# HOW DO YOU KNOW?

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### Prologue & Powerpoint

Pictures have been more important than mathematical facility in my scientific trajectory. In experimental work, most organic chemists deal with solutions, flasks, and reactions. Intellectually they deal with pictures of molecular structures and reaction diagrams. Without pictures there would be no communication of organic chemistry, and no intellectual life for an organic chemist. Over the half-century since I became a chemist, my pictures have been chalked onto blackboards, inked onto tracing paper and restaurant placemats, photographed onto lantern slides, traced with felt-tip pens onto overhead transparencies, and scratched into the earth during hikes at summer conferences. When all else failed, they were sketched with a finger on an outstretched palm or pantomimed. Thirty years ago organic chemists adopted Macs, rather than the PCs favored by physical chemists, because the graphic software for Macs allowed them to make their pictures with a mouse.

En route to a 1999 conference in England, I realized that I had forgotten the overhead transparencies for my presentation. A former student at the meeting said I could make a “PowerPoint” and lent me his laptop. Over one sleepless night I learned the rudiments of PowerPoint and got my talk finished just in time. I’ve never looked back, and PowerPoint has become a key part of my intellectual trajectory. I sometimes use it as a way to develop my thoughts.

In 2003, when I was about to testify as an expert witness in a patent case in London’s Court of Chancery, the Queen’s counsels had an extended debate on whether I should be allowed to make my written report more easily comprehensible by presenting a PowerPoint, a first in that court. Ultimately Justice Nicholas Pumfrey agreed with barrister Andrew Waugh that “[e]xplained graphically it is a lot simpler to understand. It will assist the court.”

Kai Erikson, the obliging host of Koerner Intellectual Trajectories, faced with Pumfrey’s Choice, made the same decision, and my oral presentation to the Koerner fellowship was the first to be computer-enhanced. I hope that, within the boundaries

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**James Michael McBride,** Professor Emeritus of Chemistry, has spent his entire career at Yale since he became assistant professor of chemistry in 1966. In 2000 he was named to the Richard M. Colgate Professorship, established in 1919 “for the advancement of the intellectual teaching of the freshmen students,” a chair which “shall not be confined to any one who has passed his intellectual prime or influence in usefulness as a stimulating teacher.” He received Yale’s Dylan Hixon Award for Teaching in the Natural Sciences (1992), its DeVane Medal for Distinguished Scholarship and Teaching (1994), and the YSEA Award for Meritorious Service to Yale (1998). In 1987 he shared the American Chemical Society Award in Graduate Education for the outstanding American dissertation in chemistry with his student Mark Hollingsworth, and in 1996 he received the Chemical Manufacturers Association Catalyst Award for undergraduate education.

of decorum, future presenters can enjoy whatever mode of communication they find most suitable to their story.

PowerPoint animation is not available for this printed version, so what follows differs from the live performance.

### Roots

Although my intellectual trajectory resembles those of most in this fellowship in being conditioned by good luck, my geographic trajectory has been more sedentary than many. I was born in Lima, Ohio, in 1940. At age three I left for Chicago and then Sioux Falls, South Dakota, while my father was a medical officer in the Army Air Corps. When I was five we returned to Lima and stayed. After twelve years of Lima public schools, I entered the College of Wooster in Ohio. Two years later I transferred to Harvard and stayed to complete my Ph.D. Then I came to teach at Yale and stayed for good.

Of course, my intellectual trajectory started long before I was born. My great-grandparents were born between 1822 and 1855. Of my maternal great-grandparents, three had seventeenth-century roots in Massachusetts, Connecticut, and New York. Their forbears had migrated up toward the St. Lawrence and out to the Western Reserve, to rich farm country near the Great Black Swamp in northwest Ohio. The fourth was Scotch-Irish, born in Virginia.

My McBride great-grandfather, James, was Appalachian Scotch-Irish like his wife, Jane. My father's other grandmother was Pennsylvania Dutch, that is, German. My middle name, Michael, was the family name of her husband born in Swabia. All these ancestors were drawn toward the Great Black Swamp before the Civil War. My parents grew up on either side of the Ohio-Indiana line.

My dad considered himself a Hoosier. In *Albion's Seed,* David Hackett Fisher notes that "Hoosier was attached to the citizens of [Indiana] to distinguish them from their Yankee neighbors," and points out that the terms "Hoosier," "Cracker," and "Redneck" originated in the hardscrabble English-Scottish borders and were associated with the "paradox of poverty and pride." I doubt that my dad ever read the borders poet Robert Burns, but he certainly would have liked "The honest man, tho' e'er sae poor / Is king o' men for a' that." As an orthopedic surgeon and the son of a village doctor, he was never impoverished, but he identified with the hard-working poor and especially with racial and religious minorities. He loved instructive family vacations in the station wagon, like our round-trip to San Diego in ten days—camping. But apart from military service and an orthopedic residency, the only time he lived more than 150 miles from his birthplace was for a few months in 1931, when he began an internship in San Diego. This was cut short when he took a surgeon to task for treating a nurse badly. The only backup position he could find on short notice was in Lima, where my mother was a nursing student. I like knowing that they met when he taught her chemistry class.

