Retrospective: Charles Tanford (1921–2009)

BY WALTER GRATZER

Charles Tanford was one of the leaders of that remarkable generation of physical chemists who were drawn to biology in the decade following World War II. Their incursion into biochemistry tilted the emphasis quite abruptly, away from metabolic processes and toward the structure and thermodynamics of macromolecules. From this sprang the effulgent new discipline of molecular biology, viewed with mistrust by many biochemists, for it was, in the words of Erwin Chargaff, no more than "biochemistry practiced without a license."

Tanford was also a part of the wave of Central European émigrés who so enriched the American academic scene in the 1930s. He was born to assimilated Jewish parents in Halle, Germany. In 1929, his father, Max Tannenbaum, foreseeing perhaps what was to happen five years later, pulled up his roots and took his family to London. The next year, he changed his name to Tanford, and Charles, age 8, was sent to the very reputable University College School. In 1939, Max made another far-reaching decision and dispatched his son to New York into the care of an aunt. Charles' mother and younger sister eventually followed.

Another relative, at Max's urging, got Tanford into New York University to study chemistry. On graduating, he was enrolled as a graduate student at Princeton University with the expectation that he would work with one of the leading theoretical chemists of the day, Henry Eyring. However, the war intervened, and Tanford was drafted and sent to Oak Ridge to assist in Harold Urey's program on the fractionation of uranium isotopes.

When the war was over, Tanford returned to Princeton, but Eyring imposed the condition that he must work with another professor, R. N. Pease, on combustion in gases. This was not what he wanted to study, but the work produced a Ph.D. and two papers on what became known as the Tanford-Pease theory; this enjoyed a brief vogue before being supplanted, according to Tanford, by more elegant formulations.

At this point, chance intervened to change the course of Tanford's life and career: Walter Kauzmann arrived at Princeton as an assistant professor and ignited Tanford's enduring fascination with proteins. Rejecting the temptations of a lucrative industrial job, Tanford applied instead for a place in Edwin Joseph Cohn's protein laboratory — the only one of its kind in the country, and, in its setting at Harvard Medical School, a curious anomaly. When Tanford arrived, the main concern of the laboratory was the rigorous analysis of proteins, in respect of molecular weight, size, charge and ion binding, and it had attracted a galère of distinguished chemists. The most important for Tanford was George Scatchard, for whom he developed a deep admiration and from whom he absorbed the finer points of solution thermodynamics.

After two years, and equipped with a grasp of the mainly hydrodynamic techniques then available for the study of proteins in solution, Tanford headed for his first faculty position in the chemistry department of the University of Iowa. There, he taught a course on the physical chemistry of polymers and discovered that no satisfactory textbooks were available. It was at this point that he resolved to write his own, an undertaking that was to occupy him intermittently for eight years and resulted in the book "Physical Chemistry of Macromolecules."

In the midst of all this, he took a sabbatical year with eminent theoretician J. G. Kirkwood at Yale University. There, he developed a theoretical treatment of the electrostatic characteristics of globular zwitterionic polyampholytes, based on evenly distributed discrete ionising groups, rather than on the familiar model of a uniformly charged surface. The outcome permitted a realistic interpretation of acid-base titration profiles of proteins, many of which Tanford and his students measured in the laboratory.

In 1960, Tanford moved to a professorial chair in the department of biochemistry at Duke University Medical Center, where he remained for 28 years. He will perhaps be best remembered for his work on protein stability and the hydrophobic effect. This became central to the way in which the structure of globular proteins is perceived. He himself always emphasized the debt he owed to Kauzmann, who, if not the originator of the concept, clarified it and brought it to the attention of protein chemists. Kauzmann planted the seeds in Tanford's mind during their conversations at Princeton, and the notion that the folded state is imposed on globular proteins by the instability of the unfolded chain in water, rather than the energy of interaction in the globule, came to him as an epiphany. It led to a series of classical studies on protein unfolding by nonaqueous solvents, and especially by urea and guanidinium chloride, and on the free energies of transfer of model hydrophobic compounds from water to such media.

Throughout this period, Tanford made forays into more functional aspects of protein chemistry. Notable among these was his work on antibodies. Rival models of immunoglobulin G were in circulation. Antibodies of this kind were known to be divalent, but the disposition of the antigen-binding sites was a matter of controversy. By a tour de force of hydrodynamic analysis and inference, Tanford and his colleagues defined the lineaments of the molecule. Moreover, they separated the light and heavy chains of an antibody, denatured, refolded and reunited them, and showed that the antigenic specificity was recovered. This eliminated in one stroke Linus Pauling's "template" theory of antigenic specificity, which was based on transitions between conformational states of the protein.

Around this time, Tanford embarked on his last major undertaking, this time in association with Jacqueline Reynolds, a professor in the department of anatomy at Duke University. Together, they took a daring plunge into what were then the turbid waters of membrane chemistry. Membrane proteins were viewed with disgust by protein chemists, for they were generally insoluble in water, except in an indeterminate denatured condition in complexes with destructive detergents, such as sodium dodecyl sulfate, or fully unfolded in high concentrations of denaturants. Tanford and Reynolds found that the native states could be preserved in soluble complexes with benign detergents, which they carefully characterized. They devised a method of measuring the molecular weights of membrane proteins in this state by masking the detergent contribution to the buoyancy of the complex with D_2O. This made it possible to determine the sizes and subunit structure of these refractory proteins by sedimentation analysis.

