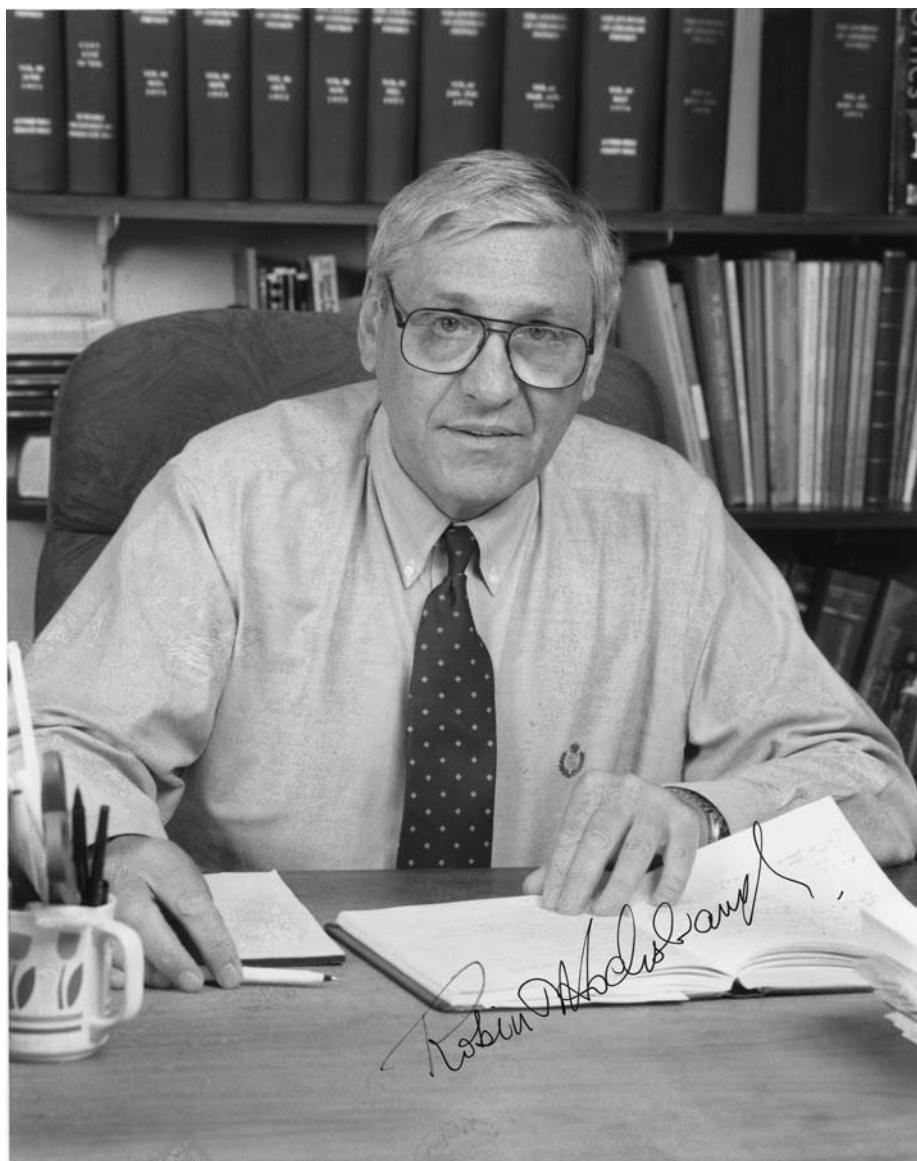




ON A RESEARCH ROLLERCOASTER WITH FRIENDS

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INTRODUCTION

This review provides a glimpse at some of the science we were excited about at the time and the way I recollect our work interfacing with the tidal wave of new chemical knowledge that was being gathered throughout those periods. I hope the people I mention, as well as those I do not, will be understanding. I could not provide a comprehensive review covering such a long period; therefore I do not adequately mention every student, postdoctoral fellow, collaborator, colleague, peer or mentor. I am certain that whatever we accomplished, and is most likely attributed to me, is in infinite measure a result of the effort, generosity, insight, and enthusiasm of all of them.

Nowadays in chemistry there are significant fractions of students and faculty who are recent immigrants to the United States. This was not so true when I started out in research. Therefore I say a little about my earliest experiences with physical chemistry and how I came to settle in the United States. My family had no scientific connections. A Swiss grandfather emigrated to Ireland then to Scotland in the late 1800s. My mother's family were Scots.

EN ROUTE TO NORTH AMERICA

I begin with a few words about how I got started in science. I was raised in Edinburgh and left school at 15 when my family planned to relocate to Belgium. We returned after several months so I took the university entrance exams without ever returning to regular school. I went into science because I seemed to be able to do it reasonably well, and I had some important positive feedback. But I was hooked on chemistry after a tutor demonstrated the Solvay process in an apparatus he had set up in his home chemistry laboratory. As a freshman at 17 my education became restricted to chemistry, physics, and mathematics. Having now raised children in the American liberal arts education system, I feel that I missed something by concentrating on scientific subjects so early.

An introductory undergraduate course on organic chemistry at Heriot-Watt University College guided me to research: The course was offered by Professor Frank

Bell, who communicated the excitement of optical rotation of intrinsically asymmetric aromatic molecules. Although he described a beautiful set of experiments that established a chemical structural basis of the optical properties, I realized that answers were not always available for the questions I asked, so it was natural that physical chemistry attracted me most because that is where I thought the answers lay. I guessed that many basic issues were not settled and there were challenges that begged for new ideas and technologies. My enthusiasm for physical chemistry was fueled further by lectures I took from Kenneth R. Buck, who had just arrived in Edinburgh from the M.G. Evans and M. Polanyi laboratory in Manchester University. He introduced me to elementary quantum mechanics. I worked with him one summer month, becoming even more interested in experimental physical chemistry by contributing to the construction of a Geiger counter with which I thought we could detect the opening of the radium safe in the university hospital one block away.

I then went to the Edinburgh University science complex at King's Buildings to earn a Ph.D. with Mowbray Ritchie, who had done his graduate work on the H_2 plus Cl_2 photochemistry with R.G.W. Norrish at Cambridge. He suggested finding a model system that would react reversibly with oxygen in light, motivated by the reversible assimilation of oxygen in biological systems. We located this beautiful set of molecules, rubrenes, that reacted with molecular oxygen in visible light and released the O_2 upon UV irradiation. Our idea was to examine the oxygen uptake and dissociation on the surfaces of various semiconductors and photoconductors. I received a generous Courtalds' scholarship for this endeavor because of its relationship to the fading of dyestuffs. The technical challenge was to measure small changes in O_2 pressure on irradiation of thin films. I soon became an expert at blowing Bourdon gauges from soda glass. All experimental physical chemists had to master glass blowing in those days: Soda glass is more difficult to handle than Pyrex, so all Mowbray's students became skilled at using a blowtorch. No graduate courses were offered at Edinburgh in those days, so I had time to spend in the library. One such visit resulted in a temporary setback when I discovered that Max Born, who was then a physics professor at Edinburgh, had participated in an experiment on the photo-oxidation of crystalline rubrene (1)! I was relieved to discover from Professor Born that the experiment consisted of placing some crystals on a window ledge at the Weitzman Institute. After this experience, I felt that my photochemistry was quite sophisticated (2). I completed my Ph.D. in three years, just enough time for me to learn that there were many areas in physical chemistry left for me to explore, but my interest in spectroscopy had been piqued.

In 1955 I was conscripted into the Royal Air Force. As a Pilot Officer I taught navigators the basic electronics associated with high-altitude radar displays used by V-Bombers. Perhaps I was given this position because, in response to the interviewer's question as to what I was reading, I said "electronics." It was only later that I realized he was asking me the topic of my degree, not what I was reading in my spare time. In the Royal Air Force I learned a lot about microwave electronics and mathematics that was useful later. All the navigators we trained were in the squadrons used in the 1956 Suez war.

