American Chemical Society AMA: Hi, my name is Paul Helquist, Professor and Associate Chair of Chemistry & Biochemistry, at the University of Notre Dame. Ask me anything about organic synthesis and my career.

AmerChemSocietyAMA [1] and r/Science AMAs[1]

[1]Affiliation not available

April 17, 2023

Abstract

Hi, my name is Paul Helquist, Professor and Associate Chair of Chemistry and Biochemistry, at the University of Notre Dame. I was a native of Northern Minnesota where I grew up literally in the "sticks" on a small lake surrounded by woods somewhere north of Duluth on the way to the Canadian border. I attended school in a small town of 2,000 people 15 miles away from our home and was the stereotypical example of the first member of our extended family to attend college. I enrolled at the University of Minnesota, Duluth, in 1965 on a free-ride scholarship, which paid for my full tuition, which was all of $400 per year in those days. I had the common problem of deciding upon a major and a career. I kept wavering back and forth among physics, astronomy, medicine, and dentistry but not yet chemistry. I initially opted for physics, but in the midst of taking some chemistry courses as required for physics majors, I was working on lab course experiments one day when a brand new, gung-ho assistant professor, Bob Carlson, came into the lab and said "Follow me." I was a little taken aback, but he took me, greatly bewildered, to his very small two-person research lab and said "This is where you're going to work" as a substitute for taking that lab course. That was a very fateful event. It was a synthetic organic chemistry lab. I quickly fell in love with the research, changed my major to chemistry, and was very fortunate to be able to publish two journal articles with Bob Carlson. My odyssey in synthetic organic chemistry continued at Cornell where I earned my M.S. and Ph.D. degrees in a little over three years under the direction of another young, super enthusiastic assistant professor, Martin Semmelhack, and at Harvard where I did postdoctoral research for a year and a half with Nobel Laureate E. J. Corey. I was then set to begin my own career at age 27, but I had tremendous difficulty making a decision about which of the positions to accept that had been offered to me at a pharmaceutical company, chemical companies, or universities. Well here I am now, after choosing the academic route and having been a faculty member for 42 years. In 1974, I began as an assistant professor at SUNY Stony, and in 1984, I was recruited to Notre Dame when it was entering a period of tremendous investment and growth in graduate and research programs. This career path has led to living and working in several places, including Minnesota, New York, Massachusetts, Indiana, and even in Sweden and Denmark, where I have held a number of visiting positions. I teach undergraduate and graduate courses in organic chemistry and run a research group, which has generated over 180 publications and patents in the following areas: development of new synthetic methods; design and development of transition metal reagents and catalysts for selective synthetic reactions; total synthesis of natural products synthesis; and applications to new pharmaceuticals, including antibacterial and antitumor agents and treatments for rare inherited diseases as part of an international network of collaborators in the U.S.A., Europe, and Asia. A therapeutic agent developed in my lab is currently being used in an FDA-approved human clinical trial. I have also served in many university administrative and service positions, as Chair of the Chemistry Board of Examiners for the Graduate Records Examination at the Educational Testing Service, as the Director of the National Science Foundation Workshop for College Teachers of Organic Chemistry, as a regional and national leader in the Siemens Math, Science, and Technology Competition, as a consultant to the pharmaceutical industry, and head of an Indiana state-wide program for clinical translational research at Indiana University, Purdue, and Notre Dame. Since 1981, I have offered special courses on

advanced synthetic organic chemistry on over 140 occasions at sites throughout the U.S.A., Canada, and Europe under the auspices of the American Chemical Society and several other sponsors. My present ACS course, "Organic Synthesis: Methods and Strategies for the 21st Century Chemist," emphasizes the latest developments in this field and is next scheduled for this coming November 7-8 in San Francisco followed by several offerings in 2017. I am very enthusiastic about answering as many questions as time permits about any of the aspects of the career area in which I have spent the last half century. I will be back at 11:00 a.m. EDT to answer your questions! I am now on line until noon EDT. I will be off line until later in the afternoon after I finish heading a faculty meeting and a few other duties. I am back again (2:00 pm EDT). I will mix the rest of the afternoon with meeting in my office with my research students and with responding to your Reddit questions. OK, I have run out to time for today at 4:45 pm EDT. I greatly appreciate the huge number of questions and responses, including ones that were in direct contrast with mine. That is what makes for a good chat room.

