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GEORGE SCATCHARD

1892—1973

A Biographical Memoir by

JOHN T. EDSALL AND WALTER STOCKMAYER

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BY JOHN T. EDSALL AND WALTER H. STOCKMAYER

GEORGE SCATCHARD'S many scientific contributions dealt almost entirely with the physical chemistry of solutions; with solutions in equilibrium and solutions undergoing change with time. The range of his studies was wide and deep, extending from the simplest mixtures of nonpolar molecules to systems containing highly polar molecules and ions, and to macromolecules, especially proteins. His involvement with proteins, at a time when most physical chemists avoided such complicated substances, stemmed initially from his close personal and scientific friendship with Edwin J. Cohn, whose laboratory at Harvard Medical School was close to Scatchard's own laboratory at Massachusetts Institute of Technology.

Many of Scatchard's papers are difficult reading for most chemists, for he commonly wrote in a highly condensed style, in which each sentence and equation carried nearly its maximum possible load of meaning. Yet he could write and talk with great simplicity and directness. His work on proteins brought him into touch with many biochemists and clinicians, and he took a deep interest in their problems. His advice and insight were crucial to a good many scientific papers on which his name never appeared.

He was born in Oneonta, New York on March 19, 1892, the second son and the fourth child of Elmer Ellsworth and Fanny Lavinia Harmer Scatchard. In an autobiographical sketch he wrote:

> Oneonta was a village of about ten thousand, on the Susquehanna in the northern foothills of the Catskills, about twenty miles south of the much better known Cooperstown. It was the largest village for fifty miles in any direction. Its most important industry was the shops of the Delaware and Hudson Railroad. It was also the site of the Oneonta Normal School which had about one boy student to ten girls in my time. It had an excellent High School Department when I was ready for it.
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> . . . I was an avid reader often for the almost mechanical pleasure of reading. . . . Except for reading I had the normal childhood of a small town boy—hiking, bird watching, swimming, skating, coasting and later bicycling. I helped organize and played on the "Oneonta Juniors" basketball team and later on the Oneonta Normal School team. I was manager then and officiated more than I played . . . I was a very shy child. My shyness was cured only when I worked in my brother's drugstore during my high school years. I still remember the agony of waiting on a customer at the beginning, but it could not last. At first I opened the store in the morning, swept and mopped the floor and snaked the hundred and fifty pound cakes of ice from the sidewalk to the icebox behind the store. On ice-cream days I fetched the cream about three blocks from the creamery, added the sugar and flavoring and turned the crank of the five gallon freezer. Later I graduated from the early morning and menial work. My brother had the theory that in the evenings when our neighbors from the hardware and clothing stores had gone home, we should do no work not directly connected with waiting on trade. My reading branched out into drug journals, the pharmacopeia, materia medica and prescriptions—the latter with difficulty. Most physicians had terrible handwriting and prescriptions were written with English or Latin abbreviations. . . . I did make myself into a good practical pharmacist, and managed the store when my brother was absent.*

Following graduation from high school, Scatchard entered Amherst College, from which he graduated in 1913 with the highest marks in his class. From the beginning his

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*G. Scatchard, "Autobiographical Note," *Equilibrium in Solutions and Surface and Colloid Chemistry* (Cambridge: Harvard Univ. Press, 1976), pp. xix–xx.

major interest was evidently in chemistry, and the background he had acquired while working in the drugstore undoubtedly influenced this choice. He records in his autobiographical notes that one of his teachers, Professor Howard W. Doughty, ". . . was one of the first people in the country, and probably in the world, to use simple physical chemistry in analytical chemistry." Scatchard assisted him in the laboratory. Doughty, although a Johns Hopkins graduate, advised Scatchard to go to Columbia for graduate work, and as Scatchard notes, "neither of us thought of any subject for my thesis other than synthetic organic chemistry." He entered the Columbia graduate school and did his thesis with Marston T. Bogert.

Edwin J. Cohn, who later became Scatchard's intimate friend and close scientific associate, was a contemporary as an undergraduate at Amherst. In his Cohn Memorial Lecture (1969, pp. 39–40), Scatchard included a passage that illuminates the character of both men:

> I did not like Cohn as an undergraduate. We were as different as our backgrounds. My family had to sacrifice to send me to college, though I earned most of my expenses working during the summer. Cohn had no financial problems. If he did not have the best of everything he had the most expensive, when his family did not know that that was not the best, which was seldom. He was an esthete. I regarded him as one of the flower children of my generation, less like those of the present than like those of an earlier generation caricaturized by W. S. Gilbert in *Patience*. . . . Cohn even fraternized with some of the faculty. I would approve of that now, but I did not then.

Scatchard's Ph.D. thesis at Columbia, submitted in 1916, dealt with 2-uraminobenzoic acid, benzoylene urea, quinazolines, and related compounds. It naturally reflected the interests of his thesis director, Professor Bogert, and was very different in character from Scatchard's later work. It did involve a study of the use of dinitrobenzoylene urea as an indicator in the pH range between 6 and 8, and this to some extent foreshadowed Scatchard's future interests in physical chemistry.

In 1917 and 1918 Scatchard was teaching organic chemistry, mostly as a laboratory assistant, and doing a little war research at Columbia under the direction of Professor W. K. Lewis of MIT. When the United States entered the First World War he proposed to leave and join the army, but Bogert and Lewis persuaded him to stay, on the ground that his work was important. Finally, he was drafted. Through the recommendations of Bogert and Lewis, he received a commission as first lieutenant in the Sanitary Corps, the only place where a chemist could be commissioned before the days of the Chemical Warfare Service. Shortly thereafter he was sent to France, where he accepted the opportunity of working with Victor Grignard, who was at the Sorbonne in the Laboratory of Georges Urbain, since Grignard's own laboratory at Nancy had been occupied by the Germans. With Grignard and G. Rivat, Scatchard developed a rapid and sensitive method for the detection of small quantities of mustard gas in air, a matter of urgent importance for troops in the field. In the course of the work Scatchard suffered burns of the throat with mustard gas and phosgene and was incapacitated for several weeks.

