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NASC 2023: showcasing diversity in North American supramolecular chemistry

Nathalie Busschaert ^a, Clifton J. Stephenson ^b, Kristin Bowman-James ^c, Lyle Isaacs ^d, Benjamin E. Partridge ^e, Ken D. Shimizu ^f, Douglas A. Vander Griend ^g, Kejia Shi ^h and Emmanuel O. Ojah ^a

^aDepartment of Chemistry, Tulane University, New Orleans, LA, USA; ^bDepartment of Chemistry, Loyola University, New Orleans, LA, USA; ^cDepartment of Chemistry, University of Kansas, Lawrence, KS, USA; ^dDepartment of Chemistry and Biochemistry, University of Maryland, College Park, MD, USA; ^eDepartment of Chemistry, University of Rochester, Rochester, NY, USA; ^fDepartment of Chemistry and Biochemistry, University of South Carolina, Columbia, SC, USA; ^gDepartment of Chemistry & Biochemistry, Calvin University, Grand Rapids, MI, USA; ^hDepartment of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, USA

ABSTRACT

Diversity in supramolecular chemistry can showcase itself in many ways. This includes the diversity of thought and topics covered in research (from fundamental science to applications in biology and materials), as well as the diversity of people (e.g. diversity in race, gender, sexual orientation, country of origin, type of higher education institute, career stage, ...). At the North American Supramolecular Chemistry (NASC) meetings, we aim to bring together the best that supramolecular chemistry has to offer in North America, create a sense of community and provide a platform for researchers at any stage of their career to present their work. NASC 2023 was the successful second edition of the NASC meeting series, and this proceedings article highlights the research and impressions of some of the speakers at NASC 2023.

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Introduction from the organisers (Nathalie Busschaert and CJ Stephenson)

The North American Supramolecular Chemistry (NASC) meeting was established to create a stronger community of supramolecular chemists across North America, and to provide opportunities for PhD students, postdocs and other early-career scientist to network and disseminate their results to a receptive audience. The first edition in 2022 was well-received and welcomed 88 attendees. A second edition was therefore held in New Orleans on December 18–19, 2023 (NASC 2023). With 74 registered attendees (including 2 keynote speakers, 12 invited speakers, 13 flash talk presenters, and 34 poster

presenters), the second edition confirmed the demand for an annual meeting of supramolecular chemists in North America. One of the most noticeable aspects of the second edition was the diversity of science and people. Supramolecular chemistry has moved on from being a niche academic subject, to a large field that covers many areas. NASC 2023 included presentations on a diverse set of topics, ranging from the fundamental physical chemistry of intermolecular interactions to crystal engineering and drug overdose treatments. Diversity of people was also showcased and can come in many forms (diversity of thought, gender, race, sexuality, disability, country of origin, ...). For example, while the first

edition was still very US-centred, the second NASC meeting welcomed a number of speakers and attendees from Canadian institutes as well. In addition, the second edition also reflected the changing demographics of the student population in North America, with increasing numbers of students with Latino or African backgrounds (in addition to the more traditional White and Asian students) and a suitable gender balance. Naturally, this diversity of people was also reflected in the 2 oral presentation winners (Kejia Shi and Emmanuel Ojah) and 3 poster prize winners (Daniil Sosnin, Fahidat Gbadamosi, and Yun-Hsien (James) Lin).

Finally, NASC 2023 also showcased an aspect of diversity that is unique to the United States higher education system. In the US, higher education can take on many forms, from doctoral universities, master's colleges and universities, baccalaureate colleges, baccalaureate/associate colleges, associate colleges, special focus colleges, and tribal colleges (Carnegie Classification). Many of these types of higher education perform research and supramolecular chemists can be found in every type of institute. A common distinction that is used in the US (e.g. by the National Science Foundation (NSF)) is between doctoral institutions, which are more research intensive and award many PhD degrees per year, and primarily undergraduate institutions (PUIs), which award few if any PhD degrees. Nonetheless, many PUIs still conduct world-class research (mostly by undergraduate students) and should therefore be part of the supramolecular research community. It has always been the aim of the NASC meetings to include faculty and students from PUIs. This is why NASC 2022 and NASC 2023 were co-organised and co-sponsored by Tulane University (a doctoral university) and Loyola University of New Orleans (a PUI), and why the cost for attending has been kept lower than most other

conferences. We consider this a win-win for both the faculty at PUIs, who are given the opportunity to present their research without the high cost of international meetings, and the PhD students and postdocs at doctoral universities, who might not be aware of the career possibilities provided by PUIs. We are happy that we could schedule several PUI speakers for NASC 2023, including a pre-meeting workshop on determining binding constants hosted by Douglas Vander Griend (Calvin University). For the remainder of this conference proceedings article, we have asked a number of our diverse speakers to provide their impression of NASC 2023 or to highlight their view of the future of supramolecular chemistry.

