Highlights

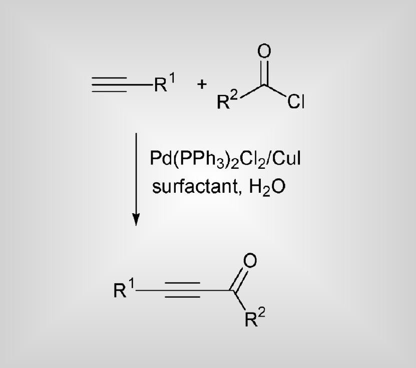
Markus Hölscher reviews some of the recent literature in green chemistry

Generation of nanosized drug particles using supercritical fluids

Drugs are often poorly soluble in aqueous solution. An attempted solution to this problem is to minimize the particle size. Among other techniques for the generation of nanosized particles, which were suggested to have a much better bioavailability with respect to larger particles, the rapid expansion of supercritical solutions (RESS) is very promising. The solute is dissolved in a supercritical fluid which is rapidly expanded *e.g. via* a nozzle into ambient air. Sun *et al.* from Clemson University have now extended this technique by expanding the supercritical solution into a liquid solvent instead of into air, which they have termed RESOLV (*J. Am. Chem. Soc.*, 2004, **126**, 10842–10843). For demonstration they chose Ibuprofen and Naproxen, which both are somewhat soluble in supercritical CO_2 and insoluble in water. By expansion of *sc*CO_2 solutions of both compounds into water, the authors found the water solution to be homogeneous initially, however, after *ca.* 15 min precipitation occurred suggesting the nanoparticles formed agglomerated to give larger aggregates. By adding poly(*N*-vinyl-2-pyrrolidone) as stabilizing agent to the aqueous solution, the nanosized particles could be protected from agglomeration. According to SEM analysis the average size of the Ibuprofen nanoparticles was 40 nm with a distribution standard deviation of 8.5 nm, whereas the Naproxen particles had a size of *ca.* 64 nm with a size distribution standard deviation of 10 nm.

Coupling of alkynes with acid chlorides in water

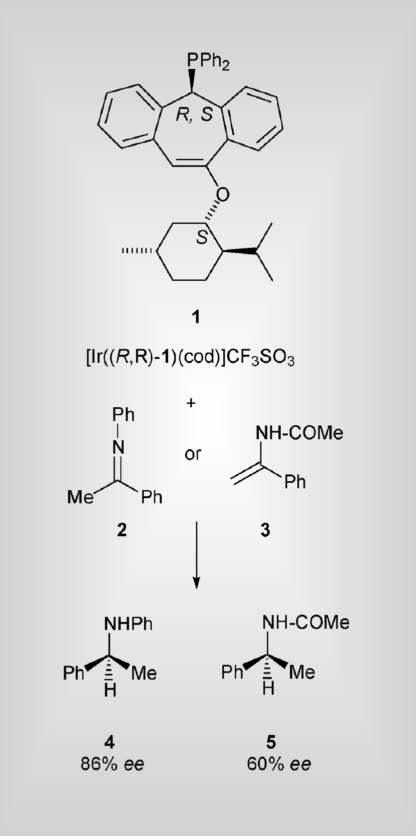
Ynones are important building blocks for the synthesis of biologically active compounds. As the traditional route, in which acid chlorides are reacted with lithium acetylides, is problematic because functional groups on the substrates need protection prior to the coupling reaction, a more efficient and milder reaction ideally in a green solvent is highly desirable. Li *et al.* from Tulane University have shown that acid chlorides can very effectively be coupled with alkynes in water, when the base and the catalyst system are carefully chosen, and when a surfactant is added to the reaction (*Org. Lett.*, 2004, **6**, 3151–3153).



Since acid chlorides hydrolyze quickly in water, the authors reasoned that the addition of a surfactant would decrease the kinetics of hydrolysis, because the surfactant prevents or diminishes the acid chloride molecules from encountering the water molecules. It was shown that a combination of $PdCl_2(PPh_3)_2$ and CuI as catalyst system and K_2CO_3 as base yielded 98% of the desired product in the coupling of phenylacetylene and benzoyl chloride when the aqueous solution contained sodium laurylsulfate as surfactant. When CuI was exchanged with CuBr the yield dropped to 92% and with no surfactant present, only 83% of the product was obtained. Other reaction conditions resulted in yields too low for practical use.

Enantioselective imine hydrogenations with Ir-complexes bearing olefins as steering ligands

It may sound contradictory to use olefins as ligands in asymmetric Ir-catalyzed hydrogenations of imines, since olefins are usually considered to be labile ligands or—not less important in this context—they are subject to hydrogenation themselves. However, olefin hydrogenation profits thermodynamically from the fact that the hydrogenation products (transition metal alkane complexes) are very labile towards dissociation into the free alkane and the transition metal complex due to the poor binding abilities of the alkane. Depending on the detailed geometrical and electronic structure of the transition metal complex under investigation, olefins might very well be used as ligands in Ir-catalyzed hydrogenations of imines, as was shown by Grützmacher *et al.* from ETH Zürich (*Chem. Eur. J.*, 2004, **10**, 4198–4205). Certain diphenyl phosphanyl-cycloheptene ligands can be chemically modified in relatively few steps to yield ligands **1** and after reaction with $[Ir(cod)_2]CF_3SO_3$ the corresponding Ir-complexes are obtained (only one diastereomer of the ligand and of the complex is shown) which can be used directly for the hydrogenation of imines **2** and **3** to yield **4** and **5**, respectively with up to 86% ee for (*S*)-**4** (conversion was >98% in all cases).



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According to NMR spectroscopy and X-ray crystal structure analysis the free ligands retain their crystallographically determined structure in solution, with only one conformer being present. This result was also found for one of the metal complexes. Since the catalytically and structure-related results clearly show that the asymmetrically substituted olefinic double bond in the ligands has a steering effect for enantioselectivity, an interesting research field for novel olefin ligands might soon develop.

Synthesis of acetic acid by direct oxidation of methane in the presence of Pd^{2+}, Cu^{2+} and O_2

A variety of alternatives for the synthesis of acetic acid from methane were published recently, reflecting the importance of this commodity in chemical industries. Bell *et al.* from the University of California reported a direct oxidation of methane in sulfuric acid (*Chem. Commun.*, 2004, 1948–1949). Important for the catalytic cycle is the addition of Cu^{2+} ions and O_2 since this inhibits the formation of Pd black (which occurs *via* reduction of Pd^{2+} to Pd^0). Reaction of CH_4 and O_2 at 180 °C with catalytic amounts of $PdSO_4$ and $CuCl_2$ in concentrated sulfuric acid yielded acetic acid (49 mM) and methanol (4 mM), with CO and CO_2 being present in the gas phase of the autoclave.

$$CH_4 \xrightarrow{Pd^{2+}, Cu^{2+}, O_2, H_2SO_4} CH_3COOH$$

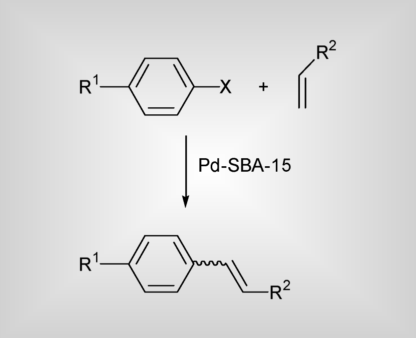
Upon variation of the reaction conditions the acetic acid production could be increased to 132 mM when the CH_4 pressure was increased to 600 psig. Other metals as catalysts, such as Hg^{2+} or Pt^{2+}, did not generate acetic acid at all.

Platinum nanowires by chemical synthesis using a polyol process

As platinum is widely used in many different applications due to its unique physical and chemical properties, much work has been devoted to the synthesis of platinum nanostructures. One goal has remained to be accomplished, which is the chemical fabrication of single crystal platinum nanowires. Chen *et al.* from the University of Washington showed recently that a simple polyol reduction process results in the formation of such nanowires (*J. Am. Chem. Soc.*, 2004, **126**, 10854–10855). In a first step, Pt^{2+} species were generated by reducing H_2PtCl_6 or K_2PtCl_6 with ethylene glycol (EG) at 110 °C in the presence of poly(vinylpyrollidone) (PVN). EG serves as reducing agent and as solvent. The Pt^{2+} species are stable at room temperature for a month, and they can be further reduced at 110 °C under air to yield nanoparticles with an approximate diameter of 5 nm. However, the addition of a small amount of $FeCl_3$ or $FeCl_2$ resulted in a distinct change at the end of the reaction, when the Pt atoms nucleated and grew as nanowires on top of the nanoparticles. Without the presence of PVN no nanowire formation was observed. By short sonication the nanowires could be released from the nanoparticles to which they were attached without being broken. The nanowires could be separated by centrifugation and redispersed in water or ethanol without the need for additional surfactants. According to TEM analyses the nanowires had diameters and lengths of *ca.* 5 nm and 100 nm, respectively. X-Ray analyses suggested a face-centered cubic (*fcc*) structure for the wires which grew in the <111> direction. Except for PVN and iron ions, the presence of air is also critical for nanowire formation since the reduction process is too fast when carried out under inert gas atmosphere, suggesting that the absorption of O_2 on the surface of the platinum nanoparticles slows down the autocatalytic reduction of Pt.

Mesoporous, Pd-coated silica as efficient heterogeneous catalyst for Heck reactions

The Heck reaction—which is the arylation or vinylation of olefins—has received considerable attention during the last decade as it provides a highly selective way to form C–C bonds tolerant to a variety of functional groups. In addition to homogeneous catalytic systems, the development of heterogeneous catalysts has also been pursued and Shi *et al.* from the Shanghai Insitute of Ceramics have recently developed an interesting and highly efficient silica catalyst for this reaction (*Chem. Commun.*, 2004, 1990–1991). The authors chose mesoporous silica SBA-15 as catalyst carrier, which was functionalized with trimethoxysilane and subsequently treated with a $Pd(OAc)_2$–THF solution resulting in the formation of colloidal dispersed Pd(0), as was shown by X-ray photo-electron spectroscopy and XRD analyses. This means that the Pd^{2+} ions were completely reduced *in situ*. The surface area of the Pd-SBA-15 amounted to 379 $m^2\ g^{-1}$, only slightly smaller than that of the parent silica (408 $m^2\ g^{-1}$) indicating the incorporated Pd occupied only very limited space. The pore width was *ca.* 66 Å according to BJH pore size distribution analysis. Also no Pd clusters were found.



When this catalyst was applied to Heck reactions using styrene and methyl acrylate or using 4-bromoacetophenone and methyl acrylate, full conversion and high selectivites were achieved. In the case of 4-bromoacetophenone–methyl acrylate full conversion was reached in 50 min with 99% selectivity, using as little as 0.02 mol% catalyst. Leaching was less than 0.4 ppm as determined by ICP analyses. Recycle experiments showed the catalytic activity to be retained without significant loss for up to 5 reaction cycles.

Solvent-free preparation of primary imines from (2-hydroxyaryl)ketones†

Ylva Bergman, Patrick Perlmutter* and Neeranat Thienthong
Centre for Green Chemistry, School of Chemistry, Monash University, PO Box 23, Victoria, Australia. E-mail: patrick.perlmutter@sci.monash.edu.au;
Fax: +613 9905 4597; Tel: +613 9905 4522

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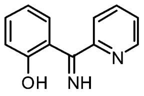
Primary imines can be readily prepared from (2-hydroxyaryl)ketones by reaction with ammonium iodide and piperidine under solvent-free conditions.

Introduction

Primary imines can be prepared from ketones by a number of different methods including employing, *inter alia*, ammonia in an alcoholic solvent,[1] ammonia in DMF[2] or toluene[3] with Lewis acid catalysis, ammonium chloride and ammonia in THF,[4] formamide[5] and liquid ammonia.[6] Recently, Mizufune *et al.* published an excellent scaled up (multikilogram) route to benzoxazines such as **2** in which ammonium iodide/piperidine was employed as the amine source in order to avoid the use of ammonia.[7]

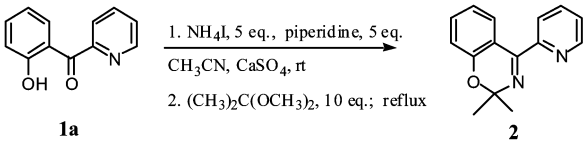
These reactions presumably proceed *via* imines such as **3a**, however these were not isolated. We were interested in preparing such imines for use as precursors to a range of new metal ligands based on the benzoxazine nucleus and considered that it might be possible to ameliorate the published reaction conditions by running these conversions under solvent-free conditions[8] and using fewer equivalents of reagents. In this report we disclose our findings on such a study.



3a

Results and discussion

As shown in Scheme 1 the original conditions involved the use of five equivalents each of ammonium iodide and piperidine. Table 1 summarises the studies carried out into variation of these conditions. The reduction in the volume of acetonitrile was first examined. It was quickly established that the solvent could be completely omitted from this reaction and the product imine was still formed in good yield (compare entries 1 and 2 in Table 1). The necessity of the presence of the calcium sulfate was examined next. It was found that this too was unnecessary with imine **3a** again being formed in good yield (entry 3).



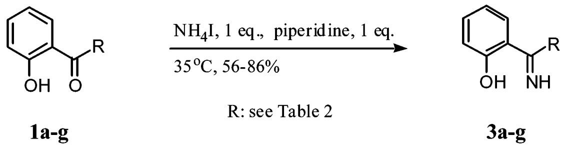
Scheme 1

Table 1 Influence of variation of conditions on the yields of **3a**

Entry	$CaSO_4$/ equiv.	CH_3CN	NH_4I/ equiv.	Piperidine/ equiv.	Reaction temp./°C	Time/h	Yield (%)
1	4.6	Yes	5	5	rt	3.5	73
2	4.6	No	5	5	rt	3.5	83
3	0	Yes	5	5	rt	3.5	72
4	0	No	5	5	rt	3.5	100
5	0	No	5	1	rt	3.5	78
6	0	No	1	1	rt	3.5	17
7	0	No	1	1	rt	40	71
8	0	No	1	1	35	24	73

Running the reaction without solvent or calcium sulfate appeared to proceed significantly more efficiently (compare entries 1 and 4). Reducing the number of equivalents of piperidine and ammonium iodide was possible although this led to a significant diminution in yield and efficiency (compare entry 4 with entries 5 and 6). When using 1 equivalent of piperidine and ammonium iodide and the same reaction time as with 5 equivalents, the yield of the reaction was very low (entry 6). However, by increasing the reaction time (entry 7) and temperature (entry 8) a better yield was achieved. Increasing the temperature significantly above 35 °C led to product decomposition. Substituting ammonium chloride for ammonium iodide led to very disappointing yields ($\sim$10 to 20% for 2-hydroxybenzophenone (**1b**) and 2-hydroxyacetophenone (**1e**)). In accord with the Mizufune group's findings, these reactions can be run in open vessels, seemingly insensitive to atmospheric moisture.

Having established a simplified reaction protocol (Scheme 2) we applied the modified conditions to a range of ketones in order to establish any limits to this process (Table 2). For comparison most reactions were run for the same period of time (40 h) rather than to complete conversion. The balance of material was unreacted ketone. Several important trends emerged. First, the 2-hydroxy group is essential (compare entries 1 and 2 as well as entries 3, 4 and 5 in Table 2). Second, non pyridyl benzophenones (entries 3, 7 and 8) also react well. The 2-hydroxy group must be free as the corresponding methyl ether showed no reactivity at all (compare entries 3 and 6). The requirement for a 2-hydroxyl group on one of the ketone



Scheme 2 The modified imine synthesis protocol.

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† Electronic supplementary information (ESI) available: analytical data for reaction products. See http://www.rsc.org/suppdata/gc/b4/b412192a/

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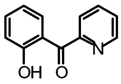
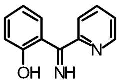
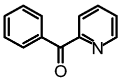
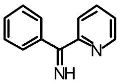
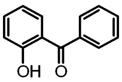
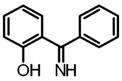
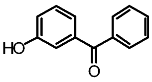
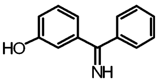
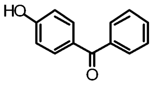
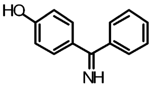
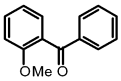
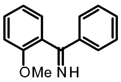
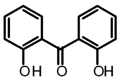
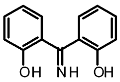
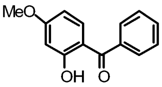
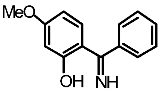
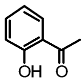
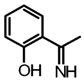
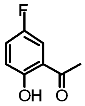
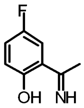
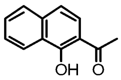
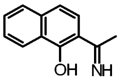
Table 2 Formation of imines under solvent-free conditions

Entry	Ketone	Product	Time/h	Yield (%)
1	 **1a**	 **3a**	40	78
2	 **4**	 **5**	40	NR
3	 **1b**	 **3b**	40	56
4	 **6**	 **7**	40	NR
5	 **8**	 **9**	40	NR
6	 **10**	 **11**	40	NR
7	 **1c**	 **3c**	40	86
8	 **1d**	 **3d**	40	47 (75)[a]
9	 **1e**	 **3e**	40	80
10	 **1f**	 **3f**	40	85
11	 **1g**	 **3g**	40	25 (77)[a]

[a] 68 h.

aromatic moieties suggests that hydrogen-bonding[9] is important in stabilising the tetrahedral intermediate initially formed on ammonia addition to the carbonyl group.

Conclusion

In conclusion we report a solvent-free method for the preparation of primary imines which requires no desiccant and only stoichiometric quantities of each component of the reaction. It was also determined that a minimum structural requirement for successful imine formation was the presence of a 2-hydroxyl group attached to one of the ketone moieties. Hydrogen bonding also appears to be important as protection of the 2-hydroxyl, as its methyl ether, completely inhibits imine formation.

Experimental

Typical procedure

Piperidine (27 μL, 0.27 mmol) was added to a mixture of 2-(2-hydroxybenzoyl)pyridine (**1a**) (50 mg, 0.25 mmol) and ammonium iodide (40 mg, 0.27 mmol). The resulting mixture was heated to 35 °C for 40 h. For an analytically pure sample the product mixture was isolated by chromatography on silica gel using ethyl acetate:hexane (1:4) to remove any unreacted ketone followed by ethyl acetate to obtain the pure imine **3a** as a yellow solid. Satisfactory IR, MS, ^{1}H and ^{13}C NMR spectroscopic and elemental data were obtained on all new imines.

Acknowledgements

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COMMUNICATION

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A new theory for ionic liquids—the Interstice Model
Part 1. The density and surface tension of ionic liquid EMISE

Jia-Zhen Yang,*[a] Xing-Mei Lu,[b,c] Jin-Song Gui[c] and Wei-Guo Xu[a]
[a] *Department of Chemistry, Liaoning University, Shenyang 110036, P. R. China*
[b] *The Institute of Salt Lakes, The Chinese Academy of Sciences, Xining 810008, P. R. China*
[c] *Department of Chemistry, Shenyang Normal University, Shenyang 110032, P. R. China*

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This paper reports measurements of the surface tension of ionic liquid EMISE (1-ethyl-3-methylimidazolium ethyl sulfate) using the forced bubble method at 278.15 to 323.15 K and densities of EMISE using a Westphal balance at 278.15 to 338.15 K. At the same time, a new theoretical model, the interstice model, is put forward. Applying the model, an expression of the average volume of the interstices, *v*, was obtained. The calculated volume fraction of the total interstices is 0.12 for ionic liquid EMISE and is in good agreement with that of the majority of materials which exhibit a 10～15% volume expansion in transition from the solid to liquid state. The value of the thermal expansion coefficient calculated from the model is 5.24 × 10^{-4} K^{-1} and is in good agreement with the experimental value 5.37 × 10^{-4} K^{-1} at 298.15 K.

1. Introduction

Ionic liquids (ILs) are viewed as a novel class of green benign solvents, which promise to have widespread application in industry, possibly replacing currently used organic solvents, due to unique properties such as negligible vapor pressures, broad liquid temperature ranges, and high specific solvent abilities. In particular, after the IL $EMIBF_4$ was synthesized in 1992,[1] many new air- and water-stable ILs were reported,[2–5] and have recently received increased attention from both the industrial and academic communities. In spite of their importance and interest, accurate values for many of the fundamental physical–chemical properties of this class of ILs are either scarce or even absent.[6] And to our knowledge, no theoretical models based on statistical thermodynamics are at present available.

As a continuation of our previous investigations,[7–11] this paper reports a new theoretical model for ionic liquids, the interstice model, which may make successful predictions of experimental results. According to the new model, an expression of the average volume of the interstices, *v*, was derived. The interstice volume fraction calculated using the model is 0.12 for IL EMISE and is in good agreement with that of the majority of materials which exhibit a 10～15% volume expansion in transition from the solid to liquid state. In order to further test the model, the density and surface tension of the ionic liquid EMISE (1-ethyl-3-methylimidazolium ethyl sulfate) were measured. The value of the thermal expansion coefficient, α, calculated using the model, is in good agreement with experimental results.

2. Experimental

2.1 Chemicals

Deionized water was distilled in a quartz still and was used to calibrate the instruments. Its conductivity was (0.9 to 1.2) × 10^{-4} S m^{-1}. Diethyl sulfate of AR reagent grade, obtained from Bejing Chemicals Co., and 1-methylimidazole of AR reagent grade, obtained from ACROS, were used as supplied. Toluene was AR reagent and was purified by a standard method.

2.2 Synthesis of 1-ethyl-3-methylimidazolium ethyl sulfate

1-Ethyl-3-methylimidazolium ethyl sulfate is a new ionic liquid which is prepared by alkylation of 1-methylimidazole with diethyl sulfate in toluene as an inert solvent following the scheme shown in Fig. 1.[5]

An equimolecular amount of diethyl sulfate was added dropwise to a solution of 1-methylimidazole in toluene cooled in an ice-bath under nitrogen at a rate that enabled the reaction temperature to be maintained below 313.15 K. Formation of the IL product was immediate and caused the initially clear solution to become opaque, followed by biphasic separation of the toluene solution and formation of a denser IL phase. After addition of the diethyl sulfate, the reaction mixture was stirred at room temperature for 2 h. The upper, organic phase was decanted and the lower, IL phase was washed three times with toluene, dried by heating at 348.15 K under reduced pressure to remove residual organic solvents, and finally *in vacuo* to yield the resulting EMISE as a colorless ionic liquid. The ^1H NMR spectra of the product matched that given in the literature.[5] The electrochemical window of EMISE was measured by cyclic voltammetry at 303.15 K. The result shows reductive and oxidative limits of −1.40 and 2.40 V, respectively, relative to a Al/Al^{3+} reference electrode, which gives an electrochemical potential window of 3.8 V which was the same as our previous paper.[11]

2.3 Measurement of density and surface tension

First, a Westphal balance was corrected with water. Then, the density of ionic liquid EMISE was measured using the Westphal balance at 278.15 to 338.15 ± 0.1 K. The experimental error is about ±0.0001 g cm^{-1}.

The surface tension of EMISE was measured by the forced bubble method using equipment which was corrected with water at 278.15 to 323.15 ± 0.1 K. The experimental error of the surface tension is ± 0.1 × 10^{-4} N m^{-1}.

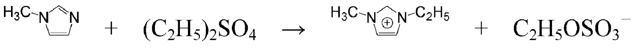

Fig. 1 The preparative route to 1-ethyl-3-methylimidazolium ethyl sulfate IL.

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3. Results and discussion

3.1 The properties of pure EMISE

The density values, ρ, and surface tension, σ, of ionic liquid EMISE are listed in Table 1. Each value in Table 1 is the average of three determinations.

The experimental values of ln ρ against $(T - 298.15)$ were fitted by the least-squares method and an empirical equation $\ln \rho = 0.206689 - 5.37 \times 10^{-4}(T - 298.15)$ was obtained. The correlation coefficient is 0.9999, standard deviation $s = 8.7 \times 10^{-5}$. The coefficient of thermal expansion of pure IL EMISE, α, is defined by following equation:

$$\alpha \equiv \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_p = -\left(\frac{\partial \ln \rho}{\partial T}\right)_p \qquad (1)$$

where V is the molar volume of ionic liquid EMISE. A value of $\alpha = 5.37 \times 10^{-4}$/K^{-1} was obtained. From the experimental density, the molecular volume of EMISE, V_m, was calculated using the following equation:

$$V_m = M/(N\rho) \qquad (2)$$

where M is molar mass (236.285 g mol^{-1}), N is Avogadro's number and $V_m = 0.3190$ nm^3 for EMISE at 298.15 K. According to the data of Fannin *et al.*,[12] $V_m = 0.3756$ nm^3 for EMIAlCl$_4$ (AlCl$_3$/EMIC equals unity) at the same temperature. The increment of molecular volume is 0.0566 nm^3 when $C_2H_5OSO_3^-$ is replaced with $AlCl_4^-$.

Glasser and Jenkins[13,14] have established a good linear relationship between standard entropy and molecular volume for both ionic solids and organic liquids. Recently, Glasser's empirical equations were extended to ionic liquids:[15]

$$S^0(298)/\text{J K mol}^{-1} = 1246.5\ (V_m/\text{nm}^3 \text{ per formular}) + 29.5 \qquad (3)$$

and $S^0(298)$/J K^{-1} mol^{-1} = 427.1 for EMISE. Similarly, $S^0(298)$/J K^{-1} mol^{-1} = 497.8 for EMIAlCl$_4$. This shows that the change in standard entropy was 70.7 J K^{-1} mol^{-1} when $C_2H_5OSO_4^-$ was replaced with $AlCl_4^-$.

3.2 The interstice theory for ionic liquids

For pure ionic liquids, a new theory was put forward on the basis of the following assumptions: 1. Due to their large size and asymmetric shape, the ions may not be closely packed and lots of interstices between ions may come into existence. 2. In order to calculate the volume easily, the interstice is regarded as a bubble. 3. There are 2N interstices for 1 mole of 1-1 ionic liquid, where N is Avogadro's number. 4. An interstice in an IL can move about like an ion or other particle; in the movement the interstice does not vanish, but can be compressed and expanded. This extra feature of motion of an interstice is called the breathing motion.

To quantify the interstice theory, it is necessary to derive an expression for calculation of the interstice volume. According to the fourth assumption given above, the interstice can make thermal movements like an ion. The dynamical state of an interstice is specified in the same way that one describes the dynamical state of an ion or a material particle. Thus, one must specify three position and three momentum coordinates: x, y, z and P_x, P_y, P_z. In addition, in order to characterize this breathing motion, it is sufficient to specify the interstice radius r and the radial momentum P_r corresponding to the breathing motion.

Table 1 Surface tension, σ, and density, ρ, of EMISE

T/K	278.15	288.15	298.15	308.15	318.15	328.15	338.15
ρ/g cm^{-3}	1.2430	1.2362	1.2296	1.2230	1.2162	1.2099	1.2037
σ/10^{-4} N m^{-1}	50.42	49.48	48.79	47.95	47.44	47.01	

According to classical statistical mechanics, the probability, pdr, of the interstice radius being between r and r + dr is

$$p\mathrm{d}r = c\mathrm{d}r\int \exp(-E/kT)\mathrm{d}x\mathrm{d}y\mathrm{d}z\mathrm{d}p_x\mathrm{d}p_y\mathrm{d}p_z\mathrm{d}p_r \qquad (4)$$

where c is a constant, E is the total energy of the interstice.

$$E = E_q + E_p \qquad (5)$$

where E_q is the potential energy of the interstice and E_p is its kinetic energy, which is given by:

$$E_p = \frac{P_x^2}{2m_1} + \frac{P_y^2}{2m_1} + \frac{P_z^2}{2m_1} + \frac{P_r^2}{2m_2} \qquad (6)$$

where m_1 is the apparent mass of the interstice in its translational motions, and m_2 is the apparent mass in its breathing motion.

By integrating eqn. (4), the result is:

$$p\mathrm{d}r = Ar^6\exp(-E_q/kT)\mathrm{d}r \qquad (7)$$

where A is a constant which is independent of the radius.

If an interstice in an ionic liquid is considered to behave similarly to a bubble, the surrounding ionic liquid exerts an inward pressure, p_i, on the bubble surface and, inside the bubble, vapor exerts a outward pressure, p_0, on the surface. The total work required to increase the bubble size, the volume work, is then $(p_i - p_0)\frac{4}{3}\pi r^3$ and the surface work $4\pi r^2\sigma$, equals the potential energy of the interstice, E_q:

$$E_q = (p_i - p_0)\frac{4}{3}\pi r^3 + 4\pi r^2\sigma \qquad (8)$$

When the diameter of the bubble is less than 10^{-5} cm, $r < 10^{-5}$ cm,

$$(p_i - p_0)\frac{4}{3}\pi r^3 \ll 4\pi r^2\sigma$$

and the volume work is negligible compared to the surface work. The potential energy of the interstice therefore reduces to:

$$E_q = 4\pi r^2\sigma \qquad (9)$$

The evaluation of the constant, A, in eqn. (7) is achieved through the following. The probability that an interstice has some radius must be unity, $\int_0^\infty p\mathrm{d}r = 1$ that is:

$$\int_0^\infty Ar^6\exp(-4\pi r^2\sigma/kT)\mathrm{d}r = 1 \qquad (10)$$

The integral in eqn. (8) corresponds to the standard formula and therefore

$$A = \frac{16}{15\pi^{1/2}}\left(\frac{4\pi r}{kT}\right)^{7/2} = \frac{16}{15\pi^{1/2}}a^{7/2} \qquad (11)$$

where $a = \frac{4\pi r}{kT}$. Substitution of eqn. (9) and (11) into (7) yields:

$$p\mathrm{d}r = \frac{16a^{7/2}}{15\pi^{1/2}}r^6\exp(-ar^2)\mathrm{d}r \qquad (12)$$

Then the average volume of an interstice in an ionic liquid is:

$$v = \int_0^\infty \frac{4}{3}\pi r^3 p\mathrm{d}r \qquad (13)$$

The integral of eqn. (13) can be evaluated:

$$v = 0.6791(kT/\sigma)^{3/2} \qquad (14)$$

According to eqn. (14), the average volume of the interstices is $v = 16.54 \times 10^{-24}$ cm^3 and the total volume of the interstices is $\Sigma v = 2Nv = 23.4$ cm^3. The volume fraction of the interstices, $\Sigma v/V$, is 0.12 for ionic liquid EMISE and this is in good agreement with that of the majority of materials which exhibit a 10 to 15% volume expansion in transition from the solid to liquid state.[16,17]

The molar volume of the ionic liquid, V, consists of the inherent volume, V_i, and total volume of the all interstices, $\Sigma v = 2Nv$, that is:

$$V = V_i + 2Nv \tag{15}$$

If the expansion of IL volume only results from the expansion of the interstices when temperature increases, then calculation of the expression α can be derived from the interstice theory:

$$\alpha = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_p = \frac{3}{2}\frac{2Nv}{VT} = \frac{3Nv}{VT} \tag{16}$$

The value of α (cal.) = 5.24×10^{-4} K^{-1} at 298.15 K and is in good agreement with α (exp.) = 5.37×10^{-4} K^{-1}. The relative difference between α (exp.) and α (cal.) is only 2.4%.

