Robert A. Alberty
1921–2014

BIOGRAPHICAL *Memoirs*

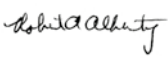
A Biographical Memoir by
Gordon G. Hammes
and Carl Frieden

NATIONAL ACADEMY OF SCIENCES

ROBERT ARNOLD **ALBERTY**

June 21, 1921–January 18, 2014

Elected to the NAS, 1965



By Gordon G. Hammes and Carl Frieden

Robert A. Alberty maintained an enthusiasm for science throughout his entire life. His presence at meetings was easily detectable, as he was blessed with an unmistakable and booming voice that conveyed his latest scientific interests and above all his continual commitment to the science enterprise. Alberty directed this passion to thermodynamics and kinetics in particular, especially as applied to biological systems, and his research in these areas established a rich legacy for modern biophysical chemistry. He was a "triple-threat" scientist, excelling not only in research but also in teaching and university administration.

Alberty (Bob to all who knew him) was born in Winfield, Kansas, but when he was five years old his family moved to Lincoln, Nebraska. Even as a boy, he displayed a strong interest in science, exemplified by a basement chemistry laboratory and photographic dark room that he built in the family's home.

When he entered the University of Nebraska in 1939, Alberty had been planning a career as a chemical engineer, but then he discovered that this would require extensive coursework in drafting and surveying. Because he had already learned surveying from his grandfather, he saw no need to take college courses in the subject. Thus he became a chemistry major. His undergraduate research involved measuring the pressure of surface films with the Langmuir balance. Alberty obtained both a bachelor's (1943) and master's (1944) degree from the University of Nebraska. His master's thesis was on the phase equilibrium of the benzene-isobutyl alcohol-water system. In that same year, 1944, he married Lillian Wind, whom he had met when they were both officers in their high-school chemistry club. They enjoyed 66 years together until her death in 2010.

Alberty continued his graduate education at the University of Wisconsin, no doubt influenced by some pleasant summers his family had spent in Madison. His research project, under Professor Jack Williams, involved making new medical products from blood plasma; specifically, Alberty used ultracentrifugation and electrophoresis to fractionate blood proteins and isolate gamma globulins (antibodies), which were used on the battlefield (during the ongoing World War II) to strengthen the immune systems of soldiers. His Ph.D. thesis (1947) involved the study of boundary spreading in the electrophoresis of gamma globulins. As part of this project, he was fortunate to interact with some of the great protein chemists of that era: John Edsall, Lewis Longsworth, Larry Oncley, and Michael Heidelberger.

Bob Alberty *circa* 1947.

Alberty became an instructor at the University of Wisconsin in 1947 and continued his doctoral research, developing both the theoretical and experimental aspects of protein electrophoresis. This technique was at that time one of the few quantitative methods available for characterizing the size and charge of proteins. However, he was eager to move on to a new field—enzyme kinetics—having been especially intrigued by the thinking of Linus Pauling with regard to the complementary structures of enzymes and substrates. Pauling had suggested that enzyme-substrate interactions were similar to those of antibodies, such as gamma globulins, when interacting with small molecule antigens. In 1950, Alberty received a Guggenheim Fellowship to spend time with Pauling at Caltech. During that period, Alberty began his studies of the enzyme fumarase, developing a spectrophotometric assay using the first Beckman DU spectrophotometer with a chart recorder. After having noticed that the absorbance

between 0 and 0.1 was almost linear, he had special chart paper made for the recorder, which greatly improved researchers' ability to make measurements.

Up to this time, Alberty's research program had been primarily supported by the Wisconsin Alumni Research Foundation. However, this source alone became insufficient, and he applied to the Office of Naval Research for additional funds. The result was that he received one of the first National Science Foundation (NSF) research grants, as the newly formed NSF funded some of the proposals submitted to the Office of Naval Research. This grant allowed him to expand his research program into the field of enzymology.

