# Harden M. McConnell: The Science Speaks for Itself



The majority of the more than 150 scientists who have worked with Harden M. McConnell, as graduate students, post docs, and senior colleagues, attended a symposium on April 4, 1992, at Stanford University, celebrating Harden's 65th birthday. As an outgrowth of that symposium, these scientists have organized special issues of the *Biophysical Journal* and *The Journal of Physical Chemistry* to present current aspects of their work, and his. Several other scientists whose work has been influenced by McConnell's contribute articles also. The symposium and these papers provide powerful testimony to the profound impact that Harden McConnell has had in the fields of chemical physics, molecular biophysics, and cellular biophysics. McConnell's influence comes not only from his own impressive publication list, but also from the scores of scientists whose careers he has inspired, by his example of intellectual brilliance, and personal integrity.

The purpose of this introduction is to provide the reader of this issue of the *Biophysical Journal* with a *brief* history and a *brief* bibliography of some of the contributions that Harden McConnell has made to areas of biophysics that have evolved from theoretical and experimental chemical physics. There is no better history of his work than the work itself. The following short selection of references to McConnell's papers covers some of the fields he has influenced. These references also provide a glimpse of the course of careers of some of the authors of this volume, from their early publications with Harden, to now. The complete publication list of over 370 papers by McConnell, and additional biographical information, will be published in *The Journal of Physical Chemistry* special issue.

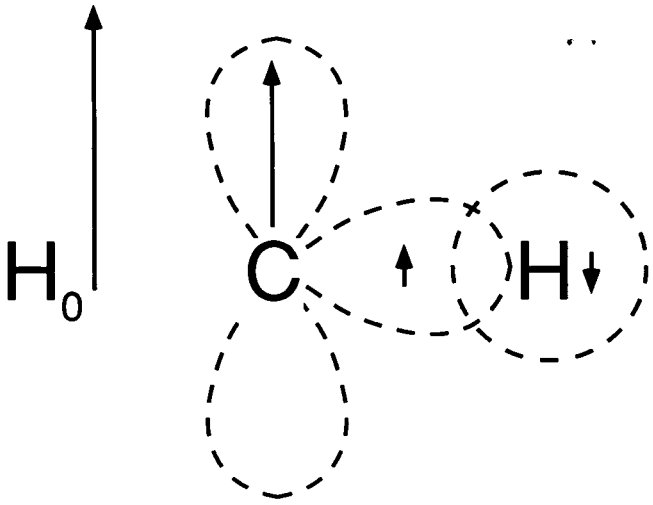
McConnell graduated from George Washington University in 1947 and became a graduate student at Caltech with Norman Davidson. Caltech graduate students were required to present original propositions. For one of his propositions, McConnell independently worked out a theory of spin-correlation dependent multiplet splittings in diatomic hydrides and presented it as part of his thesis in 1950. His thesis research resulted in four papers, the first of which bore the title "Investigation of possible interactions between thallium (I) and thallium (III) in solution and in the crystalline thallium sesquihalides" (1). These four thesis papers also included an often quoted one on chloro-bridged copper dimers titled "Optical interaction between the chloro-complexes of copper (I) and copper (II) in solutions of unit ionic strength" (2). This thesis work was followed later by the first measurement of the rate of electron transfer between metal ions by NMR, in this case between $Cu^{+}$ and $Cu^{++}$ ("Rate of electron exchange between cuprous and cupric ions in hydrochloric acid solutions by nuclear magnetic resonance" (3)).

