

Young Career Focus: Prof. Dr. Alexey Sukhorukov (N. D. Zelinsky Institute of Organic Chemistry, and D. Mendeleev University of Chemical Technology, Russian Federation)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Prof. Dr. Alexey Sukhorukov (N. D. Zelinsky Institute of Organic Chemistry, and D. Mendeleev University of Chemical Technology, Russian Federation).

Biographical Sketch



Prof. Dr. A. Sukhorukov

Alexey Sukhorukov received his M.Sc. from D. Mendeleev University of Chemical Technology (Russian Federation) in 2007 and his Ph.D. from the N. D. Zelinsky Institute of Organic Chemistry (Russian Federation) in 2009 with Professor Sema Ioffe. After working as a research associate and senior scientist, he defended his habilitation thesis on the CH-functionalization of nitrates in 2018. In 2020, he was promoted to a head of a newly created department (Laboratory of organic and metal-organic nitrogen-oxygen systems) at the same institute. He also holds the position of Full Professor at the Organic Chemistry Department of D. Mendeleev University of Chemical Technology (Russian Federation). Prof. Sukhorukov has been a recipient of several awards, including the Thieme Chemistry Journals Award (2021), The Moscow Government Award for Young Scientists (2019), and the Gold Medal of the Russian Academy of Sciences (2010). His research interests cover the chemistry of nitrogen-oxygen compounds, stereoselective synthesis of pharmaceutically relevant molecules, reaction mechanisms, and chemistry of diamondoid molecules.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. Dr. A. Sukhorukov My research activity is primarily focused on the chemistry of compounds having nitrogen-oxygen bonds (NO-compounds). I believe that the role of these compounds is underestimated, especially in organic synthesis, medicinal and coordination chemistry. Indeed, the history of chemistry gives us amazing examples, wherein NO-compounds have made a tremendous impact on the development of some critical spheres of human activity. I shall give two examples not from the military sphere to justify this. One is the introduction of synthetic fertilizers based on nitrates (produced via nitrogen fixation), the event that brought the agricultural industry to a substantially new level. Another example is the discovery of the role of nitric oxide as a signaling molecule in many physiological and pathological processes (Nobel Prize for Physiology and Medicine, 1998). This led to the development of nitric oxide donors as new-generation pharmaceuticals for the treatment of cardiovascular disorders.

Being incorporated into the organic framework, the nitrogen-oxygen linkage provides unique reactivity. The ease of the cleavage of the N-O bond can be exploited to construct more stable carbon-carbon and carbon-heteroatom bonds via umpolung and redox-neutral processes. This concept has been recognized only recently, and its synthetic potential is being actively explored.^{1,2} Our group is very much involved in the development of N-O cleavage-driven synthetic transformations, C-H functionalization processes in particular.^{3,4}

Another aspect of my interest in NO-compounds is their underestimated potential for medicinal chemistry. Until recently, heterocycles having exocyclic nitrogen-oxygen bonds were considered as rather exotic among natural products.

The situation changed in the early 2000s when numerous marine metabolites and alkaloids possessing an isoxazoline and 1,2-oxazine ring (five- and six-membered heterocycles with an exocyclic N–O bond) were isolated and shown to have promising physiological properties, in particular, anti-cancer and anti-inflammatory activities.^{5,6} This greatly stimulated research on the medicinal chemistry of NO-heterocycles. In the near future, the emergence of new scaffolds based on NO-heterocycles can be anticipated. I am proud that our team, together with our collaborators, is contributing to this field.

While my students are doing experiments, I spend time writing review articles, book chapters and highlights on topics related to our research. This helps me to expand my knowledge in chemistry, find synthetic challenges and get new ideas.

SYNFORM *When did you get interested in synthesis?*

Prof. Dr. A. Sukhorukov As a kid, I used to mix things at home pretending to be a chemist. During school times, I had a small chemistry lab at home. I got a book called “*Experiments without Explosions*”, which contained many exciting experiments to be done safely at home. While my friends were playing football, I used to wash test-tubes, preparing for the next experiment. When studying in high school at Moscow Chemical Lyceum, I got a strong interest in organic chemistry intrigued by the ability of artificial organic synthesis to create complex molecules derived from nature. At university I used to read “*Classics in Total Synthesis*” by Professor K. C. Nicolaou,⁷ the book which strengthened my desire to become an organic chemist. At that time, I didn’t realize how difficult it is to do target-oriented multistep synthesis, especially when you do it with your own hands. So difficult, but so exciting!

