Charles Tanford

1921–2009

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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and Gerald R. Grimsley

NATIONAL ACADEMY OF SCIENCES

CHARLES **TANFORD**

December 29, 1921–October 1,, 2009

Elected to the NAS, 1972

By C. Nick Pace
and Gerald R. Grimsley

SCIENTIFIC IMPACT

On October 1, 2009, Jacqueline (Jackie) Reynolds notified me that Charles Tanford had died. I forwarded her message to the people on my email list who study proteins. The replies below were received the same day along with many others, who expressed similar thoughts.

"Sorry to hear this news. He was one of my scientific heroes. I named the position of the transition state on the reaction pathway from denaturant dependence as betaT in his honour, a name that has stuck. Farewell to a great protein scientist. His name will live on."—Alan Fersht

"Thank you for sharing the passing of one of the giants of our field, it is truly remarkable how much insight his classic experiments provided to our understanding of protein folding, experiments that still are carefully considered in the way we think about protein folding today."—Jeff Kelly

"It's a very sad day. Charlie was truly a legendary biophysicist. I, for one, learned a huge amount from his work and writings, particularly his lucid books."—Ken Dill

"Very sorry to hear of Charles Tanford's passing. A great scientist, an original thinker and a major impetus for the way that I and many others think about the folding problem."—Bob Matthews

"Thanks so much Nick for sharing this notice of the passing of a great historical figure in our field...his intellectual influence on me and others was enormous."—Paul Schimmel

"I'm really sad to hear that Nick. He was one of the giants of biophysical chemistry in the last century, and his work influenced me enormously."
—Wayne Bolen

"Sad News. He was truly a great scientist." —Neville Kallenbach

These sentiments reflect the enormous impact that Tanford had on those of us who study proteins.

Early years and education

Tanford was born Karl Tannenbaum on December 29, 1921, in Halle, Germany, but the family lived in Leipzig. His mother, Charlotte (Eisenbruck) Tannenbaum, was a Leipzig girl but his father, Majer (Max) Tannenbaum, was born in Brzesko, Poland. Both parents were Jewish. The family lived in Leipzig for more than a decade and had a thriving business there, although Tanford was not sure what the business was. This period is discussed in more depth in a 2003 personal recollections article by Tanford in which he had this to say:

In particular, I never took an interest in science, never longed for a chemistry set, never took clocks apart to see how they worked, never scooped tadpoles from ponds. In fact, I didn't take much interest in any of my academic subjects. I loved cricket, that most numerical of sports, I collected stamps, I was a pretty good chess player, I read Dickens and Dorothy Sayers but not much else.[1]

Because the Nazi party was gaining strength, his father, perhaps foreseeing what was to happen a few years later, pulled up his roots and took the family to England in 1929. (Many of the Tannenbaums' extended family members, who stayed in Germany, perished in the gas chambers.) The following year, the family changed their name to Tanford and Charles was sent to the very reputable University College School. At the outbreak of the war in Europe, his father made another far-reaching decision and sent Charles to New York to live with an aunt. This was a turning point in his life, and as he says:

I left home…when I was 17 and soon discovered a resonance with American society and a vocation for chemistry in particular. I obtained an excellent education and an undergraduate degree in chemistry at NYUs uptown branch in the Bronx; I went on to Princeton for a PhD in physical chemistry.[1]

After receiving his bachelor of arts degree from New York University in 1943, Tanford enrolled at Princeton as a graduate student in chemistry with the expectation of working with Henry Eyring, one of the leading theoretical chemists of the day. But the war intervened and Tanford was sent to work on the Manhattan Project at Oak Ridge for a year. He assisted in Harold Urey's program on the fractionation of uranium isotopes. (The members of the laboratory were told that it was required for energy generation.) So, he participated in a small way on the creation of the first atomic bomb and said: "I felt a sense of exhilaration when the news broke of its successful use, and my view has not changed in retrospect. Unlike many of my contemporaries, I feel no guilt."[1] The war over, Tanford then earned a PhD in chemistry from Princeton in 1947.


Charles Tanford 1947.

Tanford did postdoctoral work in protein chemistry in the lab of Edwin Cohn and John Edsall at Harvard University. He began his independent academic career at the University of Iowa in 1950 and moved to Duke University in 1960. In 1970, he was named the James B. Duke Distinguished Professor. He retired in 1988, moved to Easingwold in the North of England, and began a second career writing about the history of science.

