed to be the first observed chemical activation of an organic free radical. A mechanism was proposed involving disproportionation of the triphenylmethyloxyl radical **13** (Equation 1.5), but further substantiation of this mechanism appears warranted.

$$\underset{\mathbf{2}}{Ph_3COOCPh_3} \longrightarrow \underset{\mathbf{13}}{2Ph_3CO\bullet} \longrightarrow Ph_3COPh \; +Ph_2C{=}O^* \xrightarrow[-Ph_2C=O]{Ph_3C\bullet(s)} Ph_3C\bullet(T) \qquad (1.5)$$

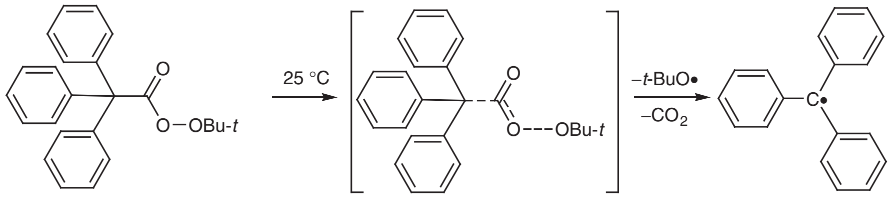
1.3 Other routes to triphenylmethyl radicals

Gomberg had already used phenylazotriphenylmethane **21** in the classic preparation of tetraphenylmethane **22** in 1897 (Equation 1.6).[9a,b] Wieland, *et al*, in 1922,[9c] showed that $Ph_3C^\bullet$ **1** was formed in this reaction, and proposed that phenyl radicals were also formed (Equation 1.6). Triphenylmethyl radicals were generated thermally from the perester **23** even at 25 °C (Equation 1.7)[10a] and at much higher temperature from the significantly less reactive *N*-triphenylacetoxy 2,2,6,6-tetramethylpiperidine **25** (Equation 1.8).[10b] Reactivity studies demonstrated that both **23** and **25** reacted thermally via concerted two-bond cleavage (**24** and **26**, respectively) forming triphenylmethyl radicals **1** and carbon dioxide.



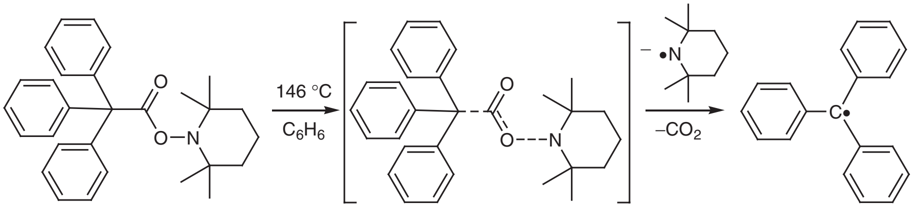
(1.6)

21 **1** **22**



(1.7)

23 **24** **1**

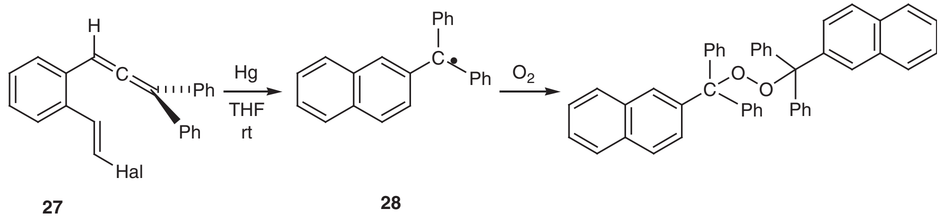


(1.8)

25 **26** **1**

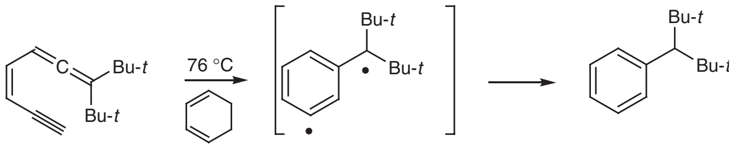
Many other dissociations of triarylmethyl substituted compounds can form triarylmethyl radicals,[10c] including, for example, formation of the radical 4-$Me_2NC_6H_4(Ph)_2C^\bullet$ by photodissociation of 4-$Me_2NC_6H_4(Ph)_2CSiMe_3$.[10d] Pulse radiolysis of trityl derivatives Ph_3CR (R = 2-naphthS, PhO, PhNH, PhNMe, and $PhCH_2$) in *n*-BuCl led to observation of $Ph_3C^\bullet$ by generation of the radical cation *n*-BuCl($^{+\bullet}$) by electron removal followed by free electron transfer (FET) forming Ph_3CR($^{+\bullet}$), which dissociated to $Ph_3C^\bullet$ and to Ph_3C^+ by separate reaction channels.[10e] These were proposed to form from two different conformations of Ph_3CR($^{+\bullet}$), both from a planar radical cation, which follows the thermodynamically favored pathway generating $R^\bullet$ and Ph_3C^+, and from a twisted radical cation, which produces the thermodynamically unfavorable product pair R^+ and $Ph_3C^\bullet$.[10e] Triphenylmethanol at high temperature and pressure in subcritical water gave $Ph_3C^\bullet$, as detected by EPR spectroscopy, and **1** was also formed in supercrtitical water, as shown by capture with hydrogen donors giving Ph_3CH.[10f] A number of triphenylmethyl derivatives have been found to have potent anticancer properties,[10g] although there is no suggestion that this is due to triphenylmethyl radicals.

A novel route for generation of triarylmethyl radicals was by reaction of 1-(haloalkenyl)-2-allenylbenzenes **27** in tetrahydrofuran (THF) at room temperature in the presence of mercury, resulting in cyclization to 2-naphthyldiphenylmethyl radical **28**, as detected by EPR (Equation 1.9).[11a] The radical formed a head-to-tail dimer involving the phenyl group, and was captured by oxygen to give the peroxide (Equation 1.9).[11a] Several related ene–yne cyclizations have been examined, including a route to a di(radical) **29**, which forms **30** (Equation 1.10).[11b–d]



(1.9)

27 **28**



29 **30**

(1.10)

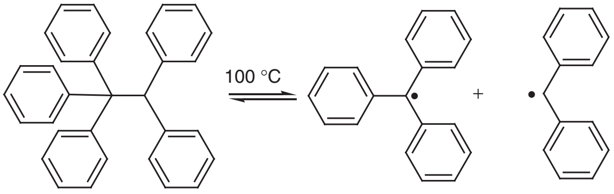
1.4 The persistent radical effect

The persistent radical effect[12] is an important phenomenon in radical chemistry that was first discovered through studies of triphenylmethyl radicals. One manifestation of this effect is seen in the reaction of carbon tetrachloride with phenyl radicals and triphenylmethyl radicals generated from phenylazotriphenylmethane **21**, which gives excellent yields of chlorobenzene and of 1,1,1-trichloro-2,2,2-triphenylethane **31** (Equation 1.11).[12]

$$\underset{\mathbf{21}}{Ph_3CN{=}NPh} \xrightarrow[-N_2]{\Delta} \underset{\mathbf{1}}{Ph_3C\bullet} \quad +Ph\bullet \xrightarrow{CCl_4} PhCl \quad +CCl_3\bullet \xrightarrow{\mathbf{1}} \underset{\mathbf{31}}{Ph_3CCCl_3} \qquad (1.11)$$

The azo compound **21** decomposes into phenyl and trityl radicals, together with a molecule of nitrogen. The more reactive phenyl radical then abstracts chlorine from carbon tetrachloride and radical coupling of the trichloromethyl radicals with the persistent trityl radicals **1** produces **31**. It is striking that only *unsymmetrical* coupling takes place, and no appreciable amount of hexachloroethane is formed. The explanation is that formation of even trace amounts of hexachloroethane would also lead to formation of the dimer **5** of triphenylmethyl in equilibrium with the monomeric radical. Therefore, the concentration of triphenylmethyl will greatly exceed that of the transient trichloromethyl radical, and since the rates of reactions of trichloromethyl with itself and with triphenylmethyl are both close to the diffusion limit, unsymmetrical coupling will predominate. However, the concentration of triphenylmethyl will remain essentially constant, since for every trichloromethyl formed another triphenylmethyl is also produced. Experimental confirmation is provided by EPR examination of the reacting solution, which shows a high concentration of the triphenylmethyl radical.

This phenomenon was correctly analyzed in 1936 by Gomberg's student Bachmann, who studied the role of triphenylmethyl in the reaction of pentaphenylethane **32** solution at 100 °C (Equation 1.12).[12f] This ethane dissociates rapidly and reversibly into triphenylmethyl and diphenylmethyl, but dimerization of the diphenylmethyl radical **33** to form detectable quantities of tetraphenylethane (which is stable under the reaction conditions) seldom occurs.



