Supramolecular Science
Where it is and where it is going

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A retrospective analysis of the last 30 years of research activity in chemistry and related disciplines leads us to the conclusion that the emergence of **supramolecular science** has produced an explosive outburst of creativity and expression on the part of many scientists (Figure 1). Their accomplishments have already had a profound effect upon the development of contemporary scientific thought and practice. In directing the focus very much toward the noncovalent bond, the supramolecular approach has allowed scientists not only to create some quite remarkable molecules and supermolecules of incommensurable beauty, but also to look at relatively old phenomena, like clathrate formation and liquid crystallinity, in a new light and from a different perspective.

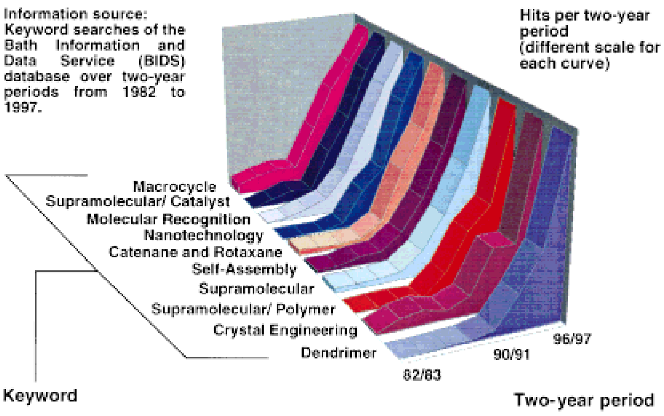

Figure 1. A collection of graphs illustrating the relative growth within each area for ten new research areas in chemistry. Each graph shows the percentage of hits in the indicated (keyword) research areas over two-year periods between 1982 and 1997, taking the period 96/97 as 100% in each case. The total number of hits in the period from 1982 to 1997 from Macrocycle through to Dendrimer were, in order, 4338, 215, 3219, 201, 425, 3181, 2774, 512, 194, and 887.

Approaches to **chemical synthesis and catalysis** have been fundamentally affected by the new type of thinking, which has given rise to the supramolecular synthesis (noncovalent synthesis) of both supermolecules and supramolecular arrays, as well as assisting in the synthesis (self-assembly with covalent modification) of a wide range of molecular receptors, often with prescribed and selective molecular recognition properties. Selective recognition has also been achieved in the transition states of chemical reactions with consequent implications for both asymmetric synthesis and catalysis. Supramolecular catalysis has been influenced greatly by biomimetic design principles and by molecular modeling. This important area will continue to be increasingly influenced by combinatorial practices in synthesis and computational approaches to the design of catalysts and the rationalization of their mechanism of action. The spontaneous self-assembly of complementary components has produced molecules and supermolecules of nanoscale dimensions with a wide range of different architectures, including some that resemble boxes, grids, rods, squares, and tubes, not to mention fractal–type displays and rings interlocked with each other and with dumbbell-shaped components.

In the realm of **materials science**, the influence of supramolecular chemistry has been enormous. There are hopeful signs that the kinetic process of crystal growth can be controlled and even engineered by appealing to weak noncovalent bonding interactions between strategically located donors and acceptors in molecules and ions. Surface and interfacial phenomena are being studied and understood increasingly in the context of supramolecular concepts. Dendrimers are providing the perfect haven for the design

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and synthesis of macromolecules (polymers) with functional features. The rapid growth in the construction of wires, switches, and logic gates on a molecular scale augurs well for the fabrication of macroscopic devices with information processing and storage capabilities built on uniquely small scales. Nanoscience is a reality. The challenge that now has to be met is to harness this nanoscience at a nanotechnological level.

In the area of the **life sciences**, chemists have used supramolecular concepts to understand the mode of action of enzymes, to synthesize DNA intercalators, and to develop new diagnostic and therapeutic agents. The study of the aggregation of lipids and other self-organizing molecules has shed light on the mechanism of membrane formation. Artificial nanotubes have been produced which alter the extent and rate of transport of ions and other biologically relevant entities across membranes. Autocatalytic processes, in which a reaction product acts as the catalyst for its own synthesis, has brought molecular self-replication onto the chemists' agenda, with all the implications it has for the origin of life. Complex molecular ecosystems, in which highly interactive and interdependent molecular species can display properties far beyond those of the sum of the species, are already being touted in the scientific community.

Since December 1991, the **Scientific Affairs Divison of NATO** has generously funded a **Special Programme on Supramolecular Chemistry** and, in so doing, has helped to accelerate the growth of supramolecular science. The Programme has undoubtedly contributed to what will surely be regarded by historians of science as a golden age in chemistry when creativity came to the fore in large measure. Aside from providing 93 Collaborative Research Grants to scientists in at least 17 different countries (Figure 2), it has nurtured 23 Advanced Research Workshops, 20 Research and Lecture Visits, and one Advanced Study Institute. At the beginning of September, more than 100 leading supramolecular scientists, at all stages in their research careers, will descend upon Lerici in Italy for four days to celebrate the success of the Special Programme with a fitting finale that will be forward-looking in substance and spirit. To mark the occasion, five eminent researchers, who are right at the forefront of the field, have been invited to write **Concept Articles** on areas of supramolecular science in which their contributions have been seminal. Let us introduce these articles to you.