Tanford married Lucia Brown while at Harvard and they had three children, Vicki, Alex, and Sarah. They were divorced in 1968, and soon thereafter he began a professional and personal relationship with Jackie Reynolds, a fellow biochemist, that lasted until his death.

Scientific accomplishments

Tanford published more than two hundred articles during his scientific career. His first was an experimental study, "The Mercury-Sensitized Reaction between Hydrogen and Nitric Oxide," and it was published while he was an undergraduate at New York University.[2] At Princeton, Tanford had planned to work with Henry Eyring, but Eyring required that he work with R.N. Pease for his PhD. (Eyring was Tanford's favorite teacher at Princeton, and he thought that Eyring would have won a Nobel Prize if he had stayed at Princeton and not moved to the University of Utah.) Tanford's PhD work led to three theoretical papers on the combustion of gases, two in the *Journal of Chemical Physics* on what became known as the Tanford-Pease theory.[3] Tanford said that this theory was later supplanted by more elegant formulations.

Tanford with Jackie Reynolds.

Near this time, chance intervened to change the course of Tanford's life and career. Walter Kauzmann returned to Princeton in 1946 during Tanford's final year, having decided to become a protein physical chemist after reading the Cohn and Edsall treatise, *Proteins, Amino Acids, and Peptides*,[4,5] as well as other books on proteins while he was in a cabin in the Colorado mountains. Kauzmann recalled:[4]

> *Tanford attended my informal lectures on proteins and we talked a lot about the subject. He decided that his future lay with proteins rather than with flames, and he went on to a postdoctoral position in the Cohn*

> *group at Harvard, and, of course, to a very distinguished career in protein chemistry. So perhaps I can claim him as one of my most important discoveries.*

Tanford began his career as a protein chemist in the lab of Cohn and Edsall at Harvard Medical School. His research there led to his first paper on proteins,[6] a careful experimental study of the hydrogen ion titration of human serum albumin and a theoretical analysis of the results based on the model of Linderstrøm-Lang.[7] In the acknowledgements section of this paper, Tanford:

> *…expresses his gratitude to Dr. E. J. Cohn for suggesting this problem, and to Drs. J. T . Edsall, J. L. Oncley, George Scatchard, and W. L. Hughes, Jr., for many invaluable discussions.*

This experience with some of the most important physical chemists working on proteins, and the lectures by Kauzmann, left Tanford well equipped to begin his work on proteins. He was especially indebted to Scatchard and had this to say:

> *The shining light for me during my Boston years was, however, neither Cohn nor Edsall, but George Scatchard, a professor at MIT without formal academic Harvard appointment, but despite that a vital member of the Harvard group. He was the most memorable among all my mentors, with an unmatched comprehension of solution thermodynamics—the modern inheritor of the depth of comprehension that J. Willard Gibbs had had 70 years earlier.*[1]

Tanford wrote the interesting obituary of Scatchard for *Nature*.[8]

The Cohn and Edsall lab, established in 1920, was unique.[9] It was a physical chemistry department in a medical school and the members had no teaching duties. Their work was especially important during the war years because of their expertise in blood proteins and blood transfusions, and because the laboratory produced materials for clinical applications, especially by the military, such as serum albumin for use as a plasma expander. As Tanford wrote:[1]

> *The department's single-minded concentration on proteins was unparalleled, with no digression to metabolic pathways, genetics, enzyme kinetics, or other aspects of biochemistry that would have been considered essential concerns had they been part of a typical medical school*

> *Biochemistry Department…The upshot of the experience for me personally was to create in my mind a passion for proteins and an indelible picture of a globular protein—the category that includes most enzymes, antibodies, and binding proteins…globular proteins interested me the most intensely and continued to do so in the years to come for a different reason, which was that they are proteins that can be crystallized and subjected to x-ray analysis. They were capable of yielding—and as the years went by they did yield—increasingly precise details of molecular structure and organization."*

At Iowa, Tanford's main teaching duties were the undergraduate physical chemistry course and graduate courses in thermodynamics and kinetics. This took up six lecture hours per week plus time for laboratory supervision. Despite this heavy teaching load, he still found time for research and writing a book. He continued his studies of the hydrogen ion equilibria of proteins and other related topics. Titration curves were determined for bovine serum albumin, insulin, lysozyme, and ribonuclease. The study of bovine serum albumin in 1955 was cited over five hundred times[10] and the figures used in several textbooks.

