ELSEVIER

Biophysical Chemistry 100 (2003) 99–103

Biophysical Chemistry

www.elsevier.com/locate/bpc

Thinking about John T. Edsall

Alexander Rich*

Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139-4307, USA

Received 26 April 2002; accepted 27 May 2002

After entering Harvard College as a freshman in the fall of 1942, I experienced the usual confusion of a young student without a clear goal in mind. It took me almost 2 years to decide that I wanted to study biochemical sciences after having flirted with philosophy and physics. My first contact with John Edsall was probably in the spring of 1944 when I began taking a biochemistry course, and John was the head of the biochemical sciences tutorial program. Of course, this was in the middle of World War II, and I had already enlisted in the Navy V12 Program and remained at Harvard in that program. Like many others, however, I left college in mid-1944 to undertake a more active form of military duty and remained away from Harvard until the beginning of the Spring Term of 1946. At that time, I returned to complete undergraduate training and do an undergraduate thesis in biochemical sciences. John Edsall agreed to supervise my thesis, and this led to my introduction to Raman and infrared spectroscopy with some focus on the amino acids that John had been studying for many years.

1. Research work with John Edsall

At that time John Edsall's office was in Harvard Medical School in Edwin J. Cohn's Department of Physical Chemistry on the top floor of Building C. John had his office there, as well as laboratory space that contained the Raman spectrometer. This instrument was a Hilger E439 glass spectrograph and the measurements were made by isolating individual mercury lines with selective filters. The work was carried out in a darkroom, and many hours were spent accumulating spectral data.

John Edsall had initiated this study in the late 1930s and had already discovered that amino acids in solutions existed as zwitterions. Although this fact seems obvious today, at the time it was a novel discovery. My work involved extending this study initially to a number of less common amino acids, such as cysteine and cystine. This made it possible to identify the stretching frequency of the SH bond of cysteine. In addition, the S–S stretching bond of cystine was identified.

The important innovation was the extension of the research to the dipeptide glycyl–glycine, which was studied both as a dipolar ion and as a cation. Formation of the peptide bond was associated with the disappearance of the C=O frequency of 1740 cm^{-1} and its replacement by a lower frequency vibration near 1400 cm^{-1} [1]. Several vibrations were found in the range of 1000 cm^{-1} which were identified as stretching frequencies of the molecular chain. It had already been shown in X-ray diffraction work that the C–N distance of the peptide linkage is approximately 1.29 Å, indicating a high degree of resonance and of double-bond character in the peptide linkage. This work from CalTech provided definitive proof of the planarity of the

*Tel.: +1-617-253-4715; fax: +1-617-253-8699.
E-mail address: cbeckman@mit.edu (A. Rich).

PII: S0301-4622(02)00267-3

peptide bond. A stretching frequency near 1700 cm^{-1} was tentatively identified as related to the C–N peptide bond stretching frequency.

This work served as a good introduction to molecular spectroscopy, and it fired my enthusiasm for learning more about the details of molecular conformation. This work was eventually published in the JACS [1], where it was No. 7 in the series of Raman spectra of amino acids and related compounds that John Edsall had been pursuing.

My interactions with John Edsall were somewhat formal at that stage. I was quite awed by his command of a wide body of information in biophysical chemistry, and I enjoyed discussing problems of science with him. We often sat in his small office and talked, and I was continually impressed by the large pile of letters that were neatly stacked on his desk, no doubt awaiting replies. At that time it was difficult for me to envision having that much correspondence. In later years, however, as similar piles of that type accumulated on my desk, I began to understand that it was an intrinsic part of the life of a scientist. Of course, this was well before the days of email and fax or widespread use of the telephone, especially for long-distance calls.

During that period the Cohn Laboratory had a weekly seminar which was held in Edwin J. Cohn's rather spacious office, with an invited speaker frequently coming from out of town. I vividly remember the talks delivered by Lars Onsager of Yale University. He spoke with such a heavy Norwegian accent that it was often difficult to follow the line of his presentation. Those meetings were especially interesting because of the wide variety of people who assembled. The laboratory was a particularly active one with permanent members including Larry Oncley and John Ferry. It was just recovering from its wartime operations in which it played a heroic part in fractionating blood and making blood products available for the armed services. It was a magnet for many post-doctoral fellows, especially from abroad. Visitors flowed through the laboratory in large numbers. I was especially impressed when John Edsall introduced me to J.D. Bernal, who was visiting from London. I came to know Bernal rather well in the mid-1950s when I spent over half a year in Cambridge, England. But the memory of his first visit to the Cohn Laboratory is vivid in my mind even today.

One thing bothered me at the time. It was the fact that Edwin Cohn had a very lavish office, while John Edsall was relegated to rather cramped quarters, both in his office and in space for his experimental work. I only gradually realized that there was a complex relationship between these two men. It was clear to me that John Edsall was the better scientist although Edwin Cohn seemed to be brilliant in publicizing his work and also was helpful in bringing out the best work from his associates.

