John A. Schellman

1924–2014

BIOGRAPHICAL *Memoirs*

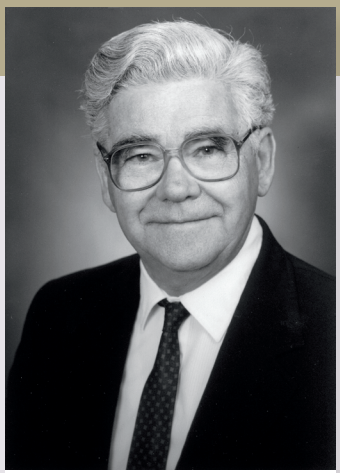
A Biographical Memoir by
Robert L. Baldwin
and Peter H. von Hippel

NATIONAL ACADEMY OF SCIENCES

JOHN ANTHONY **SCHELLMAN**

October 24, 1924–December 16, 2014

Elected to the NAS, 1982



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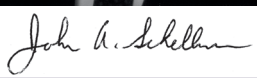

By Robert L. Baldwin[1] and Peter H. von Hippel[2]

John Schellman was born into a working class family in Philadelphia on October 24, 1924. His family was of German-Irish extraction and his father was a skilled machinist. Like many others, his father lost his job when the machine shop in which he worked closed during the Great Depression. He then took a job as a milkman, delivering milk and eggs in a horse-drawn wagon, with John often riding along with him on his rounds. John's mother had a fine voice and made extra money for the family by singing Irish ballads in the local taverns, with John sometimes accompanying her on the piano, which he had taught himself to play. However, money was always tight and the family spent some time on relief. At one point John "borrowed" his father's social security number to get work as an underage busboy in a local restaurant.

John and his siblings attended the local Catholic Schools in South Philadelphia, where they received a good education, although a bit heavy (at least for John) on Catholic theology. From childhood John was unusually interested in, and curious about, many things in the world around him, and he (with his older sister Mary) often spent time at the great science and art museums in downtown Philadelphia. The museums were free, but he and Mary were only able to go on Sundays because the regular streetcar fare was 7.5 cents (a significant sum), while on Sundays families were allowed to ride free. John and Mary would wait at the streetcar stop until a large family got on board, and then would simply climb on with them, pretending to be part of the group. John said this usually worked, although occasionally the conductor would catch them and then they had to try again on the next streetcar.

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John especially enjoyed his high school chemistry classes, and almost burnt the family house down when one of the experiments he was trying at home ignited in the basement near a cache of celluloid film. He had very few peers who shared his breadth of interests, but going to college was clearly out of the question due to the family's limited finances. John spent the year after graduation working first in a factory job and then in the laboratory of the Philadelphia Gas Works, which was a real laboratory doing applied research. While there he took a night course in chemistry at Temple University.

For John, the onset of World War II changed everything. He was drafted into the Army, but he was very shortsighted and thus not suited (in the Army's opinion) for combat service. Fortunately his interests in chemistry, together with his obvious quantitative abilities, landed him a corpsman's position in the Army medical laboratory at Walter Reed Hospital in Washington. He was soon promoted to head of the laboratory, even though he was among the youngest of those working there. His Army experiences changed his life in other ways as well. John always made friends easily and due to the vagaries of the draft a number of his Army and medical laboratory colleagues were highly intelligent and interesting university graduates. They included a young philosophy professor from Notre Dame, who tutored John through the equivalent of several college courses, as well as several well-educated Jewish refugees recruited for their German language skills. These friends introduced him to a broader world of ideas and books that he had never known, and also to classical music, which soon became one of his life-long passions. He attended symphony and chamber music concerts as often as possible, and later learned to play the cello, and to pick out classical pieces on the piano. Indeed, when John retired from active research work at the age of 80 he enrolled—as a regular student—in the year-long "Survey of Music" course in the University of Oregon's School of Music and Dance. This course was very demanding and required of all music majors. John participated fully and is fondly remembered by several faculty members as one of the outstanding students in the class.

