Robert H. Grubbs

1942-2021

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

ROBERT HOWARD **GRUBBS**

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Elected to the NAS, 1989

By Timothy M. Swager and Dennis A. Dougherty

Robert H. Grubbs made pioneering advances in organometallic chemistry and propelled polymer chemistry into a new era in academic chemistry departments. The dominant focus of his career was on the catalysis of olefin metathesis, and his efforts transformed this reaction from an organometallic curiosity into a mainstay reaction used in most organic synthesis laboratories in the world and in large-scale industrial processes. He introduced the first and only olefin metathesis catalysts that work under ambient atmosphere and even in water. These catalysts are known as Grubbs Catalysts, and the different generations of these catalysts provide for different levels of activity and selectivity in the metathesis reaction. These catalysts are widely used in organic synthesis, chemical production, and polymer synthesis. Grubbs' innovations in polymers spanned the design of polymers with high strength and durability, photonic and electronic materials, and biomaterials for medicine.

Robert Howard (Bob) Grubbs was born February 27, 1942 in his family home, which was built by his father in a place called Howards Grove described as half way between Calvert City and Possum Trot in rural Kentucky. His humble country roots were readily apparent, and Bob was famously known as a most unassuming, friendly person. In his own biography, Bob described his early life as indirectly preparing him to be a synthetic chemist. He liked to build and fix things around the farm and work with machinery. He transferred this interest to making molecules and to understanding how reactions work. It was in his studies as an undergraduate at the University of Florida in the laboratory of Professor Merle Battiste that Bob realized his passion for studying reaction chemistry and in particular deducing reaction mechanisms.

Bob was a tall man, standing 6 foot 6 inches and originally thought he might try some basketball at Florida, but fortunately he found he was better as a chemist. He did continue to play on intramural teams well into his 50s as a full professor. At the

University of Florida, Bob received a BS in Chemistry in 1963 and a MS Degree in 1965. At that time Battiste facilitated his journey to the laboratory of Professor Ronald Breslow at Columbia University to pursue his PhD. Breslow was studying antiaromaticity in organic compounds, and Bob was interested in understanding how metal complexation could stabilize these highly reactive antiaromatic organic compounds. This resulted in his studying the chemistry of iron stabilized cyclobutadiene compounds, and he received his PhD from Columbia University in 1968. Bob's interest in organometallic chemistry was deep, and he made many contributions this field and its applications throughout his entire career.

Upon arriving in New York City, Bob's country background was apparent, and he was known by his birth name of Bobby, or Bobby Howard, rather than Robert. Breslow suggested to Bob that he should change his name to Robert, which would be more acceptable in academic circles. As a result, at the beginning of his graduate experience he legally changed his name from Bobby Howard Grubbs to Robert Howard Grubbs. However, those who knew him in his younger years continue to call him Bobby or Bobby Howard, including Helen O'Kane of Brooklyn, whom he met during his postdoc in New York and married in 1967.

Bob's research on iron cyclobutadiene compounds in the Breslow laboratory likely influenced his decision to do postdoctoral studies at Stanford University with Professor James Collman, who was very active at that time in organometallic iron chemistry. After completing a short NIH Fellowship (1968-1969) in Collman's laboratory, Bob joined the faculty at Michigan State University. During his postdoctoral research he had become intrigued by a mysterious metal catalyzed reaction that became known as olefin metathesis. This reaction effectively cuts carbon-carbon double bonds ($R^1R^2C{=}CR^3R^4$) in half and reassembles them into mixtures of new alkene products ($R^1R^2C{=}CR^3R^4$, $R^1R^2C{=}CR^1R^2$, $R^3R^4C{=}CR^3R^4$). This problem first captivated Bob's interest as an unsolved mechanistic problem in organometallic chemistry, although perfecting this process and its applications became a major focus of his entire career.