In John Edsall's post-doctorate years, he worked with Alexander von Muralt, and they published papers in the early 1930s dealing with the physical chemistry of muscle proteins. One of the methods they employed was double-refraction of flow. This was a method widely used in the 1930s and 1940s to study the rotary diffusion constants of elongated molecules. When long molecules are exposed to a shear gradient, they align themselves, and this alignment can be measured quantitatively through a study of birefringence. It was necessary to look at the birefringence established by the gradient. Limitations in the field were often related to the instruments that were available. One of the projects that John embarked on in which I also participated was in the design and construction of an instrument for measuring double-refraction of flow, using a concentric cylinder apparatus in which the annulus between an inner and outer cylinder was filled with liquid. The outer cylinder rotated, but the inner cylinder did not. Relatively large velocity gradients can be obtained using this instrument [2]. A zirconium arc lamp was used as a light source, together with an interference filter, and sheets of selected polaroid were used as polarizer and analyzer. When the liquid is at rest and the field is observed between crossed polaroids, it is dark. However, on rotating the outer cylinder, the velocity gradient makes the elongated molecules line up. When the gradient is established, there are four points in the annulus where the light is occluded. The plane polarized light entering the liquid is generally converted into elliptically polarized light which is not extinguished by the analyzer. The birefringent liquid acts like a cylindrically symmetric uniaxial

crystal. At the four points 90° apart, where the optic axis is parallel or perpendicular to the incident plane of vibration, the liquid transmits plain polarized light which is then extinguished by the analyzer. The four darkened segments in the annulus are called the Cross of Isocline. A description of this instrument was published in the *Review of Scientific_Instruments* [2]. The machine was very compact and could be put on a stand with rolling wheels. It became somewhat popular and was manufactured and sold by an instrument maker in Brooklyn, New York. The experience of working with this instrument and helping to design it was one that I found very instructive, and it clearly showed me that John Edsall's analytic abilities extended into the practical realm of machine design.

In this paper we described the unusual motion of the Cross of Isocline, as seen on rotating the analyzer. The darkened areas move together with a scissors-like motion. This was a property of the Sénarmont compensator which was used to measure double-refraction of flow. At a later time I analyzed the movement in a paper published in 1955 [3]. In doing this work in 1950–1951, I cast around for a molecule that was elongated and decided to use DNA in order to measure its properties. This work was carried out before DNA gained its subsequent popularity as a carrier of genetic information.

2. John Edsall as a role model

After receiving my undergraduate bachelor's degree in June of 1947, I stayed on at Harvard Medical School to complete the last 2 years of my M.D. and therefore maintained contact with John Edsall during this period. The third and fourth clinical years of medical school were quite stimulating, but it was clear to me that my bent was toward continuing basic research, rather than medical practice. I spoke several times with John Edsall about the relative merits of going on to do a post-doctoral fellowship immediately after finishing medical school, vs. taking an internship and then going on to do research. John told me that he had faced a similar dilemma as he was finishing medical training at Harvard. However, in his case, the situation was made somewhat more difficult since his father was then the Dean of the Medical School. John's commitment to carrying out research work made him decide to go on directly into research, rather than carrying out an internship. For me, this was an important issue because it showed me that it was possible to do science directly, without having the 'insurance' associated with an internship. Thus, I decided to follow the same course of action. This was not a decision widely shared among any of the other members of my medical school class, and many considered this an unsound career decision.

Late in 1948 at the beginning of my senior year, John and I discussed various laboratories where I might apply to do post-doctoral work. He suggested a number of outstanding scientists: Linus Pauling, Melvin Calvin, Henry Eyring, Walter Kauzmann were among them. I wrote letters to all of these individuals, and they accepted me as a post-doctoral fellow, if I could come with my own fellowship. Here, again, John Edsall played a key role. He urged me to apply for a National Research Council fellowship which was, at the time, virtually the only type of post-doctoral fellowship available. NIH had not started a post-doctoral fellowship program, and the NSF had not been established. I believe it was John Edsall's supporting letter that made it possible for me to receive this fellowship. I wrote to Linus Pauling, saying that I was pleased to accept his invitation and would arrive there in the fall of 1949.

In retrospect, this was perhaps the most crucial decision in the development of my research career. John Edsall had spent a year (1940–1941) in Pasadena, California, as a visiting scientist at the Gates and Crellin laboratory where Linus Pauling was Chairman of the Chemistry Department. He told me how strongly he was impressed by Linus' command of chemistry and the great contributions he had made in understanding the three-dimensional structure of proteins. In retrospect, I recognize that this was a most fortunate decision in helping me to develop as a structurally oriented biochemist.