In the spring of 1957 I was interviewed in the Dorchester Hotel in London by Charles A. McDowell, the Chairman of the Chemistry Department at the University of British Columbia (UBC), and some faculty. There were many young scientists going to Canada from the United Kingdom, Australia, and New Zealand at that time, and research opportunities seemed promising because of funding from the National Research Council of Canada. My decision whether to move to North America became easier after Charles and colleagues showed me pictures of what they claimed were faculty members catching salmon from the beach behind the faculty club: I had no option but to accept the position, and by late August 1957 I was en route by Cunard liner and transcontinental train to Vancouver. At that time the culture barrier to moving directly from Scotland to the United States seemed insurmountable.

MOLECULAR SPECTROSCOPY AND THE UNITED STATES

At UBC I began studying gas-surface reactions to seek quantitative descriptions of the mechanisms of reactions of O_2 with thin films of aromatics but I soon became much more interested in the spectroscopy, theory, and photophysics of molecules. During this transition period I greatly benefited from discussions on spectroscopy and quantum mechanics with C.E. (Chris) Reid, a faculty colleague at UBC who, with Gerhard Herzberg, had made the first measurements of the triplet state of ethylene using a liquid cell. I became convinced that molecular spectroscopy was the most exciting direction for me to pursue. My impression was that new computational methods were making predictions that needed to be verified and challenged by experiment, and the possibilities for designing experiments to explore light-induced processes seemed unlimited. I set up a simple experiment to measure quantum yields of fluorescence and phosphorescence as a function of excitation wavelength with a Beckman DU monochromator; this experiment became the subject of a talk I gave entitled "Internal Conversion in Organic Molecules" at the Ohio State Symposium on Molecular Structure and Spectroscopy Meeting in 1959, my first trip to the United States and my first opportunity to meet the scientists whose papers I had been reading. There was some interest in my result that the higher excited states of aromatic molecules could show increased efficiencies of nonradiative transitions (3). The Columbus meeting was an important gathering place for theorists and experimentalists in both isolated molecule and condensed-phase spectroscopy, and I recall energized discussions with John Platt, Klaus Rudenberg from Iowa State, and others from the Chicago theory group. Mike Kasha chaired the session in which I talked, and I enjoyed meeting Don McClure, Mostafa El Sayed, Herb Broida, Norman Sheppard, Otto Schnepp, and G. Wilse Robinson, all experimentalists who worked with molecules in the condensed phase.

Although I was still in my twenties and it was risky to change fields as a junior faculty member, UBC granted me leave for the 1961–1962 year. My first

stopping point was the National Research Council in Ottawa, where I was hosted by William G. Schneider. Bill had done seminal work on low-temperature spectroscopy and photoconductivity of molecular solids. He had just published his famous book with J.A. Pople and Harold J. Bernstein, which was the first comprehensive treatise on the emerging discipline of high-resolution nuclear magnetic resonance (NMR) spectroscopy. Being in Ottawa allowed me to conduct high-resolution absorption and fluorescence experiments at liquid-helium temperatures on crystals of molecules having $n \rightarrow \pi^*$ transitions. I was greatly helped and encouraged by Alec Douglas in Gerhard Herzberg's laboratory where I photographed the spectra of the $n \rightarrow \pi^*$ transitions of phenazine and was encouraged to find sharp spectral lines that could be analyzed. I spent the remainder of my leave with Michael Kasha who had invited me to visit Florida State University in Tallahassee. Mike was an inspirational colleague, and in that environment the seeds of many of my subsequent research ideas became more firmly planted. Mike had just launched the Institute of Molecular Biophysics for which a building was being built when I was there. I had fruitful discussions on group theory with the young faculty member Bill (W.C.) Rhodes who was working on the optical spectrum of DNA. Many visitors, including Theodor Forster, Robert Mulliken, Bernard and Alberte Pullman, William T. Simpson, and others, overlapped with my stay, so this was an extremely stimulating environment. In January 1962 I gave a talk on the luminescence of excitons at Per-Olow Lowdin's Sanibel Symposium (4). This meeting influenced my thinking about moving from Canada, and I had discussions with many individuals about opportunities in the United States, including D.S. McClure then at the RCA Princeton Laboratories. Don had carried out landmark experiments on mixed crystals and molecular excitons that were technically innovative and had strong relationships to theory: I found this style of research to be the most exciting. After teaching for the 1962–1963 academic year I moved from UBC to the faculty at the University of Pennsylvania, with a Sloan Fellowship obtained while in Canada and new research plans that needed resources, such as high-magnetic fields, that were not available to me in Vancouver. Two recent graduates from UBC who had both participated in an undergraduate course I had co-taught with the inorganic chemist Neil Bartlett (later at University of California Berkeley) on group theory and crystal field theory in 1962 accompanied me to Penn and became my first students, Bob (R.D.) McAlpine and Gerry (G.J.) Small. Bob went to the Canadian atomic energy laboratory at Chalk River and Gerry became a Distinguished Professor at Iowa State University where he made seminal contributions to the mechanisms of photosynthesis. I had many influential colleagues at UBC particularly David C. Frost, the electron spectroscopist; Chris Reid, who I mentioned earlier; Bill (W.R.) Cullen, the inorganic chemist; Gerry (G.B.) Porter, the photochemist with whom I wrote a *Quarterly Review* in 1960 on photooxidation; Jim (J.N.) Butler, the gas phase kineticist from Kistiakowsky's lab who left at the same time to join the Applied Physics Department at Harvard University; and Jack Halpern, the physical inorganic chemist who also moved around the same time to the Chemistry Department at the University of Chicago;

all of whom with their families contributed to our scientific and social life in Vancouver.

One of the interesting changes that has occurred in the lives of young professors only became clear to me as I was writing this perspective: Out of the 30 papers I had published when I moved to Penn in 1963, 26 of them had me as the sole author!

MOLECULAR CRYSTALS AND MAGNETIC FIELD EFFECTS

Aromatics, their heterocyclics, and other conjugated systems were important objects in the early days of large molecule spectroscopy. Their spectra were accessible by infrared (IR), visible, and near UV methods, and the involvement of π -electrons in the lowest energy transitions meant they were theoretically tractable by rapidly advancing molecular orbital theory. Furthermore the states and the transitions among them were easily characterized with group theory. Therefore there existed a strong expectation that their electronic, vibrational, radiative, and nonradiative properties could become quantitatively understood, so in the 1950s and 1960s these molecules in gases, solutions, glasses, and crystals were a test bed of the fundamental processes involved in polyatomic molecular spectroscopy, photophysics, photochemistry, photoconductivity, and exciton theory. That early investment has had a significant impact on current activity on light-emitting devices and other molecular solid-based materials.

My research interest was in the triplet states of molecules: They form exciton bands in crystals, and the properties of the bands yielded information about the wave functions of the excited states, spin-dependent interactions, and especially the intermolecular potentials. The spectroscopy of molecular crystals had been launched in the 1930s by Russian physicists Obriemov and Prikhoto in Kiev, where many great contributors to molecular physics, such as A.S. Davydov, I. Rashba, V. Broude, I. Sheka, and V.M. Agranovich, originated. In 1944 Prikhoto observed splittings in the singlet spectrum of naphthalene, which, in 1948, were interpreted by A.S. Davydov to arise from interactions between translationally inequivalent molecules—hence the term Davydov splittings. Emmanuel Rashba told me that the reason why so many Russian physicists in Kiev became interested in molecular physics early on was because the research was relatively inexpensive. The spectra of molecular crystals became more deeply understood in the 1950s through the work of David P. Craig (Canberra) and his colleagues who significantly extended Davydov's theory to include the coupling by crystalline interactions of different free-molecule transitions and a full analysis of the molecular origins of the coupling. In 1960 Mike Kasha had just finished translating Davydov's classic book on molecular excitons, and he asked me to read the final proof for him (5). I finally got to meet Davydov in 1970 when he was first permitted to travel to the West to spend a week in Philadelphia at a meeting I organized. We had invited

Agranovich, Rashba, and Broude to Philadelphia in 1970 through the Academy of Sciences of the former Soviet Union, but they were not permitted to come. I finally met them all in Estonia in 1973. By then my research interests had turned to the triplet states of the aromatic and heterocyclics, to magnetic and electric field effects on their spectra, and to ultrafast phenomena.