The study of the kinetics of enzyme-catalyzed reactions was in a rudimentary state at the beginning of the 1950s, consisting mainly of the routine measurement of maximum velocities and Michaelis constants, often with impure enzymes. An understanding of what these parameters meant in terms of mechanism was limited by the Michaelis-Menten mechanism proposed many years earlier. Detailed studies of the pH- and temperature-dependence of enzyme reactions, the use of isotopes, consideration of multiple substrates, and the development of fast-reaction technology remained to be done. Alberty was one of a small number of scientists who recognized that these options were ready for development using quantitative physical chemistry methodology, which required pure enzymes, robust theoretical frameworks, and the use of modern physical chemistry experimental techniques. His work in these areas set a standard for the field, and the principles he uncovered are still important to researchers today.

The Alberty laboratory's study of the enzyme fumarase represented one of the most complete and incisive studies of an enzyme at that time, providing the first careful analysis of what information could be obtained from steady-state kinetics, and were generalizable to other enzymatic reactions. Although his primary interest was in kinetics, he also used many other methods, such as nuclear magnetic resonance (NMR), in this research.

Alberty focused on fumarase for several reasons: it was relatively simple as a single-substrate and single-product reaction, involving the interconversion of fumarate to L-malate by the addition of water across the double bond of fumarate; the equilibrium constant was close to unity, so that the reaction could be studied in both directions; and a continuous spectrophotometric assay was available. Obtaining purified fumarase was no easy matter. It involved trips to the Oscar Mayer slaughterhouse to obtain the starting material—fresh pig hearts—and required extensive purification thereafter. Members of

the Alberty research group had to be adept at dodging pig hearts thrown to them by the workers (usually laughing) cutting them out of the slaughtered pigs.

In 1953, Robert Bock and Alberty demonstrated the relationship between the steady-state parameters and the equilibrium constant, a relationship that had been suggested much earlier by J. B. S. Haldane. In 1954, Carl Frieden crystallized fumarase and determined its physical properties. The framework for the analysis of the pH dependence of the steady state-parameters was developed with Vincent Massey (1954). Subsequently, Alberty determined that plots of the maximum velocity versus pH, and of the maximum velocity divided by the Michaelis constant versus pH, could be used to derive information about the ionization constants of the protein side chains required for catalytic activity. Moreover, the fact that the maximum velocities for the forward and reverse reactions had different pH dependences implied the occurrence of at least two intermediates in the traditional Michaelis-Menten mechanism.

In 1957 the Alberty group, using the then-new method of NMR, determined the stereospecificity of the addition of water to the double bond of fumarate. In 1958, Alberty and Gordon Hammes noted that the second-order rate constant for the combination of substrates with enzymes was unusually large, and they applied the theory of diffusion-controlled reactions to calculate maximum rate constants for these reactions. Subsequently, the second-order rate constants for the binding of substrates and inhibitors to many enzymes were found to approach the values expected for diffusion-controlled reactions. In 1960, inspired by the work of Manfred Eigen, Hammes and Alberty published a paper on the kinetic relaxation spectrum of simple enzymatic reactions, the first treatment of enzymatic reactions using this methodology.

In 1959, Leonard Peller and Alberty published a definitive analysis of exactly what kinetic and equilibrium information could be obtained from steady-state enzyme kinetics. This analysis, of a multiple intermediate mechanism for a single substrate and product, remains a landmark publication in the enzyme kinetics field. The researchers demonstrated that traditional Michaelis constants and maximum velocities could be used to determine lower bounds for all of the rate constants in an enzymatic reaction mechanism containing an arbitrary number of intermediates. They also showed that the ionization constants derived from steady-state kinetics are generally complex constants, except for those derived from plots of the maximum velocity divided by the Michaelis constant versus pH. These plots usually can be used to derive ionization constants of the enzyme without bound substrate that are critical for catalysis. Moreover, these plots

should be identical for the forward and reverse reactions. Peller and Alberty, together with Victor Bloomfield, subsequently followed up this work with a similar analysis of multi-substrate enzyme reactions (1962–63).

