

for a particular correspondence between the lattice spacing in the c -direction and the period of the pair wavefunction. In the extreme high-field limit, the superconducting phase should return with a critical temperature increasing, instead of decreasing, with the magnetic field. This spectacular high-field 're-entrance' mostly involves electrons pairing with parallel instead of antiparallel spins.

Lee *et al.*¹ have stressed that the survival of superconductivity at magnetic fields exceeding by a large amount the paramagnetic limit suggests parallel spin pairing. In fact, by measuring the temperature at which the resistivity reaches zero under a magnetic field, they are detecting the melting of a lattice of magnetic vortices, rather than the temperature dependence of H_{c2} . But their conclusion that $H_{c2} \gg H_p$ is still valid.

A lot of work must be done before we can unambiguously claim that these materials show the re-entrance of superconductivity

predicted for the high-field regime. In particular, higher fields (above 20 tesla) and lower-temperature experiments with accurate field alignment should be feasible in the near future.

We do not foresee very high critical temperatures in quasi-one-dimensional superconductors, so it isn't clear what applications they might have. But they are important materials for testing our models of superconductivity and, more generally, the theory of electrons in low-dimensional spaces. □

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Oceanography

The limits to growth

Louis A. Codispoti

That the availability of nutrients and light controls carbon fixation by oceanic plants is a proposition that attracts little debate. But there has been hot discussion over just what nutrients limit this process and the applicable timescales. The traditional argument has centred around the relative importance of phosphorus and nitrogen¹. More recently, iron and other trace metals have received considerable attention, and experiments² have shown that carbon fixation in some parts of the ocean can be limited by iron.

Most investigators agree that fixed nitrogen can be limiting over shorter time intervals, but those who favour phosphorus as the ultimate controlling nutrient over periods of more than 10,000 years may feel their hackles rise when they read Paul Falkowski's latest paper on page 272 of this issue³. Falkowski asserts that it is nitrogen, not phosphorus, that limits primary productivity on geological timescales. He bases his arguments, in part, on a discussion of the evolutionary history of the enzyme systems involved in nitrogen fixation and denitrification which seem to be the main source and sink, respectively, for oceanic fixed nitrogen.

Denitrification seems to have evolved independently several times, leading to diversity in the enzymes and microbes responsible. This is not so for nitrogen fixation and, to quote Falkowski, "...the sequence of the genes encoding the catalytic subunits for nitrogenase [the nitrogen-fixing enzyme] is highly conserved in cyanobacteria and other eubacteria, strongly suggesting

an ancient, common ancestral origin".

A key point is that nitrogenase, which seems to have originated before the atmosphere was well oxygenated, has requirements for iron and for anoxia that are not well-matched to present-day oceanic conditions.

Jupiter's moons

Virgin Callisto

The nymph Callisto wanted to remain a virgin, like her hunting companion

Artemis. Inevitably, she was seduced by Zeus (or Jupiter), and then got turned into a bear for her pains by the jealous Hera. But sometimes the real world is kinder than myth: the Galileo spacecraft has discovered that Jupiter's outermost large moon (right) is a virgin aggregate of rock and ice.

The difference between Callisto and its siblings is striking. Unlike Io, Europa and Ganymede, Callisto shows no evidence of an internal magnetic field (D. A. Gurnet *et al.* and K. K. Khurana *et al. Nature* **387**, 261 and 262; 1997). In the other moons, the field probably comes from a molten iron core, which

formed when the moon got hot enough for ice, rock and metal to melt and separate. And indeed, Callisto's gravitational field shows that, unlike the other moons, it has a fairly uniform density, with maybe just a thin surface ice layer (J. D. Anderson *et al. Nature* **387**, 264; 1997).

Why is Callisto so different from Ganymede, which is almost the same size? Early heating of the two moons, from accretion and internal radioactivity, would have been about the same. But Ganymede may once have passed through an orbital resonance, where it was melted by tidal heating from Jupiter; Callisto, unlike her namesake, appears to have avoided such warm embraces.

Stephen Battersby



hemipelagic sediments. They are also present in suboxic portions of the oceanic water column, which occur at depths of a few hundred metres, and are persistent features in a few areas and occur sporadically in others. In addition, the denitrification rate is sensitive to small redistributions of dissolved oxygen and organic-matter fluxes, and to glacial/interglacial changes in continental-shelf area^{1,7}. Because the sites of increased nitrogen fixation and denitrification are different, and because these processes respond to different forcing, imbalances should be expected at least on timescales shorter than the oceanic circulation time of about 1,000 years¹.

An example of the difficulty for nitrogen fixation in today's ocean is provided by the Arabian Sea. Denitrification in the suboxic portion of this region's oxygen minimum zone¹ helps to provide waters that have low ratios of inorganic fixed nitrogen (nitrate, nitrite and ammonium) to phosphate to the sunlit upper layers. In addition, high rates of nitrogen fixation are favoured by a high iron supply⁸. Nevertheless, a search of the extensive, high-quality data on inorganic nitrogen and phosphate collected by myself and colleagues during a complete annual cycle in the Arabian Sea has, to date, found no evidence for sufficient nitrogen fixation to redress the effects of denitrification. Relative to the ~16:1 fixed-N:P ratio (by N and P atoms) of uptake during carbon fixation³, the prevailing ratios are quite low and, in surface waters with low nutrient levels, phosphate was more abundant (relative to the 16:1 ratio). The point is that it takes more than a simple increase in the iron supply to redress deficiencies in fixed nitrogen, and details of both the supply and demand sides must be carefully considered.