the WINNOWER

REDDIT

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AMERCHEMSOCIETYAMA R/SCIENCE

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You had the fortune of working during the real growth period of organic chemistry, but things seem to have flattened out now. We can make almost anything we want with existing methodology, and most academic total synthesis targets aren't economically viable to produce at scale.

What do you think the future of organic chemistry is in our world of chemistry as a mature science?

nate

Yes, synthetic organic chemistry has become a mature field, but at the same time, tremendous improvements in such aspects as enantioselectivity, catalytic efficiency, and environmental friendliness continue to be made. Having said that, many organic chemists have reached a fork in the road in terms of how to best apply synthesis. Many have chosen the biological chemistry route, and many have chosen the materials science route, both of which require efficient synthetic methods. Applications in these and other technical fields will continue to be major needs into the future, and plenty of people need to be trained to implement these applications. The resulting development of ever better therapeutic agents, biochemical tools, and materials will have long-lasting effects on our world.

In a synthetic sense, what do you consider to be the most challenging structure you've worked on and what made it so? How did you solve the problem in the end?

Yoyoguy902

Our most challenging target molecule, and which ended in a successful synthesis, was iejimalide B, a marine natural product containing a very richly functionalized macrolide core and having potent activity as a VATPase inhibitor. We needed to develop two different end-game strategies, both of which were published, to accomplish an efficient synthesis. The target compound and its analogues have potential use in cancer treatment upon development of more selective forms and/or tissue specific drug delivery methods to avoid toxic side effects. These are typical ongoing challenges for many small molecule drugs.

-How do you explain such a "successful" career in synthesis, was it just the right place at the right time leading to more lab synthesis or did you put in extra work? The right connections with the right lab. In short is there a secret to your success?

-If you've moved around so much how's your family life?

-Most scientist's careers only list the successes they have accomplished. Have you been part of notable synthetic failure's? Months or years on projects that ultimately lead to no data or data that leads to a dead end, a problem unsolved? I am sure there is plenty of this idea doesn't work and move onto another, but more than that.

-How has innovation usually occurred in your lab? Is it the right person with the right background? A lot of research? Luck, happenstance? A spur of the moment idea? Or is it always a systematic way of solving a specific problem with an informed opinion, the scientific process?

chemistryquestionacc

Essentially all scientists have experienced some combination of failure and success in their research. One of my earliest professors liked to say that experiments were successful only 10% of the time. The Nobel Laureate H.C. Brown used to calm down disappointed students who obtained only 10 or 20% yields on newly attempted reactions by saying that such a yield was only a few kilocalories away from a 90% yields. Sometimes the best-planned projects can end in failure because of unforeseen roadblocks. It is important, though, to keep in mind the old adage about “making lemonade out of lemons”. If one is able to understand the underlying basis of a failure, it can sometimes be turned around, i.e. don’t just stop dead in the tracks of a failure but try to learn from it. Another key point is always to be on the lookout for unexpected results. I have seen cases of students who became disappointed that a given reaction did not give the targeted product, and sometimes they just wanted to pour the product into a waste container. I always advise them to do the appropriate detective work to find out what happened instead of the originally desired result. In several cases, this further fine combing of the data has led to the discovery of new reactions that we simply were not looking for in the first place and have gone on to develop them into very useful methods. The key is to remain observant and vigilant, and to look for the unexpected. A recent example of this kind of discovery is the subject of our next paper to be published.

A key contributor to success is having the right mentors at the right time. I was fortunate in this respect going right back to my school years when two teachers encouraged me to go to college when it was a totally foreign concept in my family. The great mentorship continued in college and beyond with my three research mentors who have maintained good contacts with me throughout my career. Yes, hard work also pays off. One of them would say that putting in 10% extra effort was like compounded interest: “a 10% interest rate has a doubling time of 7 years.” I have also been blessed with a great family, which has been with me the whole way. Living in different places, including different countries, is something that my children in particular have cherished.