It is noted that there are probably certain semantic confusions between the name of this theory and that of the hole model of fused salts.[18] In fact, there is a great difference between the interstice theory and the hole model. The hole theory is designed to describe spontaneous density fluctuations of molecular extent that occur in liquids as the constituent particles move about under thermal agitation. In the unmelted crystal, one such important density fluctuation that appears in equilibrium at high temperatures is the unoccupied lattice site, or missing particle. On account of the rigid geometrical structure of the crystal, such a small low-density region can be equal in size to only one characteristic elementary volume, determined by the crystal structure. Furthermore, motion of these empty regions can proceed only by discrete jumps, produced by the shift of a particle in the crystal into a neighboring unoccupied site. However, the situation in the liquid is much less restrictive, since extra freedom of particle movement accompanying the melting of the rigid crystal implies not only a continuum of possible sizes and shapes for the low-density regions, or "holes", but also that movement of these holes may occur by a relatively continuous drift, rather than by discrete jumps. However, in the interstice theory, the inherent interstices exist in ionic liquids on account of the large size and great asymmetry of the ions and can not vanish during thermal movement.

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TUTORIAL REVIEW

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Products and processes for a sustainable chemical industry: a review of achievements and prospects

Jean F. Jenck,[a] **Frank Agterberg***[b] **and Michael J. Droescher**[c]
[a] *ENKI Innovation, 3 chemin des Balmes, F 69110 Sainte-Foy, France. E-mail: jenck@enki2.com*
[b] *Cefic (European Chemical Industry Council) – Research & Science, Avenue E van Nieuwenhuyse 4, B1160 Brussels, Belgium. E-mail: agt@cefic.be*
[c] *Corporate Innovation & Technology, Degussa AG, Bennigsplatz 1, D-40474 Dusseldorf, Germany. E-mail: michael.droescher@degussa.com*

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This review aims to show that industrial sustainable chemistry is not an emerging trend, but is already a reality through the application of 'green' chemistry and engineering expertise. A large number of current industrial case studies are presented, as well as new developments from the chemical industry. The case studies cover new chemistry, new process design and new equipment. By articulating the requirements for industrial application of sustainable chemistry, this review also seeks to bridge any existing gap between academia and industry regarding the R&D and engineering challenges needed to ensure green chemistry research enables a more sustainable future chemical industry.

1. Introduction

According to the Organisation for Economic Cooperation and Development (OECD), industrial sustainability is defined as the continuous innovation, improvement and use of clean technologies to reduce pollution levels and consumption of resources. In practical terms, industrial sustainability means employing technologies and know-how to use less material and energy, maximizing renewable resources as inputs, minimizing generation of pollutants or harmful waste during product manufacture and use, and producing recyclable or biodegradable products.

The chemical and process industries are well placed to embrace and drive the challenge of industrial sustainability as they enable so many other sectors in the value chain, such as construction, building, transportation and health, to provide high quality products and services. The chemical industry creates materials for multiple consumer markets, which need to be produced, used and recycled by manufacturing processes that are clean, safe and economical. These processes should use the minimum of resources with the ultimate goal of using only renewable and recyclable feedstock.

The global chemical industry represents a significant part of world trade and economic activity with 10 million employees and a combined turnover of some €1300 billion excluding pharmaceuticals, and at €1841 billion including

Jean Jenck was born in France in 1951. He carried out his doctoral research with J. E. Germain at Lyon University, from which he received a PhD in 1977. He spent a sabbatical year in 1982–3 at Stanford University with M. Boudart. During 25 years at Rhone-Poulenc (1974–1999), he gained extensive practical experience in R&D, Process Development, Engineering, Industrial Investments, which continued at Rhodia where he became Technology Advisor in 2000. During his industrial carrier, he has invented, developed and operated numerous processes in petrochemicals, intermediate and fine chemicals. He has also implemented and managed several academia–industry cooperations. Since 2003, he has led a consultancy firm in the field of Sustainable Technologies for the Process Industries.

Dr. Jean F. Jenck

Frank Agterberg was born in the Netherlands in 1966. In 1996 he received a PhD in inorganic chemistry at the University of Leiden, The Netherlands. Frank joined DSM in 1994 where he held various research positions in manufacturing process development, focused on applied catalysis. In 1999 he became responsible for innovation management tools evaluation and implementation. In 2002 he joined the research & science department of Cefic, the European Chemical Industry Association, where he is responsible for research policy and innovation issue management.

Michael Droescher was born in Germany in 1949. In 1975 he received a PhD in the field of polymer science at the University of Mainz, Germany. He then became a Wissenschaftlicher Assistent in Freiburg, spent a Postdoc year at IBM in the US in-between, went through Habilitation (Dr. of Science) for Macromolecular Science at the University of Freiburg in 1981, and is now adjunct professor at the University of Muenster. In 1982 Michael joined Huels AG in Marl now part of Degussa AG, where he held different positions in R&D for Engineering Plastics. After managing a pilot plant from 1990 to 1992, he was responsible for the department Plastics and Environment. He became Managing Director of Degussa's affiliate CREAVIS Technologies & Innovation in 1998. Since 2002 he has been Senior Vice President for Corporate Innovation Management of Degussa AG.

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pharmaceuticals, representing 4–5% of world income. It contributes 9% of world trade whilst emitting only 4% of global CO_2 emissions.

The World Business Council for Sustainable Development's "Business case for Sustainable Development"[1] describes the following business incentives to promote sustainability:

- profitability, fiscal changes
- environmental conscience, legislation and regulations
- concerns from shareholders, employees, customers
- long term business viability related to public perception and image

Profitability is, in itself, a prime driver for sustainability. In 1999, the Consortium Report, a synthesis of ideas resulting from a working group gathering leaders of multinational firms, outlined "*the strategies of sustainable development to create value*". Six virtuous effects were noted: anticipation of constraints and risks, costs-reduction in consumption of resources or production of waste, innovation, competitive advantage by differentiation of products put on the market, and improvement of the company image.[2]

The chemical industry has a strong record of innovation—in products that meet customers' needs, in manufacturing processes that protect the environment and human health, and in solutions that directly address environmental problems. The European Chemical Industry Council (Cefic) is committed to Sustainable Development and has implemented a wide range of action programmes, self-monitoring systems and other voluntary initiatives including the Responsible Care Initiative[3] and programmes such as Product Stewardship, Education–Industry Partnerships,[4] VEEP (Voluntary Energy Efficiency Programme)[5] and SUSTECH (Collaborative Research and Development in Sustainable Technologies for the Process Industries).[6]

This review examines how industry is creating new, more sustainable value by implementing 'green' chemistry and engineering concepts, with a focus on, but not limited to, Europe. We will first look at the issues and challenges facing green chemistry and engineering, then review a selection of implemented processes before examining key disciplines that we believe require research support to further progress sustainability in the industry.

2. Issues and challenges of green chemistry and green engineering

For the chemical industry, *innovation* is its lifeblood ensuring continuous improvement in performance and enabling more sustainable production and use of its products. Innovation is critical: the challenge for business is not only to provide service to our consumer society, but to innovate new ways of doing so with markedly lower reliance on materials, energy, labour and waste. If technology was in the recent past viewed as a cause of environmental degradation, it is now recognized for its key contribution to sustainability by decoupling economic growth from environmental impact[7] and for being vital for enabling downstream industries' sustainability.

Most chemical companies now set environmental and societal targets:

DuPont has set four goals for 2010 "as part of its sustainability mission":

- derive 25% of revenues from non-depletable resources, up from 14% in 2002.
- reduce global carbon-equivalent greenhouse gases (GHG) emissions by 65% (1990 as base year)
- hold energy use flat using 1990 as a base year.
- source 10% of the company's global energy use from renewable resources[8,9]

For year 2012 compared to 2002, BASF aims to:

- cut 10% of GHG emissions per ton of sales
- cut 40% air pollutants, 30% heavy metal emissions
- have 80% fewer lost-time accidents, 70% fewer transportation accidents
- by 2008, the company will have "all relevant information" on chemicals handled in volumes of more than 1 ton per year.[10]

The goal of achieving sustainability, including its dimension of clear benefits to society and equity, is socio-political and cannot be achieved by technology alone. Yet there is a global *technology challenge*, especially in the chemical sector, as sustainability can be attained by the development of environmentally benign processes, integration of material constraints, costs and safety, and further increases in energy and material efficiency in producing goods and services.[11] The challenge lies in improving the chemistry, the selection of raw and auxiliary materials and in the smarter design of chemical manufacturing facilities.

The principles of '*Green Chemistry*'[12] gave a tangible framework to reduce environmental impact of products. Improving industrial sustainability requires goals not only at the molecular and product levels, but also at the process and system levels. '*Green engineering*' focuses on how to achieve these goals through technology.[13] When designing new materials, products or processes scientists and engineers are provided with a framework, beyond baseline engineering quality and safety specifications, based on 12 principles that consider environmental, economic and social factors:[14]

- mass and energy in and outputs should be as inherently non-hazardous as possible
- prevention of waste is better than clean up
- minimize energy in separation/purification processes
- maximize mass, energy, volume and time efficiency in product/process
- output-pulled is preferred to input-pushed
- energy is main criterion for choice between recycle, reuse or disposal
- durability must be targeted (no eternal life)
- avoid one-size-fits-all, minimize excess
- minimize material diversity in multicomponent products
- integration & interconnectivity are a way to industrial ecology
- design for performance in a commercial "after-life"
- favour mass and energy inputs from renewable sources

Technical innovation alone will not suffice to ensure that sustainable technology is adopted. Correct framework conditions are required to enable successful investment in green chemistry and engineering. These include:

- Correct market conditions—including incentives to increase research and access to finance for new (and potentially risky) innovation
- Cost-effective regulation—that does not inhibit change through over regulation
- Appreciation by society—a demand for new products and systems that is real

Recent initiatives such as the European Commission's Environmental Technology Action Plan (ETAP)[15] indicate a potential improvement in the framework conditions for investment in such technologies going forward.

The following current technical challenges will be used to highlight industry innovations in the next section:

- Renewable resources
- Eco-efficient products
- Energy efficiency and sustainable energy
- Waste reduction and waste reuse
- Reduction of Greenhouse gases and other emissions
- Inherently safer processes

3. Examples of implemented industrial sustainable chemistry

3.1 Renewable resources

Nature produces a formidable 200 billion tons of biomass per year by photosynthesis, only 3–4% is currently used by man for food and non-food sectors. Use of biomass can play an important role in sustainable development and handling global warming issues in two major areas of development:

- biomass for energy uses, directly or indirectly
- biomass as base resource for chemicals, materials and products

More specifically for the chemical industry, we can distinguish three main areas:

1. The use of *renewable raw materials* replacing fossil fuel feedstocks, where new enzyme and whole cell systems convert biomass into fermentable sugars and then downstream products
2. *Bioprocesses* replacing traditional chemical processes to make many organic and other chemicals
3. Development of *new bioproducts* such as chemicals, new plastics, high performance polymers.

With respect to the objective of reduced CO_2 emissions, the use of biomass to replace fossil fuel resources is the most important group of technologies. In particular, liquid *biofuels* for sustainable transport, such as biodiesel (produced from vegetable oil) and bioethanol and its derivative ETBE (produced from plant sugars). Other liquid biofuels, such as biomethanol and its derivative MTBE, have been derived from lignocellulosic material. Biodiesel is a C16–18 fatty acid methyl ester. Some 1.5 M tons per annum (tpa) are produced in Europe. Bioethanol is traditionally produced by the fermentation of simple sugars, from starches of potatoes, corn, wheat and other plants. Other feedstocks such as waste products from the beverage, food and forest industries are also used. Research is also being carried out into producing ethanol from agricultural residues such as rice straw, sugar cane bagasse and corn stover, municipal solid waste and energy crops. Bioethanol is used as an automotive fuel, mixed with gasoline to form a fuel called "gasohol." In the US, ethanol-blended fuels account for 12% of all automotive fuels.

Oleochemicals derived from natural fats and oils from animal, marine or vegetable sources are used in detergents and cosmetics, additives for plastics, rubber and textiles, in the production of paint and surface coatings and a variety of applications in the food and pharmaceutical industries. The oleochemical industry already uses mainly renewable raw materials such as palm oil, palm kernel oil and coconut oil.

In the field of biopolymers in 1997, Cargill and The Dow Chemical Company formed a 50–50 joint venture[16] to develop a novel synthesis of polylacticacid (PLA), a polymer formed from corn-derived dextrose. *NatureWorks*™ PLA is the first synthetic polymer class to be produced from annually renewable resources. It is fully compostable in commercial facilities, or recyclable back to the monomer. The two key technical advances for large-scale low-cost production are the synthesis of lactide and efficient vacuum distillation. The Cargill–Dow process has better than 95% yield, requires 30–50% fewer fossil resources than conventional plastics, and results in a 30–60% reduction in GHG emissions. Cargill–Dow has invested more than $300 million in the venture. The first plant built in Nebraska (USA) has an annual capacity of 140 000 tons.[17] Future plants will be able to use various other biomass feedstocks, such as agricultural waste.

Through metabolic engineering an *Escherichia coli* K12 microorganism produces 1,3-propanediol (PDO), in a simple sugars fermentation process developed by DuPont and GENENCOR. In a pilot plant operated by Tate & Lyle, the PDO yield reaches 135 $g\,l^{-1}$ at a rate of 4 $g\,l^{-1}\,h^{-1}$. PDO is used for the production of PTT (polytrimethylene-terephtalate), a new polymer which is used for the production of high quality fibres branded Sorona.[18] Production is predicted to reach 500 ktpa by 2010.

Examples of biopolymers are: *xanthane*, a polysaccharide obtained by fermentation and used as a viscosifier in food, sauces, paints and even cement; *Biopol*, a natural-based polyester developed by ICI;[19] the copolymer poly-3-hydroxybutyrate/-3-hydroxyvalerate is produced from wheat carbohydrates by fermentation using *Alcaligenes eutrophius*. Recent developments using modified enzymes at Metabolics are expected to improve both yields and product properties. Researchers have succeeded in manipulating the genetic code of plants and microorganisms in order to produce polyhydroxybutyric acid.[20]

Dow Corning and Genencor are collaborating on an ambitious 35 M US$ project to make bio-based organosilicones. This so-called "Silicon Biotechnology" is expected to yield unique biologically mediated organosilicon-based materials for application in diagnostics, biosensors, controlled delivery of active ingredients and personal care products.[21]

The use of the enzyme 'nitrile hydratase' by Mitsubishi Rayon was among the first applications of biotechnology in the chemicals industry making acrylamide.[22] The conventional process involved hydration of the nitrile with sulfuric acid and/or the use of copper catalysts.[23] The enzymatic transformation in a batch reactor (kept at 5 °C to avoid polymerization) results in $>99.99\%$ conversion, selectivity and yield to reach a productivity of $\sim 2\ kg\,l^{-1}\,d^{-1}$.

Degussa produces L-threonine, an aminoacid for *animal nutrition*, in a plant expanding to 30 000 tpa, in Slovakia.[24] After researchers genetically engineered a new strain of *Escherichia coli* bacteria to make it stable, improve its productivity, and reduce sensitivity to fermentation products and conditions, the improved process removes up to 90% of the fermentation broth, leaving the remainder to inoculate the next batch, in a 'repeated fed-batch procedure'. Due to the higher purity of the broth, only one crystallization step is required to get the pure product.

Many industrial bioprocesses have been developed in the field of *pharmaceuticals*. For antibiotics such as cephalosporins, DSM began to explore biocatalysis in the early 1980s. Compared to the former chemical route, the bio-coupling of the 7-ADCA synthon results in reduction of total waste by 67%, of organics reagents and solvents by 80%, of steam by 60% and of liquid N_2 refrigerant by 100%.[25]

The traditional multi-step chemical process for the production of vitamin B2 (riboflavin) has been replaced by fermentation at BASF and Hoffman Laroche, resulting in 95% less waste and 40% cost reduction. Vitamin C (ascorbic acid) is also produced by a biotechnological method.

Biotechnology has improved the production of certain *crop protection chemicals*, such as glyphosate: DuPont has announced a new process for this broad-spectrum herbicide, by oxidation of glycolic acid using enzymes cloned from spinach and yeast. This greatly reduces the number of steps in the overall process and reduces loss of product to waste streams.[26]

White biotechnology is especially useful for producing chiral molecules:

- 2 000 tpa of 99% pure chloro-2 propionic acid are produced by Avecia using a dehalogenase enzyme[27]
- Ajinomoto: L-DOPA from catechol, pyruvate and ammonia[28]
- Degussa: chiral aminoacids in hollow-fibre modules[29]

21 biotechnology case studies can be found in the 2001 OECD report: "Application of Biotechnology to Industrial

Sustainability".[30] Additional cases are given in a review on 'Biotechnology for Industrial Sustainability' published in 2001 in South Korea.[31]

3.2 Eco-efficient products: increased functionality/mass ratio

Knowing which material functionality is desired and the required chemical functionalities to deliver that material property, various tools are available to the skilled scientist to selectively introduce these based on assessment of their sustainability

Life Cycle Assessment (LCA) is an important tool which determines all environmental impacts from 'cradle to grave'. Historically, most product management approaches have dealt with 'end-of-pipe' solutions. Today, more holistic approaches consider the life cycle of a product or device (and any part of the production process), from raw material to the final disposal, including re-use or recycling.[32] Life Cycle Inventories (LCI), popularly known as 'cradle to factory gate' studies, form part of the complete LCA which also includes a LC-impact assessment. The Ecosol group in Cefic (13 European surfactant producers) used LCI to compare the 7 most important surfactant types. Henkel[33] used LCI and LCA to show a clear advantage of oleochemical over petrochemical surfactants.

BASF has been using eco-efficiency since 1996 as a way to deliver the right product at the right time.[34] The company compared the ecological footprint of the dyeing process for blue denim[35] using indigo powder from plants, biotech-derived indigo granules, synthetic indigo in conventional dyeing or an electrochemical process. The analysis showed the electrochemical process to be clearly favourable in terms of its environmental impact and a new plant was constructed. BASF's share of the jeans dyeing market has since risen from 2 to 40%.

Few pigments are available in the colour range from red to yellow, such as cadmium sulfoselenide, lead molybdate and bismuth vanadate; they have excellent performance characteristics, but their toxicity is environmentally undesirable. Rhodia developed Neolor™, non-toxic inorganic pigments based on cerium sulfides used in automotive coatings, engineering plastics, ceramic coloring and packaging, where high opacity, thermal stability and light-fastness are required.

Many products designed to ecological rules can be cheaper to produce and use, providing higher value for their users. BASF produces a biodegradeable polyester called Ecoflex, a copolymer of 1,4-butanediol, adipic acid and terephtalic acid. It has good thermoplastic properties and forms semitransparent packaging.[36] The film is fully compostable. Luviset® polyurethane copolymers were developed by BASF to reduce VOC emissions in the production and use of hair sprays, whilst Neopor® building insulation incorporates infra-red absorbing/scattering components that keep more heat in and reduce energy use.[37]

For carpet backing applications, The Dow Chemical Company developed Biobalance Polymers, polyurethane polymers that are manufactured with a portion of the polyol coming from a renewable resource, the soybean plant. These carpet backings can also be manufactured with post industrial waste and a non-woven outer surface made from 100% recycled PET. Synalox™ is a polyglycol lubricant[38] having cleaner profiles than fossil fuel-based equivalents but is biodegradable whilst maintaining and improving performance characteristics.

DEEDMAC is a fabric softening cationic surfactant developed by Procter & Gamble. Inclusion of two weak ester linkages allows a 99%+ removal in sewage treatment and a much improved ecotoxicology profile.[39]

Two examples from Rhodia illustrate the usefulness of *nanotechnologies* for sustainability:

- HDS (Highly Dispersible Silica) is used by Michelin for its "green tyre" which significantly improves performances in term of rolling friction and consequently in the energy consumption of the vehicle, and its adherence to wet road surfaces. Silica, in aggregates of a few nm, replaces the traditional carbon black. The final properties are controlled at the very first stage of synthesis: acid neutralization of sodium silicate. Washed and dried, the silica is produced in various forms: powders, micropearls, granules, to avoid dusting during its handling.[40]
- Cerium oxide nanoparticules, pure or doped with iron, find a new application in pollution abatement in diesel engines. Perfectly dispersed in the gas oil, the 5 nm cerium oxide particules are trapped in the very heart of the soot particles, which are then oxidized in the exhaust filter. The cerium oxide particules are totally retained in the catalyst bed. The effectiveness of this nano catalyst is such that the addition of <10 ppm in the gas oil allows the complete combustion of soots in a few minutes. 2 litres of EOLYS™ allows the effective depollution of a diesel engine during up to 150 000 km.[41]

3.3 Energy efficiency

General points can be made about process improvement that will lead to improved energy efficiency. Fine control of reaction parameters to obtain better yield and selectivity leads to easier, less energy intensive downstream separation. The introduction of new energy-efficient separation technologies, such as membranes, also helps. Process design to minimise multiple drying steps in a process will also significantly reduce energy consumption.

Polimeri Europa has developed new zeolite-catalyzed ethylbenzene and cumene processes which overcome all the traditional drawbacks of conventional alkylation technologies. Benzene and ethylene or propylene are reacted in a simple fixed-bed alkylator. Di-alkylated products are recovered by transalkylation with benzene to produce additional ethylbenzene or cumene. Due to the very high chemical selectivity in both alkylation and transalkylation reactors, almost stoichiometric yields are reached. Energy consumption has been dramatically lowered compared to both aluminium chloride, phosphoric acid or gas-phase zeolite technologies, mainly due to negligible amounts of impurities in downstream distillation. The non-corrosive nature of the catalyst allows low-cost construction materials. The catalyst is completely regenerable and at the end of its life, after burning, the catalyst is a safely disposable, inert material. A plant is currently under construction.[42] Cumene technology has also been moving towards zeolite-based processes and in its Italian plant, Polimeri Europa has experienced seven years of trouble-free continuous operation.[43]

A new coating concept was developed by BASF jointly with plant builders Dürr Systems and car company Daimler Chrysler for painting the Mercedes A-class model cutting paint consumption by up to 20% and reducing emissions and energy consumption. Developed in only 24 months, the process consists of 3 consecutive "wet on wet" coating applications: an anti-corrosion dipcoat, without heavy metals; a water-based coat; and a solvent-free powder-slurry clearcoat deposited by electrostatics. Only one final drying is necessary.[44]

Combining operations is an effective method to reduce energy use. Reactive distillation is an early version of a *Multifunctional Process*: in the late 1970s, Eastman Chemical installed in Kingsport (USA) a tower reactor integrating esterification of methanol with acetic acid and distillation of methyl acetate in one single vessel, with a liquid-phase catalyst.[45] Another example is the 'Texas tea-bag' developed by CD Tech, for etherification of isobutene and methanol, with solid ion-exchange catalyst beds inserted inside distillation columns. A recent review of Reactive Separations[46] gives examples of the incorporation of up to nine functions into one single piece of equipment.

Besides reactive distillation and separations, another active field of function combination is the coupling of membrane technology to a reaction process, to remove a reaction-limiting component. Examples are pervaporation for removal of water in enzymatic esterifications and membrane nano-filtration of a product in fermentation processes. Two developments by TNO are:

- a membrane slurry reactor[47] for fine chemical hydrogenations, where very fine and active metal catalyst particles are removed from the slurry phase.
- gas cleaning where bacteria usually do not cope with dry and acidic conditions: filamentous mould is grown on perlite inert material, feeding on aromatic compounds.[48]

In this important field of membranes, new concepts are appearing, such as the non-porous elastomer membrane (selective one-way flow permeating across the membrane) commercialized by Membrane Extraction Technologies (MET) in the UK.[49] MARS (Membrane Aromatic Recovery System) is a novel process for separating toxic organic compounds from point-source waste streams. The first commercial-scale installation of MARS is now underway at Degussa AG's Fine Chemicals Site in Knottingley, UK, where the process is treating several thousand litres per day from one effluent stream, recovering the *p*-cresol content. This represents a rapid lab-to-plant scale-up for the MARS process, which went from initial proof-of-concept processing 5 litres per day in the lab during 1999, to pilot trials treating 1000 litres per day in 2001, to process scale operation in 2003. Using MARS, effluent streams can be treated not only to remove these toxic chemicals, but to recover them with a quality that allows for their re-use.

3.4 Waste reduction

There is a clear business case for waste reduction as drives for 'zero' targets show. For example, by developing new technology for manufacturing a key component of Lycra, DuPont earned an added 4 M$ a year, while cutting 2 ktpa of waste.[50]

Sumitomo Chemicals and Enichem combined two catalytic technologies for a 70 ktpa caprolactam plant: instead of the classical route with hydroxylamine sulfate, a toxic and corrosive reactant, cyclohexanone is directly ammoximated by NH_3 + H_2O_2 over a Ti-MFI type zeolite. For rearrangement of the intermediate oxime to final caprolactam, a catalyst replaces oleum. Co-production of ammonium sulfate, with poor fertilizing properties, causing economic and environmental concerns to manufacturers, is completely eliminated, as well as NO_x and SO_x gaseous emissions related to hydroxylamine and oleum/sulfuric acid production.[51]

Süd-Chemie[52] in a new route to make metal oxides, instead of nitric acid attack followed by base precipitation, reacts the metal with mild, aqueous carboxylic acid in presence of air, leading to 95% reduction of process water (75 tons less waste discharged per ton product) and zero nitrate disposal. In addition to environmental and costs benefits, customers found better performance from the new oxides as catalysts.

In the electronics sector, silicon chip fabrication plants generate up to 15 000 tons of wastewater in a typical day, and large amounts of alcohol are used as a drying agent. SC Fluids[53] has commercialized the SCORR process, where supercritical CO_2 is used rather than wet treatment to remove photoresist masks and post-etching residues. SCORR soaks the semiconductor device in CO_2 added with 1% propene carbonate; then pressure pulses dislodge the resist, the CO_2 being recycled.

3.5 Waste reuse

New material from waste by-products is not a new concept: 'From waste to value'. The basic idea is to make new material using secondary materials and by-products from *another industry*. In 'design-for-environment' environmental factors are included at the beginning of the product-process design.

An example is the extraction of squalene from olive oil waste streams (rather than from shark livers) developed by Uniqema.[54] Squalene is used in formulations for health, personal care and cosmetics. Uniqema also developed a process to recover waste frying oil to produce high grade stearine, used for example in rubber tyres.[55]

High grade carbon fibres are made by Conoco from low value 'bottom-of-the-barrel' pitch, thereby transforming a low-value, low-utility product to a versatile high value material. This carbon fibre business known as Cevolution started in 2002 with a 3 600 tonnes capacity process. Carbon fibres, a light-weight yet strong material, open the door to non-traditional, more durable applications (from car-body panels or 'smart' asphalt, to high capacity batteries).[56,57]

A source for aromatic dyes based on anthracenes and carbazoles is coal tar, a by-product from coke used in metallurgy. An improved static crystallisation eliminates solvents and reduces energy use. A new plant with twice the capacity of the classical extraction process is to be implemented soon at Ruetgers.[58]

Woodstalk brand fibreboard, shelving and flooring underlay are manufactured by Dow BioProducts Ltd. at its facility in Elie, Manitoba, Canada.[59] These alternatives to conventional fibreboard and plywood are made from wheat straw fibre, an annually renewable resource, instead of wood. The wheat-straw fibre used to produce Woodstalk boards would otherwise have been burned after the wheat harvest, adding large quantities of smoke and other products of combustion, such as carbon monoxide into the air. This use of straw residue—conventionally considered a waste product—provides a secondary revenue for farmers in the Winnipeg area.

3.6 Emissions reduction

Increased energy efficiency and use of renewable energy sources will continue to reduce the industry's CO_2 emissions. However it has been estimated that 40% of the emission of VOC (volatile organic compounds), equivalent to around 15% of global anthropogenic GHGs, originate from organic solvents widely used in the chemical and related industries. Some are also highly flammable or toxic. Efforts have been made to replace them by alternative media, such as water, super-critical solvents, ionic liquids and "neoteric solvents". The principle of using these alternatives has been demonstrated but still few industrial processes are industrialized.

Supercritical fluids (SCF) are popular in the extraction industry: for example SC CO_2 for decaffeination of coffee or dry cleaning processes. In chemicals, a 'veteran' process is the Unicarb spray-coating commercialized by Union Carbide in the early 1990's where the majority of traditional solvents are replaced by co-solvent modified SC CO_2. The technique is now implemented in the automotive and furniture industry.[60]

Supercritical fluids have been demonstrated as clean 'green' solvents in industrial synthetic chemistry. In 2002, Thomas Swan commissioned a multi-reaction SCF reactor, a commercial-scale continuous facility.[61,62] The full scale 1000 tpa plant located in Consett (GB) cost 1.7 M GB£.[63] Reactions using SCF are hydrogenations (*e.g.* of isophorone), Friedel–Crafts alkylations and acylations, hydroformylations and etherifications. Friedel–Crafts reactions in continuous SC CO_2 use alcohol instead of chloride, acid resin instead of $AlCl_3$ or HF, and have no other by-product than water.

DuPont built a manufacturing facility in Fayetteville (USA), the first phase of a total investment of 275 M US$ for a tetrafluoroethylene SC polymerization unit. Fluorinated vinyl polymers are non-explosive when mixed with CO_2[64] and can be continuously polymerized in the SC medium.