In the beginning, the proposed mechanism for olefin metathesis involved a vaguely formulated intermediate with four CRR' groups from the alkenes arranged around a metal with multiple dashed lines, indicating single and double bonds being broken or made. The field of organometallic chemistry was still in its infancy, but recently discovered new types of compounds were expanding mechanistic hypotheses. Metal carbenes, in which a transition metal was described as having a double bond to carbon (M=CRR') had been discovered a few years earlier by E. O. Fischer (Nobel Prize, 1973), and an expanding class of (L)xM=CRR' structures had been isolated and were undergoing reactivity studies by noteworthy chemists, including Charles Casey and Richard Schrock. If metal carbenes engaged in 2+2 cycloaddition reactions with alkenes, they would generate metallocyclobutanes, which are four membered rings in which one of the ring framework atoms is a metal. Disassembly by a 2+2 cleavage can give a new M=CRR' and scrambled alkenes (i.e. olefin metathesis). This mechanism was proposed first by Yves Chauvin, although at the time the full scope of M=CRR' reactivity was not understood. The argument against a carbene catalyst was that the resultant metallocyclobutane intermediate would more likely undergo reductive elimination to generate a cyclopropane and a reduced metal center. To examine this mechanistic quagmire, Bob designed experiments using deuterium-labeled alkenes with an in situ generated tungsten catalyst. His seminal studies established that M=CRR' groups and metallocycles were the likely intermediates in the olefin metathesis reaction, as shown below.

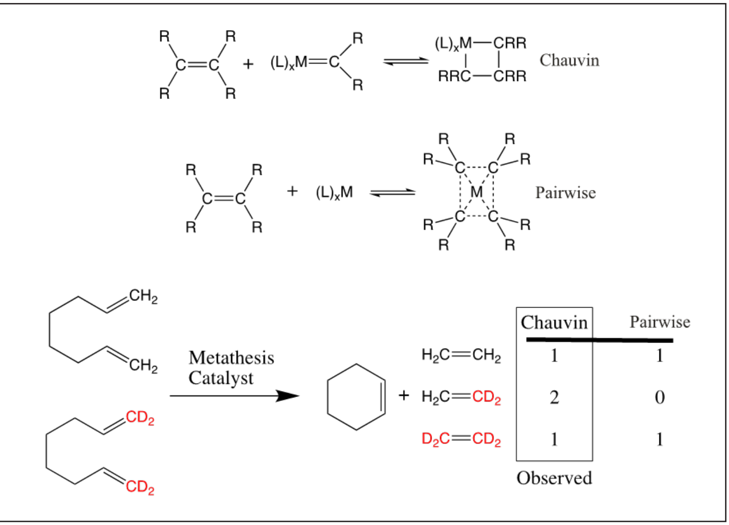

Figure 1: Two of the early mechanistic proposals for olefin metathesis. Using selective labeling experiments as shown at the bottom, Grubbs confirmed the Chauvin mechanism.

In 1978, Bob moved to the California Institute of Technology, and the combination of his program and that of John Bercaw established Caltech to be a hot-bed of organometallic chemistry. At that time there were still no isolated M=CRR' compounds that were capable of catalyzing olefin metathesis. However, a titanium metallocene complex had been isolated by Fred Tebbe at DuPont, which when activated by a pyridyl group had metathesis activity. The Tebbe reagent released a reactive $Cp_2Ti{=}CH_2$ group when a pyridyl group coordinated to the $AlCl(CH_3)_2$ group. Although these compounds were highly air and thermally sensitive, the Grubbs group was able to isolate and characterize the metallocycle formed with isobutylene. The Tebbe Reagent, unlike the earlier Fisher carbenes, was nucleophilic at the carbon and was able to convert carbonyls into alkenes (C=O-->C=CH$_2$) in high yields. Grubbs made use of this reaction in a number of contexts and showed its high versatility relative to the classical approach to this transformation with phosphorous ylids, which is known as the Wittig reaction.