As far as your career is concerned at Notre Dame, do you feel any pressure from the university to keep your research within the bounds of the Catholic church and their doctrines?

I come from a mormon community (consider myself exmormon), and I often wonder this about the scientific research at BYU.

tonusbonus

The Catholic affiliation of Notre Dame has not been an issue whatsoever in my research or research program. The atmosphere here has been very open with faculty, students, and academic visitors coming from a diverse range of backgrounds.

As a student at Notre Dame who was just in his organic chemistry lab doing a Diels-Alder reaction, my jaw pretty much hit the floor when I saw this on the front page. As a current physics in medicine major, my question would be, what about chemistry was more appealing and interesting to you than physics?

redhotrunner

Both physics and chemistry continue to fascinate me. I have frequent interactions with several faculty members in physics, and I could imagine myself having been very happy pursuing either field. Within physics, my favorite subspecialty is Astrophysics, and I enjoying speaking with colleagues in the field

about their work. I even sneak into some of the seminars, which is something I also did way back in my graduate student and postdoctoral days. When it came time to make a choice of fields, I knew that I liked many types of lab work, but perhaps it was a combination of the enthusiasm that Bob Carlson brought to my first research work and the clear relationship to developing products such as therapeutic agents that finally swayed me to one side of the fence. On the other hand, the possibilities of using advanced imaging techniques to discover the nearest habitable planet to our sun…….Maybe I still have not decided! At the same time, I fully realize that everybody has individual interests that are not uniformly shared with others. It is great that we are free to choose.

I am an analyst in a research lab in the food industry and recently we have been hosting year long internships for the local university. Being an analytical lab, we typically will hire chemistry students. On top of prep work, analysis and occasional instrument maintenance, I like to give each student the opportunity to run their own research project.

While the role of advisor is extremely rewarding, I have had difficulty at times keeping these students on task. While some may get bogged down in the literature and project planning to the point of never actually getting started on data collection and analysis, others will go forward with a scatter shot of samples to run on and instrument without remembering to write down what the heck they were trying to prove. I've also had a student agonize over a data set for weeks before asking for help in making sense of it all.

I've tried my best to nip this behavior in the bud when I start to see the signs, but I am myself only a few years out of my masters. Could you please provide any insight into how to maintain a positive working environment while encouraging decipline and good research practices? A lot of these issues would be fixed if I learned how to be a better leader. Any resources you might be able to point me towards would also be helpful!

skipper590

I make myself available as much as possible every afternoon to meet with my research co-workers. I need to reserve my mornings for teaching, teaching preparation, and other functions. I do not insist that they see me every day, and I do not hover over them in the lab every day, but I have an open door policy whereby they can drop in to tell me the latest. If I have not seen one of them for a few days, then I will pay that co-worker a friendly visit to ask how things are going. When I meet with my co-workers, I ask to see their original data, their notebooks, a clear written outline of experiments, and appropriate literature precedents in support of their plans. They are required to write a biannual research report in the format of an ACS journal article, complete with experimental and supporting information, just as required for a journal submission. I sit down with them in front of a large-screen monitor in my office, and we go through their reports together in real time and make edits as needed. I use the same approach in writing manuscripts for publication. The co-worker supplies a first draft, which we then polish in real time together until it is ready to submit. I have also adopted approaches to assure that my co-workers keep up to date in the scientific literature related to their work. Using these approaches, my co-workers learn first-hand what is expected of them, and they leave here well prepared to carry on such functions themselves in their own careers.

Thank you for the AMA, Prof. Helquist.

I am a pharmacist with a master's in synthetic organic chemistry, decided on a career change and currently studying computer engineering.

What is some software athat synthesticians need, but don't have an adequate solution for?