In 1956, Tanford was awarded a Guggenheim Fellowship to study at Yale with J. G. Kirkwood, one of the foremost theoretical chemists of the day. In addition, his office was next to that of Lars Onsager, another theoretician who won a Nobel Prize in 1968 for his work on the thermodynamics of irreversible processes. Tanford's interactions with these groups gave him a better appreciation of the importance of theoretical studies in chemistry and biochemistry.

Tanford's project at Yale was to improve the theoretical treatment of the acid-base properties of proteins. The older Linderstrøm-Lang model represented the protein molecule as a sphere with a continuous and uniform distribution of charge on its surface.[7] In the new model, discrete charges were placed at fixed positions on the surface of the protein.[11] In his paper related to the new model, the abstract ends with: "General equations are obtained which express the titration curve as a function of the locations of ionizable sites and of their intrinsic properties. It is concluded that the intrinsic properties may themselves be quite sensitive to the location of the dissociable site with respect to the surface of the protein molecule." This paper triggered an interest in the factors that determine pK values of the ionizable groups of proteins that continues to the present day. The work from this period is summarized in a review published in 1962.[12]

In an interesting aside, Tanford pointed out:

> *The calculations were laborious. There were no computers then and Kirkwood didn't even have a mechanical calculator—tables of logarithms were still used to multiply and divide, and the values of Legendre polynomials (which occurred as factors in the equations) were copied by hand from tabulations in heavy books that had been prepared by the WPA (Works Progress Administration) as part of Franklin D. Roosevelt's program to alleviate unemployment and lift America out of the great depression.*[1]

Tanford taught a course on the physical chemistry of polymers at Iowa and decided to write a textbook. His goal, he said, was to teach himself what he did not understand. His ten years of work led to the publication in 1961 of *Physical Chemistry of Macromolecules*.[13] He has written an interesting recollections article about the book, in which he noted: "There were two reviewers and their criticism was scathing; I had got it all wrong, they said, and the book was declared unpublishable."[14] When he met with the publishers he told them "…that I had every confidence in what I had written and would not change a word." The book was a great success and has now sold over twenty-five thousand copies; it has been republished, unaltered. For many of us, it was an essential reference book for our teaching and research.

Tanford moved to Duke University in 1960 and he expanded his research into new areas. When I arrived in 1962, he had a group studying antibody structure, a group studying various aspects of protein folding, including the denatured state, and he was thinking about hydrophobic bonds which led him into the area of membranes and membrane proteins. Lab meetings were held at 3 pm on Friday afternoons and generally lasted until at least 6 pm. This was when we learned from Tanford. (Tanford and Bob Hill taught an excellent course on proteins and enzymes at Duke that was also a great learning experience.) The lab was so crowded that my desk also served as my lab bench. We had two Beckman Model E ultracentrifuges (one inherited from Hans Neurath) and, shortly after I arrived, a Cary 60 spectropolarimeter #3. (The first two had gone to Elkan Blout and Henry Eyring.)

It was an exciting time to be in the lab. The experiments that led to the characterization of the denatured state of proteins were under way, and Yas Nozaki was overseeing solubility measurements on amino acids and peptides that led to the ΔGtr values for urea and GdnHCl used to understand how these compounds unfold proteins. The studies of protein folding were reviewed by Tanford in a 1968 article that has been cited over 2,200 times, his most cited paper, and in a continuation article.[15,16] These articles paved the way for the explosion of research in protein folding that occurred when site-directed mutagenesis became available.

Charles Tanford in 1964.

When Tanford arrived at Duke, Phillip Handler encouraged him to work on more biological problems. One of his first ventures was to use hydrodynamic techniques to study the structure of antibodies (immunoglobulin G). There were several competing models for the structure including a cigar-shaped model with antigen binding sites at both ends that had been proposed by Gerald Edelman, who later shared a Nobel Prize for his work on antibodies.[17] Tanford's group showed correctly that antibodies in fact have a three-domain structure with antigen binding sites on two of the domains.[18] This was subsequently confirmed more directly with electron microscopy by Valentine and Green.[19]

Later Tanford's group separated and denatured the light and heavy chains of an antibody, and then they showed that the chains could be refolded and reunited to form an antibody with the same antigen specificity that it had originally. This showed that the three-dimensional structure is determined by the amino acid sequence, not by interactions with the antigen.[20] This was also shown by Haber.[21] This proved that Pauling's template theory of antigenic specificity was not correct.

