Benign by design. New catalysts for an environmentally conscious age*

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Abstract: There is a pressing need for: (i) cleaner fuels (free of aromatics and of minimal sulfur content) or ones that convert chemical energy directly to electricity, silently and without production of noxious oxides and particulates; (ii) chemical, petrochemical, and pharmaceutical processes that may be conducted in a one-step, solvent-free manner, and that use air as the preferred oxidant; and (iii) industrial processes that minimize consumption of energy, production of waste or the use of corrosive, explosive, volatile and nonbiodegradable materials. All these needs and other desiderata, such as the *in situ* production and containment of aggressive and hazardous reagents, and the avoidance of use of ecologically harmful elements, may be achieved by designing the appropriate heterogeneous inorganic catalyst, which, ideally should be cheap, readily preparable, and fully characterizable, preferably under *in situ* reaction conditions. A range of nanoporous and nanoparticle catalysts, designed, synthesized, characterized, and tested by the authors and their colleagues, that meet most of the stringent demands of sustainable development and responsible (clean) technology is described. Specific examples that are highlighted include: (a) the production of adipic acid (precursor of polyamides and urethanes) without the use of concentrated nitric acid or the production of greenhouse gases such as nitrous oxide; (b) the production of caprolactam (precursor of nylon) without the use of oleum and hydroxylamine sulfate; and (c) the terminal oxyfunctionalization of linear alkanes in air. The topic of biocatalysis and sustainable development is also briefly discussed, and a cautionary note is sounded concerning fast screening methods for the discovery of new inorganic catalysts.

INTRODUCTION

So overwhelmingly obvious is the need to expedite the arrival of universal clean technology that merely by highlighting a term such as "environmentally conscious age" we risk eliciting a strong sense of *déjà vu*. Everyone knows that there exists nowadays an exigent need to:

- produce clean fuels—free from aromatics and sulfur, and free also from irritant particulates when the fuel is burnt;
- minimize the consumption of energy;
- minimize the production of waste; and to

- cease using corrosive, or explosive, or volatile or nonbiodegradable materials in the course of industrial and other production.

We acknowledge also that it is prudent to discourage—even when it is still legal—the use of:

(a) noxious or expensive solvents to effect chemical conversions, or
(b) aggressive, ecologically harmful oxidants such as dichromates, perchlorates, periodates, concentrated nitric acid and other such reagents.

As a result both of societal and self-imposed scientific pressure, the whole landscape of energy provision (and related considerations) is now in a state of continual upheaval. And while it is not part of our concerns to assess the potential impact of new, as yet imperfectly harnessed, sources of energy such as tidal, fusion, wind, and geothermal power, we must, as chemists, face

(i) in the shorter term, new ways of converting chemical energy directly to electricity; and
(ii) in the longer term, harness solar energy in a multiplicity of different ways.

At the same time, we must achieve cleaner and more efficient ways of converting existing, fossil-fuel (carbon)-based sources of energy, such as oil, coal, natural gas, and biomass into useful products and simultaneously aspire toward sustainable development, as well as sustainable energy (its extraction, conversion, and storage).

Here, we portray the crucial role that catalysts play in all these endeavors. But we also show how new catalysts may be designed, atomically defined, and utilized for specific, highly desirable—sometimes hitherto unobtainable—molecular and/or manufacturing targets.

SOME HISTORICALLY RELEVANT FACTS

Forty years or so after Volta discovered the Voltaic pile, the lawyer-scientist W. R. Grove invented the fuel cell, in which, using platinum as electrocatalyst, he "burnt" H_2 in O_2 silently and directly into electricity. A century and a half later, we are now on the threshold of the fuel-cell age. Transport and local sources of power (thanks to the availability of a natural gas grid in most countries) are about to be transformed. In some vehicles, liquefied hydrogen is stored "on board", in others one uses either liquefied natural gas or gasoline in conjunction with an appropriate "reforming" catalyst, to generate the combustible fuel (H_2).

Electric vehicles powered by H_2-based fuel cells present no environmental problems. The only gas emitted is water vapor! It was societal and legal pressure, particularly in California, that was chiefly responsible for the development of such (clean) electric cars. It was also societal and legal pressure in California and elsewhere that was principally responsible for the Clean Air Act (and the Huskie amendments) of the U.S. government in the early 1970s. This required a diminution of auto-exhaust emissions by 90%.

It is gratifying to note that, thanks to the pioneering research efforts of Johnson–Matthey, UK and others (who developed the three-way auto-exhaust catalyst consisting of supported Pt, Pd, and Rh), a significant fraction of the 900 million or so motor vehicles now in use on the roads of the world are fitted with catalysts for the abatement of atmospheric pollution.

Although advances in the harnessing of solar energy are not central to the topics discussed here, and developments in photovoltaics or photoelectrochemistry are not of concern to us at present, it is nevertheless important that solar-thermal arrangements should demand our attention. For a number of years workers in the former Soviet Union [1] and in Israel [2] have used solar energy to drive endothermic reactions (e.g., $CH_4 + H_2O \rightarrow CO + 3H_2$ or $CH_4 + CO_2 \rightarrow 2CO + 2H_2$) thereby producing "syngas" ($CO + H_2$ mixtures) in a clean manner. By converting solar energy in this way into chemical energy, the former may be indefinitely stored and then released (using a catalyst such as Ni to effect the reverse reactions, e.g., $3H_2 + CO \rightarrow CH_4 + H_2O$) as and when required. Such "cycles" may be repeated indefinitely, provided the catalyst does not lose its efficacy. Alternatively, the "syngas" generated by