Krumpetify

For 50 years, chemists and computer scientists have been working to develop effective computational protocols for design of syntheses. They would be useful not only research but also in teaching. There are in fact many computational tools available for these purposes now, and I am a user of some of them, but improvements in performance and accessibility at reasonable cost can still be targeted in further efforts. The potential user base is huge if really powerful tools could be provided not only to major research organizations but also to the tens or hundreds of thousands of students who study only undergraduate organic chemistry.

Over the years what is the best chemistry joke you have ever heard?

PowerShark5000

I still enjoy the ones based upon the names of the elements, such as “What do you do with an old chemist? – you barium. Or which elements make for really bad jokes? – Co, Rn, and Y. Or how does an organic chemistry prefer to commute to work? – on a bicyclo. Or if Al Kane is too saturated to meet with me today, can I see Al Keene instead? – no, he is undergoing hydration therapy. Or why did the dentist drop two teeth into a container of water? – to make a two molar solution. Or all of those benzene ring jokes about orthodox, paradox, Ferris wheel, and Mercedes Benzene. Or what is H2O4? – silly, it is for drinking, washing, bathing, swimming, etc. Or what has three bases but no acids? – baseball. Or all of the jokes about people having tough times in various situations because it is amino world.

Hey Dr. Helquist! I'm glad you're doing this- it's always nice to see someone on the other side of the hurdle! As a polymer chemist, I've done enough organic to feel grateful that I don't have to do more!

Considering the state of funding and the uncertain long-term prospects for new academics (scraping up funds, increased adjunctand non-tenure PhDs, increasing undergrad load), do you think that new PhDs should commit themselves to doing a postdoc and try to establish an academic career?

As someone who's going to graduate in a couple of years, I think more of applying to industry more than ever. I'm reasonably sure I'd hate it, but the security and cash it offers is pretty damned attractive after six years of long hours without vacations.

I hate the idea of doing a postdoc and getting a position, only to sweat for years and end up without tenure. Does it seem that funding is getting better or staying the same? How is your retention of new faculty?

Without a "love of science" argument, is the life of an academic one you'd still aspire to as a 27 year old, when your other option can have a higher salary out of the gate than after 2-4 years of postdoc and extra years of digging for tenure?

trentlott

There is an abundance of academic positions available. With over 3,000 colleges and universities in the U.S., and with a wide range of heavily research-oriented and heavily teaching-oriented institutions and everything in between, there are many types of positions from which to choose. In nearly all cases in which research is a component of an academic position, postdoctoral research experience is essentially required. It is not necessary for many of the more teaching-oriented positions, but postdoctoral experience, including teaching postdoctoral positions, can be beneficial.

Research funding is a major challenge for all of us in academics. It has become tighter, but whether the

situation will change is tied up in many issues at the national level.

The tenure years can be very trying, but success in achieving tenure leads to good security. In industry, it can be the other way around: security in the first few years but increased volatility of positions as the years go by.

Graduate and postdoctoral training in organic chemistry, especially organic synthesis, has a reputation for being extremely challenging, not just because of the nature of the work, but also due to the prevailing attitudes of professors in the field. Expectations for working very long hours, and weekends, are nearly universal in the field, as typified by the very famous case of the Carreira letter. This work culture, enabled by the absolute control possessed by advisors over their students' futures in the field, are characterized by many as deeply exploitative.

Do you agree that the work culture and student/advisor power dynamic in academic organic chemistry labs is problematic, and if so, what reforms would you propose? What are your expectations for researchers in your lab, in terms of working hours?

theytsejam

In any field of endeavor, it takes only a few limited examples to set the wrong tone for the entire discipline. Just remember that in all facets of life there are extremes on either side of an issue and the sweet spot is usually somewhere in between. Most scientists whom are know, including some of the most successful ones, lie closer to this middle ground.

Thank you for posting this AMA!

I am currently finishing up my undergrad in chemistry, I have been doing undergrad research for about a year now. I am looking to start grad school next year with the hopes of continuing organic synthesis work.