32 **1** **33**

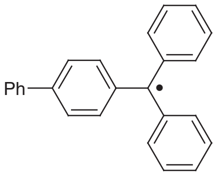
(1.12)

The decomposition of $Ph_3CN{=}NPh$ **21** in benzene has also been subjected to kinetic analysis[12g] and the effect of less persistent radicals, such as *t*-alkylperoxyls, which do decay irreversibly but only by relatively slow processes, was analyzed.[12a] A recent review on this subject is available.[12h]

1.5 Properties of triphenylmethyl radicals

The theoretical basis for the understanding of free radicals was first provided by G. N. Lewis in 1916.[13a,b] His clear recognition of the electron pair bond and the possibility of odd electron systems was heavily influenced by the work of pioneers such as Gomberg, Schlenk, and Wieland, who had shown remarkable prescience in formulating free radical structures without using the principles of electron pair bonding. The theoretical study of the triphenylmethyl radical was later provided by Erich Hückel at the 1933 Faraday conference on free radicals, which brought together many, but not all, of the pioneers in this field.[13c]

The electron-nuclear double resonance (ENDOR) and EPR spectra of triphenylmethyl **1**, (4-biphenylyl)diphenyl-methyl **34**), bis(4-biphenylyl)phenylmethyl **35**, and tris(4-biphenylyl)methyl **4** radicals were measured in 1968 by Maki *et al*.[13d] and the signals for specific protons were assigned based on the observed and calculated spectra. Computations of the spin density distributions were compared to the experimental values. Other spectroscopic measurements of triarylmethyl radicals include the laser induced fluorescence and emission spectra.[13e]



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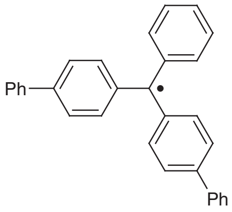

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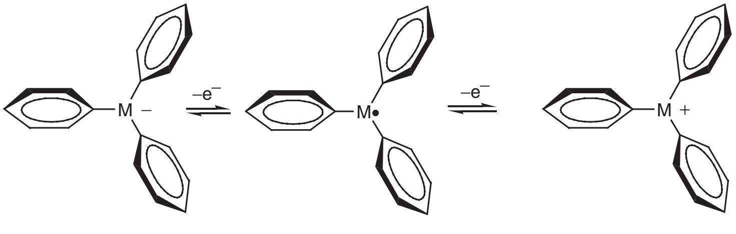
Studies of reactions of triarylmethyl radicals include kinetic measurements of hydrogen atom abstraction from thiols,[14a] electrochemical generation by oxidation of triaryl anions and the subsequent further oxidation to the carbocations,[14b] and reduction of carbocations to the radicals using cyclic voltammetry.[14c]

The oxidation/reduction potentials of triphenyl- or tributyl-substituted silicon-, germanium-, or tin-centered radicals **36** were measured in acetonitrile, tetrahydrofuran, or dimethylsulfoxide by photomodulated voltammetry and through oxidation of the corresponding anions using linear sweep voltammetry for comparison to those of the carbon analogues (Equation 1.13).[15] The order of reduction potentials follows Sn > Ge > C > Si, and is C > Si for the two oxidation potentials. Computational methods gave qualitative interpretation of the experimental results by considering a combination of effects, such as charge capacity, resonance stabilization, and solvation effects.

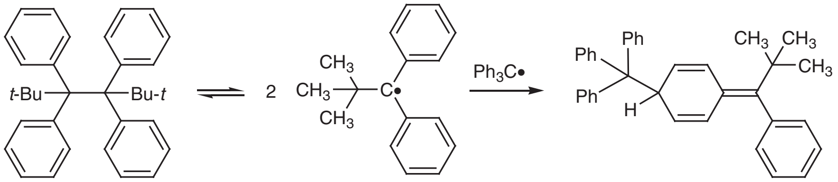


(1.13)

36 (M = C, Si, Sn, Ge)

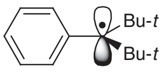
1.6 Steric effects and persistent radicals

In his first paper Gomberg[1a] recognized that steric factors make a contribution to the stability of the triphenylmethyl radical, and Conant and Bigelow[16a] reported in 1928 the reversible dissociation at 50 °C of 1,2-(di-*tert*-butyl)tetraphenylethane **37** to the yellow radical **38** (Equation 1.14),[16a] which reacts rapidly with oxygen. The radical **38** generated in the presence of $Ph_3C^\bullet$ forms the mixed dimer **39** (Equation 1.14).[16b] The di-*tert*-butylbenzyl radical **40** was stable for several days in solution at room temperature, and the EPR spectrum indicated the phenyl group was twisted into coplanarity with the singly occupied p orbital, preventing spin delocalization.[16c,d] Other work showed that purely aliphatic radicals without β hydrogens, such as di-*tert*-methyl **41**,[17a] and tri-*tert*-butylmethyl **42**,[17a] and even triisopropylmethyl **43**[17b] were sufficiently long lived in solution for direct observation by EPR. These radicals also did not dimerize but decayed by other undetermined routes. Such radicals with kinetic stability have been classified as persistent radicals.[17c]



(1.14)

37 **38** **39**



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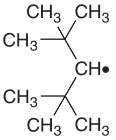

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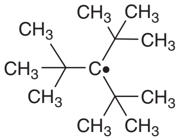

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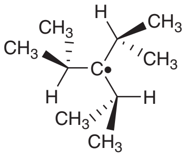

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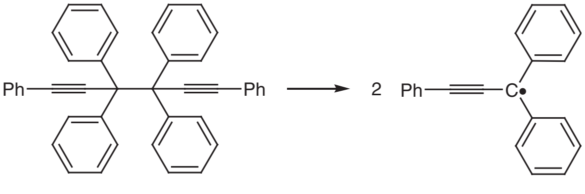
The importance of resonance stabilization of triarylmethyl radicals was emphasized by Pauling and Wheland in 1933.[17d] It had already been shown by Marvel and Munro that alkynyl groups with minimal steric barriers were also effective at promoting dissociation of the ethane **44** by stabilization of diarylmethyl radicals **45** (Equation 1.15).[17e]



(1.15)

44 **45**

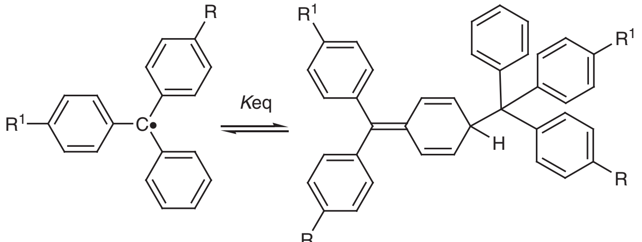
1.7 Substituted triphenylmethyl radicals and dimers

The effect of substituents in stabilizing triarylmethyl radicals has been measured by determining the equilibrium constants for dissociation of the dimers of a large number of such radicals by EPR spectroscopy

Table 1.1 Equilibrium constants for the dimerization of triarylmethyl radical derivatives 46 and correlation with substituent constants

R, R^1	σ	$\sigma^\bullet$	$\sigma^\bullet + 0.01\sigma$	log$K$	R, R^1	σ	$\sigma^\bullet$	$\sigma^\bullet + 0.01\sigma$	log$K$
H,H	0.00	0.0000	0.0000	−3.48	H,NO$_2$	0.78	0.0630	0.0710	−2.55
H,*t*-Bu	−0.20	0.0080	0.0055	−3.10	*t*-Bu,*t*-Bu	−0.20	0.0080	0.0055	−2.39
H,CF$_3$	0.54	−0.0086	−0.0019	−3.15	CF$_3$,CF$_3$	0.54	−0.0086	0.0019	−2.82
H,CN	0.70	0.040	0.0400	−2.66	CN,CN	0.70	0.0488	0.0488	−2.03
H,PhCO	0.42	0.0554	0.0554	−2.49	PhCO,PhCO	0.42	0.0554	0.0607	−2.05
H,Ac	0.50	0.0597	0.0597	−2.70	MeO,MeO	−0.28	0.0185	0.0150	−2.63
H,MeO	−0.28	0.0185	0.0185	−2.82	Ph,Ph	−0.01	0.0615	0.0614	−1.57
H,Ph	−0.01	0.0615	0.0614	−2.56	PhO,PhO	−0.32	0.0185	0.0145	−2.78
H,PhO	−0.32	0.0185	0.0145	−3.21	MeS,MeS	0.00	0.0630	0.0630	−1.72
H,MeS	0.00	0.0630	0.630	−2.78					

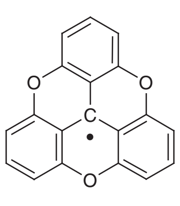
(Equation 1.16).[18a] A Hammett-like equation was found correlating log$K$ with $\sigma^\bullet + 0.01\sigma$, which relates the monomer/dimer equilibrium constants with the radical stabilizing parameter $\sigma^\bullet$ with a minute contribution from the polar substituent constant σ (Table 1.1). Captodative effects were not found in this study,[18a] but an ENDOR study showed that radicals **46** (R = PhO; R^1 = CF$_3$, CN, phenyl) are stabilized with respect to dimerization to **47** by 0.6, 1.2, and <0.2 kcal/mol over the amounts expected on the basis of substituent additivity, suggesting some influence of captodative effects.[18b]



46 **47**

(1.16)

