

Inert Free Radicals (IFR): A Unique Trivalent Carbon Species

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Perchloro-organic compounds can be viewed as constituting a chemical domain analogous to that of conventional organic chemistry. To each compound belonging to the latter—and containing at least one hydrogen atom—there can be imagined a corresponding related member belonging to the former as a result of replacing all hydrogens by chlorine atoms (perchlorination).

The initiation of this “perchloro-organic” chemistry can be ascribed to the pioneering syntheses, by Faraday and Julin in 1821, of hexachloroethane, tetrachloroethylene, and hexachlorobenzene.¹ The field then remained almost dormant for nearly 140 years in spite of numerous dedicated efforts to develop and enlarge its scope. In fact, Wheland² and Tatlow,³ both highly respected chemists, at one time concluded that perchloro-organic chemistry was destined to remain a barren deserted field. However, this prognostication was fallacious, partly as a result of the fortuitous discovery, by Ballester and Molinet⁴ in 1954, of an extremely powerful—yet selective—chlorinating agent now known as the BMC reagent.^{5,6} This proved to be the master key to unlocking and revealing perchloro-organic chemistry to represent a domain astonishing rich in new compounds, new reactions and even new phenomena.^{7,8} In retrospect, it appears that the major obstacle to earlier success can be attributed to the bulkiness of the chlorine atom, approximately eightfold that of hydrogen, and the inadequacy of earlier exhaustive chlorinating agents. The latter were either too weak or space-demanding to substitute chlorine for all of the hydrogen atoms or, when forced by stringent experimental conditions, brought about chlorinolysis with the cleavage of carbon-carbon bonds and resultant molecular fragmentation.

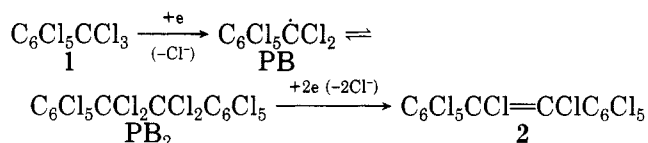
The significant breakthrough in perchloro-organic chemistry came with the synthesis, in 1954,^{4,5} of perchlorotoluene which had defied numerous preparative efforts since 1869.⁹ Repulsion forces between the methyl chlorines and those on adjacent ortho positions are so great that molecular models based on standard scalar atomic building blocks (Fisher-Hirschfelder-Taylor, Stuart-Briegleb, etc.) cannot be constructed. Because of its evidently highly strained distorted nature,^{5,10} perchlorotoluene readily undergoes a number of sterically assisted reactions, including thermolysis,¹¹ photolysis,¹² and condensations.¹³ It is therefore all the more remarkable that the BMC reagent⁵ is able to in-

sert all eight chlorine atoms without molecular breakdown or other side reactions.

Perchlorobenzyl Radicals (PB Series)

A free radical is a molecule, or molecular fragment, possessing atomic or molecular orbitals occupied by one electron (semiooccupied orbitals). As a consequence, such molecules have a net electronic *spin* which is generally experimentally observable in paramagnetic behavior. Most of these species, with their “lone electrons”, exhibit extremely short half-lives (much less than 1 s) because of either their high reactivity toward most chemical substances or their occurrence as transient high-energy intermediates in many common chemical reactions.

Some reactions of perchlorotoluene (1) appear to take place through the intermediacy of an unusually stable, nonstrained perchlorobenzyl radical (PB). One such example is the reduction of perchlorotoluene by either stannous chloride or by iodide ion¹⁴ to yield the isomeric (cis and trans) perchlorostilbenes (2). However, all



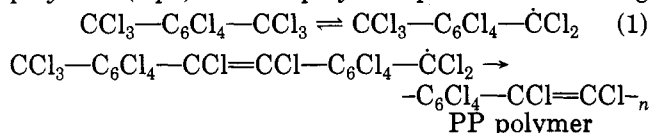
attempts to isolate the postulated intermediate perchlorobibenzyl (PB₂) have been unsuccessful, although, from 2*H*-heptachlorotoluene, the corresponding overcrowded but nonstrained bibenzyl is the major reaction product, along with lesser amounts of the isomeric stilbenes.¹⁴ The PB radical, perchlorobenzyl, has been prepared by ultraviolet photolysis of perchlorotoluene in the presence of copper and exists in equilibrium with its dimer PB₂.¹⁵ The facile dissociation of PB₂ into PB, as well as its evident ready vicinal dechlorination to the

- (1) Faraday, M. *Ann. Chim. Phys.* 1821 (2), 18, 48.
- (2) Wheland, C. W. “Advanced Organic Chemistry”, 3rd. ed.; Wiley: New York, 1960; pp 5-8.
- (3) Tatlow, J. C. *Endeavour* 1963, 22, 89.
- (4) Ballester, M.; Molinet, C. *Chem. Ind. (London)* 1954, 1290.
- (5) Ballester, M.; Molinet, C.; Castañer, J. *J. Am. Chem. Soc.* 1960, 82, 4254.
- (6) Fieser, L. P.; Fieser, M. “Reagents for Organic Synthesis”; Wiley: New York, 1967; p 1131.
- (7) Ballester, M. *Bull. Soc. Chim. Fr.* 1966, 7.
- (8) Ballester, M.; Olivella, S. In “Polychloroaromatic Compounds”; Suschitzky, Ed.; Plenum Press: New York, 1974; pp 1-196.
- (9) Beilstein, F.; Kuhlberg, A. *Justus Liebigs Ann. Chem.* 1869, 39, 393.
- (10) Ballester, M.; Castañer, J. *J. Am. Chem. Soc.* 1960, 82, 4259.
- (11) Ballester, M.; Molinet, C.; Rosa, J. *An. R. Soc. Esp. Fis. Quim., Ser. B.* 1961, 57, 393.
- (12) Ballester, M.; Castañer, J. *An. R. Soc. Esp. Fis. Quim., Ser. B.* 1966, 62, 397.
- (13) Ballester, M.; Castañer, J. *An. R. Soc. Esp. Fis. Quim., Ser. B.* 1970, 66, 487.
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- (15) Olivella, S.; Ballester, M.; Castañer, J. *Tetrahedron Lett.* 1974, 587.