My mother's family were not so well-to-do and were certainly frugal, but she didn't seem to notice. These Yankees were gentler and more cultured than Dad's

Hoosiers. As one of only two orthopods in several counties, he was busy day and night, so my mother was more involved in raising me than he was, and more of her culture rubbed off on me, except that he insisted that I not have to take music lessons if I didn't want to. Unfortunately, I didn't. Both of them campaigned vigorously for civil rights and were locally recognized for their efforts. Dad was particularly proud when one of the African American athletes whose higher education he had sponsored (despite the warning from a pessimistic assistant principal) earned a Ph.D. and became assistant HUD secretary for public housing.

I have two brothers, five and eight years younger. My first teaching experience came when I was in third or fourth grade. I sat my middle brother and a cousin at coffee table "desks" in our living room and taught a lesson. I have found that learning something new is never properly satisfying until I have taught it to someone.

Northwestern Ohio is rich in agriculture, but I thought of myself as a city boy in a town of 50,000 with thriving commerce and industry. Still, I do remember being skeptical when a high school civics teacher claimed that Lima ranked high on the priority list of Soviet cold-war targets. In the 1890s the Lima oil field had been the world's largest producer. By my time Lima refined petroleum from elsewhere, but more important were its factories – electric motors, steam shovels, steam locomotives, most American school buses, Cadillac funeral coaches. Of these only the automated refinery remains, and Lima is mostly a service provider in the Rust Belt. When I was growing up, Lima's compact Fourth Congressional District was represented by Republican William McCullough, who supported strong gun-control legislation and school busing. LBJ called him "the most important and powerful political force" in passing the 1964 Civil Rights Act. Now the Fourth District is extravagantly gerrymandered and represented by the founding chairman of the House Freedom Caucus.

### School and College

There weren't other kids my age in the immediate vicinity of our home on the fringe of Lima, but at Theodore Roosevelt Elementary School I found close friends with whom I could play unsupervised sports and read – comic books mostly. I had subscriptions to *Walt Disney's Comics* and *Looney Tunes & Merry Melodies*. Perhaps they conditioned me for visual communication, despite my lack of skill in the graphic arts. Some comic book stories featured "science," which was so respected in postwar popular culture that no TV commercial for antacids was complete without a pitchman in a white lab coat pouring "concentrated stomach acid" on a white handkerchief. One uncle far away was a chemist, but there were no other scientists in the family, except my father, who had pretended to teach my mother chemistry. Postwar America encouraged scientific careers, but to the extent I thought about it, I supposed I'd be a doctor, like my father and grandfather.

Every other week in the summer I'd get an armload of books from the library's Bookmobile. They weren't great literature, and I don't remember many of them, though I certainly enjoyed the *Doctor Dolittle* series. That I carried so many books back and forth to school was probably the reason that as a high school senior I received the class's least-coveted award, a gold cup on a pedestal labeled "Most Studious–1958." The cup was two inches high.

In junior high I worked as a page at the Lima Public Library. In retrospect, I'm sure that this was because my mother's aunt was a librarian. While preparing this talk, I became more keenly aware of the influence Aunt Mar had on me. My first exposure to classical music was listening to "The Voice of Firestone" on her console radio. In junior high I ate lunch at her home, which was full of Arts and Crafts objects and family heirlooms. Her desk at the library was stacked with fascinating leaves from medieval manuscripts, because Lima's library served as the sales agent for Otto Ege, the Cleveland biblioclast whose collection was acquired by Yale's Beinecke Library in 2015.

I started college at Wooster, 125 miles from Lima. Two of my closest friends started at Harvard, but I applied only to Wooster, partly I suppose because, like me, it was Presbyterian. The frieze in the reading room of its 1906 Library is emblazoned with the names of great thinkers: Copernicus, Raphael, Demosthenes, Michelangelo, Calvin (of course), Lavoisier (the chemistry program was particularly strong), Moses… and Darwin! In 1923 Charles Wishart, Wooster's beloved president, had fought the forces of fundamentalism in the Presbyterian Church and defeated William Jennings Bryan in the campaign for Moderator of its General Assembly. Wooster was a great place, and I loved it there – partly because of the president, Howard Lowry, a Matthew Arnold scholar and a very wise man. One of his sayings was "There is no college that is not the best for someone." Wooster was certainly the best place for me then, and best for many others. Lowry was an inspiring public speaker. He began one baccalaureate talk by establishing a rule for commencement speakers, "Realize that not all you say will be heard."

