The Search for New Environmentally Friendly Chemical Processes

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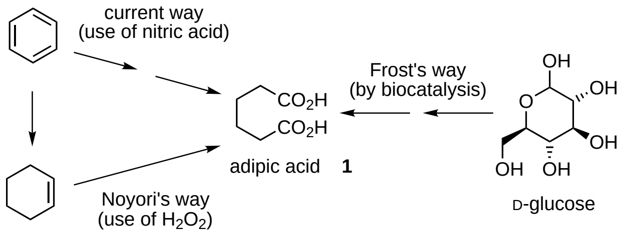
The environmentally conscious design and use of chemical processes focuses on minimizing hazards for human health and the environmental risks of chemical products and manufacturing.[1] Because a high level of environmental protection can be highly cost-intensive, for instance by proper disposal of toxic waste, the development and implementation of such processes may also offer a competitive advantage from an economical point of view. Hence, the efforts to consolidate economic growth and ecological balance, often encompassed in the expression "sustainable development", are becoming stronger in industry.

An example of a new, environmentally benign synthesis of a well-established intermediate in the chemical industry was recently presented by Noyori and co-workers. They disclosed a "green" route to adipic acid (**1**), the annual production of which runs up to 2.2 million metric tons worldwide.[2]

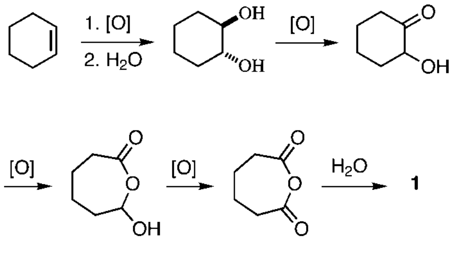
The usual industrial synthesis of this compound, which is an intermediate utilized in the production of nylon-6,6, brings about a problematic oxidation step: cyclohexanone and cyclohexanol—both obtained from benzene—are oxidized by nitric acid (Scheme 1). Although efficient technologies to reduce the emmission of nitrous oxide have been developed and implemented in industrial processes, the use of nitric acid as an oxidant still leads to a significant emission of N_2O, which is believed to play a role in the development of such phenomena as smog and acid rain, and which has been implicated in atmospheric ozone depletion and global warming. It is reckoned that N_2O emission from the nylon-6,6 production accounts for 5 to 8 % of the total amount released by man.



Scheme 1. Currently employed process for the manufacture of adipic acid (**1**) and environmentally friendly alternatives.

In comparison to the traditional manufacture of adipic acid the alternative catalytic route proposed by Noyori et al. reveals several features that represent an improvement in terms of pollution prevention. First, the oxidant is now 30 percent hydrogen peroxide, a well-known "environmentally friendly" oxidant from which the sole by-product is water.[3] Furthermore, the oxidation reaction is both solvent- and halide-free. An additional advantage of the synthetic route from Noyori et al. is the mild reaction conditions required as opposed to the high temperature and pressure that are involved in the manufacture with nitric acid.

The oxidation by H_2O_2 is made possible through the presence of a catalytic amount of a tungsten oxide along with a phase transfer catalyst. This catalyst system had been applied before in a biphasic manner in the oxidative transformations of olefins and alcohols.[4] Now, these two previously studied reactions have been combined to give a new one whose mechanistic pathway is suggested to involve the epoxidation of cyclohexene in the first step and, after hydrolytic epoxide opening, two alcohol oxidations and a Baeyer-Villiger rearrangement. Subsequent hydrolysis of the resulting anhydride eventually affords the product (Scheme 2).



Scheme 2. Proposed reaction pathway for the synthesis of adipic acid (**1**) by oxidation of cyclohexene with 30 % hydrogen peroxide.

There are other routes to adipic acid (**1**), but none of these or the aforementioned ones eliminates both the problem of nonrenewable petroleum-based feedstocks and the risky use of toxic substances at the same time. A biocatalytic alternative elaborated by Frost and Draths opens up a new perspective: they were able to establish a thoroughly "green" synthesis of adipic acid (**1**) that used an *Escherichia coli* mutant to convert D-glucose into *cis,cis*-muconic acid,[5] whose subsequent

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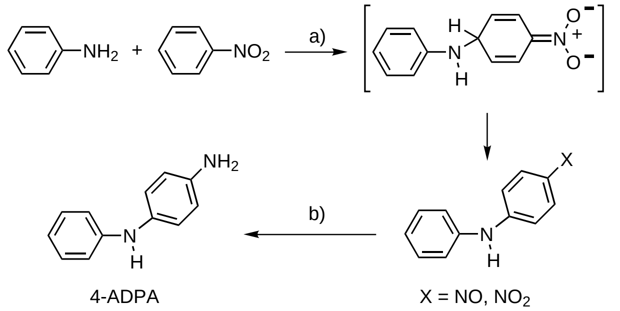
hydrogenation affords the desired adipic acid (Scheme 1). The presumably higher cost of this process notwithstanding, the microbial conversion of D-glucose derived from crops might turn out to be a competitive alternative route, for it circumvents the use of environmentally hazardous reagents as well as starting materials that stem from nonrenewable resources. To put it in other words, it avoids ever-rising costs for the handling of chemical waste and for precious nonabundant chemicals. However, scale-up and processing problems, and the need for an appropriate restructuring and adaptation of agricultural production and chemical industry provide obstacles to a switch of processes.

