Green Chemistry

Cutting-edge research for a greener sustainable future

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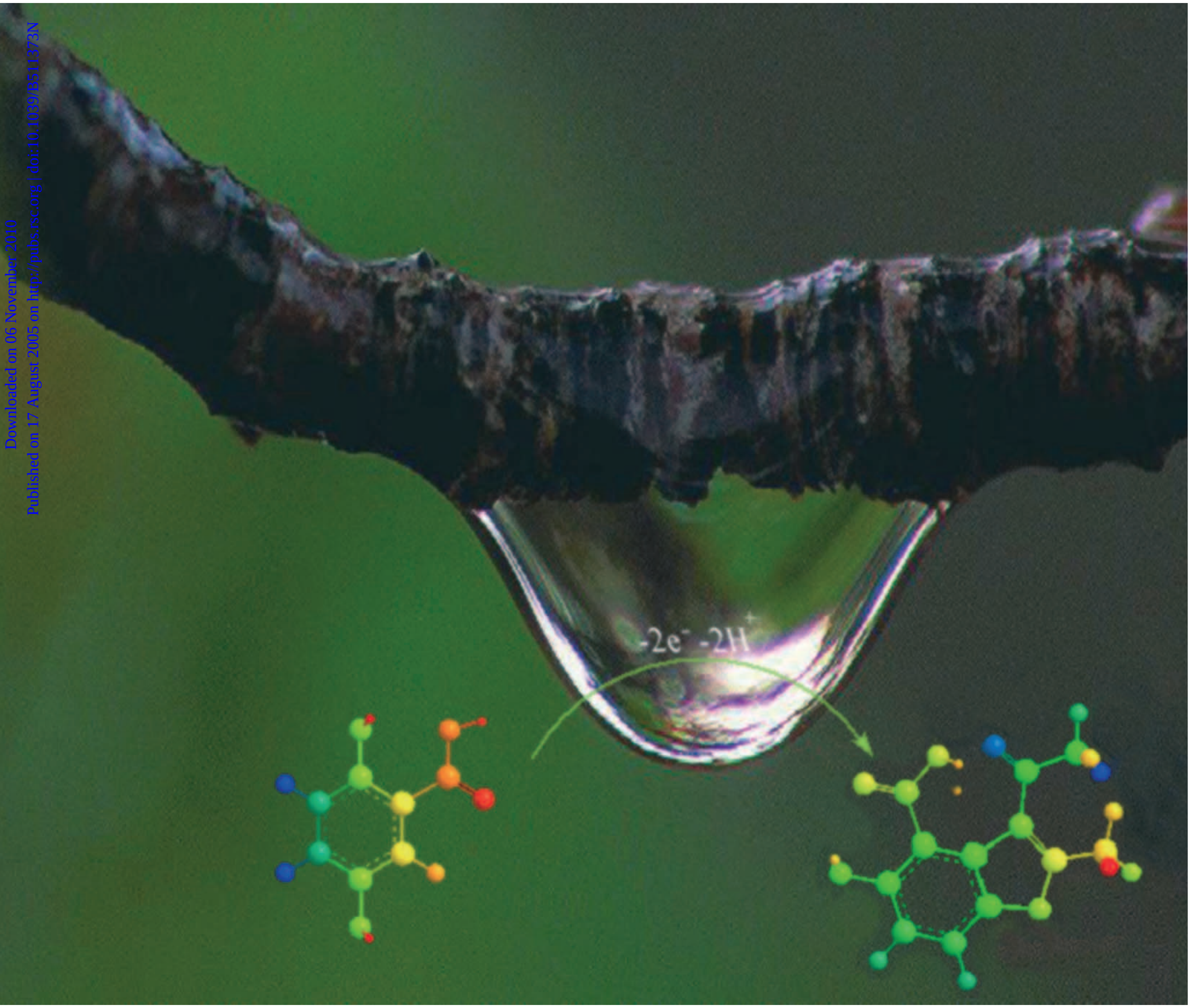
Volume 7 | Number 9 | September 2005 | Pages 625–688



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The cover image represents aqueous electro-organic synthesis in the absence of organic solvents as a means for achieving green synthesis.
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CHEMICAL TECHNOLOGY

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Chemical Technology

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CONFERENCE REPORT

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Conference on Knowledge-based Materials and Technologies for Sustainable Chemistry; Tallinn, Estonia, 1–5 June 2005

The conference "Materials and Technologies for Sustainable Chemistry (MTSC)" was aimed at promoting interdisciplinary collaboration across the fields of new solvents and reaction media, catalysis and biocatalysis and materials, providing researchers with a new impetus to explore the different areas of sustainable chemical processes.

View Online

Downloaded on 06 November 2010
Published on 17 August 2005 on http://pubs.rsc.org | doi:10.1039/B511374C

Green Chemistry

Cutting-edge research for a greener sustainable future

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Green Chemistry (print: ISSN 1463-9262; electronic: ISSN 1463-9270) is published 12 times a year by the Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, UK CB4 0WF.

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HIGHLIGHT

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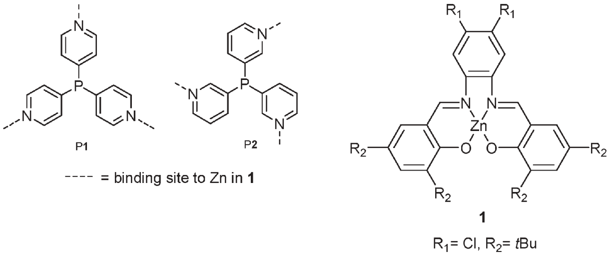
Highlights

Markus Hölscher reviews some of the recent literature in green chemistry.



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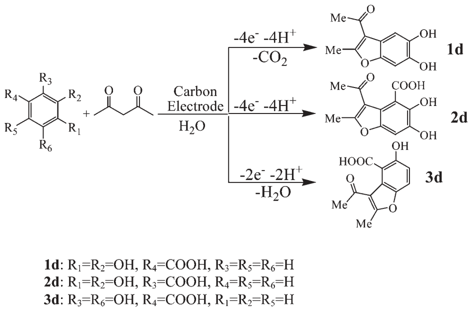
Diversity in electrochemical oxidation of dihydroxybenzoic acids in the presence of acetylacetone. A green method for synthesis of new benzofuran derivatives

Davood Nematollahi* and Mohammad Rafiee

Electrochemical oxidation of some dihydroxybenzoic acids has been studied in the presence of acetylacetone as the nucleophile in aqueous solutions, without toxic reagents and solvents at a carbon electrode in an undivided cell, using an environmentally friendly method.



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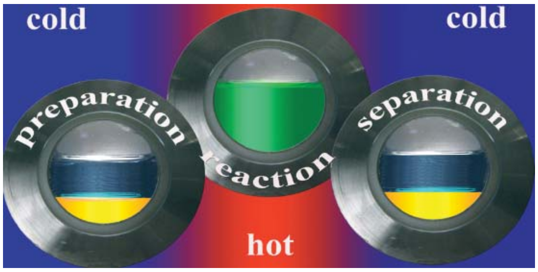
Selection process of new solvents in temperature-dependent multi-component solvent systems and its application in isomerising hydroformylation

Arno Behr,* Guido Henze, Dietmar Obst and Barbara Turkowski

In isomerising hydroformylation catalyst leaching could be reduced decisively by using open temperature-dependent multi-component solvent systems. Hansen-Solubility-Parameters were an efficient tool to select suitable green solvents.



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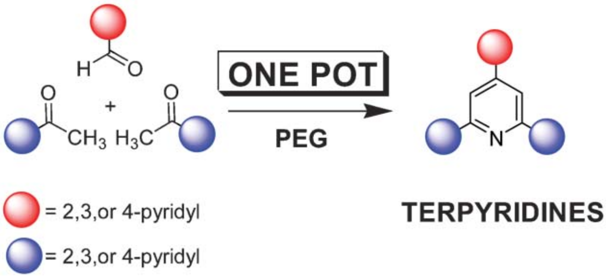
Poly(ethyleneglycol) (PEG): a versatile reaction medium in gaining access to 4′-(pyridyl)-terpyridines

Christopher B. Smith,* Colin L. Raston* and Alexandre N. Sobolev

4′-Pyridyl terpyridines are formed in a simple, one-pot procedure in poly(ethyleneglycol) (PEG) with high purity.



