

## A BRIEF HISTORY OF CARBON RADICALS

MALCOLM D. E. FORBES

*Department of Chemistry, University of North Carolina, Chapel Hill, NC, USA*

It may seem difficult to believe, but research on carbon-centered free radicals is about to close out its second century. In 1815, Gay-Lussac reported the formation of cyanogen (the dimer of  $\cdot\text{CN}$ ) by heating mercuric cyanide.<sup>1</sup> Numerous experiments involving pyrolysis of organometallic compounds followed, most notably from Bunsen,<sup>2</sup> Frankland,<sup>3</sup> and Wurtz<sup>4</sup> in the 1840s. All of these reactions suggested the existence of what we now know to be carbon-centered free radicals, but physical methods of detection were still many decades away, and the field became somewhat stagnant in the latter half of the nineteenth century. From high-temperature gas-phase dissociation reactions, it was well accepted that inorganic compounds such as elemental iodine could exist in equilibrium with their atomic “radical” forms. In 1868, Fritzsche’s observation of color changes due to formation of charge transfer complexes between picric acid and benzene, naphthalene, or anthracene represented the first evidence for the existence of carbon radical cations in aromatic systems.<sup>5</sup> However, the attempted isolation of neutral compounds with trivalent carbon was an idea that had definitely fallen out of favor by the 1880s. This lack of interest was amplified by the flourish of new ideas surrounding tetravalent carbon (pushed experimentally by the vapor density method for determining molecular weights<sup>6</sup>) and by the geometrical insight provided by van’t Hoff’s proposal of tetrahedral carbon in 1874.<sup>7</sup>

Because of this status quo, the field was turned completely upside down with Gomberg’s report in 1900 of the preparation of the triphenylmethyl radical.<sup>8</sup> Apart from the influential support of Nef,<sup>9</sup> Gomberg’s result was met with much skepticism.

But as is typical in the scientific endeavor, healthy criticism can provoke new experiments to prove or disprove a novel result, and the carbon radical skeptics were slowly won over. The year 1900 marked the beginning of what we might call the “wet chemistry” era of research on carbon-centered free radicals, although it should be noted that there were also many gas-phase experiments that were useful in establishing radical reactivity patterns. For example, Goldstein’s experiments with cathode ray tubes provided the earliest physical method of detection of carbon-based radical cations in the gas phase.<sup>10</sup> On the theoretical side, strong support for the existence of carbon-centered free radicals came from G. N. Lewis in 1916, whose ideas about valence shells and the octet rule had just begun to emerge.<sup>11</sup> Lewis was also the first to recognize that molecules with unpaired electrons would exhibit paramagnetism.<sup>12</sup> It is rather astounding to realize that both of these hypotheses predate the advent of the quantum theory; in regard to molecular structure, Lewis had an unmatched level of insight for his time.

The 1920s saw a flurry of activities in both thermal and photochemical investigations of gas-phase organic reactions, and chemists such as H. S. Taylor began to hypothesize carbon-centered radicals as reactive intermediates in certain mechanisms.<sup>13</sup> In 1929, Paneth and Hofeditz reported their ingenious “mirror” experiments involving thermolysis of vapor-phase  $\text{Pb}(\text{CH}_3)_4$  and other organometallic compounds. Their results clearly demonstrated that alkyl radicals were reasonable postulates as reactive intermediates in these reactions.<sup>14</sup> In solution-phase organic chemistry, free radicals were beginning to be proposed as intermediates whenever “forbidden” chemistry was observed. This included reactions such as autooxidation of carbonyl compounds and the sulfite ion studied by Bäckström in 1927,<sup>15</sup> and in other reactions by Haber and Willstätter a few years later.<sup>16</sup> There was even an early suggestion by Staudinger in 1920 that free radicals were involved in the polymerization reactions of olefins.<sup>17</sup> Carbon-centered radical cations were the subject of many gas-phase ion investigations in the early part of the twentieth century, led by the instrumentation developments of Thomson and Aston.<sup>18,19</sup> Their work during these years built directly on Goldstein’s cathode ray results and lay the foundation for the emerging field of organic mass spectrometry.