Impressions of NASC-2023 speakers

The need for a regional supramolecular chemistry conference (Kristin Bowman-James)

Kudos to the organisers of the 2nd North American Supramolecular Chemistry (NASC) meeting in New Orleans in December 2023! Although I was unable to make last year's inaugural celebration, I became aware of this new conference series several years ago while it was still in the early planning stages. At that time, I was contacted by Kristin Hutchins (University of Missouri-Columbia) who told me about Nathalie Busschaert's brain-child and asked if I would be willing to serve on the Advisory Board. The idea of a regional conference series highlighting early career researchers seemed way overdue, although several such venues can be found in Europe and the UK. My worry was that given so many other conference series there would not be enough interest in yet another, despite the good cause of promoting early career researchers. I was so wrong! This second event

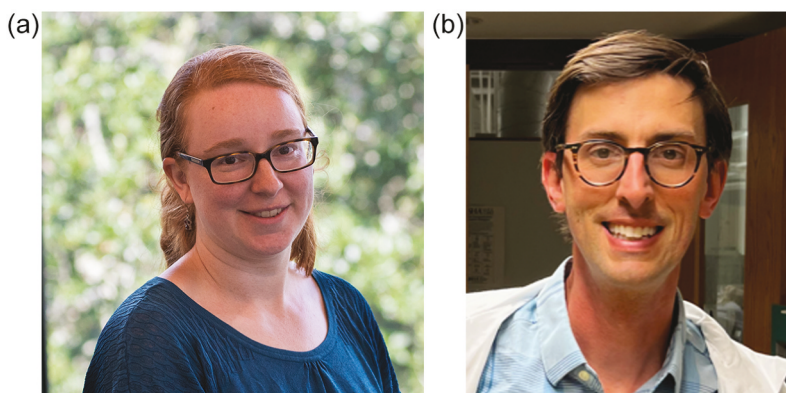


Figure 1. (a) Nathalie Busschaert. Chair and founder of the North American Supramolecular Chemistry (NASC) meeting. Assistant Professor at Tulane University. (b) Clifton J. (CJ) Stephenson. Co-organizer of the North American Supramolecular Chemistry (NASC) meeting. Professor at Loyola University of New Orleans.



Figure 2. Kristin Bowman-James. Keynote speaker at NASC 2023. Distinguished professor at the University of Kansas.



Figure 5. Ken D. Shimizu. Invited Speaker at NASC 2023. Professor at the University of South Carolina.



Figure 3. Lyle Isaacs. Invited Speaker at NASC 2023. Professor at University of Maryland, College Park.



Figure 6. Douglas A. Vander Griend. Invited speaker and workshop leader at NASC 2023. Professor at Calvin University.



Figure 4. Benjamin E. Partridge. Flash Talk Presenter at NASC 2023. Assistant professor at University of Rochester.



Figure 7. Kejia Shi. Flash talk presenter at NASC 2023 and winner of the 'best talk' prize. PhD student in the group of Bradley Smith at the University of Notre Dame.

attracted over 70 attendees, so clearly Nathalie has pulled it off! Key to its success is, first and foremost, the science. While a few established researchers gave talks, it was especially exciting to hear from very talented and promising early career researchers, e.g. senior postdocs and junior faculty members. The congenial environment provided by Nathalie and her colleagues made everyone feel comfortable, and

discussions and exchange of ideas freely occurred throughout the meeting. New Orleans is also an exciting and hospitable town, especially around the holidays. As a result of all of the above, the North American Supramolecular Chemistry series is off to a great start and will surely become the conference to attend in the upcoming years.



Figure 8. Emmanuel O. Ojah. Flash talk presenter at NASC 2023 and runner-up of the 'best talk' prize. PhD student in the group of Nathalie Busschaert at the Tulane University.