Non-combustion 'chemical' GHG include nitrous oxide (N_2O), a main coproduct in nitric acid manufacturing and in stoichiometric oxidation by nitric acid. In adipic acid manufacture about 300 kg N_2O is coproduced per ton of final product.[65] The industry was alerted to the issue in the early 1990s and different abatement technologies have been industrialized by the major producers of adipic acid: catalytic decomposition of N_2O by DuPont,[66,67] incineration with N_2O acting as an oxidant in a burner by Bayer[68] and partial oxidation to NO_x, recovered to recycle nitric acid by Rhodia.[69] Abatement of N_2O emissions throughout the sector has risen from around 38% in 1990 to 81% in 2000. This represents 598 ktpa of N_2O not released to the environment; equivalent to 175 M tons of CO_2 in terms of GHG emissions.

3.7 Safe processes

Safe use of new technologies is best ensured by a systematic approach to risk assessment and management. Frequently, what makes a product fundamentally useful also makes it hazardous. "Benign-by-design" processes try to use only passive controls, with no human intervention needed.

3.7.1 Benign by design. The methyl isocyanate disaster at Bhopal, India, in 1984 drew attention to the necessity to reduce the inventories of dangerous reactive intermediates and to produce them at the closest point to their use. This brings us to the concept of 'inherent safety'. It is[70] a cost-effective methodology seeking to remove hazards in the first instance. This pro-active approach is based on the following principles:

- intensification: reduction in the quantity of hazardous materials
- substitution: use of safer materials
- attenuation: run at safer operating conditions (room T and P, liquid phase)
- effect limitation: change design and operation for less-severe effects
- simplification: avoid multi-product or multi-unit operations
- error tolerance: more robust equipment, fault tolerant processes, *etc.*

Process minimization, a key inherent safety technique, can lessen the consequences of potential mishaps.[71]

Many examples of substituting hazardous materials can be found. Avoiding phosgene as raw material, Polimeri Europa (formerly EniChem) has pioneered the development of dimethylcarbonate (DMC) produced by methanol oxycarbonylation, with O_2.[72] The DMC process was initiated in 1983, accounting today for 70 ktpa worldwide, and a further 50 ktpa production being scheduled to go on stream during 2004. The oxidative carbonylation is a 'clean' technology: the catalyst allows high selectivity, resulting in minimization of by-products. Catalyst life is practically endless and there is no need for catalyst disposal. The only co-products are water and CO_2, which is efficiently reutilized as a carbon source in CO generation.

As a product, DMC is an eco-friendly substitute to toxic reactants, such as phosgene and chloroformates in carbonylations, or methyl halides or dimethylsulfate in methylations. These reactions are carried out in an excess of DMC itself, allowing easier separation, reduction in energy consumption and lower probability of losses. DMC based reactions require only small amounts of base catalyst, so that salt coproduction is negligible. Only CO_2 and methanol are released and recycled. DMC is used in industrial processes from fine chemistry to lubricants and polymers.

The catalytic production of propylene oxide with H_2O_2[73] as an alternative to chlorine and water as the sole final by-product is under development in these processes:[74]

- UHDE and Degussa: fixed bed reactor, licenced to SASOL for 60 ktpa in South Africa
- The Dow Chemical Company and BASF: a 300 ktpa unit to start up in 2007
- A related example by Sumitomo: oxidation with cumylperoxide in Japan
- Nippon Shokubai: 99% selectivity obtained with silicotungstates
- Lyondell: using more sustainably produced H_2O_2 made *in situ* from H_2 and O_2

Polimeri Europa has developed a new metallocenic catalyst based on titanium and magnesium, to replace nickel and aluminium for hydrogenation of SBS rubber. The environmental impact is significantly reduced and nickel is eliminated from the process.[75]

In industrial bleaching, hydrogen peroxide is replacing chlorine in bleaching of paper, textiles, *etc*. But the process is still not quite sustainable, as large quantities of clean water are needed. One way to treat the H_2O_2-containing wastewater is to use enzymatic systems. Catalayses extracted from extremophile microorganisms show promising performance. Attaching these enzymes to polymer beads in packed columns is currently scaled-up to industrial bleaching processes.[76]

3.7.2 Distributed manufacturing. Rather than manufacture a product in one location and then transport it to different customers, it is increasingly common to employ 'distributed manufacturing', where smaller volumes are produced at a number of remote sites, thus avoiding transporting of toxic, flammable materials, storage with high safety risks, and distributing the potential environmental impact. A better approach would be to produce 'on-site on-demand', in continuous mode followed by immediate consumption of the reagent keeping inventory to a minimum. Interox makes 1 ton per day of peroxysulfuric acid in a 20 cm^3 tubular reactor with only 1 second residence time.[77] This is delocalised production of Caro's acid, for 'on-site on-demand' use without any intermediate storage. Kvaerner[78] has developed a modular, point-of-use, skid-mounted generator, delivering phosgene over a wide range of rates. DuPont makes 5 tpa of HCN (useful for pharmaceutical or gold metallurgy) in a system also having the unique feature of using inductive energy to provide the endothermic reaction heat.[79]

3.7.3 Continuous processes. Many industrial processes, particularly in 'speciality chemicals', are scaled-up versions of laboratory experiments, due to the constant pressure to improve time-to-market, and are therefore performed in single-stage batch mode frequently far from the technological, economic and ecological optimum. This approach is fast and reliable, but it generates waste up to 2–3 orders of magnitude greater than the amount of product.[80] A current trend is to switch to continuous processes, which are much easier to control than inherently dynamic batch processes. Quality of product and process safety are also easier to achieve in continuous steady-state systems where each molecule experiences the same heat profile, concentration gradient and mixing characteristics leading to a purer final product with a narrow property distribution.

"The goal is to do everything on a continuous basis", primarily to minimize inventories of hazardous materials. Phoenix Chemicals[81] makes 120 tpa of an active pharmaceutical ingredient in a plant that fits on top of an office desk, the reactor being as small as a tea cup, and much less expensive than batch vessels. Phoenix's concept of VRT 'variable residence time' reactors is currently used to produce a hydroxynitrile intermediate for Lipitor.[82]

Some new technologies are a bridge between *batch* and *continuous* processing: Air Products & Chemical[83] has commercialized the monolith loop reactor (MLR), especially for gas-transfer limited hydrogenations. The monolithic catalyst developed by Johnson Matthey[84] is a honeycomb with parallel channels, a varied number of cells per unit section area (up to 100 cm^{-2}), with 1–5% precious metal bonded to the inner surface of each channel. The catalyst is installed as part of an external loop on a conventional tank reactor; coupled with gas ejectors, improving 100× the gas–liquid mass-transfer rate. For a 10 m^3 reactor, the MLR module has a 0.3 m^2 footprint and is easy to place and remove. This technology eliminates the use of catalyst slurries, avoids filtration and extensive inter-campaign washing.[85]

Dow Pharma developed a semicontinuous Swern oxidation process:[86,87] an intermediate synthesized in a compact continuous reactor is immediately quenched (by triethylamine) in a batch vessel: the traditional batch cryogenic conditions are no longer needed.

3.7.4 New business models. In a search for a safer way to deliver chlorinated solvents, The Dow Chemical Company developed a model that allows customers to continue to use these products and their excellent cleaning efficiency, while simultaneously reducing emissions and providing risk management throughout the life-cycle of the products. In 1992, Dow Deutschland and Recycling Chemie Niederrhein funded a joint-venture to offer chlorinated solvents in a closed-loop delivery system.[88] In 1998, Safechem Umwelt Service GmbH[89] became a fully owned subsidiary of Dow. The Safe-Tainer system consists of two double-skinned containers, for the safe delivery and return of solvents to and from customers (such as metal cleaning companies). Used solvent is then recycled. Solvent lifetime and efficiency is maximized through specially designed stabilizer packages and solvent maintenance tools. More than simply a set of two containers, the Safe-Tainer system enables reduction of emissions and volume while providing maximum customer support.

4. Key developments for the future

The examples described in the previous section necessarily are incomplete but reflect the wider picture. They also prove that sustainability has to be assessed on a case-by-case basis. Two major questions emerge: what is the impact of these developments and what are the promising technology areas for the future?

Development and implementation of more sustainable chemical technologies have enabled the industry to decouple economic growth from increased environmental impact. As an example the European Chemical Industry has increased production by over 35% since 1990 but its energy consumption is at roughly the same level as 1990 and its CO_2 emissions have reduced. Furthermore the industry has improved the sector's competitiveness with labour productivity increasing by 59% over the period 1992–2002.[90]

The chemical industry is a diverse and complex sector. Establishing industry wide priorities for research is not easy, however we believe that the following nine research areas can—if properly supported and sponsored—make a significant contribution to improved sustainability of the chemical industry in the next decade:

1. 'white' (industrial) biotechnologies
2. process intensification and 'meso'-technologies
3. multiscale process design and 'scale-out'
4. catalytic processes
5. green 'neoteric' solvents
6. new activations
7. new materials
8. thermo-economics
9. industrial ecology

4.1 White (industrial) biotechnology

Biobased sustainable industrial chemistry is very high on the international agenda. The OECD publication 'Biotechnology for Clean Industrial Products and Processes: Towards Industrial Sustainability' (1998)[91] and many other publications such as the USA Roadmap for Biomass Technologies,[92] note that biotechnology is a powerful tool for achieving industrial sustainability, and is gaining ground for the production of commodity chemicals. Much development has already been done on the possible uses of biomass for production of materials:

- direct use of specific materials from plants and trees, for construction materials, paper, textiles, *etc.*,
- specific products based on specific constituents of crops (oil, fibres *etc.*) by (chemical) conversion *e.g.* for specialty chemicals, biodegradable polymers, *etc.*
- generic conversion of biomass to basic constituents: 'building blocks' such as CO, H_2, CH_4 but also ethanol, acetone *etc.* through fermentation
- potential for production of high added-value products (pharmaceutical products and agrochemicals)

Industrial biochemistry seems to be more acceptable to the general public than agricultural biotechnologies, and in the long term, the production of chemicals should be increasingly based on biomass as raw material; including non-food resources, restricted residues and wastes.[93]

Chemistry and Chemical Engineering have essential contributions to make in:

- developing the technologies for conversion of biomass into energy carriers and chemicals
- research on which biomass materials are most suited and where and how arable land and water resources can be developed and exploited
- determining the metrics and indicators for the assessment of the effectiveness of sustainability projects

There are economic challenges for the development of 'White Biotech': feedstocks such as vegetable oils and glucose can be expensive, the enzymes used to convert the material require a high investment in research and long development times. It is also clear that speciality chemicals, with lower volumes of production, are likely to see the most profound early impact from biotechnology.

In "*Bio-Refineries*", biomass is used for the production of high added-value chemicals, fibres and fine chemicals, together with the production of energy carriers, preferably in liquid phase for higher energy content and easier transportation. Certain technological bottlenecks need to be investigated: a weak point is pyrolysis to obtain "bio-crude-oil/bio-fuels". Pyrolysis has not been investigated from the Chemical Engineering point of view, nor considered as a part of the holistic production system *viz*: pyrolysis – stabilisation of the produced oil-refining – use as fuel or raw material. This could be one of the main production routes in a bio-refinery concept.

A parallel approach is the concept of "*Bio-Cascade*", using crops in such a way that all constituents of a plant (oils, proteins, fibres, cellulose, secondary metabolites and remaining wastes for energy use) result in a total product mix that offers the highest economic value. Biomass can be used as an energy carrier by gasification and also as a source for base chemicals *via* the Fischer–Tropsch reaction to 'bio-oil', later refined to liquid fuel.

Further biomass utilisation can establish innovative production networks:

- separation of lignin from cellulose for different downstream product lines
- use of solar energy in combination with use of biomass
- insertion of biotechnology in normal processes for certain steps
- advanced generation of hydrogen by biological processes

Ethical considerations imply that real biomass residues—and not food—are used for chemical feedstocks, and almost exclusively for bulk applications. Even spoiled wastes can be converted to intermediates. Choren[94] has begun production of ~30 kg h^{-1} of synthetic diesel fuel from renewable resources, using the entire biomass of plants, including waste timber: Carbo-V is a three-stage gasification process.[95]

New processes for commodity chemicals, such as succinic acid and ethylene glycol, are in the pilot stage. Shell has recently invested in enzyme producer Iogen to develop a process making a high octane alcohol by fermentation. DuPont has entered a 6-year alliance with Diversa in a bio-refinery project to produce sugars from corn and biomass (including husks, straws, stovers) and develop fermentation processes to co-produce bioethanol and value-added chemicals (such as 1,3-propanediol).[96]

Vegetable oils (rapeseed, palm) can be used as energy carriers or for production of chemicals. Comprehensive LCA based on ecological indicators (finite energy resources, global warming *etc.*) conclude[97] that:

- biobased sources have clear advantages over fossil fuel counterparts
- transesterified biofuels are better than pure vegetable oils
- vegetable oils are preferred feedstocks to produce surfactants

Biocatalysis is also increasingly important in polymer science[98]

4.2 Process intensification and 'meso-technologies'

The key motivation for industrial process intensification is "*doing more with less*". Process Intensification (PI) was first designed as a strategy to reduce the size of chemical plants,[99] thus decreasing capital intensity. This concept led ICI, as an early adopter in the late 1970s, to industrialize the Higee technology, a radical rethinking of distillation, operated under a radial gravitational field. The DSM Urea 2000$^{\text{Plus}}$ process is a more recent illustration of PI as a "size reducer": the new plant is only ~20 m high compared to the previous 50 m.[100]

PI takes a broader dimension as a method to give full potential to physico-chemical transformation by minimizing diffusional limitations. It is about adapting the process to the chemical reaction, choosing the technology best suited to each step of the process and adapting the size of equipment to the reaction, rather than adapting the physico-chemical transformation to existing and often unsuited apparatus. The goal is to replace large, expensive, inefficient equipment by a smaller, more efficient and less costly plant. It is also to combine multiple operations in fewer apparatus.

PI, by its engineering approach, coupled with development of apparatus, techniques and sensors, leads to dramatic improvements in manufacturing and processing including: decreasing size/production ratio, energy consumption, waste production and using smaller, more compact, safer and better controlled (therefore more economic) installations. "*PI is a potentially lucrative way to generate products in a more concise environment that is safer, cleaner and less expensive*".[101]

The rationalization of the method, the existence of intensified tools of variable sizes allow technologies for 'sustainable manufacturing' using eco-efficiency (mass, energy), intrinsic safety (benign-by-design) with improved quality of the product. Good results are anticipated from PI for three reasons:

- in the short run (next 5 years) it is the major lever to improve Process Safety
- in the medium term: it brings (break-through) technological innovation as an answer to societal constraint
- it also enables greater control to improve and guarantee the quality of products, thus differentiating their end-use properties

During the 5th International Conference on "PI for the Chemical Industry" (Maastricht 13–15 October 2003),[102] papers were presented by industries from a variety of subsectors: oil (Norsk Hydro: intensified gas treatment), natural gas (Kvaerner: membranes for sweetening, dehydration), petrochemicals (Sabic and The Dow Chemical Company: energy efficient cracker), intermediates (DSM: urea-melamine process), specialities (TNO: conversion batch mixing to continuous operation), and equipment (Davy Process: gas/liquid ejector for oxidation).

In spite of an innate conservatism often anchored in common sense,[103] the industry is developing intensified equipment and processes.[104] Like other new concepts, many barriers exist to implementation of PI: incremental debottlenecking and expansion is preferred in slow-growth times, a first-of-a-kind process faces a high investment hurdle, plant managers are naturally conservative, risk averse and ask for full-scale demonstrations of new concepts to reduce risk. PI requires a totally new mindset to traditional batch operations and changes can have a high regulatory cost.[105] There is also a technological aspect: the current portfolio of process intensification unit operations is too limited (reaction and heat exchange, reactive separations). We need innovative integrated equipment. Certain aspects, such as pressure drop, plugging of microchannels, fouling of microdevices, are still largely unexplored.

In most synthetic chemistry order is created in molecules at the expense of exothermic bond formation. At the industrial scale, if the removal of the heat is the limiting step, the intrinsic chemical possibilities must be degraded in order to 'cool down' the reaction, by dilution in a solvent, by lower concentrations, by slow feed of the reagent, by partial deactivation of catalyst, by voluntary diffusional limitations. Therefore the transformation appears to be 'slow'. Intensified equipment intends to give full capacity to the intrinsic capacity of the transformation. Some examples of such novel apparatus include: *Rotating Packed Bed reactors*,[106] *Compact reactor-exchangers*,[107] *Spinning-Discs Reactors*,[108] *Spinning tube-in-tube reactors*,[109,110] *Static mixers*,[111] *Intensified static mixers*[112] and *Oscillating baffled reactors*.[113]

A further innovation in process design can be made through *microtechnologies and structured devices*, an unprecedented opportunity to explore radical innovation for a new generation of high-precision production devices.[114] New structured components fabricated at low-cost in various materials (corrosion-resistant metals, plastics, ceramics, and also in convenient, efficient and cheap glass), bring formidable possibilities for intensification for sustainable processes due to very efficient mass and heat transfer and added control of the process, especially in continuous plug flow.

Smaller apparatus is better for mass and energy transfer due to:

- decrease of linear dimensions leading to higher gradients of physical properties, higher driving forces for heat transfer or mass transport
- increase of surface to volume ratio leading to increase of the effective exchange surface (microreactors give surface-to-volume ratios of up to 200 000 m^2 m^{-3})

- decrease of volume giving smaller material hold-up and improved safety conditions

Microstructured equipment already exist as laboratory tools: µ-mixers, µ-extractors and µ-contactors, µ-reactors (chemical, electro-, photo-), thermal µ-exchangers, µ-separators are used to acquire basic data in R&D, diagnostics, optimization and process development, where their power to generate information rapidly is recognized. Micromixers are especially well developed, with wide geometric configurations such as caterpillar, impinging jets and interdigital. For production tools, the paradox between macroscopic chemical production and microscopic size of the reactors can be solved by numbering-up. Nature does not scale-up, just more cells are fabricated to produce more compounds. This paradigm remains valid: a production unit could be made by a simple replication of the experiment undertaken in the laboratory on a 'chip' or microdevice in thousands of similar devices. CPC developed the Cytos microreactor: six reactors operated in parallel constitute a mini-plant producing 30 tpa of dye pigments at Clariant.[115]

The advantages of the very homogeneous temperature and concentration fields in microstructures have been demonstrated repeatedly. Strongly exothermic reactions, for example, can be kept under better control, and reactions of explosive mixtures can be safely realized in these inherent safe types of reactors. Degussa[116] commissioned DEMIS™ in 2003, for a total project cost of 4.6 M€, with epoxidation of propene using vaporous H_2O_2, catalyzed by titanium silicalite, as a model reaction. New gas-phase reactions are an attractive alternative to save on solvents. Running the process in microstructures under explosive conditions also increases space-time yield and selectivity. 4 m high, 1.4 m in diameter and weighing 9 tons the exterior measurements hide the world's first pilot-scale microstructured reactor for heterogeneously catalyzed gas-phase syntheses. The truly 'micro' aspect lies hidden within the safety container, in microstructured installations that are modular in design. Like a plate-type heat exchanger, capacity can be increased by connecting additional modules.

Merck KGaA[117] has developed a vitamin H intermediate continuous process (in less than 2 years), replacing a 5 m^3 batch reactor operating at -20 °C by a few mini-reactors running in parallel reducing selectivity to by-products from 28 to 7%.

Microreactors can be used for a broad range of reactions, such as gas, liquid, gas–liquid or multiple-phase reactions and even the manufacture of solids using microreactors is under development.

The 'Super-focus' micro-mixer developed by IMM[118] for hyper-fast organic reactions has a characteristic mixing time of ~3.5 millisecond. Other applications include precipitation by anti-solvent technique, for example of PLGA microspheres for active delivery.

Microfluidics[119] is developing a 0.7 $m^3\ h^{-1}$ prototype of MMR (Multiple-stream Mixer-Reactor) where reagents are mixed at a residence time of 1 second with local energy dissipation of 10^{10} W kg^{-1}, to manufacture nanosuspensions of solid drugs for direct bloodstream injection.

Small-scale is not restricted to microtechnologies and numbering-up. What is needed is an adequate and optimal (not minimal) characteristic length (or characteristic time, or energy dissipation) related to intrinsic kinetic parameters. A millimetre size is often sufficient and economically optimal. Such structured equipment at the right length/time (µm, mm, cm) are called '*Meso-technologies*'.

4.3 Multiscale process design and "scale-out"

Multiscale Process Units are large-scale systems constructed from meso-technologies. Two examples illustrate the concept of 'scale-out':

The Segmented Flow Tubular Reactor (SFTR)[120] consists of a micro-mixer, then a segmenter in which the reaction mixture is split with an immiscible fluid (kerosene) into liquid droplets in a continuous mode. Each micro-batch droplet circulates through a tubular reactor with identical residence times (quasi plug-flow and no back-mixing). At the end, the micro-droplets are collected in a decantor. A SFTR pilot-plant, operated by Bubbletube,[121] proved the robustness and versatility of the process to make inorganic metallic salts with well-controlled particle size and a narrower size distribution.

Axiva developed a 2000 tpa plant making specialty polyacrylates: monomer and initiator are fed to an array of 32 micromixers, then 4 tubular static reactors, then 1 finishing tube. The result is a polymer of improved quality with narrow chain length distribution for Aventis.[122]

Integrated Multiscale Design sets the stage for a true paradigm shift in the principles of chemical process design: rather than adapting the operating conditions and chemistry to available equipment, the process structure, architecture and equipment are adapted to the physico-chemical transformation. Production units can be created by integration and interconnection of diverse, small-scale locally structured elements into large-scale macro-production units. Many developments of multi-scale technology are expected for chemical manufacturing including: delocalized production for on-site on-demand manufacturing ($COCl_2$, HCN, ClO_2); high yield and compact design in organic synthesis; multi-scale polymerization–control of molecular weight distribution; much safer production (*e.g.* millichannel reactors for nitration); processes with intrinsic safety (*e.g.* no detonation with pure O_2); new activations (*e.g.* electrochemical and photochemical processes); product homogeneity in liquid formulation (*e.g.* generation of small droplets in micromixers); and product homogeneity in solid formulation such as multi-scale generation of uniform microparticles.

In Europe, an Industrial R&D Consortium is under construction. The goal of the IMPULSE Project (Integrated Multiscale Process Units with Locally Structured Elements) is to demonstrate the feasibility of production by multiscale assembly in: gas–liquid reaction, exothermal liquid–liquid reaction, non-miscible liquid–liquid reaction, electro-chemical synthesis, photo-activated synthesis, structuring liquid–solid (suspensions), and structuring liquid–liquid (emulsion) reaction.

4.4 Catalytic processes

Catalysis is a central part of industrial chemical synthesis: about 75% of current chemical processes make use of catalysts in four main areas: environmental protection (35%), chemicals (23%), oil processing in refineries (22%) and polymers (20%).[123] Efficient homogeneous and heterogeneous catalysts, biocatalysts, photocatalysts, electrocatalysts, *etc.* ensure that chemical reactions are high yielding and economical, that they avoid by-products and decrease energy inputs. Key to increasing economical as well as environmental added value, catalysts are the most important tool for sustainability and profitability of chemical production processes, with three global objectives:

- new environmentally safe 'zero-pollution' processes
- enabling new raw materials sources (*e.g.* alkanes and renewables),
- energy conversion, with a focus on hydrogen technology.

There is plenty of scope for improvement and expansion in the use of catalysis in synthesis, with higher yields resulting in less waste and less energy. At the Informex meeting 2004: "The catalysis buzz was unmistakable".[124] Many fine chemicals syntheses are still carried out with classical organic reactions: stoichiometric quantities of salts have often to be separated and discarded. For certain active ingredients for medicines or crop-protection agents, the amount of waste produced can sometimes exceed the target product by a factor of 100. For example, the production process for the pain relief drug Ibuprofen: while non-catalytic processes generate over 30 kg of waste per kg of active ingredient, the catalytic method produces less than 1 kg of waste.

For catalysis, we believe that the challenge is more in improved engineering of numerous existing catalytic systems than in discovery of new catalysts. For new catalytic processes big improvements are expected from the coupling of a catalytic reaction with either another reaction or a separation process. Invention of new catalysts is not a priority: the innovation will come from the engineering aspects.

New catalysts are nevertheless of interest for customised polymers, stereospecificity, self-repairing abilities, reconversion of large molecules to starting materials. One particular field of interest is activation of methane and other C1-feedstock, as natural gas grows as a competitor to oil for feedstock.

4.5 Green solvents

Novel solvents offer possibilities for reduced emissions and other sustainable characteristics.

Supercritical fluids (SCF): SC CO_2 has already been mentioned as an implemented technology. Other SCF examples include: SC propane or SC dimethylether developed by Härröd Research[125,126] for the hydrogenation of fatty acid esters. The productivity of SC single-phase hydrogenation is typically 100 × higher than the traditional gas–liquid technologies.[127] A pilot plant using palm and rape-seed oils produces 10 kg h^{-1} of "top quality" product in a compact unit. SC acetone is proposed for dehydration of fructose to make hydroxymethylfurfural.[128] SC water, although highly corrosive due to hydroxyl radicals, is used by Takeda Chem at 374 °C and 224 atm to recycle toluene diisocyanate by hydrolysis of residue.[129] SCF are also used in innovative and promising ways to design solid-state morphology of particles.[130]

Ionic liquids (IL) are organic salts with low melting point (usually < 100 °C). As their vapour pressure is extremely low, essentially no solvent is lost by evaporation. Another advantage is the large range of temperature for use, typically extending over 200 to 300 °C. These 'green' characteristics have attracted a lot of attention during the last decade, a rediscovery of pioneering industrial work started in the 1970s (Pt/Sn-catalyzed oxo synthesis in chlorostannate salts)[131] and in the 1980s with the development of 'melt catalysts' at the industrial pilot scale. 'Melt catalysts', equivalent to liquid-supported organometallic catalysis, combine the intrinsic advantages of both homogeneous catalysis (inherent high selectivity, easier mass and heat transfers, confidence in reproducibility and heterogeneous catalysis (ease of product–catalyst separation). Application examples include:

Texaco[132] converted syngas into acetic acid, esters, alcohols and glycol using a 'ruthenium melt catalyst' dispersed in quaternary ammonium or phosphonium ILs, especially bromides.

Rhone-Poulenc used tetrabutylphosphonium chloride (MP 65 °C, thermal stability up to > 300 °C, excellent amphiphilic newtonian behaviour) to stabilize zero-valent palladium catalysts for carbonylation of dienes.[133] The reaction products are flash-distilled from a concentrated Pd-matrix,[134] with the additional advantage of removal of high-boilers by extraction with alkanes.[135]

Organochloroaluminates are another readily available class of IL. They dissolve nickel complexes and, despite their high moisture-sensitivity, IFP has developed and commercialized an alpha-olefin process by oligomerization of ethene.[136]

Various salts of alkyl derivatives of imidazole are room-temperature ILs. The BASIL (Biphasic Acid Scavenging utilizing Ionic Liquids) process recently disclosed by BASF uses an imidazole derivative as HCl scavenger.[137] The solvent-free process produces an intermediate for its Lucirin® photoinitiator with increased yield and could simplify a broad range of pharmaceutical industry processes.

Some disadvantages of ionic liquids are their high viscosity due to hydrogen bonding, frequent air and moisture sensitivity and some ILs are biocides so cannot be considered as truly 'green' solvents.

4.6 New activations

Energy sources such as UV light, microwaves or ultrasound can be used in a controlled way to increase the efficiency of a chemical reaction, thus making it more eco-friendly. However few commercial applications are documented.

Power ultra-sound has dramatic effects at the lower end of the frequency spectrum (20–100 kHz). In liquids, cavitational collapse produces intense heating and extreme pressures, causing high-energy chemistry to occur. Moving sonochemistry to the plant is not easy. However, Accentus (GB) has developed large-scale insonation, for a low-cost ultrasound crystallization technology (C^3 Technology), with a much better control of size than jet mixers or conventional stirred tanks. No direct contact of the source with the process fluid reduces wear.[138] Undatim uses ultrasound instead of adding chemicals as anti-scaling agent. 'Sonoxide' crystallizes $CaCO_3$ in cooling tower water. The ultrasound also generates short-lived oxidizing species, preventing growth of algae. Advanced cleaning oxidants are generated when 'Sonoperoxone' irradiates water with 10 ppm ozone and < 100 ppm hydrogen peroxide is added.[139]

Microwave-assisted reactions are known for their short reaction time and often improved selectivity. Reaction engineering aspects, including scale-up, now attract much attention.[140] In environmental cleaning, Kobe Steel plans to market within 5 years a process to remove chlorine from PVC by 1.2 kW microwave irradiation. Possibly 100% of organic chlorine can be extracted and recovered in the form of HCl. This technique will be more economic than current technology such as incineration.[141]

Acoustic waves are an alternative to mechanical milling, Artolith and Krause Maschinenbau developed acoustic milling:[142] pressure waves are generated between 2 disks counter-rotating at 30 000 rpm with a gap as small as 200 μm. Introduced in the centre of the disks, materials are transformed to nanometric powders with no crushing. The process is more 'hygienic' and costs are claimed to be 10 times less.[143]

Electrons are a 'green' alternative to ozone and/or hydrogen peroxide treatment of aqueous effluent. The water treatment industry already uses electrical methods such as oxidation and reduction, electrodialysis and electroflocculation. In electrocatalysis, a recent example is the cleaning of distillery effluents by oxidation on RuO_2-coated titanium electrodes.[144] Sophisticated techniques such as a fluidized bed with vitreous reticulated carbon cathodes show the best performance.

