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Science Concentrates

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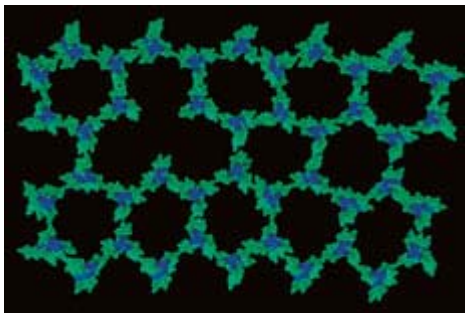
Cell wall model proposed



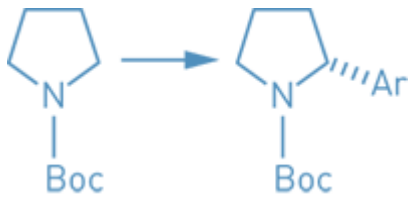
The structure of the bacterial cell wall, which is a target for antibacterial drugs, has been difficult to clarify because of its complexity and the difficulty in obtaining individual components. The cell wall is formed from a peptidoglycan scaffold consisting of repeating disaccharide units of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM), with a pentapeptide attached to each NAM. University of Notre Dame chemistry professor Shahriar Mobashery and coworkers have obtained a 3-D NMR structure of a 2-kilodalton synthetic fragment of this scaffold (*Proc. Natl. Acad. Sci. USA*, published online March 9, dx.doi.org/10.1073/pnas.0510182103). From this fragment, they predict that the longer native peptidoglycan strand is a right-handed helix with three repeats per turn and threefold symmetry along the

helical axis; each strand can cross-link with up to three neighboring strands. They extrapolate to a model of the bacterial cell wall with a layered honeycomb pattern of varying pore sizes (top view shown), depending on the number of cross-links. Waldemar Vollmer of the University of Tübingen in Germany cautions that the model is "highly speculative" and "contradicts a number of experimental data."

More Ar near Earth's surface

Testing a 180-year-old theory of chemist John Dalton, researchers have measured a diffusive separation between heavy and light molecules in the near-surface layer of Earth's atmosphere. Ralph F. Keeling and coworkers at Scripps Institution of Oceanography, La Jolla, Calif., found a detectable separation effect through precise measurements of the argon/nitrogen ratio (*Science* **2006,** *311*, 1429). On nights in February and April 2005, they took air samples in Borrego Sink, a 2-km depression in a California desert plain 140 meters above sea level that is rimmed by mountains. Ar/N_2 ratios were found to be higher near the surface relative to the air aloft and the air back in La Jolla. Dalton proposed that gravity would produce changes in atmospheric composition at different elevations, but subsequent measurements could find no separation below 100 km, where presumably the tendency to separate is overwhelmed by turbulent mixing. The Scripps group believes its observations were attributable to temperature gradients and aided by low winds.

Easy access to 2-arylpyrrolidines



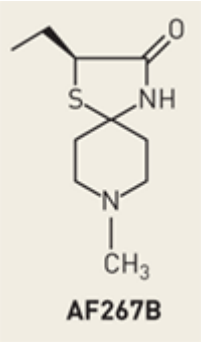
The most convergent and reliable method yet for constructing 2-arylpyrrolidines-a structural motif found in many biologically active compounds and chiral auxiliaries used in asymmetric catalysis-has been developed by process chemists at Merck Research Laboratories in Rahway, N.J (*J. Am. Chem. Soc.*, published online

March 1, dx.doi.org/10.1021/ja0605265). Kevin R. Campos and coworkers report a one-pot, enantioselective process that can be used to prepare a broad range of functionalized 2-aryl-*N*-Boc-pyrrolidines from *N*-Boc-pyrrolidine with high enantioselectivity (shown; Boc = *tert*-butoxycarbonyl, Ar = aryl). The methodology relies on the asymmetric deprotonation of *N*-Boc-pyrrolidine with *sec*-butyllithium and the chiral diamine (–)-sparteine, followed by transmetalation with zinc. The 2-pyrrolidinozinc reagent generated is then coupled to functionalized aryl halides at room temperature using a palladium catalyst. Preliminary unpublished results suggest that the arylation reaction will be applicable to other substrates as well, Campos notes.

Theory probes molecular space

To search for new drugs, catalysts, and other useful molecular structures, chemists riff on known chemical themes, assemble chemical libraries with combinatorial methods, and gather ideas from experimentally derived structure-function relationships. Even so, David N. Beratan of Duke University and his colleagues argue that today's experimental and theoretical methods for designing molecules can investigate only tiny plots of the vast landscape of possible chemical structures (*J. Am. Chem. Soc.* **2006, 128,** 3228). In an effort to bushwhack into more of that territory, Beratan, Weitao Yang, and their coworkers have developed a molecular-design framework based on a "linear combination of atomic potentials," which theoretically can represent any molecule. In goes a target property, such as electronic polarizability, together with a limited roster of molecular fragments. Out comes a "property landscape" whose highest point corresponds to the molecule that is optimal for the target property. The most ambitious combinatorial chemists might be able to investigate mere millions of structures, Beratan says, but his team's new technique can, for some properties, troll through a billion trillion possible structures.

Drug eases Alzheimer's in mice



AF267B

The experimental drug AF267B (shown) improves memory and reduces brain pathology in a transgenic mouse model of Alzheimer's disease, according to University of California, Irvine, neurobiologist Frank M. LaFerla and colleagues (*Neuron* **2006,** *49*, 671). As the disease develops in humans and in the team's transgenic mice, amyloid plaques and neurofibrillary tangles of tau protein accumulate in the brain; levels of the neurotransmitter acetylcholine also decline. AF267B mimics the missing neurotransmitter. When the drug binds to acetylcholine binding sites known as M1 muscarinic receptors in the transgenic mice, levels of α-secretase increase. This enzyme limits production of amyloid-β and therefore prevents the development of both plaques and tangles. LaFerla says AF267B is the first treatment that reduces levels of both of these pathological hallmarks of Alzheimer's. A clinical trial to assess the compound's safety in humans is under way. UC Irvine neurobiologist James L. McGaugh says the work "suggests the exciting prospect of possibly preventing the development of Alzheimer's disease."

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