Manuel Ballester was born in Barcelona, Spain. He graduated at the University of Barcelona and received his Dr. Sc. degree from the University of Madrid in 1949. After postdoctoral research work at Harvard University with Paul D. Bartlett and a year in the Aerospace Research Laboratories (Wright-Patterson AFB, Ohio) as a visiting scientist, he returned to the University of Barcelona as professor of chemistry. Presently, he is professor and director of the Institute of Applied Organic Chemistry of Barcelona (CSIC). His research includes kinetics and mechanism of organic reactions, quantitative studies on ultraviolet spectrum of benzenes, and the development of the Perchloro-Organic Chemistry.

nonstrained perchlorostilbenes, may be attributed to its high frontal strain.

PB is the first benzyl-type radical isolated with appreciable stability at room temperature. Other perchlorobenzyl-type radicals have been detected as intermediates in a number of reactions, such as the polyreductocondensation of highly strained and distorted perchloro-*p*-xylene,⁵ to yield an overcrowded, nonstrained polymeric chlorocarbon,¹⁶ as a prototype of the general class of polyperchloro-*p*-phenethylenes or PP polymers (eq 1). These polymers possess outstanding

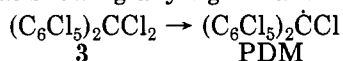


thermal stability—up to 500 °C and beyond—as well as extreme inertness to many reactive reagents.¹⁷ This remarkable behavior is due to three principal factors: (a) steric shielding of the molecular backbone by the space-filling chlorine atoms; (b) high strength of the C(sp²)-Cl bond; and (c) inertness of the chlorine attached to an sp² carbon toward a direct attack.

The exceptional persistence of the perchlorobenzyl radicals is due mainly to steric shielding provided to their trivalent (α) carbon atoms by the four neighboring chlorines (two α and two ortho) and also to the molecular steric strain in any would be products. Nevertheless, although PB can exhibit exceptional stability for many months under a variety of special conditions, it is a chemically active free radical and is immediately oxidized in air.

Perchlorodiphenylmethyl Radicals (PDM Series)

In view of the above-mentioned results, it was reasoned that further enhanced stability in trivalent carbon radicals might be achieved by replacing an α -chlorine in the PB radical by the much bulkier pentachlorophenyl group. This goal, of synthesizing the perchlorodiphenylmethyl radical (PDM), was achieved surprisingly easily. Perchlorodiphenylmethane (3), a chlorocarbon that had been obtained earlier in very small yield by perchlorination of α,α -dichlorodiphenylmethane with the BMC reagent,^{7,18} was readily converted by a variety of reducing reagents—iodide ion, stannous chloride, or ferrous chloride. The product, obtained in good yield and quality, was the orange-red crystalline PDM radical which is stable for months even in air without showing any significant change.^{19,20}



PDM is completely dissociated (does not dimerize), even in the solid state, as is corroborated by magnetic susceptibility measurements. Moreover, it is remarkably passive toward concentrated sulfuric acid, concentrated nitric acid, chlorine, bromine, hydroquinone, and *p*-quinone. In solution, however, its half-life in air at room temperature is about 3 days.

(16) Doorenbos, H. E. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* 1969, 10, 1351.

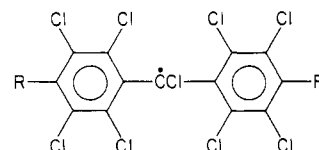
(17) Ballester, M.; Castañer, J.; Riera, J. *J. Am. Chem. Soc.* 1966, 88, 957.

(18) Reference 8, p. . .

(19) Ballester, M.; Riera, J. *J. Am. Chem. Soc.* 1964, 86, 4505.

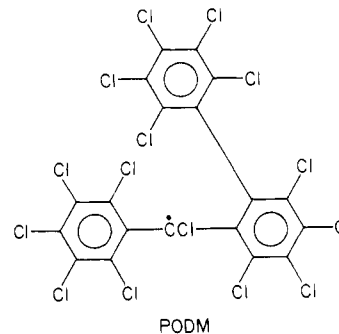
(20) Ballester, M.; Riera, J.; Castañer, J.; Badia, c.; Monsó, J. M. *J. Am. Chem. Soc.* 1971, 93, 2215.

Other completely dissociated, ring-substituted PDM class radicals have been synthesized and isolated in the solid crystalline state.^{20,21} Some differ significantly in stability from that exhibited by the parent PDM radical. For example, the 4,4-dimethoxy-substituted radical 4, in solution, oxidizes easily in air to the corresponding 4,4-dimethoxybenzophenone.²¹ Contrariwise, the perchloro-4-phenyldiphenylmethyl (PPDM) and perchloro-4,4-diphenyldiphenylmethyl (PDDM) radicals are substantially more stable than PDM, with solution half-lives of about 15 days.²⁰



PDM, R=Cl; R'=Cl
PDDM, R=R'=C₆Cl₅
PPDM, R=Cl; R'=C₆Cl₅
4, R=R'=CH₃O

It was then reasoned that the stability of radicals in the PDM series might be increased significantly by providing an extra steric shield for the central trivalent carbon atom, as through replacement of the vicinal (ortho) chlorine of the PDM radical by the much bulkier pentachlorophenyl group to give perchloro-2-phenyldiphenylmethyl (PODM).