Perhaps a subliminal reason for the resistance to the notion of nitrogen rather than phosphorus limitation is that acceptance of the potential importance of the coupling between nitrogen fixation and denitrification, and its relationship to fluxes of iron, organic matter and oxygen, plunges us into new levels of complexity in attempting to predict changes in the ocean's ability to fix carbon. The overall turnover rate between nitrogen fixation and denitrification in the sea is on the order of 100 Tg N yr⁻¹ (Tg = 10¹² g), with my best guess for the denitrification rate being 200 Tg N yr⁻¹ or more. Falkowski points out that an imbalance between nitrogen fixation and denitrification of 3 Tg N yr⁻¹ can largely explain changes in the atmospheric carbon dioxide record over the last interglacial/glacial-maximum cycle, so the sensitivity of the system is frightening. Moreover, we must add the vagaries of the aerial iron supply that seems to be the main source of iron for the open ocean. This supply is very unevenly distributed and dominated, in some regions at least, by weather conditions prevailing over periods of only a

few days⁸. If we add oceanic nitrous oxide and other complications to this picture, the situation becomes even more daunting⁹.

A cautionary note that emerges is that simple 'solutions' for problems in such a complex system are likely to have unintended consequences. Take the idea of iron fertilization, which might superficially be looked upon as 'good' because it should increase carbon fixation² and nitrogen fixation. There is debate about the efficiency of iron fertilization, but, if it has a significant effect, the increased downwards flux of organic material might increase the nitrous oxide flux from the ocean⁹, and increase denitrification (remember that the compensating process, nitrogen fixation, requires about a hundred times more iron than does carbon fixation). Other deleterious outcomes are also possible⁹. Along with many colleagues¹⁰, I fear how governments might simplistically apply our increasing knowledge of the 'leverage' of iron and other trace chemicals to oceanic biology. Applying simple solutions to such a poorly understood, poorly coupled

and highly sensitive system is likely to be a recipe for disaster.

Although the complexity of the system is indeed daunting, can we continue to avoid paying more attention to the processes that influence the nitrogen fixation/denitrification couple? □

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Synthetic chemistry

Cancer drugs better than taxol?

Cameron J. Cowden and Ian Paterson

The clinical and commercial success of taxol* (1, Fig. 1) in cancer chemotherapy has stimulated a worldwide search for compounds with a similar mode of action but superior properties — particularly activity against drug-resistant tumours. The epothilones are a new class of natural cytotoxic compounds produced by a cultured strain of the myxobacterium *Sorangium cellulosum*, which are attracting increasing attention and excitement from chemists, biologists and clinicians^{1,2}. They work in the same way as taxol to stop cancer cells from proliferating³, and based on initial *in vitro* studies, they may be better drugs, in that they are active against some taxol-resistant cancer-cell lines. In the past six months, no fewer than five total syntheses of epothilone A (2) have been reported (from the groups of Danishefsky, Nicolaou and Schinzer)⁴. To add to these exciting results, Nicolaou *et al.* (page 268 of this issue⁵) report the synthesis of both epothilones A (2) and B (3), as well as an epothilone analogue 4 with greater tubulin-assembly activity than either of the naturally occurring epothilones or taxol.

The microtubule cytoskeleton plays an important part in cell mitosis, which relies on polymerization and depolymerization of the protein tubulin. Many established anti-cancer agents such as the vinca alkaloids and colchicine work by inhibiting microtubule assembly; taxol is unusual in that it pro-

motes the formation of stable bundles of microtubules, killing the cell by inhibiting microtubule disassembly. Despite having little structural similarity, the epothilones as well as discodermolide^{6,7} (5 in the figure), work in the same way as taxol. In fact, the epothilones and discodermolide competitively inhibit the binding of taxol to tubulin polymers, probably indicating overlap between their respective binding sites.

Of these compounds, the epothilones are structurally the simplest, and hence amenable to the synthesis of analogues. With a range of analogues, relationships between structure and activity can be found. The structures of the epothilones (2 and 3) include a 16-membered macrocyclic lactone, and differ only in the presence of a hydrogen or methyl group at C12. They both have seven chiral centres with a range of functionality, including a thiazole-containing side chain and an epoxide. Although the epothilones can already be made by fermentation, chemical synthesis will allow access to a wide range of structural analogues.

The new total synthesis⁵ of epothilone A is notable in that the initial steps are undertaken on a substrate attached to a resin (Fig. 2). Such solid-phase chemistry is now common practice for the production of combinatorial libraries, primarily in pharmaceutical companies, but is novel in the area of complex natural product synthesis as seen here. The key step is the C12–C13 bond-forming reaction of compound 6 orchestrated by the rutheni-

*Bristol-Myers Squibb has registered Taxol as a trademark and wishes the scientific community to use the name paclitaxel.