absorption of solar energy may be used for a variety of other purposes, including the Fischer–Tropsch synthesis of alkanes, alkenes, or alkanols (depending upon the precise nature of the catalyst). It may also be converted to methanol, using the well-known and well-tried ICI catalyst consisting of metallic Cu on ZnO (Fig. 1).
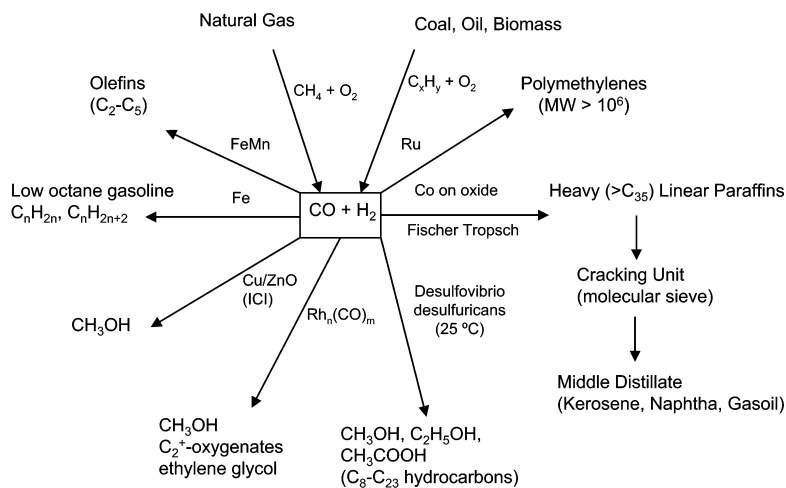

Fig. 1 Fischer–Tropsch synthesis of hydrocarbons, olefins, oxygenates, gasoline, and other fuels from mixtures of CO and H_2 (syngas).

While on the subject of Fischer–Tropsch processes—using the "appropriate" catalyst to produce the desired end product—we turn our attention to the most effective presently available method of obtaining sulfur-free petrol (gasoline) or any other hydrocarbon fuel. By pursuing a gas-to-liquids (GTL) policy, so strongly advocated by most governments and multinational oil companies at present, one may obtain fuel (for transport or heating) that is essentially free (less than 1 ppm) from any sulfur impurity. (This means that upon combustion little or no acid rain is produced). There are many ways in which the fuel (be it kerosene, gas-oil, or naphtha) may be obtained, via the Fischer–Tropsch process, from natural gas. There is, for example, the so-called Shell middle distillate synthesis process (SMDS) for converting CH_4, via syngas, into fuels outlined in Fig. 2 [3].

SGP stands for the Shell gasification process, HPS for heavy paraffin synthesis, HPC for heavy paraffin conversion, HGU for the hydrogenation unit and WPU for the wax production unit.

The SMDS process makes very efficient use of raw materials and energy. The Fischer–Tropsch catalyst, consisting of supported cobalt, is prepared in such a way and used under such conditions that α (the propagation parameter—see, for example, ref. [4]) is greater than 0.95 (thereby securing production of paraffins in the range C_{35} to C_{120}). Under the operating conditions, the production of low-molecular-weight hydrocarbons is minimized, and the main products are heavy hydrocarbons, which are selectively hydrocracked down to the size of molecules in middle distillates. Paraffins are distilled into essentially three fractions: gas-oil (otherwise known as diesel), kerosene, and naphtha. The products contain virtually no aromatics. Indeed, the product liquid is as transparent as water. Neither do the products contain low-boiling hydrocarbons. They may be used as such or blended with fuels from oil refineries to suppress the content of carcinogenic aromatic species.

Another popular method for the production of fuels with a low sulfur content involves rigorous catalytic hydrodesulfurization using WS_2 or MoS_2-based catalysts. Considerable advances [5] have been made in this branch of catalysis recently, and lower and lower sulfur contents in fuels have been
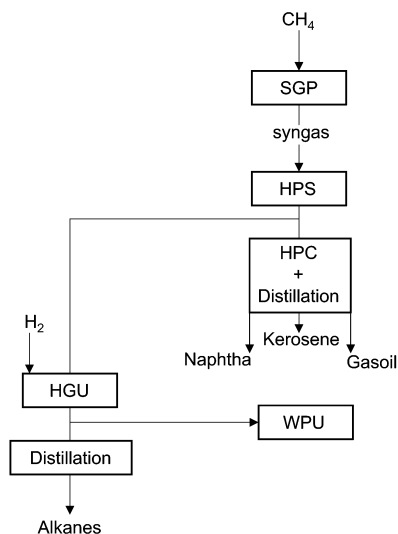
Fig. 2 Shell middle distillate synthesis process for converting syngas into other fuels (after ref. [3]).

attained. The Queensland Clean Fuels Project, backed by the Australian Government and many multi-national companies as well as leading process technologists such as Kvaerner in the UK, achieves a new grade of clean fuels, starting from oil (not natural gas), via the catalytic hydrodesulfurization route. The SASOL-Chevron method, however [6], starts from coal (as a means of producing the syngas), and proceeds via the Fischer–Tropsch process to sulfur-free, clean fuels, in much the way the Shell process does.

It is interesting to note that so "clean" has gas-oil become through these new methods of production that there is a strong case for abandoning the term "diesel oil" to describe such fuels [6]. The word diesel has pejorative overtones, because carcinogenic and particulate products were hitherto always associated with diesel oil.

CLEAN TECHNOLOGY VIA CATALYSIS

Table 1 summarizes the salient features of the approaches currently being undertaken [7,8] to achieve environmentally clean process. Much publicity has been given recently to the merits of both supercritical CO_2 and ionic melts as potentially important means of avoiding noxious and environmentally unacceptable organic solvents in the chemical technology of the future. These two approaches doubtless have their parts to play, although it remains to be recognized if the problems associated with the solubility of key reactants and products in supercritical Co_2 will prove to be a limiting factor. It also remains to be seen if the toxicological tests that have yet to be applied to many potentially useful ionic liquids will eliminate doubts as to their ecological acceptability.

