Science AMA series: I'm Phil Baran, and I'm here to talk about our work at the Baran Laboratory where we try to simplify the way molecules are created. I'm also a MacArthur Fellow "genius grant recipient". AMA!

Phil-Baran [1] and r/Science AMAs[1]

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Abstract

I'm Phil Baran and I teach Organic Chemistry at the Scripps Research Institute. I also head the Baran Laboratory, a vibrant and passionate team of graduate students and postdoctoral scholars vigorously trying to uncover Chemistry's many hidden secrets in the pursuit of useful reactions that can simplify the way molecules are created in the lab. In a nutshell, we like to pursue problems whose solution can have a rapid impact in areas that are important to modern society such as the invention of new pharmaceuticals, agrochemicals, or materials. Our general philosophy to making complex molecules in the laboratory has been summarized in multiple locations but suffice it to say we are aiming for syntheses that are as close to "ideal" as possible. With regards to inventing methodologies we like to focus on tangible and practical ways of forging bonds that are meaningful to as many folks as possible. In that regard, we are most enthusiastic about solving specific unmet needs in reactivity that have a high likelihood of being "translational". Finally, we like to collaborate as much as possible with industry as the fastest return on tax payer money happens when fundamental science and real-world problems come face to face. To learn more about our research, check out our Blog, Open Flask (http://openflask.blogspot.comhttp://openflask.blogspot.com/), our website (http://www.scripps.edu/baran/html/home.html), or follow us on Twitter (@baranlabreads). When I was awarded the MacArthur Fellowship (aka "genius grant") in 2013, they said that I my research "is not only enhancing our ability to make fundamental structures for a broad range of medicines and materials, but is also strengthening the intellectual foundations of organic chemistry." https://www.macfound.org/fellows/884/ I was on earlier today, Monday, February 13, to answer your questions, and will pop in intermittently later to answer some more, if you'd like to go ahead and keep asking. So ask me anything!

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REDDIT

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PHIL-BARAN R/SCIENCE

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To learn more about our research, check out our Blog, Open Flask (http://openflask.blogspot.comhttp://openflask.blogspot.com/), our website (http://www.scripps.edu/baran/html/home.html), or follow us on Twitter (@baranlabreads).

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Hi Prof. Baran. Last year, I attended a talk where a discussion started about arduous work hours in the lab for grad students. Many grad students agreed that 70-80 hours in the lab were the norm. Paul Chirik then expressed that today's organic chemists were "2 steps away from ISIS level insane" and that we need to stop idolizing "the Phil Baran work ethic of setting up cots and sleeping in the lab."

What is your take on the current state of graduate school for chemistry PhD students? Many would agree that long, hard hours over 5 years is just the "price of admission" to a high profile chemistry career. Others though would argue that the process needs to be reformed. Do you believe that mental health issues need to be addressed in PhD programs?

In the UK, PhD students generally are in school for 3 years and only do research. This is because during undergraduate, there is a better foundational education, and therefore classes don't have to be taken during the PhD process. Also, it is treated a lot more like a job in comparison to US programs. Do you think there needs to be a program (or general college education) reform in America? Thank

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you!

BaranThrowaway

I love Paul's sense of humor. He's a great person and scientist.

I honestly don't know why our lab has this stereotype. I think people assume that the lab is run like synthesis labs in the past. It is true that I used to sleep in the lab. It is true that some students will sleep in the couch in my office on occasion. But it is NOT true that I require or encourage this unless someone has a huge discovery and I joke to them "get out the sleeping bags" with a big smile.

The truth is, and our lab really is like an OPEN FLASK, students are simply encouraged to pursue their passion. Some of them get extremely excited and sleep is something they don't want to engage in at times. When I was in graduate school there were periods that were so exciting for me that I couldn't sleep if I wanted to because of the adrenaline of excitement.

There are no official working hours or vacation requirements. People work any hours of their choosing. These days people understand that in order to get a good job one needs a significant accomplishment. The nature of science is that this generally requires long hours. It's really that simple. I'm assuming that if one tries to master anything you probably need to work hard.

Regarding the "state of graduate school for chemistry PhD students", I think it's always a good time to enter, if and only if, its one of the only things that makes you happy. If one is not sure or doesn't really like or can't handle repeated failures then this is not a great path. I think often its easy to come to the unfounded conclusion that if something is really hard then the effort is not worth it. One can give you a long list of reasons why pursuing a PhD these days in chemistry is a bad idea (lack of jobs, over qualification, "poor conditions" of grad school, etc.) but if it is your passion then none of those reasons should phase you. For the same reason you can't convince an aspiring musician or painter to choose another profession, the best chemistry students don't care if they will have a job - they love what they do.

I'm not sure how the process can be reformed (the UK system sounds great) but I can say that in my own group most students these days are graduating in about 4 years. At Scripps we don't have undergraduates to TA so grads can focus on their research (and get paid to do so unlike med school!). I always tell students it is the best time of their life and basically like a daycare center. You get to play in a sandbox, socialize with your friends, learn, and you get fed. As advisors we even change your "diapers" when you make a mistake. Graduate school can be stressful of course and I don't want to make light of that but I think an empathetic advisor can help make the experience more enjoyable.

Regarding the mental health issue I think most institutes have a psychologist on staff (we do at Scripps) and I personally have an open door policy.

Thanks for doing this AMA! I attended one of your lectures back in 2008 in Munich and it was one of the most energetic lectures I've ever heard. I have a few questions for you:

- What is the secret to secureing research grants for a postdoc position? Do you really have to "save the world"? In direct conntection: what is your take on fundamental research without any possible application and how does one justify it other than "it's really interesting stuff"?
- How do you see the ethical responsibility of scientists working just for the science vs. the potential applications of their research? E.g. working on explosives because it is interesting vs. constructing new bombs / working on efficient synthesis of a toxin vs. using it as harmful means? (sorry for the exaggeration)
- How do the thought processes of organic, inorganic and physical chemists differ, or do they not

differ at all?

- What is the best way to eat a strawberry?