Triarylmethyl radicals **9** and **48** fully substituted with 2,6-oxygen substituents on all three rings were prepared and characterized by EPR.[19a] The radical **9** had a twisted geometry as shown by EPR, and did not dimerize. As noted above, **9** was obtained in crystalline form and its X-ray structure determined; this was consistent with the interpretation of the EPR spectrum.[6a] The radical **49** with only two oxygen bridges was quite sensitive to oxygen and was extensively dissociated in the solid state, and the 2,6-hydrogens cause twisting out of the plane,[19b] while the dimer of **48** is undissociated in the solid, with a central C–C bond length of 1.63 Å measured by X-ray.[19a,c,d]



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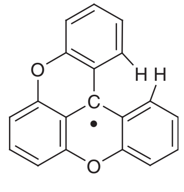
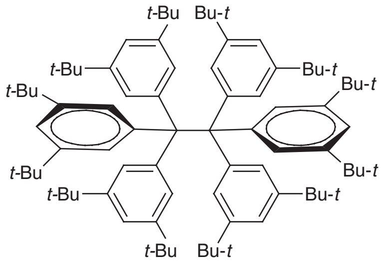


49

Other hexaphenylethane molecules with structures determined by X-ray include **50**, which is restricted from forming a head-to-tail dimer by the bulky substituents, with a central C–C bond length of 1.67(3) Å.[19e] A different type of hexaphenylethane derivative is typified by **51**, which had already been already prepared in 1933 for R = hydrogen,[19f] and has the central bond constrained by its intramolecular character. The central C–C bond of **51** (R = MeO) was measured as 1.670(3) Å,[19g] and related examples with similar intramolecular constriction have bond lengths that are even longer.[19h,i]



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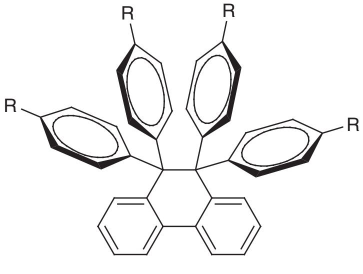
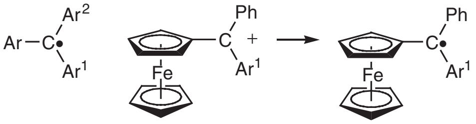


51

A variety of triarylmethyl radicals **52** with electron donating substituents were prepared by reduction of the corresponding carbocations using cyclic voltametry (Table 1.2), including the ferrocenyl substituted radical **53** (Equation 1.17).[20a] These showed strong downward shifts in the reduction potentials due to the strongly electron donating substituents, and reversible redox behavior was even observed in aqueous solution.



52 **53** (1.17)

The bis(diphenylpentafulvene) iron complex **54** was also prepared, for which the structure was considered as either the bis(radical) **54a** or the bis(fulvene) **54b**.[20b] The fact that the X-ray and calculated structure (Figure 1.1) showed the exocyclic groups on the same side of the molecule was taken as favoring the

Table 1.2 *Triarylmethyl radicals **52** studied by cyclic voltammetry*

Ar	$Ar^{1'}$	Ar^2
2,4,6-$(MeO)_3C_6H_2$	2,4,6-$(MeO)_3C_6H_2$	2,4,6-$(MeO)_3C_6H_2$
2,4,6-$(MeO)_3C_6H_2$	2,6-$(MeO)_2C_6H_3$	2,6-$(MeO)_2C_6H_3$
2,6-$(MeO)_2C_6H_3$	2,6-$(MeO)_2C_6H_3$	2,6-$(MeO)_2C_6H_3$
4-$MeOC_6H_4$	2,6-$(MeO)_2C_6H_3$	2,6-$(MeO)_2C_6H_3$
2-$MeOC_6H_4$	2,6-$(MeO)_2C_6H_3$	2,6-$(MeO)_2C_6H_3$
Ph	2,6-$(MeO)_2C_6H_3$	2,6-$(MeO)_2C_6H_3$
Ferrocenyl	Ph	2,6-$(MeO)_2C_6H_3$
Ferrocenyl	2,6-$(MeO)_2C_6H_3$	H

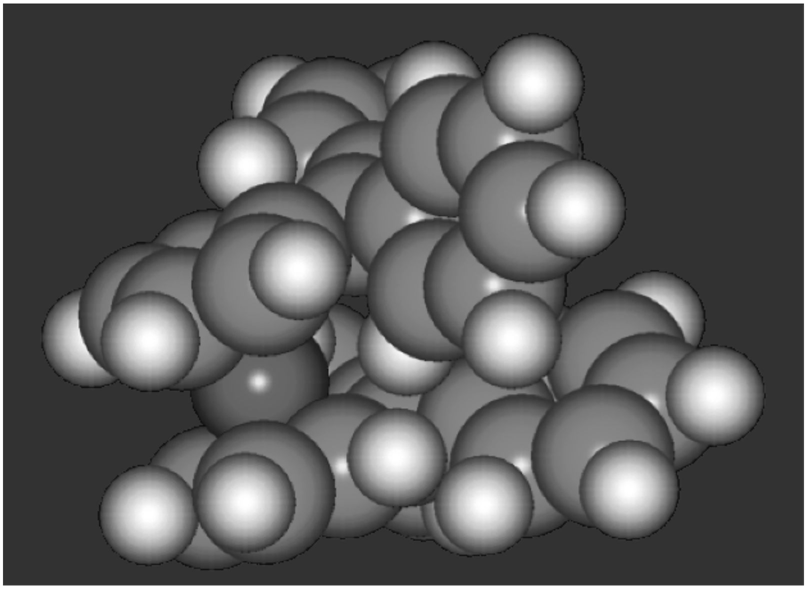
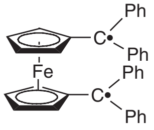
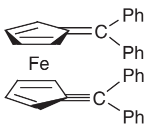


Figure 1.1 Calculated structure of ***54a***. (Reproduced by permission of Professor Mathias Tacke.)

diradical structure, with some attraction between the two radical sites.[20b] Later computational studies agreed with this conclusion, and also found that the diradical was a ground state singlet.[20c]



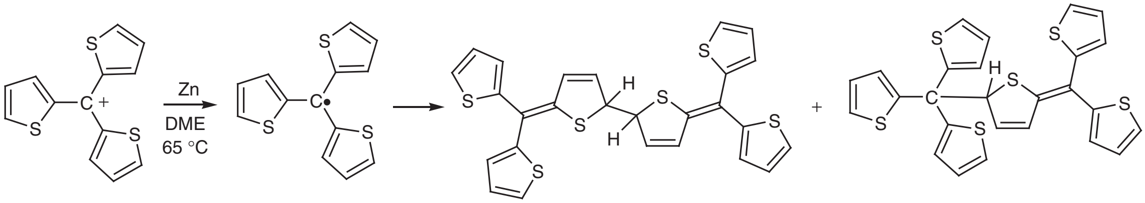
54a



54b

1.8 Tris(heteroaryl)methyl and related triarylmethyl radicals

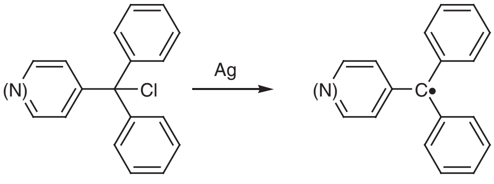
Tris(2-thienyl)methyl and tris(3-thienyl)methyl radicals generated by zinc reduction of the corresponding carbocations were directly observed by EPR and characterized by their distinctive spectra.[21a] Tris(2-thienyl)methyl radical **55** generated by reduction of the corresponding cation with zinc dimerizes to a mixture of the tail to tail dimer **56** and head to tail dimer **57** (Equation 1.18).[21b]



55 **56** **57**

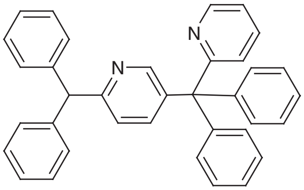
(1.18)

The 3- and 4-pyridyldiphenylmethyl radicals **58** were generated by treatment of the corresponding triarylmethyl chlorides with silver in benzene at room temperature (Equation 1.19), while the corresponding conversion of the 2-pyridyl isomer required silver in tetrahydofuran with ultrasound activation.[22] All three radicals were observed by EPR and characterized by their distinctive spectra, and all formed dimers by head-to-tail coupling involving addition to a pyridyl ring. Dimers **59** and **60** from the 2- and 3-pyridyl radicals, respectively, resulted from hydrogen migration in the initial coupling products. The 4-pyridyl radical gave the *N*-trityl bonded dimer **61** that, upon heating at 70 °C, rearranged to **62**, proposed to form by dissociation to the radical followed by dimerization involving a phenyl ring and irreversible formation of the product by hydrogen migration. In the range −27 to −15 °C reversible formation of the initial dimers was observed. Bond dissociation energies were determined that were about 42 kJ/mol larger than for the corresponding dimer of triphenylmethyl radical, and the greater stability of the pyridyl dimers was attributed to reduced steric repulsions in the pyridyl dimers due to the absence of two hydrogen atoms. Other factors, such as lower stability of the pyridyl radicals or attractive interactions between the nitrogen atoms and the other groups in the dimers, may also be involved.