Use of molecular containers as *in vivo* sequestrants (Lyle Isaacs)

Over the past five decades, research in supramolecular chemistry has delivered a deep understanding of a wide range of non-covalent interactions, showed how they could be used to self-assemble more complex systems, and ultimately demonstrated their use in chemical, materials, and even biological applications. Within the field of supramolecular chemistry, macrocyclic hosts (e.g. crown ethers, cyclodextrins, calixarenes, cyclophanes) play a starring role due in large part to their pre-organisation which imparts selective binding towards suitable guest molecules. Over the years, the Isaacs group has studied the synthesis and molecular recognition properties of macrocyclic and acyclic cucurbit[*n*]uril-type receptors, demonstrated their ultratight binding towards hydrophobic cations (e.g. ammonium ions) in buffered water, and showed that they could be used as components of sensing systems, separations materials, solubilising excipients, and sequestrants that control the chemical and biological properties of their guests. At NASC 2023, Dr. Isaacs presented his group's recent work on the synthesis of sulphated pillararenes (e.g. P6AS) and comparison of their molecular recognition behaviour towards hydrophobic cations with that of the well-known water soluble pillararene (WP6, carboxylic acid substituted). Binding studies show that P6AS binds much more strongly to tertiary and quaternary (di)ammonium ions than WP6 does. Drugs of abuse are an important class of hydrophobic cations and P6AS was shown to bind to methamphetamine, MDMA, mephedrone, fentanyl, and PCP with K_d values in the $10^7 - 10^8 \text{ M}^{-1}$ range in PBS buffer which renders them of potential utility as *in vivo* sequestrants for drugs of abuse. Open field tests showed that the behavioural change (locomotion) seen for mice dosed with

methamphetamine (0.5 mg/kg) or fentanyl (0.1 mg/kg) could be counteracted by treatment with P6AS (35.7 mg/kg for methamphetamine; 5 mg/kg for fentanyl) five minutes or 15 minutes later, respectively. This work, along with the growing body of literature from other groups, establishes that select supramolecular hosts have sufficient binding affinity, binding selectivity, and biocompatibility to function as sequestrants even within complex *in vivo* settings.

Supramolecular design using multiple noncovalent interactions (Benjamin E. Partridge)

Many years ago, when I was an undergraduate student in my native United Kingdom, I attended my first ever conference: an RSC MASC meeting. Those meetings serve a special role for the UK supramolecular community by bringing together chemists once a year for a short, highly focused, and topical meeting. The lack of a similar style of meeting in the US had been a longstanding void for our community. Fortunately, NASC has filled this void and, as a first-time attendee this year, I was delighted to find that the organisers have established a similarly topical and collegial meeting on this side of the pond. It is especially exciting that NASC provides an accessible platform for chemists across career stages to share their science, with a particular emphasis on creating opportunities for early-career scientists to present their work. I look forward to seeing NASC grow from strength-to-strength in the coming years.

A recurring theme of the December 2023 meeting was understanding and leveraging multiple noncovalent interactions in a single system. Natural systems serve as the ultimate inspiration for achieving unprecedented structural control and elegant functionality using synergistic interactions: consider, for example, the plethora of intermolecular encounters that enable the function of the ribosome. To design synthetic systems that approach the structural and functional complexity of natural systems, it is necessary to understand how non-covalent interactions operate both in isolation and in concert. Supramolecular chemists have long excelled at addressing the former, by studying individual motifs and interaction types. During NASC 2023, we heard how this research continues apace with the latest advances in pnictogen and chalcogen bonding, molecular balances and rotors, and host-guest chemistry.

Excitingly, ever more attention is being paid to addressing the latter need, that is, understanding how to model and build systems with multiple competing interaction modes. The challenges are many: theoretical approaches must be developed to model competition

and inhibition between different binding modes; synthetic routes must be created to endow low-symmetry building blocks with multiple site-specific functional groups; and characterisation techniques must be advanced to allow full interrogation of increasingly sophisticated supramolecular structures. As was communicated by several speakers at NASC, there is much excitement and activity aimed at addressing these challenges, and with good reason: success could represent a paradigm shift in our ability to craft synthetic systems, enabling new materials that utilise noncovalent interactions with the same sophistication and precision as Nature.