Electron beams are the subject of extensive R&D, due to the availability of generators at reasonable cost. Waste water disinfection can be realized on thin films, as hydroxyl radicals generated by the electrons destroy the most resistant pollutants.[145]

In solventless processes, mechano-chemistry or 'dry chemistry' uses no volatile solvents. The reagents are mixed in their physical form. An example is a Wittig reaction realized in a totally solvent-free medium and energetized by mechanical shocks between steel beads.[146] Reactive extrusion is another technique attracting interest. A way to bring energy into solvent-free processes with solid reagents is microwave irradiation.[147] As microwaves directly excite ions and polar molecules, ionic liquids (due to their dielectric properties) are ideal media for microwave irradiation.[148]

4.7 New materials

Product engineering and emerging product-oriented technologies consistently call for new and smarter materials. Obviously due to competition and IPR considerations there are few products currently in development that are disclosed publically prior to market launch. General trends in development include bioplastics, self-healing polymers, polymer conductors, mass-production of fullerene compounds, organic ferro-magnetic materials, functional polymers and hybrid materials. Innovation in smart materials is expected for emerging market needs in: energy systems, ultra-thin coatings, microelectro- and mechanical systems and for construction (low weight, high strength).

The field of *application of polymers* is continuously broadening, for example in electronic components, where polymeric printed circuits could replace silicon, giving a definite advantage of easier recycling.

In the *detergent* industry, AISE (International Association for Soaps and Detergents) enrolled more than 170 companies in a voluntary code of good environmental practices in 1997. AISE is now preparing the HERA project committed to deliver human and environmental risk assessments on household cleaning products.

Materials for energy systems is a particular strong field including: nanocarbons for hydrogen storage, polymers for membranes and high temperature applications. BASF in the area of hydrogen and methanol fuel cells for vehicles developed nanocubes for hydrogen storage. A metal–organic framework has demonstrated the ability to absorb and store high hydrogen loading.

Hydrogen-storing metal alloys can carry a maximum of 2.6% of their weight in H_2. Liquid organic hydrides (LOH) can serve as a hydrogen storage, transportation and supply system.[149] Some LOH can even be directly fed as vapour to the anode of a Proton Exchange Membrane fuel cell. The development of efficient proton exchange membrane fuel cells for vehicular use is being undertaken by Daimler, Ford and Ballard Systems.[150] The system will deliver vastly reduced emissions compared to current internal combustion technology.

Nanotechnology (as shown in section 3.2) is receiving much attention at the moment, but much R&D work on nanoscale material stops at the laboratory scale. Work must continue and expand to macroscale to enable processing and handling in an industrial context. Nanocomposites with multi-functional properties show great potential, but are unlikely to be on the market within one to two decades. The priority lies in the design of materials incorporating full life-cycle considerations. Too much research is spent on bench-scale trial-and-error schemes. Prediction of material properties at one end (knowledge-based) and the manipulation of material structures at industrial level at the other end (industrial data bases and benchmarks) should be promoted and integrated.

4.8 Thermo-economics

"In a world rapidly running out of fossil fuel, the second law of thermodynamics may well turn out to be the central scientific truth of the 21st century".[151] *Exergy*, defined as 'ordered motion', is a thermodynamic concept based on entropy that fuses energy and material quality information in a measure that is both descriptive and of physical significance. Exergy could be a suitable concept in the development of a sustainable industry as it clarifies quantification of resource depletion, waste emissions and process losses. It measures the physical value of inputs and outputs, thus relating to economic value. Non-sustainability could be penalized by its amount of exergy.

Due to its flexibility across the breadth of industrial application and its potential as a tool for quantitative assessment, the concept of an exergy quantifier is now being investigated.[152] More work is necessary on the practical application and adaptation of exergy analysis to the specific problems embodied by the material and energy flows through industry including: calculation of exergy in an industrial setting, exploring the significance of environmental ground states and establishing the requisite databases for performing analyses. LCEA, Life-Cycle *Exergy* Analysis, is a superior tool as it solves the problem of classic Life Cycle Analysis when comparing different substances.[153]

4.9 Industrial ecology

Much of industry currently uses a strictly linear production process: extracting raw materials and fossil energy, processing the material and energy, and returning the waste back into natural systems. *Industrial Ecology* aims to incorporate the cyclical patterns of ecosystems into designs for industrial production processes that will work in unison with natural systems. The seminal article "Industrial Ecology: An Environmental Agenda for Industry" in 1992[154] outlined six principal elements:

- industrial ecosystems: cooperation among various industries whereby the waste of one production process becomes the feedstock for another
- balance industrial input and output constrained by natural systems: safe interface of industry with nature, in terms of location, intensity, and timing, and developing indicators for real-time monitoring
- dematerialization of industrial output: decrease of materials and energy intensity in industrial production
- improvement of the efficiency of industrial processes: re-design production processes and patterns for maximum conservation of resources
- development of renewable energy supplies for industrial production: a world-wide energy system that functions as an integral part of industrial eco-systems
- adoption of new national and international economic development policies

Industrial Eco-Parks are extended, multi-industry networks that try to fulfil these principles. In the Kalundborg Eco-Park in Denmark,[155] fluxes of energy, steam, water, refinery gas, sulfur, biomass and liquid fertilizers, fly ash and other waste are exchanged between the Kalundborg City, Asnaes (energy), Gyproc (gypsum), Novo Nordisk (pharma enzymes), Bioteknisk Jordrens (soil cleaning), Statoil (refinery) and a fish farm. It is reported that the 75 M€ initial investment brings ~15 M€ annual savings[156] to the partners.

ValuePark® is the industrial park concept of the Dow Olefinverbund GmbH in Central Germany.[157] Its key objective is to promote and attract investment through the establishment of an integrated value-creating network of raw material suppliers, downstream investors (strategic customers) and service providers. ValuePark investors benefit from long-term synergies which arise from using shared services and the existing infrastructure. By integrating the company's strategic partners and customers on site, the ValuePark also contributes to the economic development of the region and supports the value-creation process of the petrochemical business.

Tools for systematic design of industrial ecology networks are still in their infancy but a few are already available: DIME, FaST, DIET and GIS.[158]

Industrial symbiosis, like any natural ecosystem needs:

- diversity, for an ecology based on waste to resource
- proximity, because transportation costs can quickly offset other advantages
- and most importantly cooperation, which needs improvements in communication and mutual confidence

5. Conclusions

Industry has made great progress in adopting processes and chemistry that have sustainable characteristics: our selection of examples is of necessity limited but we hope reflects the wider picture. Future progress requires technical and political challenges to be addressed. Industrial Biotechnology appears to be a particularly fruitful area for building industrial sustainability and has so far not faced the issues of public acceptance associated with agricultural biotechnology.

Radical improvements can also be achieved by new process design including new reactor configurations, integration of operations both within and between enterprises and through a focus on recycling and reusing materials.

Many barriers exist to limit the implementation of radical improvements to industrial performance: incremental debottlenecking of plant and expansion is preferred in times of slow growth and a 'first-of-a-kind' process faces a high investment hurdle. The economic and regulatory environment needs to support investment in new technologies that demonstrate sustainable advantage but carry higher technical risk than conventional operations.

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PAPER

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Highly efficient deep desulfurization of fuels by chemical oxidation

J. M. Campos-Martin, M. C. Capel-Sanchez and J. L. G. Fierro*
Instituto de Catálisis y Petroleoquímica, CSIC, c/ Marie Curie, s/n, Cantoblanco, 28049 Madrid, Spain. http://www.icp.csic.es/eac/index.htm. E-mail: jlgfierro@icp.csic.es; Fax: +34 915854760

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This paper describes the oxidation of several model S-containing molecules with hydrogen peroxide in a two liquid–liquid (L–L) phase system with a phase transfer catalyst under atmospheric pressure in the 333–353 K temperature range. The influence of the reaction temperature, the nature of the substrate, the solvent, the molar ratio of the oxidant (H_2O_2) and the S-containing molecule were examined. The reaction rates of the oxidative desulfurization (ODS) reaction were found to increase with the temperature, and with the molar ratio of H_2O_2 and the S-containing molecule. The potential of this methodology is illustrated by the complete S-removal from a 5.0 wt% dibenzothiophene mixture at 353 K, under excess of H_2O_2 oxidant in less than three hours of reaction. In addition, the ODS reaction was strongly enhanced when the water solvent was replaced by acetonitrile. The very high ODS reaction rate observed with the acetonitrile solvent could be explained in terms of the much higher solubility of the sulfone reaction product in this solvent and also by its very low surface tension, which facilitates the transfer of products and reagents at the polar–apolar interface. Finally, the very mild sulfoxidation reaction was applied to a kerosene fraction. The results revealed that S-levels below 25 ppm are achieved at 353 K upon using a H_2O_2 : substrate molar ratio of 2.5 : 1.

Introduction

The oil industry is facing increasing pressure to remove organic sulfur compounds from transportation fuels. The sulfur content in fuels is an environmental concern because upon combustion sulfur is converted to SO_x, which not only contributes to acid rain, but also poisons catalytic converters for the treatment of exhaust emissions. The sulfur level in diesel fuels is currently limited to 500 ppm, in both Japan and USA and 350 ppm in EU. However, new regulations will cut diesel sulfur from current levels to very low ones: US Environmental Protection Agency (EPA) Tier II to 15 ppm by June 2006,[1] and EU to 50 ppm by the beginning of 2005 and 10 ppm by January 2009.[2] These specifications represent a new and challenging task for both scientists and refineries, because the remaining sulfur (less than 500 ppm) is likely to be contained in refractory compounds that are difficult to desulfurize. In addition, in attempts to meet the growing demand for clean fuels, the implications are complex, not only as regards the need for a highly active desulfurization catalyst but also from the standpoint of refinery. Each refinery must meet unique circumstances, such as diesel blend components and hydrogen availability.

Current hydrodesulfurization technology (HDS) is able to desulfurize aliphatic and acyclic sulfur-containing compounds quite efficiently when adopted at industrial scale. This process, however, is limited when treating dibenzothiophene (DBT), especially in the case of DBTs having alkyl substituents at position 4 and/or 6.[3] Thus, the production of ultra-clean light oil inevitably requires severe operation conditions and, especially, highly active catalysts. In the development of any alternative energy-efficient desulfurization process, a radical approach not limited to conventional HDS technology is required. To eliminate undesirable sulfur-containing compounds or to convert them into more innocuous forms, several processes other than HDS have been employed. Such processes include oxidative microbial transformations,[4] physical extraction with a liquid,[3] selective adsorption on suitable materials,[5] and catalytic oxidation.[6,7]

Regarding microbial transformation, certain enzymes have been identified that are able to biotransform sulfur compounds found in fuels, including those that selectively remove sulfur from dibenzothiophene heterocyclic compounds.[8] In this regard, Energy Biosystems has made important efforts to develop a biodesulfurization process.[4] This basically involves the removal of sulfur-containing hydrocarbon compounds from distillates or naphtha streams using bacteria. The distillate stream is first mixed with an aqueous solution containing the bacteria. Enzymes in the bacteria first oxidize the sulfur atoms at the water–hydrocarbon interface and then cleave some of the sulfur–carbon bonds. The sulfur leaves the process in the form of hydroxyphenyl benzene sulfonate, which can be used commercially as a feedstock to produce surfactants. The properly designed pilot plant combines biodesulfurization to produce diesel fuel containing 50 ppm of S.[4]

The greatest advantage of oxidative desulfurization (ODS) as compared with the conventional HDS processes is that it can be carried out in liquid phase under very mild conditions—at near room temperature and under atmospheric pressure. In ODS reactions, the divalent sulfur can be oxidized by the electrophilic addition reaction of oxygen atoms to form the hexavalent sulfur of sulfones. The chemical and physical properties of sulfones are significantly different from those of hydrocarbons in fuel oil. Therefore, they can easily be removed by separation operations such as distillation, solvent extraction, adsorption, and decomposition. Many types of oxidants have been used and several consequences of ODS methods have been reported.[9–18] Oxidants such as nitrogen oxides, nitric acid, hydrogen peroxide, ozone, t-BuOOH, oxygen, air and peracids can be used. The oxidation of thiophene derivatives with H_2O_2 is known to take place in the presence of HCOOH, CCl_xCOOH (x = 1–3), CF_3COOH,[19–21] methyltrioxorhenium(VII),[22] vanadium acetylacetonate,[23] phosphotungstic acid,[24,25] titanium molecular sieves,[26] and vanadium silicates.[27]

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In a series of previous papers, it has been reported that tungsten catalysts are very effective for the oxidation of thioethers into sulfoxides and sulfoxides into sulfones using H_2O_2 as the oxidant in a two liquid–liquid (L–L) phase system with a phase transfer catalyst (PTC).[28] Such a biphasic oxidation reaction follows the cycle illustrated in Scheme 1, where phenylphosphonic acid acts as an accelerator. In the polar phase, the catalyst precursor H_2WO_4 is rapidly oxidized by H_2O_2 according to: $H_2WO_4 + 2\ H_2O_2 \rightarrow H_2[WO(O_2)_2(OH)_2] + H_2O$. The resulting bisperoxotungstate compound is transferred to the apolar phase by $H^+–Q^+$ ion exchange with the phase transfer agent (Q^+). The bisperoxotungstate compound in the apolar phase oxidizes thioethers into sulfones, and can then be regenerated at the L–L interface with H_2O_2 or transferred to the polar phase where it reacts with hydrogen peroxide. Then the obtained sulfones are transferred to the polar phase due to the solubility of sulfones in a polar solution, giving the production of a sulfur free apolar phase.

Within this context, the aim of the present study was twofold. On the one hand, we studied the oxidation with H_2O_2 of several model molecules in a two liquid–liquid (L–L) phase system with a phase transfer catalyst (PTC). On the other hand, we wished to obtain basic information about the applicability of the oxidation method with hydrogen peroxide in the selective transformation of organic sulfur compounds contained in kerosene and light oils. The desulfurization results were highly dependent on the temperature, the nature of the substrate or solvent, and the molar ratios of the reagents. The influence of these factors on performance was examined.

Results and discussion

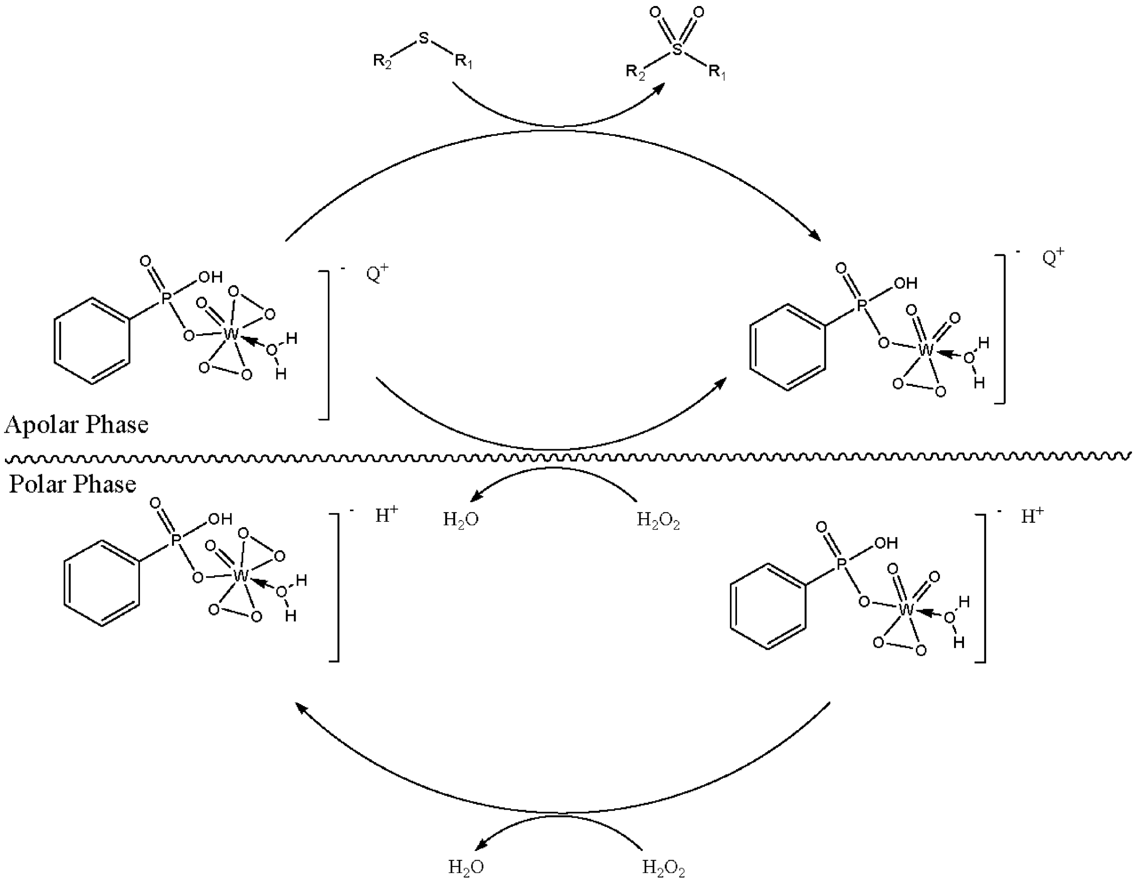
Organic sulfides, thiophenes, benzothiophenes, and dibenzothiophenes are the major sulfur-containing compounds present in liquid hydrocarbon fuels. A series of experiments was conducted with the aim of evaluating the reactivity of several model organic sulfur compounds in the H_2O_2–PTC oxidation system. Under the experimental conditions used, the oxidation reaction of sulfur compounds by hydrogen peroxide led to the corresponding sulfoxides (1-oxides) and sulfones (1,1-dioxides) as major products (Scheme 2). The direct decomposition of H_2O_2 was not observed under our experimental conditions, because tungstate does not cause unproductive decomposition of H_2O_2.[28]

Influence of the reaction temperature

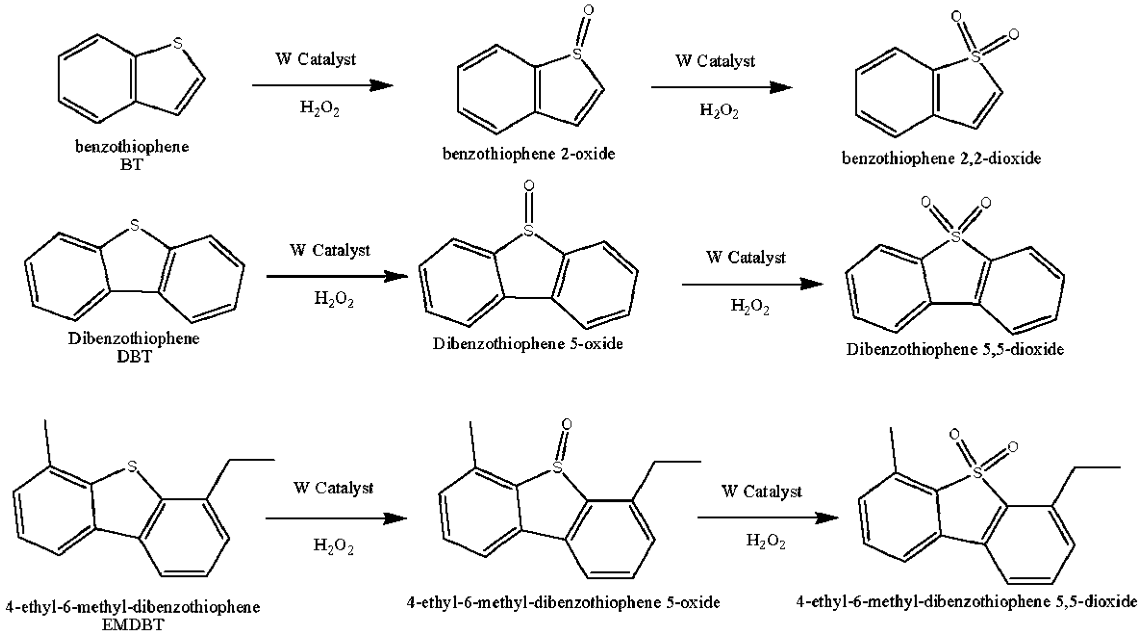
Firstly, the effect of temperature on the kinetics of the disappearance of DBT was investigated. In these experiments, water—as the solvent—and DBT—as the S-containing model compound to be desulfurized—were selected. The concentration of DBT was set at 1 wt% (1747 ppm S). The conversion profiles of dibenzothiophene (DBT) in the ODS reaction *versus* the reaction time at three different temperatures (333, 343 and 353 K) are shown in Fig. 1. A rise in the reaction temperature from 333 to 343 K led to a remarkable increase in the reaction rate at all times. However, the increase in the reaction rate at temperatures in the 343–353 K range was less pronounced. This restriction appears to be due to the nature of the phase-transfer catalysis, in which some mass-transfer limitations at the aqueous–organic interface are involved. In view of these results, the reaction temperature employed for comparisons was set at 353 K.

Influence of the H_2O_2 : substrate ratio and substrate concentration

The above experiments were carried out with an excess of hydrogen peroxide (H_2O_2 : DBT = 40 : 1 molar ratio).



Scheme 1 Catalytic cycle of sulfur compounds oxidation. $Q^+ = CH_3(n\text{-}C_8H_{17})_3N^+$.



Scheme 2 Simplified reactions of sulfur compounds following the ODS process.

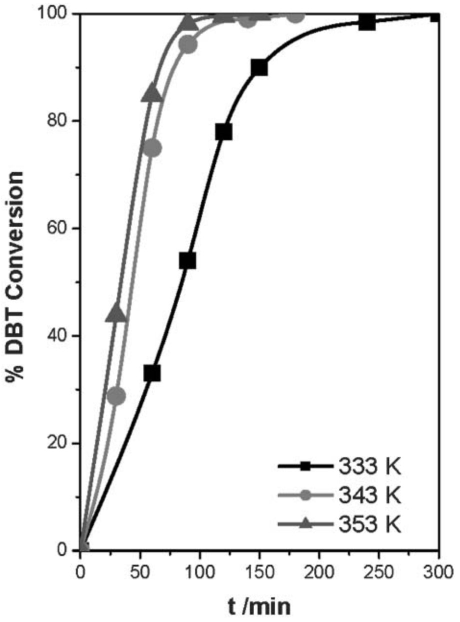


Fig. 1 Influence of temperature on the conversion of dibenzothiophene. Conditions: 1 wt% DBT in hexadecane (1747 ppm S), H_2O_2 : substrate = 40 : 1 (molar ratio), solvent = water.

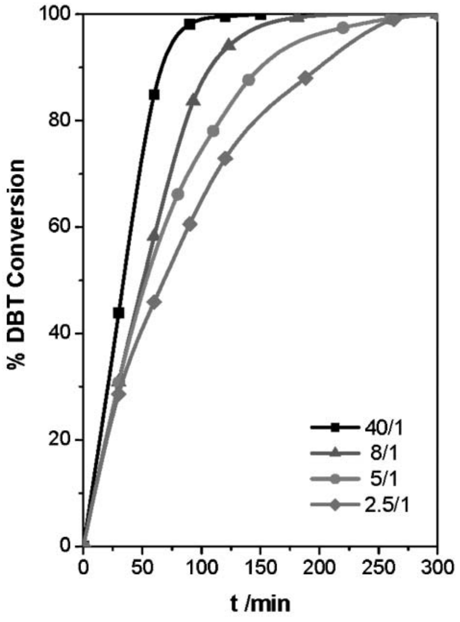


Fig. 2 Influence of the H_2O_2 : substrate ratio on the conversion of dibenzothiophene. Conditions: 1 wt% DBT in hexadecane (1747 ppm S), T = 353 K, solvent = water.

However, according to the stoichiometry of the reactions depicted in Scheme 2, only 2 mol of H_2O_2 are consumed per mole of sulfone (R–SO_2) produced. Thus, it was of interest to explore the influence of the hydrogen peroxide concentration on the kinetics of DBT conversion. Several H_2O_2-to-substrate molar ratios were selected, including 40 : 1, 8 : 1, 5 : 1 and 2.5 : 1. The lowest H_2O_2 concentration (H_2O_2 : DBT = 2.5 : 1 molar) was set slightly above the stoichiometric ratio (H_2O_2 : DBT = 2 : 1 molar) in order to avoid limitations of the oxidant reagent and to achieve complete conversion of DBT. The DBT conversion values as a function of the reaction time for H_2O_2 : DBT molar ratios of 40, 8, 5 and 2.5 are plotted in Fig. 2. As can be seen, the hydrogen peroxide-to-DBT ratio had a strong influence on the reaction rate. Working with an excess of H_2O_2 oxidant (H_2O_2 : DBT ratio of 40, 8 and 5), the reaction rate was very high, and it decreased for a H_2O_2 concentration close to the stoichiometric one (2.5). In all cases, complete DBT conversion was reached at reaction times of less than 300 min.

In order to examine the influence of the DBT concentration on the kinetics of the removal of S-containing compounds, additional experiments were conducted by raising the DBT concentration. Thus, DBT concentrations ranging from 5.0 to 0.2 wt%—that is, from 8735 to 349 ppm S—were selected while maintaining the oxidant-to-substrate ratio constant (H_2O_2 : DBT = 8 : 1). Fig. 3 plots DBT conversion as a function of the reaction time for different DBT concentrations. The conversion levels of DBT were very high for all DBT concentrations, although the reaction rate was much higher than expected for initial concentrations of DBT of 5.0 and 1.0 wt%. This finding clearly indicates that the hydrogen peroxide concentration is very important in the rate equation describing the oxidation of

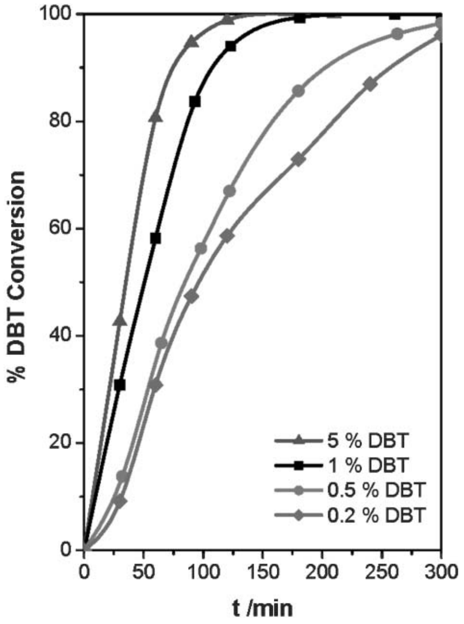


Fig. 3 Influence of substrate concentration in the conversion of dibenzothiophene. Conditions: H_2O_2 : substrate = 8 : 1 (molar ratio), T = 353 K, solvent = water.

S-containing compounds with H_2O_2 in liquid phase. Intuitively, this behaviour can be explained on the basis of the notion that excess H_2O_2 was employed in all cases, but the final concentration of H_2O_2 for the DBT concentration of 5.0 wt% was much higher than for the reaction with 0.2 wt% DBT.

Solvent effects

Not only the reaction temperature, hydrogen peroxide and DBT concentrations bear influence on the kinetics of the ODS reaction of DBT. The nature of the solvent also plays a very important role in liquid-phase catalytic reactions. The solvent has an important effect on the outcome of the reaction, *i.e.*, on yields, by-product formation, and reaction kinetics, although this effect is strongly dependent on the type of catalyst used and on the nature of the substrate. Thus, we explored the influence of the solvent on the ODS reaction of DBT. As can be seen in Fig. 4, the kinetics of the ODS reaction were found to depend strongly on the type of solvent. The reaction rate was significantly higher when acetonitrile was used as solvent instead of water. Use of acetonitrile as solvent produced a double effect: (i), the formation of a precipitate was prevented, and (ii), an almost four-fold increase in the reaction rate was observed. This enhancement in the ODS reaction rate can be ascribed to a double effect. On one hand, because acetonitrile is a much better solvent than water for the reaction products, the formation of micro-droplets of sulfones is avoided and the reaction rate is favored by removal of reaction products from the apolar phase. This effect was previously observed with other catalytic systems,[26] using biphasic and monophasic reaction media. On the other hand, acetonitrile as a solvent exhibits a much lower surface tension than water, which facilitates the transfer of products and reagents at the polar–apolar interface, notably increasing the mass transfer along the interphase.

Influence of the nature of the substrate

Although the kinetic work was basically conducted with the DBT substrate, other S-containing molecules were employed to perform the ODS reaction. These compounds included benzothiophene (BT) and 4-ethyl-6-methyl-dibenzothiophene (EMDBT). Since these compounds are present in middle distillates, their relative ODS rates allow them not only to be ranked in terms of reactivity but also permits evaluation of the potential of the ODS process in fuel desulfurization. Comparison of the reactivity of different sulfur-containing compounds revealed that reactivity depends on the type of S-containing molecule to be oxidized (Fig. 5). The relative ranking of the reaction rate was: BT : DBT : EMDBT = 1 : 2.5 : 2. In principle, this order of reactivity is unexpected because the BT molecule, with a relatively accessible sulfur atom, would give rise to a higher oxidation rate than in the more sterically hindered S-containing DBT and EMDBT molecules. The explanation for the above trend can be visualized in terms of S–C bond stabilization in the BT molecule. In the case of DBT, and to a lesser extent that of EMDBT, the inducing effect of the aromatic rings elicits an increase in the electron charge density of the S atom, meaning that the reaction can be oxidized more

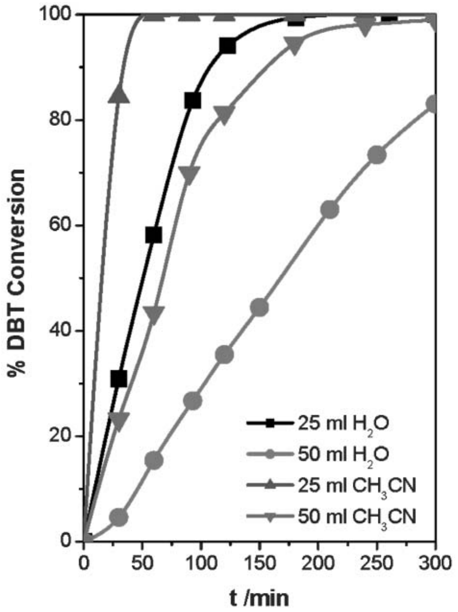


Fig. 4 Influence of solvent in the conversion of dibenzothiophene. Conditions: 1 wt% DBT in hexadecane (1747 ppm S), H_2O_2 : substrate = 8 : 1 (molar ratio), T = 353 K.