The contemplation of membranes and their relation to the various states of amphiphiles, such as lipids, led to the culmination of Tanford's thinking about hydrophobicity. This he set out in a typically lucid and elegant book, encompassing the nature of detergent micelles, surface layers and membranes, "The Hydrophobic Effect: Formation of Micelles and Biological Membranes," and in an article in Science in 1978. With the new methods they had honed, Reynolds and Tanford made a number of inroads into membrane biology: With the neurophysiologist Arthur Karlin, they studied the acetylcholine receptor and, with Walther Stoeckenius, the structure of bacteriorhodopsin. They fractionated the proteins of the red cell membrane and determined their molecular weights, and, while on sabbatical leave in Germany, they immersed themselves deeply in the action of ion pumps.

Tanford's professional collaboration with Reynolds had long since blossomed into domestic harmony, he and his wife having divorced in 1968. In 1988, he and Jackie decided to retire. They settled in the small country town of Easingwold in Yorkshire and melted into its community. But they were far from idle, as they began a new joint career as historians of science. Tanford already had published a delightful popular book on membranes and surfaces, "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." Next, there emerged a typically original joint concept: "The Scientific Traveller: A Guide to the People, Places and Institutions of Europe" — a guidebook for the scientifically inclined tourist. It was so well received that the publisher demanded, and got, a second and equally captivating volume, "A Travel Guide to Scientific Sites of the British Isles." But the most important joint venture was still to come: "Nature's Robots: A History of Proteins" — a work of meticulous scholarship, delivered with style, wit and a fine narrative sweep.

Hilaire Belloc, historian and poet, wrote his own epitaph:

When I am gone, I hope it may be said
His sins were scarlet, but his books were read.

Tanford, alas, is gone, but his books and his papers are indeed still read.

Charles Tanford was 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. The following are thoughts and reflections from several of his friends and former colleagues.

When I was in graduate school, Charlie Tanford was one of my heroes. What I liked about Tanford's work was that he was interested in big-picture questions and found meaningful ways to get insights. As far as I know, he invented the idea of hydrophobicity scales and was the first, with his associate Yashuiko Nozaki, to determine such a scale for amino acids. He developed simple conceptual models of micellization and protein stability based on such ideas.

Tanford wrote with outstanding clarity and simplicity. He composed another "bible" in the field, called "The Hydrophobic Effect," in 1973, with very psychedelic 1970s lettering on the front cover. He once told me the story of how that book came about. In his early career, Tanford had been a protein chemist. Over time, his interests shifted to membrane proteins. He was simply looking for some rules for how to pick the right detergent for solubilizing membrane proteins so that he could then move forward and study them. He told me that, after 15 years, he never figured it out, but, even so, he wanted something to show for that effort, so he wrote that book.

Ken A. Dill
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Charles Tanford was one of the great pioneers of protein biophysical chemistry. His data and ideas in the large number of areas he ploughed stand the test of time. His work on the effects of denaturants on protein denaturation is the basis of modern kinetic studies on the mechanism of folding. In his honor, I named the "beta value" for the position of the transition state for folding on the reaction coordinate as defined by solvent accessible surface area, "β_T."

Alan Fersht
Herchel Smith professor
of organic chemistry
University of Cambridge

Charles Tanford was one the great protein chemists of the 20th century. Equally comfortable with experimentation and theory, his contributions were numerous and fundamental, especially those on both protein denaturation and the hydrophobic effect. He was also an exceptional writer. His textbook, "Physical Chemistry of Macromolecules," was a staple for a generation of biophysics students (including myself), and his reviews in Advances in Protein Chemistry established a paradigm for understanding protein-folding thermodynamics. Upon retirement, he wrote several popular books, each with flair and each reflecting his distinctive view of the subject material. His work conditioned the way we all think about proteins.

George D. Rose
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Tanford's contributions on the hydrophobic effect, amino acid solubilities and protein stability are well known. What is less known is that he was also a pioneer in structure-based thermodynamics calculations. In 1957 he published, with John G. Kirkwood, a continuum electrostatics model of proteins. At the time, this was probably the most important paper in the field since Linderstrøm-Lang's contributions 33 years earlier. The Tanford-Kirkwood model, as it is still known today, was a perfect marriage of Kirkwood's mathematical skills and Tanford's deep knowledge of ligand binding and multiple equilibria. With characteristic insight, Tanford, working with Robert Roxby, cast the model as an algorithm that could be solved with an iterative procedure. In 1972, they used it to calculate the proton titration curve of lysozyme starting from the coordinates of the crystal structure. He did not go back to work on this problem, but he sparred and watched closely and with curiosity over the shoulders of younger scientists working in Frank Gurd's lab to improve Tanford-Kirkwood calculations. Generations of scientists were stimulated by Tanford's work in protein electrostatics and continue to work on problems that Tanford first brought to the forefront.

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