Although somewhat out of the mainstream of the research being done in Alberty's laboratory, he and Rex Smith determined the equilibrium constants for hydrogen-ion and metal-ion binding to nucleotide phosphates (1953, 1956). This work stemmed from his discovery, using electrophoresis, of impurities in commercial preparations of adenosine triphosphate (ATP), and it demonstrated his early recognition of the importance of knowing all of the individual ionic species present in biological solutions. He returned to this issue later in his career with the development of the thermodynamics of biological systems, a topic discussed a few pages below.

Being a member of the Alberty research group was a wonderful experience, and not just for the richness of the group's findings. Group meetings were very open, with Alberty continually posing new ideas and encouraging others to do so as well. Students and postdocs were allowed to choose research problems from the myriad of resulting suggestions—basically anything was okay as long as it was relevant to the overall goals of the lab. Similarly, the parties at the Alberty home—attended by his entire family, the research group, and whomever they wished to invite as guests—were memorable. The Albertys had three children: Nancy (born December 18, 1945), Steven (April 8, 1947), and Catherine (January 25, 1952). Catherine Alberty Baxter commented in a eulogy for her father that his students and postdocs at Wisconsin were themselves like family.

The important contributions of Alberty's research program at the University of Wisconsin were well recognized by the science community. He received the Eli Lilly Award from the American Chemical Society in 1955, was elected to the National Academy of Sciences (NAS) in 1965 and to the American Academy of Arts and Sciences in 1968, and received honorary degrees from Lawrence College and the University of Nebraska in 1967.

Alberty was especially interested in the development of young scientists, and many of his graduate students and postdocs went on to distinguished careers both in academia and industry. The NAS counts two of his trainees and two scientific "grandsons" among its members.

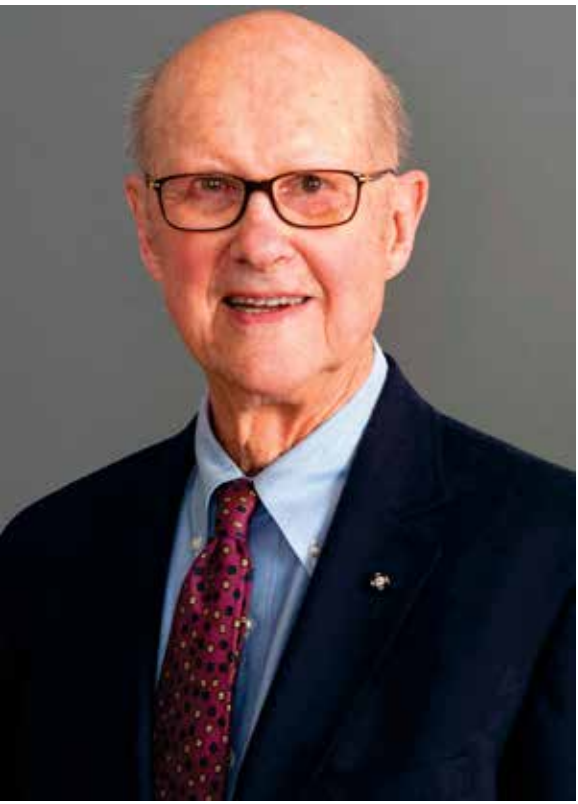
Because of his reputation as a caring advisor and mentor to students and young researchers, Alberty was urged to participate in university administration, and in 1961 he became associate dean of letters and sciences at Wisconsin. The dean, Edwin Young,

was an economist, and he relied on Alberty to take care of the sciences. In 1963 Alberty became dean of the Graduate School. This position is one of the most important and powerful at Wisconsin because the dean also is chair of the Research Committee, which receives a large annual grant from the Wisconsin Alumni Research Foundation (WARF) and in turn makes research grants to faculty. WARF itself is funded from income generated by patents awarded to the University of Wisconsin, most notably for the addition of Vitamin D to milk and the synthesis of warfarin—a commonly used anticoagulant ("blood thinner") for human patients as well as a rat poison. WARF also supports many graduate students through fellowships and research assistantships.