One of my favorite professors at Wooster was Frances Guille. François Truffaut based his movie *L'Histoire d'Adèle H* on her unscrambled edition of the coded diary of Victor Hugo's eccentric daughter. Miss Guille's most important influence on me was as the leader of a study trip on French language and culture after my freshman year. In Paris I actually lived for a month in a garret room, because I was the only male in this group of seventeen. For a freshman from Lima who had grown up with only brothers and had never even visited New York, this experience was an eye-opener in many ways.

The other professor who influenced me most was Theodore R. Williams, who arrived for my sophomore year. Wooster's first African American faculty member, he would win national recognition as an analytical chemist and educator and was an unparalleled inspiration and mentor. Ted was devoted to students and chemistry, to the college, and to chamber music. I never think of him without feeling humble. He liked saying, "There is no limit to what you can accomplish, if you don't worry about who gets the credit." In 2005 more than a thousand friends attended Ted's memorial service, where the Gryphon Trio volunteered to play, ten days after they had given a concert at Yale.

During my sophomore year, Lima friends were suggesting that I join them at Harvard. Ted Williams said that would be a good idea. Bill Rogers, a Wooster classmate, also provided useful advice. As a student at Harvard summer school Bill had been agog, until a regular Harvard student told him, "Yeah, at first you feel pretty small, but then you decide you're as good as the next guy—maybe a little better." So I was somewhat prepared when I went to Cambridge, where people would pass on the sidewalk without greeting one another.

Harvard broadened me in unexpected ways. On election eve in 1960, two months after I arrived, a Lima friend and I took the MTA to a Back Bay hotel where Henry Cabot Lodge, the running mate of Richard Nixon, who had already received our absentee votes, was rumored to be appearing. He didn't show, so we went over to the Boston Garden for the jam-packed Kennedy rally. The next day there was a photo on page 16 of the *Boston Globe* showing JFK leaving the dais while shaking my hand. Since then I've voted Democratic.

My favorite group at Harvard was the University Choir with its sublime organist-choirmaster John Ferris. Even more sublime was the star soprano, Florence Staplin, who joined during my second year of graduate school. Within six months of our first date we were married, and certainly no one has been more influential on my intellectual trajectory. As a graduate student in American literature she became particularly influential on my writing. Later, when I was drafting a Yale committee report (perhaps the one recommending the Pass/Fail option), there was only time for her to edit the first half before I had to present it to my committee colleagues. After a quick read, Bob Wyman said that the first half was great, but the rest needed work.

Boston Garden, election eve, 1960: Pat Lawford, Jack Kennedy, Tip O'Neill, Mike McBride

### Harvard Chemistry

The Chemistry department at Harvard was particularly influential on my trajectory. Like the faculty at Wooster, many of these chemists thought of themselves as educators as well as researchers. For more than thirty years Louis Fieser had taught elementary organic chemistry, the course I took the year I transferred. He had written many popular textbooks. In his lectures and in our textbook, a short version he had just published for nurses, I found his historical anecdotes particularly appealing. He distributed excerpts from his more comprehensive textbook-in-progress that had hundreds of "academic trajectory" footnotes, for example the one describing himself: "Louis F. Fieser, b. 1899 Columbus, Ohio, Ph.D. Harvard (Conant); Bryn Mawr College, Harvard University."

I never met Fieser's own doctoral mentor, James Bryant Conant, who had become the president of Harvard in 1933. When Alfred North Whitehead declared, "The Corporation should not have elected a chemist to the presidency," Corporation member Grenville Clark had reminded him, "Eliot was a chemist, and our best president too."

"I know," Whitehead replied, "but Eliot was a bad chemist."

Conant was more than a good chemist and a reforming university president; he was a key organizer of scientific research during the Second World War and became U.S. High Commissioner for Germany afterwards. He was deeply involved in making American secondary and higher education a meritocracy. He took the lead in revitalizing Harvard's history and philosophy of science program and personally taught the undergraduate general education course "On Understanding Science."

Conant's own Ph.D. mentor was organic chemist E.P. Kohler, who did important research but was not peripatetic like Conant. Kohler thought his job was teaching graduate research students and undergraduates. It is said that in his whole thirty years at Harvard he only went to one meeting away from Cambridge.

In 1932 Conant had written, "We may rest confident that the fascinating art of organic chemistry will yield only slowly to the devastating inroads of an exact science." He was right then, but times were changing.