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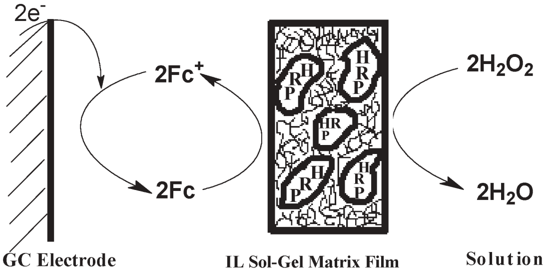

A novel room temperature ionic liquid sol–gel matrix for amperometric biosensor application

Yang Liu, Lihong Shi, Meijia Wang, Zhiying Li, Hongtao Liu and Jinghong Li*

A novel type of ionic liquid (IL) sol–gel hybrid material was developed to immobilize enzymes for amperometric biosensor application.

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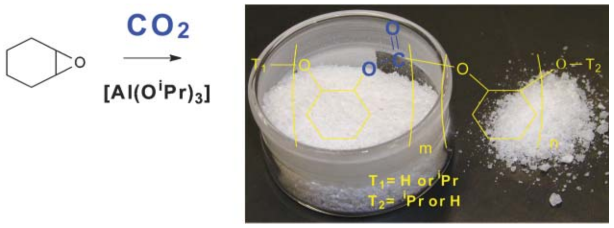

Aluminium triisopropoxide: An inexpensive and easy-to-handle catalyst of the copolymerisation of cyclohexene oxide with CO_2

Thomas A. Zevaco,* Annette Janssen, Jakub Sypien and Eckhard Dinjus*

Aluminium triisopropoxide reacts with carbon dioxide and cyclohexene oxide to produce polyether-carbonates in high yields with molecular weight up to 11 000 g mol^{-1} and a fair-to-good selectivity of the CO_2-insertion (up to 33% carbonate).

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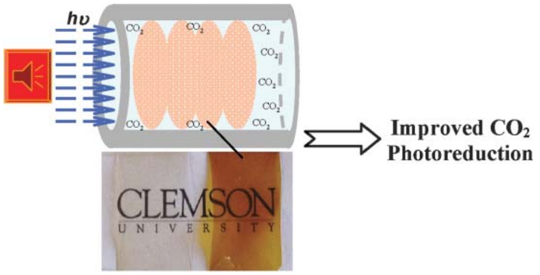

Metal-coated nanoscale TiO_2 catalysts for enhanced CO_2 photoreduction

Pankaj Pathak, Mohammed J. Meziani, Linette Castillo and Ya-Ping Sun*

Nanoscale TiO_2 particles embedded in the hydrophilic cavities of Nafion membrane films were coated with silver for significantly improved photoconversion of CO_2. These catalytic films are stable both chemically and photochemically, and reusable in repeated reactions.

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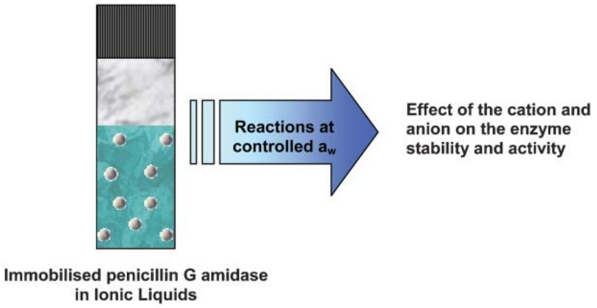

Stability and activity of immobilised penicillin G amidase in ionic liquids at controlled a_w

Alessandra Basso, Sara Cantone, Paolo Linda and Cynthia Ebert*

Penicillin G amidase is highly stable in [bmim][PF_6] and [bmim][BF_4] and synthetic activity in these ILs is comparable to that obtained in toluene.

PAPERS

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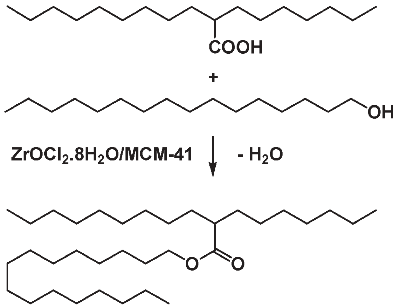
$ZrOCl_2 \cdot 8H_2O$ catalysts for the esterification of long chain aliphatic carboxylic acids and alcohols. The enhancement of catalytic performance by supporting on ordered mesoporous silica

Kshudiram Mantri, Kenichi Komura and Yoshihiro Sugi*

Esterification of higher aliphatic acids with cetyl alcohol gives the esters in high yield using $ZrOCl_2 \cdot 8H_2O$ catalyst supported on MCM-41. The catalyst can be recycled for further reactions without loss of activity.



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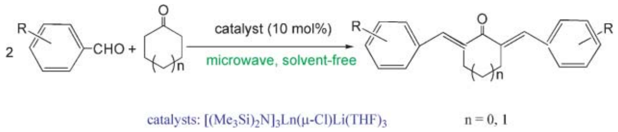
A solvent-free synthesis of α,α′-bis(substituted benzylidene) cycloalkanones catalyzed by lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ under microwave irradiation

Lijun Zhang, Shaowu Wang,* Enhong Sheng and Shuangliu Zhou

Under solvent-free and microwave irradiation conditions, cross-aldol condensation reactions of cycloketones with aromatic aldehydes catalyzed by lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ gave the corresponding *E*,*E*′-α,α′-bis(substituted benzylidene) cycloalkanones in high yields.



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Conference on Knowledge-based Materials and Technologies for Sustainable Chemistry; Tallinn, Estonia, 1–5 June 2005

DOI: 10.1039/b510805p

The field of Green Chemistry is growing rapidly. Developing sustainable products and practices is becoming increasingly important for human society and is reliant on scientific and technological developments, underpinned by chemistry.

The vital sphere of human activity in chemistry and the chemical industry has suffered from a "dirty" and "environment-unfriendly" image, which has decreased the interest in taking up a career in chemical industry or academia. *Kates et al.*[1] *suggest that during the late 1980's the science community became "increasingly estranged from the societal and political processes that were shaping the sustainability agenda." The emergence of Green Chemistry as a branch of science which does not stand in isolation but seeks to engage with the fields of the environment, commerce, politics and the public is working to redress the situation.*

The conference "Materials and Technologies for Sustainable Chemistry (MTSC)" was aimed at promoting interdisciplinary collaboration across the fields of new solvents and reaction media, catalysis and biocatalysis and materials, providing researchers with a new impetus to explore the different areas of sustainable chemical processes.

Keynote lectures, technical presentations and poster presentations provided a good forum, covering a wide range of fundamental aspects, instrumental developments and applications of new materials and technologies in the context of sustainable development. Strong themes included ionic liquids, biocatalysis and supercritical fluids.

MTSC was the biggest international chemistry conference to be held in Estonia since independence from the USSR in 1991; its location encouraged participation from many new EU member states and accession countries across Eastern Europe.

The conference was organized by Tallinn University of Technology, University of Tartu and the University of Nottingham, UK, with financial support from the European Commission.

Estonia is a small country with only 1.5 million inhabitants, but it has made a rapid entrance into the technological world, currently boasting well over a million websites. It is very important to start the new era for Estonian science with green chemistry and sustainability problems—and it was a good start with many influential chemists in this area attending.

Workshop

The conference kicked off with a workshop held in the new building of the Faculty of Science of Tallinn University of Technology. Access to these lectures was free for local graduate students and this was used actively, with around 50 young researchers attending.

The workshop covered new reaction media: supercritical fluids, ionic liquids, and fluorous phase solvents, together with catalysis and biocatalysis, giving a coherent introduction to the green chemistry field. Young scientists looking to broaden their scientific interests had the possibility to obtain professional advice from the best academic experts including some leading names in green chemistry: Professor Ken Seddon from Belfast, Professor Istvan Horvath from Budapest, and Professor Roger Sheldon from Delft. These lectures presented both cutting edge science together with discussions on the place of chemistry today and in the future, showing that good science and green chemistry are not contradictory.

Emphasis

The conference emphasis focussed on environmentally benign solvents, different catalytic systems, new developments and applications in analytical chemistry. There were 50 oral presentations and 60 poster presentations reporting results on high efficiency and selective catalysts in organic synthesis and biochemistry; the use of alternative environmentally friendly solvents for development of new technological processes; on nanomaterials and their use. The oral presentations in this conference were divided into four groups: new solvents and reaction media, catalysis and reactions, micronization and new analytical methods, new materials.