Thanks for taking the time :)

Zylooox

Thanks for your kind comments! First question: It really depends on the country and grant system. Some countries are very difficult (like the NIH in US) and although you don't need to save the world you might be judged on your choice of postdoctoral advisor (if its too close to your PhD you might be penalized). It really is unpredictable as if you get a friendly study section it might score well and vice versa. I can't tell you the "secret" to getting this funding as if I were to apply today I most certainly would not be funded (I was told this by many folks).

Regarding fundamental research: I love it. But I also love research that has an application. I don't think scientists need to choose one or the other. It's possible to do both. I've written about this elsewhere (http://blogs.sciencemag.org/pipeline/archives/2016/05/09/dont-wait-for-the-public-sector) but the bottom line is I think the taxpayers have a right to expect something useful from their funds.

• For the second question, luckily we have not engaged in any collaborations where this is a problem. We share the same moral compass as all of our collaborators thus far (pharmaceutical companies) in that we would love to contribute, if even in a small way, to the development of new medicines.

• Although I'm not sure about your third question, I do know that the ultimate way to eat a strawberry is straight off the vine. There are great strawberry fields here in San Diego and we love to take the kids there during the right season.

Hi Dr. Baran

I'm a big fan of yours so thanks for coming by! I've read a many of your papers and one trend that I've noticed is that your lab often performs *tons* of optimization reactions. Is this a top-down thing or do your students and post-docs just decide to do it? Any reason why DOE isn't relied on as much?
Also, since you have your own line of chemicals at Sigma Aldrich, what are some directions you'd like to see academic/private collaborations go?

Thank you
joy

jokes_on_you

Thanks!

I don't think our group is unique in doing tons of optimization reactions. Perhaps we just admit it more often? I don't know. DOE is something we'd like to do more of in the future. At the moment we can rely on some of our collaborators (such as BMS process) to help us with that.

Regarding Sigma-Aldrich and other companies, we wrote a review on this topic and it has some ideas for future directions: http://pubs.acs.org/doi/abs/10.1021/ar500424a

Hi Dr. Baran! You and other prolific science bloggers that talk about more complex science geared towards scientists in the field and in adjoining fields has really become a major source of science news for me. How do you feel about bloggers like Derek Lowe and where do you get your news and opinions in the scientific community?

Spenbo38

Derek's blog is more interesting to me than C&E news and other blogs like "Wait but Why?" (http://waitbutwhy.com) are more interesting than most anything I've seen in the mainstream media. Blogs are a nice way to explore the opinions of interesting people and those that are actually in your community rather than a reporter that, at their core, may not really "get it".

I think the media is 3-5 years behind the curve. These days getting news directly from the source is easier and faster than waiting for a reporter to tell me what I can easily read myself.

As Elon Musk recently said (in a Tweet): "Reading the source material is better than reading other people's opinions about the source material"

Professor Baran - I really appreciate the effort that you and your students have placed on making Supporting Information documentation more accessible & interactive, particularly given the complexity associated with some of your reaction setups. As an editor of JACS, do you perceive a more multimedia (pictures, videos, etc) approach to Supporting Information going forward, or is this something that you would prefer to be unique to your brand?

BenJimi440

Thanks! Great question. I was just talking to a reporter from Chemistry World the other day about reproducibility, etc. in science.

I think that if one publishes a method these days it should be accompanied with as much multimedia as possible as data storage is cheap and theres no way to capture EVERY aspect of a method just with text. I think it should be a journal requirement that new methods have photographic or video guides along with FAQ section that can troubleshoot as many possible situations as possible. It is extra work for sure but can save countless hours by people in the community that might actually want to use the method described. I honestly can't think of a downside to increased transparency – especially given that much of this kind of research is funded by the public!

Hi Prof. Baran! It's really awesome you're doing this AMA. I've been hoping you would for a while. I've got a few questions:

1. How many post-doc applications do you tend to get daily/weekly?
2. So what's the latest on taxanes? Last year you published an article where you were missing only (formally) two oxidations to get to taxol oxidation state. Any progress there? Also, have you seen the work by Wong and Robertson on taxane oxidation using mutant P450 cytochromes? Any thoughts on that?
3. This is kinda personal, so feel free to ignore the question if it's uncomfortable, but have you ever suffered from the impostor syndrome? It's supposed to be big in academia and I'm curious if there's a level of validation beyond which a scientist's safe from it. If you've had it, what helped you cope?
4. Is there something you'd like to see in the chemistry community that'd really help you and your group do your work? Like more negative result discussion in papers, industry cooperation, or whatever. Anything come to mind?
5. Any cool lab techniques you haven't seen people commonly use that've really helped you out during your PhD? Or any favorite tricks you feel warrant sharing?

Anyway, whether you choose to respond to this post or not, this has been a valuable thread for me

already. A lot of great insights from you and others. So, again, thanks and keep up the good work!

totesnotathrowaway_1

Thx!

1. probably 4-5/week
2. We are very close. We have a solution to C–1. Just working out stereochemistry of C–2 and then one oxygen left. We are not fundamentally opposed to using enzymes for one of the oxygen atoms. Such a union of synthetic biology and synthesis would be cool.
3. No but I think I get more credit than I'm due. The wonderfully creative students and postdocs that come to Scripps really deserve the accolades. I have 3 kids and when I get home it's like a mad house so theres really no time left in the day for me to get self-reflective or overthink. We're just trying to do useful stuff. Thats it.
4. More openness in everything would be good. I would like to see the ACS retract their open access repository initiative that could have a negative impact on chemists as nobody will reveal unpublished work at a conference for example. There is a place for peer review and to short-circuit the whole system by having such a system for simply depositing half-baked work won't be good.
5. Two-dimensional TLC got me through grad school.

Hi. Dr. Baran! So glad to see you on reddit doing this. I am currently a graduate student in Dr. Daniel Romo's total synthesis/methodology group in Texas and I am working on a synthetic problem right now and so my question is this:

Have you seen any examples/ think it is possible to trap a secondary alkoxide generated from a chelation controlled addition onto an alpha-alkoxy aldehyde with a methylating agent, where the nucleophile for the addition is RMgX, RZnX, RCeX... etc.? Thus forming a methyl-ether from an aldehyde. This must be done in one step to make this particular route viable.