In 1950 McConnell joined the Mulliken-Platt-Roothaan research group in the Physics Department at the University of Chicago, and became interested in experimental tests of theories of molecular electronic structure. McConnell's move to Shell Development Company in Emeryville, California, afforded him the opportunity to analyze early electron and nuclear magnetic resonance results in terms of molecular electronic structure. During the period 1952-1956 he developed some of the first interpretations of nuclear magnetic resonance spectra in terms of group theory ("Analysis of spin-spin multiplets in nuclear magnetic resonance spectra" (4)) and molecular orbital theory ("Molecular orbital approximation to electron-spin coupled nuclear spin-spin interactions in molecules" (5)). In 1956, the Chemistry Department at Caltech, chaired by Linus Pauling, appointed McConnell as an Assistant Professor. The culmination of McConnell's efforts to give a theoretical foundation to paramagnetic resonance spectroscopy of organic radicals began to appear in the 1956-1957 period. The paper "Electron densities in semiquinones by paramagnetic resonance" (6) presented the simple equation that has come to be known as the "McConnell Equation," which states that for $\pi$-electron radicals, the electron-proton isotropic hyperfine splitting constant $a$ is proportional to the $\pi$-electron spin density $\rho$ of the carbon adjacent to the proton:

$$a = Q\rho.$$

The proportionality constant $Q$ is approximately $-22.5$ gauss. McConnell's theory predicted that the sign of the proton hyperfine coupling in aromatic hydrocarbon radicals would be the opposite of the carbon spin density ("Theory of isotropic hyperfine interactions in pi-electron radicals" (7)). Analysis of the proton hyperfine interactions in malonic acid radicals demonstrated that it is a $\pi$-electron radical with negative proton hyperfine interaction. A familiar figure (top of next page) from the paper titled "Radiation damage in organic crystals" (8) demonstrates how spin polarization, by a magnetic field, of the $\pi$-radical on the malonic acid $\alpha$-carbon results in spin polarization in the CH bond.

McConnell had become Professor of Chemistry in 1959 and Professor of Chemistry and Physics in 1963 at Caltech. In 1964, he moved to Stanford University. He was elected to the National Academy of Sciences of the United States in 1965. During the period of the Caltech-Stanford transition, he was actively engaged in studies of excitons ("Paramagnetic Excitons in Molecular Crystals" (9)). The beginnings of his interest in applying magnetic resonance techniques to biological macromolecules were also being kindled then; his first "spin labelling" paper used the radical ion of chlorpromazine as a




DNA intercalation agent ("Interaction of the radical ion of chlorpromazine with deoxyribonucleic acid" (10)). In the same year, the paper that laid the framework for applications of nitroxides to studies of macromolecules appeared ("Nitrogen hyperfine tensor and g tensor of nitroxide radicals (11))." Nitroxides were rapidly converted into protein modification reagents ("Spin-label study of hemoglobin conformations in solution" (12)) and probes of membrane structure and dynamics. There followed an explosion in biophysical applications of spin labelling. The rapid pace and high productivity of this field in the late 60's and early 70's was due largely to the thoroughness and breadth of the effort of one closely connected group of researchers. This single extended scientific family developed in parallel not only the synthetic chemistry and spectroscopic methods, but also performed the key biological applications. Perhaps most importantly, the entire effort was based on McConnell's deep insight into magnetic resonance theory and his ability to apply these theoretical principles to develop methods for the quantitative analysis of nitroxide EPR spectra. This was particularly evident in the development of methods for studying molecular dynamics.

The greatest biophysical impact of spin labelling has been in the field of membrane structure and dynamics.

Photos taken at the symposium in honor of Harden M. McConnell, April 4, 1992, at Stanford University. Shown, clockwise from upper left, are Norman Davidson, McConnell, Alvin Kwiram with Linus Pauling, the audience of McConnell colleagues, and McConnell.

