

thetic routes from several academic groups (by Novartis process chemists) has resulted in an almost combinatorial-style synthesis of discodermolide, readily adaptable to analog preparation, that has provided more than 60 g of active pharmaceutical ingredient to enable its clinical development as an anticancer drug (14).

Of course, the opportunities for total synthesis are not restricted to the discovery of anticancer drug candidates. In the case of anti-infectives, analog design may allow us to circumvent drug resistance, in a manner that again cannot be matched by standard methods for antibiotic development. The recent report of a general synthetic route to tetracyclines and analogs shows the potential that lies in this area (15). From the outset, this synthesis was designed to access multiple analogs of tetracycline and could be achieved in consistently high overall yield (5 to 7% over 14 steps).

Synthetic developments have thus enabled the designed modification of natural product templates in ways that cannot be

readily achieved by biosynthetic means, yet potentially allow large-scale and commercial syntheses. However, despite important advances in synthetic methodology, the typical time scale for the development of truly practical synthetic routes toward complex natural products, and therefore useful derivatives, is still rather lengthy. At present, the development of new drugs seems limited not by our ability to synthesize a given natural product, nor to make analogs, but rather to do so with efficiency and flexibility, and within the short time scale required to compete with high-throughput synthesis and combinatorial chemistry. Despite the challenges that researchers face in the development of such rapid and scalable natural product syntheses, the unbeatable potencies associated with natural molecules selected by evolution should secure their future as a mainstream source of therapeutic agents for many years to come. Furthermore, the continual isolation of an increasing range of novel bioactive secondary metabolites suggests that we have

barely scratched the surface of nature's vast library of small-molecule ligands.

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APPLIED PHYSICS

Molecular Orbitals Tell the Story

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To understand the rich physics of molecular nanostructures and solids, there are times when high-resolution photoemission data are all we need to build a detailed picture of the electronic structure. At other times, structural information from x-ray diffraction or scanning tunneling microscopy (STM) can reveal precisely what is going on at the molecular level. But the most intriguing questions often leave us wishing that we could simply get in there and take a good look at the single-molecule level. On page 468 of this issue, Wachowiak *et al.* describe how they have done precisely this in order to observe the molecular distortion in an insulating monolayer of K_4C_{60} by using a combination of topographic and spectroscopic STM at low temperature (1).

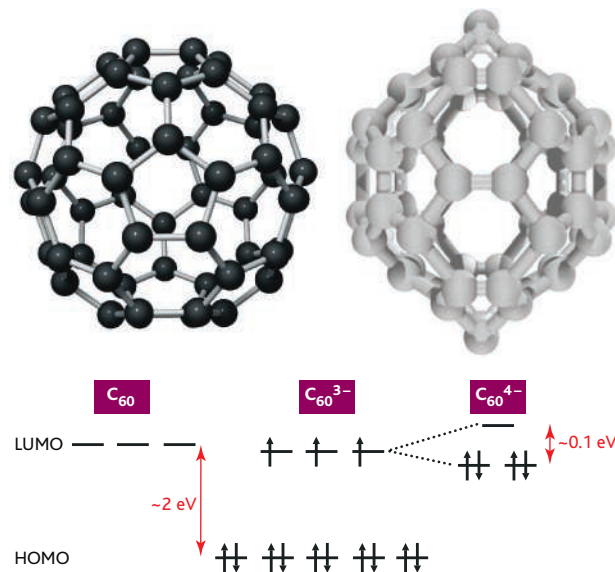
The particular distortion in question results from the Jahn-Teller (JT) effect, a phenomenon with a long history. JT distortions arise when a system is degenerate—that is, it exhibits two or more distinct states with exactly the same energy. Nature tries

to avoid this situation if there is an energy saving to be made by a molecule undergoing a physical distortion so as to split the energy levels apart. JT distortions are thought to play a key role in the electronic

properties of the alkali metal (A) fullerides A_nC_{60} , which range from insulating to metallic (2) and even high-temperature superconductivity (3).

There are technological considerations as well. C_{60} is an ideal building block for molecular devices because electrons can easily be donated to the fullerene cage from other molecules, atoms, and surfaces. In the case of A_nC_{60} , about one electron is transferred from each alkali-metal atom that sits in the interstitial sites of a C_{60} crystal or monolayer. So where do these electrons go?

Pure C_{60} is insulating. Its highest occupied molecular orbital (HOMO) is a fivefold degenerate band with a full complement of 10 electrons, whereas the lowest unoccupied molecular orbital (LUMO), some 2 eV above it, is a threefold degenerate band that could hold 6 electrons but is in fact completely empty. C_{60} is therefore a band insulator (see the figure). Additional electrons donated from the alkali-metal atoms are transferred into the LUMO, and on this basis we can intuitively understand why K_3C_{60} is metallic (because it has a half-filled conduction band). Perhaps the more compelling question, then,



Squeezed fullerenes. Geometric and electronic structure of doped C_{60} molecules. (Top left) Undoped and undistorted insulating C_{60} . (Top right) JT distorted C_{60}^{4-} . (Center) The addition of electrons into the threefold degenerate LUMO of C_{60} and C_{60}^{3-} and (center right) the JT splitting of the LUMO for distorted C_{60}^{4-} .

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