I felt a warm sense of friendship in dealing with John Edsall. He had the ability to speak to a student in a way that boosted the student's sense of self-worth. He was always considerate and recep-

tive to new ideas. Although he was friendly, he still maintained the formality of a New England gentleman, a combination that I found both stimulating and somewhat awe-inspiring. I always referred to him as 'Dr Edsall'. That changed only after more than 10 years of our association, being replaced later by the less formal 'John'.

3. Caltech and NIH

After leaving Harvard Medical School, I immersed myself in the totally different experience of southern California living at CalTech. As I came to know more about Linus Pauling, I realized that he held John Edsall in very high regard and that probably it was John's letter to him that initially opened the way for his accepting me as a postdoctoral fellow. Linus had recently described sickle cell anemia as a molecular disease, and I joined in the search for other molecular defects in hemoglobin. I learned something about the role of fetal hemoglobin in various anemias [4].

My contact with John was intermittent for some time, but intensified considerably in 1953 when Linus Pauling organized a conference on the structure of proteins and nucleic acids at CalTech in the fall. John Edsall came to this meeting, and we spent many hours walking around Pasadena, talking about what was happening at the laboratory at Harvard Medical School. I clearly remember the concern he expressed over the fact that Edwin Cohn was experiencing some episodes of transient confusion that I suspected were associated with small hemorrhagic events in the brain. Sadly, this turned out to be true, since Edwin Cohn died of a stroke not long afterward.

The conference was exciting since many attendees were scientists from England as well as from the United States. Max Perutz gave a paper describing his discovery of the phasing power of a mercury derivative, the key event leading to the ultimate solution of the structure of hemoglobin. Both Watson and Crick were at the meeting and spoke about their newly proposed structure of DNA. My contribution was to present results of modeling studies of ways in which DNA and proteins might interact, most of which subsequently turned out to be incorrect.

I moved to NIH in the following year, where I set up a section on physical chemistry and began focusing my research on RNA structure. John visited Washington frequently and several times came to our house in Bethesda near NIH. John's appearance then at age 65 was somewhat unchanged from his appearance 10 years earlier when we had first met, and he did not change appreciably since then. Thus, John appeared older than his years in his early life, but in his later life he appeared younger than his years. This always struck me as a remarkable paradox.

We carried on a long-term dialogue on the nature of proteins and the manner in which their properties were a consequence of both the structure and composition of each protein. John assumed the editorship of the *Journal of Biological Chemistry*, and it kept him very much abreast of what was happening in this broad field. I have always marveled at his comprehensive grasp of many different facets of protein research.

At one point John Edsall arranged a lecture for me at Harvard College, where he had now moved his office and laboratory. This visit gave me a good chance to learn more about his current work and also to tell him about my own research on RNA structure.

4. Back to Cambridge, Massachusetts

In 1958, I accepted a position in the Biology Department at MIT and, from that point on, my contact with John Edsall was more continuous. We frequently saw each other at seminars and interacted both socially and professionally. In more recent years, we had made a point of having lunch together every 2–3 months. These lunches offered a very pleasant vehicle for exchanging opinions on scientific, political and social events. I have a vivid recollection of having an extended lunch discussion with John about the voting habits of his father David. As Dean of Harvard Medical School, he interacted with many of the prominent members of the Boston business community, and they generally assumed that he voted as a Republican. However, he was a staunch Democrat, and John explained to me in some detail the position that he took in the election of 1896. I was struck by the fact that the date of this lunch was 1996, and the topic of our

conversation concerned voting patterns a hundred years earlier.

From my perspective the contacts with John Edsall were stimulating and often inspiring. He showed steadfast devotion to scientific issues, while at the same time maintaining a moral rectitude about what is appropriate in science. In particular, I have always been greatly impressed by the principled stand he took in declaring that he would turn down an NIH budget if support for Linus Pauling's research was withheld on political grounds. This occurred at the height of the hysteria of the McCarthy era. His willingness to stand up for proper and just behavior provided a model of how a scientist should act in a democratic society.

I feel privileged to have had continuing contact with John Edsall over a 60-year period and am very grateful that he had such an impact on my scientific development.

References

[1] J.T. Edsall, J.W. Otvos, A. Rich, Raman spectra of amino acids and related compounds. VII. Glycylglycine, cysteine, cystine and other amino acids, J. Am. Chem. Soc. 72 (1950) 474–477.

[2] J.T. Edsall, A. Rich, M. Goldstein, An instrument for the study of double refraction of flow at low and intermediate velocity gradients, Rev. Sci. Instr. 23 (1952) 695–701.

[3] A. Rich, Use of the Sénarmont compensator for measuring double refraction of flow, J. Opt. Soc. Am. 45 (1955) 393–395.

[4] A. Rich, Studies on the Hemoglobin of Cooley's Anemia and Cooley's Trait, Proc. Natl. Acad. Sci. 38 (1952) 187–196.