Like many physical chemists I considered the control of molecules by external forces to be the holy grail. While in Canada I had been interested in the effects of static magnetic fields on triplet state spectra and energy transport and had attempted some optical measurements using electron paramagnetic resonance magnets. The electron paramagnetic resonance of the naphthalene triplet had been measured recently (6) to yield the zero-field splittings and spin-density distributions, and it dispelled any doubts that existed about the triplet nature of the long-lived emitting states of organic molecules. The electron paramagnetic resonance experiments used conventional approximately 10-kG magnets, bringing the triplet splittings into the microwave region. We thought it would be necessary to bring these splittings into the range of approximately $10\text{--}20\text{ cm}^{-1}$ for them to be studied directly by absorption and emission spectroscopy in condensed phases, and fields in the 120-kG range would be required to satisfy $B_0 \geq \gamma/g_e\beta_e\hbar c_0$, where γ is the spectral width in the solid. It has to be understood that the magnitudes and origins of the spectral widths in organic condensed phases were not known. Bitter solenoid magnets with sufficiently large fields were under construction in the new Laboratory for Research on the Structure of Matter where I had chosen to set up my labs, but we decided to carry out the high-field Zeeman experiments at the National Magnet Laboratory at the Massachusetts Institute of Technology (MIT). Prior to the availability of superconducting magnets, my postdoctoral fellows, students, and I spent considerable time commuting between Philadelphia and Cambridge accompanied by a complete spectroscopy lab. This experience convinced me of the immense value of shared facilities, where cutting-edge, unique technologies could be accessed by individual users from a wide range of fields to enlarge the scope of their research. It was unusual for chemical research to be supported at the National Magnet Lab, but the solid-state physicists at MIT were generous to us during these adventures. The lessons I learned from these experiences were a key factor in how we originated and operated the NSF and NIH Laser Research Resources at Penn.

The singlet-triplet transitions were nine to ten orders of magnitude weaker than allowed transitions both because of the small spin-orbit coupling and the planarity of conjugated systems, but the spectral lines were sharpened at low temperature so that the transitions became observable in crystals having thicknesses in the range of approximately 1–2 cm. In 1965 George Castro, who had studied with Jim (J.L.) Hornig at Dartmouth, brought new crystal growth expertise to our operation and improved our ability to grow very large, relatively strain-free molecular crystals. Later George became Director of Chemical Research at IBM.

The Zeeman experiments involved photographing the visible and UV spectra of the singlet-triplet transitions of various molecular solids in light polarized in

multiple ways relative to the magnetic field. We were understandably ecstatic when, in 1965, George Castro developed the first photographic plate that clearly showed the splitting of all the visible spectral lines of aromatic molecules into triplets. These spectra directly gave the spin-orbit symmetries of the three triplet substates at zero field and hence completely characterized the spatial part of the triplet wave function (7). This experiment began a productive era of research into the spectroscopic and dynamical properties of triplet states and triplet excitons that was joined by many others, such as Peter Trommsdorff from Grenoble, who reported Zeeman measurements on the p-benzoquinone crystal. In 1970 I served on Peter's Jurie de These after which we became fast friends and collaborators in electric field, nonlinear optical, and proton transfer experiments. He is still at Josef Fourier University.

The Zeeman spectroscopy proved useful for understanding triplet excitons and the delocalization of the excitations. The triplet exciton bands were thought to be formed by overlapping charge distributions of nearby molecules. One of the most-studied crystals was anthracene: a prototype for both spectroscopic and photoconductivity research. The bandwidth of the anthracene triplet exciton was approximately 20 cm^{-1} , and the first molecular orbital computation of molecular exciton bands (8), introducing the idea that the coupling mechanism was electron exchange, had reproduced this value. The Zeeman measurement on oriented molecules was powerful because the triplet spin quantization, determined by macroscopic symmetry, permitted the symmetry species of the exciton states to be determined; hence the signs as well as the magnitudes of the intermolecular exchange interactions could be determined (9). Prior to these studies it had been assumed, incorrectly, that the triplet states of, say, a dimer were the usual plus and minus states separated by the Davydov splitting and that these states would be identifiable in polarized-light experiments as the magnitudes of the squares of the sum and differences of the two transition dipoles. Through Dick Clarke's work (10) we discovered that each Davydov component in the exciton spectra had its own distinctive multiplet of states, Zeeman splitting pattern, and a different polarization for each spin state. We concluded definitively from the Zeeman experiments that the theoretical computations had predicted almost the correct magnitude for the triplet exciton splitting of anthracene but had the wrong sign: The wave functions did not compute the exchange accurately enough at the large separations between molecules in crystals. Richard Clarke became a professor at Boston University.

Many processes that were first examined in molecular solids have proven to be essential in understanding primary processes in photosynthesis as well as in other areas of biophysical chemistry and materials science. We became particularly intrigued by the topological characteristics of energy transfer. On the basis that the packing of molecules in crystals should establish a dimensionality for the energy transport, we searched widely for systems where the delocalization of the exciton was well confined to one and two dimensions. The first of many such materials we discovered was 1,4-dibromonaphthalene (11). John Whiteman, who graduated in 1971 and made an outstanding career at Rohm and Haas, made a

detailed study of it using isotopic substitutions to break up the band structure to create various levels of energy disorder and well-defined clusters of molecules. He demonstrated unequivocally that the crystal contained linear chain excitons created by the overlap of charge distributions on neighboring molecules in the stacks and that the interstack coupling was tiny. This was an exciting discovery that interested many other groups because the theory for chains and other low-dimensional systems was directly testable for a wide variety of properties, such as the density of states, energy transport, interactions of excitons with chain motions, magnetic resonance, coherent hole and electron transfer, and coherent properties of excitons. It was at the meeting in Philadelphia in 1970 that I first met Charles (C.B.) Harris from the Chemistry Department at Berkeley, who initiated studies of the optically detected magnetic resonance of coherent excitations in one-dimensional organic crystals. There were even notions that such low-dimensional materials may have useful properties, and at that time both Dupont and IBM had already mounted major research initiatives on molecular solids.

STARK-ZEEMAN EFFECTS ON SPECTRA

In the 1967 National Bureau of Standards tabulation of dipole moments information is given for the electronically excited states of only four molecules: NH, CO, formaldehyde, and propynal. There were no excited-state dipole measurements for the vibronic levels of any of the aromatic or heteroaromatic molecules that dominated condensed matter research, although electric dichroism measurements had been reported on isotropic solutions. Crystals at low temperature displayed sharp spectra, which suggested to me that Stark effects of specific vibronic transitions should be observable in conventional electric fields if the dipole moments changed on excitation by even small fractions of a Debye unit. A postdoctoral fellow Lewis J. Noe was willing to try a Rube Goldberg version of a Stark effect experiment in 1967 by crystallizing an organic ketone in a submicron-thick layer between two SnO-coated quartz plates, which were connected to a commercial battery: The spectrum of the 0–0 transition at 4.2 K showed a Stark splitting when the circuit was made. This discovery was an excuse for celebration because a first-order Stark splitting of a nonrotating molecule had not been previously reported (12). We quickly completed our plan to conduct the experiment with field modulation, controlled field orientations, and polarizations of light. By 1973 excited-state dipole moments for tens of molecules had been reported (13), and new states of molecules discovered by Stark-induced mixing of *gerade* and *ungerade* states (14). Lew Noe went on to become a professor at the University of Montana.

I was particularly pleased that we were able to measure the signs and magnitudes of the dipoles for many different vibronic and electronic states of the same molecule in the same media where the local field was nearly identical for each transition. In the case of the carbonyl $n \rightarrow \pi^*$ transition benzophenone, a molecule influential in triplet-state photochemistry at the time, the dipole moment changed more upon

excitation of the zeropoint vibrational states of the singlet rather than the triplet $n\pi^*$ state. This finding was in contrast to what had been measured recently for formaldehyde molecules in the gas phase by Buckingham & Ramsay (15). Our result showed that the charge distributions of $n\pi^*$ states in aromatic ketones were different from those in small isolated molecules. The Stark effect measurements frequently allowed us to distinguish various electronic states in regions where spectra were perturbed and to characterize the local electric fields in anisotropic media or to advance knowledge of excited-state wave functions.