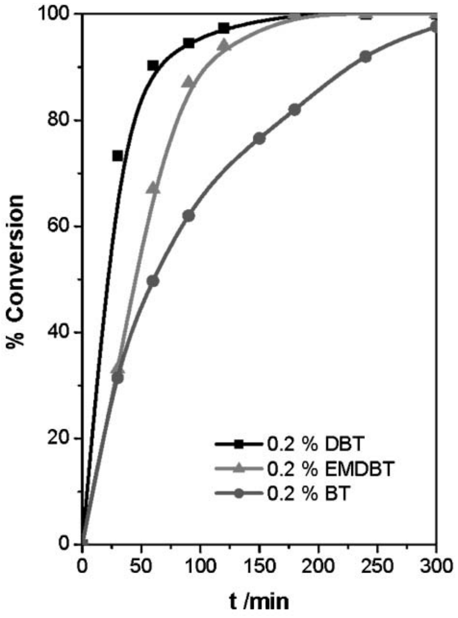


Fig. 5 Influence of the nature of the substrate in the conversion. Conditions: 0.2 wt% sulfur compound in hexadecane H_2O_2 : substrate = 8 : 1 (molar ratio), T = 353 K, solvent = acetonitrile.

easily by hydrogen peroxide. The slightly slower reactivity of EMDBT with respect to DBT appears to be related to the steric hindrance of the ethyl and methyl groups at positions 4 and 6 in the DBT molecule, which hinders the formation of reaction intermediates prior to being oxidized.

It appears that sulfur-containing compounds such as BT, DBT, and specifically EMDBT, which are only sparingly desulfurized by hydrodesulfurization catalysts and processes, readily become oxidized with H_2O_2 under very mild reaction conditions. As a consequence of the very high reactivity observed, this methodology could possibly be employed in the deep desulfurization of fuels. In any case, much further work is needed to efficiently combine reactivity with the downstream separation processes to recover the solvent and to extract sulfones selectively.

Oxidative desulfurization of kerosene

The oxidation reaction of the S-containing compounds present in a commercial kerosene fraction (1291 ppm S) was carried out by applying the optimal conditions found in the preceding section of synthetic feeds of DBT. These optimal conditions are: acetonitrile as a solvent and a reaction temperature of 353 K. In addition, two H_2O_2 : S molar ratios of 8 : 1, in excess of the oxidant, and of 2.5 : 1, approaching the stoichiometric ratio, were employed in this study. Due to the strong influence of the concentration of hydrogen peroxide in the apolar phase on the reaction rate, the amount of solvent was lowered (25 mL) by an appropriate amount in order to render the initial concentration of H_2O_2 equal in both cases. According to these reaction conditions, the rate of S removal in the kerosene cut was very high for the two H_2O_2 : S ratios investigated (Fig. 6), although the extent of sulfur oxidation in the region of very high conversion levels was slightly higher for the highest concentration of hydrogen peroxide (H_2O_2 : S = 8 : 1). However, at reaction times of 2 h, the remaining sulfur concentration in the kerosene was below 25 ppm in both cases. In previous work, liquid-phase extraction of sulfur compounds with acetonitrile solvent following operation conditions similar to those employed here were described, but very low sulfur removal was reached ($<$7%).[26] Thus, the large sulfur removal yield observed in the present work ($>$99%) is attributed to the catalytic ODS process. These results are of great relevance as they offer a simple way to remove the refractory S-containing molecules present in middle distillates under very mild reaction conditions. According to this methodology, the removal of sulfur up to levels of about 10 ppm fulfills the limits established by the EPA Tier II normative to be applied by June 2006, and are even below that recommended by EU to be operative by the beginning of 2009.

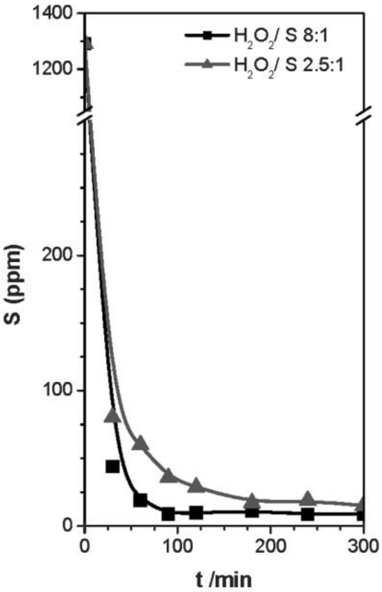


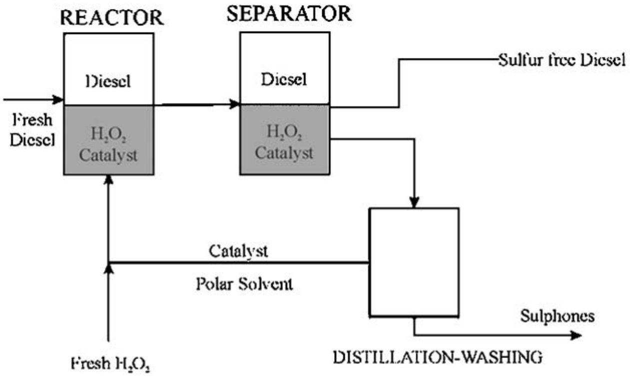
Fig. 6 Sulfur removal from kerosene (1291 ppm). Reaction conditions: T = 353 K, solvent = acetonitrile, H_2O_2 : substrate = 8 : 1 and 2.5 : 1 (molar ratio), same initial H_2O_2 concentration, T = 353 K, solvent = acetonitrile.

A tentative interpretation can be advanced to explain the almost constancy of the sulfur content in the kerosene for reaction times longer than 2 h. This explanation assumes that the extraction of oxidized S-containing compounds is not quantitative, since they can remain in the acetonitrile fraction solubilized in the hydrocarbon phase. Support for this interpretation comes from the moderate degree of solubility of acetonitrile in kerosene, which reaches 6.7 wt% at 353 K and decreases to 1.7 wt% at 313 K.[29] Since the sulfoxides and sulfones produced in the ODS reaction are highly soluble in acetonitrile, these compounds present in the solubilized acetonitrile fraction in the hydrocarbon phase may contribute to the overall sulfur analysis. In any case, much work is still needed to clarify this point.

Sulfur removal from liquid fuels according to the ODS reaction can be conducted on an industrial scale following a very simple strategy as depicted in Scheme 3. In a first step, organic sulfides are oxidized to sulfones, which are then transferred to the polar phase. Subsequently, the two liquid phases can be separated by decantation: the apolar phase is the deeply desulfurized fraction, and the polar one should then be distilled and washed to recover high added value sulfones while simultaneously recycling the solvent and catalyst.

Economical assessment

The ODS process can be considered not to be a competitor of the traditional HDS one. It appears to be complementary of it since hydrotreatments not only remove S and other heteroatoms from refinery streams but also improve the quality of the fuels. The ODS is specifically designed to be integrated in the final processing steps to decrease remaining sulfur to the levels fixed by environmental legislations. Thus, it seems appropriate to compare the ODS with the revamping or modification of an HDS unit able to perform a deep desulfurization and reach the same low S-levels which can be achieved with the coupled standard HDS and ODS technologies. Thus, a scenario in which the ODS technology is applied to a refinery stream containing 500 ppm of sulfur is compared with another which implies revamping an HDS unit. Such a revamping involves high investment costs and an increase in the operation costs of the order of 0.6 Euro per barrel (€ bbl^{-1}).[30] Such a cost is still higher than that required in the ODS, in which the cost of the raw H_2O_2 reagent, with a cost of 0.5 € kg^{-1} H_2O_2,[28] is 0.095 € bbl^{-1}. By adding indirect costs together with other



Scheme 3 Scheme of an ODS process.

costs (catalyst, solvent, recycling and separation steps), a final cost around 0.25 € bbl^{-1} is obtained. This comparison highlights the favourable economic incentive of the ODS process with respect to the cost introduced by the revamping option of current HDS units.

Conclusions

This work demonstrates that the desulfurization of DBT, and also of BT and EMDBT, can be effectively accomplished by oxidation with hydrogen peroxide under very mild reaction conditions; namely, atmospheric pressure and temperatures close to ambient (333–353 K). The principal conclusions derived from this work are as follows:

(i) As expected, the plots of DBT conversion *vs.* reaction time indicated that the ODS reaction is activated, first-order kinetics appearing with respect to the organic substrate. (ii) The hydrogen peroxide concentration exerts a strong influence on the rate of S removal; interestingly, in an excess of oxidant at 353 K starting with a DBT concentration as high as 5.0 wt%, an almost complete disappearance of DBT occurs at three hours of reaction time. (iii) The use of acetonitrile solvent instead of water proved to be highly effective for the ODS reaction. This enhancement in the reaction rate can be explained as being due not only to the higher solubility of the sulfones in acetonitrile, which facilitates their removal from the apolar phase, but also to the lower surface tension of liquid acetonitrile, which facilitates the transfer of products and reagents at the polar–apolar interface. (iv) S removal by the ODS reaction from BT, DBT and EMDBT is easy and can be almost completed under the very mild conditions imposed by this reaction. This very high reactivity makes the ODS reaction promising for the deep desulfurization of middle distillates.

The results show that the sulfoxidation reaction can be used to decrease the sulfur content of kerosene in the absence of hydrogen and without the need for high-pressure equipment.

Experimental

The catalytic sulfoxidation of sulfur-containing organic compounds with hydrogen peroxide was carried out in a 250 mL glass batch reactor, equipped with a magnetic stirrer, a thermometer and a condenser. In a typical experiment, 90 g of the sulfur compound solution in *n*-hexadecane (Aldrich) and 0.03 g of Aliquat® 336 (trioctylmethylammonium chloride, Aldrich) were heated to the reaction temperature. Then, a solution of hydrogen peroxide (70% w/w, kindly supplied by Solvay Química, S. L.), 0.0188 g of tungstic acid (Aldrich) and 0.012 g of phenylphosphonic acid (Aldrich) in 25 mL of solvent (water or acetonitrile) was added drop-wise to the apolar phase. Aliquots were taken from the reactor at different reaction times; the total amount withdrawn from the reactor was less than 10% in order to avoid interferences in the reaction results due to changes in the total mass inside the reactor. The apolar phase was recovered by decantation and analysed by GC-FID equipped with a capillary column (HP-WAX, 25 m, = 0.2 mm, 1.0 μm film thickness). The hydrogen peroxide concentration was determined by standard iodometric titration.

The desulfurization of kerosene (kindly provided by Repsol-YPF) by oxidation with H_2O_2 was also investigated. In a 250 mL glass batch reactor, 90 g of kerosene (1291 ppm sulfur) and 0.030 g of Aliquat® 336 were heated to 363 K. Then, a solution of hydrogen peroxide, 0.0188 g of tungstic acid and 0.012 g of phenylphosphonic acid in 25 mL of acetonitrile was added drop-wise. The amount of sulfur in the apolar phase was determined by X-ray fluorescence using a TXRF EXTRA-II Rich & Seifert instrument.

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PAPER

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Indium tribromide in poly(ethylene glycol) (PEG): a novel and efficient recycle system for chemoselective deprotection of 1,1-diacetates

Zhan-Hui Zhang, Liang Yin, Yong-Mei Wang,* Ju-Yan Liu and Yi Li
Department of Chemistry and the State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China. E-mail: zhanhui@mail.nankai.edu.cn; Fax: +86(22)23502654; Tel: +86(22)23504439

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Poly(ethylene glycol) (PEG) has been used as a medium for deprotection of 1,1-diacetates with easy recyclability of solvent and indium tribromide catalyst for the first time. Several aryl 1,1-diacetates were deprotected to the corresponding parent aldehydes in high yield. The procedure is operationally simple and environmentally benign.

Introduction

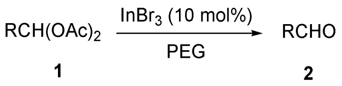
The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, that are widely used in organic synthesis have posed a serious threat to the environment. To address some of these issues, attempts have been made to develop solvent-free processes, which to some extent have succeeded in achieving some chemical transformations.[1] Despite such advances, in performing the majority of organic reactions, solvents play a critical role in making the process "liquids" and allowing molecular interactions to be more efficient. In such situations, the search for alternative reaction media to replace these organic solvents has attracted much attention from academia and industry.[2] One of the recently developed methods is to use water as solvent for organic reactions,[3] but its use is limited due to the hydrophobic nature of organic compounds and the sensitivity of many catalysts to aqueous conditions. Fluorous phases[4] have achieved adaptation and enjoy increased utility due to the advantage of being highly hydrophobic. Supercritical fluid media[5] are also attractive solvent alternatives for a variety of chemical and industrial processes but, at the same time, they need high pressure. Ionic liquids[6] have attracted interest due to their advantageous properties such as tunable polarity, high thermal stability, negligible vapour pressure and recyclability. However, ionic liquids require tedious preparation and their environmental safety is still debatable.

Recently, liquid polymers or low melting polymers have emerged as alternative green reaction media with unique properties such as thermal stability, commercial availability, nonvolatility, immiscibility with a number of organic solvents and recyclability. PEGs are preferred over other polymers because they are inexpensive, completely nonhalogenated, easily degradable and of low toxicity.[7] Many organic reactions have been carried out using PEGs as solvent or co-solvent, such as Heck reaction,[8] asymmetric dihydroxylation,[9] Suzuki cross-coupling reaction,[10] oxydehydrogenation of alcohols and cyclic dienes, oxidation of sulfides and the Wacker reaction[11] and partial reduction reaction of alkynes.[12] The use of PEG as a recyclable solvent system for the metal mediated radical polymerisation of methyl methacrylate and styrene has also been reported.[13]

The need for protection of aldehydes in organic synthesis is well documented and there are many groups available to achieve this purpose.[14] In recent years 1,1-diacetates have been introduced as suitable protecting groups for aldehydes due to their stability in mildly acidic and basic media and ease of chemoselective preparation in the presence of ketone.[15] In addition, they can be converted into other useful functional groups by reaction with appropriate nucleophiles[16] and used as carbonyl surrogates for asymmetric synthesis.[17] The synthesis of optical aldehydes by lipase-catalysed resolution of the corresponding 1,1-diacetates has been reported.[18] The cleavage of 1,1-diacetates can be carried out under strong acidic conditions using hydrochloric acid,[19] or sulfuric acid.[20] However, these catalysts can also affect other acid-sensitive groups. Mild Lewis acids such as $CeCl_3{\cdot}7H_2O/NaI$,[21] $Sc(OTf)_3$,[22] $BiCl_3$,[23] zirconium(IV) chloride,[15f] and heterogeneous catalysts[24] such as montomorillonite clays,[25] expansive graphite,[26] and zeolite,[27] have also been applied for deprotection of 1,1-diacetates. Many of these methods suffer one or more drawbacks, which include use of harmful volatile organic solvents or large amounts of solid supports, unsatisfactory yields, expensive reagents, longer reaction times, tedious work-up procedures or the necessity for an additional microwave oven. Herein, we have developed a convenient and efficient procedure for the deprotection of 1,1-diacetates using a catalytic amount of $InBr_3$ in PEG (Scheme 1).

Results and discussion

Initially, the cleavage of α,α-diacetoxytoluene in the presence of 1 equiv. $InBr_3$ in PEG-400 was investigated at room temperature. No deprotected product was obtained even if the mixture was stirred for 24 h. To our satisfaction, rapid conversion was observed when the reaction was carried out at 80 °C in PEG. We have also investigated the efficiency of the catalyst in less than stoichiometric amounts. The deprotected benzaldehyde was obtained in high yield using 10 mol% of $InBr_3$. A lower catalyst loading could be used with only a marginal drop in reaction rate (Table 1, entries 1 and 2). In

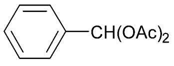
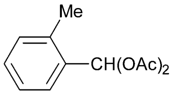
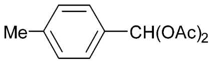
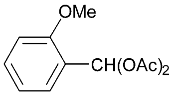
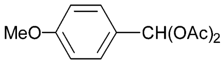
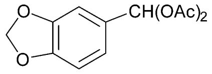
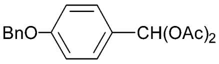
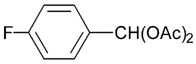
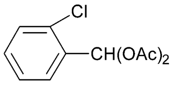
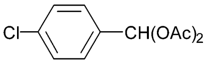
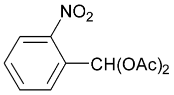
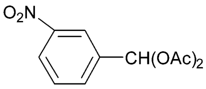
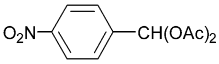
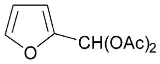
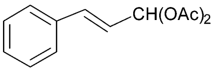
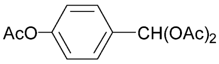
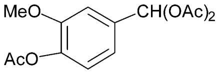
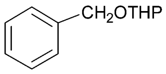
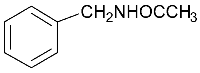
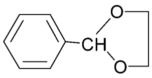


$$\underset{\mathbf{1}}{RCH(OAc)_2} \xrightarrow[\text{PEG}]{InBr_3\ (10\ \text{mol\%})} \underset{\mathbf{2}}{RCHO}$$

Scheme 1

DOI: 10.1039/b410583d

Table 1 Deprotection of 1,1-diacetates using $InBr_3$ in PEG 400 at 80 °C

Entry	Substrate	Time/min	Yield (%)[a]
1		60	95[b]
2		40	96[c]
3		50	93[d]
4		20	95
5		18	95
6		20	94
7		15	93
8		18	94
9		15	95
10		20	94
11		35	92
12		60	94
13		50	95
14		18	94
15		180	92
16		180	93
17		25	92
18		60	93
19		15	94
20		25	95
21	$CH_3(CH_2)_8CH(OAc)_2$	120	Trace
22		180	No reaction
23		180	No reaction
24		60	94

[a] Yield refers to isolated pure products. [b] 1% $InBr_3$ was used. [c] 5% $InBr_3$ was used. [d] 60 °C.

these cases, a lower temperature could also be applied but resulted in a longer reaction period (Table 1, entry 3).

Having established the preferred reaction conditions, the deprotection of several representative 1,1-diacetates was performed to demonstrate the versatility and uniqueness of the present reaction conditions (Table 1). As shown in Table 1, aromatic as well as α,β-unsaturated 1,1-diacetates, were converted to the parent aldehydes in high yield. The presence of electron-donating and electron-withdrawing groups on the aromatic ring makes an obvious difference to the reaction rate for the deprotection of 1,1-diacetates. Substitution of an electron-withdrawing group onto the aromatic ring severely retards the deprotection. The reaction with (4-methylphenyl)-methanediol diacetate (entry 6) was complete within 20 min whereas with 3- and 4-nitrobenzylidene diacetates (entries 15 and 16) the reaction times were extended to 3 h. Therefore, this method could be applied to chemoselective deprotection of aryl 1,1-diacetates due to differences in their electronic effects.

We have also tried the reaction of 1,1-diacetoxydecane (entry 21), as an example of an aliphatic aldehyde 1,1-diacetate, in PEG for 2 h in the presence of the catalyst. Only a trace of decanal was obtained under these conditions. Therefore, chemoselective deprotection of an aromatic aldehyde 1,1-diacetate in the presence of an aliphatic aldehyde 1,1-diacetate could also be achieved.

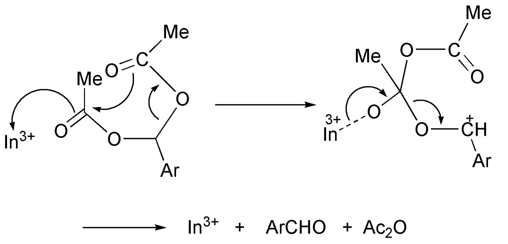
It should be noted that the treatment of (4-acetoxyphenyl) methanediol (entry 19) and (4-acetoxy-3-methoxyphenyl) methanediol (entry 20) with $InBr_3$ gave only the cleavage product of 1,1-diacetate, in more than 90% yield in a short reaction time. These results demonstrate that the reaction conditions allow for selective cleavage of aryl aldehyde 1,1-diacetates in the presence of the phenolic acetate. Moreover, the reaction conditions are sufficiently mild not to affect the methyl (entries 5 and 6), methoxy (entries 7 and 8), methyleneioxy (entry 9), benzyloxy (entry 10), chloro (entries 12 and 13) functionalities.

To ascertain the applicability and limitations of this new method, we studied the possibility of the cleavage of the tetrahydropyranyl (THP), amide and acetal groups using this catalytic system. We found that THP (entry 22) and *N*-acetyl (entry 23) groups remained intact, but acetal (entry 24) can be cleaved under the same conditions as in the 1,1-diacetates case.

After removing the reaction product by ether extraction of the reaction mixture, the mother liquor could be reused and subjected to a second run of the cleavage process by charging with the same substrates. The results of the first experiment and our subsequent experiments were almost consistent in yield (96%, 95%, 93%, 94%) for the cleavage of α,α-diacetoxytoluene. During the deprotection, the acetylated product of the terminal alcohol moiety of PEG was observed by ^{1}H NMR and ^{13}C NMR. However, this had no influence on the use of PEG in the next cycle.

Although a detailed mechanism of the reaction was not clear at this stage, the hydroxamate test identified the presence of acetic anhydride in the reaction products and neither additional water nor anhydrous conditions affect the reaction rate. We assumed the reaction proceeded *via* a unimolecular decomposition of 1,1-diacetate to give an aldehyde and acetic anhydride (Scheme 2).

In summary, we have developed, for the first time, a novel and efficient protocol for the selective cleavage of aromatic and conjugated aldehyde 1,1-diacetates using indium tribromide in PEG medium under mild reaction conditions. The advantages of the present protocol are the simplicity of operation, the high yields of deprotected products, the recyclability of the catalyst and preclusion of the usage of volatile organic solvents. Moreover, its compatibility with sensitive functionalities such as OMe, OBn, OAc, and double bonds with regard to economic



Scheme 2

and ecological considerations allows us to believe that this method may represent a valuable alternative to the existing reagents reported in the literature.

Experimental

Typical procedure for deprotection of acylals

A mixture of 1,1-diacetates (**1**, 1 mmol) and $InBr_3$ (36 mg, 0.1 mmol, 10 mol%) in PEG-400 (5 mL) was stirred vigorously at 80 °C for a specified time as required to complete the reaction (Table 1). After completion, as indicated by TLC or GC, the reaction mixture was cooled and extracted with diethyl ether (2 × 5 mL). The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: hexane–ethyl acetate) to afford pure aldehyde **2**. The remaining mother liquor containing $InBr_3$ was recovered and recycled in subsequent reactions. The products were characterized by their melting points or boiling points, IR, ^1H NMR spectra, TLC and by comparison with their authentic sample.

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PAPER

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$Hf[N(SO_2C_8F_{17})_2]_4$ as a highly active and recyclable Lewis acid catalyst for direct esterification of methacrylic acid with methanol in a fluorous biphase system

Xiuhua Hao, Akihiro Yoshida and Joji Nishikido*
The Noguchi Institute, Kaga, Itabashi-ku, Tokyo 173-0003, Japan.
E-mail: nishikido@noguchi.or.jp; Fax: +81 3 5248 3597; Tel: +81 3 5248 3596

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The activity of $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst for the direct esterification of methacrylic acid with methanol was studied and compared with representative acid catalysts including the present industrially employed H_2SO_4 and Nafion® SAC-13. It was found that $Hf[N(SO_2C_8F_{17})_2]_4$ in a fluorous biphase system (FBS) is most effective based on initial rate analysis and yield. In the simulated industrial solution (the reaction mixture was preliminarily doped with H_2O, $H_2O/MAA = 1.6$ mmol), the initial rate with $Hf[N(SO_2C_8F_{17})_2]_4$ was shown to be about 9 times that with H_2SO_4. Meanwhile, an excellent yield (86%) and selectivity (97%) were obtained with $Hf[N(SO_2C_8F_{17})_2]_4$, which are superior to the other evaluated catalysts. Furthermore, the immobilized fluorous phase was completely recovered and reused without loss of its catalytic activity either in the simulated industrial solution (both with and without preliminarily doping with H_2O) or in the practical industrial solution.

Introduction

Methyl methacrylate (MMA), as an important industrial raw material, is widely used in the production of organic glass, lacquer, adhesive, *etc.*[1] For the manufacture of MMA, several industrial processes have been developed. Amongst these, a typical method involves oxidation of methacrolein to methacrylic acid (MAA) followed by esterification of MAA to MMA, which suffers from undesirable large quantities of aqueous wastes including MAA and water. In order to treat the industrial wastes, the direct esterification of MAA with methanol was generally employed by using a large amount of strong acids such as sulfuric acid, which causes serious environmental problems.[2] On the other hand, a Fluorous Biphase System (FBS), as a new phase separation and immobilization technique, brings about potential advantages over classical homogeneous catalysis and can be shown to be one of the environmentally-benign technique candidates.[3] Nevertheless, wide industrial use of FBS is now hampered by the possible environmental impact of perfluorocarbons. The engineering aspects of FBS processes on an industrial scale need to be investigated to meet environmental concerns (*e.g.*, elimination of leakages and complete recycling of the effluents).[4]

Our recent works on FBS have found that metal complexes (*e.g.*, Sn, Hf and Yb) with bis(perfluorooctanesulfonyl)amide ponytails are excellent active and recyclable catalysts in the fluorous immobilized phase for Baeyer–Villiger oxidation,[5] Diels–Alder reaction[6] and Friedel–Crafts acylation,[7] which have even proved satisfactory in a continuous-flow reaction system at bench-scale.[8]

As an initial approach to industrial application, the direct esterification of MAA with methanol to MMA was carried out to investigate the potential of $Hf[N(SO_2C_8F_{17})_2]_4$ in FBS. The accelerating performance of $Hf[N(SO_2C_8F_{17})_2]_4$ was compared with other commercially available and well-known acid catalysts employed in the industrial processes including H_2SO_4 (98%), Nafion® SAC-13 and DIAION® PK216H. Furthermore, the recyclable performance of $Hf[N(SO_2C_8F_{17})_2]_4$ was investigated in FBS under mild operating conditions without recourse to any technique to remove H_2O during the reaction.

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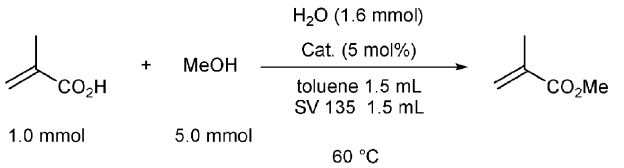
Results and discussion

The catalytic activities of different kinds of catalysts in a simulated industrial solution were first investigated both with and without preliminarily doping with H_2O (Scheme 1). In Figs. 1 and 2, the time courses for the representative catalysts are shown, where the production rate (within the range of 30% yield) of MMA is plotted against the reaction time. Their approximate linear equations were calculated with the least squares method assuming no MMA production at the initial reaction time.[9] In this paper, the inclination of the linear equation was defined as the initial rate. In Table 1, the initial rates r and the relative initial rate ratios r_{rel} (based on the initial rate of H_2SO_4) both with and without doping with H_2O are summarized. It can be seen that all of the catalysts without doping (*r1*) gave distinctively higher initial rates than those with doping (*r2*), which revealed H_2O inhibition during the reaction. How to minimize the inhibitory effect of H_2O (either from the preliminary doping or from the by-product) will be the object of our further studies. It also can be seen that $Hf[N(SO_2C_8F_{17})_2]_4$ is most active, regardless of whether H_2O was used for doping or not, even though H_2SO_4 showed a relatively higher activity than the other listed ones. The significance of this result lies in the initial rate using $Hf[N(SO_2C_8F_{17})_2]_4$, which was about 9 times that using H_2SO_4 with preliminary doping with H_2O.

In order to further optimize the reaction conditions, the



Scheme 1 Direct esterification of MAA in the simulated industrial solution with or without doping with H_2O (1.6 mmol).

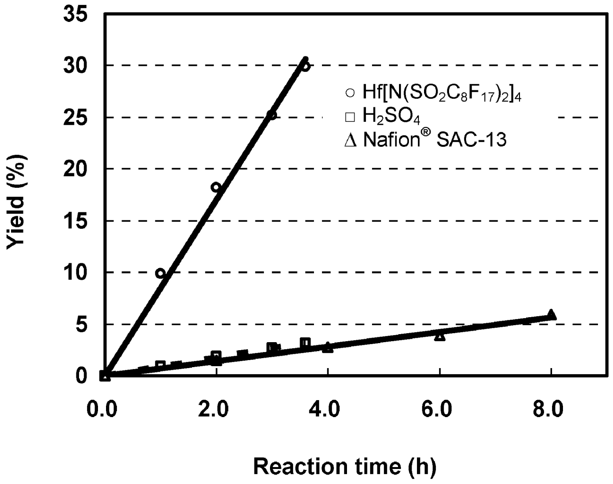


Fig. 1 Yield of MMA *vs.* time in the simulated industrial solution with preliminary doping with H_2O. Reaction conditions are given in Scheme 1.

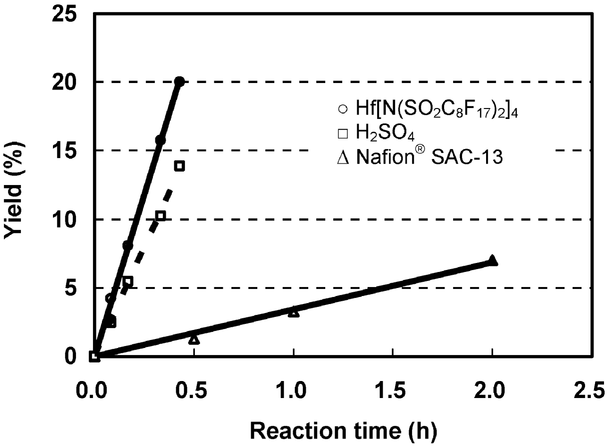


Fig. 2 Yield of MMA *vs.* time in the simulated industrial solution without preliminary doping with H_2O. Reaction conditions are given in Scheme 1.

catalytic activities of different catalysts were investigated in FBS when the reaction time was confined to 8 h. During the reaction period, the by-product H_2O was not removed. As summarized in Table 2, no product was obtained in the absence of the catalyst (entry 15). With respect to Hf^{IV}-based catalysts, $Hf[N(SO_2C_8F_{17})_2]_4$ (entry 1) showed a significantly higher activity than $HfCl_4{\cdot}2THF$ (entry 2) and $HfCl_4$ (entry 3), even though the latter catalysts are the well-known efficient catalysts in the direct esterification.[1c] In addition, $Zr[N(SO_2C_8F_{17})_2]_4$ (entry 4) and $Sn[N(SO_2C_8F_{17})_2]_4$ (entry 6) can also be thought to be effective catalysts, but $ZrCl_4$ (entry 5) and $HfCl_4$ (entry 7) were much less active. These results indicated that the unique complex of $–N(SO_2C_8F_{17})_2$ ligand with metal (*e.g.*, Hf, Zr and Sn) is highly significant for the present direct esterification system, which is also certified by the activity comparison for $Sc[N(SO_2C_8F_{17})_2]_4$ (entry 8) and $Sc(OSO_2CF_3)_3$ (entry 9), $Yb[N(SO_2C_8F_{17})_2]_4$ (entry 10) and $Yb(OSO_2CF_3)_3$ (entry 11). On the other hand, H_2SO_4 (entry 12), Nafion® SAC-13 (entry 13) and DIAION® PK216H (entry 14) are well-known industrially used Brønsted acid catalysts for the direct esterification of α,β-unsaturated carboxylic acid, but their catalytic activities were significantly lower in the present mild reaction system. Accordingly, 5 mol% $Hf[N(SO_2C_8F_{17})_2]_4$ was considered to be the best catalyst on account of the good yield of 86% and excellent selectivity of 97%.