We have pursued several studies aimed at replacing multi-step, expensive, and environmentally harmful processes with single-step, solvent-free, benign ones. We now summarize below the essence of many of these alternative routes, which apart from their intrinsic merit in providing simpler and less expensive ways of reaching a particular goal, also have the added advantage of requiring less expenditure of energy. The task in finding the best catalyst is, as ever, endeavoring to design the most active, the most selective, and the most stable agent. Over and above the strictly chemical criteria, one wishes

Table 1 Desiderata for engineered porous oxide catalysts.*

High activity, high selectivity, longevity, and durability

Freedom from restrictions imposed by diffusional considerations (reactants and products)

Capable of facilitating regio-, shape-, and enantioselective processes

Should operate under mild conditions and be environmentally, economically, and atom efficient

Should be able to facilitate an increasing number of solvent-free conversions

Possession of isolated, well-defined (single-site) active centers, the atomic architecture of which may be delicately modified

Capability of yielding detailed mechanistic understanding of catalytic action

*Between them certain microporous (3.5 to 14.5 Å apertures) and mesoporous (15 to 250 Å) oxides satisfy all these desiderata.

**Table 2** Helpful approaches toward clean technology.*

Solvent-free processes or those that involve benign (nonvolatile and biodegradable) solvents

Single-step conversions

Air or oxygen as preferred oxidant

Hydrogen as preferred reductant

Raw materials that are sustainable

*Most of these approaches may be realised by developing the necessary heterogeneous catalysts.

to have a physically robust (attrition-resistant) catalyst, or at least one that survives recycling or re-activating in a fatigue-free situation.

It has transpired [9–11] that nanoporous catalysts possess supreme advantages as materials well-suited to cope with the challenges posed by clean technology (Table 2). Not least among their advantages are the fact that active centers are readily accessed by the reactant species, and also that these solids behave as if they have three-dimensional surfaces so that their chemical properties may be readily interrogated using both simple and sophisticated physicochemical methods, generally under *in situ* conditions. Such interrogation of the active sites elucidates their precise nature (under conditions of catalytic turnover), and this helps greatly in designing new, superior catalysts. In a sense, they are the *reducto ad absurdum* of the clay catalysts which proved eminently successful as vehicles for a wide spectrum of organic reactions [12]. The microenvironment present in the interlamellar regions of, for example, montmorillonite clays (Fig. 3) is conducive for many proton-catalyzed reactions. Indeed, one of us (J. M. Thomas) devised an attractive, so-called atom economic method of producing the desirable solvent ethyl acetate (which has very low volatility and is biodegradable) by the proton-catalyzed addition of acetic acid across the double bond in ethylene, a process that was patented, and that has since been commercialized by BP in Hull (UK), using a more physically robust catalyst—see Figs. 3A and B—than the clay one used originally [13].
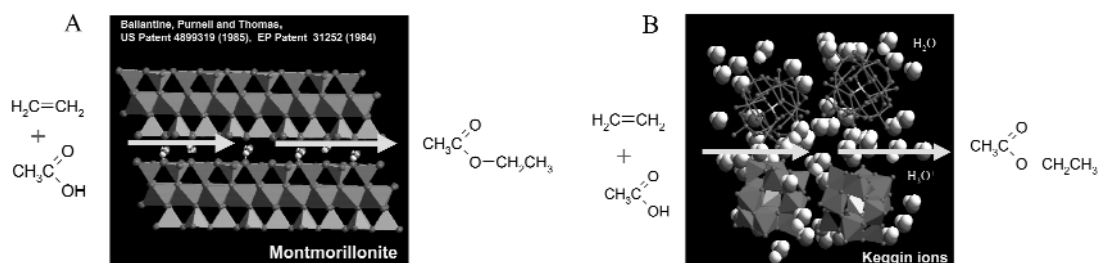
Fig. 3 (A) The proton-rich nature of the interlamellar regions of a montmorillonite clay catalyzes the addition of acetic acid to ethylene so as to yield ethyl acetate. (B) So also do the interstices between certain Keggin ions of polyoxometalates.

THE ADIPIC ACID STORY

One of the principal commercial methods of producing adipic acid nowadays starts with cyclohexane and involves a sequence of aggressive and ecologically unsatisfactory reagents (Fig. 4). Note in particular that vast quantities of N_2O (a greenhouse gas) are produced in this process, and that the multi-step production line entails use of many solvents, as well as several homogeneous and heterogeneous catalysts. Our method [7] of producing adipic acid (Fig. 5) is a solvent-free, one-step process involving just one, readily preparable nanoporous catalyst (FeAlPO-31), that has been described and characterized fully (by XAFS and other methods) elsewhere [14]. A detailed comparison of the old and new methods of converting cyclohexane to adipic acid is given in Figs. 4 and 5.
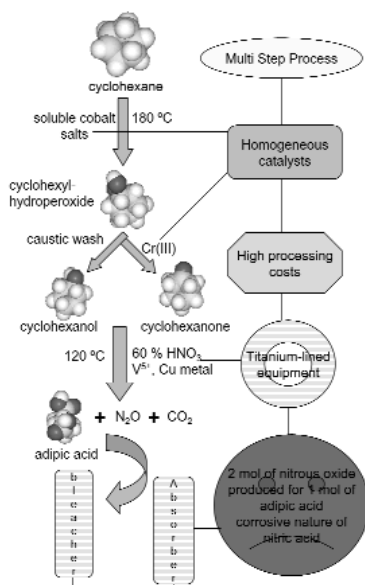

Fig. 4 The current industrial multi-step route for the manufacture of adipic acid using aggressive oxidants and reagents.
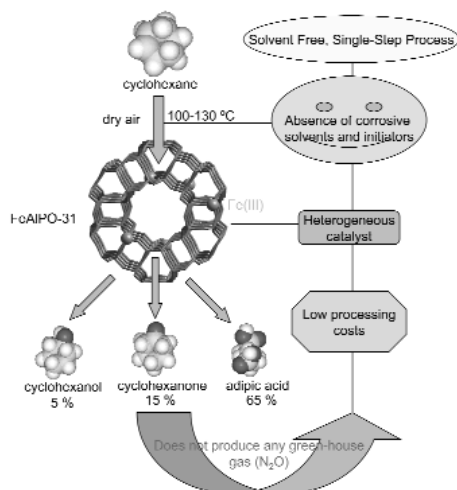
Fig. 5 An alternative one-step, solvent-free process using a microporous heterogeneous catalyst and air as oxidant.