For some triplet states the zero-field, triplet-spin dipole-dipole interaction and the exciton splittings in molecular aggregates were often of the same order of magnitude so that the combined Stark-Zeeman effect measurements could be configured to yield the signs and the magnitudes of the spin interactions at zero field by controlling the relative magnitudes of the Stark energy, $\Delta\mu \cdot E_0$, and the Zeeman energy, $g_e\beta_e B_0$. Tom Lin's experiments showed how to combine magnetic and electric fields to locate and assign all otherwise-overlapping spin-orbit eigenstates of triplet states and excitons: Clyde Hutchison told me that Tom's 1968 paper (16) was, for a while, required reading for the physical chemistry students at the University of Chicago. Tom became a professor at the University of Washington in St. Louis.

The Jahn-Teller effect had intrigued chemists for decades; this issue led us to examine spectra of orbitally degenerate states. In condensed phases our interest was in the effect of crystal fields on electronic structure and the static Jahn-Teller effect. Even a system as simple as D_{3h} s-triazine, whose spectroscopy was well-known in the gas phase, challenged a number of research groups all using the then-popular methods of low-temperature Stark and Zeeman spectroscopy and all of whom at one time or another were convinced that the lowest energy singlets and triplets were both degenerate states. Involved in these illuminating controversies about s-triazine's putative degenerate states were a number of individuals who went on to make significant impacts on other areas of chemistry, including Tom Lin and Ahmed Zewail, who were my students; Rick Smalley, who was a student of Elliot Bernstein at Princeton; Douwe Wiersma, who had recently returned to the Netherlands after being a postdoctoral fellow in my group; and my ex-student Gerry (G.J.) Small, who was based in Canberra with David Craig's group. I recall that Elliot and I joined our two students, Rick and Ahmed, at the Philadelphia American Chemical Society meeting in 1972 to discuss differences that had arisen in their work on s-triazine: Later they would both win Nobel Prizes—but in quite different fields. Benzene with its sixfold symmetry representing the archetype Jahn-Teller system among large molecules and the elucidation of the D_{2h} pseudo Jahn-Teller distortions arising in the $^3B_{1u}$ state from its coupling to the orbitally degenerate state were accomplished by John Wessel and Ahmed Zewail in what was to be our first and last use of the 105-kG Bitter solenoid magnet that had been installed at Penn (17). John Wessel, who had come from Don McClure's group in Chicago, works at the Aerospace Corporation, and Ahmed Zewail, who after postdoctoral work with Charles Harris became a professor at Cal Tech and won the Nobel Prize for femtochemistry.

RADIATIONLESS TRANSITIONS AND SPECTRAL SHAPES

Throughout the 1950s and 1960s questions relating to the mechanisms of radiationless transitions occupied many researchers in chemical physics and photochemistry. The challenge to find a quantum mechanical description of radiationless transitions was taken up by many research groups. For example, I recall a wonderful one-on-one discussion with James Franck of the Franck-Hertz experiment and the Franck-Condon principle on the roof café of New York University in 1963, during a meeting on photoconductivity of organic materials organized by Harmut Kallman, where Dr. Franck described to me his idea that nonradiative transitions were a special case of resonant energy transfer involving downward transitions from the excited state, coupling to upward transitions to the background states. However, following pioneering work of G. Wilse Robinson and coworkers (18), the Bixon-Jortner model (19) provided a quantum-based description of the intramolecular character of the relaxation of excited vibronic states of large, isolated molecules.

In 1968 I attended some evening discussions at the University of Chicago on radiationless transitions led by Joshua Jortner. As I recall only a few people composed a very lively audience, including Steve Berry, Ugo Fano, Karl Freed, Bill Gelbart, and Stuart Rice. I also gave a series of evening lectures in Chicago at that time on singlet-triplet transitions and spectral manifestations of radiationless transitions. I vividly recall that Robert Mulliken came to all my talks, sat in the front row, and always had questions for me, particularly regarding spin-orbit coupling and whether we could use our methods on long crystals of ice to locate the lowest triplet state of water and decide whether it was a bound state, which was unknown at the time.

A manifestation of nonradiative relaxation that particularly intrigued me, and still does, involved the relations between spectral shapes and dynamics. Understandably most molecular spectroscopic experiments had been concerned with line positions from which important molecular constants and structures could be obtained. My first proposal to the National Science Foundation in 1963 was to dissect the sources of linewidth in condensed-phase vibronic transitions. Wilse Robinson told me much later that he gave it his highest recommendation but that my proposal probably deviated too far from the mainstream. I learned a lot from that experience; therefore I had better results the next time. A reason for studying low-temperature spectra was that the lines were sharp enough for detailed structural information to be obtained. However there was no accepted base of knowledge of the various contributions to the linewidths and spectral shapes of these molecular spectra. Charles Marzocco, a graduate student who became a professor at the University of Rhode Island, had surveyed the low-temperature spectra of many large aromatic and heterocyclic molecules over broad spectral regions, and we began to realize that systematic variations in spectral character existed: Always the lowest energy excited state had the sharpest spectral transitions. It became obvious that the interstate coupling and the densities of coupled states were playing key roles

in determining the spectral shapes. Even in condensed phases the vibronic spectra manifested intramolecular vibrational and electronic relaxation dynamics. This idea was based on observations of dozens of molecular spectra at low temperatures (20), and the corresponding diffuseness in gaseous spectra was summarized later in a beautiful article by Byrne & Ross (21). I benefited from many discussions with Ian G. Ross, from Canberra, on the spectral manifestations of the breakdown of the Born-Oppenheimer approximation. In 1971 he visited Philadelphia, where we continued to discuss the effects of perturbations in spectra even while attending the U.S. Open golf championship in Merion, Pennsylvania. I visited Canberra in 1972 and continued these discussions with Ian while camping in the Outback. The theoretical and experimental activity on spectral dynamics during these few years by many research groups firmly established a correct physical picture of the relations between frequency domain spectroscopy and relaxation.

The inter-relationships between time and frequency domain spectroscopy became more obviously relevant when laser pulses began to be used in experiments. In the early 1970s researchers were asking about how to describe properly the time dependence of Raman and fluorescence of molecules in the presence of dephasing collisions. These topics had been introduced using somewhat different language in the 1930s by Weisskopf and Wigner and in the 1950s by Heitler, but the resurgence of interest in this problem by many theory groups stemmed from experiments at Bell Labs (22) on the resonant light scattering of molecular iodine. An M.D./Ph.D. student, Joel Friedman, who later joined that Bell Labs group and then became a professor at Albert Einstein University, was working with me on the basic quantum mechanics of the resonant light scattering (23) when the Bell Labs paper appeared. He later conducted experiments to show how the spontaneous emission time profile would depend critically on the type of light source that was used to excite the resonance. We sent the theoretical paper to the new international journal *Chemical Physics*, edited by G. Wilse Robinson in the United States. The quantitative description of how these scattering processes would show up in condensed-phase experiments was not obvious to us. The theory needed to consider the effects of frequency fluctuations on the emission. Fortunately I was able to persuade Corinne Nye, an excellent student who became a physician, to carry out some experiments that would demonstrate precisely what was happening. She used a narrow-band laser to examine the resonance emission of a single vibronic level of azulene at different excitation frequencies across the band. The results showed clearly that there were two types of emission: One was resonance Raman scattering, with a line width of the narrow-band laser, and the other was fluorescence, with the full dephasing width of the transition. The fluorescence emission was being induced by the fluctuations in the resonance frequency. The Raman part shifted predictably with the excitation laser frequency, but the so-called fluorescence emission remained centered at the peak (24). This experiment highlighted our contribution to a fruitful period of chemical physics experiments and theory (25) aimed at questioning the mechanisms of the interaction of different types of pulsed-light fields with molecular resonances in the condensed phase.