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. Dr. A. Sukhorukov The primary role of organic synthesis is to prepare molecules of the target structure in the most efficient and least time-consuming manner. In this sense, I always considered organic chemists as a sort of molecular architect. However, the way we assemble molecules is far from what I would call ideal. We do multi-step synthetic sequences, produce lots of side- and by-products, and waste litres of toxic organic solvents for compound isolation/purification, to end up with only a few milligrams of target compound from 10 grams of starting material. In comparison, Nature assembles molecules much more efficiently through biocatalysis and self-assembly routes. That is why catalytic cascade reactions, click chemistry and bioinspired syntheses are the key topics for the future development of organic synthesis.

Looking towards the future, I believe scientists will create a sort of a molecular 3D printer, a machine, which will do the job for synthetic chemists. Although some attempts are being made in this direction,⁸ automated organic synthesis in a general sense is still science fiction. But even if such a machine is created, this does not mean that there will be nothing more to investigate in organic chemistry.

Thus, I anticipate that the way we do organic synthesis will dramatically change in the future. And I wish our research will contribute to the development of practical syntheses.

SYNFORM *Could you tell us more about your group’s areas of research and your aims?*

Prof. Dr. A. Sukhorukov Our laboratory has broad research interests that focus on the chemistry of nitrogen–oxygen compounds (major research topics are shown in Figure 1). We are particularly keen on studying the reactivity of NO-compounds (nitro derivatives, oximes, NO-heterocycles, etc.), development of new synthetic methods, total synthesis of bioactive molecules, and finding new applications for NO-compounds in the fields of medicinal chemistry, click reactions, domino-transformations and coordination chemistry. Our team is also interested in studying reaction mechanisms using combined techniques including detection/isolation of chemical intermediates, DFT calculations and *operando* spectroscopy.

In the last ten years, we have developed a set of methods for the umpolung C–H functionalization of nitronates based on pericyclic processes, transition-metal-promoted reactions and nitrosoalkene chemistry (Figure 1, a). The driving force of these reactions is the cleavage of the weak N–O linkage, which provokes the formation of new carbon–heteroatom bonds. This methodology was efficiently applied as a key stage in the asymmetric total synthesis of several natural products and drug candidates (Figure 1, b). Moreover, our synthetic approach provides access to libraries of polysubstituted NO-heterocycles (1,2-oxazines, isoxazolines, isoxazoles), among which some compounds with promising pharmaceutical profiles were identified (Figure 1, c).

Another topic of our research is the chemistry of diamondoid molecules, in particular adamantanes and diamantanes doped with multiple heteroatoms (Figure 1, d). Despite their chemical beauty, these highly symmetrical structures are of interest from both fundamental and practical perspectives. Adamantane-like structures are usually expected to be very stable. However, this is not always true, and for reasons that are not completely understood, not all combinations of heteroatoms in the adamantane cage result in stable structures. Moreover, the synthesis of new heteroadamantanes is always tricky. From my experience, a reasonable route

suggested on the basis of a retrosynthetic analysis would definitely not work here. But if you are lucky, you'll find a self-assembly synthesis, which is absolutely unexpected from the first glance. In our lab, we design such self-assembly approaches to heteroadamantanes of hitherto unknown types, study their structure using experimental and computational methods, and try to find useful applications for these molecules in cooperation with our collaborators.

SYNFORM What is your most important scientific achievement to date and why?

Prof. Dr. A. Sukhorukov Probably, my most significant achievement to date is the synthesis of 1,4,6,10-tetraazaadamantane ('isourotropin' or TAAD).⁹ This highly symmetrical

diamondoid molecule is the first isomer of hexamine (urotropin) synthesized since the discovery of the latter by the Russian chemist Alexander Butlerov in 1859.¹⁰ Hexamine is a unique molecule both from structural and application points of view. I can mention that it is the oldest applied synthetic pharmaceutical, and the first organic compound for which X-ray diffraction analysis was performed. I believe 'isourotropin' and its derivatives will also find interesting applications in chemistry and related fields. Thus, we have shown that the incorporation of the 'isourotropin' motif into lipophilic biomolecules enhances their water solubility. We also developed a controllable click-declick methodology based on the coupling of boronic acids with quaternary derivatives of 'isourotropin'.¹¹ This technique is already being used by other researchers to construct click conjugates.¹² Coordination