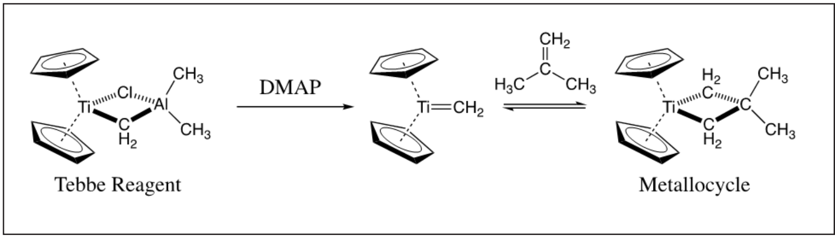

Figure 2: Grubbs conducted reactions with the titanium carbne generated from the Tebbe reagent to produce an metallocycle that could be isolated, further confirming the metallocycle-carbene equilibrium as being central to the olefin metathesis mechanism.

Bob had an enduring interest in polymers, and while at Michigan State he conducted studies of polymer-supported organometallic catalysts, preparing polymer particles containing metallocenes and metal phosphine catalysts. He also continued to work on metallocycles, and in a classic study Grubbs proved that his metallocycles could initiate living polymerizations of the strained cyclic alkene, norbornene. The term 'living' implies that the terminal reactive species that is forming the polymer chain is persistent, and after a first monomer is consumed a second monomer can be added to produce a block polymer. When living polymerizations display proper kinetics, the polymer blocks are uniform in length, and block polymers assemble into organized microstructures that depend on their compositions. In the early 1980s, the best living polymerizations were being performed by organolithium reactions, and so the Grubbs metallocycle route opened up new avenues of research. Realizing the opportunities provided by living polymerizations, Bob launched a polymer program, beginning with pioneering contributions to the synthesis of conducting polymers that made use of Ring-opening Olefin Metathesis Polymerization (ROMP). In the 1980s, few top-tier academic chemistry departments had polymer chemistry as a core research area, and the majority of polymer research in the US was being performed at select institutions that focused on all aspects of polymers (chemistry, physics, and engineering). Grubbs' many successes throughout the years and those of his many academic offspring would lead to a transformation in polymer chemistry, and presently nearly every major chemistry department has research efforts in polymers and soft materials.

Figure 3: Bob Grubbs in Crellin Laboratories after moving to Caltech.

In the late 1980s, a series of tungsten carbenes had been produced by the groups of Jean-Marie Basset, John Osborn, and most notably by Richard Schrock. The Schrock catalyst had fewer ligands, didn't require any dissociative reactions prior to reaction with alkenes, and displayed exceptional activity. However, all of these catalysts and the earlier titanium-based systems had the limitation that they had very Lewis acidic character and low functional group tolerance. The metathesis literature had seen reports of ill-defined, catalyst precursor mixtures containing late transition metals (e.g. Ir, Rh, Re, and Ru) that could display metathesis activity. These metals could be stable to polar functionality because of their "softer" electronic structure. As a result, as early as 1980, Bob had students attempting to find isolable catalysts from late metals that had metathesis activity. The first clue came from a project involving the ring opening polymerization of a norbornene ring analog, wherein the bridging methylene is replaced with an oxygen to create polymers that would assemble into ion channels, with the bridging oxygens forming an organized tetrahydrofuran-like tunnel in the polymer films. It was found that $RuCl_3$ had high ROMP activity in protonic solvents, including ethanol and water. The activation of the $RuCl_3$ was enhanced by the monomer, and after a number of detailed mechanistic studies deducing aspects of the system including the oxidation state of the Ru, in 1995, Grubbs introduced a group of compounds that gave birth to the Generation 1 Grubbs catalyst.[6] This first catalyst was produced by reacting Ru(II) chloride with 3,3-diphenylcyclopropene, but by using $N{=}N_2CHPh$ as the reactive group that produces a Ru=CHPh, the highly stable Grubbs catalysts quickly became widely used in chemistry labs throughout the world. The Gen 1 Grubbs catalyst was shown to produce living ROMP and thus block copolymers. The catalyst could also be used for ring-closing olefin metathesis reactions that could be used on highly functionalized systems as a late stage macrocyclization strategy. Grubbs also went on to show how dynamic equilibria in the ring closing olefin metathesis reaction could give rise to complex supramolecular complexes. Over the next 25 years, Grubbs would go on to create many active Ru catalysts, catalysts with different selectivity, and even water-soluble catalysts that could be used in aqueous solutions. The Gen 1-3 catalysts are widely used, as well as related more stable catalysts developed by the group of Amir Hoveyda. More than a dozen different types of Grubbs catalysts are commercially available and some of the better-known variants are shown here.