As a senior in 1961–62, I took physical chemistry with George B. Kistiakowsky, a distinguished research chemist who had personally armed the first atomic device atop the 100-foot firing tower of the "Trinity" test at Alamogordo. He had just returned to Harvard from serving as Eisenhower's science adviser—the first science adviser to a president. For some reason he seemed to think that teaching physical chemistry to us was not quite as interesting as advising Eisenhower. In the first lecture he explained that we had a textbook that talked about thermodynamics; thermodynamics was quite straightforward; we could just read that for ourselves in the textbook; he'd lecture only about quantum mechanics. Consequently I didn't really understand either thermodynamics or quantum mechanics for years and years. But like Fieser, Kistiakowsky was charming and told great stories.

In 1916 Conant had completed a two-part Ph.D. thesis: organic chemistry with Kohler and physical chemistry with his future father-in-law, T.W. Richards, the first

U.S. Nobel Laureate in Chemistry. Conant's student Fieser focused his research on classical organic chemistry, but a younger Conant student, Paul D. Bartlett, put physical and organic chemistry together more intimately than Conant had done. Bartlett became the American father of physical-organic chemistry, which uses precise conceptual and experimental tools of physical chemistry to study the structure and behavior of organic molecules. I struggled with physical chemistry in my senior year, perhaps because my math study had been truncated in transferring to Harvard, where I was advised to take only four courses each semester. But I reveled in Bartlett's physical-organic chemistry, which was transforming organic chemistry from a memorized art into an almost deductive science. Fieser's ebullient historical stories had been amusing, but I later discovered that though he could be a good historian, some of them had only a tenuous factual basis. By contrast Bartlett's understated accounts brimmed with the authority of logic and the excitement of discovery. He addressed fundamental questions: How are atoms really arranged in organic molecules? How do they move around as one molecule becomes another, and why? This was a very different approach to organic chemistry and one that really resonated with me.

I had thought seriously about medical school, but I liked chemistry and was so taken by Bartlett and his course that I decided on graduate school. I finished that spring semester with a "straight" in grades: in Bartlett's physical-organic chemistry I got an A; in Kistiakowsky's physical chemistry, a B; in non-chemistry courses I got a C and a D. Fortunately I had already been awarded an NSF fellowship for graduate study. Faced with the choice between Berkeley and Harvard, I asked two teachers for advice. August Maki, a young Berkeley Ph.D. who taught the Harvard physical chemistry lab, inquired about my specific interests and told me that Harvard was "king" in physical-organic chemistry. Bartlett said that Professor Wilson would tell me I'd be crazy not to change schools for graduate work, and that Professor Woodward would tell me I'd be crazy not to stay at Harvard. His own opinion was that changing had its advantages, but that not many undergraduates exhausted the teaching potential of the Harvard department. I decided to stay at Harvard and work with Bartlett, who had grown up in Indiana and liked to hike and ski and sing and write poetry. Every year in graduate school I audited his course. It was nominally the same one I had taken as a senior, but it changed significantly each year. He remains my principal scientific hero.

### Graduate School: From Electron Flips to Solid-State Organic Chemistry

Bartlett had pioneered a pattern for research in physical-organic chemistry, which was to choose a question of current theoretical interest and then design and synthesize a new molecule whose reaction rate, or products, or physical properties would provide an experimental answer to the question. The question I chose for doctoral research was "How rapidly can electrons flip over?" Bonds between atoms are formed by a pair of electrons. A bond can be broken by heat or light to give two molecular fragments, called "radicals," each of which bears one of the electrons from the original bonding pair. Electrons act like magnets that can point either north or south. This orientation has particular chemical relevance for pairs of electrons. When two electrons point in opposite directions, they can form a bond joining the radicals into a single molecule, but if the electrons are parallel, bond formation is impossible. An important open question for organic chemists in the mid-1960s concerned the rate at which an electron can "flip," changing its orientation so that two adjacent radicals, which could not bond because their electrons were parallel, convert into an anti-parallel pair that can bond.

There was no direct way to measure the rate of electron flipping, but I hoped to design, prepare, and study a molecule that would allow comparing that rate with the rate of molecular rotation in solution, which could be measured. Some radicals look different from the front and back. If I could prepare a molecule that, when heated or illuminated, would generate two such radicals front-to-front, and if they bonded quickly to one another, the product should be front-to-front. But if it took longer for a bond to form, for example because an electron had to flip first, there might be time for one of the radicals to turn around, and the product would be front-to-back.

It took most of my third year to design and prepare a suitable molecule for this study. I was on the brink of performing the crucial experiment when I came to Yale for a job interview just before Christmas in 1965. The interview was successful, and with the job offer in hand I returned in good cheer to the lab. There I was stunned to find that my radical pairs gave a completely random mixture of front-to-front, back-to-back, and front-to-back products, even when they were prepared with anti-parallel electrons so that bond formation would be as rapid as possible.

