

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Isaacs, Lyle

eRA COMMONS USER NAME (credential, e.g., agency login): ISAACS

POSITION TITLE: Professor of Chemistry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Chicago	B.S.	06/1991	Chemistry
University of California, Los Angeles	M.S.	06/1992	Organic Chemistry
Swiss Federal Institute of Technology, Zurich	Ph.D.	08/1995	Organic Chemistry
Harvard University	Postdoc	06/1998	Supramolecular Chem.

A. Personal Statement

For his independent work at the University of Maryland, Lyle Isaacs is recognized as a world leader in the area of cucurbit[n]uril (CB[n]) molecular containers. The focus of this work has been manifold: 1) developing a thorough mechanistic understanding of the CB[n] forming reaction, 2) using this mechanistic understanding to create new members of the CB[n] family of molecular containers with exciting new structures, and 3) investigating their unique molecular recognition properties. For example, we have discovered the ultra tight affinity binding of CB[n] toward its best guests and used CB[n]-type receptors to regulate the enzymatic activity of bovine carbonic anhydrase, to perform homotropic allsteric binding, and to trigger the decloaking of cytotoxic nanoparticles in the cell. In more recent work, Isaacs and collaborators (Briken and Eikermann) have explored the use of acyclic CB[n] type molecular containers as: 1) a solubilizing excipient for insoluble drugs, and 2) as an *in vivo* reversal agent for neuromuscular block induced by rocuronium, vecuronium, and cis-atracurium. Acyclic CB[n] compounds (a.k.a. Calabadions) do not display toxicity in both *in vitro* and *in vivo* assays which sets the stage for their further development as reversal agents for diverse biomedical applications. Over the past five years, the Isaacs group has provided blind challenge data for SAMPL3, SAMPL4, and SAMPL5 by synthesizing cyclic and acyclic CB[n]-type receptors and measuring their binding properties toward appropriate guest molecules. We have found the SAMPL challenges to be scientifically stimulating, and our participation has led our work in new directions. Accordingly, Dr. Isaacs has both the scientific expertise and a high level of enthusiasm to serve as a co-investigator on this project.

B. Positions and Honors**Positions and Employment**

10/95 – 6/98	Harvard University, NIH postdoctoral fellow (with George M. Whitesides)
6/98 – 8/04	University of Maryland, Assistant Professor, Department of Chemistry and Biochemistry
8/04 – 8/08	University of Maryland, Associate Professor, Department of Chemistry and Biochemistry
8/08 – present	University of Maryland, Professor, Department of Chemistry and Biochemistry
7/10 – 6/13	University of Maryland, Director, Chemistry Graduate Program

8/12 – present Director, UMD Chemistry Graduate Assistance in Areas of National Needs (GAANN) Program

Other Experience and Professional Memberships

1991 – present Member, American Chemical Society
2001 – present Member, American Academy of Arts and Sciences
2005 – present Member, Maryland Nanocenter
2007 Organizer of the NSF Workshop on Cucurbit[n]uril Molecular Containers
2009 – present Member, International Advisory Board of the International Conference on Cucurbiturils
2009 – present Member of the Editorial Board of the Journal of Systems Chemistry
2010 – 2016 Member, International Advisory Board of the International Symposium on Macrocyclic and Supramolecular Chemistry
2013 Organizer of the International Symposium on Macrocyclic and Supramolecular Chemistry
2015 Local Co-Organizer, American Chemical Society, National Organic Symposium
2015 Co-organizer of the “Molecular Containers” symposium at Pacifichem 2015

Honors & Awards

U.S. Department of Defense Graduate Fellow (1991)
Silver Medallion Dissertation Award (ETH Zürich, 1996)
National Institutes of Health Postdoctoral Fellow (1996 – 1998)
National Science Foundation Career Award (2000 – 2004, declined)
Cottrell Scholar, Research Corporation (2001 – 2006)
Junior Faculty Award, College of Life Sciences, University of Maryland (2001)
Outstanding Invention of 2010 “*Molecular Container to Enhance Solubility of Drugs*” University of Maryland, Office of Technology Commercialization.
Elected Fellow, American Association for the Advancement of Science (2013)

C. Contribution to Science

Dr. Isaacs has made internationally recognized and highly cited contributions to science at all stages of his career development. Dr. Isaacs has published a total of 134 articles in peer reviewed journals. These publications have received over 8000 citations in the literature. Dr. Isaacs has an h-index of 47.