The recycling performance of $Hf[N(SO_2C_8F_{17})_2]_4$ was also investigated either in the simulated industrial solution (both with and without preliminarily doping with H_2O) or in the practical industrial solution. The operation was quite similar to that we have reported for Baeyer–Villiger oxidation,[5] *i.e.*, the catalyst was completely immobilized in the fluorous phase and the fluorous solution was directly used in the subsequent reaction.[10] As shown in Table 3, even after $Hf[N(SO_2C_8F_{17})_2]_4$ was recycled 5 times, the GLC yield was still higher than 82% both with the simulated industrial and the practical solutions, which confirmed there was not only no loss of the catalyst amount but also no depression of the catalytic activity during the repetition.

$Hf[N(SO_2C_8F_{17})_2]_4$ complex in FBS can be thought to be an extremely active catalyst for the direct esterification of methacrylic acid with methanol. Its effectiveness was not only confirmed by its accelerating ability in the initial rate and yield, but also by the easy recycling operation without loss of its catalytic activity. These results showed an excellent potential for its industrial application: (1) an excellent accelerating effect superior to the traditional acid catalysts; (2) no requirement for the removal of water; (3) complete immobilization in the fluorous phase and reuse for subsequent reaction; (4) high yield and selectivity under mild conditions. The large-scale operation is currently being studied.

Experimental

General

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL JNM-ECA600 (600 MHz) instrument using tetramethylsilane (δ 0.00), chloroform-d (δ 77.0) and α,α,α-trifluorotoluene (δ −63.20) as internal standards, respectively. GC analysis was carried out on SHIMADZU GC-1700AF. GC–MS measurements were performed on Hewlett-Packard G1800A GLS. Atomic emission spectra were taken on IRIS/AP (Nippon Jarrell Ash Co.). Products after isolation were qualitatively identified by GC–MS, ^1H and ^{13}C NMR, and quantitatively analyzed by GC with *n*-nonane as an internal standard, comparing their retention times with those of the authentic samples.

Table 1 Comparison of initial rate in the simulated industrial solution[a]

		Without doping with H_2O		With doping with H_2O	
Entry	Catalyst	$r1$/mmol $mmol_{cat}^{-1}$ h^{-1}	$r1_{rel}$[b]	$r2$/mmol $mmol_{cat}^{-1}$ h^{-1}	$r2_{rel}$[c]
1	$Hf[N(SO_2C_8F_{17})_2]_4$	9.89	1.59	1.68	8.84
2	H_2SO_4	6.21	1	0.19	1
3	$Sc(OSO_2CF_3)_3$	1.92	0.31	0.12	0.63
4	Nafion® SAC-13	0.72	0.12	0.11	0.57
5	DIAION® PK216H	0.21	0.03	0.12	0.63
6	$Yb(OSO_2CF_3)_3$	0.21	0.03	0.02	0.10

[a] Reaction conditions are shown in Scheme 1; the catalysts in Entry 4 and 5 are insoluble while the others are soluble. [b] Relative rate $r1_{rel}$, $r1_{rel} = r1catalyst/r1H_2SO_4$. [c] Relative rate $r2_{rel}$, $r2_{rel} = r2catalyst/r2H_2SO_4$.

Table 2 Comparison of yield and selectivity in the reaction time of 8 h[a]

Entry	Catalyst	Yield (%)	Selectivity (%)
1	$Hf[N(SO_2C_8F_{17})_2]_4$	86	97
2	$HfCl_4 \cdot 2THF$	35	54
3	$HfCl_4$	29	40
4	$Zr[N(SO_2C_8F_{17})_2]_4$	81	85
5	$ZrCl_4$	51	82
6	$Sn[N(SO_2C_8F_{17})_2]_4$	75	92
7	$SnCl_4$	35	45
8	$Sc[N(SO_2C_8F_{17})_2]_3$	52	85
9	$Sc(OSO_2CF_3)_3$	49	80
10	$Yb[N(SO_2C_8F_{17})_2]_3$	19	66
11	$Yb(OSO_2CF_3)_3$	11	55
12	H_2SO_4	50	60
13	Nafion® SAC-13	19	76
14	DIAION® PK216H	9	55
15	None	0	0

[a] Reaction conditions are shown in Scheme 1 (without doping with H_2O) except that H_2SO_4 and DIAION® PK216H were conducted in a mono organic solvent (toluene, 1.5 mL); the catalysts in Entry 13 and 14 are insoluble while the others are soluble.

Typical procedure

A (Table 1, without doping with H_2O). A 10-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with MAA (86 mg, 1.0 mmol), methanol (160 mg, 5.0 mmol), $Hf[N(SO_2C_8F_{17})_2]_4$ (205 mg, 0.05 mmol), and a solvent mixture of toluene (1.5 mL) and GALDEN® SV135 (1.5 mL; purchased from Solvay Solexis K.K.). The tube was placed in an organic synthesizer and stirred continuously at 60 °C. After settling for 10 sec, the reaction mixture turned into an upper toluene phase and a lower fluorous phase. The MMA yield was determined by sampling aliquots (GC analysis) of the upper toluene phase.

B (Table 1, with doping with H_2O). The operation conditions and procedure were the same as those described in Typical procedure *A* (*i.e.* the same amounts of MAA, methanol, $Hf[N(SO_2C_8F_{17})_2]_4$ and a solvent mixture of toluene and GALDEN® SV135) except that additional H_2O (29 mg, 1.6 mmol) was added at the beginning of the reaction.

C (Table 3, without doping with H_2O in the simulated industrial solution). With the same experimental equipment described in Typical procedure *A*, the same amounts of MAA, methanol and $Hf[N(SO_2C_8F_{17})_2]_4$ were added to the mixture of toluene (1.5 mL) and GALDEN® SV135 (1.5 mL). The reaction mixture was stirred continuously at 60 °C for 8 h. Once the stirring was stopped, the reaction mixture settled down and turned into two liquid phases within 10 sec., *i.e.*, an upper toluene and a lower SV 135 phase. Pure MMA was obtained from the upper phase after silica gel chromatography and reduced pressure evaporation (86 mg). The lower fluorous phase containing the catalyst was reused in the subsequent recycling reactions, to which toluene (1.5 mL), MAA (86 mg, 1.0 mmol) and methanol (160 mg, 5.0 mmol) were added. The other operations and procedures (*e.g.* stirring at 60 °C for 8 h, product separation) were the same as those described above for the first cycle. The procedure was repeated a further four times. The yields of MMA were 85, 86, 83 and 85% in the succeeding four reactions, respectively.

Selectivity = produced MMA/converted MAA in mmol.

D (Table 3, with doping with H_2O in the simulated industrial solution). The operation conditions and procedure were the same as those described in Typical procedure *C* except that additional H_2O (29 mg, 1.6 mmol) was added at the beginning of every recycle reaction.

E (Table 3, in the practical industrial solution). The industrial solution, which was composed of MAA 31 wt%, H_2O 10 wt%, MMA 17 wt% and unknown composition 42 wt%, was purchased from the related chemical corporation.

The industrial solution (277 mg) was dissolved in a solvent mixture of toluene (1.5 mL) and GALDEN® SV135 (1.5 mL), then methanol (160 mg, 5.0 mmol) and $Hf[N(SO_2C_8F_{17})_2]_4$ (205 mg, 0.05 mmol) were added. The experimental procedure was the same as that described in Typical procedure *C*.

F (Synthesis of $Hf[N(SO_2C_8F_{17})_2]_4$ complex). A mixture of $HN(SO_2C_8F_{17})_2$ (5.89 g, 6.0 mmol), $HfCl_4$ (0.48 g, 1.5 mmol) and anhydrous methanol (10.0 mL) were added to a flask. The reaction mixture was stirred continuously at 50 °C for 15 h. After being cooled to room temperature, the mixture was evaporated and dried at 80 °C/0.01 mmHg for 16 h to give white powders of hafnium(IV) bis(perfluorooctanesulfonyl)-amide complex in 97% yield (5.96 g). $Hf[N(SO_2C_8F_{17})_2]_4$ elemental analysis: calcd C 18.75, Hf 4.35; found C 18.65, Hf 4.33. ^{19}F NMR δ −126.2, −121.1, −114.2, −81.5.

G (Polymeric catalysts). DIAION® PK216H (Mitsubishi Chemical Corporation) was dried under vacuum at 40 °C/0.01 mmHg for 8 h prior to use (exchange capacity 3.35 mequiv. g^{-1}).

Nafion® SAC-13 (Aldrich) was used as received (a nafion–silica composite catalyst containing 13% nafion, exchange capacity 0.8 mequiv. g^{-1}).

The molar amount (acid active site) was calculated by

$$(\text{exchange capacity, mequiv. } g^{-1}) \times (\text{amount, g}) \times k$$

where $k = 1$ for DIAION® PK216H; $k = 0.13$ for Nafion® SAC-13.

Table 3 Recycles of $Hf[N(SO_2C_8F_{17})_2]_4$ complex

	In the simulated industrial solution				In the practical industrial solution[d]	
	Without doping with H_2O[b]		With doping with H_2O[c]			
Cycle[a]	Yield (%)	Selectivity (%)	Yield (%)	Selectivity (%)	Yield (%)	Selectivity (%)
1	86	97	85	97	85	90
2	85	95	85	96	85	97
3	86	98	84	96	82	96
4	83	99	83	100	83	100
5	85	98	84	99	84	99

[a] Cycles of the lower fluorous catalyst phase. [b] Reaction conditions are shown in Typical procedure *C* and data were obtained after 8 h. [c] Reaction conditions are shown in Typical procedure *D* and data were obtained after 16 h. [d] Reaction conditions are shown in Typical procedure *E* and data were obtained after 16 h.

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10 Typical recovery result: the complex $Hf[N(SO_2C_8F_{17})_2]_4$ was recovered from the fluorous phase without apparent weight loss, *i.e.* 203 mg modified catalyst was recovered after the original 205 mg was recycled for 5 times. The recovered $Hf[N(SO_2C_8F_{17})_2]_4$ catalyst was characterized by elemental analysis: calcd C 18.75, Hf 4.35; found C 18.72, Hf 4.33.

PAPER

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An economical and green approach for the oxidation of olefins to enones†

Padma Marwah, Ashok Marwah and Henry A. Lardy*
Department of Biochemistry - Institute for Enzyme Research, University of Wisconsin-Madison, 1710 University Avenue, Madison, WI 53726. E-mail: halardy@wisc.edu

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A new and optimized water-based procedure for the oxidation of steroidal olefins and benzylic compounds to α,β-enones, using household laundry bleach and aqueous *tert*-butyl hydroperoxide at sub-ambient temperature, is described. This simple methodology is not only economical but is also environmentally friendly. Issues of reactivity, selectivity and scope of the reaction were investigated with a variety of steroidal olefins and benzylic compounds.

Introduction

Steroidal α,β-enones are an important class of compounds because of their bioactivity, commercial value and synthetic utility in various arenas such as cancer chemotherapy,[1] sterol biosynthesis,[2] metabolites of vitamin D,[3] synthesis of Squalamine, a novel polyaminosterol with interesting biological activity[4] *etc*. A thermogenic steroid, 7-oxo-dehydroepiandrosterone (7-oxo-DHEA), a metabolite of the human body's most abundant hormone DHEA, has attracted interest in recent years since it has many of the beneficial effects associated with DHEA but unlike DHEA, is not converted to androgens or to estrogens *in vivo*.[5] 7-Oxo-DHEA is more effective than DHEA in inducing thermogenic enzymes,[6] in production of interleukin-2 by isolated T cells,[7] and in enhancement of memory in old mice.[8] 7-Oxo-DHEA, is currently available as a nutraceutical,[9] and is suggested to be useful in the prevention of primary Raynaud's attacks.[10] Extensive use of 7-oxygenated steroids in our various study models[11] prompted us to find and develop a simple, cost-effective process for the synthesis of these therapeutically interesting compounds, with an implication for subsequent manufacturing and commercialization.

tert-Butyl hydroperoxide (TBHP) assisted allylic oxidation of Δ^5-steroids to α,β-enones has been the subject of numerous investigations employing a variety of transition metal oxidants such as chromium,[3,12] copper,[13] cobalt[14] and ruthenium compounds.[2a,4] Aqueous TBHP-based procedures provide a feasible approach for allylic oxidations, although the use of a non-aqueous solution of TBHP under anhydrous reaction conditions is not uncommon.[13,14] However, use of high-strength TBHP solution in combination with transition metal salts is usually unacceptable because such oxidations are exothermic and require more precautions especially when carried out on a large scale.[15] Furthermore, the toxic nature of oxochromium (VI) reagents, high cost of some of the specialty reagents such as ruthenium, contamination of product with trace metallic impurities *etc*., are additional disadvantages which often make such processes unattractive from the industrial and environmental point of view.

We report a new, efficient, one pot procedure for the synthesis of steroidal α,β-enones and benzylic carbonyl compounds utilizing an environmentally benign oxidant, sodium hypochlorite[16] (household laundry bleach) in combination with aqueous TBHP (70% or less): a relatively safe and inexpensive peroxy reagent,[15] with or without the use of organic solvents. This biphasic reaction was performed at sub-ambient temperature, preferably at 2–5 °C, without the use of a phase transfer catalyst, affording α,β-enones in good to excellent yields. This environmentally friendly water-based allylic oxidation process, requiring fewer reagents, no specialty chemicals, no expensive anhydrous or aprotic solvents and employing mild reaction conditions and easy work-up, has overcome many of the 'green' issues associated with this type of chemical transformation, and has provided a milder and inexpensive approach for the synthesis of this important class of compounds.

Results and discussion

At ambient temperature, the reaction response of sodium hypochlorite (bleach) when added into a mixture of substrate and aqueous *tert*-butyl hydroperoxide (TBHP, 70 wt%) was exothermic with brisk evolution of oxygen. The oxidation of organic compounds performed under these conditions was of little synthetic value due to low product yield (entry 18, Table 1). Therefore, optimization of bleach-mediated allylic oxidation of compounds was attempted, targeting 3β-acetoxyandrost-5-en-17-one (DHEA-Ac, **1**) as the substrate. The scope and limitations of the present methodology were studied, and are summarized in Table 1 and Scheme 2. Interestingly, the oxidation of DHEA-Ac (**1**) proceeded smoothly at low temperatures and in absence of any organic solvent, surfactant or hydrotropic agents (entry 1 & 2, Table 1) and the corresponding enone was isolated in excellent purity and in preparatively useful yields. This allylic oxidation, which could be carried out under mild conditions in aqueous medium, and without the necessity for organic solvents, provided a very feasible approach to run the reaction in a convenient and cost effective way for subsequent scaling up studies.

Product composition analysis (performed by liquid chromatography–mass spectrometry, using electrospray ionization (LC-MS-ESI)) of the reaction mixture from one of the solventless experiments (entry 3, Table 1), showed the absence of the starting material and presence of the desired enone, 3β-acetoxyandrost-5-en-7,17-dione (7-ODA, **14**), as the most abundant peak in the chromatogram, as shown in Fig. 1 (diode array UV detection at λ_{205} and λ_{240}). Among the minor products, 3β-acetoxyandrost-5-ene-4,7,17-trione (**15**, Table 1, Fig. 1), which was often encountered as one of the most likely over-oxidation products and usually a contaminant in most

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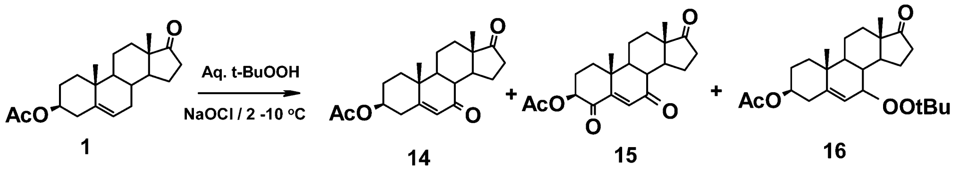
† US patent[28]

DOI: 10.1039/b408974j

Table 1 Optimization of hypochlorite–TBHP induced allylic oxidation of DHEA-Ac (**1**)



Entry#	TBHP[a] mol equiv.	Bleach[b] (%)	Temp./°C	Solvent	Conversion[c] (%)	Selectivity (%)[d] 14	15	16	Y/P[e] (%)
1	6.0	5.25	2–5	—	75	87[f]	1	1	72/62[g]
2	10.0	5.25	2–5	—	100	95	2	3	60/99
3	10.0	5.25	8–10	—	100	95	2	3	60/99
4	6.0	5.25	2–5	Water	90	67	1	1	45/80[g,i]
5	6.0	5.25	2–5	EtOAc	100	96	2	2	64/98
6	6.0	5.25	2–5	DCE	100	98	1	2	66/99
7	6.0	5.25	2–5	EtOAc–hexane[h](4 : 1)	97	96	2	1	69/98[g]
8	6.0	5.25	2–5	EtOAc–PE[h] (4 : 1)	97	97	2	1	71/98[g]
9	6.0	5.25	2–5	EtOAc–*t*-BuOH[h] (3 : 1)	100	96	2	2	66/99
10	6.0	5.25	2–5	DMP	100	97	2	1	62/99
11	6.0	5.25	2–5	PE–EtOAc (3 : 1)	90	99	t	1	66/96[g]
12	6.0	5.25	2–5	Heptane	85	74[i]	t	4	60/75[j]
13	6.0	5.25	2–5	Toluene	85	51[i]	t	4	55/60[j]
14	1.5	5.25	2–5	EtOAc	70	75[i]	t	5	38/90[j]
15	2.5	5.25	2–5	EtOAc	80	83[i]	1	5	48/90[j]
16	4.7	5.25	2–5	EtOAc–*t*-BuOH (3 : 1)	95	89[i]	2	5	61/95[g]
17	10.0	5.25	2–5	EtOAc	100	96	2	2	70/99
18	6.0	5.25	22	EtOAc	100	96	2	2	38/97
19	6.0	10–13	2–5	EtOAc	100	96	2	2	64/98
20	6.0	2.5–3	2–5	EtOAc[h]	95	92	1	2	55/95[g,j]

EtOAc = Ethyl acetate; DCE = Dichloroethane; PE = Petroleum ether; DMP = Dimethoxypropane; t = trace (less than 0.5%). [a] 70% aqueous solution. [b] Bleach solution was added as fine droplets over 9–10 h. [c] Calculated based on LC–MS, rest is unreacted starting material. [d] Calculations based on LC–MS analysis of reaction mixture. [e] Yield of the isolated technical product without crystallization, and Purity as determined by LC–MS. [f] Contains 6% 7-OOH along with some other unidentified oxygenated compounds. [g] Contains starting steroid as major impurity. [h] Reactions were done in presence of sodium carbonate monohydrate (10 mol%) in the reaction mixture. [i] Also contains 7-OH, 7–OOH, and other unidentified oxygenated compounds. [j] All reaction mixture impurities were present.

oxidation reactions of DHEA-Ac (**1**), accounted for 3% abundance in this oxidation. A simple work-up without column chromatography or crystallization afforded compound **14** in 99% purity (Fig. 2) and in 60% yield. Allylic *tert*-butyl perether and allylic *tert*-butyl ether, which are often the major by-products produced in the TBHP mediated oxidation of compounds with endocyclic olefinic linkage[15] were present in only trace amounts at the end of the reaction. Allylic *tert*-butyl ether was not detected and allylic *tert*-butyl perethers (7-OOt-Bu, **16**, Table 1, Fig. 1) were formed during the course of the reaction but only small amounts (2–3%) remained at the end of the reaction. The presence of diastereomeric 7-hydroxy and 7-hydroperoxy compounds during the course of the reaction was confirmed by LC–MS analysis, but they were subsequently converted to enone. It may be noted that in solventless oxidation of DHEA-3-Ac (**1**), 8–10 mol equivalents of TBHP (entry 2) were required to effect complete conversion as lower amounts led to incomplete oxidation (entry 1) and

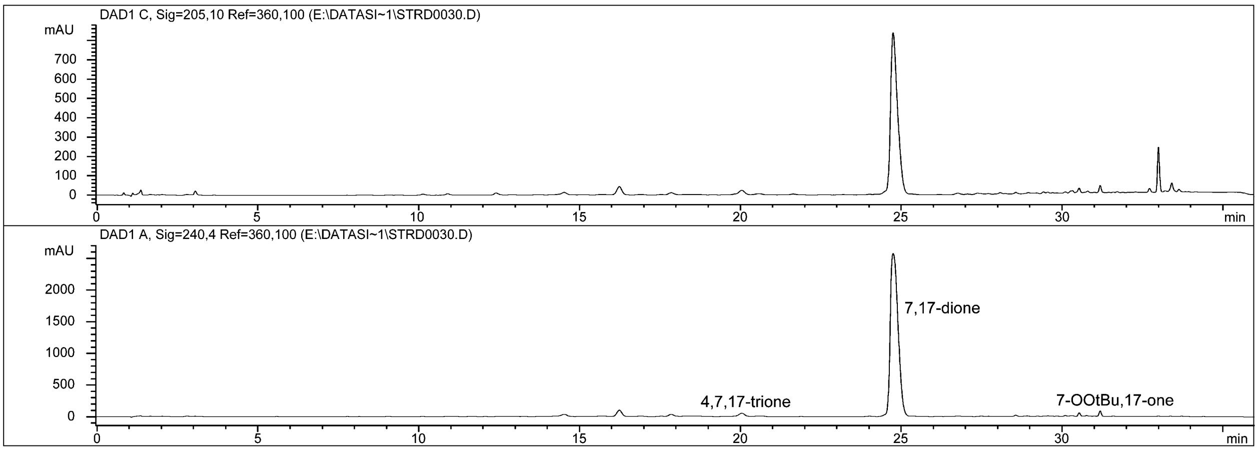


Fig. 1 Oxidation of DHEA-Ac (**1**) using *tert*-butylhydroperoxide and bleach (5.25% available chlorine) at 8–10 °C. (entry 3, Table 1). HPLC-chromatogram of the reaction mixture. Chromatographic conditions: Agilent's 1100 LC-MS-ESI system. LC column: Zorbax-SB C_{18} (4.6 × 75 mm, 3.5 μm) with a guard column, at 40 °C. Column flow rate: 0.8 ml min^{-1} and the eluent was monitored at 205, 240 and 280 nm with a reference wavelength of 360 nm. Linear gradient (% acetonitrile–water) 20 : 80 at $t = 0$, 45 : 55 at $t = 25$, 94 : 6 at $t = 32$ to 34 min and 20 : 80 at $t = 36$ min; 0.1% formic acid at 0.088 ml min^{-1} was added post column. MS (Method A): drying gas (N_2) 13 l min^{-1}; drying gas temperature 350 °C; nebulizer pressure 50 psi; capillary voltage 4500 V; and fragmentor 80 V.

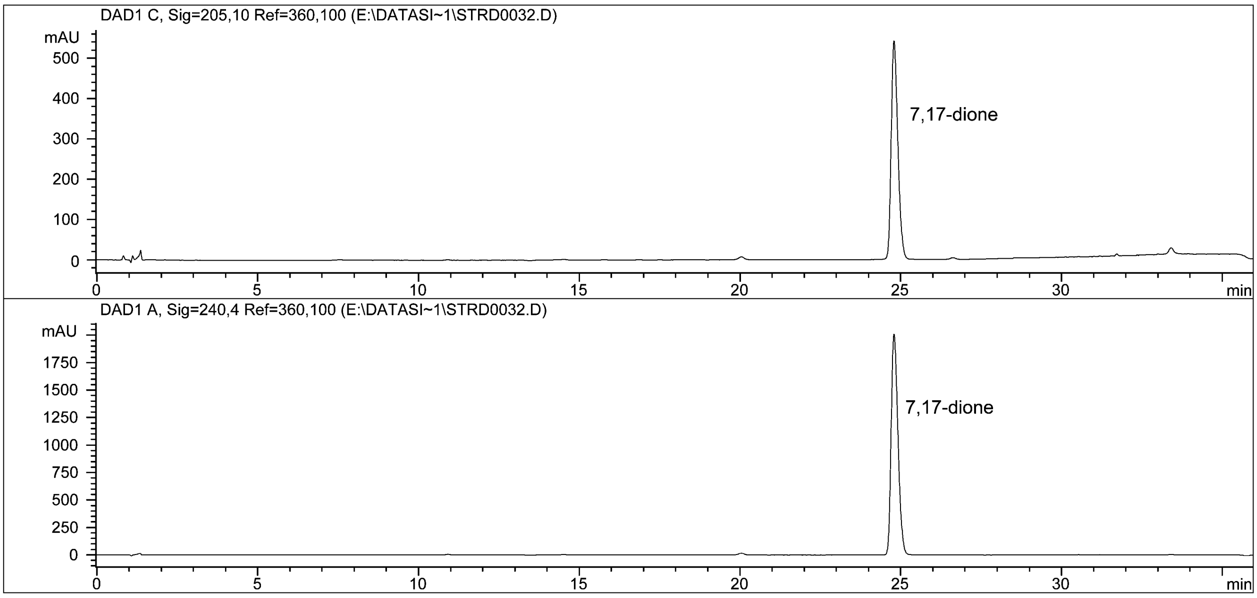


Fig. 2 LC-chromatogram of 7-oxo-DHEA-3-acetate (**14**) isolated from the reaction mixture. DHEA-Ac (**1**) was allylically oxidized using aqueous *tert*-butylhydroperoxide and bleach (5.25% available chlorine) at 8–10 °C. (entry 3, Table 1). Chromatographic conditions as in Fig. 1.

contaminated product. However, 6 mol equivalents of TBHP were enough to complete the same reaction in the presence of suitable organic solvent(s).

Allylic oxidation in which hydrogen abstraction is the dominant reaction, is a process involving free radicals induced by low oxidation state transition metal species. The mechanism of the reaction of the hypochlorite–TBHP combination used for lipid peroxidation has been reported[17] as a free radical reaction in contrast to the formation of singlet oxygen during hypochlorite reaction with hydrogen peroxide[18]. The present hypochlorite reaction with TBHP, which induced allylic oxidation, was exothermic and hypochlorite reacted fast with TBHP at room temperature generating a lot of oxygen *in situ*. This required the reaction to be performed preferably at 2–5 °C. In order to study the mechanism, progression of this oxidation (DHEA-Ac, **1**) was monitored and samples were collected every 10 min for the 1st hour of the reaction followed by 20 and 30 min intervals; reaction intermediates were identified using LC–MS analysis. Formation of both isomers of allylic–OOH, –OH, and allylic *tert*-BuOO– was observed. Area% (UV λ_{205}) was calculated for all the compounds during a 9 h run and the data were plotted with reference to time (Fig. 3). In the first 10 minutes, products identified were diastereomeric allylic-OOH's, allylic-*tert*-butylperether and α,β-enone. As the reaction progressed, the amount of allylic-OOH's increased during the first 50 min (to 8–12%) and then started to decline; these intermediates were completely consumed by the end of the 6th hour. Both allylic hydroxyls, whose concentration increased from <1 to 8.5% were eventually oxidized completely in 6 hours, whereas both allylic *tert*-BuOO compounds, whose concentrations increased from <1% to a maximum of 3.8% in 6 h, were eventually reduced to 0.5% at the end of 9th hour in this experiment. Since both allylic-OH's and allylic-OOH's were consumed and probably converted to α,β-enones, it is quite probable that more than one reaction pathway is functional (Scheme 1). Another reaction was conducted simultaneously under the same conditions except that a radical inhibitor, butylated hydroxy toluene (BHT, 20 mol%) was added into the reaction mixture. In this experiment, allylic oxidation was inhibited until BHT was consumed, suggesting that the reaction of hypochlorite with TBHP does involve free radical stages and *tert*-butylperoxy radical is the most probable free radical (Scheme 1), which initiates the formation of olefin radical, and is likely responsible for the formation of allylic *tert*-butylperoxy ether. It seems that an allylic radical thus formed from the

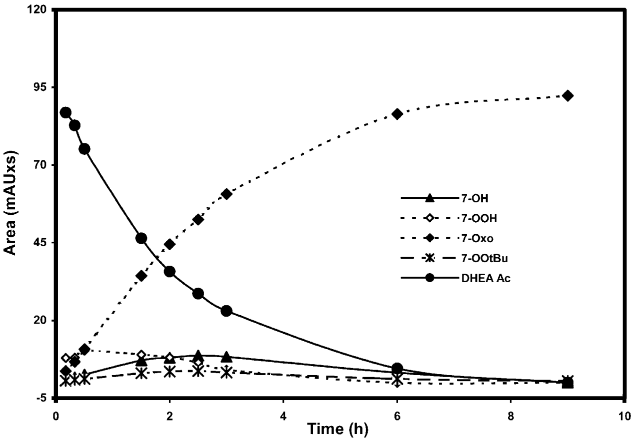


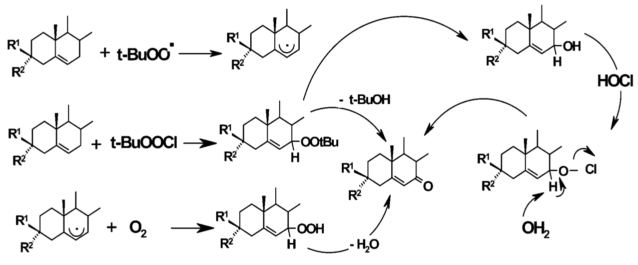
Fig. 3 Oxidation of DHEA-Ac (**1**) using hypochlorite and *tert*-BuOOH: reaction products were identified by LC–MS and the progress of the reaction was monitored by LC–MS of the reaction mixture at various intervals. LC–MS conditions as mentioned in Fig. 1.