THE CAPROLACTAM STORY

The conversion of cyclohexanone to the oxime and its subsequent Beckmann rearrangement to ε-caprolactam are vital stepping stones in the manufacture of nylon-6 [15]. On an industrial scale, one popular procedure is that depicted in Fig. 6A. Note that aggressive reagents such as hydroxylamine sulfate and
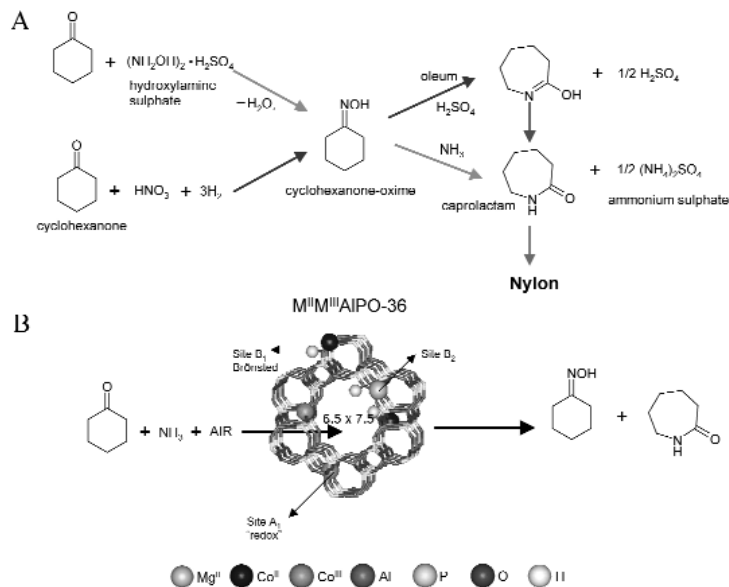
Fig. 6 (A) Industrial routes for the manufacture of ε-caprolactam, starting from cyclohexanone, using hydroxylamine sulfate and oleum. (B) A one-step, solvent-free route for the production of ε-caprolactam, using a mixture of air and ammonia, and a bifunctional nanoporous catalyst. In $M^{II}M^{III}AlPO-36$ (M≡Co, Mn), the framework M^{III} ions are the redox active centers (A_1), whereas M^{II} ions have associated ionizable OH bonds attached to the framework, and these are the Brønsted (B_1) acid sites. Mg^{II} ions in the framework also have neighboring ionizable OH ions (B_2 sites).

oleum are used, and that large quantities of (unwanted) ammonium sulfate are generated as by-products. We have recently shown [16] that a bifunctional nanoporous catalyst may be designed so as to achieve a one-step, solvent-free production of oxime and ε-caprolactam with a mixture of air and ammonia (see Fig. 6B). The catalyst in question is designated $M^{II}M^{III}AlPO-36$ in which there are both Brønsted active sites and redox sites (the locus of the framework M^{III} ions, where M^{III} is usually Co^{III} or Mn^{III})—see Fig. 6B. It is to be noted that, with our designed molecular sieve catalyst:

- hydroxylamine (NH_2OH) is readily formed *in situ* inside the pores from NH_3 and O_2 at the M^{III} active redox sites;
- the NH_2OH converts the cyclohexanone to its oxime both inside and outside the nanopores, and, likewise, at the Brønsted active sites, the oxime is isomerized to the caprolactam inside the pores of the catalyst; and
- O_2 yields NH_2OH more efficiently than H_2O_2 or tertiary butyl hydroperoxide at the redox active sites.

THE TERMINAL OXYFUNCTIONALIZATION OF ALKANES

It is much easier to burn saturated hydrocarbons (such as linear alkanes) completely in air or oxygen than it is to introduce at certain regions along the chain just an oxygen atom or two, i.e., to convert them, in a regioselective manner, into alkanols, alkanoic acids, or aldehydes and ketones. The very name, paraffins, from the Latin *parum affinis* (slight affinity) betrays their inertness. Linear alkanes such as *n*-hexane resist attack by boiling HNO_3, conc. H_2SO_4, chromic acid, or $KMnO_4$. On top of that, the prospects of oxyfunctionalizing the terminal carbon atoms look particularly bleak when it is borne in mind that the C–H bond dissociation energies decrease from 104 to 95 to 91 kcal mol^{-1} in proceeding from primary to secondary to tertiary carbon atoms.

But terminally oxidized alkanes, such as linear alkanols (or dialkanols) or acids, are extremely desirable potential feedstocks for the chemical industry. There is, therefore, an acute need to devise ways of selectively oxidizing the terminal methyl groups. (In addition to this practical consideration, there is also the scientific challenge posed by the American scientist J. D. Roberts called the Barton challenge [17], which entails finding a way of selectively converting *n*-hexane to adipic acid.)

As described elsewhere [10,11,18], our strategy for effecting solvent-free, one-step, oxyfunctionalization in a regioselective fashion entails the use of a nanoporous catalyst that permits only end-on


| ◯ Al | ◯ P | ⬤ O | ⬤ Co | ◯ C | ◯ H |
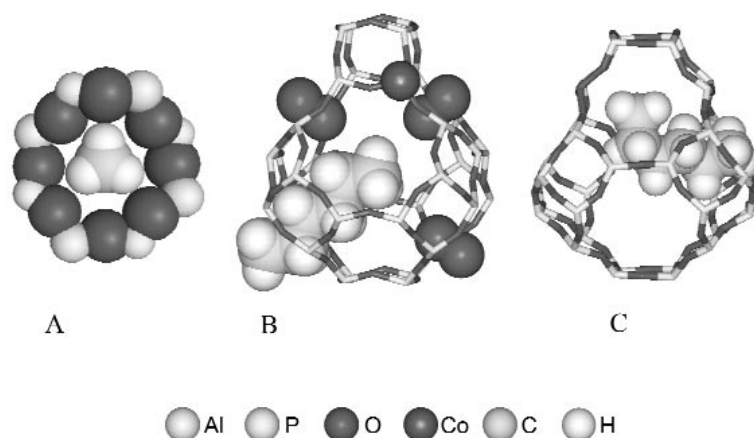
Fig. 7 Only end-on approach of alkane chains can secure access to active sites situated inside the chabazitic cages (aperture dia. 3.8 Å) of MAlPO-18 catalysts (A & B). The energy-minimized configuration (C) adopted by *n*-hexane inside the cages of the AlPO-18 framework.