Side note: I am also exploring additions to a dimethyl acetal, but addition to an aldehyde would be way more amenable to the rest of the synthesis.

christmichaeli

Thanks for the question. Say hi to Dan for me. He's one of the greats of natural product total synthesis and I've always been inspired by his work.

To answer your question it should be possible but I think you'll need a hard electrophile and two great ones (MeOTf and Me3OBF4) can be found in this classic Evans paper: TL, 1994, 35, 7171-7172. Hope that helps!

Hi Prof. Baran,

I always find it interesting to hear, outside of their own work, what chemistry interests academics. Would you be able to share with us some of your favorite total syntheses over the last 5 years, or so? The next "Classics in Total Syntheses" perhaps?

Thank you!

phil-baron

Sure there are so many great syntheses, a few that just pop into my head are Reisman's ryanodol, Maimone's ophiobolin, Shenvi's jiadifenolide, Burns' ladderanes, Krische's bryostatins, Boger's magnificent N-H analog of Vancomycin, Myers' erythronilide, Sarpong's complanidine, Herzon's batzellidine, Movassaghi's communensin, Trauner's Exiguamines, I could keep going for much longer.

Seriously it's good that I'm not writing the classics series because I'd never be able to make a small list!

Hi Dr. Baran,

I want to commend your lab on not only the work ethic clearly required for the success you've had, but the methodical and intuitive planning of your syntheses. I, and I'm sure many other chemists, really appreciate the depth of your publications. I particularly enjoy your publications for the simple fact that, unlike many other synthetic publications, you publish troubleshooting and synthetic routes that were attempted, but didn't work (for instance "Total synthesis of taxane terpenes: cyclase phase"). This gives greater insight into how you approach synthetic challenges. Also, running reactions in distilled liquors is pretty cool.

As your lab focuses much of your efforts on terpene synthesis, I have a few questions:

Terpene scaffolds are notably absent from many drugs despite their incredibly diverse scaffolds and their ubiquitous utility in Nature. Do you think this is due to the difficulty in functionalizing these elaborate scaffolds for SAR studies, use in combinatorial chemistry, and lack bioavailability (cLogP)?

You tout a biomimetic approach to terpene synthesis (cyclization followed by oxidation). Do you see any benefit in adding oxidation prior to scaffold generation?

I am a synthetic biologist/ mechanistic enzymologyist/ combinatorial biochemist (think Yi Tang, Bradley Moore, Jay Keasling, and Chaitan Khosla hybrid). Organic chemistry is incredibly useful, but I believe that combination between these fields is far from where it should be for the development of mixed synthetic strategies that could be paradigm shifting. How do you think the biosynthetic community could better aid organic chemists? Do you see any lack of inquiry that the chemists would benefit from?

Thanks!

calumnncsuchemist

Thanks for your kind comments and great questions.

• Regarding terpenes in medicines, there are actually quite a few. Consider all the steroids out there (cortisols, the pill), taxol, ingenol mebutate, vitamin D, artimenisin, just to name a few. That said, there aren't as many terpenes in drugs as pyridine-containing compounds of course! I think synthesis is a bottleneck for sure and the lack of terpene-skeletons in HTS libraries so med. chemists don't often have them as starting points for a drug discovery program.

• Regarding your second question yes I think strategically placed oxidation into a scaffold is a necessary prerequisite for a successful "two-phase" approach to terpene synthesis. For a discussion, see: https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0030-1258123

• For your third question I think the best example of this is the industrial synthesis of Artimenisin where Sanofi and Keasling's team at Berkeley teamed up. I think there is a great opportunity for more synthetic biologists to team up with more synthetic chemists - both groups could help each other. In fact, we just started such a collaboration.

What's with those IKA ads? A question you brought up on twitter.

Personally, I tought it was funny but a lot of people criticized it. I do hope though we won't see you in IKA sponsored shirts on conferences.

BEchemist

I replied elsewhere on this page but I guess I just don't take myself so seriously (neither does Jin-Quan). IKA gave us equipment to do these shoots, it is a great and ethical company, the products are awesome, and nobody was harmed.

Phil, I'm from the other campus. Two questions: 1. What are the advantages to working at a purely soft money institution like TSRI versus the conventional land grant institutions? 2. Will the merger with Calibr (California Institute for Biomedical Research) will have any profound impact on your research?

hawkeye807

1. More freedom I suppose. Since we have to raise our own money there is less bureaucracy here and forging new collaborations with industry is easy. Also since students don't need to spend long hours TAing undergrads they can focus on research on day one and graduate earlier.
2. I think so. What Pete Schultz built at Calibr is remarkable (like everything he does). We already have a super exciting collaboration that is leading to a clinical candidate. That work is under review now...

Hello Professor Baran :) Do you think Chemistry has place for young doctors? That is , any possibility of doing research in the field? I'm asking this because in MedSchool our knowledge in "pure" chemistry is not that deep. The same way Radiology and Nuclear Medicine allows us to do a PhD in physics for example , would be interesting to know your point of view about Chemistry . Thank you!

weblupin

Sure! There are lots of great chemists that are MD/PhD or straight MDs with awesome knowledge of chemistry.

My hero in this regard is Richard Lerner. Aside from his amazing legacy of building Scripps, he is a rare breed of doctor that can speak in molecules and in one instant describe phage display concepts and in the next sentence lecture you on the stereochemistry of the Diels-Alder.

Hi Phil,

Thanks for doing this AMA. I've been anxiously anticipating this day since your blog started becoming viral, and I am so glad it has finally came. I have a few questions that I would like to hear your insight:

- can you tell us what your daily iternary is as a PI?
- as your group rose to fame and increase in size and diversify in talent wise, do you find it harder to manage everyone's progress and if so, what is your tactics in human resource management?
- what kind of soft skills do you think is lacking in graduate students nowadays for preparing their future career?
- personally I find areas in biology and physics more integrated with data science, but organic chemistry hasn't been diverging from the trial-and-error approach i.e. we still need to roll up our sleeves and perform numerous optimization experiments for one single reaction. How do you foresee that organic chemistry can benefit from technological advancement in big data?

theUnXpected

• In around 545a, brief lunch around noon, 40 mins at the gym (1 min walk from the lab) at some point, home by 615. In between my door is always open or its closed when I'm on the phone or doing a reddit AMA :) but people can just knock or walk in. • It gets harder to keep the lab with the same culture it had

in 2003 but I try my best. I try to meet with students as often as possible and empower talented postdocs and senior graduate students to run their projects without me micro-managing. • Hmmm. Perhaps conflict resolution and time management.
• The problem with big data and organic chemistry is that even if a computer screams in my student's face "THIS WON'T WORK DARNIT!!" reactions are easy enough to simply try. Some of the best discoveries and inventions are ones that a computer would not predict.

