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JOHN WARREN WILLIAMS

*1898—1988*

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*A Biographical Memoir by*

ROBERT L. BALDWIN AND JOHN D. FERRY

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J. W. Williams

# JOHN WARREN WILLIAMS

*February 10, 1898–March 5, 1988*

BY ROBERT L. BALDWIN AND JOHN D. FERRY

JOHN WARREN WILLIAMS had broad research interests, ranging from basic physical chemistry to the nature of the antigen-antibody reaction. Williams was one of the first to deduce molecular structure from measurements of dipole moments using theory formulated by P. J. W. Debye. He became interested in macromolecules, and, after a sabbatical year with The Svedberg, Williams established the leading American school for the development of physical methods, especially ultracentrifugation, for studying biological macromolecules. He also made important contributions to the determination of size distributions for flexible polymers. He had a strong guiding influence on the evolution of colloid chemistry to modern macromolecular chemistry. His students include well-known chemists and biochemists.

John Warren Williams was born in Woburn, Massachusetts, on February 10, 1898. His parents, both born in Portland, Maine, first met much later in Massachusetts and were married in 1896. His father, Charles Sampson Williams, graduated in chemistry from the University of Maine and had some graduate work at Harvard. His mother, née Genevieve Allen, was a graduate of Gorham Normal School in Maine and taught high school in Massachusetts before her marriage. She instilled in her children a firm respect for schol-

arship. Most of Charles Williams's career was spent as a chemist for the Travelers Insurance Company in Hartford, Connecticut. Jack, as he was always known (he disliked the name John), acquired an early interest in science in his father's laboratory.

Jack Williams attended Trinity College in Hartford, but his undergraduate years were interrupted by brief service in the U.S. Navy during the First World War. After the war, he enrolled in chemical engineering at the Worcester Polytechnic Institute and received a B.S. degree in 1921. He wanted to continue with graduate work, and since Ph.D. degrees were not offered in chemical engineering at that time, he changed to chemistry. His choice of the University of Wisconsin at Madison was probably influenced by Farrington Daniels, who had taught at Worcester Polytechnic and joined the Department of Chemistry at Wisconsin in 1920. His graduate research there, supervised by Daniels, was concerned with the heat capacities of binary mixtures of organic liquids, and he received his Ph.D. degree in 1925.

Williams was then immediately appointed instructor in chemistry at Wisconsin, and remained there for his entire career, advancing to full professor in 1938 and becoming emeritus in 1968. He married Lois Mary Andrews in 1925. She was born in New Britain, Connecticut, and they met in high school in Hartford. Their daughter, Janet Andrews, was born in 1931.

Williams's first independent research began with measurements of the dielectric constants of liquid mixtures. His interest in the electrical properties of matter was probably influenced by close contacts with the departments of physics and mathematics, where Max Mason and Warren Weaver were collaborating on their classic treatise, *The Electromagnetic Field*. After one exploratory paper, Williams undertook a long series of studies in which the dipole mo-

ments of polar molecules were calculated from precise measurements of the dielectric constants of their solutions in nonpolar solvents. He used Debye's theory, which involves extrapolation of the molar polarization of the polar component to infinite dilution. Jack Williams built his own instruments for both resonance and bridge methods, and meticulously purified his materials. By mid-1927, he and his students had determined the dipole moments of some thirty compounds and shown that, in several cases, the results were essentially independent of the choice of the nonpolar solvent.

Debye, whose laboratory at Leipzig was the world center for research on dipole moments (and, of course, solutions of electrolytes and other aspects of electrochemistry), had given a course of lectures at Wisconsin in the spring of 1927, and became acquainted with Williams's work. Williams was awarded a National Research Council Fellowship to spend the academic year 1927–28 abroad, mostly with Debye at Leipzig. There, and after his return to Madison, he continued his thorough and sustained investigations of dipole moments of more than a hundred compounds, including many mono and disubstituted derivatives of methane, ethane, benzene, diphenyl, and cyclohexane. Some of these were synthesized by collaborators at Leipzig. The results were analyzed in terms of vector addition of moments of bonds and substituent groups, including deviations from planarity in aromatic compounds, and free or restricted rotation around bonds as influenced by steric hindrance.

Williams's fellowship abroad in 1927–28 included two months with J. N. Brönsted at Copenhagen, and his work there on activity coefficients of strong electrolytes was briefly continued later in Madison.