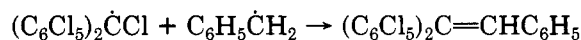
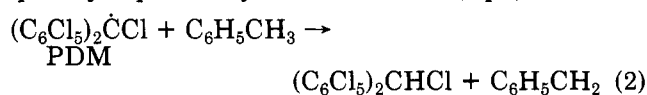


The radical PODM has been synthesized and, as expected, has a longer half-life, about 3 months.²² It appears that the contribution of the α chlorine in PDM-type free radicals to their chemical passivity is significant and decisive. Accordingly, it has been found that whenever an α -H-decachlorodiphenylmethyl radical is formed, it either attacks its neighboring molecules or else it dimerizes. The resulting dimer dissociates at temperatures above 160 °C.^{21,23}

Reactions of the PDM Type of Radicals

The PDM-type free radicals display an interesting range of reactivities.

(a) They extract a methyl hydrogen from boiling toluene to produce a benzyl radical which is subsequently captured by the PDM itself (eq 2).

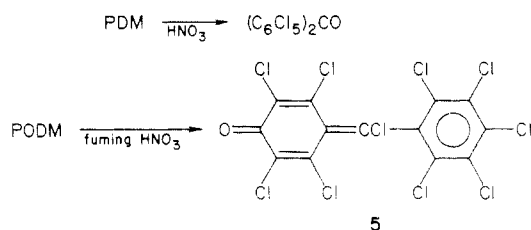


(21) Barrios, M. Doctoral dissertation, University of Barcelona, 1965. Ballester, M., et al., forthcoming publication.

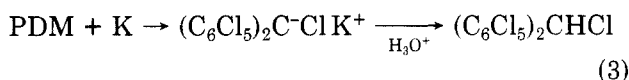
(22) Ballester, M.; Castañer, J.; Riera, J.; Pujadas, J. *J. Org. Chem.* 1984, 49, 2884.

(23) Reference 8, pp 123-128.

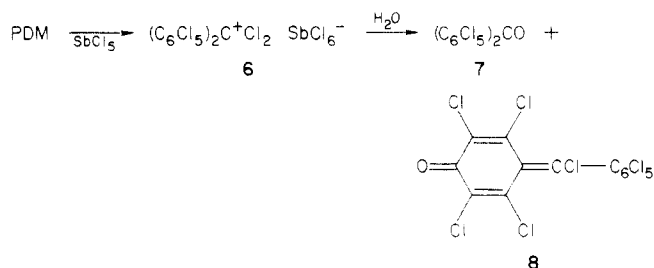
(b) The PDM radicals react very slowly with concentrated nitric acid to give the corresponding benzo-phenones. The more sterically hindered perchloro-2-phenyldiphenylmethyl radical (PODM), as expected, is less sensitive to the concentrated acid,²² but even it reacts immediately with fuming nitric acid, to yield perchloro-*p*-quinomethane **5**.



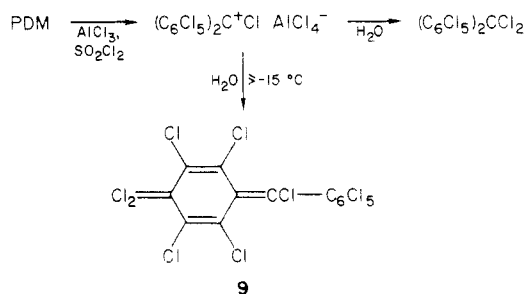
(c) The PDM-type radicals react with either metallic sodium or potassium to give the corresponding diphenylcarbanion salts (eq 3).²⁰



(d) The radical PDM reacts with antimony pentachloride, giving an excellent yield of perchlorodiphenylcarbenium hexachloroantimonate (**6**) readily isolated in crystalline form.²⁴ Upon hydrolysis of this salt, a mixture of perchlorobenzophenone (**7**) and *p*-quinomethane **8** is obtained. Formation of the latter,



by attack at the para carbon, is driven by the steric shielding around the trivalent (positive) carbon of **6**. If aluminum chloride (in sulfuryl chloride solvent) is used instead of antimony pentachloride, carbenium tetrachloroaluminate is formed. Unexpectedly, hydrolysis of this salt at room temperature yields the corresponding perchlorodiphenylmethane.²⁴ If the temperature is lower (-15°C and below), the major product becomes the isomeric chlorocarbon **9**. The radicals



PPDM²⁴ and PODM²² featuring monosubstitution by perchlorophenyl at the para and ortho positions, respectively, behave analogously. However, the disubstituted homologue PDDM does not give the isomeric chlorocarbon but the "normal" one instead.²⁵ This is

(24) Reference 8, pp 173-175.

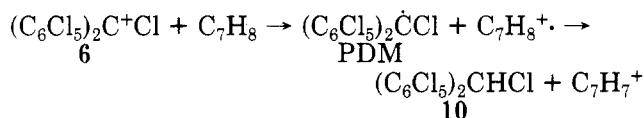
(25) Reference 8, pp 130.

undoubtedly attributable to the powerful shielding of both distant (para) positions by the double substitution by the bulky pentachlorophenyl group and the forbidding strain it imposes on isomeric chlorocarbon formation.

These results suggest that the tetrachloroaluminate salts are actually chlorine-bridged ion pairs.

The Two-Step Hydride-Shift Mechanism

As observed in other carbenium ions, **6** reacts with cycloheptatriene (C_7H_8), an excellent hydride ion donor. The products are the expected α *H*-undecachlorodiphenylmethane (**10**) and tropilium (C_7H_7^+) hexachloroantimonate.²⁶ Although the reaction is rapid at



room temperature, the PDM free radical can be easily detected as a transient species by electron *spin* resonance (ESR).^{26,27} This indicates that the hydride shift from cycloheptatriene to carbenium ion **6** occurs in two steps: an initial one-electron transfer from the hydrocarbon, followed by a hydrogen atom shift from the resulting tropilium radical cation, C_7H_8^+ , to the neutral PDM radical. (It has been ascertained that, under the given reaction conditions, PDM itself does not react with cycloheptatriene.) The unveiling of this two-step mechanism for the hydride shifts was made possible because the hydrogen atom shift in the second step was slowed due to steric shielding in the intermediate PDM.