Hi Prof Baran, thanks for doing this AMA!

Can you comment on the somewhat controversial definition of a "step" in the context of organic synthesis? The research lab I work in is pretty deeply divided on the issue, even if it's just semantics.

BecauseChemistry

Well I was wondering when this would come up.

I think we will stick to our current definition, one that is agreed upon by many. But we will also in the future pay attention and learn from the criticism that was posted on our blog. So we will report syntheses with step counts but also point out isolations, operations, etc. In other words we will strive to be more self-critical and point out the weaknesses of our routes rather than the strengths.

Syntheses should not be judged by a single number but there is no reason to abandon this number as a useful and important variable to evaluate an important aspect of efficiency.

Hi Professor Baran. You've been a co-founder of multiple companies and you've recently started a new company Vividion.

Can you share some unique challenges that professors and students might face when trying to commercialize their research?

What changes do you think academic institutions can make to make this process easier?

Do you have any advice for students who intend on creating a start up?

normankhoo

Well let me address Vividion - this is a super exciting company that would not exist were it not for the brilliant science emanating from Ben Cravatt's group. Hey Macarthur foundation, are you looking for a real genius? That's Ben.

Jin-Quan and I are bringing our unique blend of chemistry there but I want to make it clear that the company would not exist without Ben's game-changing science.

My first company, Sirenas, is also very exciting and based on the vision of it's co-founder Ed Esquenazi. If you are company looking for composition of matter for an undruggable target, the platform we have developed there is incredibly powerful.

The biggest challenge of starting a company is finding funding but it's just the beginning. it's a marathon not a sprint. Once the money arrives the real challenge is turning a profit, bringing in revenue, and creating something sustainable.

Academic institutions can make this easier by having dedicated incubators on campus that have reduced lease rates and allow for use of community core services such as NMR.

Students that want to create a start up should do as much due diligence as possible on the market they

seek to serve.

1. Do you believe that there has been a considerable decrease in pure, curiosity-based research? If so, do you think that this is tied to a utility-driven grant system and do you find that the deliberate efforts of your group to provide meaningful "pure" discoveries help to bridge this disconnect?
2. What does a typical Baran flash column setup look like? A silica gel slurry with cotton and sand? A fritted column targeting an Rf of 0.3? Dry loaded with a gradient for better separation? Inquiring minds would like to know!
3. As someone who has applied to the chemistry graduate program at TSRI (emphasized La Jolla), should I assume my acceptance is a no-go if I haven't heard anything at this point?

Thanks so much for taking the time to do an AMA!

AllenesOnMyJeans

1. I can speak to the case in organic chemistry and the answer is absolutely yes. I answered a little of this above (please read my essay on this topic if interested). I think as a community we can lament this all we want - it won't change anything. Its perhaps best to just look for alternative places to fund your research and if you can't then try your best to find problems that are interesting to you from a fundamental perspective but also might have some useful downstream application. Again, fundamental and applied science are not mutually exclusive!
2. Haha we have many different setups but my favorite for most applications are columns that we make out of test tubes. Silica gel has gotten a lot better over the years so you don't need to use so much to get a good separation. Perhaps we should do a blog post on this?
3. I am no longer on the committee but since the first recruiting weekend is coming up I assume that is correct. I'm sorry about that - you can always reach out to the grad office for clarification.

Hi Phil! I'm a chem grad student considering entering academia. Obviously not everyone can make it as a PI at are R1 institution. What, in your opinion, does it take to make it as a PI at the highest level, and what differentiates these PIs from those at less prestigious research institutions?

mynewsonjeffery

Gee – I don't know if I'd think of it this way. There are lots of cool discoveries that take place at "less prestigious research institutions". All I can say is that when I was a grad student I didn't think about what I would do after grad school. I kind of just realized that it would be a good fit to teach and explore. Its quite a blessing to be able to do that. My advice would be to just follow your passion, work as hard as you can, and don't look back. You can make an awesome contribution to society and science no matter where you end up.

Professor Baran,

First question, are you ever accidentally referred to as Batman in emails? My autocorrect wanted to replace your name with Batman.

Secondly, what is your emphasis on creating reactions that have a high yield of a specific product (is very selective) vs. a reaction that is easier and quicker, but produces more waste product.

Thanks!

imnothappyrobert

Haha I've been called many things (mostly too vulgar to post here) but not that :)

Regarding your second question it's all about the purpose. For example, if I was in process chemistry I would need a reaction that creates a high yield of specific product with minimal waste. If I were in medicinal chemistry I would simply need a small amount of product in the minimum time in order to evaluate SAR. Waste and atom economy in that setting are largely irrelevant. If I were in radiochemistry I would base all my attention on minimum exposure to radioactive steps and cost of the SM. Atom economy, catalyst loading, yields of non-radioactive steps, all nearly irrelevant.

- What are the most under-appreciated skills and thinking processes that a fresh graduate student has to learn when he/she starts a PhD in total synthesis and in method development, respectively?
- Nickel or Palladium? Magnesium or Zinc?

chemochemchem

• Most underappreciated? Hmmmm. Probably attitude. Students that have a negative and pessimistic attitude (this project is stupid, this reaction will never work, etc.) are almost always proven right.

• I don't discriminate against people or elements :) Although you won't catch us doing Uranium or Thallium chemistry any time soon...

First, thank you for doing this AMA.

I'm an undergraduate in physics thinking to go into bio/chemical physics for grad school. My main motivator is the question "How do we start with molecules and get an organism?"