Keynote lectures were presented by Prof. Terry Collins of Carnegie Mellon

University, who reminded us of the scale of some industrial problems which green chemistry aims to rectify; Prof. Walter Leitner from Aachen, Editor in Chief of "Green Chemistry"; Prof. Irina Beletskaja from Moscow State University, Academician of the Russian Academy of Science; Prof. Christian Reichardt from Marburg, author of the well-known book "Solvents and Solvent Effects in Organic Chemistry"; leading Swedish chemist Prof. Jan-Erling Bäckvall from the University of Stockholm; Prof. Sabeet Verpoote from University of Groningen in the Netherlands and Prof. Martin Schröder from the University of Nottingham, newly elected Doctor of Honours of Tallinn University of Technology.

As part of the conference program there were two round-table discussions: firstly on ionic liquids chaired by Prof. Kenneth Seddon from QUILL and Dr Mathias Maase from BASF, and secondly on supercritical fluids, chaired by Prof. Manuel Nunes da Ponte from Lisbon and Prof. Walter Leitner from Aachen. Both round-tables were extremely well attended, with many of the attendees actively participating in the discussions; that on ILs covering sources of ILs, safety, toxicology, recycle, extractions, and applications, whereas the SCF discussion covered successful high pressure processes, perceived barriers to SCF commercialisation and breaking technologies—electronics cleaning and extraction of trichloroanisole (which causes "corking") from wine corks. Participation of representatives of companies including BASF, Merck, Chematur, UHDE brought to the table the industry view of alternative solvent use. The comment from the chairmen was: "We were very pleased with the feedback, and felt most people had appreciated the event, and had learnt a lot from it".

Oral presentations

Neoteric solvents

Supercritical fluids focussed on supercritical water and its applications in chemical synthesis and clean waste destruction. Prof. Gerd Brunner form Hamburg spoke about reactions of biopolymers in sub- and supercritical water, whilst Prof. Jerry King, now affiliated with the University of Arkansas, gave a presentation devoted to optimization of sub-critical water-based processes, whilst Dr Kari Hartonen from the University of Helsinki presented the results of deuteration in pressurised hot D_2O.

Presentations on ionic liquids demonstrated their different applications as solvents: Prof. Jean-Yves Nedelec from France presented ionic liquids as solvents for organic electrosynthesis; Prof. Stefan Toma from Slovakia gave examples of the behaviour of organocatalysts in ionic liquids; Dr Annegret Stark from Germany and Dr Jyri-Pekka Mikkola from Finland discussed catalysis in ionic liquids and presented results about supported ionic liquid catalysts for fine chemicals. Representatives from BASF and Merck presented examples of how the chemical industry can benefit from the use of ionic liquids and outlined the trends in development of new ionic liquids. Ionic liquids seem to be a very fashionable topic at the moment and researchers, including those at Tallinn University of Technology, are actively trying to find the right niches for them.

A review of these two sessions is not complete without mention of two of the most colourful Englishmen: Professor Kenneth Seddon and Professor Martyn Poliakoff. They have many things in common: both are from islands, have a good sense of humour and make wonderful presentations. Their excellent reviews gave a very good idea of the contemporary level of research in the field of ionic liquids in one case and reactions in supercritical fluids in the other case.

Catalysis

A key area of green chemistry, catalysis, was well represented in this conference. The first plenary presentation from Prof. Terry Collins, of Carnegie Mellon University, Pittsburgh, USA, set the targets of research for sustainable development and continued to describe results of his work at the Institute for Green Oxidation Chemistry.

Green catalytic oxidation systems have been developed, designed to move the elemental composition of oxidation technology away from chlorine and toxic metal ions toward the much safer natural oxidants, hydrogen peroxide and oxygen. Nontoxic catalysts, called "TAML® activators" have been designed, which have unprecedented technical performance as peroxidase enzyme mimics for large-scale oxidation applications.

A review was presented by Prof. Walter Leitner highlighting some recent examples from his laboratory of the development of new catalysts and catalytic transformations for atom economic and highly selective bond formation reactions. Furthermore, he discussed new approaches to the fundamental problem of catalyst recycling and immobilization, which are based on the use of $scCO_2$ either alone or in multiphase combinations. These new techniques allow for continuous or semi-continuous processes combining organometallic, nanoscale or enzymatic catalysts with the process design of heterogeneous catalysis.

Solutions to problems in bio-catalysis were discussed by Prof. Roger A. Sheldon from Delft. He spoke about a new family of cross-linked enzymes, termed cross-linked enzyme aggregates (CLEA®). CLEAs have many advantages in the context of industrial applications. The method is exquisitely simple and amenable to rapid optimisation, which translates to low costs and a short time-to-market. It is applicable to a wide variety of enzymes, including crude preparations, affording stable, recyclable catalysts with high retention of activity. In contrast to CLECs, there is no need for the enzyme to be available in crystalline form and the technique can be applied to the preparation of combi-CLEAs containing two or more enzymes.

Hydrogen storage

Some papers were devoted to new materials related to uses in solar energy, hydrogen energy and fuel-cells—currently the most highlighted topics in contemporary material science.

Although hydrogen is abundantly available and environmentally benign, storage of hydrogen at acceptably favourable conditions and with high energy density is still an unresolved problem. Prof. Cor Peters from Delft University of Technology outlined the requirements for vehicle onboard hydrogen storage—enough H_2 for 500 km of

travel, and how the competing technologies currently rank in terms of the mass and volume of the storage device required to contain this amount of gas. Also, he reminded us that it is not only a requirement to get the H_2 into a material; you must also be able to get it out easily! He presented the gas clathrate hydrate of hydrogen as a solution for hydrogen storage with high energy density. Experimental results were reported on the phase behaviour of hydrogen clathrate hydrate in presence of certain selected promoters. The stability conditions for the hydrate phase were measured within a temperature range of 271–282 K and pressures up to 14.5 MPa.

Microfluidics

Prof. Sabeth Verpoorte in her presentation provided a short introduction to microfluidics technology, followed by some examples of its application in the chemical and life sciences. Since the early nineties, researchers from a wide range of disciplines have adopted this technology to perform not only analytical tasks, but synthetic chemical, biochemical, and biological tasks as well. Just over a decade young, microfluidic technologies have enabled the miniaturization of established analytical techniques, thereby enhancing achievable performance, especially with respect to reduction of analysis times. Clearly, the ability to control solution transport in the nL to pL range so predictably can be exploited to develop completely new approaches to conduct chemical and biological processing.

Prof. Mihkel Kaljurand's (Tallinn University of Technology) presentation was complementary to the previous one, being dedicated to performing reactions inside the capillary, simultaneously with their electrophoretic separation. In the plug-mode of electrophoretically mediated microanalysis (EMMA), reactants are introduced into the capillary inlet as separate bands. Upon the application of an electric field, the two bands merge together due to the differences of their electrophoretic mobilities. The reaction takes place and the resultant products migrate away from the reaction zone and separate. Thus, the detector can individually determine the amount of nonreacted substrate and products. The contact time depends on the mobility differences of the reactant/product mixture as well as on the background buffer electroosmosis.

Ethics and the environment

On the conference program were several interesting presentations relevant to green chemistry: Prof. P. Aarne Vesilind's lecture "The moral challenge of green science and technology" addressed the issue of ethics and the pressure which free market capitalism places on the environment. With the news that the UK government has recently announced that it is to consider personal carbon allowances, perhaps the status quo of "Business as usual" is about to be challenged. Dr David Highfield outlined the current status and future challenges of Green Chemistry, whilst Prof. Jürgen Metzger presented renewable feedstocks for sustainable chemistry: new syntheses with oils and fats. Perhaps the most impressive presentation was that of Prof. Eric Beckman, well known from his work on supercritical fluids. His lecture; "How Green Chemistry supports and sustains the greening of the built environment", highlighted the fact that buildings have an enormous impact on resource use and energy consumption, and chemistry can have an enormous impact on the greening of buildings. One example quoted was the use of PVC and the search for alternatives. Data on emissions of a cocktail of volatile organic compounds within the home showed the importance of the problem and need for large scale actions to affect the greening of "the home as a chemical reactor".

COST D29

The European Science Foundation COST Chemistry action D29 "Sustainable/Green Chemistry and Chemical Technology" is closely related to the thematic area of this conference.

Action D29 is going through mid-term evaluation and therefore COST D29 ran its network meeting and workshop as a part of the conference. Ongoing studies from 11 networks including 93 research groups from 20 different countries were represented. The session was actively visited by other conference participants and action D29 got wide attention. The results were discussed and put into the same framework as other problems of green chemistry in the lecture by Prof. Istvan Horvath in the final plenary session

SuperGreenChem

The Marie Curie Training Network SuperGreenChem held a meeting for its young researchers during the conference, where the young researchers reported their progress in studies and training. As the theme of the network is related to supercritical fluids it was a good opportunity for young members of the network to meet outstanding specialists in the field. Tallinn University of Technology is a partner of this network which consists of 13 laboratories around Europe.