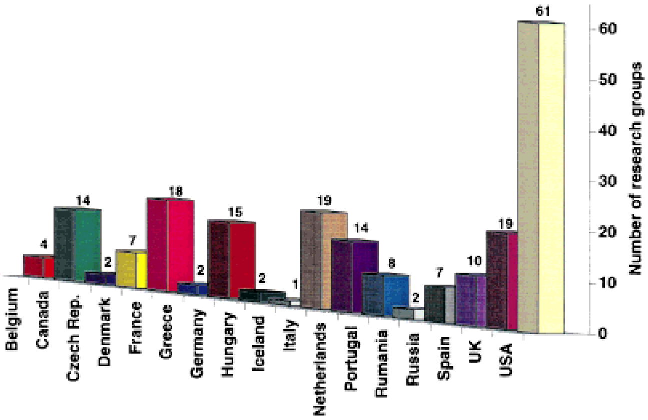

Figure 1. Histogram summarizing the number of research groups in 17 different countries that have participated in the 93 Collaborative Research Grants funded by NATO under their Special Programme on Supramolecular Chemistry in the period 1992 to 1998.

Diederich and Smith[1] highlight, in an authoritative and wide-ranging sweep of the contemporary literature, how functional dendrimers have been fashioned to exhibit some of the characteristics and properties of nature's large biomolecules. The processes they focus on include molecular recognition and catalysis, as well as energy and electron transfer. Their treatment draws attention to the three constitutionally different regions of dendritic (super)structures—namely, their central cores, their branching regions, and their external shells—and how these distinct regions have been utilized and exploited as the sites in which to locate functioning entities and reporter units in dendrimers. They look to the future in optimistic vein and see an increasing emphasis on much more highly designed molecular structures containing recognition units and the potential for self-assembled superstructures to express functions that are additional to those found in the individual molecular and supramolecular building blocks. Containing a mechanical bond, [2]rotaxanes (molecules comprised of a cyclic component threaded onto a dumbbell-shaped one) provide yet another distinct and unique structural environment to investigate supramolecular phenomena within a molecular domain. In their survey of transition metal-containing rotaxanes, Chambron and Sauvage[2] illustrate how these intriguing molecules allow nondissociative translational motions of extremely large amplitudes to be effected by stimuli that are either photonic, electronic, or chemical in nature. They trace the progress—much of it made in their own research laboratories—from controlled molecular motions to electron transfer between chemically nonconnected chromophores. This essay is a tribute to the methods of template-directed synthesis of interlocked molecular compounds that have added considerably to the repertoire of synthetic chemists during the last 15 years. One feels that this is a field which is very much still in its infancy and that there is a lot to be done beyond catenanes, rotaxanes, and knots.

Against the backcloth of a comprehensive coverage of nanotubular arrays, Ghadiri et al.[3] focus on assemblies based on cyclic DL-α-peptides and cyclic β-peptides, while noting that the virtues of structures with mixed α- and β-amino acids await detailed investigation. They describe how the outside surface properties of peptide nanotubes can be influenced by the choice of substituents and how the internal diameters can be controlled by the numbers of amino acids present in the cyclic structures. While eight-residue cyclic DL-α-peptides do well at mediating sodium and potassium ion transport through lipid membranes, a cyclic decapeptide possessing a 10 Å internal diameter can transport glucose. Drug delivery systems beckon with even larger arrays, as do numerous catalytic and materials science applications.

The last two articles both anticipate the emergence of hosts that self-assemble themselves around guests that are templates or transition state analogues, with real and effective catalysis one of the prizes to be won. A revealing survey of the use of calixarenes and resorcinarenes (cavitands), lined around their upper rims with either interdigitating ureas (as well as other appropriately curved building blocks lined with complementary hydrogen-bond donors/acceptors used in the construction of supramolecular capsules) is provided in a characteristically clear and succinct manner by de Mendoza.[4] He draws attention to the need to now start lining the inner surface of significantly large capsules with noncovalent bonds that are directed inwards. In his exquisite essay, Sanders[5] poses a not unreasonable question, despite some modest accomplishment in the design and synthesis of enzyme analogues that preside over reactions involving 1) transformations, 2) fissions, 3) fusions, and 4) transfers: why are there so few enzyme analogues and why is catalysis so elusive? He puts in a well-reasoned plea for introducing more flexibility into preorganized systems and suggests that a combinatorial approach to self-assembling catalysts around suitable transition-state analogues using thermodynamically controlled reactions might be the best way to identify leads that could subsequently be optimized by appropriate synthetic modifications. In coming to terms with the intellectually stimulating appraisal and daring new agenda advanced and advocated by Sanders, one is reminded of the dictum that has been attributed to the late Noel Coward: The secret of success is the capacity to survive failure.

In three decades, supramolecular scientists have moved progressively from the investigation of molecular recognition as an end in itself to the exploitation of molecular recognition with specific goals in mind. We have learnt the lesson the hard way that it is a very long haul from fanciful concepts to real applications. Now, however, that applications are in sight at long last, we can look back with some considerable satisfaction on a journey and an experience that has always been pleasurable and stimulating, and, above all, has provided us with endless intellectual challenges and rewards. On behalf of everyone who has been a beneficiary of this Special Programme, we would like to thank the Scientific Affairs Division of NATO most warmly.

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[1] D. K. Smith, F. Diederich, *Chem. Eur. J.* **1998**, *4*, 1353–1361.

[2] J.-C. Chambron, J.-P. Sauvage, *Chem. Eur. J.* **1998**, *4*, 1362–1366.

[3] J. Hartgerink, T. D. Clark, M. R. Ghadiri, *Chem. Eur. J.* **1998**, *4*, 1367–1372.

[4] J. de Mendoza, *Chem. Eur. J.* **1998**, *4*, 1373–1377.

[5] J. K. M. Sanders, *Chem. Eur. J.* **1998**, *4*, 1378–1383.