In the late 1960s, Tanford began his long and productive collaboration with Jackie Reynolds. With Tanford's interest in the hydrophobic effect and Reynold's background in protein-lipid interactions, the lab moved into the area of membranes and membrane proteins with great success. They showed that the native states of membrane proteins could be preserved in soluble complexes with benign detergents, and these states were carefully characterized. They also devised new methods of measuring the molecular weights of these proteins and this allowed them to determine the size and subunit structure of membrane proteins. The two papers they published together in 1970 were cited more than 1,500 times and revolutionized the study of membrane proteins.[22,23]

The following year, Nozaki and Tanford published the first hydrophobicity scale.[24] And in 1973, Tanford's thoughts about hydrophobicity, membranes, and cells were set out in a typically lucid and elegant book: The *Hydrophobic Effect: Formation of Micelles and Biological Membranes*, which met with great acclaim.[25] This led later to a landmark paper published in *Science* titled "The Hydrophobic Effect and the Organization of Living Matter."[26] In the following years, Tanford's research remained focused on topics related to membranes and membrane proteins such as bacteriorhodopsin and the acetylcholine receptor.

Tanford had a long and very distinguished academic career. Thirteen of his articles were cited more than five hundred times. He became a member of the National Academy of Sciences in 1972 and served as president of the Biophysical Society in 1979-80. He received the Alexander von Humboldt Prize and the Merck Medal for Biochemistry. He held the highly coveted Eastman Visiting Professorship at Oxford University and was a visiting professor at Harvard and other distinguished institutions.

Tanford's second career

Tanford and Reynolds retired from Duke in 1988 and moved to England. They settled in the small country town of Easingwold in Yorkshire. This is where their second career began. Tanford first published a delightful book titled: *Ben Franklin Stilled the Waves: An informal history of pouring oil on water with reflections on the ups and downs of scientific life in general.*[27] This was first published in 1989 by Duke University Press and later in 2004 in a paperback version by Oxford University Press.[28] Lubert Stryer wrote a foreword for the 2004 version and had this to say:

> *My curiosity was piqued fourteen years ago when I saw Tanford's "Ben Franklin Stilled the Waves "on a shelf of new books. I had known Tanford as a distinguished biophysicist and physical chemist and had learned much from his earlier scientific works. What did Tanford have in mind in writing about Franklin and the pouring of oil on water? The unconventional title prompted me to read the book, which proved to be enlightening and delightful…Reading "Ben Franklin Stilled the Waves" a second time was much like savoring wine that has become richer and deeper with the passage of time.*[28]

Next Tanford and Reynolds conceived and wrote a typically original joint venture: *The Scientific Traveler: A Guide to the People, Places and Institutions of Europe*.[29] This is a guidebook for the scientifically inclined tourist, with information about memorials of famous scientists in churches, cemeteries, and public squares, as well as fossilized laboratories and traces of historic experiments. It was so well received that the publisher requested and got a second equally captivating volume, *A Travel Guide to Scientific Sites of the British Isles*.[30] Both of these books were illustrated with photographs taken by Tanford, and they are great resources for any scientist who wants to visit the sites where important scientific discoveries were made.

But Tanford and Reynolds' most important joint venture was their last book, *Nature's Robots: A History of Proteins*, which was published in 2001.[31] This is a work of meticulous scholarship, delivered with style, wit, and a fine narrative sweep. The last line of Henryk Eisenberg's review in *Nature* was "…anyone interested in proteins will find *Nature's Robots* an absorbing and often exciting story, as well as a major contribution to scholarship."[32]

In addition to these books, Tanford and Reynolds wrote many interesting book reviews and obituaries for *Nature*.

Some personal observations

I will conclude with a few personal observations on Tanford during my time in his lab. Tanford suggested three possible projects for my PhD research. One caught my interest. Kauzmann's seminal review showed convincingly that hydrophobic bonds stabilize proteins, and model compound data showed that they become stronger as the temperature increases.[33] Tanford pointed out that this did not make sense because everyone knows that proteins unfold at higher temperatures. My project was to figure this out. He suggested that I work on β-lactoglobulin because we had more than twelve grams of it in the freezer, given to him by Serge Timasheff and Bob Townend.