NONLINEAR MOLECULAR SPECTROSCOPY

One important impact of the new laser technology on chemistry was the introduction of nonlinear molecular spectroscopy. The first years of nonlinear spectroscopy in chemistry were exciting, not only because of what we learned, but also because of the discovery of amazing electromagnetic phenomena that were new to chemists. Our progress was dependent on advances in laser engineering as illustrated by the following example. For the 10 years prior to 1973, two-photon spectroscopy experiments had been accomplished at a few wavelengths on crystals, other solid materials, and liquids. Solid-state pulsed lasers often experienced strong two-photon absorption, but they were neither tunable nor useful for spectroscopic detail, even though they did allow assignments of electronic state symmetries from their anisotropy. Ted (T.W.) Hansch's invention of a movable diffraction grating as the rear reflector of the nitrogen-pumped dye-laser system suddenly created an unprecedented opportunity for us to carry out high-resolution two-photon molecular spectroscopy. Fortunately, we had just completed construction of a 0.1-MW nitrogen laser in 1972, with the help of the Bell Labs machine shops, when we received a preprint of his paper (26), so John Wessel and Ho-Nan Sung were immediately able to create a widely tunable narrow-band source, and by the next year, at John's urging, we completed a paper on continuously tunable two-photon spectroscopy (27), showing the fully resolved vibronic spectrum of the hitherto undetected $g \rightarrow g$ electronic transitions of biphenyl and the $g \rightarrow g$ vibronic transitions of benzene vapor (28). A year later, postdoctoral fellows John Wessel and Bob (R.G.) Bray observed the first rotationally resolved two-photon spectrum (29), using NO at low pressures. John Wessel later took a research position at Aerospace, and Bob Bray went on to do seminal work on local-mode spectroscopy with M.J. Berry before joining the Allied Corporation.

Tunable two-photon spectroscopy became a popular field leading to the multiphoton ionization methods. During an evening Harvard/MIT seminar in 1974 I was presenting slides containing many two-photon molecular spectra, some with hundreds of sharp transitions, when a voice from the back of the darkened room exclaimed "Unbelievable!" The comment had come from Mark Levinson, then working with N. Bloembergen on the Doppler-free two-photon spectra of sodium atoms and coherent anti-Stokes Raman scattering: I do not think they had realized the richness of molecular spectra.

The second- and third-order nonlinear optical processes induced by lasers tunable through multiple molecular resonances exposed vibronic properties not obtainable from linear spectroscopy. As a result, during the 1970s there was much exploration through experiments and theory of nonlinear optical methods applied to molecular structure and dynamics. Although we had found some fruitful spectroscopic approaches and line-narrowing techniques using second-order sum and difference frequency generation (30, 31), we decided to concentrate on coherent Raman processes to obtain level-specific information about molecular vibrational relaxation, which was always a theme of my interests. Finding new nonlinear

signals was always an adventure, and dephasing-induced coherent emission (DICE) fell squarely in this category (32). The experiment was hard for molecular spectroscopists to accept because it measured the vibrational spectra of excited states without directly populating them. Postdoctoral fellow John Andrews, who has since had a successful career at Xerox, proved the effect unequivocally in a dilute mixed crystal having well-characterized sharp transitions. The experiment was based on anti-Stokes Raman spectroscopy: Visible pulses centered at ω_1 and ω_2 were chosen so that $\omega_2 - \omega_1 > 0$ was tunable through a frequency region that bracketed the frequencies of both the ground and excited-state vibrations, whereas ω_1 was tunable near the electronically excited-state 0–0 transition. The strong anti-Stokes coherent signal at $2\omega_1 - \omega_2$ was measured. Remarkably, this coherent signal did not decrease but rather increased with increasing temperature: The coherent emission was being induced by the pure dephasing (32). Quantitative comparisons of the experiment with Bloembergen's general equations for the third-order susceptibility enabled us to show that the coherent signal in the condensed phase arose because an exact cancellation between certain pathways in the nonlinear response no longer occurred when there was a pure dephasing contribution to the line width. This experiment enabled us to make accurate measurements of the pure dephasing of the spectral linewidth free from relaxation contributions.

Nonlinear spectroscopy was also an essential method in our attempts to understand the relaxation of molecular vibrations in the condensed phase. Although no general predictive theories of vibrational relaxation existed, there were preconceived notions as to the relaxation times, usually considered to be in the picosecond regime for large molecules. The coherence decay time of a vibrational transition is determined by population relaxation, which involves energy transfer to the solvent and intramolecular relaxation, and a dynamic distribution of vibrational frequencies that generates pure dephasing (33). However, we had learned from the work of postdoctoral fellow Izo Abram (34) that the vibrational excitation transfer between molecules in a solid motionally narrows the inhomogeneous contribution to the vibrational transition, and if the temperature is sufficiently low, the pure dephasing contribution can be caused to vanish. The net result was that coherence measurements displayed exponential coherence loss with the time constant of the population relaxation. This result enabled many measurements of vibrational relaxation using both time and frequency domain nonlinear methods such as coherent anti-Stokes Raman spectroscopy (CARS) (35). Izo Abram later moved to the French Telecom/CNET Laboratory in Paris.

Our first clues that the vibrations of aromatic molecules could have very long T_1 lifetimes came from measurements in naphthalene, which exhibited a lifetime of 88 ps for a mode at 1380 cm^{-1} (36, 37). The vibrational population relaxation rates of these large molecules all showed a high degree of mode selectivity. However it was even more surprising when graduate student (and my long-time tennis partner and coach) John Trout and postdoctoral fellow Steve Velsko discovered that carbon isotopes in natural abundance could strongly influence the coherence lifetime of vibrations. In crystalline natural benzene the coherence time of the

606-cm⁻¹ mode was 95 ps, but it was 2.65 ns in the pure carbon-12 isotopomer (38): This exceptionally long lifetime showed vibrational energy relaxation of a large molecule occurring on the same time range as that of small molecules in rare gas matrices. The cost of synthesizing isotopically pure ¹²C₆H₆ benzene turned out to be an excellent investment that eventually saved us a fortune. John Trout now has a successful career with Dupont, as has Steve Velsko at Livermore National Laboratory.

These particular nonlinear methods, however, were not useful in dilute solutions where the pure dephasing was fast and there was no comparably fast energy transfer between vibrators, so studies of isolated molecules in dilute solutions required developments in ultrafast laser methods. Nevertheless, this period of discovery and learning about optical nonlinear methods produced general principles of nonlinear molecular optics and spectroscopy (39, 40) that became an integral part of our research in almost all the scientific avenues we followed thereafter.

PICOSECOND TO FEMTOSECOND PROCESSES

The advances in laser methodology in the 1960s were dramatic, and the availability of various lasers dispersed the traditional molecular spectroscopy community into a wide range of entirely new avenues of research. Our spectroscopic work always had a significant dynamics slant, so when the opportunity arose to make real-time measurements of intramolecular processes it was not possible to resist. In early 1969 I persuaded our Chairman, David White, to provide the resources to purchase our first Nd-glass laser. The case was made with the help of Peter Rentzepis of Bell Labs, who, in the previous year, had published his paper on the pump/probe kinetics of azulene, which reported a time-domain measurement of a picosecond molecular process. I had met Peter in 1968 and invited him to Penn. Later, as an adjunct professor, he made welcome contributions to our picosecond lab. The generation and characterization of 8 to 10 picosecond pulses was technically manageable, but I thought it was challenging to perform meaningful experiments with them.

Our early experiences with mode-locked Ruby and Nd-glass solid-state lasers were a change from the other experiments we were doing with high magnetic and electric fields and moderately high-resolution spectroscopy of crystals in liquid helium. Their repetition rates were in the range of one shot per minute. Only one type of oscilloscope—the Tektronics 519—had enough band width to resolve the mode-locked pulse trains and allow us to inspect the extracted single pulses. Its fleeting signals needed to be stored by means of a Polaroid camera, so the laboratory became an ocean of discarded Polaroids. Approximately 95% of the laboratory time was spent aligning the laser. Proving the significance of results presented challenges because of the high energy (approximately 20 mJ), high peak powers, and large peak-to-peak fluctuations. I thought the suggestion by Alfano & Shapiro (41) that their super-continuum may be used as a probe for kinetic spectroscopy was a big step forward; this discovery stimulated the subsequent

development of various approaches to transient absorption spectroscopy on the picosecond timescale.