Since your research is in basic molecular structure I'm curious to know your thoughts regarding this "Origins of Life" problem. Have you thought about it? What do you think are the major gaps in understanding? Where would you start to look for patterns? Etc.

Thanks in advance.

lbman

This is an intriguing area. Three of my treasured colleagues, Donna Blackmond, Ram Krishnamurthy, and Reza Ghadiri, are doing cutting-edge research in this area. As my now ex-colleague Albert Eschenmoser has said something along the lines of "The origin of life won't be discovered, it will be invented!" . I look forward to what people discover and invent in this thought provoking area.

Dr. Baran, Do you think there is group or institution based bias in the review process? For example, for papers or grants that come from big labs or institution vs others. Do you think the blind review that does not reveal the authors and institution of the papers for the referees will be better ?
Thanks for doing this.

Chem109

Probably but that is hard to do in practice for fields that are relatively close-knit. I'd bet even if many groups blinded everything you'd pretty much know who wrote it just based on Figure settings :)

There's bias in anything that involves humans.

Hi Prof. Baran, thanks for doing this.

What is your view on how synthetic problem solving skills can/should be taught to undergraduate o-chem students? Are there certain skills you think are reserved for upper level courses or should students be taught how to disconnect molecules as soon as they are learning reactions in Organic I?

Here_For_Da_Beer

Disclaimer: I only teach graduate level synthesis.

I think that undergraduates should learn as much mechanism and basic reactivity as possible but once they know enough reactions then retrosynthetic analysis is a great way to teach critical thinking in general. Students should be exposed to this as early as possible in my view (at least I was at NYU).

Let me put it this way: I would not want to send my kids to a doctor that didn't get at least a B in organic chemistry.

Greetings Prof. Baran. What are in your opinion a must read organic chemistry books.

Chysce

To name a few: all the classics books, the Kurti/Czako named reaction book, Anslyn/Dougherty physical organic, March, Larock, and of course https://itunes.apple.com/us/book/portable-chemists-consultant/id618463142?mt=11

Hello Professor Baran,
I'm a second semester OChem student at a local community college in San Diego. What advice would you give to a Chemistry major about to transfer to university? What can I do to best prepare myself for a job in industry or to ensure success in chemistry classes?

One last request, I am the president of our college's chemistry club, and we love guest speakers! I'd love to invite you or anyone from your lab to come to our local community college to speak. It's in the South Bay.

Thank you for doing this AMA! I'm excited to read the answers and learn more about your work.

BREEZE_BLOCKS

Try to get an internship at a company or in the group of a academic chemist. At the beginning it's like the karate kid - just wax on and wax off and learn to catch flies with chopsticks :) Once you know the techniques you will go far. When you're not in the lab do lots and lots of problems.

For second request please send me an email directly!

Hey Prof. Baran - your work is really cool.

As an aspiring chemist/undergraduate who's interested in synthesis, I have a question: what level of purity do you shoot for/try to achieve in your syntheses? For instance - if you see triethylamine peaks in an intermediate, do you carry it on to the next step or not? Is that "sloppy" or "efficient"? (assuming of course that it won't interfere with anything)

I'd also be interested in seeing a blog post about this "Baran column" setup.

cwagen

Thanks! great suggestion. We will add this discussion to the blog post on "Baran lab purity" :)

Hi Phil, can you expand on what is meant by "ideal", when you say...

syntheses that are as close to "ideal" as possible

Can you give an example of a reaction that you've synthesized that has simplified how a molecule is created?

Also, have you done any work on genetically encoded molecules?

subroutines

Great question - we have published a review on this that clearly articulates what we mean: http://pubs.acs.org/doi/abs/10.1021/jo1006812

One of my favorite examples in there was the welwitindolinone story. The molecule basically looks like a combination of Carvone (from spearmint) and indole (from coal tar) so one of my first graduate students, Jeremy Richter (now at BMS), just decided to invent a way to put the two together.

Hello. I am a materials chemist (solid state materials), I enjoy your work on organic electrochemistry. I recently started as an assistant professor, I am wondering if you have any advice that would be valuable to a new faculty member.

Your group is rather large, where do you apply to obtain enough research funding to sustain such a large group? (certainly NSF, DOE, NIH, and AFOSR wouldn't be enough)

In terms of student/postdoc recruitment what is most important attribute to finding the best student. I tend to think that GRE and GPA are not that important, but I haven't been around long enough to make correlations yet.

NanoChemist

Thanks!

My advice to new faculty members is to rely on yourself entirely at the beginning - work in the hood as much as you can and fiercely instill the techniques and thinking skills you'd like to see into your first batch of students as that will be passed on from class to class. Focus as much as you can on getting results in the first year or two rather than applying for a million grants (stay close to the hood). Also I'd recommend never losing your temper with your students and treat people the way you were or would have liked to be treated when you were a student.

For funding we rely on >50% of our funds to come from Industry.

For recruitment GRE and GPA are really not great predictors of success. Sometimes the really good test takers fall apart when they are told to invent something. The best attributes are drive/persistence and some undergraduate research (or even a publication). Often students from unusual backgrounds or older students that realize graduate school is what they want thrive.

hi Prof. Baran What is your take on the future of synthesis research? Do you think that President's D. Trump policies will hurt in one way or another the domain of synthesis ? would graduate student prefer europe over the states for their phd and postdoc ? in the grand scheme of things do u think that synthesis is a domain that flourishes or shrinks and why is that ? best of luck

anthitecht

I'm going to answer your first question and steer away from anything remotely resembling politics.

I think the future of synthesis is still very bright. This question gets asked very often and perhaps much too often than is warranted given the TINY amount of public $ that is spent on this field relative the amount of interest and utility it generates. Every few years some grand old expert comes out and declares "Enough! Ok synthesis is mature!" but over an over again they are proven wrong. Computers and machines are not taking over any time soon either. When the day comes that we have replicators like on Star Trek then we will be in trouble.

As a very young chemist interested in organic chemistry the reactions I am learning in class seem vastly less complex then those I see in research papers and ACS conferences. Is my lack of understanding just my youth thus I need more time studying the field or is it something else? Additionally, if this is unrelated, do you have any advice on transitioning from entry level organic chemistry to more advanced organic chemistry?