The year 1937 was an auspicious one for free radical chemistry, with the publication of an extensive review on solution-phase free radical mechanisms by Hey and Waters.<sup>20</sup> At about the same time, Kharasch proposed the now well-accepted mechanism for anti-Markovnikov addition of  $\text{HBr}$  to alkenes in the presence of peroxides,<sup>21</sup> a reaction he had initially reported with Mayo 4 years earlier.<sup>22</sup> Also in 1937 came Flory’s definitive paper on the kinetics of vinyl polymerization reactions, confirming the nature of these reactions as free radical propagations.<sup>23</sup> This work on polymers eventually led to one of the largest spurts of industrial growth of the twentieth century. The year 1937 was noted by Walling in his excellent monograph<sup>24</sup> as the beginning of the general acceptance of carbon-centered free radicals as viable reactive intermediates in solution-phase organic reactions at ordinary temperatures.

In terms of physical methods, by 1937 there had been only a few advances beyond the mirror technique of Paneth or the invoking of “forbidden reactivity” in solution to establish that a mechanism involved free radicals (or not). As noted above, mass

spectrometry was one field where radicals and radical cations from organic structures were beginning to be postulated and actively studied.<sup>25</sup> Optical absorption, usually carried out in frozen glasses with unstable radicals, was also a common early technique,<sup>26</sup> and this was an important component of Gombert's description of the triphenylmethyl radical. With Lewis' recognition of the link between radicals and paramagnetism, the magnetic susceptibility experiment came to be used in the study of stable free radicals.<sup>27</sup> A bit later, scavenging studies were carried out to establish radical mechanisms<sup>28</sup>, and the early days of flash photolysis allowed coarse structural and kinetic studies of radicals to be performed for the first time.<sup>29</sup> However, prior to World War II (WWII), there were no high-resolution methods available that could definitively establish the structural (and magnetic) properties of carbon-centered radicals. The War would change this situation quickly.

The threat of airborne bombing raids on major cities during WWII led to intense efforts for the early detection of aircraft, and it was quickly recognized that radio and/or microwave frequency electromagnetic radiation could be used for this purpose.<sup>30</sup> This research in radio physics and engineering led to the availability of high-powered RF sources and sensitive detectors, the potential of which was immediately exploited by chemical physicists for the detection of magnetic resonances due to spin angular momentum in atoms and molecules. Such resonances had been predicted from the quantum theory two decades earlier, but had eluded detection.<sup>31</sup> Purcell and Bloch in the United States, and Zavoisky in Russia (then the USSR), refined these RF experimental techniques to demonstrate "proof of principle" magnetic resonance spectroscopies (Purcell and Bloch discovered and reported NMR independently in 1946,<sup>32,33</sup> while Zavoisky reported the first EPR spectrum of a paramagnetic species in 1945<sup>34</sup>). While the EPR experiment is more directly relevant, both experiments played key roles in understanding mechanistic organic chemistry involving carbon-centered free radicals. The impact of these techniques on the field cannot be overestimated, and both spectroscopic methods are widely used in the study of radical reactions to the present day.

Just a few years after the discoveries of electron and nuclear magnetic resonance phenomena, commercial EPR and NMR spectrometers appeared, and the early 1950s can be considered the dawn of the "spectroscopic era" of research on free radicals. In the United States, the research groups of Weissman in St. Louis and Hutchison in Chicago were soon studying the structures and molecular dynamics of radicals and triplet states. Weissman in particular was developing workable models for simulating solution EPR spectra.<sup>35</sup> In 1958, Hutchison and Mangum reported the first EPR spectrum of an organic triplet state,<sup>36</sup> ending years of speculation and argument about the nature of phosphorescence (much earlier, G. N. Lewis had correctly predicted that the phosphorescent state of an organic molecule was the excited triplet).

Activity in magnetic resonance of free radicals has not let up, and a cursory literature search found almost 80,000 publications related to EPR spectroscopy at the time this book went to press. More than half of these papers are devoted to carbon-centered radicals. In 1963, new photochemical techniques and advances in spectrometer sensitivity led to the first direct observations of free radicals in liquid solution at room temperature.<sup>37</sup> Soon after, it was commonplace to see *g*-factor (chemical shift)

and isotropic electron–nuclear hyperfine coupling constants for novel radicals being published on a regular basis in what we now refer to as “high-impact” journals.