Perchlorotriphenylmethyl Radicals (PTM Series)

In view of the unusual and interesting chemical behavior of the PDMs, it was considered desirable to investigate the replacement of the α -chlorine in the PDM radical by the much bulkier pentachlorophenyl group, i.e., to attempt the synthesis of perchlorotriphenylmethyl radical (PTM).

The trivalent carbon of the PTM radical, if it existed, might be expected to be extremely well shielded and, if the extrapolation from the observed chemical inertness of PDM is valid, to display even greater resistance to chemical attack. Unfortunately, the same reasoning would suggest the probability of encountering insurmountable difficulty in basing synthesis on the logical chlorocarbon precursor perchlorotriphenylmethane. Substantially less steric crowding for the case of PDM was barely overcome during its synthesis by an analogous route.

Consequently, it was decided to attempt the synthesis of the PTM radical from a less strained precursor, namely, α *H*-pentadecachlorotriphenylmethane (**11**). Although overcrowded by chlorine substituents, it was nevertheless accessible in high yield from triphenylmethane by reaction with the BMC^{4,5} reagent mentioned earlier. Then, by alkaline treatment with dimethyl sulfoxide, compound **11** was converted almost quantitatively into the carbanion **12**. Subsequent oxidation by iodine produced the free radical PTM in

(26) Ballester, M.; Riera, J.; Castañer, J.; Rodríguez, A. *Tetrahedron Lett.* 1971, 2079.

(27) Ballester, M.; Castañer, J.; Riera, J.; Rodríguez, A.; Rovira, C.; Veciana, J. *J. Org. Chem.* 1982, 47, 4498.

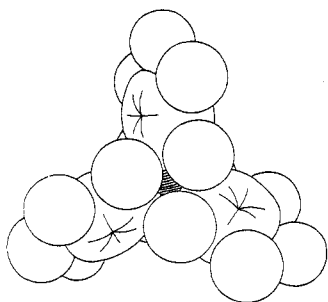
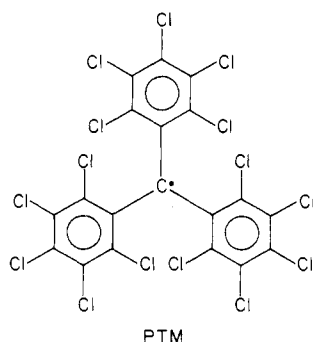
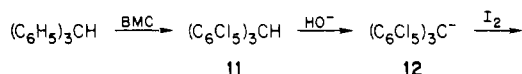


Figure 1.

excellent yield.²⁰ (This new synthetic path, via conversion of relatively nonstrained precursors into carbanions with follow-on oxidation, has now been used very successfully in high-yield syntheses of a number of PDMs and other perchlorocarbon radicals.)



Perchlorotriphenylmethyl, here called PTM, is a deep red, crystalline solid which is shown by physical measurements²⁰ to be completely dissociated into the free radical form, yet is stable to oxygen. In solution at room temperature in contact with air, its half-life, extrapolated from spectral measurements, is estimated to be of the order of 100 years. Moreover, in addition to being unreactive to typical radical scavengers such as nitrous oxide, nitric oxide, hydroquinone, *p*-quinone, and toluene, it is also inert toward aggressive chemicals such as concentrated sulfuric acid, concentrated nitric acid, chlorine, bromine, and others. Thermally, it withstands temperatures up to 300 °C in air without significant decomposition.^{20,27}

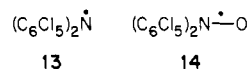
Numerous other radicals of this class, the PTMs, with various substituents in one, two, or three para positions have now been synthesized and also display similar nonreactivity.^{20,27-29} Therefore, such trivalent carbon species, although free radicals, possess a general stability higher than that of the overwhelming majority of "normal" tetravalent carbon compounds and materials. Consequently, these substances are called "inert free radicals" (IFRs) instead of just "stable" or "persistent" free radicals.

Figure 1 shows the space-filling model of the nonstrained, but extremely overcrowded radical PTM, with its propeller blade-like pentachlorophenyl groups. It may also be noted that the trivalent (central) carbon atom is completely shielded by the six ortho chlorines

and the three benzene rings. The normally reactive radical site is enveloped in a "cage", somewhat analogous to the trapping of gaseous molecules such as oxygen, carbon monoxide, and methane in clathrates by hydroquinone, and is unable to approach within chemical bonding distance to other reagents. The high tilt or dihedral angle, evident in the model, between each flat perchlorophenyl group and its neighbor, as well as with respect to the plane of their three bonds to the trivalent (trigonal sp^2) central carbon atom leads to a weak overlap between the π -orbitals of the rings and any p orbital of the latter. As a result, there is significant steric inhibition to any lone-electron delocalization into the three rings, and it is observed that the odd electron (*spin*) resides mainly at the trivalent carbon.³⁰ This undoubtedly also contributes appreciably to the inertness of the PTMs, since attack on sites other than the central carbon, such as the phenyl ring carbons, is also inhibited.