Excellence in Estonian science

The Estonian partners organizing the conference; the University of Tartu and Tallinn University of Technology are the two centres in Estonia performing

research and development in chemistry. Prof. Ilmar Koppel from Tartu, Prof. Margus Lopp and Prof Andres Öpik from Tallinn gave presentations during plenary sessions of the conference.

Prof. Koppel's lecture summarised the work ongoing in Tartu involving designing substances with certain properties and performing studies of acid–base properties of compounds, as these properties largely determine their reactivity and applicability in various fields of chemistry and related sciences. Dr Ivari Kaljurand from his group introduced the self-consistent Brønsted acidity and basicity scales in several polar and low polarity media (acetonitrile, THF, heptane); Prof. Peeter Burk explained where these principles are applied to gas phase reactions—the protonation of simple species such as cubylamine and cubane leads to remarkable isomerization reactions in the gas phase.

Prof. Lopp presented work of synthetic chemists in Tallinn on asymmetric oxidation with the aim of binding substrate and reagent into one catalytic complex and forming the complex as an "artificial enzyme". On their way towards this catalytic complex they have found that different "flat" organic molecules (such as cyclic ketones, diketones *etc.*) are good substrates for an "artificial enzyme". His co-worker Dr Tõnis Kanger gave a talk on another aspect of asymmetric synthesis—hydrogenation of ketones, where phosphene-free non-aromatic catalytic systems are used.

Prof. Öpik gave a review on a matter directly related to sustainable development—new materials for better capture and use of solar energy. He presented results of electrically conductive polymers. A number of photovoltaic structures based on the photoactive inorganic polycrystalline semiconductors $CuInSe_2$ and $CuInS_2$ in combination with electrically conductive polymers like polyaniline and polyparaphenylene were prepared using electrodeposition and casting techniques.

Two other talks demonstrated good achievements in analytical science—Dr Danilkin spoke about the wide-range linearity of thermoluminescence response against radiation dose and a high sensitivity CaF_2:Mn extreme dosimeter which has been built in the University of Tartu.

Dr Niilisk from the Institute of Physics at the University of Tartu demonstrated their micro-Raman spectroscopy system and its application for structural analysis of oxide thin films grown by atomic layer deposition (ZrO_2, HfO_2, and TiO_2) and pulsed laser deposition (TiO_2, mixed TiO_2/Cr_2O_3 films) on various substrates (amorphous silica, Si(100), MgO(100), and r-cut sapphire).

Enzymatic reactions are obviously good examples of "green" catalytic processes. Prof. Jaak Järv from Tartu focused on structures of the transition state of the catalytic step(s), and comparison of these structures with those assigned to the activated complexes of conventional chemical reactions of similar compounds. The results demonstrate significant differences of the structure of the transition states of the enzymatic processes if compared with our understanding about the mechanism of the same chemical processes under conventional conditions.

If we add here the work on alternative solvents going on in Tallinn University of Technology by Dr Mihkel Koel, then these talks represented the main directions of Estonian chemistry contributing to clean technology. This conference certainly gave a positive impact for further and wider developments in Estonian green chemistry.

Mihkel Koel, Tallinn University of Technology

Paul Hamley, University of Nottingham

References

1 R. W. Kates *et al.*, Sustainability Science, *Science*, 2001, **292**, 641–642.

Highlights

DOI: 10.1039/b510730j

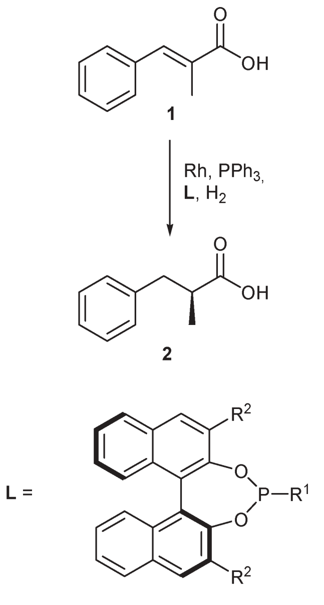
Markus Hölscher reviews some of the recent literature in green chemistry

Molecular oxygen oxidizes nitrobenzene selectively in the presence of polyoxometalate catalyst

Selective liquid phase oxidations of arenes to the corresponding phenols is a challenging though important task. Even more problematic is the oxidation of deactivated arenes such as nitrobenzene. Neumann *et al.* from the Weizman Institute investigated the use of polyoxometalate $H_5PV_2Mo_{10}O_{40}$ as a catalyst in oxidations of nitrobenzene with molecular oxygen.[1] The authors found nitrobenzene to be oxidized selectively (>99%) to 2-nitrophenol unter a pressure of 2 bar of O_2. Isostructural catalysts $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ were inactive and also the corresponding *n*-butyl salt of the parent catalyst showed no activity indicating both vanadium and a proton source to be necessary for catalytic activity. Isotope experiments showed ^{18}O to be incorporated in the nitrophenol, proving the oxygen source is indeed O_2. The reaction mechanism is by far not understood presently, however, spectroscopic and other experiments indicate the formation of a nitrobenzene–catalyst–H_3O^+ complex to be the starting point of a radical process, which was supported by the observation of a spin-trapped radical intermediate by EPR spectroscopy during the reaction.

Drastic enhancement of enantioselectivity and conversion by combining chiral and achiral ligands in Rh-catalyzed hydrogenations

Enantioselective hydrogenation of dihydrocinnamic acid derivatives is an interesting synthetic target, as the products are key intermediates in the synthesis of bioactive compounds such as opioid antagonists, endothelin receptor antagonists, enkephalinase inhibitors and renin inhibitors, to name a few. Monodentate phosphorous ligands have served as versatile and highly selective ligands in rhodium catalyzed hydrogenations. As it was shown very recently that mixtures of chiral monodentate ligands can improve enantioselectivity, the question occured what would happen if chiral and achiral monodentate ligands were mixed. The groups of Feringa at the University of Groningen and de Vries from DSM Pharma Chemicals-Advanced Synthesis came up with a fascinating answer: The combination of achiral and chiral ligands can improve the enantioselectivity and the rate of enantioselective Rh-catalyzed hydrogenations drastically.[2] In screening experiments, it was demonstrated that the combination of achiral PPh_3 with different phosphoramidite ligands very efficiently increases *ee*-values and conversions in the hydrogenation of α-methylcinnamic acid.

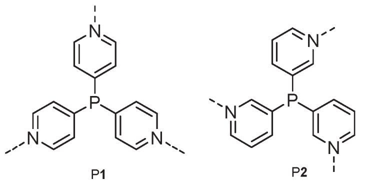


e.g. R^1 = piperidine, R^2 = Me

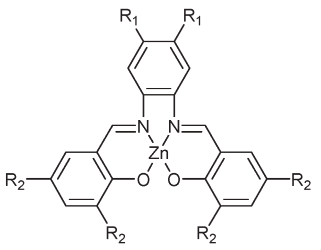
In the next step the influence of substitutents at the parent achiral ligand PPh_3 was investigated leading to the result, that among many different substituents and substituent positions the best result is achieved when a tolyl group is present in the *ortho*-position. The concept can also be applied successfully to the asymmetric hydrogenation of substituted acrylic acids, which were hydrogenated with the appropriate ligand combinations with very high *ee*'s and full conversion.

Rhodium catalyzed hydroformylation using encapsulated phosphane ligands

Homogeneously catalyzed hydroformylation is one of the important carbon–carbon bond forming reactions with simultaneous introduction of a new reactive functional group (aldehyde), useful for subsequent reactions. As high catalyst selectivity and activity adds significantly to the development of clean and simple processes, this topic has been under intense investigation with no end in sight. Van Leeuwen *et al.* from the university of Amsterdam introduced ligands encapsulated by porphyrin moieties and have very recently extended the encapsulation approach towards tripyridylphosphane ligands encapsulated by Zn-salphen complexes to form active and selective phosphane ligands for the rhodium catalyzed hydroformylation of 1-octene.[3]



---- = binding site to Zn in **1**



1

R_1= Cl, R_2= *t*Bu

P1 + 3·**1** ⟶ $(\mathbf{1})_3$**P1**

P2 + 3·**1** ⟶ $(\mathbf{1})_3$**P2**

One of the most important results of this work is the electronic and steric tunability of the phosphane ligand through the Zn-salphen unit. As an example, phosphane ligand **P1** forms an aggregate with Zn-complex **1** which can be used as a ligand for the Rh-catalyzed hydroformylation of 1-octene yielding linear to branched product ratios of 69 : 31, while the conversion is 27%. In contrast, phosphane **P2** when encapsulated with the same Zn-complex **1** is a ligand which results in a catalyst system yielding the hydroformylation products with conversions of 97% whereas the linear/branched ratio decreases to 59 : 41. This approach provides interesting new alternatives for ligand tuning.