Many sophisticated techniques for the isolation and study of free radicals and carbenes in the gas phase were devised during the spectroscopic era,<sup>38,39</sup> most of them in conjunction with the development of high-intensity CW and pulsed lasers. These experiments were not only highly complementary to magnetic resonance methods, but also had the advantage of driving computational and theoretical work because very simple structures could be studied in the absence of solvent effects with high spectroscopic resolution. An example is the landmark photodetachment experiment of Engelking et al. that led to a precise value for the singlet–triplet energy gap in methylene, the simplest carbene.<sup>40</sup> This energy gap had historically been a problem for computational chemists due to its open-shell structure, but the photodetachment method provided much guidance. The electronic structure of methylene remains one of the healthiest examples ever recorded of experiment/theory convergence in physical organic chemistry. The development of pulsed lasers in the 1960s also improved the time resolution and sensitivity of the flash photolysis experiment, and this allowed the kinetics of many radical reactions in solution to be precisely measured in real time.<sup>41</sup> It is fair to say that prior to the development of time-resolved magnetic resonance techniques in the 1970s, laser flash photolysis was the standard method for determining free radical lifetimes in solution.<sup>42</sup>

Research on carbon-centered radical cations in solution accelerated dramatically with the development of time-resolved optical absorption and emission techniques. The research group of Th. Förster in Germany pioneered photochemical methods of production of radical cations and anions, as well as exciplexes.<sup>43</sup> While the Förster group focused on structure and lifetimes, the later work of D. R. Arnold in Canada,<sup>44</sup> and of H. D. Roth in the United States,<sup>45</sup> reported the reactivity of photochemically generated radical cations from a mechanistic perspective. These studies of radical ion chemistry evolved into the field we now know as electron donor–acceptor interactions, a rich area of science in which carbon-centered radical cations are still actively studied.

Another burst of activity in free radical research occurred in the 1960s and 1970s, after several reports of anomalous intensities in the EPR spectra of photochemically or radiolytically produced radicals, and in the NMR spectra of the *products* from free radical reactions in solution.<sup>46,47</sup> These so-called chemically induced magnetic spin polarization (CIDNP and CIDEP) phenomena provided a wealth of mechanistic, kinetic, dynamic, and structural information and were a cornerstone of carbon-centered free radical research for the better part of three decades.<sup>48,49</sup> The umbrella term for this area of research is “spin chemistry,” which is defined as the chemistry of spin-selective processes.

Many new physical methods were developed in response to needs of spin chemists. In particular, the time-resolved EPR (TREPR)<sup>50</sup> and time-resolved NMR (CIDNP)<sup>51</sup> techniques were found to be of unparalleled utility in terms of mechanistic understanding of radical chemistry. Theoretical work to explain CIDNP and CIDEP phenomena was able to link, for the first time, the spin physics of radical pairs to their diffusion, molecular tumbling, confinement (solvent cages versus supramolecular environments<sup>52</sup>), and the effects of externally applied magnetic fields.<sup>53–56</sup>

Several chapters of this book show how magnetic field effects, as well as CIDEP and CIDNP spectral patterns, can be used to solve chemical problems. It should be noted that the study of how applied magnetic fields perturb chemical reactivity is a topic that is highly relevant to biological processes involving radical pairs, for example, photosynthesis.<sup>57–59</sup>

Two other major instrumentation developments had a major influence on the study of carbon free radicals. In the 1950s, George Feher developed electron–nuclear double resonance (ENDOR) spectroscopy,<sup>60</sup> which is still used to great advantage in determination of hyperfine coupling constants in biological systems.<sup>61</sup> The experiment is even run in time-resolved mode in some laboratories.<sup>62</sup> Pulsed EPR has emerged in recent years as a valuable technique,<sup>63</sup> but its utility in the study of organic radicals is somewhat limited by the current status of microwave pulsing technology. Only very narrow spectral widths ( $\sim 100$  MHz) can be excited with uniform power by such pulses without distortions of the signals. Both electron spin-echo envelope modulation (ESEEM)<sup>64</sup> and FT-EPR<sup>65</sup> are used in the study of biological free radicals, and as the microwave technology improves in the modern era, 2D<sup>66</sup> and even 3D<sup>67</sup> pulsed EPR experiments have become a reality.

It is interesting to look back on this historical perspective and note that in the “wet chemistry” era (pre-WWII), the reactivity of radicals (Bäckström) and synthetic applications (Kharasch) were “hot” experimental topics. Polymers were just beginning to be recognized as fertile areas for research on free radicals (Flory), and gas-phase spectroscopy was leading to some of the most insightful experimental observations of the time (Paneth). This book honors the efforts of these pioneers in that, while the experiments have become more complex, the fundamental relationship between structure and reactivity is still driving intellectual curiosity in free radical research. The level of computational precision regarding structure and reactivity of free radicals has grown incredibly since 1950 and now matches the sophistication of the modern experimental arsenal.<sup>68,69</sup> It is clear that the complexity of the systems that can be studied with these computational methods will continue to increase.