Electron Transfers Involving the PTMs

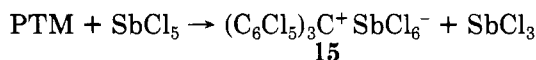
Although the synthesis of the first IFRs has been regarded as a major achievement and also as a paradigm of stabilization of highly reactive species with abnormal valence atoms, their utility in chemical applications would have been sharply curtailed by their nonreactivity. Application of the concept of steric shielding



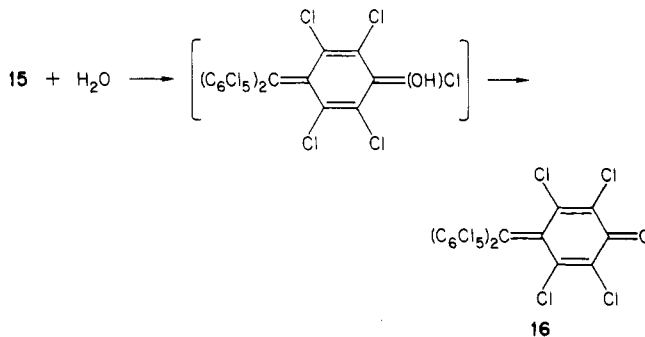
to reactive species has led to the synthesis and isolation of remarkably stable bivalent nitrogen (13)³¹ and nitroxide (14)³² radicals. Fortunately, however, it has been found that the IFRs are very active in one-electron processes.

One-Electron Donations

As with the PDMs, the radicals of the PTM series can be oxidized to the corresponding carbenium ions. For example, PTM, in solution, reacts readily with antimony pentachloride, or with aluminum trichloride in sulfuryl chloride, to give the perchlorotriphenylcarbenium ion (15). The hexachloroantimonate salt can be isolated easily in the form of green crystals.³³ As



expected from steric considerations, hydrolytic attack on the cation 15 does not take place at the extremely well-shielded central (α) carbon, which would yield the hypothetical carbinol $(\text{C}_6\text{Cl}_5)_3\text{C-OH}$. Instead, it occurs at the peripheral (para) carbons to produce perchlorofuchsonone (16).^{27,33} Similarly, alcoholysis and ammono-



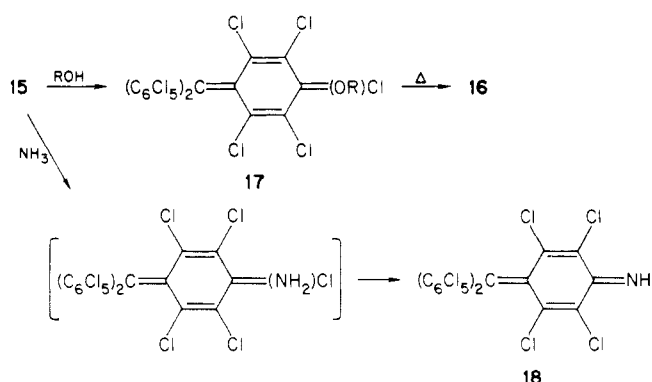
(28) Ballester, M.; Castañer, J.; Riera, J.; Ibáñez, A.; Pujadas, J. *J. Org. Chem.* 1982, 47, 259.

(29) Ballester, M.; Riera, J.; Castañer, J.; Rovira, C.; Veciana, J.; Onrubia, C. *J. Org. Chem.* 1983, 48, 3716.

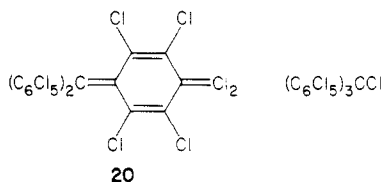
(30) Falle, H. R.; Luckhurst, G. R.; Horsefield, A.; Ballester, M. *J. Chem. Phys.* 1969, 50, 258.

lysis of ion 15 lead to the respective alkoxy (17) and imino (18) derivatives, respectively.²⁸

When tetrachloroaluminate is the counterion, the hydrolysis of carbenium ion 15 leads, under certain reaction conditions, to chlorocarbon 20. This synthesis of a low-strain isomer of the hypothetical highly strained perchlorotriphenylmethane, analogous to the

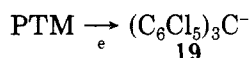


case of some PDMs, suggests the existence of chlorine-bridged ion pairs as reaction intermediates. Compound 20 is a rather unstable chlorocarbon which decomposes easily to the radical PTM.³⁴



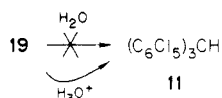
One-Electron Abstractions

As with the PDMs, the radicals of the PTM series accept an electron from alkali metals and are converted to the corresponding carbanions. For example, the PTM radical reacts with sodium or potassium to give the perchlorotriphenylcarbanion (19).²⁰ Although the



resulting salts are very stable in solution, all attempts to isolate them in solid form have failed. Invariably, the carbanions revert to their radicals by an unknown oxidation process. However, they can be isolated when the alkali ion is attached to a crown ether or when the counterion is tetraalkylammonium.³⁵

A most remarkable feature of those carbanions is their resistance to hydrolysis in neutral and basic homogeneous aqueous media.³⁵ This is also attributable to steric shielding of the α -carbon. However, hydrolysis takes place readily in aqueous *acid* media to give the corresponding α -H compounds. For example, carbanion 19 leads to 11.



The conversion of the PTMs into their carbanions can also be performed with alkaline hydroxide in ethyl

(31) Ballester, M.; Castañer, J.; Olivella, S. *Tetrahedron Lett.* 1974, 615.

(32) Ballester, M.; Riera, J.; Onrubia, C. *Tetrahedron Lett.* 1976, 945.

(33) Ballester, M.; Riera, J.; Rodriguez, A. *Tetrahedron Lett.* 1970, 3615.

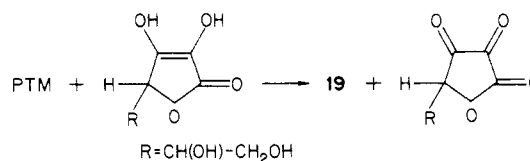
(34) Ballester, M., et al., forthcoming publication.