58

(1.19)



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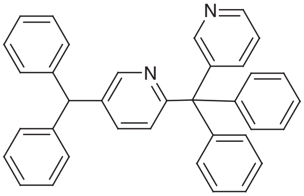

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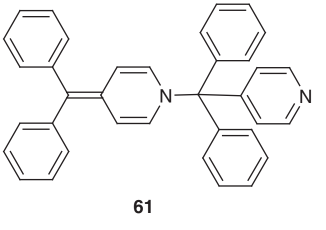

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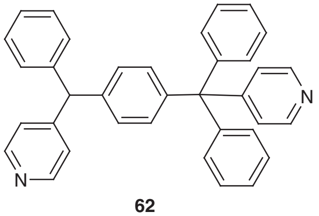
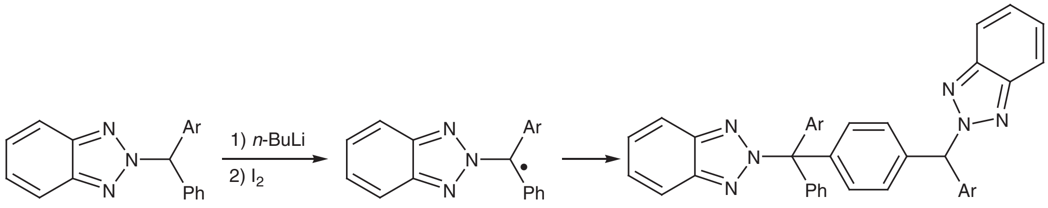


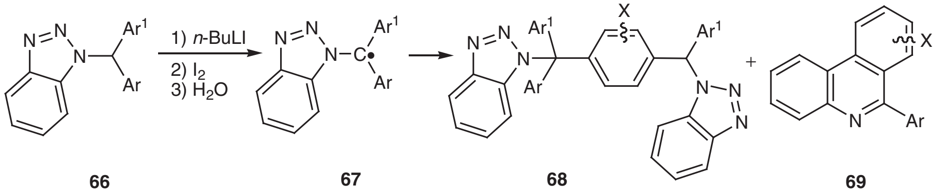
62

2-Triazolyldiarylmethanes **63** upon reaction with *n*-BuLi followed by iodine evidently gave unobserved free radicals **64**, based on the isolation of dimers **65** (Equation 1.20).[23] 1-Triazolyldiarylmethanes **66** upon reaction with *n*-BuLi followed by iodine gave the radicals **67**, which were the first triarylmethyl radicals reported with a directly attached heteroatom at the radical center. The radicals formed the dimers **68** as well as phenanthridines **69** (Equation 1.21).[24] The latter were proposed to form from loss of N_2 from **67** with cyclization (Equation 1.22). Radicals **71** generated from the corresponding triarylmethanes were detected by EPR, and gave dimers **72**, while **73** formed by loss of N_2 with cyclization (Equation 1.23).[24]



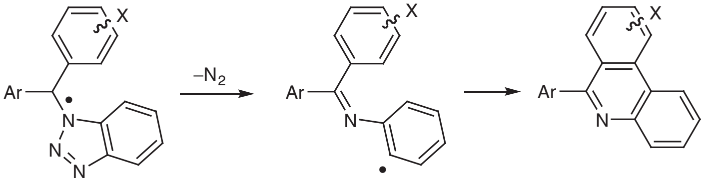
63 **64** **65**

(1.20)



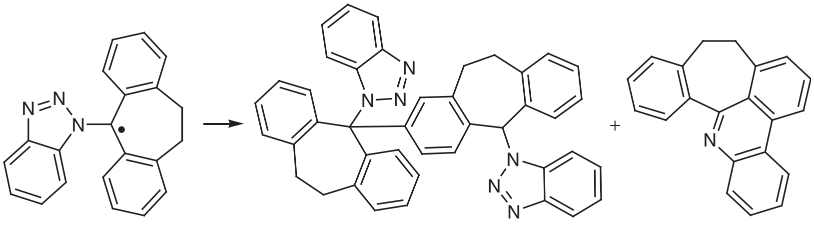
66 **67** **68** **69**

(1.21)



67 **70** **69**

(1.22)

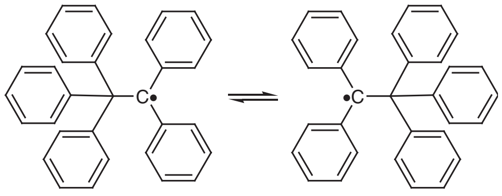


71 **72** **73**

(1.23)

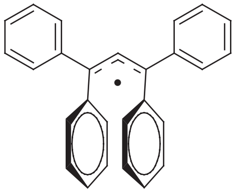
1.9 Delocalized persistent radicals: analogues of triarylmethyl radicals

The discovery by Gomberg of the triphenylmethyl radical opened the way for the discovery of a variety of related persistent radicals. Some of these are covered in greater detail elsewhere in this book. Schlenk and Mark reported the preparation of the equilibrating pentaphenylethyl radical **74**,[25a] which exists as a long lived species (Equation 1.24). Karl Ziegler and coworkers prepared the tetraphenylallyl radical **75**[25b] and the pentaphenylcyclopentadienyl radical **76**.[25c]



74

(1.24)



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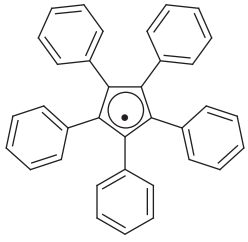
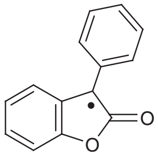


76

The long-lived radical **77** was first reported by Löwenbein and Folberth: it reversibly forms a dimer, and reacts only slowly with oxygen to give a peroxide.[25d,e] Radical **77** and its analogues have found extensive recent application as chain breaking antioxidants.[25f,g] These function by trapping peroxyl radicals and can completely suppress autoxidation. Diarylacetate radicals **78** have long been known and undergo reversible dimer formation[25h,i] and react with oxygen to form peroxides.[25j,k] Addition of the tetramethylpiperidinyloxyl radical (TO$^\bullet$) to diphenylketene gave the radical **79**, which reacted with oxygen forming the peroxide **80**, with the structure determined by X-ray crystallography (Equation 1.25).[25l]



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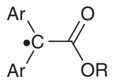

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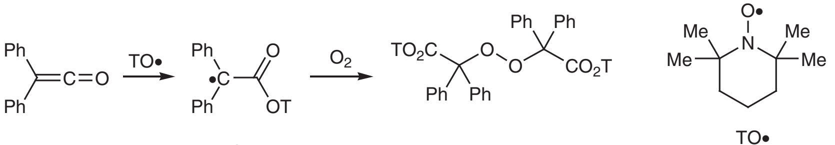
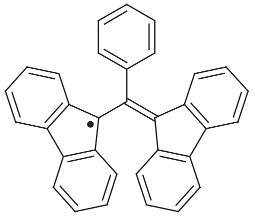


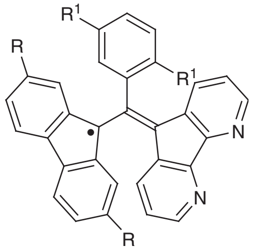
79 **80** TO•

(1.25)

The Koelsch radical **81** was prepared in 1931 but, somewhat surprisingly, even at this date, the idea of stable radicals met some resistance. Koelsch prepared and submitted for publication a report of the long lived radical, but the lack of reactivity of the radical towards oxygen seemed improbable, and the manuscript was rejected. In 1957, EPR spectroscopy of the same sample confirmed the identification, and the original manuscript was resubmitted and published.[26a] Nitrogen analogues **82** were reported in 2000.[26b] More recently, the Koelsch-type diradicals **83** and **84** have been reported and found to have singlet and triplet ground states, respectively.[26c,d]



81



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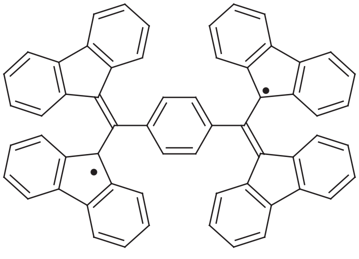

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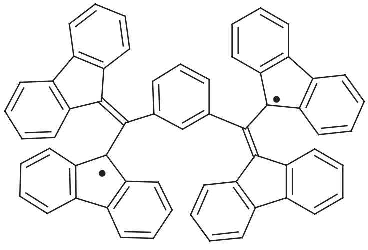
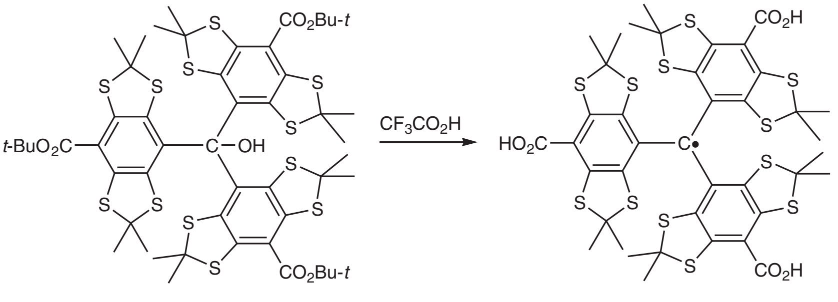


84

1.10 Tetrathiatriarylmethyl (TAM) and related triarylmethyl radicals

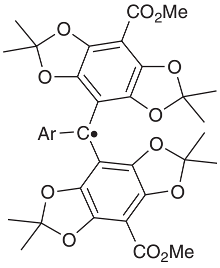
Specialized triarylmethyl radicals are finding extensive and increasing use in imaging applications using EPR spectroscopy because of their extraordinary stability in cells and tissues, narrow line widths resulting in high analytical resolution at concentrations in the μM range, and enhanced sensitivity to oxygen.[27] Derivatives which vary in their state of ionization as a function of pH show a corresponding dependence upon of their EPR spectra with pH and are being examined for a variety of biomedical applications.