The future of the field is bright: carbon-centered free radicals in chemistry and biology continue to be of broad interest and continue to be studied experimentally with high resolution and high sensitivity. Combined with the latest computational techniques, it is now possible to consider the creation of a “cradle to grave” understanding of a free radical reaction, from the characterization of the excited-state precursor by optical techniques to the structure and dynamics of the radicals themselves by EPR spectroscopy, and finally to the kinetics of formation and structures of the products by NMR spectroscopy and other analytical methods.

## REFERENCES

1. Gay-Lussac, H. L. *Ann. Chim.* **1815**, 95, 172.
2. Bunsen, R. H. *Justus Liebigs Ann. Chim.* **1842**, 42, 27.
3. Frankland, E. *Ann. Chem. Pharm.* **1849**, 71, 213.
4. Wurtz, C. A. *Compt. Rend.* **1854**, 40, 1285.

5. Fritzsche, C. J. *Jahresb.* **1868**, 395.
6. Siwoloboff, A. *Ber. Dtsch. Chem. Ges.* **1886**, 19, 795.
7. van't Hoff, J. H. *Arch. Neerl. Sci. Exactes Nat.* **1874**, 9, 445.
8. Gomberg, M. J. *Am. Chem. Soc.* **1900**, 22, 757.
9. Nef, J. U. *Liebigs Ann.* **1901**, 318, 137.
10. Goldstein, E. *Ann. Phys.* **1898**, 300, 38.
11. Lewis, G. N. *J. Am. Chem. Soc.* **1916**, 38, 762.
12. Lewis, G. N. *Valence and Structure of Atoms and Molecules*; Chemical Catalog Co.: New York, **1923**; p 148.
13. Taylor, H. S. *Trans. Faraday Soc.* **1925**, 21, 560.
14. Paneth, F.; Hofeditz, W. *Ber. Dtsch. Chem. Ges.* **1929**, 62, 1335.
15. Bäckström, H. L. J. *J. Am. Chem. Soc.* **1927**, 49, 1460.
16. Haber, F.; Willstätter, R. *Ber. Dtsch. Chem. Ges.* **1931**, 64, 2844.
17. Staudinger, *Ber. Dtsch. Chem. Ges.* **1920**, 53, 1073.
18. Thomson, J. J. *Philos. Mag.* **1899**, 48, 547.
19. Aston, F. W. *Philos. Mag.* **1919**, 48, 707.
20. Hey, D. H.; Waters, W. A. *Chem. Rev.* **1937**, 21, 169.
21. Kharasch, M. S.; Engelmann, H.; Mayo, F. R. *J. Org. Chem.* **1937**, 2, 288.
22. Kharasch, M. S.; Mayo, F. R. *J. Am. Chem. Soc.* **1933**, 55, 2468.
23. Flory, P. J. *J. Am. Chem. Soc.* **1937**, 59, 241.
24. Walling, C. *Free Radicals in Solution*; Wiley: New York, **1957**.
25. Taylor, D. D. *Phys. Rev.* **1935**, 47, 666.
26. Walter, R. I. *J. Am. Chem. Soc.* **1966**, 88, 1930.
27. van Vleck, J. H.; *Electric and Magnetic Susceptibility*; Oxford University Press: New York, **1932**.
28. Noyes, R. M. *J. Am. Chem. Soc.* **1955**, 77, 2042.
29. Norrish, R. G. W.; Porter, G.; Thrush, B. A. *Proc. R. Soc. Lond. A* **1953**, 216, 165.
30. Bowen, E. G.; *Radar Days*; Institute of Physics Publishing: Bristol, **1987**.
31. Gorter, C. J.; Broer, L. J. F. *Physica* **1942**, 9, 591.
32. Purcell, E. M.; Torrey, H. C.; Pound, R. V. *Phys. Rev.* **1946**, 69, 37.
33. Bloch, F. *Phys. Rev.* **1946**, 70, 460.
34. Zavoisky, E. K. *J. Phys. (USSR)* **1945**, 9, 245.
35. Weissman, S. I. *J. Chem. Phys.* **1954**, 22, 1135.
36. Hutchison, C. A. Jr.; Mangum, B. W. *J. Chem. Phys.* **1958**, 29, 952.
37. Piette, L. H. A new technique for the study of rapid free radical reactions. In *Sixth International Symposium on Free Radicals*, Cambridge University Press, **1963**.
38. Friderichsen, A. V.; Radziszewski, J. G.; Nimlos, M. R.; Winter, P. R.; Dayton, D. C.; David, D. E.; Ellison, G. B. *J. Am. Chem. Soc.* **2001**, 123, 1977.
39. Deyerl, H.-J.; Gilbert, T.; Fischer, I.; Chen, P. J. *J. Chem. Phys.* **1997**, 107, 3329.
40. Engelking, P. C.; Corderman, R. R.; Wendoloski, J. J.; Ellison, G. B.; O'Neil, S. V.; Lineberger, W. C. *J. Chem. Phys.* **1981**, 74, 5460.