(35) Ballester, M.; de la Fuente, G. *Tetrahedron Lett.* 1970, 4509.

ether-dimethyl sulfoxide solution. At the time, this surprising observation was attributed to the reducing character of the Me_2SO .²⁰ However, it was later found that hexamethylphosphorous triamide (HMPT) was as effective as Me_2SO . Even more remarkable, such one-electron transfer to PTM takes place immediately, even at room temperature, in aqueous tetrahydrofuran (THF) containing a tetraalkylammonium hydroxide.³⁴ A tempting esoteric rationalization for such a puzzling reduction might be the formation of a charge-transfer complex between hydroxide ion and the PTM radical and a subsequent single electron transfer to give the carbanion. The high electron affinity of the PTMs, caused by the accumulation of electronegative aromatic chlorines, would be crucial for the formation of such a complex.

The few reactions of PTMs that involve bond formation are presumably initiated by a one-electron-transfer step. As examples of this might be mentioned the following: (a) under certain conditions, hydrogen iodide reduces PTM to its corresponding α -H compound 11; (b) fuming nitric acid or oleum oxidizes PTM to fuchsone 16.²⁷

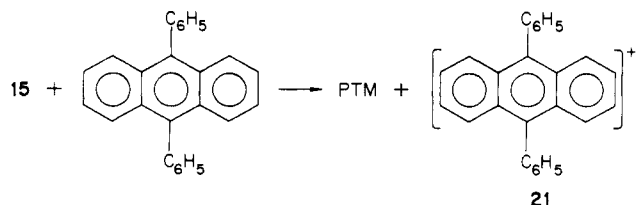
Although PTM is inert toward highly aggressive chemical species and also to organic reducing compounds such as glucose, oxalic acid, etc., it does react with ascorbic acid (vitamin C) in solution at room temperature with the immediate formation of the α -H compound 16.³⁶ This unexpected behavior proceeds with the transient formation of carbanion 19, as evidenced by ultraviolet absorption studies and the isolation of dehydroascorbic acid. This appears to be a clear-cut example of a reaction initiated by one-electron transfer.



This reduction has successfully been used in the conversion of PTMs into their α -H compounds.

In connection with the chemistry of the PTMs, the reaction of carbenium ion 15 with cycloheptatriene has been effected to give excellent yield of PTM radical.^{26,27} No α -H compound 11 was formed, which suggests that the tropylium radical ion $C_7H_5^+$ cannot release a hydrogen atom to PTM because of steric shielding.

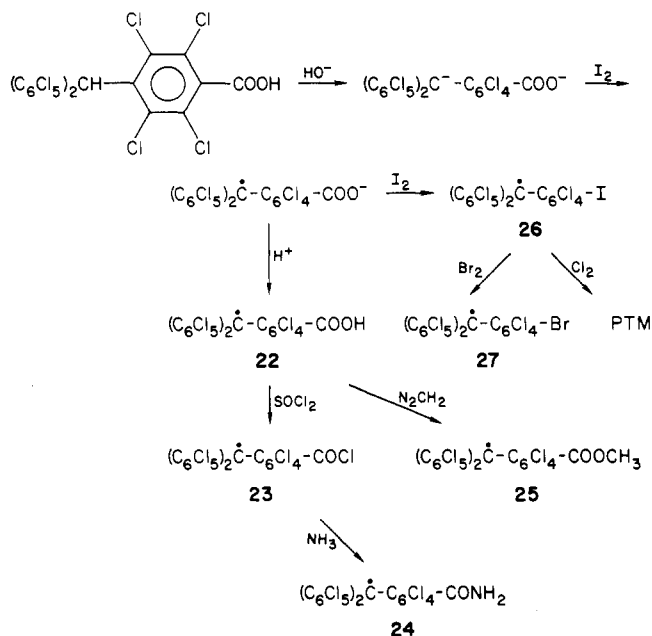
When an electron donor, 9,10-diphenylanthracene, was used instead of the hydride donor cycloheptatriene, the PTM radical was obtained, along with 9,10-diphenylanthracene radical cation (21) hexachloroantimonate. These were isolated and identified by analysis and ESR spectra.²⁶



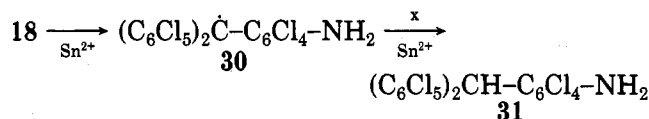
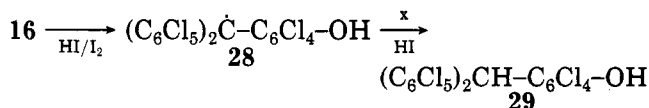
(36) Ballester, M.; Riera, J.; Castañer, J.; Casulleras, M. *Tetrahedron Lett.* 1978, 643.

Functionalized Inert Free Radicals

It has already been mentioned that substitution of one, two, or three para chlorines by other substituents in PTM does not affect the inertness of the radical. This is attributed to insignificant impact of such substituents on steric shielding around the central radical site, the α trivalent carbon, where most of the *spin* density is observed to reside.³⁰ If the substituents are functional groups, then they may react individually at their sites without disturbance to the free radical nature of the molecule. Hence, it is possible to change one member of the PTM family into another by carrying out reactions on peripheral positions. For example, one valuable functionalized IFR is the carboxy-substituted radical **22** which can be prepared via oxidation of its carbanion with iodine.²⁸ If the contact with iodine is prolonged, then iodo-substituted radical **26** is obtained as the major product of a decarboxylation oxidation process.²⁸ The carboxy radical **22** can also be converted directly to the acid chloride **23** with either boiling thionyl chloride or with phosphorus pentachloride.²⁹ In turn, the acid chloride radical **23** reacts with ammonia to yield the amide radical **24**.²⁹ Diazomethane converts the carboxy radical into the ester radical **25**.²⁸ The iodo radical **26** with chlorine or bromine at room temperature is transformed into PTM or bromo radical **27**, respectively.²⁸ Product yields for the conversions of carboxy radical **22** to IFRs **23**, **24**, and **25**, as well as those from iodo radical **26** to PTM and **27**, are practically quantitative.