Early in 1919 he was about to return to the United States, but because of the acute shortage of medical officers he was assigned, along with a dentist, to be responsible for the medical care of fifteen hundred men who were unfit for further duty and were being transferred from St. Aignan to Brest. When he pointed out his lack of medical training they said, "You can read a clinical thermometer, can't you? You're better than nobody. If they don't have you they'll have nobody." Then he was urgently called back from Brest to Paris, where his oldest sister died of meningitis. Eventually he sailed for home on the *Orizaba,* and finally arrived in New York on his twenty-seventh birthday, March 19, 1919.

He applied for and received one of the first group of National Research Council Fellowships, but gave it up to return to Amherst as a teacher of chemistry on the invitation of Alexander Meiklejohn, president of Amherst, who had embarked on his brief but highly significant career of educational reform there. Scatchard wrote: "They were exciting years for a young teacher there [in Amherst]. Meiklejohn believed that to teach well one must be learning. He also believed that chemistry and physics are so simple that to learn about them a man must do research. He brought me to Amherst to prove that research in the physical sciences could be done in a small liberal arts college with the right atmosphere."* It was indeed at Amherst that Scatchard produced the first three papers that contained his own ideas. However, in 1923 the sharp disagreements between Meiklejohn and the Amherst trustees came to a head, and Meiklejohn resigned. Scatchard, an ardent Meiklejohn supporter, resigned also. He was reawarded the National Research Council Fellowship and went to the Massachusetts Institute of Technology to work with Duncan A. MacInnes in electrochemistry. In gratitude to the National Research Council, he later undertook, with three colleagues and a student, the arduous work of tabulating the densities and thermal expansions of aqueous electrolyte solutions for the *International Critical Tables.*

A year after going to MIT, Scatchard was appointed to the teaching staff. He was associated with the Institute for the rest of his life, becoming associate professor of chemistry in 1928, professor in 1937, and professor emeritus in 1957. His activity in research, however, continued to the end of his life, and a number of his important contributions appeared in the decade after 1960.

The years at MIT, from his arrival there until the Second World War, were a time of steady development of Scatchard's

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*Scatchard, "Autobiographical Note," p. xxiv.

theoretical and experimental studies on solutions. In the following section we trace the progress and the character of these fundamental studies. The range of his scientific interests, however, extended beyond that of most members of the Chemistry Department at MIT. This was primarily due to the influence of Edwin Cohn.* We have seen that Scatchard and Cohn had not been congenial as undergraduates at Amherst. Of the close friendship that developed from 1923 on, Scatchard spoke on two occasions: first in an address on Cohn's scientific work, when Cohn received the Theodore W. Richards Medal in 1948; and then twenty-one years later in his Cohn Memorial Lecture (1969). On the latter occasion he wrote:

> Soon after I came to MIT in 1923, Cohn and I attended a reception of the Science Club of Amherst College for Niels Bohr. We stayed with a mutual friend and drove back to Cambridge together. I was surprised to find that he thought more like me than anybody I had ever met. His thoughts were more developed and polished than mine, but there was little other difference. From that day we became close friends and frequent collaborators although we never published a paper together.
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> It is difficult to realize how customs have changed since that time. When I came to MIT, I was the only one who called himself a physical chemist in the area, perhaps in the country, who would listen to a physician or even a physiologist talking science. Cohn is probably responsible for my doing so.

Cohn's field of research was the physical chemistry of proteins. Scatchard became deeply concerned with these macromolecules and developed his thinking about solutions to encompass their special properties, as well as those of simpler molecules and ions. We speak later of his work in that area; here we simply note the importance of the relation between these two very different men. Cohn was a driving,

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*See J. T. Edsall, "Edwin Joseph Cohn (1892–1953)," in *Biographical Memoirs* (Wash., D.C.: National Academy of Sciences, 1961), 35:47–83.

aggressive, dynamic organizer, with an excellent capacity for perceiving important scientific problems and arousing the enthusiasm of his associates, while maintaining rigorous standards of work in the laboratory. Scatchard was quieter; he never operated with a large group of people in his laboratory; in his thinking about the fundamentals of the chemistry of solutions he went deeper than Cohn, and his critical judgment was more rigorous and searching, with a far greater command of basic theoretical chemistry. In their complementary relation the two men were stronger than either could have been alone.

In 1928 Scatchard married Willian Watson Beaumont, always called Billie by him and their friends. He had known her since 1916, when he was a graduate student at Columbia and she was taking a degree there in education, in preparation for her career as a teacher of music. She was born and brought up in Montana and had taken two degrees in music at the University of Montana before coming east. She taught music in New York for some ten years before their marriage, and thereafter joined the Department of Music in Smith College, Northampton, Massachusetts, about a hundred miles from Cambridge. They lived in Cambridge in an apartment on Memorial Drive, overlooking the Charles River, near Harvard Square. Because of the demands of her work, she was away for just over half the week during the academic year. Each Sunday evening she took the train to Northampton, returning on the following Thursday afternoon. That evening she would go down to MIT to conduct the women's chorus there. On Saturday evenings throughout the concert season, she and George almost invariably attended the concert of the Boston Symphony Orchestra. Then, on the following evening, she returned again to Smith. This cycle was repeated, throughout the academic year, until her retirement from Smith in 1957. During George's year abroad as a Guggenheim Fellow in 1931–32, they attended several musical festivals together. He shared her deep love of music, and their life together was congenial and harmonious, in spite of the circumstances that obliged her to spend so much time away from Cambridge.