entry of the alkane chain to the redox active center (see Fig. 7). We use MAlPO-18 catalysts where M is exclusively either Co^{III} or Mn^{III}. The kind of regioselectivity that we obtain is illustrated in Fig. 8. Note that, with other comparable nanoporous catalysts where the diameters of the pores permit greater librational and other freedom to the alkane, oxyfunctionalization during the free-radical autocatalytic [18] conversion takes place at many of the carbon atoms along the alkane chain.

To achieve oxyfunctionalization at both (methyl) ends of *n*-hexane, a sufficiently large number of framework Co^{III} ions needs to be accommodated on the inner walls of the CoAlPO-18 catalyst in such a manner that two framework Co^{III} ions should be separated by *ca* 7 to 8 Å from one another inside the so-called chabzitic cage of the catalyst. With the composition $Co_{0.10}Al_{0.90}PO_4$ for the CoAlPO-18 structure (i.e., with a Co:P ratio of 0.1 instead of 0.04, as above) there is a high probability for there being two (separated) Co^{III} ions in each cage of the AlPO-18 structure, and for these two ions to be situated opposite one another, as shown in Fig. 9. This catalyst does indeed yield considerable quantities of adipic acid from *n*-hexane in air [19].
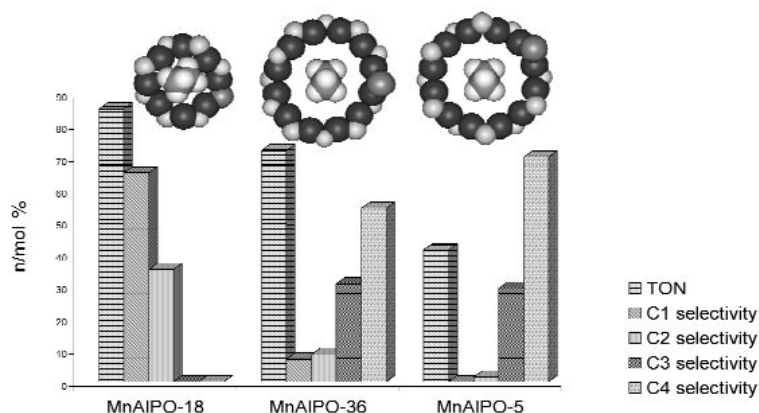

Fig. 8 Bar chart summarizing the regioselective oxyfunctionalization of *n*-octane when exposed to air and a Mn^{III}AlPO-18 catalyst. 65% of the products are oxyfunctionalized at the terminal methyl (C_1) and 35% at the penultimate methylene (C_2) carbons with virtually no attack at the C_3 or C_4 positions, in marked contrast to what occurs under identical conditions (373 K, 1.5 MPa, 24 h) with MnAlPO-36 or MnAlPO-5.
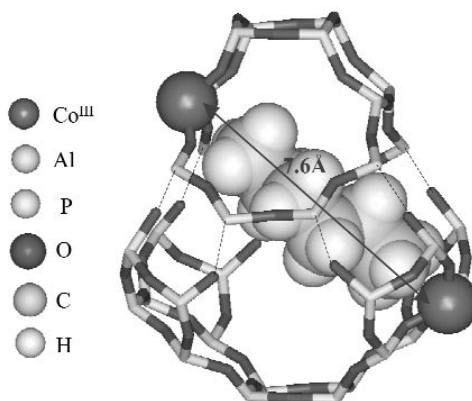
Fig. 9 With two Co^{III} ions at the opposite vertices of the chabazitic cage in CoAlPO-18 (as occurs when the composition is close to $Co_{0.1}Al_{0.9}PO_4$), their separation distance (*ca* 7.6 Å) is similar to that which separates the two terminal methyl groups in *n*–hexane. This maximizes the occurrence of oxyfunctionalization of the alkane, at both terminal ends, to form adipic acid. For clarity, the top half has been separated from the bottom one, the dotted lines indicating which atoms in the separated half link up.

BAEYER–VILLIGER OXIDATIONS

Over a century ago, Beyer and Villiger showed that cyclic ketones could be converted into lactones using certain powerful oxidants that are now frowned upon environmentally, such as peroxomono-sulfuric acid, H_2SO_5. Some milder variants have been used as oxidants in the intervening years, for example 90% H_2O_2 or H_2O_2 in the presence of inorganic materials such as $MeReO_3$. Our approach [20] relies on Mn^{III} (or Co^{III}) framework-substituted MAPO-36 in which air (or O_2) and a sacrificial aldehyde (usually benzaldehyde) are used. These constituents produce, *in situ*, perbenzoic acid, which functions as an environmentally successful oxygen donor to convert the ketone to the corresponding lactone. In effect, we are exploiting the easy autoxidation of aldehydes to promote the *in situ* formation of peroxy acids. A summary of the perceived mechanism is sketched in Fig. 10.
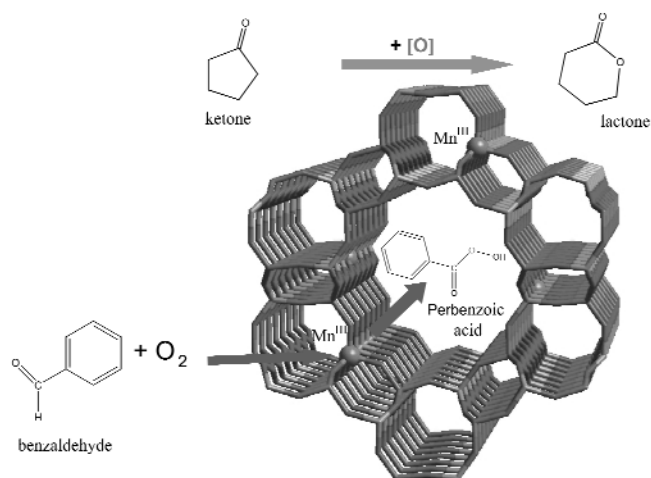
Fig. 10 Graphical representation of the reaction scheme for the *in situ* formation of the perbenzoic acid intermediate inside the micropores of the $Mn^{III}AlPO-36$ catalyst, using benzaldehyde and molecular O_2. This peroxy acid is subsequently involved in a nucleophilic attack at the carbonyl carbon, of a ketone or alkene, leading to production of the corresponding lactone or epoxide.