It soon became clear why bond formation was so slow regardless of electron flipping. The molecule I had designed had such bulky radicals that the electrons had difficulty getting close enough to form a bond. I could not possibly use my molecule to measure the rate of electron flipping! I needed a new question for my molecule to answer, and I needed to find it quickly enough to finish research, write a thesis, and start teaching at Yale in seven months.

My molecule was designed to show the relative rates of molecular rotation and bond formation, but for a relatively uninteresting reason bond formation in solution had proved to be much slower than rotation. Might I use my molecule to study a situation in which rotation was slowed down—in a more viscous liquid perhaps, or in a solid?

Then as now, most organic reactions were studied in liquids. A few were beginning to be studied in the gas phase, where absence of solvent allowed closer comparison with available theory. Almost no one was studying reaction in solids. Might freezing my samples before forming a pair of radicals by exposure to ultraviolet light give a different, more interesting result because of slower rotation in the solid?

Yes indeed! In frozen solutions the bonded product was mostly face-to-face. Moreover, a completely new product appeared, one that could be formed with even less motion of the radicals. A solid environment could be used to change the course of chemical reactions! The previous year chemists at Israel's Weizmann Institute of Science had published an impressive series of ten papers solving the long-standing puzzle of why different crystal packings of the same molecules gave different reaction products. Each packing pattern favored the product that required least atomic motion. Solid-state organic chemistry was in its infancy, and I had stumbled into it.

My first extraordinary stroke of luck during that last semester at Harvard was landing the Yale offer. The second was becoming involved in solid-state organic chemistry. The third was a suggestion from my roommate, a physical chemist working on "EPR" spectroscopy. The Chemistry department had just acquired an EPR spectrometer that could detect the radical fragments that can intervene between starting materials and products, but only if these radicals live long enough. Such reaction intermediates were almost always so short-lived that they had to be inferred; they were rarely or never observed directly. Others in the Bartlett laboratory had failed when trying to use EPR to observe reactive radicals in solution, because their intermediates did not survive long enough. But my solutions, when frozen at very low temperature, did give EPR signals. My roommate suggested using pure, single-crystal samples instead of frozen solutions. In a single crystal all molecules have identical environments and the same orientation, and by rotating a single crystal in the EPR spectrometer one could "see" the pairs of radicals from many different angles. From these results I measured the orientation of the two molecular fragments to within about 1° and the distance between them within a precision of 1 percent of a normal bond distance. Direct observation of reaction intermediates in this sort of detail was nearly unprecedented.

When Bartlett presented my results that summer at an important international symposium, he called on me to field questions. As the audience filed out for coffee afterward, Jerry Berson from Wisconsin, a leading chemist whom I had heard speak but had not previously met, smiled at me and said, "That was great work Professor Bartlett did."

### Yale and Single-Crystal Reactions

Yale was an ideal department for my budding career. Phil Lyons and Harry Wasserman were sympathetic mentors, and in the subfield of physical-organic chemistry Ken Wiberg and Marty Saunders were both mentors and models. Three years later, when Jerry Berson joined the Yale department, and Bartlett left Harvard, Yale became "king" in physical-organic chemistry. This stellar group attracted outstanding graduate and postdoctoral students, and a few of the more adventurous, or perhaps naive, were willing to risk trying the off-beat solid-state studies that I was launching. In the Berkeley College Fellowship I met Hal Wyckoff of MB&B, who volunteered to teach my sole graduate student and me how to do x-ray diffraction and also to let us use his equipment to determine the three-dimensional positions of all the atoms in our crystals. Now we could use x-rays to discover initial atomic positions of the reacting molecule and its surroundings before reaction, could use single-crystal EPR spectroscopy to determine the positions of the radical intermediates, and could use conventional chemical analysis to determine the nature of the products. The range of reactions we could study was severely limited, but the detail in which we could follow their course was unprecedented. We could even use primitive computer graphics to make Super-8 movies of our experimental reaction trajectories.

I easily convinced myself that studying solid-state reactions had both disciplinary and practical significance. It seemed to me that quantum mechanical computation for isolated molecules was developing a level of sophistication that would eventually reduce the importance of classical physical-organic methods for explaining gas phase chemical behavior, but there would still be a need for physical-organic experiments to deal with the influence from surrounding molecules in liquids or solids. Single-crystal studies could reveal such influence much more definitively than liquid studies, because structures in crystals are uniform, persistent, and determinable using x-rays and EPR. From a more practical point of view it is important that, while organic reactions are usually studied in liquids, the most important organic substances are not usually liquid. Enzymes and other biological systems are highly structured and to some extent rigid. Most pharmaceutical drugs and most explosives are crystalline solids. Natural and artificial materials, like wood, cotton, rubber, and plastics, are very viscous or solid. It is important to understand how the rules governing reactions in such media differ from those in fluids, even though such reactions are as often deleterious as they are synthetically useful.