The coming of the Second World War brought urgent new demands into George Scatchard's life. He led a triple life. He was acting director of the Physical Chemistry Laboratory at MIT and had to keep the department running in a period of great stress. He was scientific advisor in the Manhattan Project to Harold Urey at Columbia, where he did important work on the thermodynamics of the fluorocarbon systems that were needed for the separation of uranium isotopes by diffusion; he commuted weekly to New York to take part in this work. He devoted even more of his time to the work on the blood plasma fractionation project, headed by Edwin Cohn, which grew into a major enterprise, involving dozens of chemists, biochemists, and clinicians, and seven major pharmaceutical firms that produced for the armed forces the serum albumin, gamma globulin, and other products of plasma fractionation that were used in medicine and surgery. Scatchard served as an advisor on almost every aspect of the program; he was particularly concerned with serum albumin, with its osmotic action, important in the treatment of shock, and with its capacity to bind rather tightly all sorts of small molecules and ions. This led him into important researches in his own laboratory that continued long after the war; of these we speak later, in the discussion of his work on proteins.

In 1946, when the war was over, he served for six months as scientific advisor to General Lucius D. Clay, deputy military governor of the Office of Military Government in Berlin. In those chaotic days there was much confusion and conflict in dealing with the problems of a defeated and divided Germany, with four powers occupying different parts of the country. Scatchard dealt with many problems involving German science and scientists, and had some battles with the Russian members of the quadripartite committee during his first days in Berlin concerning the treatment of German scientists. After that things were calmer. He returned to the United States, to his research and teaching at MIT, at the end of 1946.

Not long after this he became a scientific consultant to the Oak Ridge National Laboratory, and for many years he and Mrs. Scatchard stayed at Oak Ridge for about six weeks each summer. He collaborated closely during those years with K. A. Kraus and J. S. Johnson, and extended his treatment of the thermodynamic properties of solutions containing charged macromolecules to a rigorous treatment of sedimentation in the ultracentrifuge. Later his collaboration with them, and with Y. C. Yu and R. M. Rush, involved studies of mixed electrolyte solutions containing many components, a subject with which he was closely concerned during the last years of his research at MIT.

He retained his mental alertness to the end of his life, but his physical energy declined gradually during his final five years. In 1970 he fell and broke his hip, and had to remain several months in a nursing home. He was then able to return to the apartment in Cambridge, but did not regain his previous energy and vitality. With Mrs. Scatchard's devoted care, his life remained pleasant and comfortable; he enjoyed seeing his friends and talking with them about science and the world in general, but he was easily fatigued and usually did not attempt to rise from his chair when visitors arrived. In December 1973, after dental surgery that required general anesthesia, he suffered a fatal heart attack and stroke.

RESEARCH ON NONELECTROLYTE SOLUTIONS

Because of the breadth and diversity of Scatchard's research work, a purely chronological account of it would lack coherence. As we have seen, he was interested in systems aqueous and nonaqueous, electrolytes and nonelectrolytes, small molecules and macromolecules, and colloidal systems where surface forces were important. Moreover, though he was concerned mainly with equilibria, he did not neglect reaction rates. Usually he would work simultaneously in several different areas, frequently with fruitful overlap between them. The divisions chosen in our description of his scientific contributions are thus certainly arbitrary and in some ways artificial.

At Amherst College, his first independent work dealt with the hydrolysis rates and vapor pressures of concentrated aqueous sucrose solutions. Assuming that mole fractions were the most fundamental units of concentration and that in sugar solutions the various hydrated species could be treated as ideal solutes with activities equal to their mole fractions, Scatchard estimated the hydration of dissolved sucrose from both the rate and equilibrium data, with satisfactory agreement between the two methods. Years later, in referring to the ideal law for the entropy of mixing, on which the above treatment fundamentally rests, he remarked drily that most attempts to justify it in physical terms were "more entertaining than convincing."

In 1931 Scatchard published what he later considered to be his first important paper, a definitive theoretical discussion of the thermodynamics of nonelectrolyte solutions. In common with other contemporary treatments, he assumed that the entropy of mixing was ideal, so that the deviations of real solutions from the ideal laws were to be related to the enthalpy changes on isothermal mixing. Such solutions had been dubbed "regular" by Joel Hildebrand. The difference among the several existing theories lay in the interpretation of the mixing enthalpy. Thus Hildebrand (largely on the basis of solubilities and other data) and Heitler (from a lattice model) regarded this quantity as a quadratic function of the composition expressed as mole fraction; Irving Langmuir preferred "surface fractions," involving estimated molecular surface areas; while Scatchard, like his predecessor J. J. van Laar, argued that a quadratic expression in the volume fractions was most suitable. Moreover, Scatchard gave the simplest and most successful formula for predicting the magnitude of the mixing enthalpy, based on what he called the "cohesive energy density" (a piece of nomenclature which has survived). Unlike its rivals, Scatchard's expression can be completely evaluated numerically from the properties (vapor pressures and densities) of the pure components, and it thus constituted a genuinely predictive theory, which he showed in the same paper to give a rather good account of the existing data for many binary nonpolar solutions. Later, in the course of demonstrating further applications of the theory in several papers with W. J. Hamer, Scatchard introduced the notion of the excess free energy, defined simply as the difference between real and ideal free energies. Today the use of excess functions provides the most commonly used procedure for characterizing the thermodynamic properties of solutions.

In the foregoing paragraph we make no attempt to describe the methodology used by Scatchard in arriving at his theory, and indeed he did not present this completely. Like essentially all physical chemists of his generation, he did not use the formal methods of statistical mechanics, but relied on more intuitive arguments. The applications of statistical thermodynamics to solutions began a few years later in England, when R. H. Fowler, E. A. Guggenheim, and their followers studied lattice models and thus defined more sharply the fundamental basis of Scatchard's and related theories. Scatchard followed these and later developments with great interest, but did not again attempt a complete theory. His mastery of the classical thermodynamics of Gibbs was, however, brought out in an important paper in 1937. In this article he showed how experimental data obtained under constant pressure conditions should be converted to a constant-volume basis for more rigorous confrontation with theory.