Calovichi_Otter

You've gotta know the basics like aldol and ester hydrolysis before moving to more complex stuff! Do as many problems as you can get your hands on. Master the basics and then move on to the recommended texts I posted above.

Hi Professor Baran,

Thank you for sharing your knowledge and experience in an open forum. In your opinion, what is it about biology that allows for such small pieces to be put together to form such complex biological structures? In other words, I recognize why atoms are attracted to one another but how is it that the jump is made from a single molecule to a homeostatic living cell that is capable of reacting to its surroundings and futher building upon itself to create complex life forms?

Jstbeechy

See above answer regarding origin of life. Several awesome scientists looking at this question now.

In your hydramination paper in Science, the SI mentions an intramolecular hydroamination that wouldn't work, giving the 6-endo product (hydration) instead of the 5-exo product (amination). Any insight on why this might be? I thought the general trend in organic chemistry is that 5-exo tends to be faster than 6-endo, so what other factor could be at play here?

thebrew221

The radical forms on the olefin to make the more stable radical which then engages the O of the NO2. After cleavage of the N-O bond the 6 endo product emerges. The net product is thus due to where the radical on the olefin forms not on Baldwin rules.

Is it true you are big into weightlifting? A postdoc in my lab was telling a story about how apparently K.C. Nicolaou thought you were working in lab too much and told you to "get a hobby" and so you started lifting and got huge.

elloyd5

I'm not huge, KC never told me to get a hobby, but I do like to go to the gym! First it's very close by, second it releases a lot of stress because it's somewhere I can go to unwind and, for a very brief period, not think about solving problems, and third I find I am more efficient at work when I'm in ok shape.

One of my favorite aspects of organic chemistry is the competition over the development of similar synthetic methods (with different advantages/disadvantages) or fundamental mechanistic controversies, a la the debate over non-classical carbocations between Winstein and Brown and resolved by Olah. Along those lines, do you have a favorite unresolved controversy (or competing views) in modern organic chemistry, whether it is related to the nature of an intermediate or perhaps competing synthetic methods (e.g., ways to perform decarboxylative cross-couplings...)? If so, where do you stand?

00413200

Hmmm. I stand at the opposite end of the spectrum here. I think a lot of these debates and controversies keep some talented students from entering the area. I know a very famous biochemist that told me she entered an ACS meeting when the carbocation debates were ongoing and watching these folks made her decide, in that instant, that organic chemistry was not the field for her.

We have a group meeting on this topic:
http://www.scripps.edu/baran/images/grpmtgpdf/Seiple_Sept_10.pdf

I don't think this kind of controversy exists today in organic chemistry (thankfully). Regarding your specific question, there is a need for many ways to do certain transformations. The best thing you can give a practicing chemist is options. So the more options to do a type of reaction the better for society.

Hi Prof. Baran, I'm a graduate student in biochemistry. My issue is not one of becoming disillusioned, but of not pursuing a specific passion.

I've wanted to do total synthesis since freshman undergrad. But I had troubles getting into a synthetic lab and eventually made the dire mistake of "settling" to wash dishes for biology labs. I did no actual research. My GPA got me into a top chemistry program anyhow, but I was rejected by the synthesis groups on account of my experience being in the wrong field. There were too many bright-eyed 1st years with the correct experience for me to compete. Even though my degree program is Chemistry, the only lab that let me in is 100% molecular biology and there is no fume hood.

I guess I'm pretty damn decent at biochemistry now, but everyday the thought of not having chased the dream plagues me. I wish I wasn't so complacent in undergrad and looked harder. I don't care about money or working hours and nobody can really convince me that I'm better off with my current path. I would feel lousy to earn a PhD in chemistry and have zero training in synthesis which is what will happen.

What do you think in general about my situation? There are many chemists who become sick of the columns and solvents and move towards biology, but I feel like there are much fewer of the reverse! I guess, post-doc in a chemical biology lab would be my last chance.

compy_mx

Well if it's your dream then why not do a postdoc in a pure synthesis group? It's never too late.

I have had students that completely abandoned successful careers to engage in synthesis. Its not unprecedented. Don't let people tell you what you can and can't do. Otherwise you'll be asking "what

if?" for the rest of your life.

Hello Dr. Baran! I really do enjoy your total syntheses, especially Phorbol. It's refreshing that you not only efficiently plan out your syntheses but also use "older chemistry," instead just opting for more well-planned retrosynthetic analysis. 2 questions:

1) Do you find that PIs, and possibly graduate students, get bogged down in natural product synthesis with developing novel chemistry instead of a well-planned retrosynthesis?

and

2) Do you still find yourself doing organic chemistry problems (e.g.-Evans physical organic chemistry course or Fukuyama mechanism problems) if you haven't already done all of them, and if so, do you have a particular favorite source/any to recommend as I enjoy the process of solving the problem and reading the reference

homerunmanjb

Thx!

1. Well I wouldn't say "bogged down". I think thats the whole point. In my view if the retrosynthesis works perfectly as planned then it's not likely that new insights into reactivity emerged.
2. As my students can attest I do them every week in group meeting. I still get stumped every now and then :) The Fukuyama book is an awesome source!

What would you think about accepting a post-doc (hypothetically) from a different sub-field? I'm currently doing an organometallic PhD and work with a lot of (highly) air-sensitive compounds, but I'd like to potentially swap fields to do organic/total synthesis, as that's always been my true interest.

Is it impossible?

elnombre91

Nooooo thats exactly what the funding agencies are looking for. Going from one field to another is a super education.

Hi Phil,

I work for Louis Barriault and I recently wrote a chapter on our Vinigrol Synthesis that will be featured in STOS. I also myself am working on a total synthesis project.

Having seen the efforts of installing the syn Me/OH at the C8/C8A position (they had tried multiple dipolar cycloadditions but not the dibromoformaldoxime), I really gained insight in how incredibly frustrating total synthesis can be.

My question is what was the most frustrating part of your Vinigrol synthesis, and perhaps further, most frustrating efforts to install some functionality in your career?