One challenge was that the American academic community of solid-state organic chemists was extremely small. I knew only of two chemists at Chicago and two more at the University of Illinois. In each case one was an organic and the other a physical chemist. Stopping by Bartlett's Harvard lab in the early summer of 1970, I was introduced to Meir Lahav, a postdoctoral researcher from the Weizmann Institute group that had recently made such a splash with their ten papers. He told me that the Israeli group would be hosting an international symposium in three months' time and that I must attend. This was the first of innumerable times over almost fifty years that he has correctly told me what I should do.

This meeting, the most influential I ever attended, took place September 14–18, 1970, a period that became known as "Black September." On September 1, cholera broke out in Jerusalem. On the seventh the Popular Front for the Liberation of Palestine hijacked and blew up Swissair, Panama, TWA, and BOAC airliners. On the fifteenth King Hussein attacked the PLO, and on the eighteenth Syria attacked Hussein. But I focused on interacting with the senior leaders in my new field, like Clyde Hutchison from Chicago, who was also using EPR spectroscopy of single crystals. He said he thought of a crystal as a "molecular ring stand" allowing one to clamp molecules and orient them for observation from different directions. He was speaking my language.

At the close of the meeting Gerhard Schmidt, its chairman and the leader of the Weizmann team, explained that this would not be my last visit to Israel and asked me to postpone participation in the conference tour in order to present my work in more detail to his group. I could hardly believe that this distinguished pioneer seemed as interested in my work as I was. He died prematurely the next year, but his successors have become my closest scientific friends.

Over the next twenty-five years, a small but adventuresome group of Yale students and I extended and refined our studies of radical reactions in single crystals. At first we thought that breaking a molecule into three or four pieces with a burst of light would generate a dog's breakfast of different arrangements of the shards, but we found that usually only one or two arrangements were generated at low temperature, and that they were as precisely defined as the molecular orientation in a perfect, undamaged crystal. On gradual warming the pieces would "click" from one arrangement to another at particular temperatures. We could sometimes trace a dozen sequential structures during reaction, many of them involving different arrangements of the same molecules.

We were able to show the inadequacy of the simplistic hypothesis that solid-state reactions always take the path that requires the least atomic motion. There is not enough room in the crystal cavity surrounding a fragmented molecule to accommodate the pieces. The fragments can be squeezed by enormous local stresses that twist them or force them further apart before they can come together again to rebond in a new pattern. In his prizewinning 1,022-page Ph.D. thesis, Mark Hollingsworth reported using changes in the rate of molecular vibration to measure a reaction-generated local pressure of some twenty thousand atmospheres.

I was not surprised that my particular line of research did not attract many imitators. It was laborious and limited in the range of reactions that could be studied, and there were no obvious commercial applications. I was just grateful that funding agencies were willing to support such detailed studies of reaction mechanism and that talented students wanted to collaborate in them. More conventional individuals might have considered these studies the chemical analogue of building ships in bottles.

### Crystal Growth

By the mid-1990s we had gone about as far into the rococo details of solid-state reactions as we could in the context of graduate student research, but a related field was still in its infancy. We had often found that the most significant challenge to our studies lay neither in preparing new molecules with complex isotopic labeling, nor in the tedious days of measuring and interpreting hundreds of low-temperature spectra for each of them. Rather it lay in obtaining the single crystals of these compounds that our studies required. This is a challenge as familiar to the biophysicist who needs single crystals to determine the three-dimensional structure of biological molecules as it is to the pharmaceutical scientist who must prepare drugs in a particular crystal form. The vast majority of commercial drugs are crystalline, and obtaining the wrong crystal form can be disastrous. In 1998 Abbott Laboratories had to withdraw Ritonavir, an important AIDS drug, from the market when it began to give different, less soluble crystals. While our work on molecular synthesis and solid-state spectroscopy had been scientific, crystal growth remained an art.

In turning our research focus to understanding the mechanism of crystal growth and dissolution, we used one very old technique and one very new one. The old technique was microscopy with polarized light, which had been popular in nineteenth-century chemistry but had been supplanted by x-ray diffraction in the early twentieth century. Using old-fashioned polarized microscopy together with x-ray studies, we were able to solve the conundrum of "optically anomalous crystals" that had been forgotten after baffling the leading nineteenth-century crystallographers. We found that the anomaly was due to errant molecular incorporation during crystal growth, a phenomenon that can now be harnessed to allow the tailoring of crystals for technological applications.