My first student to work with picosecond lasers was Bob Anderson from the Army Research Lab in Philadelphia. He along with John Wessel, Hans-Peter Lutz from Lars Lindquist's lab in Paris, and Gary Scott from Clyde Hutchison's group in Chicago were the adventurous quartet who began our effort with picosecond solid state lasers. We aimed to address a wide range of questions to expose new aspects of solution-phase dynamics, photochemistry, and radiationless transitions, but obtaining meaningful, reproducible results from these lasers was very hard work. In 1971 I rearranged all the questions we had been trying to address on a blackboard in order of how straightforward the experiment would be. We worked our way down the list over a one-year period. This approach, although it meant putting off some exciting ideas until later, was a good strategy after all. Bob Anderson graduated in 1976, by which time the group had accomplished significant, reproducible experiments on time-resolving energy transfer (42), direct measurements of inter-system crossing and its solvent dependencies (43, 44), internal conversion (45), photodissociation (46), geminate recombination reactions, and vibrational energy transfer in solids (47). In those days the authors of papers were often arranged in alphabetical order, but all played an equal role in these early ultrafast experiments. I had other people in my group in the early 1970s who were deeply interested in the ultrafast research and who contributed significantly to our developing ideas on coherence and ultrafast processes. This group included some who made extraordinary independent contributions to the ultrafast field later in their careers, such as Ahmed Zewail and Douwe Wiersma. Gary Scott became a professor at University of California Riverside, Hans-Peter Lutz a scientific director at NATO, and Douwe Wiersma a professor and now Dean at the University of Groningen.

In the ensuing year or two we tried many approaches to obtain high-quality picosecond spectra. A major breakthrough came when Bruce Weisman, a post-doctoral fellow who had come from Stuart Rice's group in Chicago and is now a professor at Rice University, and Ben Greene, who went on to a postdoctoral fellowship with Chuck Shank at Bell Labs where they developed the colliding pulse mode-locked laser and who later became a permanent staff member at Murray-Hill, combined a picosecond-generated continuum with a prototype of the Vidicon optical multichannel analyzer. Now for the first time we were able to digitize full normalized transient spectra immediately after each laser pulse (48). By 1978 we were recording reproducible transient spectra of aromatic and heteroaromatic molecules, proteins, and molecular gases. I later learned that the five papers we published using this instrument within a space of only two years (1978–1980) were all highly cited: We reported on transient spectra of aromatic molecules in solutions, hemoproteins after ligand dissociation, photoinduced isomerization in solutions, and chemical reactions under collision-free conditions. It would not have been possible using any previous picosecond spectroscopic method for us to have been certain of the many important phenomena we reported that were signalled by very small spectral effects. For example, it became clear from the solution phase

experiments that absorption spectra created on the picosecond timescale were not relaxed but were characteristic of hot molecules whose cooling times we could clearly observe. I mention some of the other applications of this spectrometer below. These experiments represented a qualitative advance in the reliability and applicability of ultrafast spectroscopy (49).

Through the 1970s many other groups used solid-state lasers to measure significant molecular relaxation processes: These groups included Peter Rentzepis and colleagues at Bell Labs, Ken Eisenthal at IBM, Maurice Windsor at Washington State, and V.S. Letokhov in Moscow. In particular, Wolfgang Kaiser and Alfred Laubereau in Munich, who were making measurements on dephasing and relaxation of vibrations, had a significant impact on my thinking. However low repetition rate solid-state lasers were soon to be replaced by ultrafast dye lasers. There were laser people from engineering and physics engaged in the development of new ultrafast detection methods and lasers. I want to mention in particular Erich Ippen and Chuck Shank from Bell Labs (Holmdell), who greatly influenced our ability to reach for more significant questions by creating a succession of ultrafast, femtosecond timescale lasers based on mode locking of continuous wave (CW) dye lasers. Most femtosecond laser experiments in chemical systems owe a great debt to the inventions of Ippen and Shank, who I first met at the International Conference on Quantum Electronics in Amsterdam in 1976 when they were already using a passively mode-locked dye laser to examine some molecular systems. The first conference on picosecond phenomena (later ultrafast phenomena) was held in Hilton Head Island in 1978, and its proceedings (50) contain contributions from many of the pioneers of the ultrashort pulse laser field. This conference was the first to bring together chemists, physicists, biologists, and engineers as a fruitful and lasting combination.

Real-time measurements of vibrational energy relaxation remained a principal objective of mine. Although significant progress in technology was being made by 1979 when Ted (E.H.) Heilweil became my student, we still had no general way to adapt these new methods to the study of molecular vibrations in condensed phases. The methods of Kaiser and Laubereau were not applicable to dilute solutions, so we built a 0.5-Hz glass laser that synchronously pumped a dye laser: One tunable pulse every 2 s was a great improvement over one fixed frequency pulse every 2 min. Excitation by the laser harmonics and the tunable-dye laser pulse allowed us to make vibrational populations by Raman gain. When Ted discovered the stimulated Raman gain from an aqueous potassium cyanide solution, we were able to use its time dependence to measure a vibrational relaxation time for the isolated CN^- ion in water. Most diatomics had lifetimes in the millisecond to microsecond time regime, so the relaxation time we measured of 25 ps for a diatomic molecule having a high frequency of approximately 2000 cm^{-1} was unexpectedly fast and difficult for many critics to comprehend: How could the molecule dispose of 2000 cm^{-1} of vibrational energy in such a short time? We had guessed that the Coulomb interactions were responsible but had no quantitative description (51). When this measurement was repeated 15 years later using stable tunable femtosecond IR

pulses based on a titanium sapphire laser and an optical parametric amplifier (52), I called Ted and told him that his earlier measurement was right on the mark, but of course he was not surprised. A recent theory of the vibrational relaxation of the ion in water shows that it is dominated by the Coulomb force fluctuations (53). Ted is a senior scientist at the National Institutes of Science and Technology, and he is a leader in the field of vibrational energy relaxation in liquids and on surfaces.

COLLISION-FREE TIME-RESOLVED EXPERIMENTS

As the ultrafast methods became more flexible I considered it more reasonable for us to use them in collision-free gas-phase experiments. The expectations for chemical reactions of isolated large molecules were not obvious, and I remember long discussions at meetings about whether processes such as isomerization could even occur without collisions. When our time-domain experiments showed that the trans to cis isomerization of stilbene occurred rapidly under collision-free conditions and that the rate was dependent on the excitation frequency (54, 55), this was an exciting discovery: It was the first isomerism that had been triggered with a range of initial energies. We now understood that isomerization corresponded to a barrier crossing and the intramolecular redistribution of a large excess of vibrational energy. I recall presenting this work for the first time at a meeting organized in Munich in 1979 by Ludwig Hofacker, my long-time colleague who was also the Editor of *Chemical Physics*. Bill (W.T.) Miller looked at the energy dependence we had obtained and suggested that it may all be explained by the Rice-Ramsberger-Kassel-Marcus (RRKM) theory. Only later did it become obvious that this was exactly the way to think about it. It was immediately obvious that the supersonic jet spectroscopy introduced by Don Levy's laboratory (56) would be ideal for a study of the photochemistry and spectrum of the isomerizing molecules. I could not interest Don Levy in stilbene, but Joshua Jortner, who was at Penn in 1979 as our first Camille and Henry Dreyfuss Visiting Professor, was very interested in the idea. However, I knew that Ahmed Zewail was very close to having a beam apparatus constructed at Cal Tech, where he would be able to measure not only intensities but also fluorescence lifetimes of the individually accessed levels, so I persuaded him to look at stilbene: The results turned out to be useful and provided a much improved measurement of the functional form of the sudden onset of the isomerization pathway, clarifying the energy dependence of the isomerization yield and providing a quantitative measure of the height of the potential barrier (57).