My questions are simply, what sort of things should a student in my position know about enter grad school (and the research community as a whole) that might not be readily available? What do you wish you knew? And what do you look for in a potential grad student?

babysalesman

A key factor in choosing a graduate school is to have a fairly firm idea of the field of research in which you are most interested and to narrow down your list to those programs that have a critical mass of faculty members in that field and closely associated fields. Try to avoid a program that has only one or maybe two faculty members in your field(s) of interest; there is no guarantee that you will get into their labs or that you will have the right feel for their labs' dynamics. Not even the finest programs in the country can be equally strong in all fields of research no matter what their overall rankings may be. There are plenty of examples of universities that are traditionally ranked at the highest levels but which have very little if any activity in a given subspecialty. Therefore, it is critical to do a lot of homework to find out which programs are strong in the field(s) of interest to you. Looking at websites, brochures, and publications is one approach, and soliciting input from your professors is another, but be aware that sometimes opinions can be far more subjective than objective and can be based upon reputations from several years ago. Reputations are slow to build and slow to die.

As someone studying chemistry at university, one of the golden questions that everyone seems to want to the answer to, me included, is what set of skills did you develop the most and gain from by

being a chemist? And as a side-question, what is the one thing you would look for in a lab member if you could only pick someone based on one attribute?

ForeignSwag

Interpretation of data to solve problems, which is a skill required in many fields. Perhaps that is a reason that organic chemists are often hired to work in many other areas.

Motivation can be more of a key to success than basic intellectual skills. Some of my most successful co-workers have been highly motivated to succeed without necessarily having the best academic records.

I have just started taking a chemistry class because I'm hoping to go to med school someday. I know I will have to take organic chemistry in the upcoming years. Any advice you might have for getting the most out of these classes?

HeraclitusOnFire

To be successful in organic chemistry courses requires getting out of the mindset that it requires memorizing everything in the lectures and the textbook. Typical exam questions are not based upon simply writing down facts from rote memory but are instead based upon working problems that you have probably never seen before. The key is to learn the fundamental concepts fully, and to learn to use them to solve problems The more problems that you take the time to do, the better. If you get a problem wrong initially and then look at the answer and say,"Oh yes, that's correct", you can just fool yourself into thinking that you have mastered the material. You need to mark the question and go back to it at a later time to make sure that you can get it right with a fresh mind.

What was it like working with a Nobel Laureate? As a current PhD student, what qualities do you think make a good scientist? Were there any pitfalls in your career that you would like to warn others about?

KnowLoitering

While I was doing my postdoctoral research, Professor Corey had not yet received the Nobel Prize, but we all knew it was just a matter of time due to his numerous accomplishments and stature in the field. I had admired his work while I was still an undergraduate and had the dream of working with him. It was one of those dreams that eventually turned into reality. While in his lab, I was amazed at how well he kept on top of the many projects being pursued by 45 co-workers. He would make the rounds of the several labs with a yellow legal pad to sketch out ideas with each co-worker, but any of us could also go to see him in his office at almost anytime to discuss problems and plans. It was also a privilege to be in the same group with other co-workers who have gone on to great success in their own careers, including some at the very top of their fields and whose names you would readily recognize.

Hey Dr. Helquest, Having so much experience in the industry while also being located in Indiana, how is the job opportunity in the area with a Master's Degree in Chemistry? (Non-Thesis) In addition, in your professional opinion is it more versatile to have a Master's or PhD in our current economy? I'm currently debating what may or may not be a relatively large life choice. Thanks.

Hodor_The_Wise

Master's degree holders are in demand, especially at chemical and pharmaceutical companies. Employers value them highly, especially when they have gained advanced lab experience beyond the standard undergraduate curriculum. They can be the "real hands" that get the greatest amount of work

done in a lab. They typically work initially, at least, under the direction of Ph.D.s and other more experienced chemists, but they can move up the ladder with time. Ph.D.s on the other hand usually design and direct their own research and the research of others from the start. They also generally have greater advancement opportunities up the scientific ladder but not necessarily up the management ladder.