During the same period, Scatchard and his collaborators, including Hamer, S. E. Wood, H. H. Gilmann, C. L. Raymond, and J. E. Mochel, constructed an accurate "equilibrium still" for the measurement of vapor pressure and composition over a range of temperatures, and produced data of then unrivalled accuracy and precision for a number of binary liquid mixtures. These results revealed complexities of thermodynamic behavior not encompassed by the earlier theory. There was, of course, strong evidence of hydrogen bonding in chloroform-ethanol. The benzene-cyclohexane system was not "regular," despite the nonpolar nature of both components, revealing a distinct positive excess entropy even at constant volume. Solutions of methanol with carbon tetrachloride and benzene were more complex still; in the latter case, the excess entropy was positive at low concentrations of methanol, but became negative at higher methanol content.

About 1950 a new equilibrium still was built and was used to investigate H_2O-H_2O_2 mixtures (then of practical interest) and also the ternary system benzene-carbon tetrachloride-methanol, for which data on the three parent binary combinations had already been obtained. At about the same time Scatchard developed a simple calorimeter to obtain heats of mixing more accurate than those derived from temperature coefficients of vapor pressures. A few years later, the final work on nonelectrolytes in his laboratory involved construction by F. G. Satkiewicz and G. M. Wilson of yet another apparatus for studying vapor-liquid equilibrium, and its use for several polar systems. Wilson found a simple and remarkably successful two-parameter equation for correlating these results,* but neither Scatchard nor anyone else has offered a complete derivation of it.

Today the simple 1931 theory still finds useful practical applications, thanks in large part to its further systematic development by Hildebrand and his students in terms of the "solubility parameter," which is the square root of the cohesive energy density. From a purely theoretical standpoint, however, it now has mainly historical interest.

INTERACTIONS OF IONS, DIPOLAR IONS, AND UNCHARGED MOLECULES

Scatchard promptly assimilated the Debye-Hückel theory of interionic attraction when it appeared in 1923.† Not long after joining the MIT faculty he initiated a comprehensive study of the freezing points of aqueous salt solutions, including salt mixtures. The results of these studies, which also involved mixed solvents (water-alcohol, water-dioxane), appeared in ten papers from 1932 to 1936. The principal collaborator in this work was S. S. Prentiss; P. T. Jones and M. A. Benedict were also involved. The experimental technique was the most precise yet devised for such measurements, and the calculation of osmotic and activity coefficients from the data followed the general approach of G. N. Lewis and his associates, but with certain refinements.

The freezing-point data in dilute solution amply confirmed the validity of the Debye-Hückel limiting law; in addition, the measurements on solutions of salt mixtures gave strong support to J. N. Brönsted's "principle of specific ion interactions" and to a corollary commonly known as Harned's

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*G. M. Wilson, *Journal of the American Chemical Society,* 86 (1964):127–30.

†Concerning Peter J. W. Debye, whose work profoundly influenced Scatchard, see M. Davies, *Biographical Memoirs,* (London: Royal Society, 1970), 16:175–232; J. W. Williams, *Biographical Memoirs,* (Wash., D.C.: National Academy of Sciences, 1975), 46:23–68.

rule. Scatchard presented the Brönsted principle in his graduate course on solutions, with a characteristic humorous twist. In his *Equilibrium in Solutions* (published posthumously in 1976) he remarked, "The theory may be stated very simply, and it is reminiscent of the famous chapter in a natural history of Ireland: '*The Snakes of Ireland.* There are no snakes in Ireland.' The principle is that the electrostatic forces are so strong that ions with charges of like sign never approach close enough for their short-range, non-electrostatic specific interactions to become appreciable" (p. 143). The students naturally remembered this quotation with pleasure. In one memorable Christmas skit, the student who played Scatchard (disguised as King Lear) received a gift from Ireland which wriggled out of its container and caused him to exclaim "Gad! Brönsted must be wrong!"

Scatchard also recognized the importance of the salting-out effect, which involves the interaction of ions with uncharged molecules in aqueous solutions. The solubility (S) in water of a molecule containing nonpolar groups generally decreases as the concentration of salt (C_s) increases, according to the equation:

$$-\log(S/S_0) = \mathrm{K}_s C_s$$

Here S_0 is the solubility of the nonelectrolyte in the absence of salt, and K_s is the salting-out coefficient. Debye interpreted salting out in terms of the preferential attraction of the highly polar water molecules around the ion, the less polar solute molecules being "squeezed out," so that their solubility diminished. In special cases, as with highly polar solutes, and with certain anions such as iodide or thiocyanate, K_s becomes negative and the solute is actually "salted in."

As was well known, proteins are also salted out at high salt concentrations, and the salting-out coefficients are much larger than for small compounds. Scatchard was well aware of this, through his discussions with Cohn, and he incorporated such interactions into his thinking from an early stage in his career.

In the middle thirties, Scatchard turned to more concentrated electrolyte solutions; in a notable review in 1936 he combined the Debye theories of ion interaction and salting-out with his own treatment of nonelectrolytes (to deal with the "specific interactions") and, with the aid of a single disposable parameter chosen to match the data for sodium chloride, produced an impressive fit of the data for all alkali halides up to concentrations of the order of 6M. At the same time, he initiated a new experimental program of measuring the activities of concentrated solutions of nonvolatile solutes (both electrolyte and nonelectrolyte) by the isopiestic method of R. A. Robinson.

The Debye-Hückel limiting law, however, was soon again to intrude on Scatchard's thoughts. T. Shedlovsky and D. A. MacInnes reported that dilute aqueous solutions of lanthanum chloride, as measured by "concentration cells with transference," displayed serious disagreement with the limiting law. A new and still more precise freezing-point apparatus was thereupon designed and built in Scatchard's laboratory by B. Vonnegut and D. W. Beaumont. Their measurements were finished in 1942 and gave results for lanthanum chloride which strongly supported the Debye-Hückel theory. Scatchard held off publication until well after Shedlovsky had discovered a computational error in the emf (electromotive force) data, bringing the disagreement to an end.