Attendees included (as identified prior to press time): (*1st row, left to right*) Dean Hafeman, John Rubenstein, Martin Itzkowitz, Himan Sternlicht, Benton Smith, Michael Seul, Krishna Balakrishnan, David Cafiso, Elizabeth Luna, Verla Kwiram, and Harden McConnell. (*2nd row*) Rosmarie Swanson, Wilse Robinson, Joel Morrisett, O. Hayes Griffith, Lubert Stryer, Lloyd Smith, Sunney Chan, Wray Huestis, Roger Kornberg, Richard Keys, and Alonzo Ross. (*3rd row*) Henry Dearman, Philippe Devaux, Zoltan Soos, Harris Silverstone, Brian Hoffman, Mark McName, James Sheats, Seiji Ogawa, Mireille Viguier, Robert Hughes, Stephen Witt, Vincent Moy, and Mamoru Nakanishi. (*4th row*) Richard Fessenden, Don Thompson, James Hyde, Dave Thomas, Jan Boeyens, Trent Buckman, Chien Ho, Alvin Kwiram, Gill Humphries, Patrick Coleman, Philippe Brulet, Betty Gaffney, Anton de Kroon, Penny Gilmer, Stephen Wu, Terry Cole, and Carl Scandella. (*5th row*) Maria Yamout, Nick Benvegnu, Jerry Tsai, Tom Theriault, Joachim Seelig, Wayne Hubbell, James Trudell, Dieter Rechtenwald, Dan Dennen, Jane McConnell, Robert Weis, Dan Leahy, Jacob Anglister, Lukas Tamm, Wallace Parce, and Karen Mason.

The fluid nature of biological membranes was demonstrated by the simple observation that the hydrophobic spin label, TEMPO, tumbled in a membrane as if in a hydrocarbon liquid ("Spin-label studies of the excitable membranes of nerve and muscle" (13)). Motion of lipids within the plane of the membrane ("Lateral diffusion of phospholipids within a vesicle membrane" (14); and "Lateral diffusion in spin-labeled phosphatidylcholine multilayers" (15)) is consistent with the fluid picture of the membrane, but "flip-flop" between two halves of the bilayer is very slow ("Inside-outside transitions of phospholipids in vesicle membranes" (16)). Phase diagrams for lipid mixtures were introduced ("Lateral phase separations in phospholipid membranes" (17)). Many of the papers appearing in this issue of *Biophysical Journal* demonstrate how spin labelling technology has developed recently.

Studies by epifluorescence microscopy of domains in lipid monolayers has revealed two-dimensional chiral shapes ("Two-dimensional chiral crystals of phospholipid" (18)). The theory of formation of these structures involves competition between line tension and in-plane dipole-dipole repulsions between molecular dipoles and has been derived independently by McConnell and collaborators ("Theory of superstructures in lipid monolayer phase transitions" (19); and "Shapes of finite two-dimensional lipid domains" (20)), and by de Gennes and collaborators (21).

Lipid bilayers supported on solid surfaces were developed to study cell-cell (cell-membrane) recognition in the immune system ("Antigen presentation by supported planar membranes containing affinity purified I-$A^d$" (22); and "Biophysical aspects of antigen recognition by T cells" (23)). This technique has allowed the kinetics of interaction of peptide and MHC class II cell-surface proteins to be studied quantitatively ("A kinetic intermediate in the reaction of an antigenic peptide and $IE^k$" (24)). Another area of molecular recognition in

immunology has employed NMR difference spectroscopy with antibodies directed to spin labeled haptens ("Structural and kinetic studies of the Fab fragment of a monoclonal anti-spin label antibody by NMR" (25)).

In 1983, Molecular Devices Corporation was founded by McConnell with the mission of interfacing silicon-based electronic devices directly with biological systems. The Light-Addressable Potentiometric Sensor (LAPS), a low-impedance device employing AC photocurrents to measure surface potential, was developed ("Light addressable potentiometric sensor for biochemical systems" (26)). The sensor has been developed into a device for detecting metabolic events in a very small population of eukaryotic cells and is being applied as a means for replacing animals in toxicology studies, and for screening for new receptor ligands and therapeutic drugs ("The cytosensor microphysiometer: biological applications of silicon technology" (27)).

The articles collected in this volume cover a wider range of topics on biology and chemistry than might normally be seen in this journal, but these articles share a remarkably consistent voice, based on fundamental physical and chemical principles, and based on the courage to apply these principles to complex biological systems. Each of these authors owes a great debt to Harden McConnell for leading the way in articulating this voice.

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