Hi there Dr. Helquist, I'm about 4 weeks off finishing my undergraduate degree in chemistry. I'm seriously considering building my career around organic synthetic chemistry because that is what I am passionate about. However, I am concerned about the level of medicinal application for organic synthesis. What are your thoughts on this?

shookfoot

Medical applications are only of several directions in which organic chemistry can be directed. Yes, essentially all small molecule drugs require at least some degree of synthesis as part of the overall development process, but keep in mind the many other areas in which synthesis plays key roles, including commodity chemicals, fine chemicals, catalysts (either metals that require elaborate organic ligands or organocatalysts), biochemical tools/probes, polymers, materials in general.

Thank you so much for doing this! I have two questions.

What was the last advancement in your field that truly startled you?

How will organic chemists change everyday life as we know it in the next 20 years?

2canSampson

The most exciting recent advances for me are the tremendous selectivities that have been seen in the activation of ordinary C-H bonds to introduce greater molecular complexity at specific sites, even in relatively complex molecules. A number of metal catalysts are being developed for this purpose. These new reactions enable the efficient construction of complex systems without the need for traditional functional group incorporation and modification.

How has organic chemistry changed over your career? Has the focus on sustainable, more environmentally-friendly synthesis affected the field?

shiruken

Environmentally friendly or “green” chemistry has also grown to be a part of the field. Any synthetic chemist working with a company needs to take into account environmental hazards of chemistry being used in the development of a process. It pertains not only to the nature of the chemicals, solvents, and waste products involved but also to overall chemical efficiency and the amount of energy consumed. We even introduce the concept of green chemistry into undergraduate lab courses.

I was born in Duluth. Great to hear about another small town, northern Minnesotan doing great things.

I attend the University of Minnesota and I was wondering if "green chemistry initiatives" are becoming the norm for chemistry departments across the country, and how far away are we from devolving practical polymers from renewable sources?

Tzack15

But I was not even so fortunate to be from a real town – only the “sticks”.

Yes, green chemistry has been adopted in much of chemistry as I have mentioned above. A huge amount of effort is being devoted to developing polymers and other materials from renewable resources. One approach is to use carbon dioxide as a component, although we have a long ways to go.

Thank you for taking the time to do an AMA. Would you please comment on the role chemical reaction modeling has on or guides research? What are the key limitations of current reaction models?

AlphaSquare

Computational and theoretical chemistry has become embedded in essentially all fields of chemistry, including organic synthesis. Yes, synthesis can still be done successfully by using empirical and phenomenological, seat-of-the-pants approaches much as the pioneers did in the 1800s, but so much more can be accomplished by taking advantage of computational methods. I have always enjoyed such work, even in my undergraduate days before the widespread availability of powerful computers, but by no means am I an expert. To address this need, my colleague Olaf Wiest and I decided to merge our groups about 15 years ago whereby he is the computational guy and I am the synthesis guy, or as he describes it to visitors, he tells me what to do (make). Students become members of our two labs jointly, and we give them a choice of doing computational work, experimental work, or ideally both. This combination of expertise has allowed us to succeed in tackling the design of new therapeutic agents based upon active site modeling and new chiral catalysts. Most of our recent publications have been joint papers.

Dr. Helquist, on the subject of instrumentalysis in Organic Chemistry, do you believe the advancements in the new instruments will soon blur the lines between the fields in chemistry? Also, what are the most astounding advances in instrumentalysis you've seen? P.S. I was the same as you in terms of a lot of different fields, but I ended up in dentistry!

Tamatone

Please see a response above.

As a forensic chemist, I've been thrown into the world of figuring out organic structures as they relate to synthetic substances and the laws pertaining to them... My question is what is your favorite website that can help with figuring out R groups and their attachments to structures, and what is your take on all the new synthetic cannabinoids and cathinones? Thanks so much!

microgoddess

I am not certain of your needs, but in a broad sense SciFinder and Reaxys are the most powerful web-based tools that organic chemists use. However, they require site licenses, which most universities have but not necessarily other organizations. Users also benefit from some training. I suggest that you visit your nearest university or college science library to find out more. Many science librarians these days are familiar with the use of these web tools.