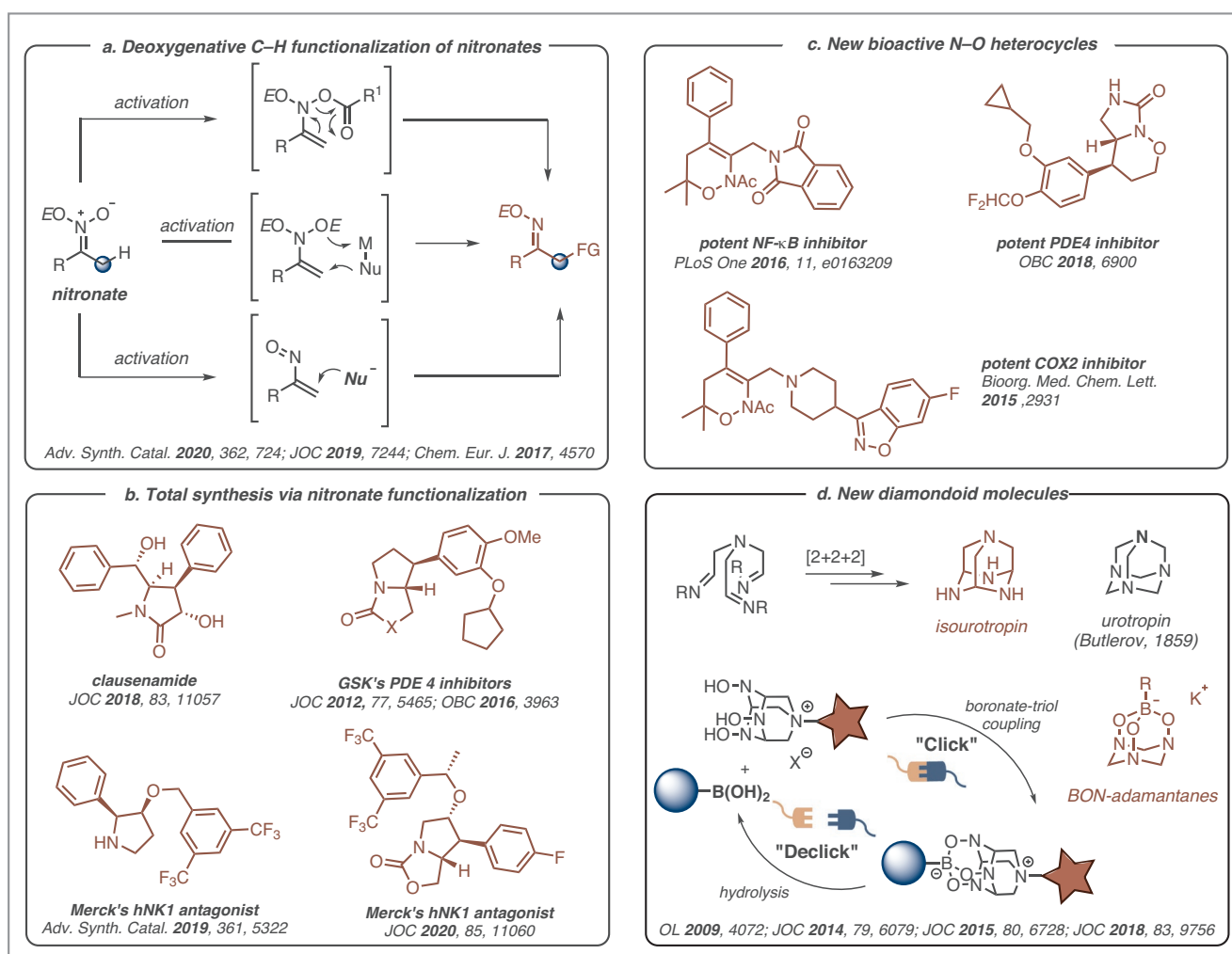


Figure 1 Overview of research areas pursued in the Sukhorukov lab

chemistry of 'isourotropin' derivatives is actively explored by inorganic chemists from the University of Idaho and the University of Marburg.¹³ Finally, our colleagues recently have shown that 1,4,6,10-tetraazaadamantane derivatives enhance the thermal and photochemical stability of perovskite films.¹⁴ I am sure we will see other examples in near future.



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