Chemical industry in the UK performs much greener

According to the Chemical Industries Association (CIA) which has a membership of 150 companies operating from 270 chemical sites (200 of which are located in the UK) british chemical industry has outperformed its own criteria for the 2004 Climate Change Agreement (CCA) target. Since 1998 the energy efficiency has improved by 19.5%, which equals a saving of *ca.* 3.5 million tons of carbon dioxide emissions. Under the agreement, companies commit to challenging energy targets up to 2010 in exchange for an 80% reduction on the Climate Change Levy (CCL), a tax on the business use of energy. Companies can purchase emmissions allowances from the UK Emmisions Trading Scheme and also generate allowances for sale or banking if they overachieve their targets. The chemical sector is the UK manufacturing's largest consumer of energy—with an annual combined energy and feedstock bill amounting to *ca.* £2.5 billion.

Kyoto in the US after all—hybrid electric shuttle buses for the Bronx

173 mayors, representing *ca.* 36 million inhabitants in US cities have signed in July 2005 the Climate Protection Agreement to meet or beat Kyoto Protocol emissions reductions goals. As one of the first actions Canadian-based internationally active company Azure Dynamic Corporation has launched a shuttle bus program in which five hybrid-electric, 20-passenger shuttle buses will be delivered to the Bronx Overall Economic Development Corporation (BOEDC). The BOEDC, established in 1981, is a community-based non-profit organization that has been a central figure in the revitalization of the borough. The Bronx contains two overlapping zones, the New York State Economic Development Zone and the federally-designated Bronx Empowerment Zone. The hybridized buses will operate approximately two to three shifts daily and are expected to drive between 160–240 miles per day. The shuttles buses will operate in areas severely underserved by public transit.

Solar power for manchester's CIS tower

More than seven thousand panels of solar cells will cover three sides of the landmark Co-operative Insurance Society (CIS) tower in Manchester and generate 180 MW h of electricity each year. This is enough energy to illuminate eight floors of the building or power 1000 desktop computers. The challenging project has been managed by EC Harris, which played a pivotal role in the planning and delivery of this technically innovative environmental initiative. Sharp electronics, the global leader in solar cell production, manufacturing a quarter of solar modules used worldwide, produces the panels for the CIS tower. This is the largest european vertical photovoltaic project to date.

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Diversity in electrochemical oxidation of dihydroxybenzoic acids in the presence of acetylacetone. A green method for synthesis of new benzofuran derivatives†

Davood Nematollahi* and Mohammad Rafiee

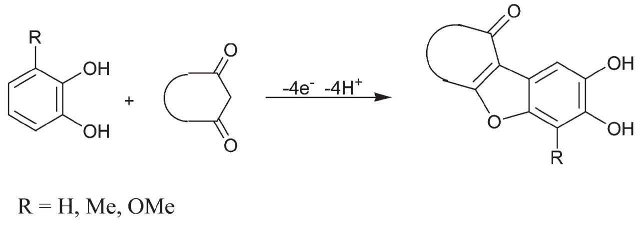
Received 8th March 2005, Accepted 22nd June 2005
First published as an Advance Article on the web 21st July 2005
DOI: 10.1039/b503408f

Electrochemical oxidation of diol derivatives of benzoic acid (**1–3**) have been studied in the presence of acetylacetone (**4**) as the nucleophile in aqueous solutions, using cyclic voltammetry and controlled-potential coulometry. The results indicate that the quinones derived from dihydroxybenzoic acids (**1a–3a**) participate in Michael addition reactions with acetylacetone (**4**) and *via* various mechanisms convert to the corresponding benzofurans (**1d–3d**). In this work, we derive various products with good yields based on electrochemical oxidation under controlled potential conditions in aqueous solutions, without toxic reagents and solvents at a carbon electrode in an undivided cell, using an environmentally friendly method.

Introduction

Because electrochemical oxidation very often parallels the cytochrome P450 catalyzed oxidation in liver microsomes, it was interesting to study the anodic oxidation of catechols in the presence of the β-diketone as CH-acidic nucleophiles. In addition, because of the pharmacological uses of benzofurans the syntheses and pharmacological properties of benzofuran derivatives have been extensively investigated.[1–8] In this direction, recently, we have investigated the electrochemical oxidation of catechols in the presence of acethylacetone and dimedone as nucleophiles. The results indicate formation of benzofuran derivatives (Scheme 1).[9]

In this work electrochemical oxidation of some *ortho* and *para* dihydroxybenzoic acids (**1–3**) has been studied in aqueous solutions in the presence of acetylacetone (**4**) as a possible nucleophile. The results indicate different mechanisms for each case. The present work has led to the development of a facile and environmentally friendly reagentless electrochemical method for synthesis of some new benzofuran derivatives in aqueous solutions with high atomic economy and safe waste (sodium chloride and acetic acid), under ambient conditions and in an undivided cell using a graphite electrode.



Scheme 1

Results and discussion

Electrochemical study of 3,4-dihydroxybenzoic acid (1)

The electrochemical study of 1 mM solution of 3,4-dihydroxybenzoic acid (**1**) in an aqueous sodium acetate solution (0.2 M) as supporting electrolyte, at a bare glassy carbon electrode has been performed using cyclic voltammetry (Fig. 1, curve a). The voltammogram shows one anodic (A_1) and corresponding cathodic peak (C_1), at 0.34 V and 0.08 V *versus* a standard calomel electrode (SCE), respectively, which correspond to the transformation of 3,4-dihydroxybenzoic acid (**1**) to *o*-benzoquinone (**1a**) and *vice versa* within a quasi-reversible two-electron process (Scheme 2, eqn. (1)). A peak current ratio (I_p^{C1}/I_p^{A1}) of near unity, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *o*-benzoquinone (**1a**) produced at the surface of the electrode under the experimental conditions. In other