Many questions still to be answered: fundamental studies in supramolecular chemistry (Ken D. Shimizu)

The study of non-covalent interactions, such as hydrogen bonds and dispersion forces, dates back to the late 19th and early 20th centuries. Pioneering work by chemists like Linus Pauling and Fritz London laid the groundwork for understanding these phenomena. Utilising hydrogen bonding, aromatic stacking, and ion-pairing has become a common practice in the design of new self-assembling systems, catalysts, and materials. The second NASC in New Orleans showcased numerous impressive demonstrations of these applications. However, the conference also featured many valuable fundamental studies on non-covalent interactions, which are the focus of this commentary.

Despite the significant contributions made by early researchers, our comprehension of non-covalent interactions and rules for self-assembly remains far from complete, and many important questions remain unanswered. Understanding the fundamental principles governing these interactions is crucial for tailoring their properties and enhancing their applications in various fields, including drug design, materials science, and nanotechnology. These examples underscored the importance of ongoing research and exploration into the intricacies of supramolecular chemistry. Presentations at NASC covered a wide array of fundamental topics and questions, ranging from deciphering the rules of molecular recognition in aqueous membrane environments to understanding the origins of non-covalent interactions. These fundamental topics in supramolecular chemistry included:

- Several presentations sought to unravel the basic rules for molecular recognition in water, in order to bind highly hydrophilic guests like carbohydrates and polyphosphates. These studies offer insights

into crucial biological processes occurring in aqueous environments.

- In a similar vein, several reports explored recognition phenomena in heterogeneous environments such as lipid membranes. These studies not only advance our understanding of membrane transport mechanisms but also hold promise for the development of targeted drug delivery systems.
- Another popular theme was the study of the origins and unique properties of relatively new non-covalent interactions such as chalcogen, pnictogen, and halogen bonding. These studies expand the toolkit for designing self-assembled structures and materials with unique properties and applications.
- Presenters discussed their studies focused on understanding the basic principles of self-assembly processes. These discussions aimed to clarify how discrete structures, like specific-sized rings or precisely folded flexible molecules, can be predictably formed.
- Multiple studies examined the principles and recognition patterns that favour the formation of discrete structures such as the construction of macrocycles of specific size and shape or the folding of flexible molecules into precise configurations.
- Several talks delved into the challenge of predicting the 3D crystalline structure of solids based on molecular interactions which are crucial for advancing materials science and tailoring condensed phase properties.
- Speakers also explored the strength, specificity, and origins of relatively noncovalent interactions involving sigma- and pi-holes, such as halogen, chalcogen, and pnictogen bonding, unveil new avenues for designing molecular recognition systems with enhanced selectivity and specificity.
- Presentations examined the challenges and rules for binding slippery perfluorinated molecules with potential applications in coatings, sensing, and environmental remediation.
- The interplay between chirality, structure, and selectivity was examined by several speakers, offering avenues for designing highly selective and efficient catalysts and sensors.
- Finally, the conference workshop focused on analytical methods to determine association constants consistently and accurately, which is fundamental to qualitatively assessing and optimising recognition systems.

From investigations into the basic rules of molecular recognition to pioneering explorations of novel non-

covalent interactions, the breadth of research at the second NASC meeting showcased the ingenuity and depth of inquiry within the supramolecular community. These fundamental studies not only underscored the importance of curiosity-driven research but also demonstrated its profound impact on shaping our understanding of the natural world, driving technological advancements, and addressing complex challenges facing society.

Better analysis, better binding constants (Douglas A. Vander Griend)

NASC 2023 continued to show how much the supramolecular community attends to binding constants. It began with a full-day workshop on quantifying binding constants with over 30 participants. Then over half of the presentations, both posters and talks, showed those capital K values: over arrows, in tables, and on graphs. And so it should be. Thermodynamic characterisation of the fascinating systems that researchers have created is key to further adapting the chemistry towards useful ends.

A binding constant is just a number, but it contains such profound insight into the balance of chemical forces that hold a multifaceted system in tension, ready to respond to its environment. And while we chemists have long succeeded in coming up with the numbers, there have also been many questions as to the reliability of those numbers as they are published, especially from within the supramolecular community.