There was much activity in the following few years on stilbene, which remained a prototype for barrier-crossing dynamics. However, my main interest continued to be the problem of the solution-phase isomerization and comparisons of solution and isolated molecule behavior.

I recall lively theoretical and experimental interest in the early 1980s in the Kramers theory of reaction rates, which predicted that isomerization rates should

go through a maximum at some value of the friction at which point the transition-state rate could be obtained. When postdoctoral fellow Guido Rothenburger, who later joined the faculty of the University of Lausanne, joined my group, he measured the rates of isomerization of stilbene in hydrocarbon solvents, but we found no maximum in the rate even at frictions as low as that exerted by liquid n-butane. It became clear that any maximum in rate must occur at lower-than-conventional liquid friction, and the direct observation of a Kramers so-called turn-over phenomenon came when an excellent student Minyung Lee, who later became a professor at Ewha University in Korea, constructed a high-pressure cell and examined the fluorescence of stilbene in supercritical fluid ethane as a function of pressure from the gas to the liquid regime. Real-time measurements of the rate of isomerism (58) showed a regime where the rate increased with increasing friction, typical of the Lindemann behavior for unimolecular reactions in gases, followed by a turnover in the isomerization rate at approximately 140 atm of ethane at 300 K. The predictions of the Kramers theory were confirmed by this beautiful experimental result in a broad sense, but understanding how the observed properties depended on the specifics of the potential energy surfaces, such as the shape of the turnover region, and complete reconciliation of the maximum rate with transition state theory continued to occupy many labs for some time to come. During this period, many other labs, including those of Graham Fleming, then at Chicago, and Jurgen Troe at the University of Gottingen, were major contributors to this important area of condensed-phase dynamics.

BIOPHYSICAL CHEMISTRY

In the 1960s I did not have the impression that many in the field of physical chemistry were very enthusiastic about the biological sciences, in the sense of encouraging research to answer biological questions. X-ray crystallography, then a component of every physical chemistry group, seemed to be an exception, and although this also was a period of discovery in conformational analysis of polypeptides and optical activity, it was less usual to find a chemistry-based group carrying out state-of-the-art spectroscopic experiments or theory on biological processes. In the time since this situation has gradually changed; experimental and theoretical biophysical chemistry has emerged as an indispensable part of the chemical sciences. I believe this evolution is strongly related to the continuing commitment of the NIH, particularly the GM Institute, to stimulate research on fundamental aspects of processes of potential importance in biology and medicine. There is also an increased awareness by physical chemists that biology offers new questions of a basic nature that are characteristic of complex systems and whose answers require a physical chemistry approach.

My research in biophysical chemistry began in the early 1960s with work on energy transfer, photophysics, and spectra of molecular aggregates, which was aimed at questions in photobiology. But my research on proteins began in 1966,

when a young M.D./Ph.D. student candidate, William A. Eaton, who was making thermodynamic measurements on proteins in the laboratory of Philip George, asked my opinion about a weak absorption band at 695 nm in the spectrum of the protein ferricytochrome-c. This band was a known diagnostic of the native protein, disappearing in denaturing solvents and on the binding of a sixth ligand. Later that day, Bill and I were engaged in our first conversation, at the local Deck Tavern, when I learned that he had a crystal of this protein. So we returned to Bill's lab, picked up crystals of cytochrome-c, kindly donated by Emanuel Margoliash, and took them to my lab where a polarizing microscope and a spectrograph were combined to create a makeshift microspectrograph, with which we photographed the spectrum of cytochrome-c in two crystal polarizations using a Wollaston prism. I was soon able to convince Bill that the 695 band was a transition polarized perpendicular to the porphyrin plane and therefore was a ligand-iron charge transfer transition. Converted by the power of group theory and spectroscopy, Bill signed on as my graduate student and wrote a beautiful thesis for the Department of Molecular Biology in 1967 on the spectroscopy of heme proteins; thus began our lifelong friendship. The results were published in the *Journal of Chemical Physics* (59), a journal that in 1967 published only one paper on a protein. Bill Eaton is now the Chief of the Laboratory of Chemical Physics at the NIH, where he makes world-renowned contributions to the molecular basis of sickle-cell disease and to the mechanism of protein folding.

For those interested in ultrafast chemistry, the advances in laser methods through the 1980s were startling, and the adaptation of the new technologies to the study of a variety of molecular processes was challenging, exciting, and rewarding. It was during this period that the dynamics of proteins began to be accessible to us.

A widely known strategy for initiating a protein conformational change was the photodissociation of a ligand. This technique had been used before with heme proteins such as myoglobin and hemoglobin, but I thought it was illuminating to obtain high signal-to-noise electronic spectra of the proteins a few picoseconds after the dissociation of the carbon monoxide ligand: For us, this achievement (60) in 1978, based on our new spectrometer mentioned above, began a major new initiative on the fast dynamics of hemoproteins spearheaded by postdoctoral fellows Don Chernoff, from the group of Stuart Rice, and Paul Cornelius, who came from the Charles Harris group in Berkeley. The questions were clear: What are the immediate and later structural responses of a protein to ligand dissociation? After photodissociation, does the ligand recombine, and what can this dynamics tell us about the potential energy surface linking ligand and metal center? In all the examples we examined there were subtle changes in the spectra that could not have been seen with earlier methods. The dissociation of CO was immediate and there was no geminate recombination. The dissociation of oxygen from HbO₂ was also immediate but we discovered a 200-ps geminate recombination of the oxygen molecules (61). The nitric oxide ligand of HbNO dissociated immediately followed by a very rapid nonexponential geminate recombination of the NO (62).

These phenomena, showing that the potential barriers for the ligand-binding step in the reactive configuration of hemoglobin were dependent on the electronic structure of the ligand, have been the subjects of many subsequent optical and IR experiments over a wide range of timescales. Later, Don Chernoff founded his own company and Paul Cornelius joined Coherent.

By 1983 femtosecond timescale deligation of the CO of MbCO had been reported by Jean-Louis Martin (63) using the Ippen and Shank design dye laser. However, I strongly believed that clarification of the protein dynamics after the ligand dissociation would require direct observations of the ligand: But such an experiment needed femtosecond IR spectroscopy, which at that time had not been developed. How to generate IR pulses by difference frequency generation was known, and we were using such methods in vibrational relaxation experiments in the mid-1980s. However, a stable, versatile, tunable IR probe source was still elusive, especially in the mid-IR where the fingerprints of complex structures were found. To address this gap we developed an approach in which a sample was pumped by an optical pulse and a tunable transmitted CW IR salt diode laser beam was upconverted by a femtosecond dye laser and detected in the visible: A scan of the CW IR laser provided a record of the IR kinetics at 200-fs time resolution and tunable over molecular vibrations (64). We later used the principles of this method in many optical pump/femtosecond IR probe applications in biophysics including vibrational energy relaxation of simple ions (64a); IR probing of the protein backbone in reactions in photosynthetic systems, such as the reaction centers of photosynthetic bacteria (65, 66) in collaboration with my Penn colleague Les (P.L.) Dutton; the isomerization in bacteriorhodopsin (67); and in basic studies of the dynamics of carbon monoxide chemisorbed on copper in collaboration with Penn physics professor Arjun Yodh (68).

The arrival of postdoctoral fellow Phil Anfinrud in 1986 coincided with the time for a major new effort in protein dynamics because I was confident that Phil was the right person to tackle the difficult experimental task of examining the carbon monoxide ligand IR spectrum after photolysis of HbCO. First Phil used the CW upconversion method to obtain a direct IR femtosecond measurement of the disappearance kinetics of the Fe-CO bond. Needless to say I sought to measure the appearance of the diatomic CO, but its IR absorption cross section was 30 times weaker than that of the metal carbonyl, so observing it was nearly unfeasible with the then-current laser methods. However, Phil and Challee Hahn accomplished it by running the IR upconversion experiment continuously for six weeks to achieve the appropriate signal-to-noise ratio. Phil, the postdoctoral fellow, had the day shift and Challee, the graduate student, had the night shift. Eventually we were able to see clearly the IR spectra of the generated CO molecules inside the protein. This femtosecond IR experiment generated a remarkable set of microscopic features that allowed us to visualize the ligand-protein dynamics with unprecedented detail (69): The free CO was seen promptly at 300 fs after optical excitation. A barrier to recombination must have formed within a few picoseconds, and the CO rapidly found locations in the heme pocket that were not more than a few angstroms from

the Fe. The deligated CO appeared in its $v = 0$ vibrational level. The flow of excess vibrational energy from the heme to the solvent was directly seen as the heme cooled within 1 to 2 ps, and the thermal equilibration with the surrounding solvent structure took 30 ps. Phil, currently a senior scientist at the NIH, has become a world leader in picosecond time-resolved structural biology by means of synchrotron-based ultrafast X-ray diffraction. Chalee is a professor at the Sunmoon University in Korea.