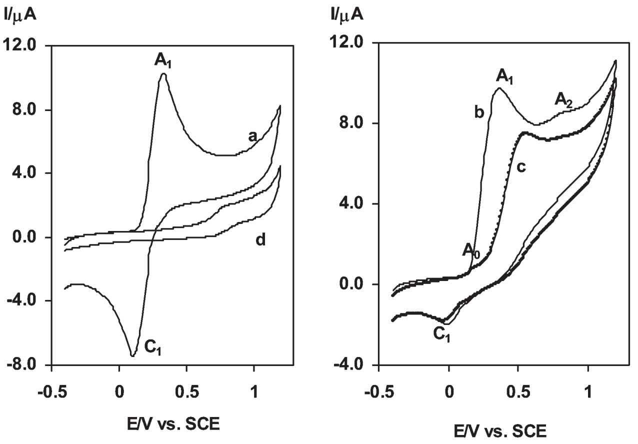
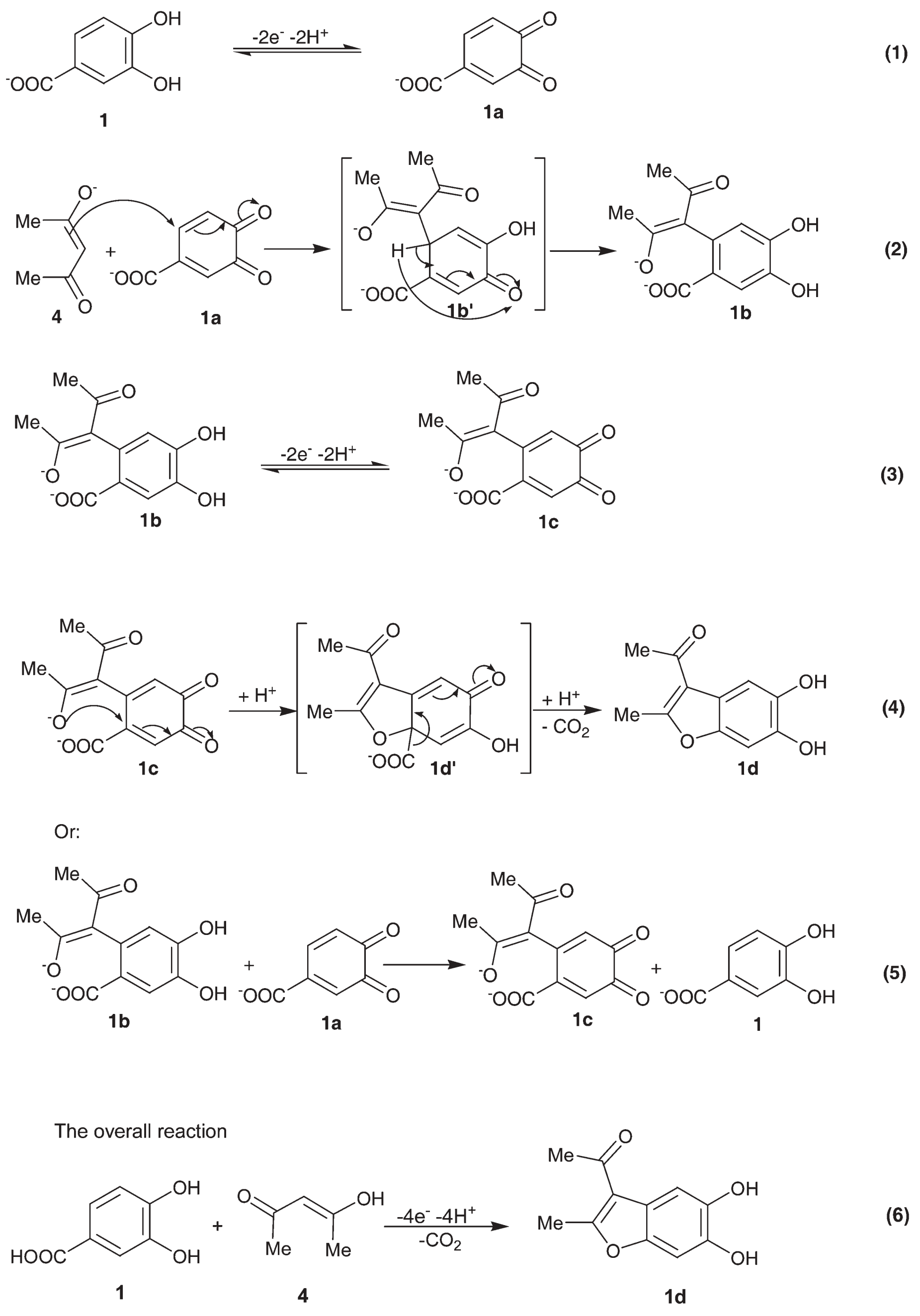


Fig. 1 Cyclic voltammograms of 1 mM 3,4-dihydroxybenzoic acid: (a) in the absence of acetylacetone, (b and c) first and second scan in the presence of 1 mM acetylacetone and (d) 1 mM acetylacetone in the absence of 3,4-dihydroxybenzoic acid. Supporting electrolyte: sodium acetate solution (0.2 M). Scan rate: 100 mV s^{-1}. $t = 25 \pm 1$ °C.

Department of Chemistry, Faculty of Science, University of Bu-Ali-Sina, Hamadan, 65174, Iran. E-mail: nemat@basu.ac.ir;
Fax: 0098-811-8272404; Tel: 0098-811-8271541

† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra. See http://dx.doi.org/10.1039/b503408f



Scheme 2

words, hydroxylation[10] or dimerization[11] reactions are too slow to be observed on the time scale of cyclic voltammetry. The oxidation of 3,4-dihydroxybenzoic acid (**1**) in the presence of acetylacetone (**4**) as a nucleophile was studied in some detail. Fig. 1, curve b shows the cyclic voltammogram obtained for a 1 mM solution of **1** in the presence of 1 mM acetylacetone (**4**). The voltammogram exhibits two anodic peaks (A_1 and A_2). The cathodic counterpart of the anodic peak A_1 nearly disappears. Comparison of voltammograms b and d reveals that the peak A_2 corresponds to the oxidation of acetylacetone (**4**) or acetylacetone linked to 3,4-dihydroxybenzoic acid (**1**). The multi-cyclic voltammetry of **1a** in the presence of **4** shows that parallel to the shift of the A_1 peak in a positive direction, a new peak (A_0) appears as a shoulder at a less positive potential in the second cycle (Fig. 1, curve c). This new peak is related to electro-oxidation of intermediate **1b**. The positive shift of the A_1 peak in the presence of acetylacetone is due to the formation of a thin film of product at the surface of the electrode.[9] In Fig. 1, curve d is the voltammogram of **4**.

Furthermore, it is seen that proportional to the augmentation of potential sweep rate, the height of the C_1 peak increases (Fig. 2, curves a–e). A plot of peak current ratio (I_p^{A1}/I_p^{C1}) *versus* scan rate for a mixture of 3,4-dihydroxy benzoic acid (**1**) and acetylacetone (**4**) confirms the reactivity of **1** towards **4**, appearing as an increase in the height of the cathodic peak C_1 at higher scan rates (Fig. 2, curve f). On the other hand, the

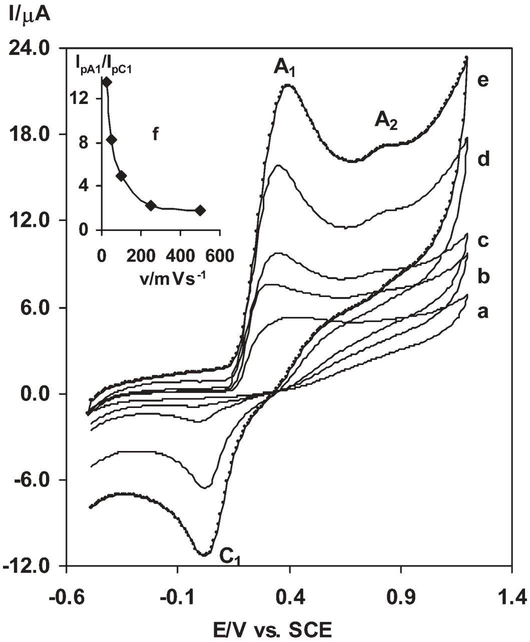


Fig. 2 Typical cyclic voltammograms of 1 mM 3,4-dihydroxybenzoic acid in the presence of 1 mM acetylacetone at a glassy carbon electrode, in sodium acetate solution (0.2 M). Scan rates from (a) to (e) are: 25, 50, 100, 250 and 500 mV s^{-1}, respectively. (f): Variation of peak current ratio (I_p^{A1}/I_p^{C1}) *versus* scan rate. t = 25 ± 1 °C.

current function for the A_1 peak, ($I_p^{A1}/v^{1/2}$), decreases on increasing the scan rate and such a behavior is seen as indicative of an ECEC mechanism.[12]

Controlled-potential coulometry was performed in aqueous solution containing 0.5 mmol of **1** and 0.5 mmol of **4** at 0.4 V *versus* SCE. Cyclic voltammetric analysis carried out during the electrolysis shows the progressive formation of a new anodic (A_0) peak, parallel to the disappearance of the A_1 peak (Fig. 3). All anodic (A_0, A_1 and A_2) and cathodic peaks disappear when the charge consumption becomes about 4e$^-$ per molecule of **1** (Fig. 3, inset). These observations allow us to propose the pathway in Scheme 2 for the electro-oxidation of **1** in the presence of **4**.

According to our results, it seems that the Michael addition reaction of anion enolate **4** to *o*-benzoquinone (**1a**) (eqn. (2)) is faster than other secondary reactions, leading to the intermediate (**1b**). The oxidation of this compound (**1b**) is easier than the oxidation of the parent-starting molecule (**1**) by virtue of the presence of an electron-donating group. The intramolecular reaction was performed *via* the 1,4-(Michael) addition reaction with an electro-decarboxylation reaction (eqn. (4)). Since the oxidation of formed dihydroxybenzofurane occurs at more positive potentials, the over-oxidation of **1d** was circumvented during the controlled potential preparative reaction. As can be seen from the mechanism shown in Scheme 2, *o*-benzoquinone **1c** can be generated through homogeneous oxidation (eqn. (5)). The synthesis of **1d** has been performed using electrochemical oxidation of 3,4-dihydroxybenzoic acid (**1**) in the presence of acetylacetone (**4**) in aqueous sodium acetate, in an undivided cell at A_1 peak potential (see Table 1).