When Alberty joined the faculty at Wisconsin, he immersed himself in the classroom teaching of undergraduate physical chemistry and soon became very successful at it. But his most lasting contributions to the undergraduate teaching of physical chemistry may be his textbooks. In 1949 he coauthored *Experimental Physical Chemistry,* a laboratory textbook that was very popular nationwide. This coauthorship continued through multiple editions. In 1955 he coauthored *Physical Chemistry* with Farrington Daniels. Ever humble and open to feedback, when Alberty taught the undergraduate course he kept a drawer full of coins, and any student who found an error in the book received a quarter (which was worth something at that time).

The textbook *Physical Chemistry* has had a long history. Its first version, by Frederick H. Getman, appeared in 1913, so that its lifetime now spans more than a century. Alberty eventually became the sole author and later took on coauthors again. Never one to stop writing, another edition of *Physical Chemistry*, written with R. J. Sibley, was published in 1992. This was followed by three more editions written over the next 13 years, with the most recent version appearing in 2005 and a new edition scheduled for 2016. Alberty's participation in the writing of this monumental book spanned some 50 years. In its various incarnations, it has proved to be the most popular and enduring physical chemistry textbook of all time. Thousands, perhaps millions, of students have learned their physical chemistry from it. Moreover, each edition was a major rewriting, with additions and deletions that made it appropriate for the standards of its day.

Although content at the University of Wisconsin, in 1967 Alberty accepted the position of dean of science at the Massachusetts Institute of Technology (MIT). Knowing this job would likely take all of his time, he decided to forgo research and closed his laboratory. It turned out that he was right, as the next several years would be difficult ones at MIT, and at many other schools throughout the nation, because of student ferment regarding



Bob Alberty, late-career portrait.

the war in Vietnam. Alberty was asked to be the administrative representative on a student center committee, a position that required constant attention. Around the same time, MIT wanted to start a medical school, with a combined M.D.-Ph.D. program being of particular interest. The National Institutes of Health, however, would only support the already-established medical school at Harvard University, and so the Harvard-MIT Medical Science Training Program was born.

During his time as dean of science Alberty was involved in many changes in the undergraduate programs at MIT. In spite of his administrative duties, he taught portions of the biophysical chemistry course for several years, but he found little time to write scientific papers. In addition to helping to develop a joint MIT-Harvard University M.D.-Ph.D. program, Alberty was involved in the establishment of the Cancer Research Center, now the Koch Institute for Integrative Cancer Research, and was the first cochairman of MIT's exchange program with Wellesley College. One of his colleagues, Robert Haslam, stated that as dean of science, Alberty "was always available to his colleagues, and always optimistic about finding funding for many endeavors to benefit chemistry and the Institute as a whole.…He liked nothing better than to convey good news about tenure."

During 1975–1977, Alberty chaired the National Research Council's Human Resources Division, which produced an annual survey of doctorates. He also served on the NRC committee that produced the report *Prudent Practices in the Chemical Laboratory* (1981); the National Academy Press sold more copies of this book than any of its previous

publications. He chaired the committee that wrote the follow-on report *Prudent Practices for the Disposal of Chemicals in the Laboratory* (1983). Alberty also became an advisor to the Dreyfus Foundation, a position he occupied for 30 years and in which he championed the support of young scientists.

"I think the moral is that sometimes in research it is a good idea to spend some time in another field, because you may come back and see your previous field in a new light."