MORE RECENT BIOPHYSICAL CHEMISTRY AND TWO-DIMENSIONAL INFRARED ECHO SPECTROSCOPY

Based on a tremendous amount of conventional IR spectroscopy, the amide-I modes of peptides appeared to have significant potential as probes of protein structure and dynamics, so we continued through the early 1990s to examine them with femtosecond IR methods. These amide transitions are basically carbonyl modes, so their vibrational states have excitonic character in polypeptides, their mode frequencies are sensitive to the local secondary structure, and they have large transition dipole moments. From my standpoint some of the questions faced in finding ways to use amide modes to expose protein structure were similar to those we had developed many years before, mentioned above, to investigate exciton topology: The highly degenerate exciton bands needed to be pulled apart into structural components by isotope replacement. But we also needed more-efficient methods of nonlinear IR spectroscopy. It was this goal of determining features of peptide structure led us to develop two-dimensional IR spectroscopy.

In 1997 the contributions of three important postdoctoral fellows coalesced to make possible the initial advances toward two-dimensional spectroscopy: Peter Hamm (now a professor at the University of Zurich) came after earning his doctorate on transient IR spectroscopy with Wolfgang Zinth at the University of Munich. Steve Palese, from Dwayne Miller's group at Rochester, had just completed the design and construction of our new hybrid Ti-Sapphire laser that was ideal for use as the pump for a stable optical parametric amplifier (OPA), which would produce femtosecond IR pulses to replace the sum frequency generation method. The electronics for a 32-element array detector on which we would disperse the transmitted femtosecond IR pulse were being put together by Manho Lim, a postdoctoral fellow who had come from Phil Anfinrud's group in Harvard and is now a professor at Fudan University in Korea. Nowadays these electronics with preamplifier circuits for every mercury-cadmium-telluride detector are commercially available, so Manho's feat was a tour de force. Manho has often wondered how the many tens of people now doing two-dimensional IR photon echo spectroscopy would fare if they had to wire their own array detectors. Based on a published design, the OPA was constructed by Peter Hamm. At last we had a tunable source of approximately 100-fs IR pulses and a sensitive array detector for high signal-to-noise nonlinear IR

spectroscopy and an extremely stable laser system. After testing this instrument on the challenging example of CN^- in dilute solutions, mentioned above, we moved on to peptides and proteins. To simplify the amide spectra and achieve results that could not be obtained from Fourier-transform IR spectroscopy, we needed to generate optimally narrowed pump IR pulses by means of a Fabry-Perot filter and use the largest possible bandwidth pulses to probe the peptide vibrations. When Peter and Manho displayed the results of these experiments as a signal contour in the two frequency dimensions of the pump pulse center and the dispersed pulse frequency, we had the first two-dimensional IR spectrum. Mostafa El Sayed was kind enough to put it on the cover of the *Journal of Physical Chemistry* (70) featuring a paper with the two-dimensional IR spectra of N-methylacetamide and three small globular peptides, apamin, scyllotoxin, and pancreatic trypsin inhibitor. We had soon used this method to determine the structure of a peptide containing five amide modes and the results were extremely encouraging (71). This two-dimensional IR experiment is analogous to the NMR double resonance and displays the coupling between the amide modes as well as their frequency distributions.

Although past laser adventures had taught me that when an experiment is working well it is unwise to change anything significant, I did urge Peter and Manho to modify the double resonance experiment to the photon echo configuration. En route to that goal in 1998 they succeeded in recording the first three-pulse photon echoes in the IR (72). In this experiment the echo signal is spatially separated from other signals and sent to a square law detector. The experiments showed clearly the photon echo peak shifts of the vibration of the aqueous azide ion and led to measurements of its spectral diffusion. We went on to use the three-pulse IR echo to examine the frequency fluctuations of the reactive sites of carbonic anhydrase and hemoglobin (73).

The final advance toward the optimized phase-locked two-dimensional IR echo method that is now in widespread use came from Matt Asplund, a postdoctoral fellow from Charles Harris' group who is now at Brigham Young University who successfully heterodyned the IR three-pulse photon echo. The heterodyning required combining the generated echo field with another pulse to act as a local oscillator. This advance enabled the echo signal field, rather than its intensity, to be obtained as a complex function of three times familiar from two-dimensional NMR—the coherence time, the waiting time, and the detection time. We were immediately able to obtain phase-controlled two-dimensional IR echo spectra by Fourier analysis along the three time variables of the third-order nonlinear response. The signal was measured by both time and frequency domain interferometry. This first experiment, which involved a dipeptide, showed the characteristic shapes of two-dimensional spectra caused by the separation of homogeneous and inhomogeneous broadening in the echo signal (74). The two-dimensional IR experiment was being performed in a manner analogous to the NMR COSY and NOESY experiments and contained all the information needed to describe the nonlinear responses. At last all the three-field nonlinear spectroscopy signals at $\omega_s = \omega_1 - \omega_2 + \omega_3$, fully characterized by their dependence on three time intervals, and their tensor elements were obtainable

from one single data set. In earlier years each of these many signals had required relatively complex instrument development.

Our discoveries of the two-dimensional IR double resonance and photon echo methods were motivated not by the contemporary research on nonlinear optics but, as I have described, by the need to find avenues to determine dynamical and structural features of biological assemblies. The two-dimensional IR method is a powerful new form of IR spectroscopy that is adaptable to both the equilibrium and nonequilibrium dynamics of structures. Many groups are contributing to the advances in two-dimensional IR theory (75) and experiment (76, 77), but a complete review of this burgeoning field goes well beyond the scope of this perspective. Using techniques of isotope replacement, we have made extensive studies of the structures and dynamics of small peptides (78, 79), α -helices (80), and proteins and have completed experiments analogous to heteronuclear NMR (81) and dynamic chemical exchange NMR (82). These two-dimensional IR spectra inform on the dynamics of the distributions of structures, the coupling between the amide units, and the conformational dynamics.

It is fascinating how the knowledge gained from studies of molecular excitons has become useful in designing experiments for multidimensional IR spectra of peptide secondary structures. The concepts we learned from the many experiments on nonlinear optics and exciton topology and the key role of isotopic substitution in discovering linear chain and two-dimensional excitons are becoming exciting new tools in secondary-structure and liquid-state structure determination. The motional narrowing of exciton vibrations discussed above for solids has become a key factor in the vibrational spectra of peptides, particularly in well-ordered helices and beta sheets. It was the high priority given to the support of physical chemistry research on basic molecular concepts that gave rise to these developments.

At the time of writing, the rollercoaster ride continues. I am optimistic that multidimensional IR experiments will enable measurements of the structural evolution of a protein along folding pathways and allow visualization of reactions occurring in enzymes. But this will require advances in laser technology and new understanding of properties of the molecular vibrations of peptides and of water. A major advance will occur if a stable, single-cycle IR pulse is available to create a multidimensional echo spectrum that allows us to visualize the complete matrix of coupled states of sections of a protein at each instant of time. I do not believe that this accomplishment will take another 50 years.

CONCLUSION

Finally, on a personal note, if I had some influence on the friends and colleagues who traveled with me on this physical chemistry research journey I would like to imagine that it was because I brought personal and spontaneous qualities to the research and an unbridled enthusiasm for new questions that helped to lead us into many different areas of chemical physics.

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