Tetrathiatriarylmethyl (TAM) trityl radicals **86** and various structural variations were originally developed in industry for use as contrast agents in Overhauser magnetic resonance imaging (OMRI),[27–29] and were first reported in the patent literature.[27c–f] Their properties are discussed in detail in Chapter 16. Important characteristics of these materials are the narrow signals promoted by the absence of inhomogeneous hyperfine couplings. An earlier preparation of these compounds[29c] has been improved by a convenient large scale synthesis of the sodium salt of **86** (known as Finland trityl).[28] The oxygen substituted analogue **87** and the methyl deuterated derivative have also been studied, and together with **86** are soluble in water with single sharp lines in the EPR spectra.[27a] The radical **86** was formed in one step in quantitative yield by treatment of the tri(*tert*-butyl ester) **85** in neat trifluoroacetic acid at room temperature (Equation 1.26).[28] Other trityl alcohols formed radicals in a similar fashion.[28]



(1.26)

85 **86**



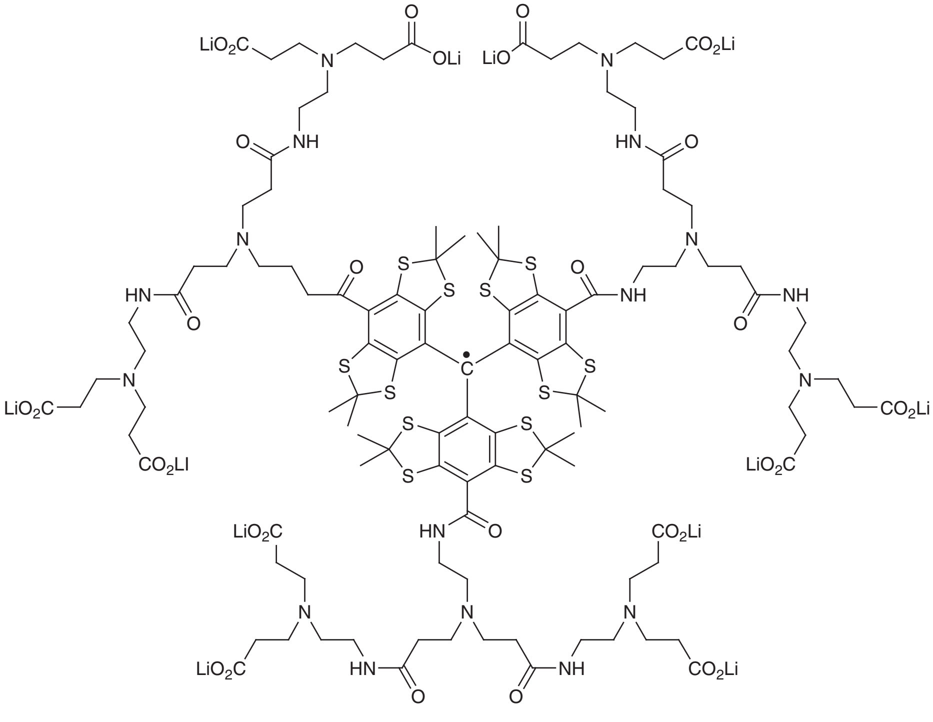
87

The presence of ionizable carboxyl groups on the TAM radicals leading to pH sensitivity of the EPR parameters has been examined, as has the presence of limited numbers of aryl ring protons leading to doublet or triplet EPR signals.[29a] These serve as dual function pH and oxygen probes. Dendritic TAM molecules were prepared in which encapsulation of the radical by the dendrimer enhances their stability and solubility in water over a wide pH range, and the copper(II) complex of **88** is a highly effective pH probe.[29f]

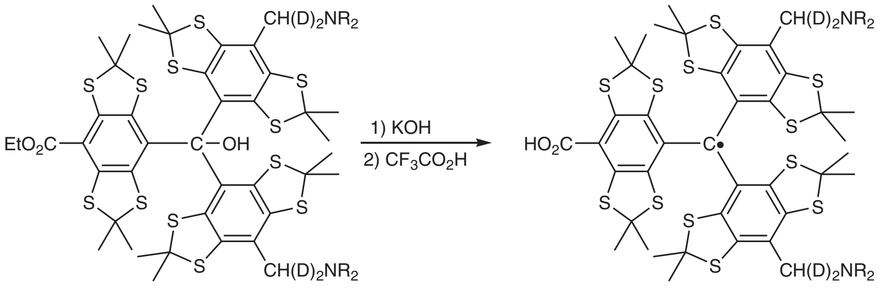
Amino substituted TAMs **90** and related derivatives were prepared by selective reduction of one or more carboxyl groups of **85** to hydroxylmethyl substituents, and these were converted to mesylates that were displaced by amino groups forming **89**. Conversion to radicals **90** was accomplished using trifluoroacetic acid (Equation 1.27), and provides derivatives useable in other pH ranges.[29b]

Collisions of these probe molecules reduce relaxation times of the probes and provide a measure of local oxygen concentration; to investigate the viscosity and frequency dependence on the EPR spectra, measurements of TAM radicals in glycerol/water ranging from 10 to 90 % concentration were carried out, including the use of deuterated solvents.[30a] The conformations of the TAM radicals in solution were investigated using ^{1}H, ^{2}H, and ^{13}C measurements,[30b] with hyperfine coupling tensors determined using X-band pulsed electron-nuclear double resonance (ENDOR) spectroscopy for two triarylmethyl (trityl) radicals used in EPR imaging and oximetry.[30b] Calculated geometries were used to predict the experimental hyperfine tensors, and these gave satisfactory agreement.[30b]

Rapid-scan EPR spectra of a 0.2 mM aqueous solution of deuterated **86** (trityl-CD$_3$) radical at 9.8 GHz using a rectangular resonator were obtained.[31a] Larger effects of magnetic field inhomogeneities were found for the extended structure of **86** than in smaller lithium phthalocyanine crystals.



88



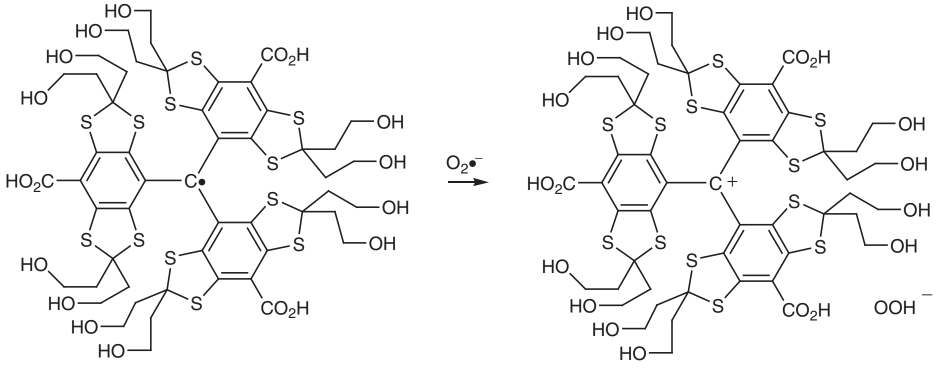
89 **90**

(1.27)

Continuous wave spectra at W-band of four triarylmethyl (trityl) radicals at 100 K in 1 : 1 water/glycerol exhibit rhombic EPR spectra.[31b] The results are consistent with assignment of the Raman process and a local mode as the dominant relaxation processes.