In 1949 another defense of Debye and Hückel was called for after A. R. Olson and T. R. Simonson at Berkeley had presented extensive measurements of salt effects on rates of second-order reactions (and also some equilibria) involving two ions with charges of like sign. They showed (in amplification of some earlier work by V. K. LaMer) that under most experimental conditions the concentration of oppositely charged ions, rather than the ionic strength, was the important controlling variable. On this basis some chemists questioned the entire Debye-Hückel theory. Scatchard again responded to the challenge, showing by numerous calculations based on the modern extended theories of J. G. Kirkwood and of J. E. Mayer and J. D. Poirier that the essential Debye-Hückel model of charged hard spheres in a dielectric continuum (now often called the "primitive model" of electrolyte solutions) could account for all the results, but that for solutions of highly charged ion species one should, of course, not expect the ionic-strength principle or the limiting law to hold except at very low concentrations. This work appeared in a symposium at the National Bureau of Standards (1953).

STUDIES ON AMINO ACIDS AND PROTEINS

Scatchard and Cohn, from about 1924 on, constantly discussed the relation of the Debye-Hückel theory and the salting-out effect to the behavior of proteins, especially the solubility of proteins in salt solutions. Addition of small amounts of salt greatly increases the solubility of many proteins in water. This was, at least qualitatively, to be expected of molecules like proteins, with their electrically charged groups, in the light of the Debye-Hückel theory. At much higher concentrations of salts such as ammonium sulfate, proteins had long been known to be salted out, the protein concentration dropping very rapidly as the salt concentration increased.

E. Q. Adams in 1915 and Niels Bjerrum in 1923, with a much greater array of evidence, had concluded that aliphatic amino acids, even at their isoelectric points, bear positive and negative charges, separated by substantial distances; that is, an isoelectric α-amino acid has the formula $^+H_3N{\cdot}CHR{\cdot}COO^-$, not $H_2N{\cdot}CHR{\cdot}COOH$, as nearly all chemists had supposed earlier. The centers of positive and negative charge, separated by about 3Å, should give rise to a large dipole moment of about 15 Debye units. Isoelectric proteins, with many positive and negative charges, should possess much higher moments than this. They might therefore be expected to interact with ions of salts, at least qualitatively, as if they were ions, even though the net charge on the protein (or amino acid) was zero; that is, the molecule was a so-called zwitterion, or dipolar ion. The nature of such interactions gave rise to intense discussion in Cohn's laboratory; and Scatchard took a most active part in the seminars there. The mathematical problems of calculating interactions between ions and dipolar ions were formidable, and taxed even Scatchard's very considerable mathematical powers. Fortunately a brilliant younger associate at the Massachusetts Institute of Technology, John G. Kirkwood, became involved in the discussions. Scatchard and Kirkwood undertook a joint theoretical research during the year 1931–32, when they and Cohn were on leave of absence in Europe. Their calculations involved a "dumbbell" model of a zwitterion, composed of two charged spheres, one positive and one negative, separated by a thin rigid connection. It soon became apparent that the activity coefficient of any such model, in the lower limit near zero ionic strength, would be a linear function of the first power of the ionic strength, not of the square root, as in the case of an ion carrying a net charge. Scatchard, in his autobiography, described a discussion with Debye in Leipzig. "When I introduced Kirkwood to Debye, he (Debye) was apparently very busy and did not invite us into his office. He asked what we were working on. I said we were correcting Bjerrum's statement that molecules with widely separated charges behave like two independent ions even in the limiting law. Debye said, 'Bjerrum must be right.' I said, 'Do you forget that at infinite dilution the ion atmosphere is at an infinite distance?' Debye said, 'That's right. Bjerrum must be wrong.' "*

The resulting paper appeared, in German, in the *Physikalische Zeitschrift* in 1932. Its fundamental conclusions were qualitatively sound, but the model was still inadequate for describing such molecules as amino acids. It was Kirkwood who carried the problem much further, by calculations on spherical and ellipsoidal models with charges appropriately placed. These provided an excellent basis of comparison with the experimental data obtained in Cohn's laboratory on amino acids and peptides; the correspondence of theory and experiment was impressive. Kirkwood went on to a brilliant career at Cornell, California Institute of Technology, and Yale—a career tragically cut short by his death from cancer at the age of fifty-two. Scatchard's relation with Kirkwood was second only to that with Cohn in its combination of personal friendship and closely shared scientific interests. Scatchard's brief memoir (1960) is at present the best account we have of Kirkwood's career.

Scatchard's freezing point studies on ethanol, glycine, sodium chloride, and their mixtures demonstrated both the "salting in" of glycine by the salt, due to electrostatic interactions, and the salting out of ethanol and the repulsive interactions between ethanol and glycine, due to the nonpolar portion of the ethanol molecule and its interaction with the positive and negative charges on the glycine dipolar ion. Related studies of solubilities of amino acids, in media containing salts and ethanol, were proceeding at the same time in Cohn's laboratory. The solubility studies were more comprehensive in scope, but Scatchard's measurements had the advantage of being carried out at very low concentrations of the solute molecules and ions, where the interaction

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*Scatchard, "Autobiographical Note," p. xxviii.

coefficients could be determined with less ambiguity of interpretation.

OSMOTIC PRESSURE OF PROTEINS AND BINDING OF IONS AND OTHER LIGANDS

Scatchard's interest in proteins had certainly begun before 1925, as a result of his constant interchange of ideas with Cohn. It was the blood plasma fractionation program in the Second World War, however, that drew him to study proteins in his own laboratory; these studies continued for the rest of his career in research.