Now that the Job's plot is dead, I judge that we have moved past the inflection point of a mini-revolution in quantifying binding constants. The optimal methodology for analysing data has been laid out and made available in programs like Sivvu.org and Supramolecular.org. It involves using all the spectroscopic data from a titration, not just one peak. No simplifying assumptions need to be made as to the presence of multiple species. Proper asymmetric uncertainty ranges can be readily calculated for each and every binding constant with bootstrapping. Replicate datasets can be correctly combined. And datasets with their best models can be readily shared with reviewers and readers so that we can benefit from the accountability necessary to make any science great.

The field of supramolecular chemistry has arrived at a place where we can quantify our binding constants with excellence and reliability to match the wonder and ingenuity of the chemical systems people study. In the reaction that takes high quality data and produces the best binding constants possible, let's drive K up into the thousands.

Controlling organic species in water using host-guest chemistry (Kejia Shi)

In the last two decades, macrocycles have found applications in solubilising and stabilising organic molecules in water. This is attributed to the energy differences between free guests and complexes. The supramolecular community has invested extensive efforts not only in studying energy changes upon complexation, but also in examining covalent bond formation and breaking related to supramolecular encapsulation. Beyond the complexation-induced pK_a shift of guest molecules, there is a fascinating exploration into how reversible chemical reactions are influenced and artificially regulated by host-guest chemistry. In a recent study by our group, we uncovered that host-guest interactions can significantly impact dynamic covalent chemistry. The kinetics and chemical equilibria of imine hydrolysis/formation undergo dramatic alterations in the presence of their complementary hosts in water. Consequently, this discovery allows for the manipulation of the association and dissociation between host and guest to regulate organic species in water. This outcome holds promise for the development of a triggering system, offering controlled drug release by releasing payloads in water.

Supramolecular chemistry and antibiotic development (Emmanuel O. Ojah)

The global crisis of antimicrobial resistance is debilitating because bacteria are indiscriminately evolving multifaceted resistance mechanisms to all known antibiotics. It is saddening that the mechanism of resistance has overwhelmed the development of new antibiotics, and investment in research and development of new antibiotics is diminishing. Mitigating antibiotic resistance requires an urgent multifaceted and multidisciplinary approach. Interestingly, supramolecular chemistry presents several non-covalent strategies with potential applications in the discovery and development of new antibiotic agents. The North American Supramolecular Chemistry (NASC) meeting has been established as an annual event to provide a web of opportunities for supramolecular chemists in North America. Reflecting on the 2022 and 2023 meetings, one could easily realise that students and early career scientists are the chief beneficiary of this meeting. The second North American Supramolecular Chemistry (NASC) meeting was a swift improved version of the maiden edition and unveiled the horoscope for a fast global participation in this annual event. The organisers of the conference did

a remarkable job in improving the inaugural event and spiced up the meeting with a fantastic hands-on workshop on modern techniques for determining binding constants. Determination of binding constants is a pivotal toolbox useful to both experimental and computational supramolecular chemists. The workshop did not only inculcate pragmatic ways of experimentally determining binding constants but also gave a guide on useful ways of reporting results of binding constants in a communally beneficial way. Generally, the NASC 2023 meeting gave several early career scientists the opportunity to learn, network and share diverse research repositories. As a drug discovery enthusiast, the 2023 NASC meeting created a great inspiration and reinvigoration to reflect on improved supramolecular strategies for developing antibacterial agents and combating the multi-antibiotic drug resistance crisis. A recommendation to the organisers as we anticipate the 2024 meeting is to design brainstorming seminars and symposia on supramolecular strategies for drug discovery and development. This would help to sharpen our vision for improving global public health and strengthen our research muscles to win the fight against antibiotic resistance.

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ORCID

Nathalie Busschaert  <http://orcid.org/0000-0002-3612-3382>

Clifton J. Stephenson  <http://orcid.org/0000-0001-6037-1370>

Kristin Bowman-James  <http://orcid.org/0000-0001-6329-5262>

Lyle Isaacs  <http://orcid.org/0000-0002-4079-332X>

Benjamin E. Partridge  <http://orcid.org/0000-0003-2359-1280>

Ken D. Shimizu  <http://orcid.org/0000-0002-0229-6541>

Douglas A. Vander Griend  <http://orcid.org/0000-0002-8828-1112>

Kejia Shi  <http://orcid.org/0000-0001-7313-2205>

Emmanuel O. Ojah  <http://orcid.org/0000-0001-6884-8102>