PERSPECTIVES: CHEMICAL ENGINEERING

Separating Rare Earth Elements

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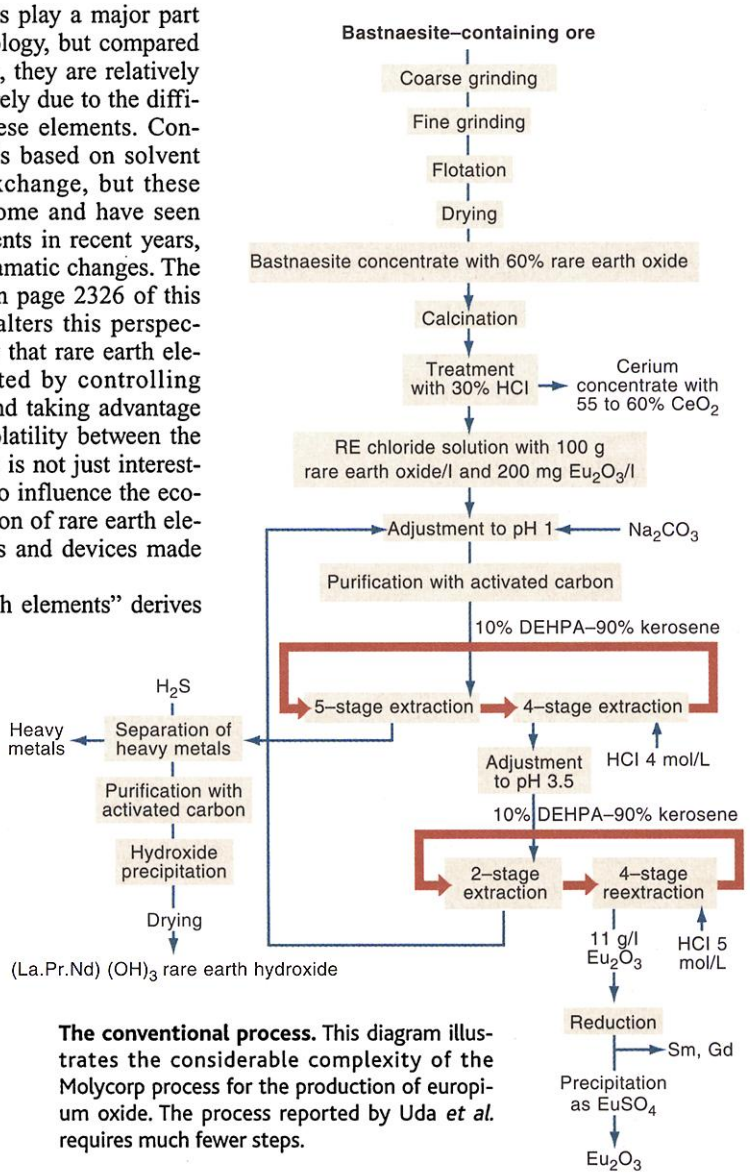
Rare earth elements play a major part in modern technology, but compared with other metals, they are relatively expensive. This is entirely due to the difficulty of separating these elements. Conventional processing is based on solvent extraction and ion exchange, but these methods are cumbersome and have seen only minor improvements in recent years, with no prospect of dramatic changes. The report by Uda *et al.* on page 2326 of this issue (*1*) completely alters this perspective. The authors show that rare earth elements can be separated by controlling their oxidation state and taking advantage of the difference in volatility between the di- and trihalides. This is not just interesting science: It may also influence the economics of the production of rare earth elements and of materials and devices made with these elements.

The term "rare earth elements" derives from the initial view that they could only be isolated from very rare minerals. Geological surveys have since shown, however, that these elements are quite abundant in Earth's crust. For example, cerium is more common than cobalt, yttrium is more abundant than lead, and lutetium and thulium are as common as antimony, mercury, and silver. But because they have very similar physical and chemical properties, rare earth elements tend to occur together in Earth's crust, making their separation extremely difficult. This is why it took almost 70 years, from 1839 to 1907, to separate and identify all rare earth elements (*2*).