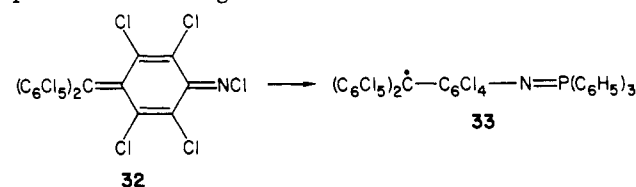


It has been found that some IFRs of the PTM series can be obtained by methods other than the oxidation of their carbanions. The reduction of fuchsone **16** with hydrogen iodide, instead of giving the expected α -H compound **29**, affords a quantitative yield of the hydroxy-substituted radical **28**.²⁷ Analogously, fuchsone imine **18**, with either stannous chloride or diethyl phosphite gives the amine radical **30** instead of **31**.²⁷

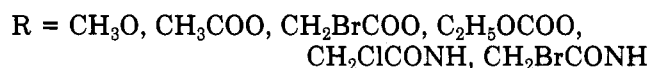
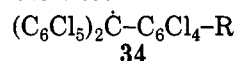


These reactions stop at the intermediate stage, probably because of a combination of the strong positive electronic effect of the OH and NH_2 substituents which opposes the relevant electron transfers and steric shielding factors. It is noteworthy that even the powerful hydroxide/dimethyl sulfoxide mixture is unreactive toward the amino radical **30**. However, the reduction of **30** to **31** can be effected by means of ascorbic acid, although rather sluggishly.

The reaction of fuchsone imine **32** with triphenylphosphine gives the unexpected and unusual phosphorus-containing radical **33**.³⁷



The inertness of radical sites in **29** and **30** allow high-yield conversions into the functional derivatives **34**, such as the methyl ester radical (via diazomethane) and the carboxylic ester and amide radicals (via refluxing acid anhydrides or chlorides), without direct disturbance to those sites.



Further evidence attest to the significance of the substituent electronic effects in the reduction of radicals **28** and **30**: (a) methoxy radical **34** cannot be reduced to its α -H compound;²⁸ (b) the reductions of molecules **28** and **30** can easily be effected by acylation, followed by hydrolysis of the resulting ester.

The Reverse Effect

Since the discovery of the organic free radicals in 1900 by M. Gomberg, the influence of substituents on radical site reactivity has been investigated extensively. Now, with the availability of IRFs, the study of the opposite effect—the influence of the radical character of a molecule on the reactivity of its nonradical chemically active substituents—has become possible. A few studies on this kind of influence, which has been called the “reverse effect”, have been reported recently. They include thermolyses,³⁸ reductive dimerizations,³⁸ bromination,³⁸ and nucleophilic substitutions³⁹ of functionalized IFRs. In all cases, an increase in reaction rate, ranging from moderate to spectacular, is observed and ascribed to stabilization of the relevant transition states by the lone-electron orbital.

Inert Spin Labeling

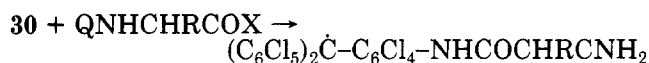
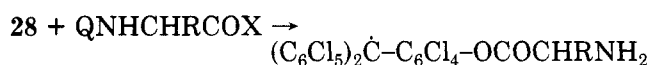
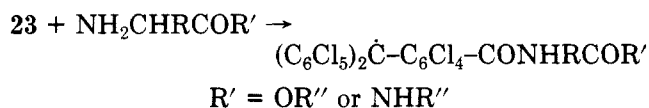
The so-called electron *spin* resonance (ESR) hyperfine structure provides valuable data on the structure

(37) Ballester, M.; Riera, J.; Rovira, C. *An. Quim.* 1976, 72, 489.

(38) Ballester, M.; Veciana, J.; Riera, J.; Castañer, J.; Rovira, C.; Armet, O. *Tetrahedron Lett.* 1982, 23, 5075.

(39) Ballester, M.; Veciana, J.; Riera, J.; Castañer, J.; Armet, O.; Rovira, C. *J. Chem. Soc., Chem. Commun.* 1983, 982.

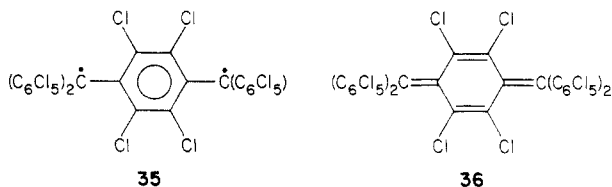
of a free radical. Consequently, structural information on a nonradical molecule can be obtained by attaching a stable free radical to it. This technique, called "spin labeling", has been used successfully in the fields of chemistry, biochemistry, molecular biology, and industrial research, with nitroxide radical as the *spin* labels. It seemed reasonable to believe that some IRFs could also be used for this purpose, with, possibly, some special benefits. Accordingly, some radical derivatives, such as hydroxy **28**, amino **30**, and chloroformyl **23**, have been successfully studied as tags for aliphatic alcohols,³⁴ amino acids,²⁹ and peptides.²⁹



Q = protecting group; X = activating group

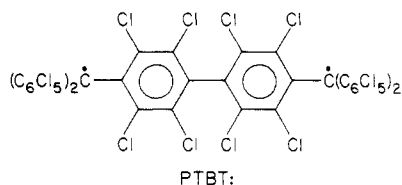
Inert Diradicals

The simplest diradical of the PTM series would be the perchloro- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-*p*-xylylene (**35**). Its synthesis has been attempted via its dicarbanion and oxidation with iodine. However, the product obtained is diamagnetic and, therefore, is not the free diradical but *p*-quinodimethane **36**.⁴⁰ This is quite a remarkable



result since the steric repulsions between the chlorine substituents on the quinonoid structure must be rather strained and distorted. These should have favored formation of the overcrowded less strained diradical.