EPOXIDATIONS OF ALKENES

The well-known ability of Ti^{IV} ions to activate peroxocompounds is what is used in many commercial and laboratory procedures for epoxidizing alkenes. By grafting a Ti^{IV} center onto the walls of mesoporous silica (starting from titanocene dichloride), thus ensuring that isolated, well-defined, four-coordinated sites are created, exceptionally powerful epoxidation catalysts are produced. Moreover, *in situ* XAFS studies leave no doubt concerning the nature of the active site: it is a coordinatively unsaturated TiOH group tripodally attached to the silica support [21]. With such insights, it is relatively straightforward to improve the performance of Ti^{IV}-centered catalysts, either by substituting a germanium atom for one of the three silicons in, or by enhancing the hydrophobicity of, the immediate vicinity of the TiOH group.

INDUSTRIAL HYDROGENATIONS

So far as hydrogenations are concerned, it is relevant to note that the chemical industry is turning increasingly for its feedstocks to biological molecules extracted from the plant kingdom, rather than to

the constituents of oil in the production of high-added-value materials. Because such molecules are too large to enter the inner surfaces of microporous catalysts, it is appropriate for mesoporous catalysts (diameter in the range 3–10 nm) to be used so as to facilitate access of reagents to, and diffusion of products away from, the catalytically active sites that are (ideally) distributed in a spatially uniform manner over the high-area solid. In a number of studies [7,8,22] we have demonstrated how large concentrations of nanoparticle bimetallic catalysts dispersed inside mesoporous silica possess the high intrinsic activity required for the solvent-free hydrogenations. The selective hydrogenation of a polyene such as 1,5,9-cyclododecatriene is quite an important procedure in the synthesis of organic and polymeric intermediates, such as 12-laurolactam, 12-aminododecanoic acid, and dodecanedoic acid, which are important monomers for nylon-12, nylon-612, copolyamides, polyesters, and coating applications.