In 1929 Williams turned his attention to the frequency dependence (dispersion) of the dielectric constant. Debye

had formulated the theory of so-called anomalous dispersion in polar liquids in terms of the rotational relaxation time of a molecule modeled as a sphere with rotary Brownian motion in a viscous medium, and several investigators had shown that the sphere radii calculated by this treatment from data on polar liquids were roughly correct but often implausibly small. Since the theory was strictly applicable to a dilute solution of a polar molecule in a nonpolar solvent rather than to an undiluted polar liquid, Williams studied nitrobenzene and nitronaphthalene as solutes and chose mineral oils as solvents with the expectation that their high viscosities would place the dispersion in an accessible frequency range (below  $3 \times 10^7$  Hz). The dispersion, when observed, corresponded to a relaxation time about ten times smaller than calculated from the solution viscosity and the estimated molecular dimensions, and in most cases the experimental frequency range was not high enough to observe any frequency dependence at all. Williams and his student J. Lawrence Oncley reached the important conclusion that the local frictional resistance to rotation of the small solute molecule surrounded by the larger oil molecules was much less than the macroscopic viscosity would imply; and that a proper test of the theory should be made with a polar solute of colloidal dimensions, large enough so the solvent could be considered as a continuum.

Subsequently, Williams and his students chose for this purpose the proteins zein, gliadin, and secalin, with molecular weights in the range of 25,000–40,000, which, unlike most proteins, are soluble in alcohol-water mixtures with conductivities low enough to make dielectric constant measurements by the same methods used for solutions in organic liquids. For zein, the frequency dependence corresponded to two relaxation times which could be attributed to rotation of an ellipsoid of revolution about its major and

minor axes; the size of the ellipsoid agreed reasonably with the molecular weight as determined by sedimentation and diffusion. Thus, the frictional resistance to rotation for a solute molecule of this size did reflect the macroscopic viscosity of the solution. (Meanwhile, Oncley at Harvard had developed an impedance bridge method for dielectric measurements over a wide frequency range on aqueous solutions with substantially higher conductivities. This permitted measurements on many other proteins; he showed how rotational relaxation times for these macromolecules could be combined with diffusion and viscosity data to estimate both the axial ratio of an ellipsoid model and hydration.)

In addition to analyzing the rotational motions of macromolecules, Williams turned to translational motion as revealed by measurements of sedimentation and diffusion. During Williams's graduate student years, The Svedberg was a visiting professor at Wisconsin and in 1923 conceived the prototype of the ultracentrifuge. After returning to his laboratory at Uppsala, Svedberg perfected the oil turbine velocity ultracentrifuge and within a few years had revolutionized the chemistry of proteins by showing that they were not heterogeneous colloids but monodisperse. In 1934-35, Williams spent a year with Svedberg as a fellow of the International Education Board, to study the technique and theory of ultracentrifugation. Then an opportunity, unusual for that period in history, presented itself.

In 1932, Warren Weaver became director of the Natural Sciences Division of the Rockefeller Foundation, and recommended an extensive program of research support in which the techniques and methods of the physical sciences would be applied to problems in the biological sciences. One item in this broad program was the installation of an oil turbine ultracentrifuge at an American university; at that time, there was none in the United States. The foundation

chose Williams's laboratory for its location. There was actually some reluctance on the part of the State of Wisconsin to accept this funding, and some of Williams's colleagues erroneously accused him of having solicited it. In the end, the grant was approved, and in 1936-37 the massive velocity ultracentrifuge was installed at Madison as well as a smaller electrically driven machine for equilibrium sedimentation measurements. The university authorities were worried about the danger of an exploding rotor, and a separate underground room was constructed to house the velocity centrifuge, separated from the chemistry building by a heavy wall. This and a similar instrument at the DuPont Laboratories in Wilmington, Delaware, were the only oil turbine centrifuges ever located in the United States.

Not long after installation of the ultracentrifuge, Jack Williams took up a problem that would interest him for many years: the isolation of antibodies and the nature of the antigen-antibody reaction. In 1939, A. M. Pappenheimer, Jr. came on a visit to Williams's laboratory and, together with Harold Lundgren, they began to measure the molecular weights of diphtheria toxin and antitoxin and to analyze the stoichiometry of the soluble complexes that are formed in antigen excess. The aim was to provide a physico-chemical framework for Marrack's lattice theory of antigen-antibody precipitation. Later Mary Petermann, who had earlier worked with Pappenheimer, joined Williams's laboratory, and they undertook the task of isolating active proteolytic fragments of antibodies. The existence of such fragments was claimed in a patent by Parfentjiev. With the ultracentrifuge they were able to demonstrate the presence of active fragments, but the time was not ready for structural characterization, particularly because modern methods of protein isolation were not available.