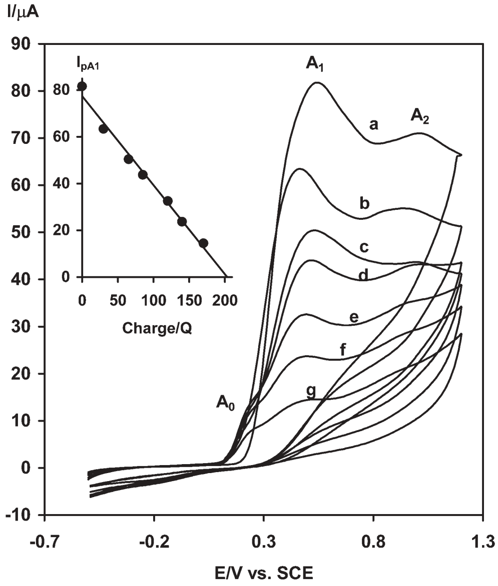


Fig. 3 Cyclic voltammograms of 0.5 mmol 3,4-dihydroxybenzoic acid in the presence of 0.5 mmol acetylacetone, at a glassy carbon electrode during controlled potential coulometry at 0.4 V *versus* SCE. After consumption of: (a) 0, (b) 30, (c) 65, (d) 100, (e)140, (f) 170 and (g) 200 C. Inset: variation of peak current (I_p^{A1}) *versus* charge consumed. Supporting electrolyte: sodium acetate solution (0.2 M). Scan rate 100 mV s^{-1}; t = 25 ± 1 °C.

Electrochemical study of 2,3-dihydroxybenzoic acid (2)

The electrochemical oxidation of 2,3-dihydroxybenzoic acid (**2**) in the presence of acetylacetone (**4**) as a nucleophile in sodium acetate solution (0.2 M) proceeds in a similar way to that of **1**. Fig. 4 shows the voltammograms of **2** in the present and absence of **4**. In this figure, curve a, is a cyclic voltammogram of **2** in the absence of **4**. The anodic (A_1) and corresponding cathodic peak (C_1) correspond to the transformation of 2,3-dihydroxybenzoic acid (**2**) to the related *o*-benzoquinone and *vice versa* within a quasi-reversible two-electron process. The oxidation of 2,3-dihydroxybenzoic acid (**2**) in the presence of acetylacetone (**4**) was studied in some detail (Fig. 4, curve b). Under these conditions, the anodic peak A_1 increases and the cathodic counterpart of A_1 disappears. Other conditions are similar to those for the electro-oxidation of 3,4-dihydroxybenzoic acid (**1**) in the presence of acetylacetone (**4**). In this case, each molecule of **2** in the presence of **4** converts to **2d**, *via* inter- and intramolecular Michael addition reactions with consumption of 4e$^-$. The overall reaction mechanism for electro-oxidation of 2,3-dihydroxybenzoic acid (**2**) in the presence of acetylacetone (**4**) is presented in Scheme 3.

The existence of a carboxylic group probably causes the *o*-benzoquinone (**2a**) derived from the oxidation of **2** to be

	Peak potentials V (SCE)				Applied	Product
Conversion	A_0	A_1	A_2	A_3	Potential V (SCE)	Yield %
1 → **1d**	0.25	0.35	0.85	—	0.35	58
2 → **2d**	—	0.35	0.90	—	0.40	53
3 → **3d**	—	0.28	0.50	0.90	0.25	94

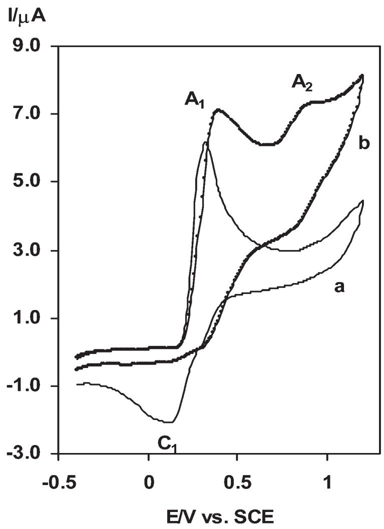
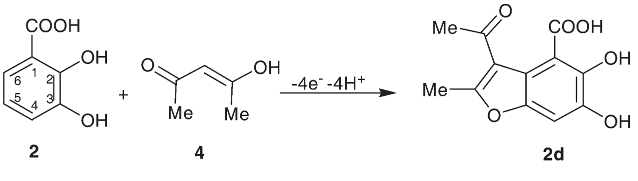


Fig. 4 Cyclic voltammograms of 1 mM 2,3-dihydroxybenzoic acid: (a) in the absence, (b) in the presence of 1 mM acetylacetone. Supporting electrolyte: sodium acetate solution (0.2 M). Scan rate: 25 mV s^{-1}; $t = 25 \pm 1$ °C.

attacked by acetylacetone (**4**) at the C-5 or C-6 positions to yield two types of products in each case. However, according to a previous report[8a] and considering the electron-withdrawing character of the carboxylic group, we suggest that *o*-benzoquinone **2a** is attacked in the C-6 position by acetylacetone (**4**) leading to the formation of the products **2d**. The electro-organic synthesis of **2d** has been performed using oxidation of 2,3-dihydroxybenzoic acid (**2**) in the presence of acetylacetone (**4**) as described for **1d** (see Table 1).

Electrochemical study of 2,5-dihydroxybenzoic acid (3)

The electrochemical oxidation of 2,5-dihydroxybenzoic acid (**3**) in the presence of acetylacetone (**4**) in 0.2 M acetate solution has been performed using cyclic voltammetry. Fig. 5, curve a shows the cyclic voltammogram obtained for a 2 mM solution of 2,5-dihydroxybenzoic acid (**3**) in the presence of 2 mM acetylacetone (**4**). In comparison with cyclic voltammograms of **1** and **2** (Fig. 1, curve b and Fig. 4, curve b), *p*-benzoquinone (**3a**) derived from the oxidation of **3** has less reactivity towards the intermolecular Michael addition reaction, appearing as a decrease in peak current ratio (I_p^{A1}/I_p^{C1}) (Fig. 5, curve b). Increasing the concentration of **4** and decreasing the scan rate caused an enhancement in the extent of chemical reaction during the time scale of cyclic voltammetry, appearing as an increase in peak current ratio (I_p^{A1}/I_p^{C1}). This voltammogram shows a new anodic peak (A_2) at higher potentials (0.51 V *vs.* SCE) and its corresponding cathodic peak (C_2), which corresponds to the transformation of intermediate **3b** to the related *p*-benzoquinone and *vice versa* (Fig. 5, curve b). The more positive E_p of peak A_2 is related to relative stability of **3b** towards oxidation due to extension of inter- and intra-molecular hydrogen bonding. Also, this voltammogram shows another anodic (A_3) in 0.92 V *vs.* SCE.



Scheme 3

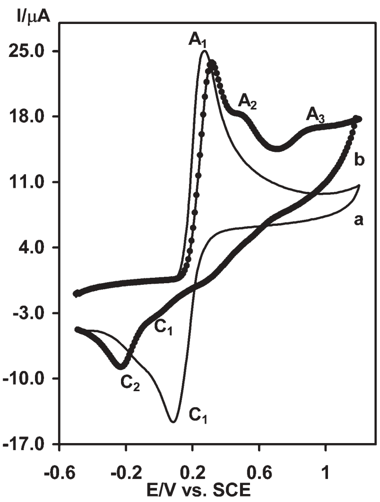


Fig. 5 Cyclic voltammograms of 2 mM 2,5-dihydroxybenzoic acid: (a) in the absence, (b) in the presence of 2 mM acetylacetone. Supporting electrolyte: sodium acetate solution (0.2 M). Scan rate: 50 mV s^{-1}; $t = 25 \pm 1$ °C.

Controlled-potential coulometry was performed in aqueous solution containing 0.25 mmol of **3** and 0.25 mmol of **4** at 0.27 V *versus* SCE. Cyclic voltammetric analysis was carried out during the coulometry (Fig. 6). It was observed that, proportional to the advancement of coulometry, anodic peak A_1 decreases, peak A_2 at first increases and then remains constant and peak A_3 nearly increases. Peak A_1 disappears and peak A_3 reaches a maximum value when the charge consumption becomes about 2e$^-$ per molecule of **3**. These observations allow us to propose the pathway in Scheme 4 for the electro-oxidation of **3** in the presence of **4**. In addition, cyclic voltammogram of the final product (after separation and purification) in acetate solution shows an irreversible anodic peak (A_3). This peak, that is related to the irreversible oxidation of benzofuran **3d**, indicates that there is no hydroquinone ring in the structure of **3d**. Hydroquinone rings show a reversible or quasi-reversible behavior.

