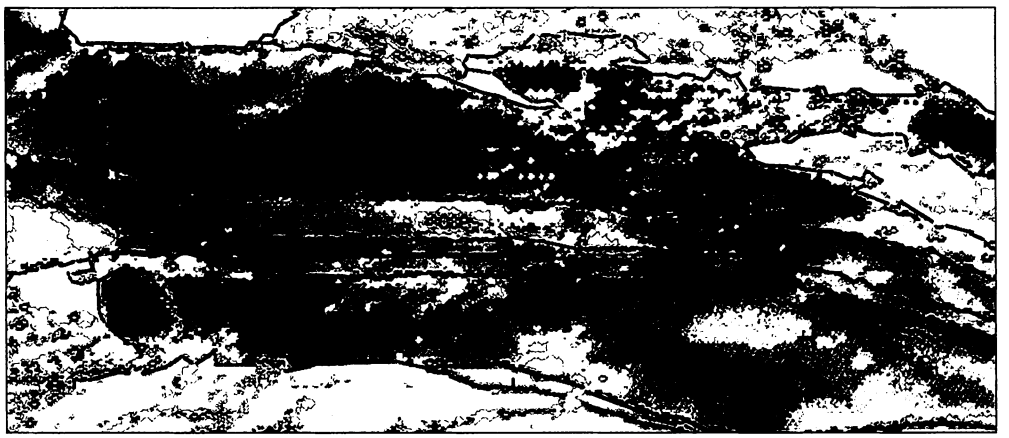


Complex orientation pattern. Orientation gradients (shades of green) inside a single copper grain (outlined by thick black lines) are induced by rotation and bending of the crystal lattice as a result of dislocation movement and pile-up during deformation. The process leading to this complex structure can now be followed directly with the method of Margulies *et al.* (*1*). The orientation map was produced by electron backscattering diffraction in a scanning electron microscope with a spatial resolution of 1 μm. The width of the map is 175 μm, and the spread of orientations is about 15°. [Adapted from (*8*)]

but these conditions are rarely fulfilled in real materials. More recent theories such as the self-consistent model (*5*) may yield more realistic predictions for texture development but are hampered by the problem that very similar final textures may be produced under wide ranges of model parameters. Tracking orientation changes of single grains inside a polycrystal directly during deformation therefore represents an important step toward understanding the deformation behavior of polycrystals and developing new and better models.

To date, orientation changes on the scale of a single grain have mostly been studied with electron microscopy, operating either in transmission (*6*) or in scanning mode (*7*). In both cases, analyses are restricted to two-dimensional sections bound by at least one free surface. Hence, orientation development of single grains in the bulk material can only be measured after the deformation process. A typical example is shown in the figure, which displays the curvature and distortion of the crystal lattice in a single copper grain after deformation (*8*). The continuous wavelike orientation gradient is caused by the accumulation of dislocations in the crystal lattice, illustrating the complex interactions between external stresses and grain deformation.

The orientation before deformation of the grain shown in the figure is not known, and, hence, its rotation path cannot be reconstructed by electron microscopy. The synchrotron-based approach of Margulies *et al.* (*1*) allows this rotation path to be tracked starting from the undeformed material. The method uses the penetration depth of a focused high-energy x-ray beam to monitor the orientation changes of lattice reflections from single grains within a deforming polycrystal. By analyzing the width of the reflections, it furthermore allows the spread of orientations resulting from the deformation within one grain to be determined. The rotation path can be compared directly with predictions from polycrystal plasticity theory, enabling the deformation behavior to be understood in detail.

The method demonstrated by Margulies *et al.* makes it possible to map orientations and their dynamic change in three dimensions, opening the opportunity to comprehend the deformation process in space as well as in time. With the rapidly increasing number of synchrotron facilities around the world, this pioneering approach should become widely applied in the future, leading to a better understanding and visualization of the complex processes in polycrystal plasticity.

References and Notes

1. L. Margulies, G. Winther, H. F. Poulsen, *Science* **291**, 2392 (2001).
2. U. F. Kocks *et al.*, *Texture and Anisotropy* (Cambridge Univ. Press, Cambridge, 1998).
3. G. Sachs, *Z. Ver. Deut. Ing.* **12**, 134 (1928).
4. G. I. Taylor, *J. Inst. Met.* **62**, 307 (1938).
5. A. Molinari *et al.*, *Acta Metall.* **35**, 2983 (1987).
6. A. Berger *et al.*, *Prog. Mat. Sci.* **32**, 1 (1988).
7. B. L. Adams *et al.*, *Metall. Trans.* **24A**, 819 (1993).
8. S. I. Wright, F. Heidelbach, *Mat. Sci. For.* **157**, 1313 (1993).