Low frequency (300 MHz) pulsed EPR with pulsed FID detection of triarylmethyl radicals injected in mice was used to obtain three-dimensional oxymetric images.[32a,b] Single-point imaging, a technique developed for solid state NMR, applied to pulsed EPR imaging yielded artifact-free spatial images.[32a] Continuous wave EPR imaging was used to obtain slice-selective images of free radicals without measuring three-dimensional (3D) projection data.[32c]

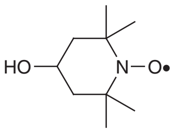
Notable among these widely studied radicals is **91**, which has been extensively derivatized for optimum properties.[27b,29a] This reacts with superoxide ($O_2^{\bullet -}$) radicals with an apparent second order rate constant of $3.1 \times 10^3\,M^{-1}\,s^{-1}$, and this was used for analysis of the superoxide.[33a,b] Assay of superoxide by monitoring the newly formed product absorption peak at 546 nm[33a] or by EPR[33b] gave good agreement with the widely used cytochrome *c* method of superoxide detection.[33a] The identity of the species giving rise to the observed absorption at 546 nm, which was stable for 12 hours, was not identified. Hydroperoxide was detected by ferrous oxidation-xylenol orange (FOX) assay,[33b] but mass spectrometric analysis did not detect a covalent adduct, and formation of an ion pair **92** of hydroperoxide anion and the trityl cation was proposed (Equation 1.28).[33a]



91 **92**

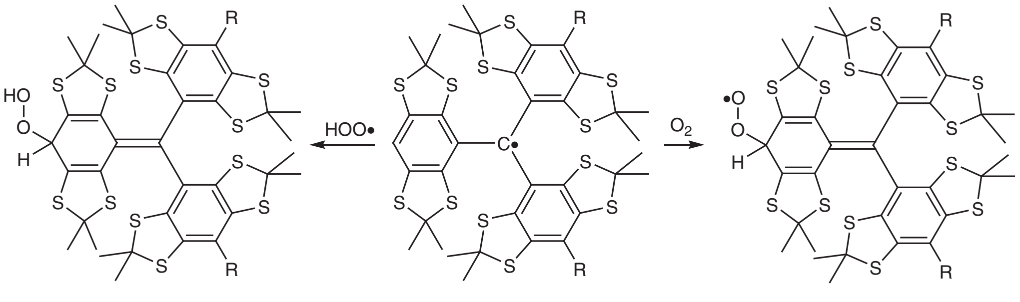
(1.28)

Dynamic nuclear polarization of the substrate by microwave irradiation of **91** permitted the measurement of the kinetics of trypsin catalyzed hydrolysis of N_α-benzoyl-L-arginine ethyl ester by ^{13}C NMR using stopped flow.[33c] Extension of this method to the study of other enzyme catalyzed reactions is anticipated. The dynamic nuclear polarization (DNP) of the triphenylmethyl radical in water has been compared to that of the 4-hydroxyTEMPO radical **93** and the latter showed considerably larger DNP enhancements up to 100 (9 GHz) and −20 (94 GHz) using continuous microwave irradiation.[33d]



93

The degradation of tetrathiatriarylmethyl radicals **86** used as oximetry probes for EPR imaging applications due to reaction with oxygen was investigated experimentally and by using computational methods.[33e] Tricarboxylate salts bearing CO_2Na groups were the most stable, and it was proposed that degradation by oxygen attack on the TAMs preferentially occurred at unsubstitued 4-positions of the aryl rings leading to hydroperoxide intermediates. Radical pathways with addition of O_2 or $HO_2^\bullet$ to **86** forming **94** or **95** were considered (Equation 1.29), as well as ionic routes, such as the addition of the anion HO_2^- to the cation of **74** forming **80**.[33e]

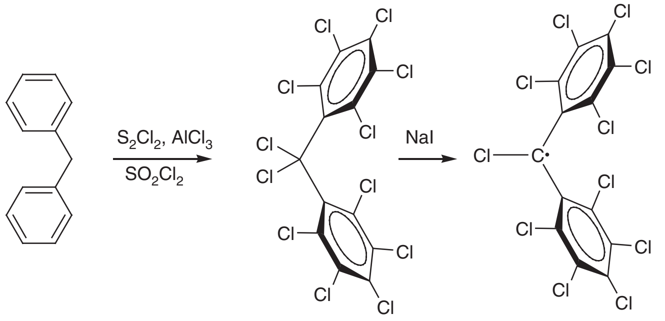


95 **86** **94**

(1.29)

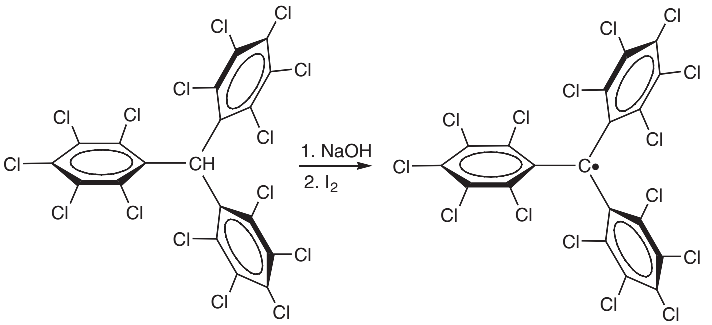
1.11 Perchlorinated triarylmethyl radicals

Perchlorination of aromatic compounds using a reagent composed of sulfur monochloride and aluminum chloride in sulfuryl chloride (SCM reagent) was introduced in 1960,[34a] and has proved very effective. In 1971 this method was applied to the formation of perchlorodiphenylmethyl **97** and perchlorotriphenylmethyl **99** radicals, both of which have lifetimes in air of decades and are characterized as *inert* carbon free radicals.[34b,c] Conversion of the chlorocarbon **96** to **97** could be effected by reduction with sodium iodide (Equation 1.30). More generally, radical **99** and its derivatives are prepared by deprotonation of the corresponding tris(pentachlorophenyl)methane **98** followed by oxidation of the anion with iodine (Equation 1.31).[34b,c] The *ortho*-chorines on the aryl rings effectively shield the central radical site, preventing reactions of the chlorinated radicals (Figure 1.2). This family is reviewed in detail in Chapter 2.



96 **97**

(1.30)



98 **99**

(1.31)

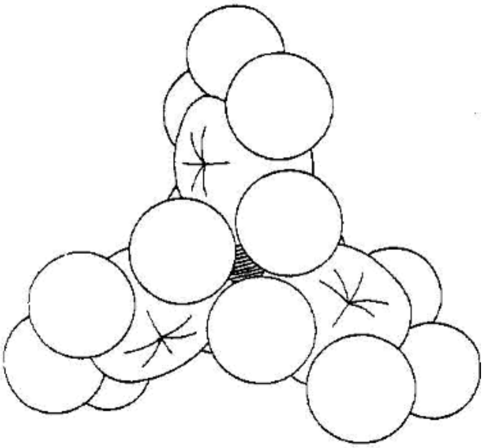
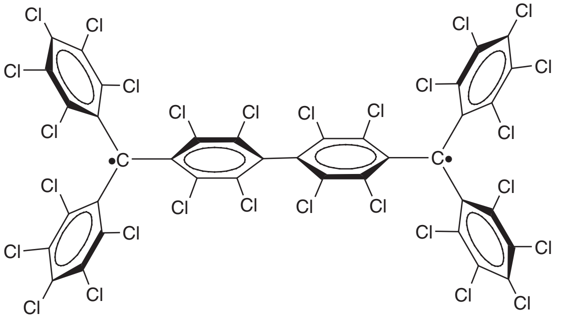
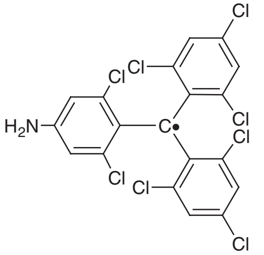


Figure 1.2 Model of the tris(pentachlorophenyl)methyl radical ***99****. (Reprinted with permission from [34c]. Copyright 1985 American Chemical Society.)*

Some of the properties of these chlorinated radicals include the formation of clathrate hosts for benzene[35a] and the use of partially chlorinated amino-substituted derivatives in magnetic materials.[35b] Their EPR properties have been determined,[36a] and monofunctionalized derivatives have been prepared and characterized.[36c] These studies have been extended to perchlorinated diradical **100**[34b] and to corresponding radical cations and radical anions, which have single electron transfer equilibria,[34e,f] and to other highly but not completely perchlorinated radicals, including the monoradical **101**[35b] and the diradical **102**.[36d]



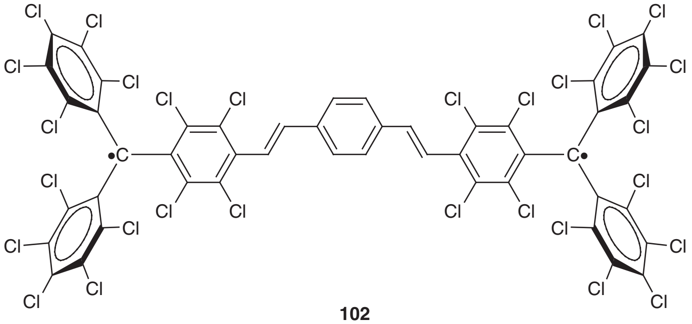
100



101

There is essentially no delocalization of the free electron into the twisted perchlorophenyl rings of these perchloroaryl radicals, but because of the steric shielding normal atom transfer reactions or radical combination reactions are strongly inhibited. While these radicals are remarkably inert to almost all reagents, they are susceptible to electron transfer, either reduction to carbanions or oxidation to carbocations.[34e,f]

Perchorinated triarylmethyl radical **103** combining perchorotriphenylmethyl and bis(4-methoxyphenyl) amine moieties was used to study electron transfer and charge transfer properties. The absorption spectrum of this highly soluble compound was studied in 13 solvents. The electronic coupling and the dipole moments of the ground and excited states were also determined.[37a]