Rare earth oxides are very expensive, costing \$20 to \$7000/kg depending on scarcity and method of extraction. The metals cost around \$80/kg more than the oxides. The report by Uda *et al.* offers an exciting opportunity to reduce these prices by greatly simplifying the number of steps in the extraction process. In the conventional process, minerals containing many rare earth elements are first dissolved in concentrated alkalis or acids. This is by far the simplest step; further separation of the rare earth elements is one of the most difficult problems in inorganic chemistry. Two methods have been used commercially. The first is based on solid-liquid systems and uses fractional crystallization or precipitation; the other is based on liquid-liquid systems and uses ion exchange or solvent extraction.



The conventional process. This diagram illustrates the considerable complexity of the Molycorp process for the production of europium oxide. The process reported by Uda *et al.* requires much fewer steps.

Liquid-liquid extraction has been the favored route since the 1960s. In this method, the rare earth element preferentially separates into an organic phase that is in contact with an acidic solution. Modern techniques usually require the organic phase to consist of two miscible phases because the active component (the "extractant") is frequently highly viscous and must be dissolved to ensure good contact between the two phases (*3*, *4*). Unfortunately, the degree of separation is often very poor, and many extraction cycles are required. The process developed by Molycorp for extracting europium oxide (*5*) shows the complexity of these methods (see the figure), with separation factors (*6*) at each stage of only 2 to 10. In contrast, the process described by Uda *et al.* offers separation factors that are increased to 500 to 600, thus greatly reducing the number of separation steps. This is achieved through an elegant combination of the thermodynamics for the formation of various halides coupled with an appreciation of the different volatility of the halides (*7*).

Rare earth elements find a wide range of applications in metallurgy, fuel cells, the coloring of glass and ceramics, and the production of magnets. In metallurgy, "misch metal" (a mixture of rare earth elements directly reduced from a mixture of oxides) is added to molten iron (*8*), and increasingly to nonferrous metals, to improve the mechanical properties. Nonferrous metals such as magnesium are used to substitute iron, for example, to make lighter vehicles.

Low-temperature fuel cells require the storage of hydrogen. This is possible using lanthanum-nickel alloys (*9*). High-temperature fuel cells use zirconia stabilized with a rare earth oxide as an electrolyte, and some of the electrode materials also contain rare earth elements. The same electrolyte is used in oxygen sensors to control the internal combustion engine and to measure the oxygen content in molten steel and copper. Furthermore, magnetocalorific effects in gadolinium alloys may allow the application of magnetic fields to remove or add heat to various systems (*10*).

Today, the largest use for rare earth oxides is still in coloring glasses and ceramics (*5*). Neodymium makes glass blue to wine red, praseodymium makes a green color, erbium pink, and holium blue. Com-

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bining rare earth elements with other elements makes other colors. For example, titanium and cerium make a yellow color.

The largest growth area for rare earth elements is magnetic applications. Samarium-cobalt and iron-neodymium-boron alloys give extremely stable magnets with high remanence and coercive field strengths (*11*). These magnets form an integral part of hard disk drives, electric motors, and compact headphones.

It is likely that the use of rare earth elements will increase, but many applications are held back by the cost of these elements. The report by Uda *et al.* may well lead to simpler and less complicated routes for the separation of these elements, reducing cost and opening up further opportunities for applications of these unique elements.

References and Notes

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6. The separation factor is the ratio of the concentrations of the rare earth element in the organic and aqueous phases.
7. Uda *et al.* used both experimental and estimated data to devise their separation process. A difference in volatility between divalent chlorides and tetravalent chlorides is already known for tin(II) and tin(IV) compounds, and the separation of volatile chlorides is used in the purification of titanium tetrachloride.
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PERSPECTIVES: NEUROSCIENCE