PERSPECTIVES: CHEMISTRY

Dynamic Combinatorial Chemistry

Jean-Marie Lehn and Alexey V. Eliseev

Combinatorial chemistry is now widely used to generate vast libraries of molecules that can be screened for biologically active substances and new materials. In a parallel development, self-assembly processes directed by molecular recognition are investigated in supramolecular chemistry. By merging features of both areas, dynamic combinatorial chemistry (DCC) offers access to a wide range of substances assembled from relatively small libraries, without the need to synthesize each substance individually. Although formulated only recently, this approach is already showing success in the search for compounds binding to specific biological and nonbiological targets.

DCC uses mixtures (libraries) of constituents that interconvert in dynamic equilibrium. The constituents are assemblies of components connected through reversible reactions or interactions; the whole set of possible self-assembled constituents forms a virtual combinatorial library. When a molecular target such as a biopolymer or a small molecule is added, some library constituents bind to it selectively and are removed from the pool of interconverting compounds. The equilibrium then shifts, amplifying the good binders and minimizing the concentration of poor binders in the library. The method thus enables the discovery of individual compounds or noncovalent assemblies that recognize small molecules or biopolymers.

DCC was conceptualized and implemented only recently in various chemical systems [see recent reviews (*1–4*)], although some characteristic features may have been implicitly present in earlier studies. Initial investigations focused on proofs of principle and on methodological procedures that established, for example, which reversible chemical transformations

J.-M. Lehn is at ISIS, University Louis Pasteur, 67000 Strasbourg, France. E-mail: lehn@chimie.u-strasbg.fr
A. V. Eliseev is at Therascope AG, Hans-Bunte-Strasse 20, 69123 Heidelberg, Germany.

can be used to generate dynamic libraries. More recently, DCC has been applied to a variety of targets, among which the biological ones are the most demanding.

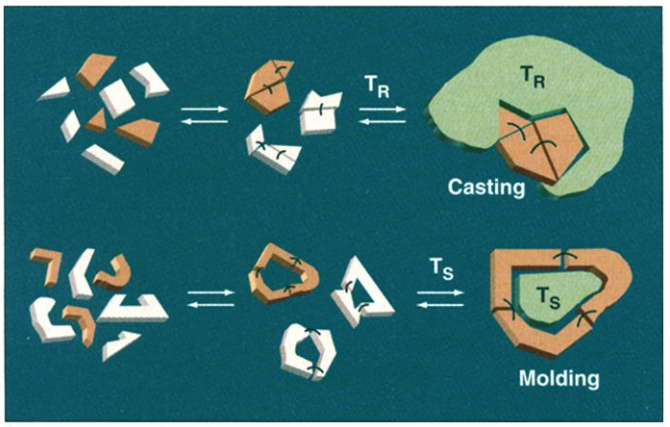
Small molecular targets may be recognized by "molding" (see the figure) (*3*), in which a receptor is formed by assembly of two or more binding moieties around the target. Such an entity containing zinc porphyrin units has been selectively amplified by interaction with a heteroaromatic target displaying zinc-binding pyridine groups (*5*). Dynamic libraries of self-assembling hydrogen-bonding capsules (*6*) and of covalent pseudopeptide macrocycles (*7*) have shown amplification of those receptors that have the best shape and electronic complementarity to tetraalkylammonium ions in chlorinated organic solvents. Similarly, the building block of a library of macrocycles was amplified through its recognition by a macrocyclic polyether (*8*).

Combinatorial chemistry has been driven mainly by applications in drug discovery, and in the long term, many DCC studies also aim for biomedical targets. Because DCC libraries "evolve" in the presence of the target, they must be compatible with aqueous solutions when "casting" a substrate for a biopolymer active site (see the figure). In one recent study, a dynamic library of disaccharides linked by a disulfide bridge was scrambled through sulfide exchange of the building blocks in the presence of the carbohydrate-binding protein concanavalin A. Equilibration led to preferential formation of the bis-mannoside constituent, which showed highest affinity for the protein (*9*). Another study investigated the dimerization of vancomycin, which may be a viable way to overcome bacterial drug resistance. Dimers connected by linkers containing disulfide or internal alkene groups were generated, and the library members were scrambled in the presence of the target by disulfide exchange or alkene metathesis. The equilibrium was thus shifted toward the strongly binding constituents that also displayed the highest antibacterial activity in an independent assay (*10*).

If the conditions of dynamic library generation are incompatible with the target, the use of preequilibrated libraries rather than fully dynamic ones may be required (*9*). For biological targets available only in very small amounts, target molecules may have to be immobilized (*9*). Alternatively, active compounds may be identified by combining an enzymatic reaction with a dynamic deconvolution procedure. This has been demonstrated for the generation of acetylcholinestarase inhibitors (*11*).