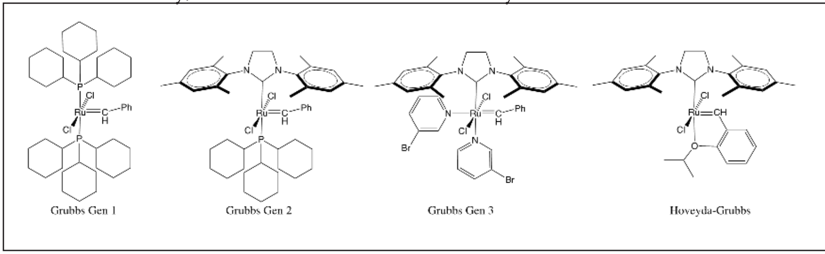

Figure 4: Select examples of Grubbs catalysts.

Bob performed a number of pioneering studies that demonstrated the power of ROMP with his catalysts in materials science. Previous workers had investigated the polymerization of dicyclopentadiene (DCPD), a very inexpensive feedstock, in an attempt to make durable composites, but with limited success. The challenge is to get complete polymerization. DCPD has one strained alkene in a norbornene-like ring system and another that is in an unstrained cyclopentene. The Grubbs catalyst selectively reacts with the more strained alkene, allowing the conversion of DCPD, a liquid, to poly(DCPD) objects with limited crosslinking that could stop bullets and endure large impacts without fracture. Just for fun, the group made a golf club, which had this polymer replacing the head. Bob loaned his poly(DCPD) club out to some golfers, who found it to perform very well. Recognizing the potential of this invention, Bob went on to found the company Materia Inc. Bob loved to tell the story about a meeting with angel investors, wherein a Hall of Fame retired Major League Baseball player was in the audience. The story went like this: Bob was showing his golf club with the plastic head and the MLB Star skeptically questions; “you claim that this club won’t break?” and Bob said “yes.” The baseball player examined the club and then left the room with club in hand. Others followed, and once outdoors the MLB Star repeatedly beat it on the concrete. He then examined the club again and stated “I’m in.” Bob indicated it was a very good day for courting angel investors. Materia went on to manufacture different Grubbs catalysts and demonstrate applications of poly(DCPD) including tractor bodies, wind turbines, and large pipes. The pipes have extraordinary chemical and mechanical stability and can be used to transport oil and gas in demanding environments, including the high pressures encountered in deep-sea environments. The remarkable aspect of the Grubbs poly(DCPD) materials and production process is that large monolithic objects are made in a single step and Materia was acquired by Exxon-Mobil in December of 2021.

There are many more chapters to the Bob Grubbs Olefin Metathesis story. He devised ways to synthesize bulk quantities of cyclic polymers,[7] paving the way for potential industrial applications of materials that had previously only been academic curiosities. His catalysts have enabled the synthesis of polymers containing peptides, carbohydrates, and nucleic acids for biological applications. His research group developed bottle brush- and dendron-monomers that produced block polymers, wherein the chains have extended structures. These materials were found to be exceptional at organizing into lamellar microstructures, in which the differences in refractive index produce a strong Bragg reflection of light. These photonic materials can be tuned throughout the visible and into the near-IR. Grubbs developed ring-closing metathesis reactions that could create macrocycles and were dependable enough to use in late state syntheses. The utility of his methods in drug synthesis is now widely recognized by the pharmaceutical industry.