41. McGarry, P. F.; Cheh, J.; Ruiz-Silva, B.; Hu, S.; Wang, J.; Nakanishi, K.; Turro, N. J. *J. Phys. Chem.* **1996**, *100*, 646.
42. Scaiano, J. C.; Johnston, L. J. *Org. Photochem.* **1989**, *10*, 309.
43. Förster, Th. *Pure Appl. Chem.* **1973**, *34*, 225.
44. Neunteufel, R. A.; Arnold, D. R. *J. Am. Chem. Soc.* **1973**, *95*, 4080.
45. Roth, H. D. *Acc. Chem. Res.* **1987**, *20*, 343.
46. Ward, H. R.; Lawler, R. G. *J. Am. Chem. Soc.* **1967**, *89*, 5518.
47. Bargon, J.; Fischer, H.; Johnsen, U. *Z. Naturforsch. A* **1967**, *22*, 1551.
48. Trifunac, A. D.; Lawler, R. G.; Bartels, D. M.; Thurnauer, M. C. *Prog. React. Kinet.* **1986**, *14*, 43.
49. Bagryanskaya, E. G.; Sagdeev, R. Z. *Prog. React. Kinet.* **1993**, *18*, 63.
50. Forbes, M. D. E. *Photochem. Photobiol.* **1997**, *65*, 73.
51. Closs, G. L.; Miller, R. J. *Rev. Sci. Instrum.* **1981**, *52*, 1876.
52. Turro, N. J.; Buchachenko, A. L.; Tarasov, V. F. *Acc. Chem. Res.* **1995**, *28*, 69–80.
53. Adrian, F. J. *J. Chem. Phys.* **1971**, *54*, 3918.
54. Closs, G. L. *J. Am. Chem. Soc.* **1969**, *91*, 4552.
55. McLauchlan, K. A.; Steiner, U. E. *Mol. Phys.* **1991**, *73*, 241.
56. Steiner, U. E.; Ulrich, T. *Chem. Rev.* **1989**, *89*, 51.
57. Hoff, A. J. In *The Photosynthetic Reaction Center*; Deisenhofer, J.; Norris, J. R., Jr., Eds.; Academic Press: New York, 1993; Vol. 2, pp. 331–382.
58. Norris, J. R., Jr.; Budil, D. E.; Kolaczowski, S. V.; Tang, J. H.; Bowman, M. K. In *Antennas and Reaction Centers of Photosynthetic Bacteria*; Michel-Beyerle, M. E., Ed.; Springer: Berlin, 1985; pp. 190–197.
59. Bowman, M. K.; Budil, D. E.; Closs, G. L.; Kostka, A. G.; Wraight, C. A.; Norris, J. R. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 3305.
60. Feher, G. *Phys. Rev.* **1956**, *103*, 834.
61. Hoganson, C. W.; Babcock, G. T. *Biochemistry* **1992**, *31*, 11874.
62. Jaegermann, P.; Lendzian, F.; Rist, G.; Moebius, K. *Chem. Phys. Lett.* **1987**, *140*, 615.
63. *Modern Pulsed and Continuous-Wave Electron Spin Resonance*; Kevan, L.; Bowman, M. K., Eds.; Wiley: New York, **1990**.
64. Rowan, L. G.; Hahn, E. L.; Mims, W. B. *Phys. Rev.* **1965**, *137*, A61.
65. van Willigen, H.; Levstein, P. R.; Ebersole, M. H. *Chem. Rev.* **1993**, *93*, 173.
66. Goldfarb, D.; Kofman, V.; Shanzer, J. A.; Rahmatouline, R.; van Doorslaer, S.; Schweiger, A. *J. Am. Chem. Soc.* **2000**, *122*, 1249.
67. Blank, A.; Dunnam, C. R.; Borbat, P. P.; Freed, J. H. *Appl. Phys. Lett.* **2004**, *85*, 5430.
68. Fokin, A. A.; Schreiner, P. R. *Chem. Rev.* **2002**, *102*, 1551.
69. Improta, R.; Barone, V. *Chem. Rev.* **2004**, *104*, 1231.