His major concern was with serum (plasma) albumin, which plays the major role in maintaining osmotic equilibrium between the plasma and the cells and tissues with which it is in contact. It was therefore a matter of great practical concern, and also of fundamental scientific interest, to determine accurately the osmotic pressure of albumin solutions under varied conditions.

Several investigators, notably S. P. L. Sörensen in Copenhagen and G. S. Adair in Cambridge, England, had made excellent use of osmotic pressure to determine the molecular weights of proteins. Scatchard's work was distinctive in extending the measurements over a wide range of both pH and salt and protein concentration, and in avoiding the use of buffers other than the albumin itself. This permitted the evaluation of thermodynamic interaction coefficients between the albumin molecules, over a wide range of positive and negative net charge, and between the albumin and the ions of the salt (sodium chloride). The experimental work (reported in 1946) was done in collaboration with A. C. Batchelder and A. Brown. In an immediately preceding paper, Scatchard developed the thermodynamic theory of osmotic pressure with a degree of rigor never previously attained; the paper makes difficult reading, even for most of the specialists in the field, but it is fundamental. Scatchard, Batchelder, and Brown determined the molecular weight of bovine serum albumin as 69,000, and they characterized the protein-protein and protein-salt interactions in great detail.

Perhaps the most striking finding to emerge from their study was the selective tendency of albumin to bind anions, such as chloride, even when the albumin molecule carried a net negative charge, which would tend to repel anions and attract cations. They found no evidence that sodium ions were bound. These observations led to Scatchard's long series of researches on ion binding by albumin. One approach, demonstrated in his work with E. S. Black (1949), was to add salts to an isoionic solution of albumin—that is, to a solution initially containing only water, albumin, hydrogen, and hydroxyl ions. The mean net charge on the isoionic albumin is close to zero. If a salt is added, the albumin selectively binds the anion, thus acquiring a negative net charge. This in turn causes the ionized carboxylic groups in the albumin to bind more protons by electrostatic attraction, thus removing H^+ ions from the solution and thereby raising the pH. The greater the anion binding, the greater the upward shift in pH. The measurements indicated that, for instance, binding of anions increased in the order chloride $<$ iodide $<$ thiocyanate.

Most of the further studies of ion binding involved electromotive force measurements. The first major studies, with I. H. Scheinberg and S. H. Armstrong, Jr. (1948), dealt with the binding of chloride and thiocyanate ions. Later Scatchard devoted much effort to the development of ion-exchanger electrodes. His reasons were well stated in a later paper:

> Ion exchangers have advantages in the electrochemical study of protein solutions because their pores are too small to admit protein molecules and because they repel ions of the same sign. Therefore, even in the presence of protein, a cation exchanger membrane behaves as a small-cation elec-

> trode and an anion exchanger membrane as a small-anion electrode in the same sense that a glass membrane may behave as a hydrogen electrode.
>
> Some advantages are that there is no oxidation or reduction at these membranes, they are not limited to ions for which there are reversible true electrodes, and the combination of a cation and an anion exchanger permits the measurement of the free energy of transfer of the salt. [Scatchard, Coleman, and Shen 1957, p. 12.]

The paper by Scatchard, Wu, and Shen (1959) reported the most accurate and comprehensive studies on ion binding by albumin by studies of pH and electrical potentials of anion-exchanger electrodes, and in more concentrated solutions by osmotic pressure measurements. They inferred from this work three classes of anion-binding sites on the albumin: a single site in the first class showing very strong binding; eight in the second class, with weaker binding; and eighteen in the third class, with still weaker binding. The ratio of the association constants, for both chloride and iodide, for the three classes, was given by the relation: $K_1 = 24K_2 = 720K_3$.

The special features of the serum albumin molecule that give it this remarkable tendency to bind all sorts of anions were still obscure, and remain obscure today. Serum albumin is unique among proteins in this respect.

Scatchard's studies on ion binding led him to an equation of extreme simplicity for plotting binding data to evaluate the number of binding sites and the association constants involved. The simplest case arises when there are n equivalent and independent sites in a macromolecule for the binding of a given ligand. In this case the data can be described by a single association constant k. If n and k are both initially unknown, the problem is to evaluate them as accurately as possible from the data. Assuming that electrostatic interactions between the charged protein and the anion could be neglected, Scatchard concluded that the best plot of the data, which would give the most appropriate relative weight to the various measurements of amount of ligand bound ($\bar{\nu}$), corresponded to the form:

$$\bar{\nu}/c = k(n-\bar{\nu})$$

where k is the intrinsic association constant, and c is the concentration of free ligand. If the basic assumptions hold, the plot of $\bar{\nu}/c$ as ordinate against $\bar{\nu}$ as abscissa is a straight line of negative slope; the intercept on the abscissa gives n, that on the ordinate gives kn. This equation, which Scatchard first employed in a discussion on "The Attractions of Proteins for Small Molecules and Ions" (1949) has proved enormously useful, and such "Scatchard plots" appear in dozens of papers every year.

Such plots may deviate greatly from linearity if binding at one site affects binding at others, or if there are different classes of binding sites with inherently different affinities for the ligand. Scatchard considered in his discussion how such factors modify the representation of the data, and how to derive information about the nature of the system from plots of the above variables in more complicated cases. Further work by others has shown that Scatchard plots for proteins that undergo important conformational changes during ligand binding (allosteric transitions) may assume quite unusual shapes.*

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*The Michaelis-Menten equation for the rate of an enzyme-catalyzed reaction is mathematically equivalent to the equation for the binding of a ligand at a set of identical and independent binding sites. This is discussed in detail by J. T. Edsall and J. Wyman (*Biophysical Chemistry*, vol. I, pp. 620–23 [New York: Academic Press, 1958]). The initial rate (v) of the enzyme-catalyzed reaction corresponds to $\bar{\nu}$, the maximum velocity ($V_{\max}$) to n, and the reciprocal of the Michaelis constant (K_M^{-1}) to k. The equivalent of the Scatchard plot, in enzyme kinetics, was apparently first proposed by Barnet Woolf of Cambridge University, and published in J. B. S. Haldane and K. G. Stern (*Allgemeine Chemie der Enzyme* [Dresden and Leipzig, 1932], p. 119). We take this information from M. Dixon and E. C. Webb (*Enzymes*, 2d edition [Academic Press, 1964], p. 69). Later G. S. Eadie (*J. Biol. Chem.*, 146