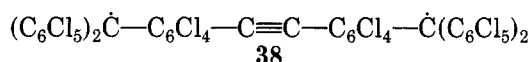
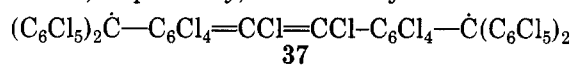
By way of contrast, the diradical PTBT \cdot , synthesized by analogous procedures, is a completely dissociated, chemically inert, non-quinonoid species.²⁰ The ultra-



violet-visible and ESR spectra of PTBT \cdot show that its two moieties are electronically independent because the two central phenylene rings of the biphenyl core are perpendicular to each other, evidently because of the great steric repulsions among the four central chlorines, as has been observed also in perchlorobiphenyl.⁴¹⁻⁴³ In fact, the UV-vis spectrum is practically congruent with that of the PTM radical.²⁰ Therefore, it appears rea-

sonable to deduce that resonance (π -electron delocalization) in PTBT \cdot : essentially inhibited.

The related ethylene- and acetylene-based diradicals **37** and **38**, respectively, have been synthesized and are

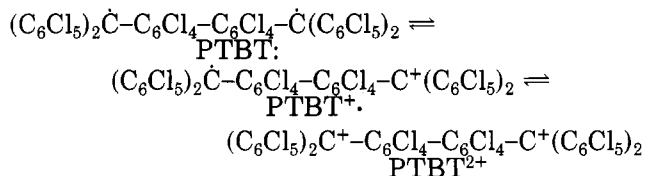


also inert.⁴¹ Their UV-vis spectra differ appreciably from those of PTBT \cdot : or PTM, indicating that electron delocalization involving their two molecular moieties is significant.

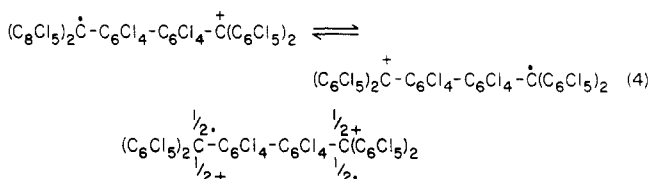
Interestingly, chlorination of diradical **38** with iodine monochloride results in an excellent yield of diradical **37**.

Spin-Charge Exchange

Diradical PTBT \cdot : is easily converted into its dicarbenium ion PTBT $^{2+}$ by oxidation with antimony pentachloride.⁴⁴ If the progress of this reaction is monitored by the electron *spin* resonance technique, it is observed that the spectrum of the starting PTBT \cdot : is replaced gradually by the new transient spectrum of radical carbenium ion PTBT $^{\cdot+}$. The hyperfine struc-



ture of this hybrid exhibits significant differences from that of PTBT \cdot :. In particular, this hybrid's coupling constants with ^{13}C nuclear *spins* are half as high as those observed in PTMs and PTBT \cdot :. This halving indicates that, within the ESR time scale, the odd-electron (*spin*) is distributed symmetrically between the two electronically equivalent moieties in the radical ion hybrid. Since the previously mentioned perpendicularity between the phenylene rings should effectively preclude π -electron delocalization, another effect must be applicable. It is postulated that in the radical ion hybrid, there is a rapid intramolecular exchange between the lone electron and the positive charge, so that the ESR technique "sees" only a structural average. This phenomenon is here called "spin-charge exchange" (eq 4).



The species PTBT $^{\cdot+}$ is viewed as being in equilibrium with PTBT \cdot : and PTBT $^{2+}$, with the relevant interconversions being relatively slow processes. Compelling experimental evidence has recently been found for an analogous spin-charge exchange in the related radical carbanion PTBT $^{\cdot-}$.⁴⁵

All of these phenomena are shedding additional light on the nature of electron and charge interactions and exchanges in organic matter.

(44) Ballester, M.; Castañer, J.; Riera, J.; Pascual, I. *J. Am. Chem. Soc.* **1984**, *106*, 3365.

(45) Ballester, M.; Pascual, I. *Tetrahedron Lett.* **1985**, *26*, 5589.

(40) Reference 8, p 154.

(41) Ballester, M.; Castañer, J.; Riera, J.; Ibáñez, A. *Tetrahedron Lett.* **1980**, *21*, 2435.

(42) Pedersen, B. F. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *B31*, 2931.

(43) Galí, S.; Miravittles, C.; Solans, X.; Font-Altaba, M. *Bull. Inst. Cat. Hist. Nat.* **1979**, *43*, 51.

Conclusion

With the discovery of the "inert free radicals" class and the unusual chemical and physical behavior of the growing number of members, it is fair to conclude that not only is a new type of organic matter being made available to science and technology but also new processes and phenomena are being unveiled. It is quite probable that these IFRs may find useful applications as tracers, inhibitors, energy transfer media, electron-active substances, thermally and chemically stable materials, enzyme and biologically active substrates. These may lead to significant contributions in such diverse fields as medicine and biochemistry, geophy-

sical, hydrologic and petroleologic exploration, high-temperature materials science, theoretical physics and chemistry, etc.

The research herein described has merely scratched the surface. It has produced exciting results that point with promise to future work within this domain undoubtedly discovering more new and unexpected delights which cannot even be guessed at now.

The author acknowledges his deep appreciation to his colleague Dr. Leonard Spialter (Dayton, OH) for his major, decisive role in the discovery and development of the IFRs.