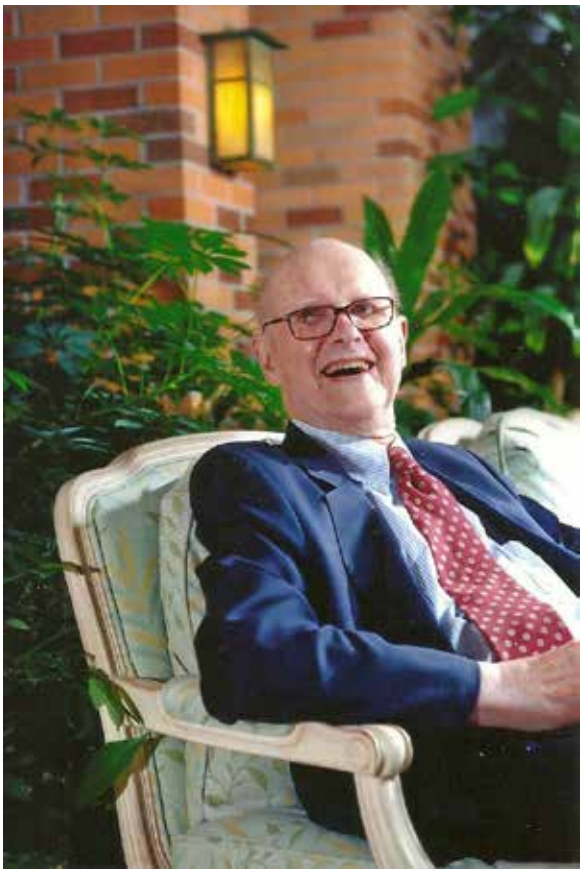
When Alberty stepped down as dean of science in 1982 he wanted to renew his interest in research. He had no desire, however, to reestablish an experimental research program of the past. Instead, he focused on the theoretical aspects of thermodynamics and kinetics. He had grown fascinated with the increasing power of computers to make calculations on complex systems and, at the same time, was increasingly concerned that fossil-fuel sources such as petroleum would eventually be depleted. Because of a long-time interest in thermodynamics, he applied for and received financial support from the U.S. Department of Energy to carry out thermodynamic calculations related to petroleum processing.

A series of papers ensued between 1983 and 1991 dealing with the thermodynamics of organic molecules. Alberty later stated in his autobiography that the 10 years he spent working on petroleum processing taught him a lot of thermodynamics that he later used for studying enzyme systems. For example, when he published a paper on the use of semigrand ensembles in chemical equilibrium calculations regarding complex organic systems (1989), he realized that this concept was needed in his research dealing with the thermodynamics and kinetics of enzyme-catalyzed reactions. In a "Reflections" article for the *Journal of Biological Chemistry* (2004), he stated "I think the moral is that sometimes in research it is a good idea to spend some time in another field, because you may come back and see your previous field in a new light."

Alberty's work on the thermodynamics of biological reactions began in 1991, and he became a professor emeritus in the Department of Chemistry at MIT in 1992. (Faculty members were required to retire at age 70.) However, his research output continued unabated after retirement as he explored the thermodynamics and kinetics of biological systems, particularly enzymes. He was especially interested in finding a consistent method for dealing with the many different ions present in biological systems—hydrogen ions, for example. The thermodynamics of enzyme-catalyzed reactions, and the use of the

rapid equilibrium assumption relative to enzyme kinetics, became focal points of his research.

In 1992 Alberty began writing a series of papers dealing with transformed thermodynamic properties of biochemical reactants at specified pH and Mg concentration. This work included a return to his interest in the hydrolysis of ATP, as well as an effort to generalize the concept to ligand binding in biochemical systems. He believed that biochemical thermodynamics needed the use of Legendre transformed thermodynamic properties because pH is an independent variable much like temperature and pressure. His research in these areas led to new types of thermodynamic functions for calculating apparent equilibrium constants and heats of chemical reactions, and it is summarized in two books: T*hermodynamics of Biological Reactions* (2003) and *Biochemical Thermodynamics: Applications of Mathematica* (2006).



Bob Alberty on his 90th Birthday.

Alberty became especially fascinated with Mathematica (a computational software program based on symbolic mathematics) as a tool for calculating thermodynamic functions, and both of the books contain computer programs and multiple illustrations for calculating thermodynamic parameters as a function, for example, of temperature, pH, or ionic strength. He also chaired a joint committee of the International Union of Pure and Applied Chemistry and the International Union of Biochemistry and Molecular Biology that issued recommendations for biochemical-thermodynamics terminology and databases (2011).