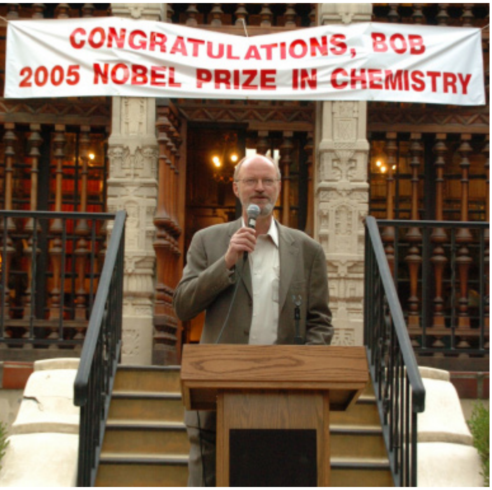

Figure 5: Bob Grubbs being celebrated at Caltech for winning the Nobel Prize.

Although Bob Grubbs was best known for his research in olefin metathesis, and it is for this work that he received the 2005 Nobel Prize in Chemistry, there were many other dimensions to his research program and entrepreneurial activities. To name just a few: he devised new conditions to produce a greatly improved anti-Markovnikov Wacker reaction;[8] and oxidation-reduction coupled catalytic cycles for the transformation of terminal alkenes in primary alcohols.[9] Grubbs remained a vibrant innovative scientist to the end, and he took on new challenges, such as designer polymers to coat electrodes to direct CO_2 reduction catalysis to give 77% yields of C_2 and higher organic products.[10]

He had a long-term interest in creating synthetic polymers to be used in cataract treatments. These methods are now FDA approved and are produced by another Grubbs startup, RxSight Inc. A noteworthy fact is that his wife Helen has received his polymer inventions as part of her treatment. These activities led to a strong connection with clinical scientists at the University of California, San Francisco Medical School. Among other inventions relevant to medicine, he formulated new chemical treatments for kidney stone reduction and removal.

As a person, Bob Grubbs was down to earth and famously interacted with young chemists as if they were peers at many scientific meetings. Generations of undergraduate and graduate students are sure to give an account of their interactions with the Nobel Laureate Bob Grubbs, as a person that never portrayed himself as special or above anyone else. His kind, gentle approach with students almost certainly contributed to the development of his coworkers, a number of which are current or certain to be future NAS members. In the US alone, nearly 100 professors studied with Grubbs, creating one of the largest academic families in the history of chemistry.[11]

Those who knew Bob Grubbs well also knew his devotion to his family. His marriage of more 54 years to Helen was tightly woven into his academic life. Helen is known to many chemists, and she attended many ACS meetings and even Polymer Gordon Conferences. Their son Professor Robert Barney Grubbs and daughter-in-law Professor Katherine Aubrecht would attend these meetings too, with Helen taking care of their daughter – Bob and Helen's first grandchild – while they were attending scientific sessions. Both Barney and Kate shared Bob's love of polymer chemistry and are on the Chemistry Faculty of the State University of New York, Stony Brook. Bob was passionate about being engaged in his children's sports activities and would travel to see his daughter Dr. Kathleen (Katy) Grubbs play basketball while in College at Yale or during her brief professional basketball career in Europe. Katy received a PhD from the University of Hawaii and is a Clinical Psychologist for the Veterans Administration in San Diego. Bob also actively watched Brendan Grubbs play college water polo, where he was an All American at the University of Southern California. Brendan went on to pursue MS and MD degrees before becoming a Professor of Medicine at the University of Southern California. The Grubbs Gang (as Bob called his family) all took an interest in, and became close personal friends, with multiple generations of students from Bob's group. The Grubbs Gang have famously made Bob's coworkers feel that they were a part of a greater extended Grubbs family.

Bob Grubbs received many domestic and international awards throughout his 52 years as a professor. These awards recognize his influence as a world leader in organic, polymer, and organometallic chemistry. Robert H. Grubbs was elected to the National Academy of Sciences in 1989 and died on December 19, 2021 from a heart attack brought on by complications from cancer treatments. He left a legacy of scientific excellence and humanity that all should aspire to emulate.

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