Cheers and thanks for your time.

UglyRyanGosling

Thanks for your great question and send my regards to Louis - few people are as fun to have a beer

with! And he's a great chemist!

The most frustrating part of vinigrol after Tom figured out the dipolar cycloaddition was actually installation of the last CH2OH group. Someone had erroneously indicated that the conversion of 9 to 10 (http://pubs.acs.org/doi/pdf/10.1021/ja908194b) was not workable so we spend a looooong time trying to figure out a workaround when Cindy Shi (now at BMS) saved the day and found the right conditions and figured out how to make the polyanion and quench with formaldehyde.

Honestly these events are not frustrating. When students start having these issues in synthesis they are greatest source of joy for me (I try to relay that to them too) – that's what makes great educational opportunities and ample chance to invent!

Hi Dr. Baran, First, thanks for making this session a reality! I've came up with some q's during lunch break. 1. What's a luck/skill ratio for a successful organic chemist (e.g. in your group)? 2. How much of your supervising style did you inherited from your mentors? Is there anything you didn't like and so don't do as a PI? 3. Do you take vacations? 4. Do you feel personal responsibility for your students'/postdocs' future? Were there anyone you didn't write a good reference letter? 5. Is there any time-management technique you are using?

That's probably it. If anything was previously answered, feel free to skip. Thanks again!

slavabernat

Let me just answer #4 = YES. absolutely I do. I care for their welfare as if they were my family.

Greetings Dr. Baran,

1. What is your take on Dr. Nocera's work with the Bionic Leaf? He recently held a symposium at Davis and I've heard a lot of mixed reviews regarding his developments.
2. I have to present mechanisms for group meeting this Wednesday. Any suggestions?
3. How was your experience working for Corey?

Keep up the good work!

KinGBee777

1. His work is outside of my area of expertise but having interacted with him and read his papers, theres a reason he is a legend in the field! I'm sure there are haters out there but I'm more inclined to think he is as amazing as people think.
2. 8 to 9 in http://pubs.acs.org/doi/pdf/10.1021/acs.orglett.6b03760
3. Was amazing! Learning from him was one of the greatest experiences of my life.

As a profession, one could say the principal workplace activity of a chemist is to incinerate money, in the form of chemicals in a fume hood, using high purity chemicals, solvents, and research platforms such as mass spectrometry, NMR, and computational chemistry facilities, in a gamble to generate a slice of IP. A sharp cliff of hard work and research training awaits the passionate budding chemistry students who scale the cliff, but realistically, it is a lot of hard work and a very difficult profession when it comes to job security.

- Particularly regarding industry growth, do you think there will be a rise in the need for classically trained organic chemists?

- Or is it one of those situations where the world will always need organic chemists, but it will never need more?
- Also, is Scripps the glowing haven we've all been led to believe by our natural product synthesis research supervisors?

analcime

Haha I don't think I'd be so cynical. There is no utopia. Every profession can be written about with this kind of negative slant. I don't agree with the sentiment of your first paragraph and I'd say that nobody's job is secure these days. I'm grateful that the sign outside my office is still there every morning. In some ways I think thats a good thing.

• I can't predict that there will be a rise but I can predict that for the foreseeable future there will be a need for people that can speak and create in the language of molecules. We're not going to be replaced by computers or other automation in my lifetime. That's my prediction.

• Regarding Scripps. It is as close to being heaven on Earth for me and many of my colleagues. I think students agree as well, but usually they don't make that admission until after they leave and experience the outside world :)

I am a chemistry undergraduate (senior), and am very impressed with your work in total synthesis. How do you choose which molecules to try to synthesize?

In other words, it seems that there are a lot of potential synthetic targets; how do you know which ones to go after?

-Metacelsus-

Target selection is based generally on the disconnect between what is known and unknown. When the gap is really large we love such problems.

Hi Phil -

It's safe to say that public funding for academic research doesn't flow as freely as it once did, and things aren't exactly looking up in the foreseeable future. You also do not shy away from sharing your opinion that private funding agencies can pick up the slack. Obviously, it's important to maintain some level of academic integrity and independence and balance the needs and interests of the students while still finding a way to keep the lights on. How does one avoid tumbling down the rabbit hole and going full-fledged CRO while still working to keep "the man" happy?

Oh and thanks for the PhD.

BrandoFromBaranLab

Hi Brandon! We miss you!! great question.

I think the key is never to agree to a collaboration where you feel you are bending your principles or taking advantage of students. Partners should let you publish, should share results, be open-minded, and respect that fact that in an academic environment you can't be expected to do things that a CRO can accomplish.

Hi Prof. Baran,

Do you think total synthesis will still have a place in the future?

I absolutely love creative, yet efficient total synthesis and want to pursue a PhD in that field, but I'm afraid the niche of total synthesis will become redundant.

critzz123

Well we've commented on this a lot on the blog and I think another post on this topic is due so stay tuned for that.

Very little $ is spent on this but it still continues to be the kind of science that people want to read about. I think Total synthesis will endure but people will need to be more creative about funding such endeavors....

Hello Phil,

I attended your last lecture in Basel and like someone mentioned before this was the most energetic lecture that I've ever visited. I will start my PhD in organic chemistry in 2018.

I have 2 questions:

1) I'm really interested in psychology and computers other than chemistry and I'm wondering how can you apply chemistry to these fields? I think that brain research might be the connection with psychology but I have no idea how chemistry can help fundamental research in computer science?

2) What is the most unusual career that you know about that evolved after organic chemistry PhD?

torn_apart

Thx!!

1. To psychology the biggest impact you can have is to invent new medicines for the neuroscience area. I have spoken to many physicians and they say there is a great unmet need for such medicines for all sorts of disorders. So become a great chemist and then invent a new medicine for this area!

For the computer science area perhaps fields like Stoddart and Leigh (molecular machines) could be a way forward as we might see computers based on such chemistry in the future.

1. Someone I know became a sculptor! Not surprising as theres a huge artistic aspect to this field.

Hi Professor Baran! Another grad student from the Romo group here. I had the pleasure to talk to you at the Nicolaou Symposium last year and really enjoyed your talk!