In World War II Jack Williams was fortunate to be as-

signed a research task that allowed him to follow his interest in antibodies. He participated in the program organized at Harvard Medical School by Edwin J. Cohn and John T. Edsall, of fractionating proteins from human plasma. Williams would use the ultracentrifuge and electrophoresis to measure size and purity of the fractionated proteins. He soon became interested in subfractionating the antibody-containing  $\gamma$ -globulin:  $\gamma_1$  and  $\gamma_2$  globulins could be observed by moving boundary electrophoresis. He enlisted the collaboration of Harold Deutsch in the Physiological Chemistry Department at Madison, and several of his own students, notably Robert Alberty, Eugene Hess, and Louis Gosting, joined in. Alberty went on to show that boundary-spreading measurements demonstrated the existence of antibody molecules with different isoelectric points within the  $\gamma_1$  and  $\gamma_2$  globulin fractions, and at Caltech John G Kirkwood built an electrophoresis convection apparatus which could separate molecules according to their isoelectric points. Later, Kirkwood's student Richard Goldberg would come to Williams's laboratory to work on his statistical theory of lattice formation in the antigen-antibody reaction, and to make novel contributions to ultracentrifuge theory. While the work on antibody fractionation and characterization was in progress, Michael Heidelberger, the immunologist, often came to Madison to see his son Charles, and he was a frequent visitor to Williams's laboratory.

Another World War II task was to study the physico-chemical properties of gelatin (which is almost non-antigenic), to evaluate its possible use as a blood plasma extender for shock victims. A short report, "Size distribution in gelatin solutions," was coauthored by George Scatchard, J. Lawrence Oncley, Williams, and Alexander Brown in 1944. Williams became deeply interested in developing ultracentrifugal methods for determining molecular weight distributions of

polymers, and after the war he developed both sedimentation velocity (boundary spreading) and sedimentation equilibrium methods. Michael Wales and later Hiroshi Fujita made notable contributions. Jack Williams considered it natural to study proteins and synthetic polymers in the same laboratory. He believed that insights into the physical behavior of polymers would be useful in understanding proteins, and vice versa, and that ultimately both would be considered part of one field, the physical chemistry of macromolecules.

After the war, Jack Williams turned his attention to improving the theory and methods of ultracentrifugation. His timing was good: biochemists in large numbers were beginning to study proteins and nucleic acids and ultracentrifugation became a major analytical tool for their study. The development of the direct-drive Spinco ultracentrifuge provided an accurate and easily operated instrument, and many biochemists began to use analytical ultracentrifuges. At that time, protein molecular weights were measured chiefly from sedimentation velocity and diffusion experiments, by use of the Svedberg equation. It had become easy to measure sedimentation coefficients accurately but the same could not be said of diffusion coefficients. Gerson Kegeles and Louis Gosting in Williams's laboratory gave a theory for the interference fringes, first observed by Gouy in 1880, that are seen when light traverses a diffusing boundary, and Gosting then went on to develop an instrument for making highly accurate measurements of diffusion in liquids. At Oxford, Coulson, Cox, Ogston, and Philpot independently obtained a theory for the outermost Gouy fringe and used it to make rapid measurements of diffusion coefficients. Louis Gosting remained closely associated with Williams's research group until Gosting's tragic early death. Gosting enjoyed explaining the intricacies of Gibbsian thermodynamics, and his

counsel, both on experimental and theoretical problems, was of great value to Jack Williams and his research group.

At the end of the 1950s, sedimentation equilibrium began to replace sedimentation-diffusion as the method of choice for measuring the molecular weights of proteins. This happened when Kensal Van Holde and Robert Baldwin, who not long before had been members of Williams's research group, used the Mason-Weaver solution to the differential equation for the ultracentrifuge to show that equilibrium could be reached in a day instead of two weeks, by using a short column of solution. The classic 1923 paper on sedimentation equilibrium by Max Mason and Warren Weaver, both then at Wisconsin, was inspired by Svedberg's extended visit to the Chemistry Department at Madison.

