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

James N. O'Shea

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*).

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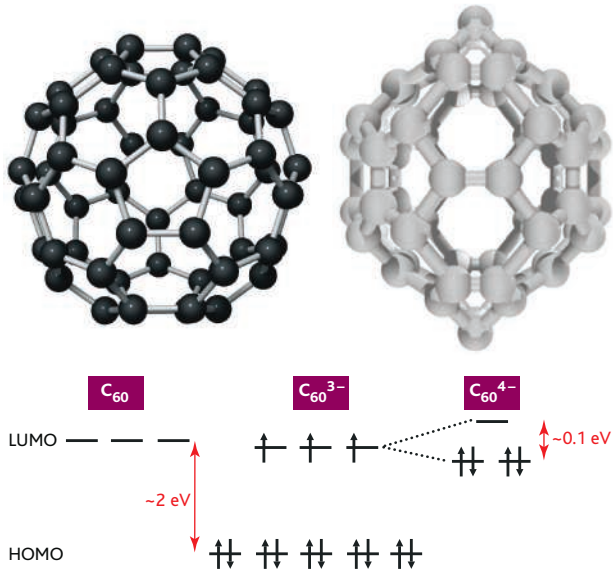
The particular distortion in question results from the Jahn-Teller (JT) effect, a phenomenon with a long history. JT distortions arise when a system is degenerate—that is, it exhibits two or more distinct states with exactly the same energy. Nature tries to avoid this situation if there is an energy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

The author is with the Nanoscience Group, School of Physics and Astronomy, University of Nottingham, Nottingham NG7 2RD, UK. E-mail: james.oshea@nottingham.ac.uk

is why K_4C_{60} and a host of other A_nC_{60} compounds are not metallic, despite having a partially filled LUMO band.

In fact, the underlying physics of both these compounds is intriguing because their strong interelectron repulsion should outweigh the energy gained by delocalizing the electrons in the crystal, thus driving these compounds to an insulating state. However, in A_3C_{60}, the orbital degeneracy of the LUMO lessens this effect by providing multiple hopping channels for an electron to reach a neighboring site (*4*, *5*). A_3C_{60} compounds, it seems, sit quite precariously on the metallic (and superconducting) side of a metal-insulator transition, so why not also A_4C_{60}?

The answer almost certainly lies in the lifting of the orbital degeneracy (*6*) of the LUMO in A_4C_{60} by the JT effect (*7*). In this case, it is a spontaneous molecular distortion arising from the coupling of degenerate electronic orbitals with certain vibrational modes of the molecule, leading to a lowering of the total energy. In A_4C_{60}, the JT distortion splits the LUMO into two lower (and now fully occupied) degenerate levels and an empty level some 0.1 eV higher in energy (see the figure).

The experiment of Wachowiak *et al.* reveals the story of the JT distortion in monolayer K_4C_{60} as told by the molecular orbitals involved. The researchers use a surface on which both the metallic K_3C_{60} and insulating K_4C_{60} phases exist simultaneously, which allows direct comparison between the two compounds from both topographic and spectroscopic points of view. Wachowiak *et al.* show clearly the metallic and insulating nature of the molecules directly beneath the STM tip by mapping the local density of states, of both occupied and unoccupied molecular orbitals, and observing the presence or absence of an energy gap at the Fermi level. When imaging the spatial distribution of the frontier molecular orbitals, they observe very different symmetries for the occupied and unoccupied states. This in itself is indicative of a JT distortion, which affects the two states in different ways, in contrast to the nondistorted molecules of the K_3C_{60} phase. However, a very powerful extension of this approach is the incorporation of detailed theoretical calculations of the expected molecular wavefunctions. Although there are three separate C_{60}^{4-} distortions consistent with a JT distortion (indistinguishable from an energetic perspective), only one of these was found to be consistent with the observed topographic images of the molecular orbitals. This combination of experiment and theory is becoming increasingly prevalent in many areas of science and has a very important role to play, especially in the study of molecular nanostructures with both imaging and spectroscopic techniques.

The work of Wachowiak *et al.* was carried out at low temperature, where infrared data for bulk K_4C_{60} have previously suggested a static JT distortion (*8*). Although structural evidence for the distortion has been observed for fully orientationally ordered Cs_4C_{60} at higher temperatures by neutron diffraction (*9*), the same cannot be said for K_4C_{60}. This has prompted suggestions that at these higher temperatures, molecular orientations in K_4C_{60} are either complex or disordered or that the JT distortion is not static at room temperature but rather exerts a dynamical effect (*10*). The molecules in the K_4C_{60} monolayers studied by Wachowiak *et al.* are certainly ordered and the JT distortion is clearly static, but is this driven to a dynamical JT effect at higher temperatures? Clearly, we have reached another question that is best answered at the single-molecule level. Indeed, there are a myriad of questions surrounding molecular interactions and the mechanisms of molecular electronics that need to be addressed. What is also clear is that the molecular orbitals of these and other systems can tell the story at the single-molecule level, and that by combining reliable calculations with high-resolution techniques that can probe these molecular orbitals, we can address many unanswered questions about the fundamental workings of molecular nanostructures.

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EVOLUTION

Changing the Cofactor Diet of an Enzyme

Andrew D. Ellington and J. J. Bull

Certain molecular processes are fundamental to all free-living organisms. The minimal set of genes necessary for life may be as small as a few hundred, as can be inferred from genome sequence comparisons across diverse organisms (*1*). Because this minimal set is so fundamental, it would be especially rewarding to understand the requirements for, and constraints on, a minimal metabolism. Understanding these parameters should also provide insights into how metabolism originally evolved. Yet such an endeavor seems fraught with one basic problem: If all life requires an essential function, how can we study life without that function?

On page 499 in this issue, Lunzer *et al.* (*2*) addresses a fundamental issue in metabolic evolution and gets around this dilemma. The authors choose a limited but relatively invariant feature of metabolism—biosynthesis of the amino acid leucine. All known forms of life need leucine. Those organisms that synthesize it use an enzyme called isopropylmalate dehydrogenase. In turn, this enzyme uses the coenzyme nicotinamide adenine dinucleotide (NAD^+) as a hydride acceptor during an oxidative decarboxylation. Not only is the use of NAD^+ by isopropylmalate dehydrogenase found in all three domains of life, but NAD^+ is the only cofactor so far found to be used by this enzyme. We can thus presume that this property of leucine biosynthesis is at least as old as the last common ancestor of modern life.

This invariant use of NAD^+ might be less puzzling were it not that a related tricarboxylic acid cycle enzyme, isocitrate dehydrogenase, uses NAD^+ as a cofactor in some species but uses nicotinamide adenine dinucleotide phosphate ($NADP^+$) in others. Why, then, does isopropylmalate dehydrogenase use only NAD^+? Although there are apparently no extant natural enzymes that could help answer this question, it can nonetheless be addressed by enzyme engineering. Studies of the reaction kinetics and mechanism of isocitrate dehydrogenase, combined with crystal structures and phylogenetic

The authors are in the Departments of Chemistry and Integrative Biology, Institute for Cell and Molecular Biology, University of Texas at Austin, Austin, TX 78712, USA. E-mail: bull@bull.biosci.utexas.edu, andy.ellington@mail.utexas.edu