This was a fortunate choice. It turned out that β-lactoglobulin is most stable at 35 degrees Celsius and unfolds at both higher and lower temperatures.[34] Consequently, we were the first to observe the cold denaturation of a protein and show that proteins can be unfolded by either lowering or raising the temperature. ΔH for unfolding was strongly temperature dependent, varying from -40 to + 40 kcal/mol between 10 degrees and 50 degrees Celsius. This was a reflection of the large change in heat capacity, ΔC_p, that accompanies protein unfolding, as shown earlier by John Brandts.[34,35] This research benefited others in ways that had not been anticipated. Efraim Racker wrote us a nice note to thank us because they began purifying their protein, ATP synthetase, at room temperature rather than in the cold room and got a better yield.

The door to Tanford's office was always open for his graduate students and post docs, and he was an excellent mentor. When he was writing a paper, his mail would pile up on the corner of his desk and would not be opened until the paper was finished. In one lab meeting, he mentioned that he did not mind us looking through the stack of mail, but we should not open his letters.

I was fortunate to have two long car rides with Tanford; they were a chance to learn about things other than proteins. In one, we were riding from Atlantic City to Durham and he explained to me why he enjoyed bird watching and classical music, two things I knew little about. Later, he would loan me records to take home and play with the hope that I would develop an appreciation of classical music. Tanford did not succeed in all of his ventures. During the other car ride, we were on our way to the 1966 Biophysics Gordon Conference with Serge Timasheff and Harold Susi. It was the day that a fellow was shooting people from a tower on the campus of the University of Texas. Three of us, but not Tanford, were in favor of capital punishment for the shooter.

Tanford called me into his office to set me straight on a few occasions. One was when I suggested that Philip Handler did not deserve to be elected to membership in the National Academy of Sciences. (Handler later served two terms as the Academy's president.) Tanford explained to me that Handler had done more than anyone to gain support for scientific research in Congress, and he certainly deserved to be a member. (Like many of us, Tanford was mightily impressed by Handler, as he has described.[1])

We celebrated Tanford's retirement on Cape Cod in 1988. At the time, Tanford suggested that his success resulted from all of the good experimental data gathered by his students. He was just being nice to us. More important than those data was Tanford's ability to take the experimental results and write the great papers that helped so many of us gain a better understanding of proteins. Few if any made a greater contribution to protein science than his.

Other observations

Tanford's career was intertwined with that of Walter Kauzmann. Here is what Jackie Reynolds had to say in 2011 about their last meeting:

> *The last time Walter and Charlie met face to face was in London approximately 10-15 years ago. They spent the day together walking down the Thames from Hammersmith to Barnes Bridge (well known to all followers of the Cambridge/Oxford boat races) discussing scientific problems both present and past. My enduring memory is of the great humility that both of them possessed in attributing everything they had accomplished in their scientific careers to both those that had gone before and to their students and post-doctoral collaborators. In particular, on this occasion, I believe they both would want the seminal contribution of G. S. Hartley (1936) to an understanding of hydrophobicity to be recognized together with the many scientists of a previous age whose work they drew on and whose scientific integrity was a guiding light in their own careers.*

Tanford was good friends with Walter Gratzer, who had this to say in an obituary:

> *Tanford was a man of strong principles and strong opinions, who relished an uninhibited debate. Both in open discussion and in print he could mug an adversary, and some there must have been who did not thank him for proving them wrong. When Dr. Johnson declared after an evening at the alehouse with his friends that they had had a good talk, Boswell replied, 'Yes, sir, you gored and tossed several people'. Tanford used to take the same kind of pleasure in an evening of good food, wine (for he was a discriminating gourmet) and talk. He was withal a bracing and genial companion, and under the formidable exterior, a kind and generous man, ever willing to spend time explaining a tricky scientific point to a student or to anyone less intellectually agile. We will remember him with pleasure and gratitude.*[36]

Final note

On February 12, 2014, the federal and provincial governments in Germany agreed to invest 39.6 million Euros to build a protein center on the campus of the Martin-Luther University in Halle-Wittenberg. The building will be named after Tanford, who was born in Halle. The announcement stated:

> *Benannt warden soll das Künftige Proteinzentrum nach dem Wissenschaftler Charles Tanford (1921-2009), einem Pionier der Proteinforschung. Auch damit soll die herausragende Bedeutung des Forschungszentrums deutlich werden. Tanford wurde unter dem Namen Karl Tannenbaum in Halle geboren. Die jüdische Familie emigrierte 1929 nach England and änderte dort ihren Familiennamen. Charles Tanford erhielt seine akademische Ausbildung in den USA und verbrachte dort sein gesamtes wissenschaftliches Leben. Er führte insbesondere grundlegende Arbeiten zur Stabilität der Proteinstruktur durch.*

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