These experiences convinced John that he had to go to college. When the war ended and he was mustered out of the military he set off—with the financial support of the GI Bill—to study chemistry at Temple University. He finished the undergraduate chemistry program at Temple in two years and, with strong recommendations from his undergraduate mentors, was admitted to graduate study in the chemistry department at nearby Princeton University. There a young assistant professor named Walter Kauzmann soon came to his attention because of Kauzmann's outstanding lectures on quantum mechanics. Kauzmann accepted John as one of his first graduate students and intro-

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duced him to theoretical and experimental physical chemistry, including early efforts to measure the kinetics of the largely mysterious process of protein denaturation.

John wasn't sure what he wanted to do after obtaining his PhD, but he thought it might be best if he got involved in some sort of practical chemistry-oriented medical research. He received a US Public Health Service (USPHS) postdoctoral fellowship from NIH and, after looking over the various possibilities, decided to accept an offer from Professor Leo Samuels at the University of Utah Medical School. He went to Utah with the ulterior motive of getting a chance to live in the Western US, the wide-open spaces of which had always fascinated him, especially in contrast with the crowded and urban East Coast where he had grown up. With Samuels, John worked to improve chemical and biological assays for different types of steroid hormones, and also explored the beautiful and lonely expanses of the National Parks of Utah. He soon found the work on steroid analysis to be uninteresting, but he never lost his enthusiasm for wilderness, which ultimately played a role in his choice of Oregon as the place where he would spend most of his subsequent career.

Thus he again had to figure out what to do next. After consulting with Kauzmann—and deciding he was still very interested in proteins—John was able to transfer his postdoctoral fellowship to the Carlsberg Laboratory in Copenhagen, Denmark, where he became a postdoctoral fellow with Kaj Linderstrøm-Lang from 1953 through 1955. This step laid the foundations for his scientific and personal life. He made groundbreaking contributions to important questions in macromolecular thermodynamics and spectroscopy throughout his career, but the 'tone' of his life's work was set at the Carlsberg Laboratory.

When John arrived in Copenhagen Linderstrøm-Lang was in the middle of painstaking efforts to establish the new field of protein folding research. Walter Kauzmann was also thinking about these issues, and as a keen observer and clear thinker was also a major participant in these developments. There was general agreement that the Carlsberg Lab was the center of this new field and many of those who would build the field in subsequent years were arriving as postdocs and sabbatical visitors to be part of the action.

John Schellman and Bill Harrington, working as postdocs at the Carlsberg Lab, made an important discovery (1) that helped to open up the area of protein folding research.

They showed, for the first time, that protein unfolding transitions were fast and reversible and thus were reactions suitable for quantitative physico-chemical analysis. They studied bovine pancreatic ribonuclease A (RNaseA), with disulfide bonds intact, and used optical rotation to probe the folding reaction on a fast (for those days) time scale. Within a few years of their discovery other workers (especially Charles Tanford (2,3), John Brandts (4-6), and Peter Privalov (7)), were developing the study of reversible protein unfolding transitions into a major field of work. The Harrington-Schellman discovery that the driving force for protein folding is simply the formation of a stable protein structure undoubtedly influenced Chris Anfinsen (8), who was then studying whether the amino acid sequence itself is sufficient to determine the folded structure of a protein. In 1956 it seemed possible that instead some auxiliary cellular process (perhaps involving free energy provided by ATP hydrolysis) would be needed to form the folded structures of native proteins.

John's choice for a postdoctoral project at the Carlsberg Lab combined the spectroscopy he had learned with Kauzmann and the interests in protein structure that motivated Linderstrøm-Lang. John decided to develop optical rotatory dispersion (ORD) as a method for measuring the α-helix and β-sheet secondary structures of proteins. Such a method was badly needed. The protein α-helix and β-sheet structures had not yet been observed directly, much less measured quantitatively. The first X-ray structure of a protein (myoglobin) at high resolution would be published only in 1960, whereas when John arrived Aase Hvidt and Linderstrøm-Lang had just obtained (9) the first hydrogen exchange (HX) results on insulin and the isolated insulin A-chain. They hoped to use the insulin HX results to learn how an isolated α-helix undergoes hydrogen exchange, but their initial HX results were not yet interpretable.

They chose this system because the A-chain could be separated from the B-chain of insulin and it was plausible from model-building that the A-chain contained a single α-helix. But it was not yet known whether their new HX results gave any information about the HX behavior of an isolated α-helix. Thus it was very important when, in 1954, Linderstrøm-Lang and Schelllman determined (10), using John's new ORD method of measuring secondary structures, that intact insulin did indeed contain an α-helix, although they also found that the isolated A-chain did not form a stable α-helix in aqueous solution under the same conditions.