$\mathrm{NaOCl + HOH \rightarrow HOCl + NaOH}$

$\mathrm{t\text{-}BuOOH + HOCl \rightarrow t\text{-}BuOH + O_2 + HCl}$

$\mathrm{2\ t\text{-}BuOOH + 2\ HOCl \rightarrow 2\ t\text{-}BuO^{\bullet} + 2\ H_2O + O_2 + Cl_2}$

$\mathrm{t\text{-}BuO^{\bullet} + t\text{-}BuOOH \rightarrow t\text{-}BuOO^{\bullet} + t\text{-}BuOH}$



Scheme 1

olefin by *tert*-BuOO$^\bullet$-induced allylic hydrogen abstraction may then be intercepted by the oxygen, generated by the reaction of HOCl and TBHP, to form an allylic hydroperoxide which is then further oxidized to α,β-enones. Reaction carried out in the presence of ethylenediamine tetraacetic acid (EDTA, 2 mol%), a metal ion sequestering agent, did not have any effect on the yield and the product composition indicating that this allylic oxidation was not being catalyzed by the presence of adventitious metal ions.

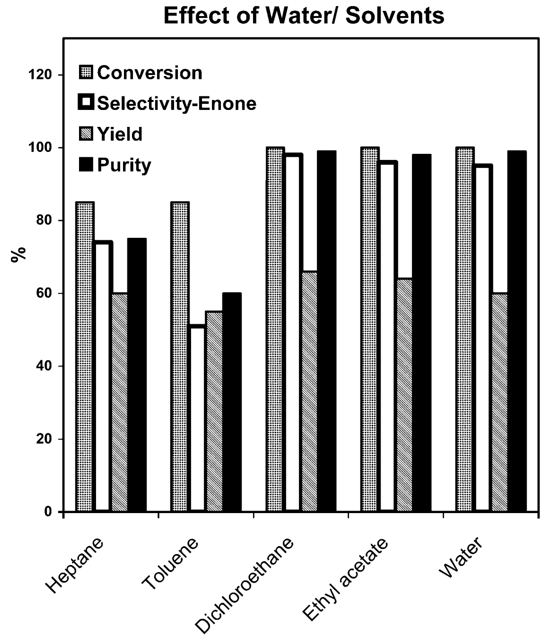
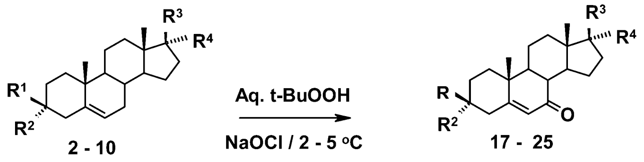


Fig. 4 Effect of reaction medium (water/solvents) on the allylic oxidation of DHEA-Ac (**1**) using bleach (5.25% available chlorine) and aqueous *tert*-butylhydroperoxide. Reaction mixture and products were analyzed by LC–MS for (i) conversion (consumption of DHEA-Ac, **1**), (ii) selectivity [formation of enone (7-oxo-DHEA-Ac, **14**)], (iii) yield of enone (**14**), and (iv) purity of isolated enone (**14**). LC–MS conditions were as mentioned in Fig. 1.

Organic solvents have been a prerequisite for allylic oxidations, which are often performed in undesirable solvents such as benzene,[13,14,19] methylene chloride[2a,3,12c] *etc.* The present oxidation provided a dual choice system, where oxidation could be performed with or without organic solvents. Since the use of solvent was not a prerequisite in this oxidation, a solubility constraint of polar and non-polar steroidal substrates was eliminated. The effect of organic solvents on the oxidation of DHEA-Ac (**1**) was studied. The oxidation was carried out in heptane, toluene, dichloroethane, ethyl acetate or in water and the results are illustrated in Fig. 4. The reaction mixtures were analyzed for % conversion of the starting material, and selectivity, purity and the yield of the steroidal enone. DHEA-Ac was oxidized efficiently in a wide variety of water immiscible solvents or mixture of solvents (entries 5–11, Table 1 and Fig. 4). Although the present reaction could be performed in water or in organic solvent(s), a slight increase in product yield was obtained by conducting the reaction in suitable organic solvent (Table 1). The use of two solvents as a reaction medium was also applied in the present methodology and interestingly a co-solvent system of ethyl acetate–petroleum ether was found to be the most suitable solvent system for the oxidation of **1** and other steroidal substrates, affording the best yields of the enones (entry 8, Table 1; entry 25 Table 2). We were able to oxidize 200 g batches of DHEA-Ac (**2**) and DHEA (**1**) smoothly in the laboratory in a solvent system of ethyl acetate–petroleum ether (4 : 1) and isolated the corresponding enone in 65–67% yield with a purity of 99% without any crystallization. Solvents such as *tert*-butanol and acetonitrile were also used either alone or as a co-solvent. Heptane, toluene and petroleum ether gave lower yields and a low purity product often contaminated with starting substrates and by products (entry 12, 13, Table 1, Fig. 4). Since this biphasic reaction was performed below pH 11, at which the equilibrium amount of HOCl becomes significant,[20] and due to the solubility of this positive form of chlorine in moderately polar solvents such as ethyl acetate, the use of a phase transfer catalyst (PTC) was not required. This was further substantiated by the fact that no significant difference in yield and reaction time was observed when tetrabutylammonium bromide was added to the reaction mixture.

The presence of TBHP in the reaction mixture was absolutely necessary for the allylic oxidation leading to α,β-enones;

Table 2 Hypochlorite and TBHP induced allylic oxidation of Δ^5-steroids (**2–10**)



		SM									
Entry #	#	R^1	R^2	R^3	R^4	Enone #	Solvent	Conversion[a] (%)	*Y*[b] (%)	*P*[c] (%)	mp/obs.°C[d]
21	**2**	OH	H	—=O——		**17**	No solvent	88	65	98[e]	234–236[24]
22	**2**	OH	H	—=O——		**17**	Water[f]	98	68	97[e]	
23	**2**	OH	H	—=O——		**17**	EtOAc–*t*-BuOH (8 : 2)	98	70	99.4	234–236
24	**3**	AcO	H	C_8H_{17}	H	**18**	DCE	100	68	96[g]	159–161[19]
25	**4**	AcO	H	AcO	H	**19**	EtOAc–PE(9 : 1)	100	71	99.8	222–224[19]
26	**5**	——EK—		AcO	H	**20**	EtOAc	100	71	99.8	252–254[25]
27	**6**	——EK—		——EK——		**21**	EtOAc	100	63	99	200–201[26]
28	**7**	MeO	H,	—=O——		**22**	EtOAc	100	76	99	227–229[27]
29	**8**	OH	H	C_8H_{17}	H	**23**	DCE	98	68	99.8	169–171[28]
30	**9**	OH	H	——EK—		**24**	EtOAc	100	68	98[h]	195–197
31	**10**	OH	H	—NPK—		**25**	DCM	100	72	98[h]	167–169

SM = starting material, EK = Ethylene ketal; NPK = Neopentyl ketal; EtOAc = Ethyl acetate; DCE = Dichloroethane; PE = Petroleum ether; DCM = Dichloromethane; Reaction conditions: 6 mol equiv. TBHP, 2 mol equiv. NaOCl in 9–10 h, 2–5 °C. [a] Calculated based on LC data. [b] Isolated technical product obtained without chromatography or recrystallization. [c] LC based purity of isolated technical product. [d] mp of the recrystallized material. [e] Contains SM as impurity. [f] TBHP (70%) : water = 1 : 1. [g] Contains 4% 7-OH compound. [h] Contains 2% deketalized product.

no formation of α,β-enone was observed in its absence. Subsequently, oxidation of DHEA-Ac was performed using different molar equivalents of TBHP in order to get an optimized value for this important variable. An initial concentration of less than 3 mol equivalents of TBHP (entry 14 and 15, Table 1, and Fig. 5) led to incomplete conversion of the starting material and reaction intermediates, whereas 6.0 mol equivalents of TBHP under the same reaction conditions in different organic solvent systems showed complete conversion of starting materials and reaction intermediates affording the desired enones (entry 5 and 6, Table 1) in excellent selectivity (>96%). However a higher concentration (10 mol equivalents) of TBHP was needed when the allylic oxidation was carried out in water; presumably TBHP acts as a solvent too. The effect of different concentrations of TBHP on the % conversion of the starting material and selectivity, purity and the yield of the product is depicted in Fig. 5. The effect of different concentrations of hypochlorite solution on the oxidation of DHEA-Ac was studied (Fig. 6). Household bleach solution containing ~5.25% available chlorine (w/v) was found to be adequate for achieving allylic oxidation in good yield and purity. Use of lower strength bleach solution (2–3%, entry 20, Table 1) resulted in poor yield, whereas use of higher concentrations of hypochlorite did not result in any advantage (Fig. 6).

During initial studies, the reaction temperature and rate of addition of bleach solution were found to be other critical parameters, which played an important role in this oxidation and required further attention. At ambient temperature, the relative rate of conversion was rapid compared to sub-ambient temperature, but the product yield was poor (Fig. 7), possibly due to degradation of the starting materials and their intermediates by bleach and rapidly generated free radicals, which also compete with oxygenation. Sub-ambient temperature (2–5 °C) was the temperature of choice (Fig. 7) for obtaining the best values for the %conversion, selectivity, yield and purity of the isolated product. Fast addition of bleach solution even at sub-ambient temperature was deleterious and led to poor yields of the desired enones. Excellent selectivity and good yield of the product could be obtained when bleach solution was added continuously in the form of fine droplets or mist for 9–10 hours to the vigorously stirred cold (2–5 °C) solution of substrate and 70% aqueous TBHP with or without organic solvent.

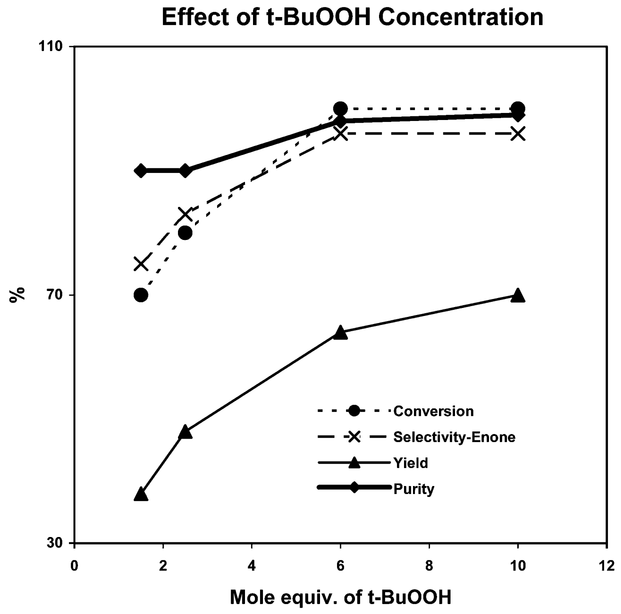


Fig. 5 Effect of *tert*-butylhydroperoxide (70% aqueous solution) concentration on the hypochlorite oxidation of DHEA-Ac (**1**). Reaction mixture and products were analyzed by LC–MS for (i) conversion (consumption of DHEA-Ac, **1**), (ii) selectivity [formation of enone (7-oxo-DHEA-Ac, **14**)], (iii) yield of enone (**14**), and (iv) purity of isolated enone (**14**). LC–MS conditions were as mentioned in Fig. 1.

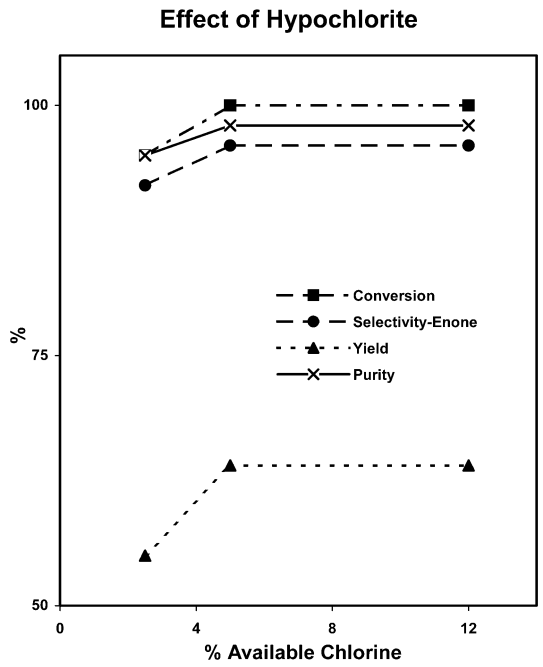


Fig. 6 Effect of different concentrations of hypochlorite solution (expressed as percentage available chlorine) on the allylic oxidation of DHEA-Ac (**1**). Reaction mixture and products were analyzed by LC-MS for (i) conversion (consumption of DHEA-Ac, **1**), (ii) selectivity [formation of enone (7-oxo-DHEA-Ac, **14**)], (iii) yield of enone (**14**), and (iv) purity of isolated enone (**14**). LC-MS conditions were as mentioned in Fig. 1.

The scope of the present procedure was further indicated by the results summarized in Table 2 for nine different Δ^5-steroidal olefins related to the androstene and cholestene series (entry **21**–**31**, Table 2), and in Scheme 3 with three benzylic compounds (**31**–**33**). In most cases examined, the reactions reached 98–100% conversion within a period of 9–10 h under optimized conditions, providing the corresponding steroidal enones in good (68–76%) yields and benzylic ketones in excellent 88–99% yields. Even Δ^4 steroid (**11**, Scheme 2) was

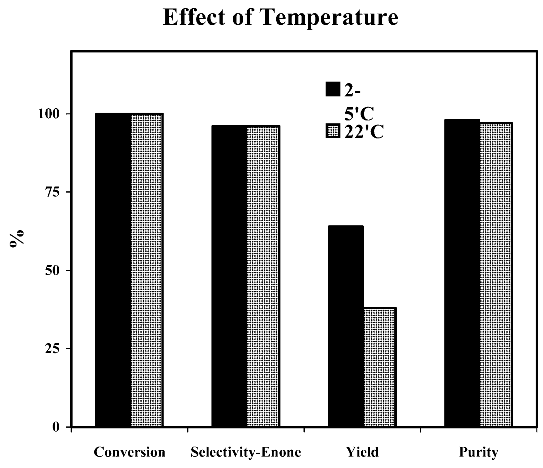
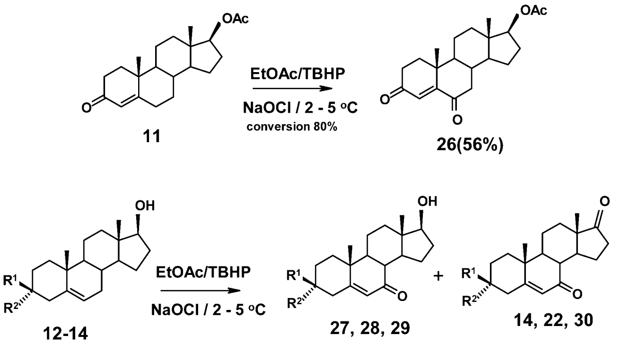
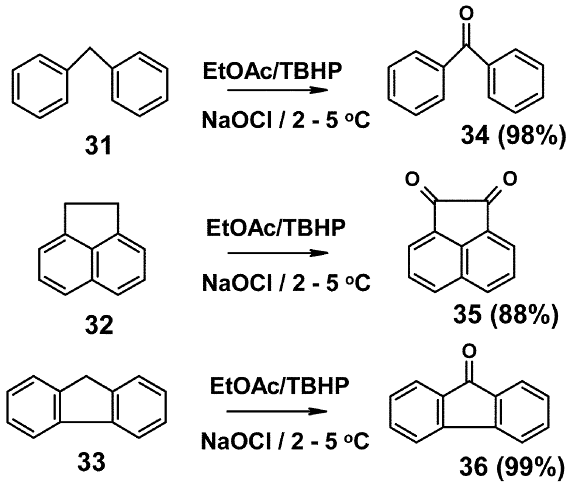


Fig. 7 Effect of reaction temperature on the allylic oxidation of DHEA-Ac (**1**) using *tert*-butylhydroperoxide (70% aqueous solution) and sodium hypochlorite solution (5.25%). Reaction mixture and products were analyzed by LC–MS for (i) conversion (consumption of DHEA-Ac, **1**), (ii) selectivity [formation of enone (7-oxo-DHEA-Ac, **14**)], (iii) yield of enone (**14**), and (iv) purity of isolated enone (**14**). LC–MS conditions were as mentioned in Fig. 1.



12.	R^1 = AcO, R^2 = H	**27** + **14** (7:3)
13.	R^1 = MeO, R^2 = H	**28** + **22** (7:3)
14.	R^1, R^2 = EK	**29** + **30** (9:1)

Scheme 2



Scheme 3 Oxidation of benzylic compounds.

oxidized at its allylic C-6 position under similar conditions and α,β-dienone **26** was isolated in 56% yield.

Bleach–TBHP-induced oxidation of steroidal olefins produced α,β-enones more selectively than those carried out using chromium,[12c,d] ruthenium,[2a] and iron[21]-based catalysts that produce a number of undesirable by-products. Since these by-products are produced in appreciable amounts (10% or more), the purification of the desired product often becomes a cumbersome task. In the present bleach-oxidized reaction mixture, the by-products that were produced at the end of reaction were far less abundant (~2% or less) compared to enone, which was detected in ~80–85% abundance. High selectivity was found towards the formation of steroidal enones even when free hydroxyl groups, at different positions, were present. Steroids with a free hydroxyl group at the 3-position (entry 21–23, 29–30, Table 2) were oxidized successfully into the corresponding α,β-enones (**17**, **23–25**) in good yields (68–70%). Interestingly, oxidation of dehydroepiandrosterone (DHEA, **2**, entry 22) could be performed in a 1 : 1 mixture of water and 70% TBHP as a reaction medium and, after almost quantitative conversion, the 7-oxo compound was obtained exclusively without the formation of the 3-oxo compound. Experiments also indicated that water could be substituted for the solvent for the oxidation of polar steroids having unprotected hydroxyl groups. Use of a small amount of water in the oxidation of DHEA (**2**) eliminated the use of an excess of TBHP, which was needed for the oxidation of the corresponding acetate (entry 2, 3 Table 1). A hydroxyl group at position 17 of the steroid molecule showed some oxidative vulnerability, which seemed to be substitution dependent. Oxidation of 17-hydroxylated Δ^5-steroids (**12–14**, Scheme 2) afforded corresponding α,β-enones with 70–90% selectivity (**27–29**, Scheme 2). Furthermore, reaction conditions were also found to be suitable for the oxidation of steroids bearing acid-sensitive groups such as ethylene ketal (entries 26,27,30,31, Table 2 and **14** Scheme 2), and the corresponding enones were obtained in good yields. All these reactions of steroidal olefins and their isolated products were analyzed for product composition, purity and structure conformation using an online LC–MS instrument equipped with a diode array UV detector (DOD, λ_{205} and λ_{240} absorbance) and an electrospray ionization mass detector, In all cases, the selectivity of steroidal enones was excellent (>96%) and a short and convenient work-up afforded them in high purity. Benzylic ketones (**34–36**, Scheme 3) were analyzed by chemical ionization mass detector using flow injection analysis.

Conclusions

The present methodology demonstrated that allylic oxidations can be accomplished cheaply and effectively, using water-based oxidants such as household bleach and aqueous TBHP, thereby meeting the dual challenge of cost effectiveness and benign nature of the process. The present hypochlorite oxidation provides a distinct advantage over other oxidizing agents, where work-up and waste disposal is usually a difficult task. The salts formed in the hypochlorite oxidation can be rinsed down the drain. Reactions can be run under aqueous conditions, quite concentrated and can be conveniently scaled-up for subsequent manufacturing and commercialization.

Experimental

Commercially available household laundry bleach (~5.25% sodium hypochlorite) was used for all general purposes. TBHP (70 wt% aqueous solution), sodium hypochlorite (10–13% available chlorine), benzylic compounds and the organic solvents were purchased from Aldrich Chemical Company. Deionized water (18 MΩ-cm) was used for the reactions. Steroids were purchased either from Steraloids, Newport, USA or were synthesized in this laboratory by known procedures. The structure of oxidized products was confirmed by known literature references, melting point (uncorrected), nuclear magnetic resonance (NMR, Brucker's 200 MHz spectrometer), and online LC–MS instrument with diode array UV-detector (Agilent's 1100 series, single quadruple LC–MS–ESI and APCI system). Reaction mixtures were analyzed for % conversion, selectivity, and purity of enones simultaneously at 205, 240 and 280 nm wavelengths, and confirmed by molecular mass measurements and their fragmentation patterns in the positive ion mode using MS–ESI and APCI detectors.

General oxidation procedure

A mixture of steroidal/benzylic compound (0.01 mol) and 70 wt% aqueous TBHP (0.06 mol) in ethyl acetate (substrate : solvent = 1 : 10; in solventless reactions substrate : TBHP = 1 : 10 mol) was stirred vigorously at 2–5 °C. Bleach solution containing 0.02 mol of sodium hypochlorite was added slowly using a minipulse pump, which allowed uniformly controlled addition of bleach over 10 h. At the end of the reaction, the solution was saturated with sodium bicarbonate (it can also be added at the beginning of the reaction) and the organic layer was separated, mixed with 20% aqueous solution of sodium sulfite (0.04 mol equiv.) and the mixture was stirred at 50 °C for

2 h (or until all the trione, if any, was gone). The organic layer was removed, washed twice with water and dried over magnesium sulfate. The solution was concentrated to 1/3 of its volume, mixed with petroleum ether (bp 35–60 °C) or n-hexane, and cooled to induce crystallization. A second crop was obtained after concentrating and crystallizing from the mother liquor with appropriate organic solvents.

Chromatographic conditions

LC-MS-ESI (method A) for analyzing steroidal substrates. Chromatography of all the reactions and the isolated products was carried out on an Agilent 1100 LC–MS system. LC was performed on a Zorbax-SB C_{18} analytical column (4.6 × 75 mm, 3.5 μm), protected with a Zorbax SB-C_{18} guard column and maintained at 40 °C. The column flow rate was set at 0.8 ml min^{-1} and the eluent was monitored at 205, 240 and 280 nm with a reference wavelength of 360 nm. An acetonitrile–water (ACN–W) linear gradient (% ACN : W 40 : 60 at $t = 0$, 92 : 8 at $t = 13$ to 20 min and 40 : 60 at $t = 21$ min followed by a 10 min post run time; 0.1% formic acid at 0.088 ml min^{-1} was added post column throughout the run.

All the compounds were analyzed for their molecular mass and fragmentation using electrospray ionization (ESI) in positive mode. Operating conditions were (optimized by flow injection analysis (FIA) of DHEA-Ac and 7-ODA): drying gas (N_2) 13 l min^{-1}; drying gas temperature 350 °C; nebulizer pressure 50 psi; capillary voltage 4500 V; and fragmentor 80 V. The samples were run in scan mode. LC-retention times (t_R) for intermediates and isolated products were checked by standard sample and area percent was calculated based on the external standard method.

LC–MS–APCI (method B) for the analysis of aromatic substrates. Benzylic compounds were analyzed by flow injection analysis using a guard column (Zorabax SB C_{18}). A LC–MS–APCI detector was used to obtain their molecular mass and fragmentation in positive mode.

3β-Acetoxyandrost-5-en-17-one (DHEA-Ac, **1**)[22]: UV λ_{max} 205; LC–MS (method A), t_R 11.01 min; MS (*m*/*z*), 353 $(M + Na)^+$, 331 $(M + H)^+$, 313 $(M + H - H_2O)^+$, 271 $(M + H - CH_3COOH)^+$, 253 $(M + H - H_2O - CH_3COOH)^+$.

3β-Acetoxyandrost-5-en-7,17-dione (**14**):[22] mp 185–187 °C, UV λ_{max} 236; LC–MS (method A), t_R 6.0 min, MS (*m*/*z*), 367 $(M + Na)^+$, 327 $(M + H - H_2O)^+$, 285 $(M + H - CH_3COOH)^+$, 269 $(M + H - H_2O - CH_3COOH)^+$; ^{1}H NMR (200 MHz), δ 5.75 (d, J = 1.4 Hz, 6-H), 4.74 (m, 3α-H), 2.06 (s, 3-AcO), 1.24 (s, 19-CH_3), 0.89 (s, 18-CH_3).

3β-Acetoxyandrost-5-en-4,7,17-trione (**15**): mp 218–20 °C; UV λ_{max} 250; LC–MS (method A), t_R 4.83 min; MS (*m*/*z*), 381 $(M + Na)^+$, 359 $(M + H)^+$, 341 $(M + H - H_2O)^+$, 299 $(M + H - CH_3COOH)^+$, 281 $(M + H - H_2O - CH_3COOH)^+$; ^{1}H NMR (200 MHz), δ 6.17 (s, 6-H), 5.29 (dd, J = 12.2, 7.08 Hz, 3α-H), 2.19 (s, 3-AcO), 1.23 (s, 19-CH_3), 0.91 (s, 18-CH_3); ^{13}C NMR δ 220, 200.5, 197.5 (CO), 169.8 (CO-AcO), 159.3 (C-5), 127.2 (C-6), 76.0 (C-3), 50.5, 45.6,44.7 (CH's), 35.5, 34.1, 30.6, 25.8, 23.9, 20.8 (CH_2's), 20.6, 18.2, 13.8 (CH_3's).

3β-Acetoxy-7-*tert*-butylperoxy-androst-5-en-17-one (**16**):[22] UV at λ_{max} 205; LC–MS (method A), t_R 13.0, 13.42 min (7**α**- and 7**β**- isomers); MS (*m*/*z*), 441 $(M + Na)^+$, 419 $(M + H)^+$, 345 (M + H − *tert*-BuOH)$^+$, 269 (M + H − CH_3COOH − *tert*-BuOOH)$^+$, 267 (M + H − H_2O − CH_3COOH − *tert*-BuOH)$^+$.

3β-Acetoxy-7α and 7β-hydroxy-androst-5-en-17-one:[22] UV at λ_{max} 205; LC–MS (method A), t_R 4.85 min (7β-OH) and 5.81 min. (7α-OH); MS (*m*/*z*), 369 $(M + Na)^+$, 287 $(M + H - CH_3COOH)^+$, 269 $(M + H - H_2O - CH_3COOH)^+$, 251 $(M + H - 2H_2O - CH_3COOH)^+$.

3β-Acetoxy-7α and 7β-hydroperoxy-androst-5-en-17-one:[23] UV at λ_{max} 205; LC–MS (method A), t_R 5.69 min. (7β-OOH) and 6.66 min. (7α-OOH); MS (*m*/*z*), 385 $(M + Na)^+$, 345 $(M + H - H_2O)^+$, 285 $(M + H - H_2O - CH_3COOH)^+$, 269 $(M + H - H_2O_2 - CH_3COOH)^+$, 267 $(M + H - 2H_2O - CH_3COOH)^+$.

3β-Hydroxyandrost-5-en-7,17-dione (**17**);[24] UV λ_{max} 242; MS (*m*/*z*), 325 $(M + Na)^+$, 303 $(M + H)^+$, 285 $(M + H - H_2O)^+$, 267 $(M + H - 2H_2O)^+$; ^{1}H NMR (200 MHz), δ 5.75 (d, J = 1.47 Hz, 6-H), 3.7 (m, 3α-H), 1.23 (s, 19-CH_3), 0.9 (s, 18-CH_3).

3β-Acetoxycholest-5-en-7,17-dione (**18**):[19] UV λ_{max} 236; MS (*m*/*z*), 465 $(M + Na)^+$, 383 $(M + H - CH_3COOH)^+$; ^{1}H NMR (200 MHz), δ 5.69 (d, J = 1.0 Hz, 6-H), 4.72 (m, 3α-H), 2.05 (s, 3-AcO), 1.21 (s, 19-CH_3), 0.91 (d, J = 6.9 Hz, 21-CH_3), 0.88 (s, CH_3), 0.84 (s, CH_3), 0.68 (s, 18-CH_3).

3β, 17β-Diacetoxyandrost-5-en-7-one (**19**):[19] UV λ_{max} 236; MS (*m*/*z*), 411 $(M + Na)^+$, 329 $(M + H - CH_3COOH)^+$, 269 $(M + H - 2CH_3COOH)^+$, 251 $(M + H - 2CH_3COOH - H_2O)^+$; ^{1}H NMR (200 MHz), δ 5.72 (d, J = 1.4 Hz, 6-H), 4.68 (m, 3α-H+17α-H), 2.05 (s, AcO), 2.045 (s, AcO) 1.21 (s, 19-CH_3), 0.8 (s, 18-CH_3).

17β-Acetoxy-3-ethylenedioxyandrost-5-en-7-one (**20**):[25] UV λ_{max} 242; MS (*m*/*z*), 411 $(M + Na)^+$, 389 $(M + H)^+$; ^{1}H NMR (200 MHz), δ 5.68 (d, J = 1.7 Hz, 6-H), 4.63 (dd, J = 6.8, 9.5, 17α-H), 3.97 (m, O–CH_2–CH_2–O), 2.05 (s, 17-AcO), 1.21 (s, 19-CH_3), 0.82 (s, 18-CH_3).

3, 17-Diethylendioxyandrost-5-en-7-one (**21**):[26] UV λ_{max} 242; MS (*m*/*z*), 411 $(M + Na)^+$, 788 $(2M + Na)^+$; ^{1}H NMR (200 MHz), δ 5.66 (d, J = 1.95 Hz, 6-H), 3.96 (m, O–CH_2–CH_2–O), 3.89 (m, O–CH_2–CH_2–O,), 1.21 (s, 19-CH_3), 0.87 (s, 18-CH_3).

