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The economies of synthesis

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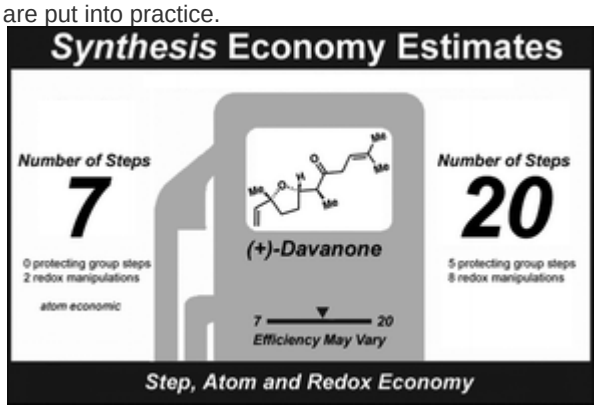
In this *tutorial review* the economies of synthesis are analysed from both detailed and macroscopic perspectives, using case-studies from complex molecule synthesis. Atom, step, and redox economy are more than philosophical constructs, but rather guidelines, which enable the synthetic chemist to design and execute an efficient synthesis. Students entering the field of synthesis might find this tutorial helpful for understanding the subtle differences between these economic principles and also see real-world situations where such principles are put into practice.



Molecular Behavior in Small Spaces

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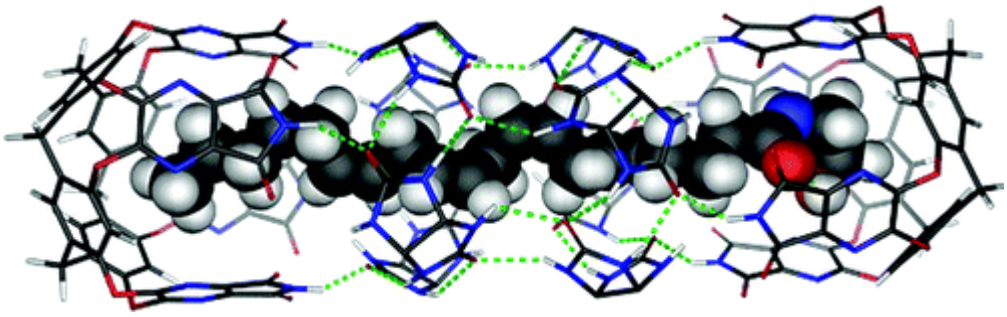

The study of physical organic chemistry in solution is a mature science, over a century old, but over the last 10 years or so, reversible encapsulation has changed the way researchers view molecular interactions. It is now clear that the behavior of molecules in dilute solution is really quite different from their behavior in capsules. Molecules isolated from bulk media in spaces barely large enough to accommodate them and a few neighbors show new phenomena: their activities resemble those of molecules inside biochemical structures—pockets of enzymes, interiors of chaperones, or the inner space of the ribosome—rather than conventional behavior in solution.

In this Account, we recount the behavior of molecules in these small spaces with emphasis on structures and reactivities that have not been, and perhaps cannot be, seen in conventional solution chemistry. The capsules self-assemble through a variety of forces, including hydrogen bonds, metal–ligand interactions, and hydrophobic effects. Their lifetimes range from milliseconds to hours, long enough for NMR spectroscopy to reveal what is going on inside. We describe one particular capsule, the elongated shape of which gives rise to many of the effects and unique phenomena. Molecular guests that are congruent to the space of the host can be

tightly packed inside and show reduced mobilities such as rotation and translation within the capsule. These mobilities depend strongly on what else is encapsulated with them. We also relate how asymmetric spaces can be created inside the capsule by using a chiral guest. In contrast to the situation in dilute solution, where rapid exchange of solute partners and free molecular motion average out the steric and magnetic effects of chirality, the long lifetimes of the encounters in the capsules magnify the effects of an asymmetric environment. The capsule remains achiral, but the remaining space is chiral, and coencapsulated molecules respond in an amplified way.

We probe the various regions of the capsule with guests of different shape. Primary acetylenes, the narrowest of functional groups, can access the tapered ends of the capsule that exclude functions as small as methyl groups. The shape of the capsule also has consequences for aromatic guests, gently bending some and straightening out others. Flexible structures such as normal alkanes can be compressed to fit within the capsule and conform to its shape. We obtain a measure of the internal pressure caused by the compressed guests by determining its effect on the motion of the capsule's components. These forces can also drive a spring-loaded device under the control of external acids and bases. We show that spacer elements can be added to give self-assembled capsules of increased complexity, with 15 or more molecules spontaneously coming together in the assembly. In addition, we analyze the behavior of gases, including the breakdown of ideal gas behavior, inside these capsules.

The versatility of these capsule structures points to possible applications as nanoscale reaction chambers. The exploration of these confined spaces and of the molecules within them continues to open new frontiers.