The United States Environmental Protection Agency (EPA), in an ongoing effort to give incentives for surmounting such barriers, presented one of its 1998 *Presidential Green Chemistry Challenge Awards* to Frost and Draths for their microbe-based synthesis. This prize is part of an EPA program that aims to promote the development and implementation of innovative chemical technologies that accomplish pollution prevention.[6]

Another recipient of an EPA green chemistry award was Flexsys,[7] which was honored for having found a novel strategy to 4-aminodiphenylamine (4-ADPA). This aromatic amine represents a key intermediate in the production of rubber antioxidants. Flexsys's current process for the preparation of 4-ADPA is based on the chlorination of benzene and requires the storage of large amounts of chlorine gas. None of the used chlorine, however, ultimately ends up in the final product, and significant quantities of an aqueous stream containing high levels of inorganic salts contaminated with organic compounds is generated. The treatment of this waste stream is awkward and expensive. Therefore, a more environmentally compatible access to 4-ADPA was sought. This was eventually achieved by utilizing a novel nucleophilic aromatic substitution reaction,[8] which consists of a base-promoted direct coupling of aniline and nitrobenzene and avoids the intermediate use of halogenated reagents (Scheme 3). By means of a nucleophilic attack of the anilide anion on nitrobenzene, a σ complex is formed first, which is then converted into 4-nitrosodiphenylamine and 4-nitrodiphenylamine by intra- and intermolecular oxidations. Catalytic hydrogenation finally affords 4-ADPA. Azobenzene, which is formed as a by-product, can be hydrogenated to aniline and thus recycled into the process. Switching to this alternative synthetic strategy effects a dramatic reduction of chemical waste and waste water, as demonstrated by Flexsys in a pilot plant operation.[9]



Scheme 3. New atom-efficient route to 4-ADPA, a key intermediate in the rubber chemicals family of antioxidants. a) Base; b) catalytic hydrogenation.

In the described novel route to 4-ADPA no extra leaving group or external oxidant is required, making this process environmentally benign and more efficient. In the light of the "atom economy" concept introduced by Trost[10, 11] this synthesis comes closer to an ideal reaction. It uses atoms so efficiently that a higher possible number of atoms out of all the starting materials ends up in the desired product. According to Trost's concept the ideal chemical reaction is a simple and selective addition that does not need any further reagents except in catalytic amounts. Hence, by obeying atom economy in the design of chemical manufacture the amount of feedstocks used and the amount of waste produced may be reduced.

However, following the concept of atom economy and eliminating waste at the source will often be difficult to realize immediately. Apart from the fact that implementing a new process while phasing out an old one takes time, in many cases novel and more efficient synthetic routes are still to be found and developed. Despite these difficulties one can also modify traditional syntheses to meet the needs for more environmentally benign processes. Such an approach to pollution prevention will not completely overcome an established, yet environmentally inefficient synthesis, but it will seek to substitute hazardous chemicals currently used in it, recycle waste streams, or find milder reaction conditions.

For instance, supercritical carbon dioxide might be a suitable replacement for organic solvents since it combines such benefits as nontoxicity, nonflammability, and the elimination of solvent residues and waste.[12, 13] Furthermore, homogeneously catalyzed reactions conducted in supercritical fluids (SCFs) exhibit increased selectivities as well as accelerated mass transfer and reaction rates as a consequence of the special physical properties such solvents are endowed with, and allow facile separation of reagents, catalysts, and products by selective precipitation.[14] Beyond its use as a mere solvent, supercritical carbon dioxide can even serve as an abundant source of C_1 building blocks in chemical synthesis, with CO_2 fixation in the form of formic acid and its derivatives being possible by means of transition metal catalysis.[15] In future its use in chemical processes that are still to be developed could eliminate toxic starting materials, which might, in addition, be derived from nonrenewable resources. Thus, supercritical carbon dioxide represents an attractive tool as to both resource substitution and a more efficient chemical technology.

We are convinced that the responsible care of industry and the increasing political concern about environmental issues will necessitate the use of "green" technologies in the long term: an assessment of the true value of pollution prevention will promote the implementation of emission- and waste-avoiding processes, and enforce the existing environmental partnership between chemical industry, academia, and governmental agencies.[16]

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Stichwörter: arenes • homogeneous catalysis • oxidations • polyoxometalates • waste prevention

[1] a) Recently, the Italian Chemical Society devoted the conference IASOC VIII to the topic of *Friendly Processes: A Recent Breakthrough in Organic Chemistry* (Ischia Porto, Italy, 1998). The *First Summer School on Green Chemistry* (Venice, Italy, 1998) was supported by the European Commission within its program *Training and Mobility of Researchers*; b) *Green Chemistry* is a new international journal published by the Royal Society of Chemistry.