These puzzling results led John to undertake three new projects, each of which had the potential to give important new insights into the protein-folding problem. John

realized that he first had to learn whether the peptide H-bond itself is stable in water. In 1936 Mirsky & Pauling (11) had proposed that protein structures are held together by hydrogen (H-) bonds and that these H-bonds had to be strong. However, the Mirsky-Pauling energetics were based on gas phase data, and it was clear to John that H-bond energetics in water should be very different. Clearly peptide H-bonds would be much weaker in water, because the -NH and -CO groups that form peptide H-bonds can also form competing H-bonds with water.

Thus John's first project was to find a way to measure the stability of the peptide H-bond in water. Kauzmann suggested studying the H-bonds made between the NH and CO groups of urea when urea forms dimers in water. Literature data were available for the heat of dilution of concentrated urea solutions in water. These data showed that urea forms dimers and/or multimers in water. John derived an equation to analyze how the number of H-bonds made between urea molecules in water should change when a concentrated urea solution is diluted. His equation fitted the available heat of dilution data well, and the results gave a value of ΔH^o of -1.5 kcal/mol for the enthalpy of the H-bond between urea -CO and -NH groups in water (12). This result suggested that, subject to the vagaries of the entropy changes that also must accompany the transitions involved, the peptide H-bond should be marginally stable in water.

John's next question was: how stable is a single α-helix in water? The entropy change on forming a helix was known to oppose helix formation, and John had just learned that its peptide H-bonds were unlikely to stabilize the helix significantly. So John set out to provide a model of the peptide helix - coil transition, based on statistical thermodynamics (13)[3], in order to estimate how the stability of a single α-helix depends on helix length. Schellman's model, in which peptide helix formation was driven by a favorable enthalpy change and opposed by an unfavorable change in backbone entropy, was adopted later by Zimm & Bragg (14) and by Lifson & Roig (15), when they used statistical mechanics instead of statistical thermodynamics to model the peptide helix-coil transition. John concluded from his study that a single α-helix should have borderline stability in water, and that helix length should be a critical variable in determining helix stability.

3. [A personal note from PvH.] When in graduate school at MIT I knew nothing of John Schellman or his work. The biophysics graduate students had formed a journal club, and when it came my turn to make a presentation I searched through the library for an appropriate subject and turned up Schellman's modeling study on helix-coil transitions (13). It struck me as one of the most interesting papers I had ever read and I gave my talk about it. Thus my very first seminar was on John Schellman's work.

John and Charlotte, just married in Copenhagen, 1954.

John's third project was designed to attempt to answer the question: how might neighboring tertiary structure affect the stability of an α-helix? He thought that contacts with the B-chain, which is present in intact insulin but not in the isolated A-chain, might well increase the stability of the vicinal A-chain α-helix. To approach this question John joined with Bill Harrington to find out how the inter-chain S-S bonds of intact RNaseA affect the stability of its secondary structures. They decided to compare the stability of the secondary structures in native RNaseA with those of oxidized RNaseA, whose S-S bonds had been broken by oxidation. They did not find any surviving secondary structure in oxidized RNaseA (1), suggesting that indeed tertiary structure and other stabilizing elements (such as inter-chain S-S bonds) might be critical in stabilizing the individual secondary structure elements of globular proteins.

Despite these major scientific contributions, John's time at the Carlsberg Lab was not all work. He took the opportunity to make many personal friends in the laboratory, as well as many non-scientific friends in the wider Copenhagen community, and kept those friends for life. He learned to speak (relatively[4]) fluent Danish, played the cello in impromptu chamber music groups and learned (from Linderstrøm-Lang) to smoke cigars. He also dated, and then married, a fellow American postdoc from Cal Tech named Charlotte Green.[5] While in Denmark John and Charlotte developed a passion for travel, and in brief excursions saw a good bit of Europe. After they had settled on an academic

4. On this point Bengt Norden tells of sailing into Copenhagen Harbor in his boat with John and Charlotte. They were hungry and John—wanting to exhibit his Danish—ordered three hot dogs for delivery to the boat from a stand on the quay. However, somehow it came out wrong and 13 sausages were delivered! The vendor became quite upset when they tried to reject the extra 10 – Bengt can't remember whether they ended up having to eat all of them.