3β−Methoxyandrost-5-ene-7,17-dione (**22**):[27] UV λ_{max} 240; MS (*m*/*z*), 339 $(M + Na)^+$, 317 $(M + H)^+$, 285 $(M + H - CH_3OH)^+$; ^{1}H NMR (200 MHz), δ 5.75 (d, J = 1.95 Hz, 6-H), 3.38 (s, OCH_3), 3.2 (m, 3α-H), 1.22 (s, 19-CH_3), 0.9 (s, 18-CH_3).

3β-Hydroxycholest-5-en-7-one (**23**):[28] UV λ_{max} 236; MS (*m*/*z*), 423 $(M + Na)^+$, 401 $(M + H)^+$; ^{1}H NMR (200 MHz), δ 5.68 (d, J = 1.46 Hz, 6-H), 3.67 (m, 3α-H), 1.2 (s, 19-CH_3), 0.91 (d, J = 6.9 Hz, 21-CH_3), 0.87 (s, CH_3), 0.84 (s, CH_3), 0.68 (s, 18-CH_3).

3β-Hydroxyandrost-5-en-17-ethylene ketal (**24**): UV λ_{max} 240; MS (*m*/*z*), 369 $(M + Na)^+$, 347 $(M + H)^+$, 285 $(M + H - CH_2OHCH_2OH)^+$; ^{1}H NMR (200 MHz), δ 5.7 (d, J = 1.2 Hz, 6-H), 3.9 (m, O–CH_2–CH_2–O), 3.68 (m, 3α-H), 1.2 (s, 19-CH_3), 0.87 (s, 18-CH_3).

3β-Hydroxyandrost-5-en-17-neopentyl ketal (**25**): UV λ_{max} 240; MS (*m*/*z*), 411 $(M + Na)^+$, 389 $(M + H)^+$, 285 $(M + H - HOCH_2C(CH_3)_2CH_2OH)^+$; ^{1}H NMR (200 MHz), δ 5.7 (d, J = 1.2 Hz, 6-H), 3.4 (m, O–CH_2–CH_2–O), 3.66 (m, 3α-H), 1.2 (s, CH_3), 1.14 (s, CH_3), 0.82 (s, CH_3), 0.71 (s, 18-CH_3).

17β-Acetoxyandrost-4-en-3,6-dione (**26**): mp 192–194 °C; UV λ_{max} 252; LC–RT (method A) 7.07 min.; MS (*m*/*z*), 367 $(M + Na)^+$, 345 $(M + H)^+$, 285 $(M + H - CH_3COOH)^+$, 267 $(M + H - H_2O - CH_3COOH)^+$; ^{1}H NMR (200 MHz), δ 6.18 (d, J = 0.7 Hz, 6-H), 4.64 (dd, J = 7.6, 9.3 Hz, 17α-H), 2.06 (s, 17-AcO), 1.18 (s, 19-CH_3), 0.85 (s, 18-CH_3)

3β-Acetoxy-17-hydroxyandrost-5-en-7-one (**27**):[29] mp 167–169 °C; UV λ_{max} 238; MS (*m*/*z*), 369 $(M + Na)^+$, 287 $(M + H - CH_3COOH)^+$, 269 $(M + H - H_2O - CH_3COOH)^+$; ^{1}H NMR (200 MHz), δ 5.7 (d, J = 1.2 Hz, 6-H), 4.7 (m, 3α-H), 3.65 (t, J = 9.5 Hz, 17α-H), 2.04 (s, 3-AcO) 1.23 (s, 19-CH_3), 0.77 (s, 18-CH_3)

3β-Methoxy-17-hydroxyandrost-5-en-7-one (**28**):[27] mp 202–204 °C; UV λ_{max} 242; MS (*m*/*z*), 341 $(M + Na)^+$, 319 $(M + H)^+$, 287 $(M + H - CH_3OH)^+$; ^{1}H NMR (200 MHz), δ 5.73 (d, J = 1.7 Hz, 6-H), 3.38 (s, OCH_3), 3.66 (dd, J = 8.5, 17α-H), 3.2 (m, 3α-H), 1.2 (s, 19-CH_3), 0.77 (s, 18-CH_3).

17β-Hydroxy-3-ethylenedioxyandrost-5-en-7-one (**29**): mp 222–224 °C; UV λ_{max} 242; MS (*m*/*z*), 369 $(M + Na)^+$, 347 $(M + H)^+$; ^1H NMR (200 MHz), δ 5.7 (d, J = 1.7 Hz, 6-H), 3.96 (m, O–CH_2–CH_2–O), 3.65 (t, J = 8.3 Hz, 17α-H), 1.22 (s, 19-CH_3), 0.77 (s, 18-CH_3).

3-Ethylenedioxyandrost-5-en-7,17-dione (**30**): UV λ_{max} 242; MS (*m*/*z*), 367 $(M + Na)^+$, 345 $(M + H)^+$, 327 $(M + H - H_2O)^+$; ^1H NMR (200 MHz), δ 5.72 (d, J = 1.7 Hz, 6-H), 3.97 (m, O–CH_2–CH_2–O), 1.23 (s, 19-CH_3), 0.9 (s, 18-CH_3).

Benzophenone (**34**):[28] mp 47–48 °C; LC–MS–APCI (method B, conditions: drying gas (N_2) 4 l min^{-1} at 350 °C; nebulizer pressure 60 psi; capillary voltage 2500 V, corona current at 7.0 µA; and fragmentor at 80 V) *m*/*z* : 183 $(M + H)^+$, 105 $(M + H - C_6H_6)^+$; ^1H NMR (200 MHz), δ 7.43–7.64 and 7.78–7.83 (m, ArH).

Acenaphthenequinone (**35**):[28] mp 250–52 °C (dec.); LC–MS–ESI (method A, positive ion), *m*/*z*: 205 $(M + Na)^+$, 183 $(M + H)^+$; ^1H NMR (200 MHz), δ 8.64 (dd, J = 1.0, 7.33 Hz, 2H-Ar), 8.33 (dd, J = 1.0, 8.33 Hz, 2H-Ar), 7.83 (dd, J = 1.0, 7.33 Hz, 2H-Ar).

Fluorenone (**36**):[28] mp 82–84 °C, LC–MS–APCI (method B, conditions: drying gas (N_2) 4 l min^{-1} at 350 °C; nebulizer pressure 60 psi; capillary voltage 4000 V, corona current at 7.0 µA; and fragmentor at 80 V), *m*/*z*: 181 $(M + H)^+$; ^1H NMR (200 MHz), δ 7.68 (t), 7.64 (t), 7.5 (m)(ArH).

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PAPER

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Green chemistry analytical method development: a revisit on the use of potassium ferrioxalate as a chemical actinometer

Ronald R. Sauers,*[a] Susan D. Van Arnum[a]† and Angelina A. Scimone[a,b]

[a] *Wright and Rieman Laboratories, Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08854, USA. E-mail: sauers@rutchem.rutgers.edu; Fax: +01 732 445-5312; Tel: +01 732-445-2626*

[b] *Natural and Physical Sciences Department, Caldwell College, 9 Ryerson Avenue, Caldwell, New Jersey 07006, USA*

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The experimental details regarding the use of potassium ferrioxalate (**3**) as a chemical actinometer are discussed with respect to the precision, ruggedness and simplicity of the method. Despite the fact that as much as a ten-fold difference between the actinometer **3** quantum efficiency and the analyte quantum efficiency was observed, these differences were compensated for by the use of multiple actinometer solutions during the quantum yield determinations. As a tool in process development, the advantages of the merry-go-round apparatus for the evaluation of the influence of experimental conditions for the quantum yield of photochemical reactions are also discussed.

Introduction

Analytical chemistry is an important component towards the development of environmentally-benign chemical processes. Suitable analytical methods are required for the detection and measurement of environmental contaminants as well as for the development of real-time, in-process monitoring of chemical processes to reduce the formation of hazardous substances.[1,2] In addition to issues regarding safety of chemical processes, analytical methodology can also be used to obtain data regarding the evaluation of environmentally-benign chemical processes.[3] An extension of this concept would be to use in-process analytical methods to evaluate the kinetics of the desired and undesired reactions in order to identify the attributes of a particular chemical transformation and to provide a base-line for comparison purposes for new processes and areas of future development.[4]

Due to competing pathways in a chemical reaction, reaction parameters such as moles of a reagent, solvent and reagent type and reaction time and temperature are typically evaluated during the course of process development. The stoichiometry, the solvents and reagents may have particular impact on the greenness of a process as increases in the amount of a reagent or changes in reagent type or solvent may compromise the ecological safety of a process. Statistical design of experiments is an approach in chemical development in which an empirical model of a chemical reaction is generated and in many cases, is the only technique which is experimentally feasible to understand a chemical reaction. This technique could also be used to assess the potential environmental impact of a process.[5] The model from a statistical design of experiments is only useful within the experimental space which was investigated, whereas a kinetic analysis of chemical reactions may be more general and would serve to truly identify the scope of a chemical process. Regardless of the technique, after this analysis is complete, the use of new process technologies or synthetic methodologies for the preparation of a target compound can be considered as possible environmentally safer alternatives. For photochemical processes, the quantum yield is the important parameter and could also be used as a selection criteria for a photochemical route.

In a similar vein for the process development of photochemical processes, the quantum yield would be an area for process optimization. The influence of solvent type, wavelength,[6] reaction temperature and the sensitivity to dissolved oxygen on the quantum yield and the product distribution would be areas which would be investigated. As many photochemical synthetic methods produce free-radicals or other kinds of reactive intermediates, reaction temperature would influence the selectivity of these reactive intermediates.[7] Although not investigated in this laboratory, reaction temperature would likely have an effect on the quantum yield for the photoisomerization of 4-acetyl-3,5-methylisoxazole (**1**) to 2-diacetyl-3-methylazirine (**2**). Flash photolysis studies and quantum yield measurements indicated that the inefficiency in this photoisomerization is due to efficient ring closure of a 1,5-diradical intermediate back to the starting isoxazole.[8] Depending on the relative activation energies for these processes, temperature may influence the rates of these processes. A Stern–Volmer analysis of the influence of quenchers for photochemical reactions could be used to preclude unwanted triplet state reactions. Desired reactions from triplet excited states could be controlled by the presence and type of chemical sensitizer.

As photochemical processes are one strategy for the development of environmentally-benign chemical processes,[9] knowledge of the quantum yield of a photochemical reaction is not only important from a fundamental perspective, but would also be useful as a selection criteria for a particular kind of substrate. For example, a class of photosensitive protecting groups which are frequently used for the protection of carboxylic acids are substituted phenacyl esters.[10] In a biochemical application, a review of the quantum yields for the deblocking of photosensitive protecting groups for carboxylic acids indicated that, in general, the quantum yields are approximately 0.1, despite the fact that the chemical yields for these deprotection reactions are virtually quantitative.[11] However, when the carboxylic acid is substituted with a 3,5-dimethoxybenzoin ester, the quantum

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† Former address: Chemical Development Department, Roche Carolina, 6173 East Old Marion Highway, Florence, South Carolina 29506, USA

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yield increased to 0.64.[12] Because of this six-fold increase in photochemical efficiency, the more efficient photochemical reaction may represent an economically feasible protecting group strategy as well as an environmentally benign approach if the spent reagent could be efficiently recycled. Such analysis is only possible, however, if the quantum yield for a particular reaction is known.

Because of their high degree of process control, microreactors are being considered as replacements for the traditional batch processing of chemical reactions.[13–15] The dependence of the quantum yield on the residence time within a microreactor for the photoreduction of benzophenone was recently described and many of the advantages of microreactors *versus* traditional photochemical apparatus were highlighted.[16] Of particular importance is that miniaturization of photochemical reactors minimized the "wall effects" associated with most preparative photochemical equipment and that they also help to attenuate the effect of absorbing solutions. In addition to the more efficient use of light, the process control in a photomicroreactor also offers advantages with respect to product selectivity, as reported for the photochlorination of toluene-2,4-diisocyante.[17] Miniaturized photochemical reactors have also been used for the photogeneration of the highly reactive reagent, singlet oxygen.[18] Knowledge of the quantum yield for these kinds of processes would also be important if photochemistry were to be considered as a sustainable technology in green chemistry.[19] An understanding of the quantum yield in solar light catalyzed processes may also be required to ascertain the potential of these processes.[20,21]

If the energy costs for a photochemical reaction or the materials of construction of a photochemical reactor do not preclude the consideration of photochemistry as a sustainable technology, the sustainability of this technology would be enhanced if photochemical synthetic methods were routinely incorporated during the identification of new chemical entities. For the synthesis of many target molecules, the photochemical approach is the only viable synthetic alternative. This distinguishing feature of photochemistry makes synthetic photochemistry a viable candidate for a sustainable technology since in some cases, there are very few other methods to prepare these compounds. As an example from these laboratories, the synthesis of oxetanes by an intramolecular Paterno–Büchi reaction has an efficiency with which very few, if any, routes could compete.[22] The synthesis of the core structure of pentacycloundecan-8-ones by a [2 + 2] cycloaddition reaction is another example of this concept.[23]

In the recent literature, there have been several reports of new actinometers and in some cases, these actinometers have been developed for specific uses such as the determination of quantum yields for reversible photochemical reactions and photochemical reactions in sun-exposed aqueous solutions.[24] A convenient method to determine quantum yields of photochemical reactions is to measure the photoconversion of a primary actinometer whose quantum yield is known at a particular wavelength and to compare the amount of the photoproduct that is formed from the actinometer per unit time to either the amount of photoproduct produced or the amount of starting material consumed by the analyte for the same time period. If the determination of a quantum yield is conducted in a manner in which the actinometer and the analyte are exposed to the same light flux, then this methodology can afford quantum yields which are both accurate and precise. In these laboratories, we have routinely used potassium ferrioxalate (**3**) as a chemical actinometer for the solution phase determination of quantum yields.[25] The quantum yield for different substrates and at different reaction conditions will serve to illustrate the precision, ruggedness and simplicity of the potassium ferrioxalate (**3**) method.[8,22]

Experimental

UV spectra were obtained on either a Perkin-Elmer UV-vis or a Cary 17D spectrophotometer.

Irradiations were conducted in a Rayonet Photochemical Reactor (Southern New England Ultraviolet Co., Middletown, CT) using 254 nm or 300 nm light sources. A merry-go-round apparatus was used in order to minimize any fluctuations in light flux. When the quantum yields were determined at 300 nm, the apparatus was housed in a Pyrex beaker to filter any short wavelength light.

In order to further ensure that both the actinometer and the analyte were exposed to the same light flux, the solution volumes of the actinometer and the analyte were identical and were irradiated in parallel in matched quartz tubes. These 13 mm tubes were outfitted with high-vacuum Teflon stopcocks and the analyte solutions were degassed by four freeze–thaw cycles using liquid nitrogen as a coolant and at a vacuum which was at least 0.05 Torr. The actinometer **3** solutions were degassed for one minute using a stream of nitrogen. In the original work by Hatchard and Parker, they demonstrated that the quantum yield for the photoreduction of actinometer **3** was unaffected by molecular oxygen.[25]

Potassium ferrioxalate (**3**) was prepared as described in the literature and was recrystallized before use.[25] Potassium tris(oxalato)ferrate (III) trihydrate is currently available from Strem Chemical Co. and Alfa-Aesar. Commercial 1,10-phenanthroline was used and was recrystallized twice from doubly distilled water. All manipulations with the actinometer **3** or with solutions of the actinometer **3** were conducted in either diffuse red light or in darkness.

Prior to the irradiation, an aqueous solution of 0.1% (w/v) 1,10-phenanthroline, a 1 M sodium acetate solution and a 0.1 N sulfuric acid solution were prepared. A buffer solution which consisted of 30 mL of 1 M aqueous sodium acetate and 18 mL of concentrated sulfuric acid was prepared by dilution to a volume of 50 mL. Doubly distilled water was used to prepare these solutions as well as solutions of the actinometer **3**. The concentration of the actinometer **3** was 0.15 M in 0.1 N sulfuric acid. After irradiation of the actinometer **3**, the actinometer **3** solutions were developed by transferring a 0.1 mL aliquot of the irradiated actinometer **3** solution to a premixed solution of 2 mL of 0.1% aqueous *o*-phenanthroline solution, 0.5 mL of buffer and 0.9 mL of 0.1 N sulfuric acid. The resulting solution was diluted to a volume of 10 mL and kept in the dark for 1 h at 25 °C after which time the concentration of ferrous ion was calculated from the absorbance of the complex at 510 nm ($\varepsilon = 11\,050$).

The absorbance at 510 nm was measured against a blank which contained all of the components except the 0.1 mL aliquot of the actinometer **3** solution. A zero time sample of the actinometer **3** solution had no absorbance at 510 nm. As a further check on the method and the quality of the reagents, a standard solution of ferrous sulfate in 0.1 N sulfuric acid was prepared and developed using the above procedure. The extinction coefficient at 510 nm was in agreement (±5%) with the reported value.

4-Acetyl-3,5-dimethylisoxazole (**1**) was prepared as described in the literature and purified by recrystallization. The recrystallized material was then further purified by sublimation.[8] *endo*-Bicyclo[2.2.1]hept-5-en-2-yl-(3,5-dimethyl-4-isoxazolyl)-methanone (**4**) was prepared as described in the literature[22] and had UV (CH_3CN) $\lambda = 306$ nm ($\varepsilon = 119.5$) and $\lambda = 228$ nm ($\varepsilon = 6800$). *endo*-Bicyclo[2.2.1]hept-5-en-2-yl-(5-methyl-3-isoxazolyl)-methanone (**5**) was similarly prepared by a

Diels–Alder reaction[22] and had UV (CH_3CN) $\lambda = 320$ nm ($\varepsilon = 77.5$) and $\lambda = 245$ nm ($\varepsilon = 2940$).

Separate solutions consisting of a 0.105 M solution of 4-acetyl-3,5-dimethylisoxazole (**1**), a 0.0295 M solution of the *endo*-isoxazole ketone **4** and a 0.0450 M solution of the *endo*-isoxazole ketone **5** in HPLC grade acetonitrile were used in the quantum yield determinations. A volume of 3 mL of the actinometer **3** solution and 3 mL of each of the analyte solutions were transferred to the specially designed quartz tubes. In the case of the norbornenyl ketone **4**, 30 mg of solid potassium carbonate was present as an acid scavenger. The glassware which either contained oxetanes **6** and **7** or was used to prepare solutions of oxetanes **6** and **7** was rinsed thoroughly with doubly distilled water and concentrated ammonium hydroxide and dried in an oven at a temperature of 120 °C for at least twelve hours.

In addition to the use of the merry-go-round apparatus, potential fluctuations from the light source were further minimized by turning on the Rayonet Photochemical Reactor for at least one hour before the commencement of the quantum yield determinations. The Rayonet Photochemical Reactor was not shut off during these experiments. Optical densities of greater than two were maintained throughout the irradiation and conversions of the actinometer **3** and ketones **1**, **4** and **5** were less than 10%.

The disappearance of 4-acetyl-3,5-dimethylisoxazole (**1**) to produce 1,1′-(3-methyl-2H-azirin-2-ylidene)bisethanone (**2**) was determined by UV spectroscopy and the concentration of ketone **1** after irradiation was determined by measuring the absorbance at two different wavelengths and by solving the simultaneous equations. Preparative experiments had shown that azirine **2** was the only primary photoproduct under these conditions. 4-Acetyl-3,5-dimethylisoxazole (**1**) had UV (CH_3CN) $\lambda = 300$ ($\varepsilon = 48$), $\lambda = 255$ ($\varepsilon = 7949$). 2-Diacetyl-3-methylazirine (**2**) had UV (CH_3CN) $\lambda = 300$ ($\varepsilon = 114$), $\lambda = 254$ ($\varepsilon = 8404$).[8]

The disappearance of norbornenyl ketone **4** at 300 nm to produce 4-(hexahydro-1,3,5-metheno-1H-cyclopenta[c]furan-1-yl)-3,5-dimethylisoxazole (**6**) was determined by UV spectroscopy. In a similar way, the disappearance of norbornenyl ketone **5** at 300 nm to produce 3-(hexahydro-1,3,5-metheno-1H-cyclopent[c]-furan-1-yl)-5-methylisoxazole (**7**) was also determined by UV spectroscopy. Preparative photolysis of isoxazoles **4** and **5** indicated that the respective oxetanes **6** and **7** were the only photoproducts at 350 nm.[22]

Because of the disparity in quantum efficiency for the actinometer **3** and those of the analytes, multiple actinometer **3** solutions were used during the course of the irradiation periods for the ketones **1**, **4** and **5**. For example, for ketones **4** and **5**, the actinometer **3** solutions were irradiated for a period of four minutes. Three actinometer solutions were irradiated for total irradiation times of 30 and 40 min for ketones **4** and **5** respectively. The extent of the photoreduction of actinometer was assessed for each one of these solutions and the results were averaged.

The quantum yield for the disappearance of starting ketone ($\phi_{(-K)}$) is equal to the moles of ketone consumed divided by the moles of absorbed photons. Moles of absorbed photons is equal to the moles of ferrous ion produced for the total irradiation time divided by the quantum yield for the formation of ferrous ion at a given wavelength. For actinometer **3**, the quantum yield (ϕ) for the formation of ferrous ion at 302 nm is equal to 1.24 and the quantum yield (ϕ) for the formation of ferrous ion at 253.7 nm is 1.28.[25]

Results and discussion

The balanced chemical equation for the photoreduction of ferric ion to ferrous ion during the photolysis of potassium ferrioxalate (**3**) is shown in Scheme 1. The concentration of ferrous ion as potassium dioxalatoferrate (II) (**8**) that is produced in this photolysis is determined by the formation of a complex with 1,10-phenanthroline and the measurement of the absorbance of this complex at 510 nm. In the original paper by Hatchard and Parker, the quantum yield for this photoreduction was determined at a variety of different wavelengths from 579 nm to 253.7 nm. This work showed that the quantum yield for the appearance of ferrous ion was very similar from 366 nm to 253.7 nm.[25]

$$\underset{\mathbf{3}}{2K_3Fe(C_2O_4)_3} \xrightarrow{h\nu} \underset{\mathbf{8}}{2K_2Fe(C_2O_4)_2} + K_2C_2O_4 + 2CO_2$$

Scheme 1

The results for the quantum yield determinations for ketones **1**, **4** and **5** are shown in Table 1. Despite the fact that the photoreduction of ferric ion to ferrous ion in the actinometer **3** is approximately ten times more efficient than the cycloaddition reaction of ketones **4** and **5** or approximately five times more efficient than the photoisomerization of isoxazole ketone **1**, the use of multiple actinometer solutions during the irradiation serves to compensate for any fluctuations in light intensity. As the method to detect ferrous ion in the actinometer solutions requires only simple dilutions and the use of a UV spectrophotometer, the described technique offers a method which is both rugged and precise.

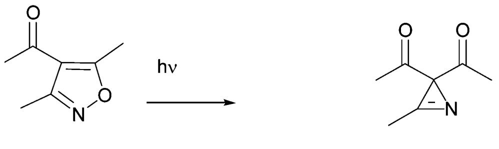
The scope of this methodology is further evident by the fact that it was used to measure precisely the photoefficiency of two very different photochemical reactions. For the first example, this technique was used to measure the efficiency of the photoisomerization of 4-acetyl-3,5-dimethylisoxazole (**1**) to 2-diacetyl-3-methylazirine (**2**) at both 254 and 300 nm. At these different wavelengths, the two different chromophores of isoxazole ketone **1** are selectively excited and the quantum yields indicate a difference in efficiency for the same photoreaction at these different wavelengths (Scheme 2). Such information is not only important mechanistically, but would be very useful in the scale-up of these processes as shorter irradiation times and perhaps, also lower costs might be expected for the more efficient photochemical process.

When the structurally-related norbornenyl ketone **4** was irradiated at 300 nm, the quantum yield for disappearance of ketone **4** to yield oxetane **6** was found to be 0.11. In the case of norbornenyl ketone **4**, the kinetics of this Paterno–Büchi reaction are determined by the very rapid rate of exciplex formation between the proximate double bond and the ketone.[22] (Scheme 3).

Norbornenyl ketone **5** yielded the expected oxetane **7**[22] with

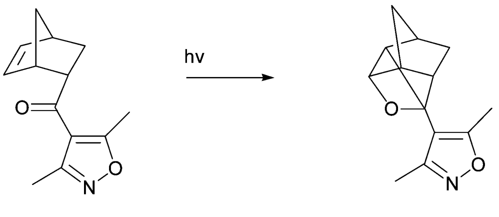
Table 1 Quantum yield determinations

Ketone	Wavelength	Quantum yield ($\phi_{(-K)}$)			Average $\phi_{(-K)}$
1	254 nm	0.20	0.26		0.23 ± 0.03
1	300 nm	0.29	0.35		0.32 ± 0.03
4	300 nm	0.109	0.101		0.11 ± 0.01
5	300 nm	0.110	0.117	0.099	0.11 ± 0.01



1 **2**

Scheme 2



4 6

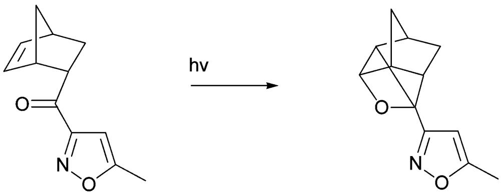
Scheme 3

a quantum yield of 0.11. In these rigid bicyclic ketones, the very rapid rate of exciplex formation governs the high chemical efficiency in these systems at the expense of other potential photochemical reactions and the long wavelength photochemistry of ketone **5** provides another example of geometric influences on photochemical reactions (Scheme 4).[22]

In initial quantum yield determinations for norbornenyl ketone **4**, the presence of a product which interfered with the UV measurement for the disappearance of starting ketone **4** was observed. On occasion, solutions of oxetane **7** rearranged to a compound which was tentatively identified as aldehyde **9** (Scheme 5). Because of this, the glassware which was used in the quantum yield determinations of norbornenyl ketones **4** and **5** was rinsed with concentrated ammonia and dried in an oven at 120 °C to remove any traces of acidic materials. For norbornenyl ketone **4**, an additional precaution was taken that solid potassium carbonate was present during the quantum yield determinations in order to prevent this rearrangement which could have compromised the use of UV spectroscopy as an analytical method to measure the disappearance of the ketone **4**.

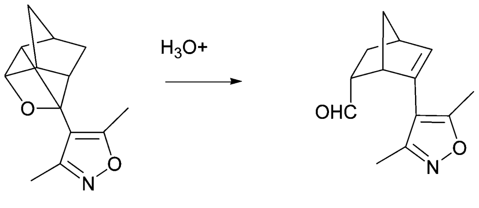
Because 3-acetyl-5-methylisoxazole (**10**) is known to be base sensitive and yields the ring-opened product, 3-oxobutanenitrile (**11**), the potassium carbonate was omitted for the quantum yield determinations for ketone **5** (Scheme 6).[26] Our pretreament of the glassware was sufficient to prevent any acid-catalyzed rearrangement of oxetane **7**.

Because potassium ferrioxalate (**3**) can be used as an actinometer in the visible and in the ultraviolet region, the establishment of this technique in a particular laboratory would make this system useful for quantum yield determinations at most wavelengths. As the quantum yield for the photoreduction of **3** is largely invariant of wavelength, this technique can also be used for quantum yield determinations from broad wavelength light sources such as the mainstay of preparative laboratory light sources, the mercury arc-lamp.



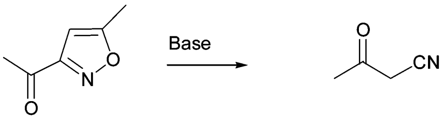
5 7

Scheme 4



7 9

Scheme 5



10 11

Scheme 6

Conclusion

The use of potassium ferrioxalate (**3**) as a chemical actinometer yields precise quantum yield values as exemplified in the data for the quantum yields for the photoisomerization of isoxazole ketone **1** at two different wavelengths and the [2 + 2] photocycloaddition of the structurally related norbornenyl ketones **4** and **5**. The use of the merry-go-round apparatus is convenient not only for quantum yield determinations at a particular wavelength and for a given substrate, but its sixteen-compartment construction can also be used to determine in parallel the quantum yield as well as the chemical yield for a particular photochemical reaction under different reaction conditions. The latter information would be particularly important if energy costs of a photochemical process and hence the quantum yield, are the determining factor for a selection of a photochemical process as a green chemistry alternative.

Despite the synthetic possibilities and the diversity of structures which are available in photochemical processes, they are underutilized in process chemistry in the pharmaceutical industries. Although the photoisomerization of provitamin to previtamin in the industrial synthesis of vitamin D_3 is a prominent example of an industrial photochemical process,[27,28] photochemical transformations are not often incorporated as a diversity element in the synthesis of combinatorial libraries, despite the fact that these methods can fundamentally change the structure of the substrate molecule. The consideration of photochemistry as a sustainable technology may serve to rectify this situtaion.

In these laboratories, we have shown that 3-acetyl-5-methylisoxazole (**10**) photoisomerizes to 2-acetyl-5-methyloxazole (**12**) and 3-cyano-2,4-pentanedione (**13**) with a quantum yield for ketone disappearance of 0.20[29] and this route was recently used to prepare oxazole **12** for its use as an intermediate in the synthesis of a series of anti-*Heliobacter* agents.[30] The solvent-free conditions used to prepare isoxazole ketone and the availability of a combinatorial route to isoxazole ketone **10**[31] would make the photochemical isomerization of isoxazole ketone **10** to oxazole ketone **12** and related molecules, an attractive green alternative to traditional approaches to oxazoles such as the Robinson–Gabriel synthesis[29,32] and at the same time, provide for a convenient way to prepare libraries of these oxazole ketones.

Using this photoisomerization of an isoxazole ketone **10** to oxazole **12** as an example to develop photochemistry as a sustainable synthetic technology, specific knowledge of the quantum yield at different conditions such as reaction temperature and the influence of chemical sensitizers would be required to maximize the chemical and quantum yield of oxazole **12** and to minimize by-product formation. The quantum yield for a particular photochemical reaction can be used to define the environmental impact of such a process. The described methodology which utilizes potassium ferrioxalate

(**3**) as a chemical actinometer represents a convenient way to conduct such studies. In conjunction with other experimental techniques such as quenching and sensitization studies and photophysical measurements, knowledge of the quantum yield of a photochemical reaction is an integral component towards the understanding of photochemical processes.

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