One of us (J. T. E.) is indebted to Scatchard for another valuable method of calculating binding constants for molecules or ions with n initially equivalent binding sites, with interactions between them. Here n is a known quantity, and the problem is to determine the n successive binding constants. Examples are ions such as Ca^{++} or Zn^{++}, with four binding sites for such ligands as ammonia or imidazole, and hemoglobin with its four heme groups, binding oxygen or carbon monoxide. Scatchard's proposal was to plot a quantity $Q = \bar{\nu}/(n-\bar{\nu})c$ (or log Q) as a function of the bound ligand, $\bar{\nu}$, which varies from 0 to n as the concentration (c) of free ligand increases. It is readily shown that the limiting value of Q as $\bar{\nu}$ approaches zero equals K_1/n, where K_1 is the first association constant; and the limiting value of Q as $c \rightarrow \infty$ is nK_n, where K_n is the n'th association constant. Knowledge of these limiting K values is an important first step in calculating the other association constants. The method demands high accuracy in determining the values of $\bar{\nu}$, in the neighborhood of $\bar{\nu} = 0$ and $\bar{\nu} = n$. The plot of log Q against $\bar{\nu}$ also reveals immediately whether the interactions between the binding sites are cooperative, with a curve that rises as $\bar{\nu}$ increases, or anticooperative, with a descending curve. Equivalent and independent groups give a horizontal straight line. On Scatchard's suggestion this plot was first used by Edsall *et al.*,*

[1942]:85) also independently derived and used the equation. Thus what we may call the "Woolf plot" anticipated the Scatchard plot by seventeen years. Scatchard was almost certainly unaware of this. It is interesting to note that the enzyme chemists have made very little use of this method of plotting their data, whereas the workers on equilibrium binding have employed the Scatchard plot in hundreds of papers.

An important discussion on the various forms assumed by the Scatchard plot, for independent sites, interacting sites, and mixed interacting and noninteracting sites, is given by A. A. Schreier and P. R. Schimmel (*Journal of Molecular Biology,* 86 [1974]:601–20) in a study of the binding of manganese ions to transfer RNA.

*J. T. Edsall, G. Felsenfeld, D. S. Goodman, and F. R. N. Gurd, *Journal of the American Chemical Society,* 76 (1954):3054. See also J. T. Edsall and J. Wyman, *Biophysical Chemistry,* vol. I (New York: Academic Press, 1958), pp. 629–35.

who were studying the binding of imidazole to Zn^{++} and Ca^{++} ions. A number of authors used it later. Since Scatchard was not listed as an author on any of these papers, we take this opportunity to note this valuable contribution.

COLLABORATIVE WORK AT THE OAK RIDGE NATIONAL LABORATORY

Scatchard's collaboration with J. S. Johnson, Jr. and K. A. Kraus at Oak Ridge began in 1950 and continued every summer for some fifteen years, during the summer periods when Scatchard was free to leave MIT. It included elaborate calculations of the distribution of charged polymers at equilibrium in a centrifugal field, the use of interference optics in such studies, and studies on silicotungstic acid in the ultracentrifuge and by light scattering. Later, with Johnson, R. M. Rush, and Y. C. Wu, he undertook extensive studies of the osmotic activity coefficients of salt mixtures. These papers show Scatchard's almost unparalleled grasp of the complexities of the thermodynamic interactions in multicomponent systems. They furnish outstanding examples of the interpretation of such complex systems in terms of simpler systems, where only one or two solute components at a time are considered.

Scatchard's last student at MIT, H. F. Gibbard, Jr., studied the vapor-liquid equilibrium of synthetic seawater solutions from 20 to 100°C, and made detailed studies of liquid-vapor equilibrium in aqueous lithium and sodium chloride solutions, over a wide range of composition and temperature.

Dr. J. S. Johnson, Jr. of Oak Ridge has provided illuminating comments on Scatchard's role as a consultant there. He wrote that his scientific group "particularly benefited, because of several common interests—ultracentrifugation, ion exchange, thermodynamics of solutions—[and because] he has a trait oddly rare, in my experience, in consultants

. . . he discusses with you your problems, rather than his. . . . His patience in explicating his ideas to us has been immense. Once one understands what he is about, intriguing subtleties frequently become apparent in his style. There are other occasions, particularly in his MIT lecture notes, when he has produced about the only worthwhile discussion of many topics. And there is no ally I'd rather have in a scientific controversy" (quoted from I. H. Scheinberg's introduction to Scatchards' *Equilibrium in Solutions* [1976]).

SCATCHARD AS THINKER, TEACHER, AND CRITIC

George Scatchard was a master of the science of thermodynamics. In his insight into the thermodynamic relations of systems containing many components, he was directly in the line of descent from Willard Gibbs. He resembled Gibbs also in his resolutely brief and austere presentation of his results. It was often not easy to follow the path by which he traveled from basic principles to final results, but those who made the effort could always verify the fact that the path was there, and that it provided a firm footing for the traveler. Moreover, deeply though he valued the elegance and rigor of pure thermodynamics, he was always concerned with the nature of molecules and their interactions. In his published work he made scarcely any use of the formal relations of modern statistical mechanics. Throughout his career, however, he was concerned to understand what he called, in one of his semi-popular lectures (1950), "the social behavior of molecules." His interests ranged from the monatomic gases to the large proteins, and his contributions to our understanding of their interactions were fruitful all along the line.