Alberty's research on biochemical thermodynamics led him to a detailed consideration of rapid-equilibrium enzyme kinetics, the assumption that all steps are in equilibrium prior to the rate-determining step of the chemical transformation. This work, involving simulations and the development of methods for extracting steady-state kinetic parameters from the data, again used Mathematica as a primary tool. He published the results in a book, *Rapid Equilibrium Applications of Mathematica* (2011), that contained computer code and many examples of enzyme mechanisms. This final publication appeared when Alberty was 90 years old.

Alberty's accomplishments covered an enormous range, and they spanned his entire lifetime. They included undergraduate and graduate classroom teaching, influential textbooks, the mentoring of young scientists, an outstanding research program concerned with enzyme kinetics, the development of new concepts in the treatment of biochemical thermodynamics, and high-level university administration. Truly a man for all seasons, he was an outstanding scholar with a warm personality enjoyed by all of his many colleagues and students.

ACKNOWLEDGEMENTS

We obtained much of the material for this memoir from the "Robert A. Alberty Festschrift" published by the *Journal of Physical Chemistry B* (Volume 114, Issue 49:16045–16676) on December 16, 2010—a document that included an Alberty autobiography. We also are indebted to Catherine Alberty Baxter for reviewing this memoir and supplying the photographs.

SELECTED BIBLIOGRAPHY

1949 With F. Daniels, J. H. Matthews, J. W. Williams, P. Bender, and G. W. Murphy. *Experimental physical chemistry.* New York: McGraw-Hill.

1953 With R. M. Bock. Studies of the enzyme fumarase I. Relation between kinetics and equilibrium. *J. Am. Chem. Soc.* 75:1921–1925.

1954 With V. Massey. On the interpretation of the pH variation of the maximum initial velocity of an enzyme (catalyzed reaction). *Biochim. Biophys. Acta* 13:347–353.

With C. Frieden and R. M. Bock. Studies of the enzyme fumarase. II. Isolation and physical properties of crystallized enzyme. *J. Am. Chem. Soc.* 76:2482–2484.

1955 With F. Daniels. *Physical chemistry, First edition*. New York: John Wiley and Sons.

1956 With R. M. Smith. The apparent stability constants of ionic complexes of various adenosine phosphates with divalent cations. *J. Am. Chem. Soc.* 78:2376–2380.

1957 With T. C. Farrar, H. S. Gutowsky, and R. A. Miller. The mechanism of the stereospecific enzymatic hydration of fumarate to L-malate. *J. Am. Chem. Soc.* 79:3978–3980.

1958 With G. G. Hammes. Application of the theory of diffusion-controlled reactions to enzyme kinetics. *J. Phys. Chem.* 62:154–159.

1959 With L. Peller. Multiple intermediates in steady-state enzyme kinetics. I. The mechanism involving a single substrate and product. *J. Am. Chem. Soc.* 81:5907–5914.

1960 With G. G. Hammes. The relaxation spectra of simple enzymatic mechanisms. *J. Am. Chem. Soc.* 82:1564–1569.

1962 With V. Bloomfield and L. Peller. Multiple intermediates in steady-state enzyme kinetics. II. Systems involving more than a single reactant and product. *J. Am. Chem. Soc.* 84:4367–4374.

1989 With I. Oppenheim. Use of semigrand ensembles in chemical equilibrium calculations on complex organic systems. *J. Chem. Phys.* 91:1824–1828.

2003 *Thermodynamics of biochemical reactions*. Hoboken, NJ: John Wiley and Sons.

2004 A short history of the thermodynamics of enzyme-catalyzed reactions. *J. Biol. Chem.* 279:27831–27836.

2006 *Biochemical thermodynamics: Applications of Mathematica*. Hoboken, NJ: John Wiley and Sons.

2011 With A. Cornish-Bowden, R. N. Goldberg, G. G. Hammes, K. Tipton, and H. V. Westerhoff. Recommendations for terminology and databases for biochemical thermodynamics. *Biophys. Chem.* 155:89–103.

Rapid equilibrium applications of Mathematica. Hoboken, NJ: John Wiley and Sons.

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