In all your years of grad school/postdoc/academia, what would you say is the most important thing you learned? Also, any advice on how to stay sane and not give into the urge to throw your RBFs out the window?

Thanks so much!

akriza

Haha, please just call me Phil.

The most important thing I've learned? Tough question. Hmmm... Maybe that one shouldn't take themselves so seriously and that everyone can teach you something.

And when the going gets tough I'd recommend going for a run or play a sport. When you hit a wall sometimes you can accelerate the solution to a problem by stepping away for a brief period and then

returning with renewed vigor.

Hi Prof Baran, We've seen multiple reports from your group mentioning the large number of experiments needed to achieve a particular transformation. This often includes the addition of relatively strange "additives" whose role isn't clear. 1) How do your students remain motivated to do conduct so many experiments to accomplish one transformation? 2) How do you go about selecting these "additives" for these transformations? Thanks!

thewhateves

Thanks!

1. Sheer love of chemistry and a desire to create something of beauty is what fuels their passion
2. Lots of brainstorming, chemical intuition, clues from the literature

As a chemist, how particular are you about your coffee?

stemcelltulsa

Double espresso, splash of 2%, dash of cinnamon, 2 splendas.

Hi Dr. Baran,

What's your take on using synthetic biology to make these molecules (e.g. using yeast to make opiates), rather than industrial-style chemical reactions?

Nemisis_the_2nd

Very exciting field. Synthetic biology is not going to solve all the worlds problems but when it works its hard to beat it. For a discussion, see:
http://www.nature.com/nature/journal/v492/n7428/abs/492188a.html

Hey Dr. Baran. I have a B.Sc in chemistry and have been fortunate to have worked as a medicinal chemist for the past 8 years. I enjoy my job and the challenge of drug discovery and organic synthesis, but I am an ambitious person and it seems very clear to me that without a PhD there is no path forward for me in chemistry, as employers would much rather hire someone fresh out of graduate school as opposed to someone who has worked their way up the ranks. How do you feel about "the glass ceiling" that exists in chemistry oriented careers for non-PhD chemists?

Entropy912

It really depends on the company. One of the best undergraduate students I had was a blackjack dealer and all of a sudden decided to go into chemistry. Long story short this person is now at a top 10 pharma company and is at the same level as a PhD chemist and running a group.

Find a company that values intellect, talent, and drive rather than titles!

So, why can't we make Buckminster Fullerene (LaC60)?

trevisan_fundador

Larry Scott did!

Dear Prof Baran, I have two questions:

1) What is your favourite natural product and why?

2) Do you now have a PhD student working specifically on reactions involving exotic solvents like Oolong tea and whiskey?

Cheers and thanks for the inspiration!

NotABiscuit

1. probably palau'amine because it was pursued for purely fundamental reasons but if we had not worked on it there are a variety of interesting methodologies we wouldn't have explored.
2. At the moment we have some students working on something even more bizarre than that... I can't say more right now but will in the future :)

Hello Professor Baran. I am currently a chemistry undergraduate student at Florida Institute of Technology and I have a question regarding REUs at Scripps Research Institute. Do you know what exactly professors who host undergraduates look for in cadidates? Additionally, what should an undergraduate research assistant expect during the summer program? Thanks for doing this AMA, you're awesome!

SweetJeff11

We simply look for students that are driven to learn. You should expect to be immersed in a lab and experience real research. I'd recommend taking advantage of such opportunities by trying to live like a graduate student. Its a great way to see if graduate school will be something that is for you.

Hello,

How would you recommend an industrial chemist dig back into synthetic chemistry with a mind towards green chemistry? Is there anyone in particular in the field doing groundbreaking work?

slawdogporsche

I think the whole field is moving in the direction of doing more with less which I think is the essence of green chemistry. I think the ultimate greenness is achieved by reducing the step count or number of operations needed to make a target (either through the use of a clever strategy or a powerful method) rather than using a solvent that is more "green".

Dr Baran,

I am a doctoral candidate working in Green/Sustainable Organic Synthesis, and I think often on the concept of an ideal synthesis. To paraphrase Hendrickson, 1975 (roughly since I don't have Journal access where I am), the ideal synthesis uses 'small, widely available molecules' and contain 'only construction reactions leading directly to the target molecule'. Do you agree with this? For example, utilisation of biomass feedstocks may require starting a synthesis from a widely available molecule with some unnecessary functionality, removal of which might not constitute a construction reaction.

Somewhat related, how do you quantify the ideality of a synthesis? Is it a case of step economy, atom economy? bonds formed/bonds broken per step? I have my own ideas, but am interested to know yours.

Do you consider there to be a recalcitrance in organic synthesis towards utilisation of Green methodologies? If so, why? Regardless, what can be done to increase utilisation?

Finally, did you enjoy your IKA race? Nothing has ever made me want to buy a hotplate more.

Edit: ref

UrbanRollmops

Great question! Yes I agree wholeheartedly with Hendrickson. He was ahead of his time for sure and really articulated everything about efficiency before chemists became interested in it. To answer how we quantify this, see http://pubs.acs.org/doi/abs/10.1021/jo1006812

Regarding green chemistry I don't see anyone resisting it. I gave my opinion on greenness on this page somewhere but I think the greatest strides can be had from new methods and strategies rather than new solvents or by chanting the word "Green" over and over again.

For the IKA race, that was so much fun. We actually filmed 2 videos and the next one was also a lot of fun. I will say the next one is super crazy and I have a renewed respect for actual actors. Hopefully Scripps doesn't fire me after the next one :)

Regarding IKA products they are the best for a number of reasons but now you don't need to take my word for it. Just get one and with a lifetime warranty you'll never need to buy another. They don't believe it's right to make money off of a product that will break. They are also a very ethical company with great integrity and they donate a lot to various charities and take very good care of their employees.

What happened with the optical rotation measurements with ingenol?

anonchemist1234

Original synthetic sample gave correct magnitude but opposite sign. Apparently this is a known issue as two different isolation folks had differing signs as well. When we made more we checked again and again and it was in fact incorrect confirmed with comparing to authentic natural material. Just a tale about the sometime spotty nature of an old polarimeter.