1. *Cucurbit[n]uril molecular container chemistry and recognition properties.* The Isaacs group is a world-leader in the area of cucurbit[n]uril molecular containers. Specifically, we are renowned for: 1) our investigation of the mechanism of CB[n] formation that allowed the creation of numerous new CB[n]-type receptors (e.g. chiral CB[n], acyclic CB[n], double cavity CB[n], chromophoric CB[n], monofunctionalized CB[n]), 2) our discovery of the remarkable affinity of CB[n] toward their guests in water (e.g. K_a up to 10^{17} M^{-1}), 3) the use of the recognition properties of CB[n] in diverse applications (e.g. homotropic allostery, chiral recognition, non-natural folding, chemical sensing, supramolecular polymers, drug delivery), and 4) our landmark review article that launched >100 groups to join the CB[n] field.

Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. The Cucurbit[n]uril Family. *Angew. Chem. Int. Ed.* **2005**, *44*, 4844-4870. (review article; cited 1158 times)

Rekharsky, M. V.; Mori, T.; Yang, C.; Ko, Y. H.; Selvapalam, N.; Kim, H.; Sobransingh, D.; Kaifer, A. E.; Liu, S.; Isaacs, L.; Chen, W.; Gilson, M. K.; Kim, K.; Inoue, Y. A synthetic host-guest system achieves avidin-biotin affinity by overcoming enthalpy-entropy compensation. *Proc. Natl. Acad. Sci.* **2007**, *104*, 20737-20742. (cited 248 times)

Huang, W.-H.; Zavalij, P. Y.; Isaacs, L. Cucurbit[n]uril Formation Proceeds by Step-Growth Cyclo-Oligomerization. *J. Am. Chem. Soc.* **2008**, *130*, 8446-8454. (cited 53 times)

Cao, L.; Hettiarachichi, G; Briken, V.; Isaacs, L. Cucurbit[7]uril Containers for Targeted Delivery of Oxaliplatin to Cancer Cells. *Angew. Chem. Int. Ed.* **2013**, *52*, 12033-12037. (cited 20 times)

2. *Biomedical Applications of Acyclic CB[n] Containers.* Dr. Isaacs research group used our mechanistic knowledge of CB[n] formation to create acyclic CB[n] containers that function well in two important biomedical application areas. First, a major problem facing the pharmaceutical industry is that many of their most promising promising drugs and drug candidates are so insoluble that they cannot be formulated on their own. Isaacs and Briken created acyclic CB[n] compounds that act as containers that solubilize and thereby formulate these drugs for in vitro and in vivo testing. Second, a major issue facing anesthesiologists is that residual neuromuscular block at the end of surgery results in patients having difficulty breathing which increases healthcare costs and mortality. Isaacs and Eikermann demonstrated that certain acyclic CB[n] compounds are able to sequester the neuromuscular blocking agent rocuronium from the bloodstream of rats and thereby allow them to regain their neuromuscular function rapidly. Acyclic CB[n] are under active development toward real world application.

Ma, D.; Hettiarachchi, G.; Nguyen, D.; Zhang, B.; Wittenberg, J. B.; Zavalij, P. Y.; Briken, V.; Isaacs, L. Acyclic Cucurbit[n]uril Molecular Containers Enhance the Solubility and Bioactivity of Poorly Soluble Pharmaceuticals. *Nat. Chem.* **2012**, 4, 503-510. (cited 82 times)

Ma, D.; Zhang, B.; Hoffmann, U.; Grosse Sundrup, M.; Eikermann, M.; Isaacs, L. Acyclic Cucurbit[n]uril Type Molecular Containers Bind Neuromuscular Blocking Agents in Vitro and Reverse Neuromuscular Block In Vivo. *Angew. Chem. Int. Ed.* **2012**, 51, 11358-11362. (cited 31 times)

Hoffmann, U.; Grosse-Sundrup, M.; Eikermann-Haerter, K.; Ayata, C.; Zhang, B.; Ma, D.; Isaacs, L.; Eikermann, M. Calabadiol, a new broad spectrum agent to reverse the effects of benzylisoquinoline and steroidal neuromuscular blocking agents. *Anesthesiology* **2013**, 119, 317-325. (cited 3 times)