An Accomplice for γ-Secretase Brought into Focus

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Alzheimer's disease (AD) is thought by many to be intimately, if not causatively, associated with the deposition of short β-amyloid (Aβ) peptides in the cerebral cortex and hippocampus of affected individuals (*1*). These Aβ peptides are liberated from β-amyloid precursor proteins (APPs) after cleavage of APPs in the membrane by β- and γ-secretase enzymes. Identified last year, β-secretase (BACE 1) is a membrane-tethered aspartyl protease that generates an Aβ fragment from the APP amino terminus (see the figure) (*2*). In contrast, the identity of γ-secretase—which cleaves APP within its transmembrane segment to generate the carboxyl-terminal Aβ fragment—has remained a mystery. Various researchers have all but declared that the serpentine presenilin proteins (PS1 and PS2) are the γ-secretases responsible for intramembranous processing of APP (and other proteins such as Notch). These declarations are likely to be tempered by the recent report in *Nature* from St George-Hyslop and his colleagues (*3*). These investigators describe a new protein, dubbed nicastrin, that associates with PS1 and PS2 and, most provocatively, affects γ-secretase processing of APP. This hints that, even if PS1 and PS2 do have γ-secretase activity, they may require help from additional proteins to cleave APP efficiently.

Some AD patients with early-onset disease carry mutations in either the *PS1* or *PS2* gene. These mutations induce a shift in the preferred γ-secretase cleavage site in APP by two amino acids. The ill-fated consequence of this shift is the generation of a slightly longer Aβ fragment (42 rather than 40 amino acids in length) called $A\beta_{42}$, which forms fibrillar clumps that are toxic to neurons (*4*). Genetic analysis of the PS homolog, *sel-12*, in the worm and phenotypic examination of mice lacking either *PS1* or *PS2* or both genes strongly suggest that the PSs facilitate signaling through the *lin12/glp1/Notch* pathway during animal development. The ability of Notch, a membrane receptor, to move to the nucleus and activate gene expression depends on its proteolytic processing within the membrane (*5*). It is intriguing that the PSs facilitate two seemingly distinct processes, namely $A\beta_{42}$ production and Notch activity. Interest in this observation escalated even further with the discovery that secretion of Aβ peptides is compromised in *PS1*-deficient neurons, resulting in the intracellular accumulation of membrane-tethered, β-secretase–derived "β stubs" (the substrates for γ-secretase). Indeed, γ-secretase activity is completely abrogated in cells derived from mouse blastocysts lacking both *PS1* and *PS2* (*6*). Concurrently, Wolfe and colleagues (*7*) demonstrated that expression of PS1, harboring substitutions of the two aspartate residues in transmembrane domains six and seven, also compromised Aβ secretion. Together these findings led to the proposal that PSs are unusual diaspartyl proteases that hydrolyze peptide bonds in membrane-associated proteins. Consistent with this observation, intramembranous processing of Notch 1 and its nuclear signaling activity are also attenuated in *PS1*-deficient cells or in cells expressing mutant PS1 (*6*). Finally, the recent demonstration that PS1 and PS2 are selectively cross-linked to potent, transition-state γ-secretase inhibitors has led many to indict the PSs as the culprit γ-secretases (*8*).

Although the notion that PS1 and PS2 are γ-secretases is appealing, the evidence is not as air-tight as it might appear. First, PSs are predominantly found in the early compartments of the endoplasmic reticulum (ER), yet intramembranous processing of APP and Notch occurs in late compartments of the secretory pathway (the Golgi and beyond) (*6*). Moreover, the rate at which APP moves through the ER is decreased in PS1-deficient neurons, suggesting that PS1 could be a chaperone (or scaffold protein), recruiting APP (or its β stubs) to those secretory compartments in which γ-secretase activity resides (*6*). In a similar fashion, it has been proposed that SREBP (a membrane-anchored protein that regulates cholesterol synthesis) is delivered by SCAP (a cholesterol-sensing ER membrane protein) from the ER to the Golgi, where it is cleaved by the Site-1 protease (*9*). Second, PS1-dependent γ-secretase processing of APP is promiscuous, generating heterogeneous carboxyl-terminal Aβ fragments, which indicates that this protease has relaxed sequence specificity. In contrast, γ-secretase processing of Notch 1 is precise, occurring at only one position in the transmembrane segment of the protein (*5*). Finally, it is now abundantly clear that accumulation of the PSs is tightly regulated through their association with limiting cel-

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