5. Charlotte had started to work as a lab assistant in Linus Pauling's lab at Caltech in 1943, when his previous lab assistant was drafted. Pauling encouraged her to obtain a BS and then a PhD, and then hired her back as a postdoc. After two years at Caltech she arrived at the Carlsberg Lab on the same day as John. He suggested that they explore Copenhagen together.

life they never missed an opportunity to spend their sabbaticals in European laboratories that were both scientifically significant and located in interesting places, including Cambridge (England), Paris (France), Padua (Italy), Gothenburg (Sweden) and Rehovoth (Israel).

After he left the Carlsberg Laboratory John studied various problems, but protein folding remained his favorite. He had learned how to analyze theoretical problems as a graduate student with Walter Kauzmann, and his PhD thesis included the development of a theoretical model of the dielectric polarization of ice (16). From this and other graduate school experiences he found that he loved tackling and solving difficult problems, both theoretical and experimental. During his time as a Chemistry and Molecular Biology faculty member at Oregon John read—for leisure entertainment—seminal theoretical papers by Einstein and others, often in their original languages.[6]

John was introduced to the protein-folding problem in his PhD research by taking part in the Kauzmann laboratory's experimental efforts to analyze the kinetics of protein denaturation, which they studied as an irreversible unfolding process. (The unfolded protein was measured by its ability to form aggregates.) John knew that someday it would be important to study reversible protein unfolding, which he later did at the Carlsberg Laboratory in collaboration with Bill Harrington.

John's main project at the Carlsberg Lab was to develop the complete structure, both in terms of theory and its experimental realization, of the ORD method for analyzing the backbone secondary structures of proteins. By the end of his ORD project at the Carlsberg Lab, John and Charlotte had learned a lot about protein secondary structures and John had learned that the measurement of ORD should be replaced by the measurement of circular dichroism (CD). Implementing CD studies of protein secondary structures became an important goal for John in his future work.

As mentioned above, John met his wife, Charlotte, at the Carlsberg Lab. They worked together and later often traveled abroad together, which they both loved. Charlotte's research specialty was finding novel structural features in proteins, such as reverse turns and helix termination motifs. The Schellman of the "Schellman motif" (α-helix termination in proteins by a characteristic sequence motif) (17) is Charlotte, not John.

6. These interests affected others in the family. One of John's and Charlotte's daughters, Heidi, became a well-known experimental physicist at Northwestern University and at the Fermilab near Chicago, and is now chair of the physics department at Oregon State University. Their daughter Lise inherited John's musical passion and became a noted costumer, leading the costume shop of the Seattle Opera for many years.

John and Charlotte in their first laboratory at the University of Oregon, 1958.

Charlotte worked together with John at Carlsberg on the ORD project. Their ORD results were published in a magnum opus (seven papers on ten proteins) (18) in 1958, after they had left the Carlsberg Lab.

John and Charlotte returned to the U.S. in 1956, when John joined the Chemistry Department of the University of Minnesota at the suggestion of Rufus Lumry. In 1958 they moved to the University of Oregon, where John had a joint appointment in the chemistry department and in the Institute of Molecular Biology and Charlotte held an adjunct professorship. John loved to hike and the outdoor life in Oregon suited him perfectly. He generously shared these enthusiasms with the authors of this memoir, and was a wonderful friend and close scientific colleague to us both over most of our scientific lives.[7]

John and Charlotte used sabbatical leaves to work and study abroad, first in Padua, Italy, with Evaristo Peggion, later in Gothenburg, Sweden with Bengt Norden, and twice at the Weizmann Institute in Rehovoth, Israel with Shneior Lifson and others. John found it easy to give valuable advice on how to solve various types of physico-chemical research problems, and he was a big help in the laboratories he visited.[8] In recognition

7. [A personal note from PvH.] I had the good fortune to be a colleague of John's at the University of Oregon from 1967 until he died. We taught Physical Biochemistry together for many years—often interrupting one another's lectures to argue and critique. We also swam, hiked and skied together. In retrospect it is fair to say that my scientific education had three critical phases: the first was as a student at a remarkable high school near Boston, and the second as a graduate student at MIT. However the third—and perhaps most valuable—phase of my education may have been the 40 years of discussions I had with John Schellman over almost daily lunches, as well as on hikes and riding up mountains on ski lifts (on the way down we generally found that staying upright occupied our full attention).