The new technique for studying crystal growth and dissolution was atomic force microscopy (AFM), a modern analogue of the phonograph in which an amazingly sharp needle scans over a surface recording its height. The height sensitivity is such that AFM can show the addition or loss of a single layer of molecules as a crystal grows or dissolves under solution. Movies we made using AFM provided the first experimental record of the theoretically important phenomenon of a "critical size." A pit on a crystal surface that was one molecule deep, and had a cross-sectional area that was 0.01 percent of that of a human hair, would remain unchanged under solution, while narrower pits filled in and wider ones expanded. The crystal was growing and dissolving at the same time.

Involvement in crystal growth studies provided a bridge from directing the research of students to working as a retiree with no lab. As at the beginning of my career, my Israeli friend Meir Lahav was my guide, telling me of the incredible work of an unconventional Spanish geologist interested in the origin of life. Cristobal Viedma had reported that grinding a mixture of right- and left-handed crystals with a solvent caused all the molecules to adopt a uniform handedness, the type of homogeneity that biology requires. At first I dismissed the report out of hand as an outrageous theoretical impossibility. Three years later, when the observation was confirmed by chemists, Lahav convinced an editor of *Nature* to ask me to write a News & Views column about it. John Tully and I advocated an explanation based on crystals growing by agglomeration of preexisting tiny crystals, rather than by addition of individual molecules. This suggestion has led to stimulating collaborations with scientists in Spain, Switzerland, the Netherlands, and the United States, as we work to develop experimental support for this idea, which has both fundamental importance and commercial potential.

### Teaching and History

This account has focused on my trajectory in research, but like my mentors at Wooster and Harvard I think of myself mostly as a teacher, and teaching has certainly shaped my intellectual trajectory. Naturally I learned a lot from my graduate research students, who were becoming the real experts in their specialties, but my vision was stretched at least as much by classroom teaching of Yale undergraduates, especially the freshmen. I took special satisfaction in being part of the team that initiated Yale's Perspective on Science and Engineering program. Each year from 1991 to 2015 it introduced select freshmen to a broad range of scientific and technological disciplines through biweekly lectures by experts, alternating with small-group discussions led by students, in which faculty volunteers from various scientific disciplines participated without holding all the intellectual trump cards. It was stimulating to interact with these students and with colleagues who were willing to contribute despite the risk of exposing their ignorance to freshmen and to each other.

During my first years at Yale, I mostly taught advanced organic chemistry to graduate students and seniors. But my assignment changed in 1972, when the organic chemists decided we should offer a special course in organic chemistry for those freshmen identified as the most promising prospective majors. This, we reasoned unsurprisingly, would be a more exciting and appropriate introduction to university science than was provided by the existing freshman course in physical chemistry.

I volunteered to develop such a course and continued teaching it most semesters over the next forty years. The original goal of attracting more chemistry majors didn't quite work out. Of the thirty-five students in the first year, only four became chemistry majors. But all thirty-five students were really special. Early on I mentioned that an Israeli theoretician had recently used a powerful computer to reckon the energy states of the helium atom to a precision of nine significant figures. Evan Koslow asked, "How is that possible, when the mass of the electron is known to only six figures?" I still have not found a theorist with a convincing answer to Evan's question. Obviously this was not going to be a standard class.

I've looked at the subsequent careers of those first thirty-five freshmen: ten went into academic medicine, four into medical practice, and three into chemistry; the rest were evenly divided among other sciences, law/business, and "other." As a member of the Committee on Freedom of Expression at Yale, one student was later chosen to write the first draft of its "Woodward Report." He became a full professor of chemistry at ETH Zurich and ultimately founded an Institute for Synthetic Biology. A second student, from one of Yale's first cohorts of freshman women, became a professor of medicine and vice president for research at Harvard. A third became a chaired professor of American literature at Brandeis. A fourth became a Howard Hughes investigator in biochemistry at UCSF. A class member from a few years later became Microsoft's first program manager. After heading the team that developed Excel, he retired to become a national-prize-winning high school math/physics teacher and then a climate and land conservation expert.

Soon I began to wonder what I should be teaching these individuals. Ultimately most were not going to care about the details of organic chemistry. Not long after the course began, our son John clarified my thinking upon becoming a three-year-old. During the whole ensuing year he would incessantly ask, "How do you know?" It dawned on me that this was the question my students should be asking. I should not just tell my students what is known, but show them how it is known, and how a science works.

Over the years the course became increasingly idiosyncratic. It became focused on two key questions, "How do you know?" and "Compared to what?" I explained that there were different ways of knowing. Divine and human authority might have their place, but not in science, which, though it may be guided by intuition and chance, is governed by experimental observation and logic. So I tried to supply the experimental evidence that led to each discovery, and to discuss the line of thinking of the discoverer. I believe that "Freshman Organic Chemistry" was the last Yale course to recognize the primacy of experiment by requiring lecture students to enroll simultaneously in the related lab course.