Figure 11 illustrates the key features of marrying the scope offered by mesoporous silica (see electron micrograph at top left) with the world of mixed-metal carbonylates (Fig. 12) that enable us to
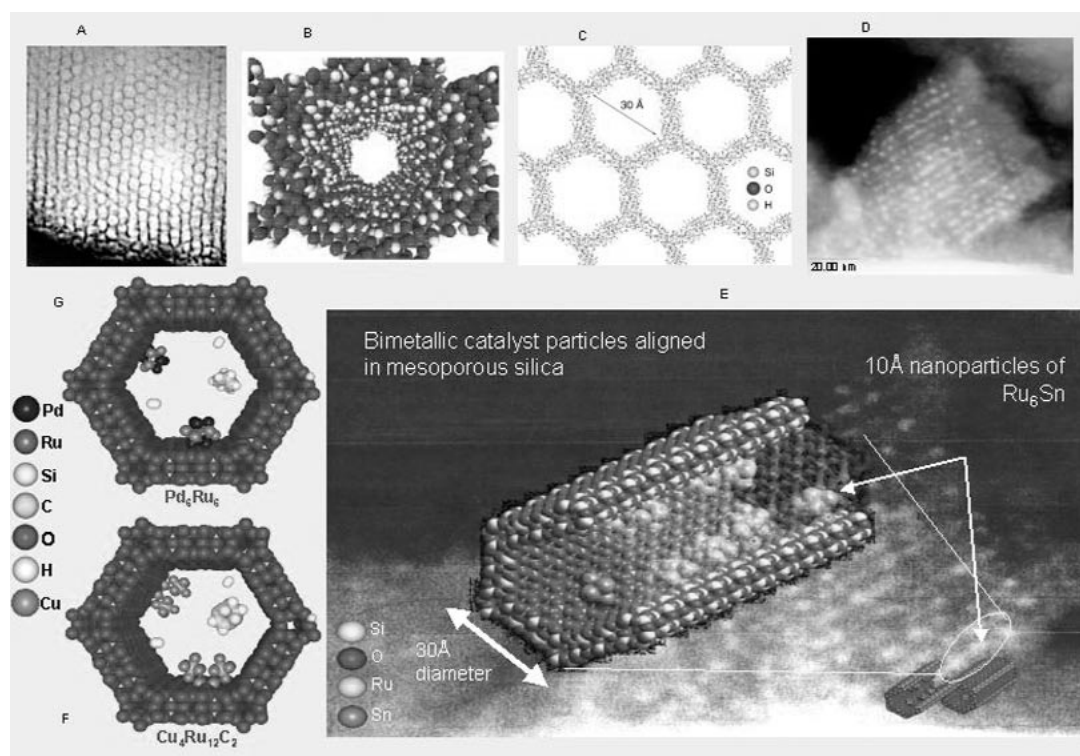
Fig. 11 Clockwise from top left: (A) HRTEM micrograph showing the regular structure of the empty channels in mesporous silica; (B) computer graphic view along the axis of a single mesopore (pore diameter $\approx$ 30 Å) showing the profusion of pendant silanol groups lining the pores that serve as the anchoring points for the adsorbed bimetallic nanoparticle carbonylates; (C) energy-minimized model of the mesopore (shown in B), which is obtained by combined molecular dynamics and computed atom–atom procedures; (D) high-angle, annular dark field electron micrograph of a Ru_6Sn/MCM-41 catalyst after catalytic use; (E) electron micrograph, with associated illustration, showing the mode of distribution of Ru_6Sn bimetallic nanocatalyst (for selective hydrogenation) within a siliceous nanopore. In the background electron micrograph the linearly arranged white spots demarcate the anchored bimetallic clusters (dia. *ca* 10 Å); (F) & (G) computer graphic models of $Cu_4Ru_{12}C_2$ and Pd_6Ru_6 nanocatalyst clusters anchored (originally in their carbonylated form via pendant silanol groups) to the inner walls of mesoporous silica. Typical reactant polyenes [1,5,9-cyclododecatriene in (F) or 2,5-norbornadiene in (G)] and H_2 are also shown in the mesopore channel.
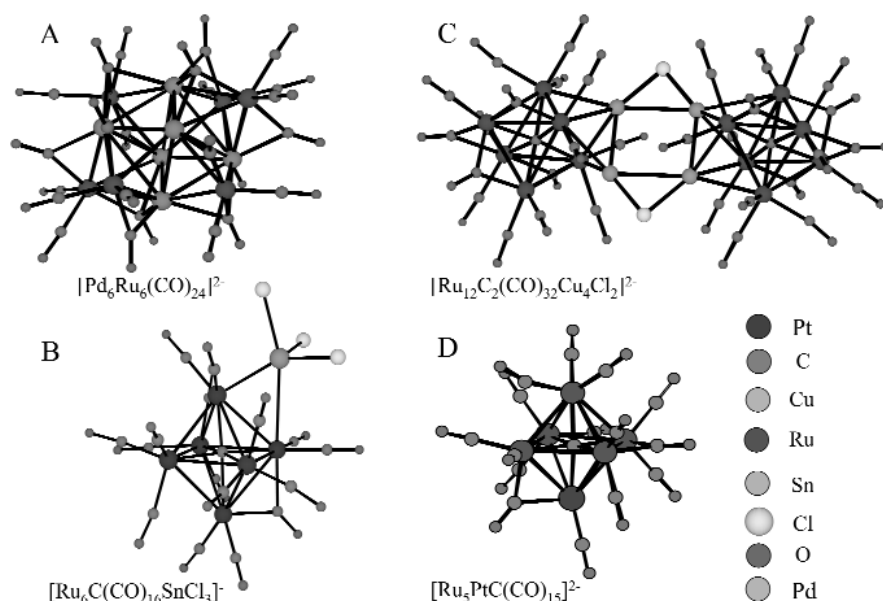
Fig. 12 Typical parent carbonylates from which naked nanoparticle (10 to 15 Å diameter, depending upon the constituents of the bimetallic core) catalysts are generated. (A) $[Pd_6Ru_6(CO)_{24}]^{2-}$, (B) $[Ru_6C(CO)_{16}SnCl_3]^-$, (C) $[Ru_{12}C_2(CO)_{32}Cu_4Cl_2]^{2-}$, and (D) $[Ru_5PtC(CO)_{15}]^{2-}$.

place powerful bimetallic nanoparticles (such as Ru_6Sn, Ru_5Pt, Ru_6Pd_6, and $Ru_{12}Cu_4C_2$) firmly inside the nanopores of the silica support.

These bimetallic catalysts exhibit high performance in the solvent-free, selective hydrogenation of 1,5,9-cyclododecatriene. With an ever-expanding range of mesoporous materials, with diameter up to 50 nm, there is abundant scope to pursue the solvent-free catalytic approach outlined here in future technology.

BIOCATALYSTS AND SUSTAINABLE DEVELOPMENT

It has long been recognized that isolated and purified enzymes when immobilized (firmly anchored) onto a high-area inert solid may retain their conformation and function effectively (and in continuous processes) rather like traditional heterogeneous inorganic catalysts. In addition they, have the supreme advantage of being enantioselective, as well as being highly specific. As a result of recent major advances in molecular biology, enzymes can now be suitably modified (improved)—by site-directed mutagenesis, for example—and, in particular, rendered more stable and durable. Such is the confidence among experts in biocatalysis nowadays that they foresee that, in the next decade, bulk chemical products will emerge from enzymatic rather than conventional chemical reactors. The other major advantage of enzymes as catalysts is that they are highly active at room temperature, and offer great scope in producing new chiral building blocks such as alkanols, amines, and hydroxy carboxylic acids.

The science and artistry of the modern protein engineer, aided by the skills of the directed-Darwinian (molecular) evolutionists, has made it possible to design biocatalysts on the basis of selecting microorganisms from extreme environments and changing their catalytic profiles by genetic modification. Moreover, by intelligent use of high (rapid)-throughput screening (and testing) methods, it is

possible to adapt biocatalysts in relatively short time to the conditions needed in large-scale chemical syntheses. In doing so, less energy will be consumed, and less waste will be produced.

