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EDITORIAL



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Aggregation of Small Molecules: From Dimers to Crystals

Gautam R. Desiraju,^{*,[a]} Mark A. Johnson,^{*,[b]} and Wolfram Sander^{*,[c]}

The aggregation of molecules through non-covalent interactions to form larger structures is a process of fundamental importance to many aspects of chemistry, such as the formation of molecular crystals, the solvation of molecules, and the formation of three-dimensional structures of proteins and other biomolecules. Crystal structure prediction from first principles is still a "holy grail" in physical science. Many molecules crystallize in polymorphic structures, which means that the thermodynamically most stable structure is not necessarily the structure that is formed under specific conditions. Rather, crystallization can be driven kinetically, resulting in metastable crystals. Some adherence to kinetically controlled processes in crystallization is manifest in the robustness of supramolecular syntheses, for example in crystal engineering.

For the success of organic synthesis, a profound understanding of kinetic control in the breaking and forming of covalent bonds is mandatory, and it is taught even in elementary textbooks of organic chemistry. In contrast, chemical pathways in-

volving the formation of non-covalent bonds are poorly understood, and in particular kinetically controlled processes are difficult or even impossible to predict. The origin of these problems is the lack of knowledge on the mechanisms for non-covalent reactions. Mechanisms at least require the characterization of stationary points in the potential energy landscape such as the structures and energies of intermediates and transition states. This information then provides a basis for investigation of the dynamics of the system. Why is that easier to achieve for reactions involving covalent bonds? Non-covalent bonds are softer and both structurally and energetically less well-defined than their covalent analogues. Small changes in the geometry of a weakly bound aggregate barely affect the energy of the system, which leads to a multitude of energetically almost degenerate structures that rapidly interconvert even at low temperatures. The small energy changes involved in aggregation also mean that the process of assembling molecules may be accompanied by disassembling, with the result that a smaller cluster is not necessarily a good model for

a larger cluster. There might be dead-ends in the assembly process that lead to the exploration of alternative routes by the system. Such discontinuities continue to pose problems in operational crystal engineering because it is more difficult in such cases to use small synthons in the design strategy for new crystals. One is necessarily obliged to employ larger and more complex synthons, with the resultant difficulties that

Gautam R. Desiraju joined the Indian Institute of Science in 2009. Prior to this he was in the University of Hyderabad for 30 years. He is currently the President of the International Union of Crystallography. He has been closely associated with the subject of crystal engineering and the structural aspects of the weak hydrogen bond for many years and has played a major role in the development and growth of these subjects. He is a member of the International Editorial Advisory Boards of *Angewandte Chemie* and the *Journal of the American Chemical Society*.



Mark A. Johnson received his B.S. in Chemistry from the University of California at Berkeley in 1977 and his Ph.D. from Stanford University in 1983 in the laboratories of Richard N. Zare and the Laboratoire de Photophysique Moleculaire in Orsay, France with Joelle Rostas. He then carried out post-doctoral studies with W. C. Lineberger at J.I.L.A and the University of Colorado at Boulder, where he interfaced mass spectrometers with supersonic jet ion sources and pulsed lasers. He started at Yale University in 1985, where he has moved through the ranks and is now Arthur T. Kemp Professor of Chemistry, and continues to be fascinated by the way solvents control the nature of electrolytes at the molecular level.



Wolfram Sander is a Professor of Organic Chemistry at the Ruhr-Universität Bochum (RUB). He obtained his Ph.D. from the University of Heidelberg in 1982 and was a postdoctoral fellow at UCLA with O. L. Chapman from 1982–84. He was Associate Professor at the Technische Universität Braunschweig from 1990–1992 before accepting his present position in 1992. His main research interest in the field of physical organic chemistry is the investigation of reactive intermediates, organic high-spin molecules, and non-covalently bound species using a variety of experimental and computational techniques.



such a methodology entails. To characterize these transient structures in the molecular assembly process, either ultrafast spectroscopy has to be used, or the aggregates have to be immobilized at extremely low temperatures. Likewise, the theoretical description of weakly bound, highly dynamical aggregates is a difficult task since dispersion might play a major role, and the localization of multiple minima on flat potential energy surfaces is highly challenging.

All of this has been recognized for many years, but it is only now that experimental and theoretical tools are available to gain the detailed insight necessary for an understanding of aggregation processes at the molecular level. To exploit this opportunity, the DFG-funded (DFG: Deutsche Forschungsgemeinschaft) Research Unit 618 “Understanding the Aggregation of Small Molecules Using Precise Methods—Interplay between Experiment and Theory” came into being. Between 2006 and 2012, a team of seven research groups located at several German universities started a close collaboration on various aspects of aggregation. In a concluding international symposium in May 2012, researchers from all over the world presented exciting results on many aspects of aggregation, obtained by using state-of-the-art experimental and theoretical methods. This special issue of *ChemPhysChem* presents some of these results, but also contributions from many other leading groups in the field.

It is fascinating to see how the complex process of aggregation is tackled by sophisticated techniques. Two contributions describe spectroscopy of weakly bound aggregates in ultracold (0.37 K) helium nanodroplets. Under these conditions, the diffusion and rotation of trapped molecules is almost barrierless, which allows the authors to observe the very first steps of aggregation controlled by long-range dipole interactions. To describe aggregation processes in the absence of any thermal activation, subtle quantum effects have to be taken into account to understand the formation of low-barrier hydrogen bonds, described in a theoretical paper. Since the ground-breaking work of George Pimentel more than 50 years ago, matrix isolation spectroscopy has been established as a workhorse technique for the spectroscopic identification of van der Waals complexes and hydrogen-bonded aggregates. This is elucidated in several contributions that demonstrate how far this technique has been developed. The combination of spectroscopy, electronic structure theory, and dynamic calculations has proven to be a powerful way to unravel the complex processes proceeding not only at ground electronic states, but also photodissociation processes by including nonadiabatic dynamics. Yet another technique employed to understand aggregation is molecular beam spectroscopy, which bridges the gap between the gas phase and the solid state by generating ever-larger aggregates in a regime where every molecule counts. Identifying building blocks of cocrystals by structurally characterizing molecular aggregates under molecular beam conditions is an important step towards understanding the formation of macroscopic crystals. How subtle, small structural variations might influence the architecture of a macroscopic crystal is impressively

demonstrated by showing the influence of deuteration on crystal packing. Perhaps the most striking aspect of most of these contributions is how tight the interplay between experiment and theory has become in this area. There is virtually no contribution from experimental groups without a very strong theoretical foundation, and all theoretical contributions are a direct offspring from collaborations with experimentalists. Spanning wide scales of temperature, time resolution and conditions, the fusion of experimental and theoretical methods paves the way for a molecular understanding of aggregation. We are not quite there yet, but we are coming closer.

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- [a] *Prof. Dr. G. R. Desiraju*
Solid State and Structural Chemistry Unit
Indian Institute of Science
C. V. Raman Avenue, 560012 Bangalore (India)
E-mail: gautam_desiraju@yahoo.com
- [b] *Prof. Dr. M. A. Johnson*
Department of Chemistry, Yale University
New Haven, CT 06520-8107 (USA)
E-mail: mark.johnson@yale.edu
- [c] *Prof. Dr. W. Sander*
Lehrstuhl für Organische Chemie II
Ruhr-Universität Bochum, D-44801 Bochum (Germany)
E-mail: wolfram.sander@rub.de