His standards of work were high, and he could be a severe critic. Charles Tanford has described this aspect of his character well:

> He did not necessarily expect others to match his own precision of thought or experiment, but he expected them to try their best. When he detected gross confusion or misconceptions, and especially when they masqueraded behind a facade of glib showmanship, he could be merciless. He will not be forgotten by anyone who presented seminars at the Harvard–MIT Physical Chemistry Colloquium when he was present. There was a perpetual frown on his face, deepening at each point where the speaker was glossing over theoretical or experimental difficulties. At the end of the seminar there was relief when he asked an innocuous question, and (depending on the personality of the speaker) either anger or a silent resolve never to err again when he rose to expose a fallacy. There are undoubtedly some who remember George Scatchard with less than affection as the result of such an encounter, but there are many more who are grateful for his example and for the effect it had of raising their own standards of what is and is not a valid piece of scientific research."*

He was involved in polemics on several occasions, when he felt it necessary to criticize sloppy work and thinking in published papers or books. For many years at MIT he taught a course in surface and colloid chemistry. In his Kendall Award Address (1962; published, 1973), "Half a Century as a Part-time Colloid Chemist," he contrasted ". . . the unionists—Einstein and Svedberg for example—who held that a colloid particle is a macromolecule, like an ordinary macromolecule only more so, as opposed to the isolationists like (Wolfgang) Ostwald who claimed that the world of neglected dimensions was subject only to its own laws." In his early days, as he said in the same article: "The textbooks on colloid chemistry . . . seemed mostly cook book or nonsense." In his own class notes on his course, posthumously published in 1976, he presented the subject in solid and rigorous fashion. The major part of the same book, *Equilibrium in Solutions,* was written for his graduate course at MIT. As one of us (W. H. S.) has written in the introduction to that book:

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*From an (unsigned) obituary in *Nature,* 248 (1974):367.

> It conveys, in the same compressed style that makes his major papers difficult, Scatchard's methodology in dealing with solutions of any degree of complexity, from noble gas mixtures to multicomponent electrolyte or protein systems. It is this breadth and the continuous subtle interplay between strict thermodynamic reasoning and intuitive molecular interpretation which are unique. Although the modern student of solutions will not find the extensive statistical-mechanical developments of the past two decades, he will find in Scatchard's chapters many guides and examples of procedures that are still viable and valuable. It is not irrelevant (or irreverent) to suggest a qualitative parallel with the papers of Gibbs, and indeed this suggestion has already been made by others. [Cambridge, Mass.: Harvard Univ. Press, 1976, p. xvii–xviii.]

In the early 1920's he submitted a paper on the activities of hydrochloric acid in solutions, by electromotive force measurements. Merle Randall in Berkeley, who reviewed this manuscript, wrote that his own freezing point measurements on this system made all other measurements obsolete, and asked that he should be permitted to discuss his measurements before anyone else. At this point, Scatchard notes in his autobiographical sketch, "I fought." Later, in 1925, at an American Chemical Society meeting in Pasadena, he met Professor William Bray of Berkeley, who said: "Scatchard, you don't look nearly as belligerent as I expected."* Bray had seen all the correspondence; he and Scatchard soon became very good friends.

Many years later (1950) Scatchard reviewed the well-known treatise on *Thermodynamics* by E. A. Guggenheim, a book with a strongly individual flavor. In his searching review Scatchard remarked that the book might well be subtitled *Pride and Prejudice.* Guggenheim, who dearly loved an argument, duly noted the comment in the preface to the second edition, and invited his readers to judge for themselves.

Although Scatchard could thus be a formidable critic, there were many workers, especially biochemists and clinical

*Scatchard, "Autobiographical Note," p. xxvi.

investigators, who found him most approachable and helpful when they came to him to discuss their problems. In personal discussions he learned to gauge the level of scientific understanding of those who came to see him, and he spent countless hours in helping to disentangle their problems and to suggest fruitful lines of approach. His formulation of the "Scatchard plot" for analyzing the binding of small molecules to proteins grew out of such discussions with the protein chemists. He was well aware of the practical importance of such phenomena, as in the stabilization of serum albumin against heat denaturation by addition of certain fatty acid anions to the solution, which permitted the solution to be heated so as to destroy the virus of serum hepatitis. For many years after World War II he worked closely with the Commission on Plasma Fractionation to help insure the quality and safety of serum albumin preparations for clinical use, and was always vigilant and helpful as an adviser.

As a teacher in undergraduate courses, Scatchard was somewhat baffling to many of the students. He did make serious efforts to present basic material simply, but many points that were elementary to him were not easily grasped by most undergraduates, and they often lost the thread of his thinking at a rather early stage. Indeed some students used to refer to the time of his lectures as the "mystery hour." This was in contrast to his capacity for patient and careful explanation when he was talking to individuals. In the give-and-take of mutual discussion he would gradually discover the difficulties that were troubling his interlocutor, and clear them away, step by step. Almost anyone who came to him with a real desire for clarification of some difficult point would leave with a better understanding than when he came.

HONORS AND AWARDS

Scatchard received the honorary degree of Sc.D. from his college, Amherst, in 1948. He was elected to the National

Academy of Sciences in 1946, and was a Fellow of the American Academy of Arts and Sciences. The award that he most valued was probably the Theodore Richards Medal of the American Chemical Society, which he received in 1954. His long concern with systems of colloidal dimensions was recognized by the Kendall Award in Colloid Science (1962).

IN THE WRITING of this memoir, Mrs. Scatchard was most helpful in commenting on earlier drafts of this biography, and in supplying photographs and other unpublished material. She died in 1976. We are indebted to Dr. I. H. Scheinberg for his personal recollections of George Scatchard, many of them embodied in his introduction to Scatchard's *Equilibrium in Solutions* (1976), which also includes the recollections of several other colleagues who were closely associated with Scatchard, the present authors among them. We thank the Harvard University Press for permission to quote some passages from this introduction, and also to include extensive quotations from Scatchard's autobiographical note in the same volume.

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