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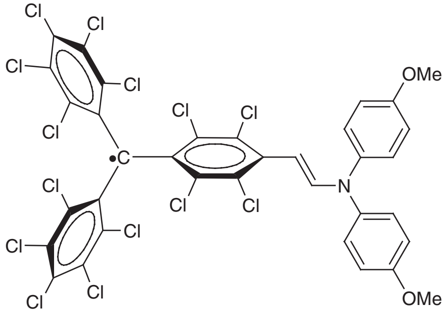
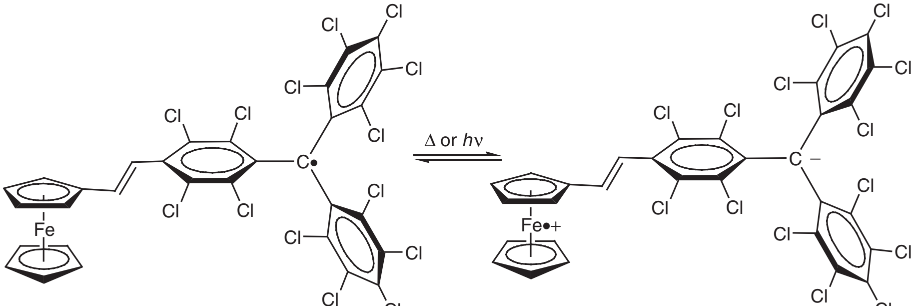


103

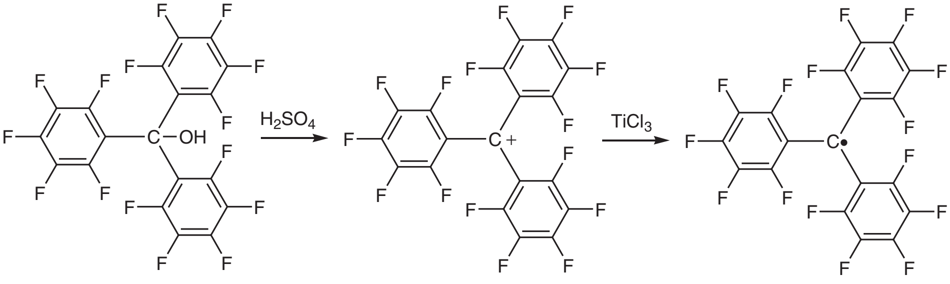
The dependence of the UV spectra of the transition from radical **104** to the zwitterion **105** was examined as the solvent composition was varied and the process changed from the normal to the inverted Marcus region (Equation 1.32).[37b] The redox properties of the two species were also examined.



104 **105**

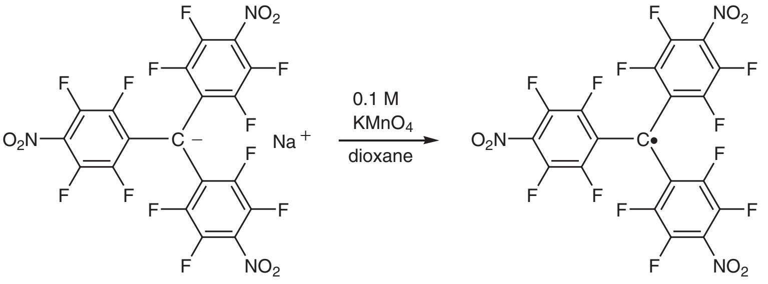
(1.32)

Perfluorinated triphenylmethyl radical **106** was generated by reduction of the corresponding carbocation and gave an EPR spectrum measured in benzene (Equation 1.33).[38a] The product was recrystallized from benzene giving material with a melting point of 158 °C containing an undetermined amount of free radicals as detected by EPR. Tris(4-nitro-2,3,5,6-tetrafluorophenyl)methyl radical **107** was formed by oxidation of the corresponding carbanion with potassium permanganate and characterized by its EPR spectrum (Equation 1.34).[38b]



106

(1.33)

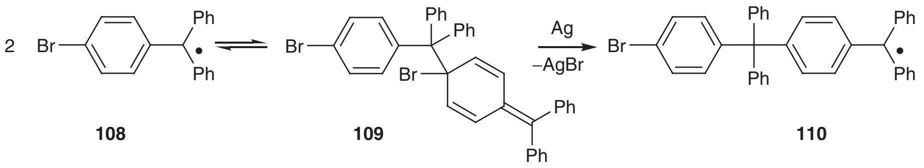


107

(1.34)

1.12 Other triarylmethyl radicals

Earlier studies of less substituted tris(4-halophenyl)methyl radicals indicated these underwent dehalogenation upon formation of unsymmetrical dimers. For example, reaction of 4-bromophenyl(diphenyl)methyl chloride with silver evidently proceeds with formation of radical **108**, and after dimerization to **109** there is loss of the allylic bromine forming **110**, which was captured as the peroxide (Equation 1.35).[39a] Previously it had been found that treatment of 4-bromophenyl(diphenyl)methyl chloride with silver resulted in loss of all the chlorine and half the bromine, in agreement with this process. Similarly 4-fluorophenyl(diphenyl)methyl chloride lost fluorine on treatment with silver.[39b,c]

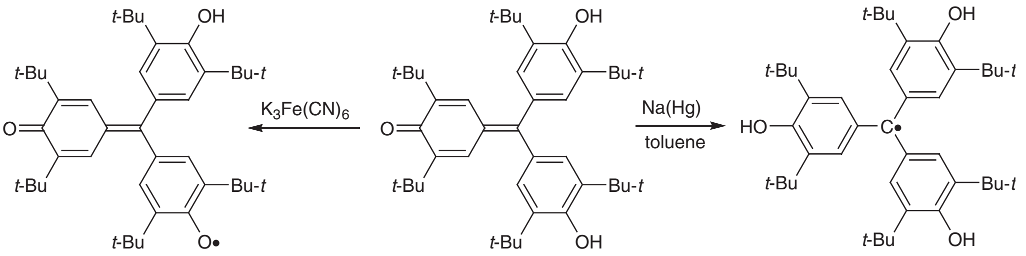


108 **109** **110**

(1.35)

Galvinoxyl-based radical **111** is a stable free radical inert to oxygen that is used as a spin trap for reactive free radicals; it is obtained by oxidation of the galvinol **112** (Equation 1.36).[40a,b] Reduction of **112** yields the triarylmethyl radical **113**, which has quite different properties from **111**.[40c] A variety of analogues of **113** have been prepared.[40c]

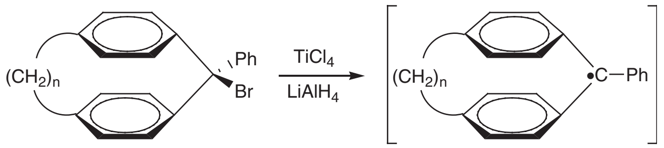
Cyclophane derived triarylmethyl bromides **114** (n = 6,7,8,9) reacted with the reducing agent obtained from titanium tetrachloride and lithium aluminum hydride ($LiAlH_4$) to form dimers **116** evidently derived from triarylmethyl radicals **115** (Equations 1.37 and 1.38).[41] The dimers either were accompanied by or converted to the fully aromatized isomers.



111 **112** **113**

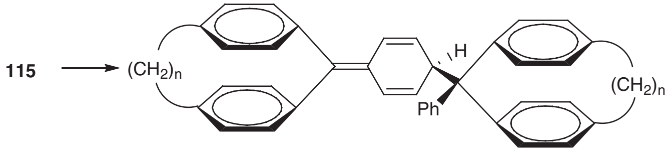
(1.36)

111 **112**



114 **115**

(1.37)



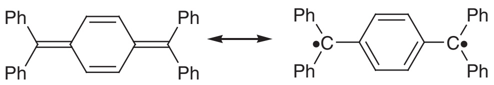
116

(1.38)

1.13 Diradicals and polyradicals related to triphenylmethyl

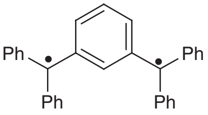
As noted in Section 1.7 a number of hexaarylethanes, such as **51**, which are potential diradicals but are constrained to close intramolecular geometries, have been prepared but do not have diradical character.[19e−i] However, **54** is proposed as a singlet diradical.[20b−d] Stable chlorinated diradicals, such as **102**, have also been prepared.[34b]

Tetraphenyl-*para*-xylylene **117** (Thiel radical) was prepared by Thiel and Balhorn in 1904 as an isolable species[42a] and has been characterized by X-ray.[42b] This species, however, has some diradical character (**117b**) and continues to attract attention after more than 100 years.