8. John's generosity in providing such assistance became legendary, and extended to colleagues and students alike. A person in need of scientific help and insight would approach John and describe the problem. John would listen carefully, but not say much, and then would conclude the session by saying he would get back to the person,

John and Charlotte on a ski trip in the 1980s.

of his contributions John received honorary doctorates from Chalmers University (Gothenburg) in 1984 and from the University of Padua in 1990.

In his research at Minnesota and Oregon John dug deeper into the problems he had opened up at the Carlsberg Lab and began to analyze the physical properties of DNA. He clarified the foundations of the subjects he studied, especially of circular dichroism and the energetics of protein folding. In 1962 John and his student Patrick Oriel (19) found that the n-pi* transition of the peptide group is responsible for the Cotton effect that is used to measure α-helix formation in ORD studies. (In CD studies, the n-pi* transition is responsible for the 220 nm CD band that is used to measure α-helix content.) Bob Woody and Nacho Tinoco independently discovered the role of the n-pi* transition in tracking α-helix formation.

In the 1970s the study of protein mutants became an important approach to the protein folding problem and John and his coworkers developed methods of analyzing the properties of mutant proteins. John's methods were widely used, both in equilibrium studies of mutational effects on protein stability (20) and in kinetic studies of how mutations affect the rates of protein folding (21). At the Institute of Molecular Biology in Oregon, George Streisinger had set up an institute-wide program of analyzing the consequences of making mutations in T4 lysozyme, and John and his coworkers took part and made significant contributions.

often leaving the questioner with the impression that John had not understood. However invariably, usually within a day or two, he would seek out the questioner with a long series of notes, equations and references, all written out on yellow paper, which not only indicated that he had understood perfectly, but also that he had generally understood more than the questioner, and often had opened up a whole new approach to the scientific issue at hand.

In 1969-70 John and Charlotte enjoyed a sabbatical at the Weizmann Institute in Israel in the research group of Shneior Lifson. John was deeply interested in the Lifson-Roig approach to understanding the polypeptide helix-coil transition. The Lifson-Roig theory (15) has the backbone ϕ and ψ angles as key variables. When the helix-coil transitions of peptides containing more than one amino acid type are analyzed (22), it is essential to interpret the results by using the Lifson-Roig approach because then the helix propensity of an amino acid can be associated with a single amino acid residue type, whereas in the Zimm-Bragg approach the helix propensity is associated with the helix H-bond, which connects two different residues. (The peptide H-bond connects the -NH of one residue and the -CO of a neighboring residue.) When John returned to Oregon after his sabbatical, he and a postdoctoral fellow, Hong Qian, wrote a classic paper (23) in which they compared the Zimm-Bragg and Lifson-Roig approaches to the study of the helix-coil transitions of peptides and polypeptides.

In 1990 John retired from teaching and became an emeritus professor at the University of Oregon. He continued to do research and to support this ongoing work he submitted a final grant application to NSF that would have spelled disaster for a lesser scientist. In essence the application consisted of a list of approximately nine questions, dealing mostly with issues of protein physical biochemistry that he stated he was working on and to which he felt he could still make useful contributions. The study section approved unanimously and the grant was funded with enthusiasm. Some of the results of that work appeared in a remarkable summary paper and overview, which John entitled: "50 Years of Research on Solvent Denaturation" (24) in which he succinctly described both the entire history of the field in quantitative terms, and also his many insights into how the various components fit together. In his spare time, John wrote detailed and illuminating accounts of the scientific careers of Walter Kauzmann (25) and (with Charlotte) of Kaj Linderstrøm-Lang (26). A *Festschrift*, dedicated to John and containing papers by his many friends and coworkers, was published in *Biophysical Chemistry* in 2002. So many wanted to honor him that the *Festschrift* filled two entire volumes (101 and 102) of the journal. References to John's important scientific contributions after leaving the Carlsberg Laboratory are listed in the *Festschrift* as well.

John Schellman died in Eugene, Oregon, on December 16, 2014, at the age of 90.

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