The dynamic libraries discussed so far are limited to a single type of connecting reaction between components. Much higher diversity may be achieved by procedures based on the simultaneous operation of two or more reversible interconversion processes, such as metal ion coordination and imine formation (*12*).

The difference in substrate-binding ability of isomers may be exploited in dynamic libraries of interconverting isomers.



Molding and casting processes in dynamic combinatorial libraries. Dynamic self-adaptation of reversible libraries driven by receptor (T_R) and substrate (T_S) target molecules. The increase in size of the selected components (red) reflects amplification/expression of the specific combination making up the preferred target-binding library constituent. The hooks represent the reversible connections between the building blocks.

For example, addition of barbiturate as a target drives a complex mixture toward a single bis-hydrazone receptor (*13*) and a large library of folding isomers toward a specific folded form of a linear molecule (*14*). This process is of special importance for biopolymers where different foldamers may have very specific substrate-binding properties. Other intramolecular processes such as tautomerism may also generate dynamic diversity (*15*). Dynamic metal ion coordination has been used successfully for efficient self- and heterorecognition in the guest-controlled assembly of inorganic cage receptors (*16*).

The relative degree of amplification in dynamic libraries depends on the difference in target affinity among the library components. A theoretical analysis of a dynamic library of polymeric chains with a given continuous distribution of target affinity has indicated that the amplification in such a system is limited to about two orders of magnitude and decreases with increasing target saturation (*17*). Efficient discovery procedures through DCC therefore require dynamic libraries with high functional diversity and distinctly different projected affinity to the target.

As noted earlier (*3*), the DCC approach also has potential in other areas, particularly materials science. Supramolecular materials are naturally dynamic owing to the reversibility of the connections linking their components. This allows incorporation or extrusion of novel components and the shuffling of those already present, thus conferring combinatorial ability. This is the case in particular for supramolecular polymers (*18*), where the monomers are linked by noncovalent interactions such as hydrogen bonds or metal ion coordination. Supramolecular materials are thus dynamic combinatorial materials and lead the way to novel adaptive materials (*19*).

DCC has been developing rapidly and may become an efficient tool in areas from drug discovery to material science, where new molecular and supramolecular entities engaged in molecular recognition and other function-driven processes are in demand. The approach takes steps toward conferring some basic features of adaptation and evolution, such as selection, mutation, and amplification, to chemical systems.

References

1. A. Ganesan, *Angew. Chem. Int. Ed.* **37**, 2828 (1998).
2. A. V. Eliseev, J. M. Lehn, *Combinatorial Chem. Biol.* **243**, 159 (1999).
3. J. M. Lehn, *Chem. Eur. J.* **5**, 2455 (1999).
4. G. R. L. Cousins, S. A. Poulsen, J. K. M. Sanders, *Curr. Opin. Chem. Biol.* **4**, 270 (2000).
5. M. C. Calama, P. Timmerman, D. N. Reinhoudt, *Angew. Chem. Int. Ed.* **39**, 771 (2000).
6. F. Hof, C. Nuckolls, J. Rebek, *J. Am. Chem. Soc.* **122**, 4251 (2000).
7. G. R. L. Cousins *et al.*, *Angew. Chem. Int. Ed.* **40**, 423 (2001).
8. R. L. E. Furlan, G. R. L. Cousins, J. K. M. Sanders, *Chem. Commun.* **2000**, 1761 (2000).
9. O. Ramström, J. M. Lehn, *CHEMBIOCHEM* **1**, 41 (2000).
10. K. C. Nicolaou *et al.*, *Angew. Chem. Int. Ed.* **39**, 3823 (2000).
11. T. Bunyapaiboonsri *et al.*, *CHEMBIOCHEM*, in press.
12. V. Goral, M. I. Nelen, A. V. Eliseev, J.-M. Lehn, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 1347 (2001).
13. V. Berl *et al.*, *Eur. J. Org. Chem.* (1999), p. 3089.
14. V. Berl *et al.*, *Chem. Eur. J.* **6**, 1938 (2000).
15. A. Star, I. Goldberg, B. Fuchs, *Angew. Chem. Int. Ed.* **39**, 2685 (2000).
16. S. Hiraoka, Y. Kubota, M. Fujita, *Chem. Commun.* **2000**, 1509 (2000).
17. J. S. Moore, N. W. Zimmerman, *Org. Lett.* **2**, 915 (2000).
18. J. M. Lehn, in *Supramolecular Polymers*, A. Ciferri, Ed. (Dekker, New York, 2000), pp. 615–641.
19. J.-M. Lehn, in *Supramolecular Science: Where It Is and Where It Is Going*, R. Ungaro, E. Dalcanale, Eds. (Kluwer, Dordrecht, Netherlands, 1999), pp. 287–304.