We looked first at modern techniques. What is the most direct evidence for the existence of molecules? We can now "feel" them with the atomic force microscope; we discussed how AFM works. We can "see" atom positions in crystals with x-ray diffraction; we studied how diffraction works and how Rosalind Franklin's curious photo revealed that DNA is a double helix with major and minor grooves. What holds atoms together in molecules? We examined rigorous but qualitative ideas in chemical quantum mechanics to learn how an outrageously nonintuitive formulation of kinetic energy shapes electron density to form the bonds that x-rays reveal. What gives molecules their characteristic reactivity? We showed how quantum mechanics explains the traditional "functional groups" of organic chemistry.

This unconventional material, much of it from the last few decades, consumed about half of the first semester, but then we turned to the really interesting question: how is it possible that chemists were not surprised by the revelations of these powerful new techniques? How could they already have known what molecules looked like, half a century or more before they could see, feel, or calculate them?

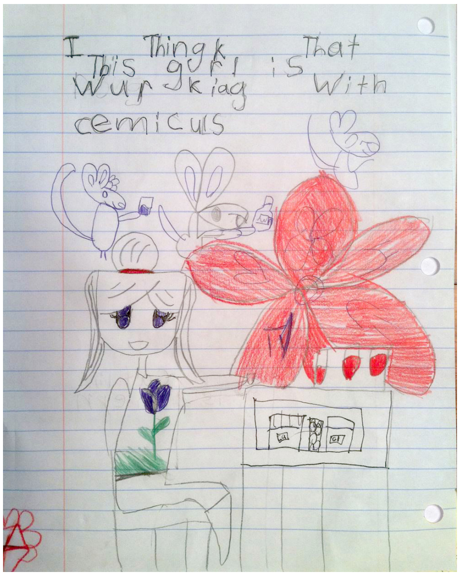
Especially since enjoying Fieser's anecdotes as a college junior, I have been intrigued by chemical history, and I have always been a hero worshipper. Over the years of teaching "Freshman Organic Chemistry" I stepped progressively further back in time to meet new personal heroes who had contributed the key insights about how molecules look and behave. Many of them were relatively unknown, modest young scientists with whom my students could identify: Moses Gomberg in Ann Arbor in 1900, J.H. van't Hoff in Utrecht in 1874, Wilhelm Körner in Palermo in 1869, Archibald Couper in Paris in 1858, Friedrich Wöhler in Berlin in 1828, Antoine Lavoisier in Paris in 1789, Carl Scheele in Uppsala in 1771. Finally I concentrated on Robert Hooke, the polymath behind the Royal Society in Restoration London whose contributions were so unjustly suppressed by Isaac Newton. We used these heroes to learn how to distinguish sense from nonsense, contrasting their work with that of pompous, narrow "authorities" like Hermann Kolbe and theosophical "occult chemists" like Annie Besant, who reported using clairvoyance to see atoms and molecules. Detailed study of the discoveries that led to our current understanding of organic chemistry, and analysis of some examples of bad "science," help students develop the most valuable scientific attribute, good taste.

### Envoi

A special reward of a career in education and science is the possibility that an intellectual trajectory starting long before your birth can extend into the future. My research group was always relatively small, and I certainly can't pretend to having launched any sort of school, but it is gratifying to see my trajectory as a ripple in the ongoing current of chemistry and to know that much of what I've accomplished probably wouldn't have happened without me. As I finish this account I am preparing to travel to the twenty-third International Congress on the Chemistry of the Organic Solid State in South Africa. The second in this biennial series was the Israeli meeting in 1970 that helped launch my research career. It is rewarding to see several of my former graduate students among many close friends on the program.

But it is equally rewarding to know that many former student collaborators creatively diverged from my specialty, and even from chemistry altogether, moving further than I did from my predecessors. Similarly, it is as satisfying to learn about the varied accomplishments of my former undergraduate students as it is to see a steady frequency of Internet "hits" on the videos and PowerPoints of the lectures from my course that were made available by Open Yale Courses. Our own daughter Anne, an alumna of the course, teaches biology at Bowdoin College and does biochemical research beyond my ken.

It is also gratifying to see the signs of scientific and educational potential in our granddaughters. In fourth grade, Caitie, with enthusiastic support from her dad, and help from a pillow pet and a phone-pole guy wire, created a video to explain to her classmates how piano dampers work. Now in eighth-grade science, she recently phoned with a question about chemical nomenclature that has challenged my colleagues as much as it did me. In second grade, artistic Annika drew a girl seated at a desk with test tubes and giant, colorful flowers, surrounded by mice bearing vials and beakers. The drawing was labeled, "I Thingk That This gurl iS Wurking With cemiculs." At age four she was given her first bike. When I said, "Annika, I really like your new bicycle," she replied impishly, "How do you know?"



*Cemicul Gurl,* by Annika McBride, age 8