[2] K. Sato, M. Aoki, R. Noyori, *Science* **1998**, *281*, 1646.

[3] *Catalytic Oxidations with Hydrogen Peroxide as Oxidant* (Ed.: G. Strukul), Kluwer, Dordrecht, **1992**.

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[5] a) K. M. Draths, J. W. Frost, *J. Am. Chem. Soc.* **1994**, *116*, 399; b) for a related approach for the synthesis of vanillin from glucose, see K. Li, J. W. Frost, *J. Am. Chem. Soc.* **1998**, *120*, 10545.

[6] The German Chemical Society awards the Wöhler prize for accomplishments in reducing the exploitment of resources in chemical processes. In 1998 Dr. Hans Peter Rath (BASF AG) was the first recipient of this prize.

[7] Flexsys America L.P. is a joint venture of Monsanto's and Akzo Nobel's rubber chemicals operations.

[8] a) M. K. Stern, F. D. Hileman, J. K. Bashkin, *J. Am. Chem. Soc.* **1992**, *114*, 9237; b) M. K. Stern, B. K. Cheng, F. D. Hileman, J. M. Allman, *J. Org. Chem.* **1994**, *59*, 5627.

[9] For a more detailed description, see http://www.epa.gov/opptintr/greenchemistry/aspa98.htm.

[10] a) B. M. Trost, *Science* **1991**, *254*,1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; c) B. M. Trost in *Transition Metals for Organic Synthesis, Vol. 1* (Eds.: M. Beller, C. Bolm), WILEY-VCH, Weinheim, **1998**, p. 3.

[11] Professor B. M. Trost (Stanford) was also honored with the *Presidential Green Chemistry Challenge 1998 Academic Award* for the introduction of this concept. See http://www.epa.gov/opptintr/greenchemistry/aa98a.htm.

[12] G. Kaupp, *Angew. Chem.* **1994**, *106*, 1519; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1452; b) M. Poliakoff, S. M. Howdle, S. G. Kazarian, *Angew. Chem.* **1995**, *107*, 1409; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1275; c) see also J. O. Metzger, *Angew. Chem.* **1998**, *107*, 3145; *Angew. Chem. Int. Ed.* **1998**, 37, 2795.

[13] Professor J. M. DeSimone (Chapel Hill) won the *Presidential Green Chemistry Challenge 1997 Academic Award* for the Design and Application of Surfactants for Carbon Dioxide. See http://www.epa.gov/opptintr/greenchemistry/aa97.htm.

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[15] a) W. Leitner, *Angew. Chem.* **1995**, *107*, 2391; *Angew. Chem. Int. Ed. Engl.* **1995**, *43*, 2207; b) W. Leitner, *Coord. Chem. Rev.* **1996**, *153*, 257.

[16] See also the announcement of the *Presidential Green Chemistry Challenge Award* by President Clinton on March 16, 1995: http://www.donlar.com/greenchemistry/index.html.

Phosphate and Vanadate in Biological Systems: Chemical Relatives or More?

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The biological function of vanadium is well established and has been documented in several review articles.[1, 2] Of particular importance is the ability of vanadium to influence phosphate-metabolizing systems and the fact that vanadium is an inherent part of enzymatic active sites. For both types of vanadoenzymes known today, the vanadium-containing haloperoxidases and the vanadium nitrogenases from the nitrogen-fixing bacteria *Azotobacter*, functional analogues are found in nature which are either more widely spread or more efficient, for example the heme-containing haloperoxidases and the conventional nitrogenases with molybdenum cofactor, respectively. This immediately leads to the question of how these enzyme systems evolved and in particular whether the vanadium-containing enzymes known today are retained functional analogues, which withstood evolutionary forces. New insight concerning these questions may be gained on the basis of newly found similarities for vanadate and phosphate in biological systems.

The widespread physiological effects of vanadium are mainly attributed to the similarity of vanadate(v) ions and phosphate ions. But there are also important differences between these two anions. At physiological pH values monovanadate is found as doubly protonated $[VO_2(OH)_2(H_2O)]^-$ species, whereas phosphate occurs in the monoprotonated form HPO_4^{2-}. This is also important for possible mechanisms of the transport systems for these two anions.[3–5] In addition vanadium is easily reduced under physiological conditions to yield cationic species. The third difference is given by the pronounced ability of vanadium to adopt higher coordination numbers. The higher coordinative flexibility of vanadium can be deliberately used for the structural characterization of phosphate-metabolizing enzymes.

Recently the crystal structures of several stable enzyme aggregates of phosphatases with vanadate as transition state analogue have been reported. Interesting examples are the protein tyrosine phosphatases,[6, 7] which are involved in signal transduction mechanisms for controlling and regulating intracellular processes (e.g. the insulin receptor system)—in

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