One of the goals of the U.S. Biomass R & D Act 2000 is to make biomass competitive with petroleum feedstocks for the production of energy and chemicals. According to a U.S. National Research Council report, there is sufficient biological waste—as much as 280 million metric tons per annum in the United States from sources such as paper, tree, crop, and wood-processing residues—to satisfy adequately the carbon needed for all 100 million metric tons of organic chemicals that are consumed annually in that country. New processes are already being developed to produce ethanol from biomass or, to be precise, from cellulosic material in wood, grass, and agricultural waste. Cellulose is readily broken down into simple sugars by cellulases, so that it might serve as a plentiful and cheaper raw material for the biocatalytic production of ethanol than present-day food starches. (Bioethanol comes from fermenting sugars, which are often generated by breaking down starches from corn, potatoes, beets, sugarcane, or wheat). Such are the prospects in biocatalysis these days that, in principle, if the right microbe or enzyme is selected (and modified) it should be possible to produce important chemicals like catechol, adipic acid, and gallic acid from carbohydrate precursors such as glucose. The attractions here are obvious: Whereas these materials would normally be generated, indirectly, from nonrenewable petrochemicals, biocatalytically they can all be generated from (renewable) carbohydrate sources. Moreover, the oxygen is already contained within the precursor: It does not have to be introduced via an external oxidant, aggressive or benign. The range of products produced this way encompasses commodity chemicals, pharmaceuticals, food additives, and fragrances.

At present, the cost of enzymes required to convert biomass to sugars remains one of the most critical barriers to commercialization. Notwithstanding these barriers, the DuPont Co. has recently

N
C
Si
O
H

tetramethyl piperidine-1-oxyl
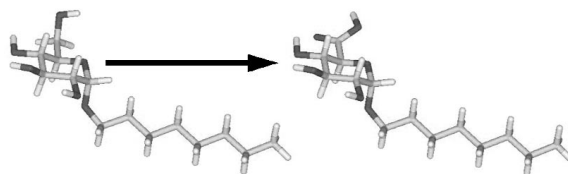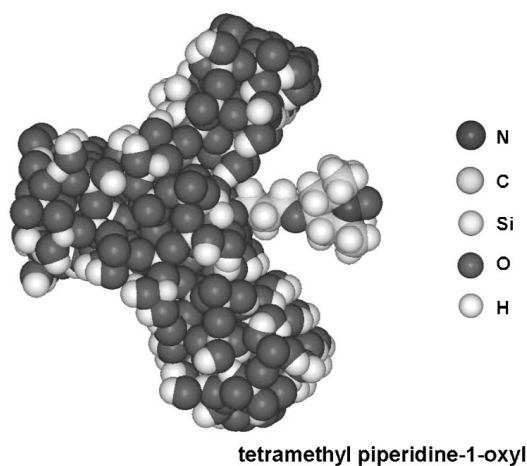
Fig. 13 Anchored TEMPO (tetramethyl piperidine-1-oxyl) catalyst (after H. van Bekkum *et al.* [24]) for the regioselective oxidation of carbohydrates.

announced that it can make 1,3-propane diol (PDO), a key component of the company's new polymer Sorona, from corn sugar instead of petroleum feedstocks. This biocatalytic approach entailed combing DNA from three different organisms into one production strain, thereby resulting in greatly enhanced productivity gain. By sequencing the genome of *Methylomonas* (a common class of microbes that utilizes methane as a source of food), it is hoped that a variety of valuable products can be made on a commerical scale.

According to a recent report in *Chemistry & Engineering News* [23], a successful biocatalytic process for the production of ascorbic acid has been developed by Eastman Kodak, and is already in the pilot plant stage. This new process is entirely aqueous and consists of but two steps, compared with several in the traditional chemical routes. It also promises to be much cheaper.

Despite the great promise of biocatalysts of the kind outlined above, it must not be thought that traditional heterogeneous catalysts have no role in this domain. Perhaps, in future, a combined bioconventional heterogeneous catalytic approach may be expected, especially if full advantage is taken of the nanoporous silicas described earlier. In this connection, it is relevant to recall the recent work [24] carried out in H. van Bekkum's group at Delft. Using an anchored TEMPO (Fig. 13) reagent with NaOCl as oxidant, remarkably high degrees of regioselectivities (for 6-carboxylation) in carbohydrate oxidation could be achieved. Such work, carried out on monomeric systems, could well constitute a first step in a new synthesis of vitamin C.

FAST SCREENING METHODS: A CAUTIONARY NOTE

Fast throughput methods of discovering the best catalysts for a particular reaction are very much in vogue. The merits of doing so are multiply attested, especially in the pharmaceutical field. But such methods are not without serious risk; and this is well illustrated in the quest for the best ammonia synthesis catalyst or for advanced new inorganic catalysts.

The synthesis of ammonia is one of the largest energy-consuming processes of the industrialized world, requiring approximately 1% of the world's power production [25]. The classic iron catalyst, derived from magnetite, performs at high temperature and at a total pressure of *ca* 130 atm. Several tons of the catalyst are used in a fixed-bed reactor. Tens of thousands of other catalysts have been tested, usually by Edisonian methods of trial and error. But the best catalyst so far found, barium (and ceasium)-promoted metallic ruthenium, was discovered not by early variants of the combinatorial exercises, but as a result of inspired chemical ratiocination on the part of Tennison *et al.* [26] (at BP Sunbury), who followed up the pioneering work of the Japanese investigators Aika and Tamaru [27]. The Ru (nanoparticles in the range 2.5 to 3.5 nm) must be supported on partially graphitized carbon. It synthesizes ammonia at a much lower temperature and much lower pressure (*ca* 85 atm) than the iron catalyst; and typical reactors such as those currently in operation in Trinidad produce some 2000 tons of ammonia per day.

Bielawa *et al.* have recently described [25] the lengthy procedure required to follow the activation of the catalyst from its as-prepared to its most effective operational state. These procedures are lengthy: Even after 45 h steady-state activity had not been reached, and experiments showed that some 120 h were needed "on stream" before constant catalytic activity was achieved. This result clearly demonstrates the dangers of conventional fast-screening methods previously used. Indeed, Bielawa *et al.* [25] have cited the specific example of Ru-based catalysts, and state that during a 30-year series of experiments on the part of eminent pioneers the most active new synthesis catalyst was not found.

When "time on stream" is short, as it invariably is in fast throughput testing, such failures will arise. The same can be said of catalysts that poison gradually during the course of use. One method of minimizing the failure rate is to use several reactors connected in parallel; and this is now frequently done.

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