117a **117b**

The first stable diradical **118**, which is analogous to triphenylmethyl, was reported by Schlenk in 1915 (Schlenk diradical)[43a] and promoted the expansion into the field of molecules containing multiple radical sites. The analogous 1,3,5-trisradical **119** (Leo triradical) was reported in 1937.[43b] This marked the beginning of the study of "high spin" molecules, which are gaining increasing attention because of the potential application of these materials as molecular magnets.[43c] The chemistry of triarylmethyl di- and polyradicals and related species in the design of magnetic clusters and organic magnets has been frequently reviewed.[44]



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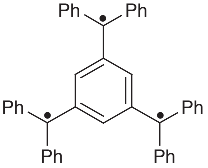
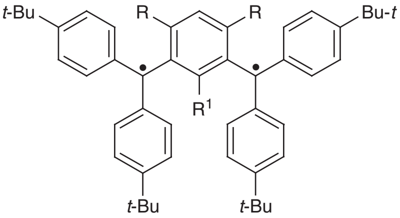


119

Many diradicals which share the topology of the Schlenk radical have been prepared, including **120** and **121**.[45a,b] Triradicals **122** have also been prepared and characterized by EPR.[45c]



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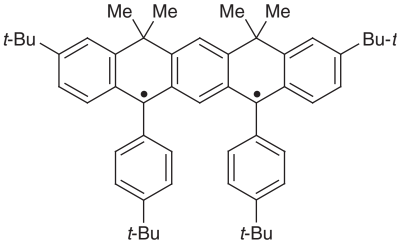

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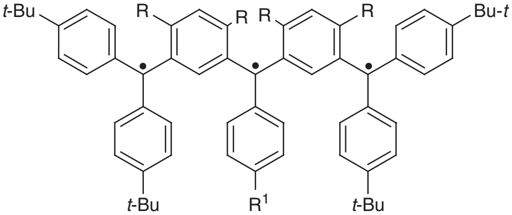
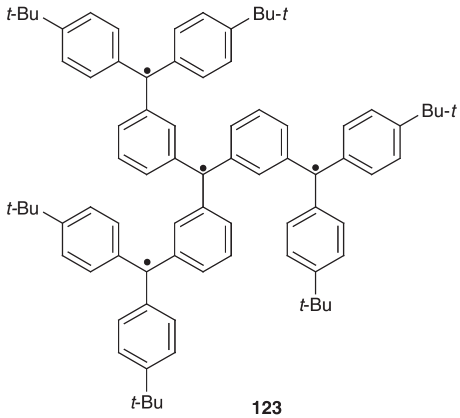


122

The tetraradical **123** was prepared by oxidation of the corresponding tetra-anion with molecular iodine, and identified by the characteristic quintet EPR spectrum. The zero field parameter [D/hc] is less than that of the triplet radical **118** and the small value of [E/hc] was interpreted as showing threefold symmetry for **123**.[45d] Analogous heptaradical **124** and decaradicals were also prepared.[45e] This work has been reviewed.[46]



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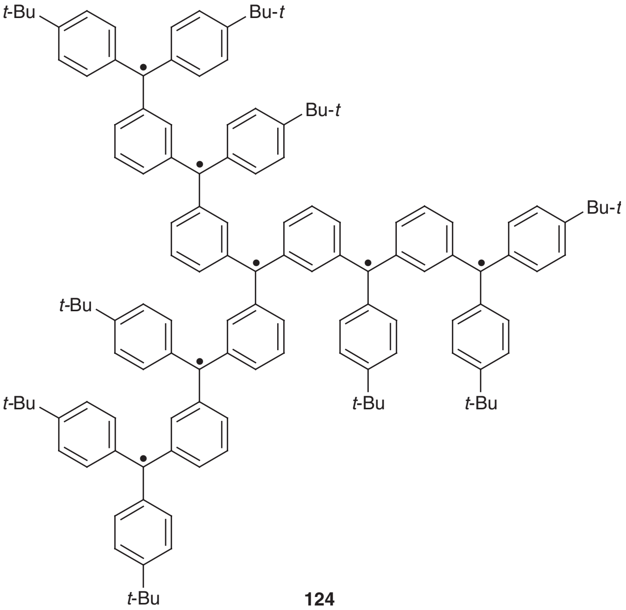
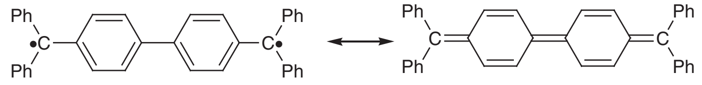
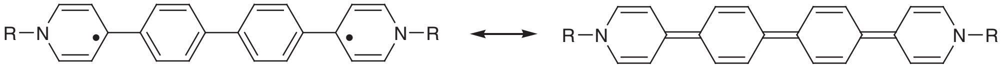


124

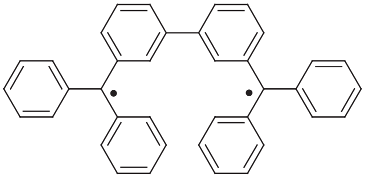
The Chichibabin hydrocarbon **125**[47a] is a further example of an extended linear polyaromatic with diradical character (**125a**) and is related to the Thiel radical **117**. It is unusual for a neutral, even-electron molecule with a closed shell electronic structure such as **125** to display magnetic activity and this species has remained of interest. In recent studies, extended viologens **126** have been compared to **125**.[47b,c] These yield ambiguous results for their electronic structure (**126b**) using EPR techniques, but **126** was recently found to have singlet character as determined using Raman spectroscopy.[47b,c] Earlier X-ray studies also favored a singlet structure for **125**.[42b] Other related diradicals include **127**,[47d] **128**,[47e] and the Muller hydrocarbon **129**.[47f]



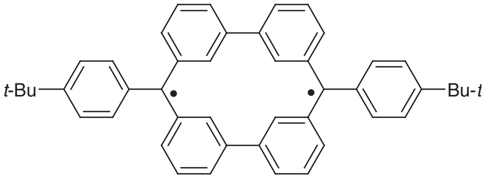
125a **125b**



126a **126b**



127



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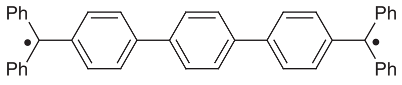
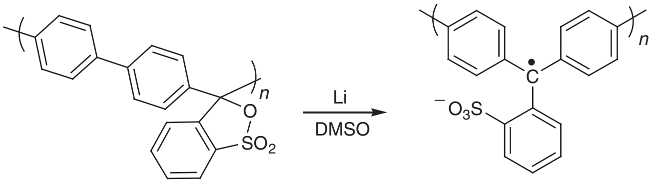
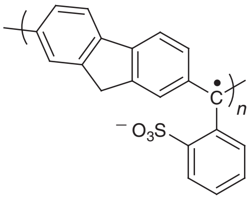


129

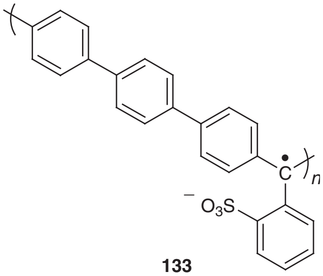
Poly(sulfonylphthalide) **130** was reduced with lithium to give poly(triarylmethyl) radical **131**, characterized by EPR and UV-Visible spectra as a diradical ground state singlet of the Chichibabin hydrocarbon type (Equation 1.39).[48] Poly(radical) **132** had similar character, while **133**, for which the formation of quinonoid structures is energetically unfavorable, led to polyradicals of the triarylmethyl type.[48]



130 **131** (1.39)

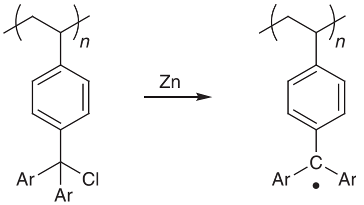


132



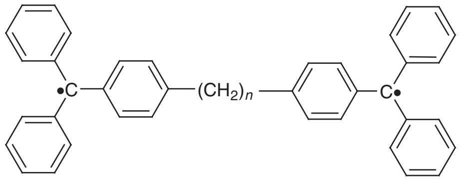
133

Polymer-based triarylmethyl radicals **135** in which the individual triarylmethyl groups are separated from one another by saturated hydrocarbon chains were generated by zinc or potassium treatment of the corresponding polymer with attached triphenylmethyl chlorides **134**, and were characterized by their UV and EPR spectra (Equation 1.40).[49a–e] Radical sites were found to be present on between 25 and 33 % of the triarylmethyl moieties.[49] These species behave as isolated radicals, with no direct spin interaction between the triarylmethyl groups.

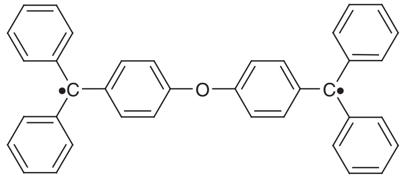


134 **135** (1.40)

A number of further related diradicals of the type **136** and **137** with insulating groups between the radical sites were obtained from reactions of the triarylmethyl chlorides with silver.[49h]



136



137

1.14 Outlook

Originally the discovery of stable triarylmethyl radicals was mainly of theoretical interest and helped lay the foundation for the electronic theory of organic chemistry. The realization of the existence of free radicals with variable levels of stability then led to many advances in chemical theory and practical application, as a variety of free radical reactions, such as polymerizations and substitutions, are of great industrial importance. Similarly, free radicals have been found to play a vital role in biological processes. Now, with the application of triaryl radicals in biology, these species are themselves of great utility, highlighting the inextricable connection between fundamental knowledge and useful application.

Acknowledgements

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