Zhang, B.; Isaacs, L. Acyclic Cucurbit[n]uril-Type Molecular Containers: Influence of Aromatic Walls on their Function as Solubilizing Excipients for Insoluble Drugs. *J. Med. Chem.* **2014**, 57, 9554-9563. (cited 1 time)

3. *The conceptualization and demonstration of multi-component self sorting systems.* Researchers in the field of supramolecular chemistry take inspiration from Nature to create non-natural receptors that perform useful recognition, transport, or catalytic function. However, a widespread misconception was that supramolecular chemists synthetic systems were not as selective as natural systems and would be incapable of functioning in complex multicomponent mixtures. The Isaacs group shifted the viewpoint of the field in a series of papers that showed that mixtures of supramolecular receptors performed their functions faithfully even with complex mixtures. The work has been highly cited and has launched numerous research groups worldwide to start research programs on self-sorting systems.

Wu, A.; Isaacs, L. Self-Sorting: The Exception or the Rule? *J. Am. Chem. Soc.* **2003**, 125, 4831-4835. (cited 196 times)

Mukhopadhyay, P.; Wu, A.; Isaacs, L. Social Self-Sorting in Aqueous Solution. *J. Org. Chem.* **2004**, 69, 6157-6164. (cited 114 times)

Liu, S.-M.; Ruspic, C.; Mukhopadhyay, P.; Chakrabarti, S.; Zavalij, P.; Isaacs, L. The CB[n] Family: Prime Components for Self-Sorting Systems. *J. Am. Chem. Soc.* **2005**, 127, 15959-15967. (cited 358 times)

Mukhopadhyay, P.; Zavalij, P. Y.; Isaacs, L. High Fidelity Kinetic Self-Sorting in Multi-Component Systems Based on Guests with Multiple Binding Epitopes. *J. Am. Chem. Soc.* **2006**, 128, 14093-14102. (cited 111 times)

4. *Development of the tether directed remote functionalization approach to regioselectively multiply functionalize buckminsterfullerene (C₆₀).* My PhD dissertation with Prof. Francois Diederich focused on the functionalization of C₆₀ as a means to tune the properties of this important class of compounds for specific applications. In the early 1990s, a major challenge to the field was that C₆₀ features 30 reactive C=C double bonds and therefore numerous regioisomers can result when two or more groups are added to the carbon sphere. My research introduced the concept of tether directed remote functionalization to create bis, tris,

tetrakis, pentakis, and hexakis adducts of C60. The work stimulated significant follow up research in numerous labs worldwide.

Isaacs, L.; Haldimann, R. F.; Diederich, F. Tether-Directed Remote Functionalization of Buckminsterfullerene: Regiospecific Hexaadduct Formation. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2339-2342. (cited 140 times)

Isaacs, L.; Seiler, P.; Diederich, F. Solubilized Derivatives of C₁₉₅ and C₂₆₀: The First Members of a New Class of Carbon Allotropes C_{n(60+5)}. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1466-1469. (cited 76 times)

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/lyle.isaacs.1/bibliography/45414278/public/?sort=date&direction=ascending>

D. Research Support

Ongoing Research Support

CHE-1404911

Isaacs (PI)

09/01/14 – 08/31/18

National Science Foundation

"Synthesis and Application of Cucurbituril Type Receptors"

This project explores the preparation of cucurbituril-type receptors and exploitation of their molecular recognition properties including ultratight host-guest binding, peptide and protein recognition, and the use of immobilized cucurbituril type receptors in bioanalytical assays.

Role: PI. Dr. Isaacs is responsible for the conception of the projects, supervision of their execution, and their dissemination in the scientific literature.

1R01 CA168365-01A1

Isaacs (PI)

04/01/2013 – 03/31/2018

National Institutes of Health

“Acyclic Cucurbit[n]uril Molecular Containers for Drug Solubilization and Delivery”

Role: Isaacs (PI), Briken (co-PI). Dr. Isaacs is responsible for overseeing the design of new acyclic CB[n]-type receptors and investigation of their solubilization ability toward insoluble drugs as well as the administrative reporting and dissemination of the results in the literature.

P200A150033

Isaacs (PI)

09/01/2015 – 08/31/2018

Department of Education

“UMD Chemistry GAANN”

This grant provides funding to the Department of Chemistry and Biochemistry to support five students from the Chemistry graduate program as GAANN fellows each year.

Role: PI, Jeffery Davis and Herman Sintim (Co-PIs).