Major advances in ultracentrifuge theory were made after the arrival in 1954 of a Japanese postdoctoral research fellow, Hiroshi Fujita. Jack Williams considered Fujita to be his best discovery. Fujita had a remarkable facility for finding analytical solutions to difficult problems, and it often took him only a day to find a solution to a new problem. Soon after he arrived, Fujita solved the long-standing problem of how the combined effects of diffusion and the concentration dependence of a solute's sedimentation coefficient determine the shape of a sedimenting boundary, and he and Victor MacCosham obtained a useful solution to the differential equation of the ultracentrifuge for molecules of intermediate sizes. Hiroshi Fujita continued to make regular visits to Williams's laboratory after he became a professor at Osaka, and his book on the mathematical theory of the ultracentrifuge became the standard work on this subject.

These improvements in sedimentation theory were particularly important for study of synthetic polymers because of the wide distribution of molecular weights, much greater

deviations from thermodynamic ideality, and also the greater compressibility of the organic liquids used as solvents, as compared to aqueous solutions of proteins. From equilibrium measurements at different concentrations and rotor speeds, it was finally possible to determine the entire molecular weight distribution as well as the second virial coefficient which characterizes the thermodynamic interaction between polymer and solvent.

Two important discoveries in polymer physical chemistry were made in Williams's laboratory. With Wilbur B. Bridgman in 1937, he measured dielectric constants of solutions of poly- $\omega$ -hydroxydecanoic acid with different molecular weights up to 14,000 and found no frequency dependence in a range where it would be expected for global rotation of the molecule. Moreover, the square of the dipole moment was a linear function of the degree of polymerization. Both observations confirmed the presence of free rotation around chain backbone bonds of such a linear polymer, at a very early stage in the development of this concept. With Kensal E. Van Holde in 1953, he determined viscosities and steady-state compliances (a measure of elastic recovery) of a series of polyisobutylene samples and found that the latter, surprisingly at the time, correlated not with the molecular weight but with the molecular-weight distribution. These discoveries were not followed up in Williams's laboratory, since they were outside the general theme of his research, but later theories explained Van Holde's results and stimulated an enormous volume of work on mechanical properties of blends and other polydisperse polymers.

Only rarely did Jack Williams's name appear on the research papers of his students and postdoctoral fellows after his work on dipole moments ended. Partly this custom reflected his modest and generous temperament, partly it reflected his policy of making students independent research

workers as soon as possible. He had a gift for developing research ability. He had a deep concern for the welfare of his students and other collaborators, and maintained contact with them and assisted them in their subsequent careers.

He was a stimulating teacher who used unconventional expositions and problems. He was especially attentive to the development of the undergraduate physical chemistry laboratory. Here he had a keen sense for spotting research talent and identifying promising students for graduate work. Through the fellowship committee of the Graduate School, he was instrumental in bringing to the university numerous graduate students who later became leaders in science. Of his own students and associates, many progressed to prominent positions and several were elected to the National Academy. He enjoyed his many international associations; he travelled widely, and was one of the first American scientists to visit the Soviet Union, in 1935.

Williams's honors included election to the National Academy of Sciences, 1952; the Kendall award in Colloid Chemistry, 1955; Nobel Guest Professor, Uppsala, 1968; and Hon. D.Sc., Worcester Polytechnical Institute, 1973.

Jack Williams was a true gentleman, always courteous and understanding in his associations with others. His conversations were livened by sparks of humor and unexpected anecdotes. He never lost his boyish smile or his contagious enthusiasm for science. His smile made him appear younger than he was. On a visit to Harvard early in World War II, he was invited to dinner by a Harvard colleague whose wife greeted Jack Williams at the door with "young man, why aren't you in the army?" He didn't tell her that he was several years older than her husband. He was fond of his summer home on Lake Michigan on the Door County peninsula of Northeastern Wisconsin. In later years, he often

spent several winter weeks at the California Institute of Technology, where he had been visiting professor in 1946–47 and 1953–54.

After retirement in 1968 at the age of seventy, Jack Williams continued work with postdoctoral associates for several years, mostly on self-association equilibria of proteins as determined from sedimentation equilibrium. Until the age of eighty-seven he kept an office in the chemistry building, where in later years he continued writing, including preparations of biographies of the two scientists who he felt had profoundly influenced his scientific career and whom he always held in high esteem: Peter J. W. Debye (NAS *Biographical Memoirs*, 1975) and The Svedberg (whose biography he did not complete). He died at Madison a few weeks after his ninetieth birthday, on March 5, 1988. His wife had died in 1980. He is survived by his daughter, Janet Williams Coussens, three grandsons, two great-grandsons, and his sister. His friends and colleagues and the scientific community will remember him with gratitude as a discerning and dedicated scientist, and a benevolent and generous person.

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