The rate of the conversion of **3b** to **3d** is as low as that by the end of coulometry and both anodic peaks (A_2 and A_3) that are related to oxidation of **3b** and **3d** respectively will be observed (Fig. 6, curve e). However, during the preparative process in acidic media, **3b** is rapidly and quantitatively converted to **3d** (Fig. 6, curve f).

The existence of a carboxylic group probably causes the Michael acceptor **3a** to be attacked by acetylacetone (**4**) at the C-3, C-4 or C-6 positions to yield three types of products in each case (Scheme 5). In this connection, the ^{1}H NMR spectrum of obtained product indicates that the coupling constants, *J*, for the two aromatic peaks (6.74 and 7.54 ppm) are 8.8 Hz, that is, in agreement with the existence of two protons in the hydroquinone ring in the *ortho* positions.[13]

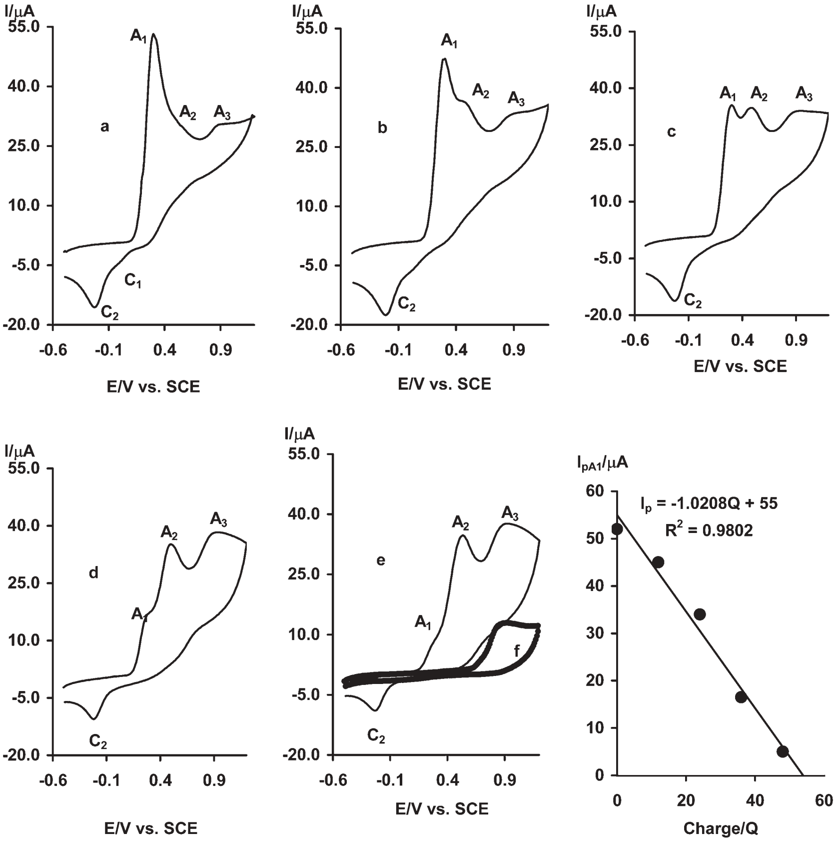


Fig. 6 Cyclic voltammograms of 0.25 mmol 2,5-dihydroxybenzoic acid in the presence of 0.25 mmol acetylacetone, at a glassy carbon electrode during controlled potential coulometry at 0.27 V *versus* SCE. After consumption of: (a) 0, (b) 12, (c) 24, (d) 36, and (e) 48 C. (f) Cyclic voltammogram saturated solution of final product after separation and purification. (g) Variation of peak current (I_p^{A1}) *versus* charge consumed. Supporting electrolyte: sodium acetate solution (0.2 M). Scan rate 100 mV s^{-1}; $t = 25 \pm 1$ °C.

Therefore, according to the ^{1}H NMR results we suggest that *p*-benzoquinone **3a** is attacked in the C-6 position by **4** leading to the formation of **3d**.

The synthesis of **3d** has been performed using electrochemical oxidation of 2,5-dihydroxybenzoic acid (**1**) in the presence of acetylacetone (**4**) in aqueous sodium acetate, in an undivided cell at a potential less than the A_1 peak potential (see Table 1).

Conclusion

The results of this work show that dihydroxybenzoic acids are oxidized in aqueous media to their respective quinones. The quinones are then attacked by the anion of acetylacetone *via* intermolecular Michael addition reaction. We observed diversity in their behavior in the steps that followed. In 3,4-dihydroxybenzoic acid (**1**), after the intermolecular Michael addition reaction and oxidation of the intermediate (**1b**) (Scheme 2, eqns. (2) and (3)), an intramolecular Michael addition reaction takes place that is accompanied by a decarboxylation reaction. We have recently reported the synthesis of this compound *via* electrooxidation of catechol in the presence of acetylacetone (**4**).[9b] In the case of 2,3-dihydroxybenzoic acid (**2**), the final product (**2d**) contains a carboxylic group and was obtained after a normal intramolecular Michael addition reaction as recently reported.[9] Contrary to **1** and **2**, in the case of 2,5-dihydroxybenzoic acid (**3**), the final product was obtained only after consumption of 2e$^-$ per molecule of **3** and a dehydration reaction. The overall reaction mechanisms for anodic oxidation of 3,4-dihydroxy benzoic acid (**1**), 2,3-dihydroxybenzoic acid (**2**) and 2,5-dihydroxybenzoic acid (**3**), in the presence of acetylacetone (**4**) is presented in Schemes (2), (3) and (4), respectively. These mechanisms show a good diversity in anodic oxidation of dihydroxybenzoic acids in the presence of acetylacetone (**4**).

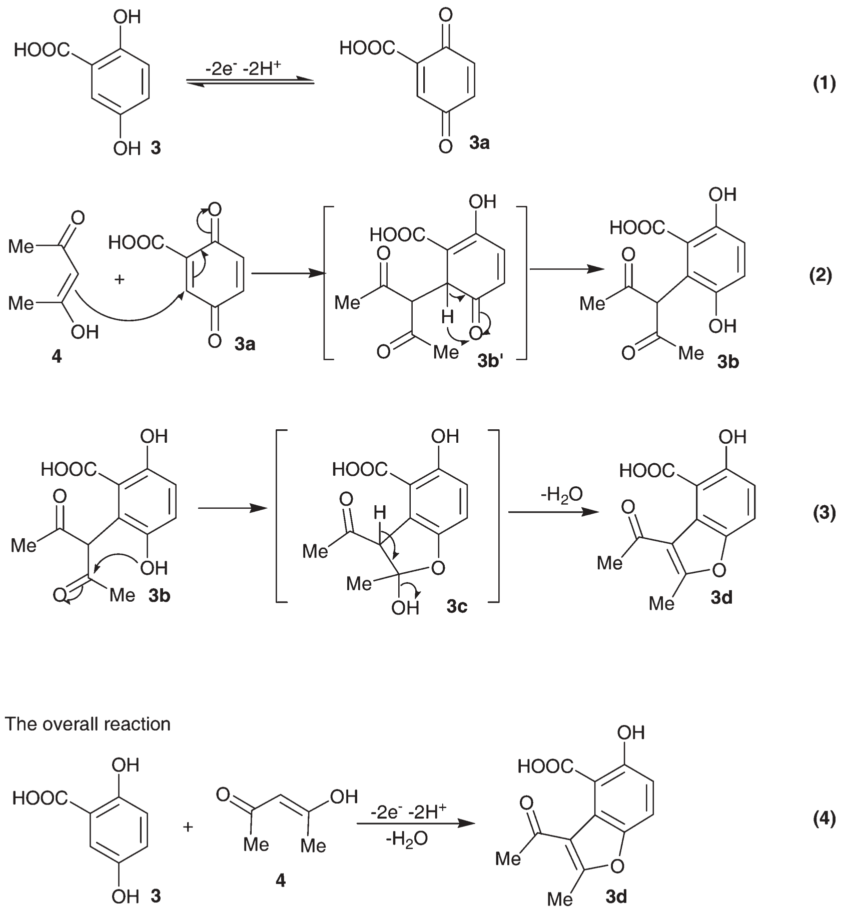
Experimental

Apparatus and reagents

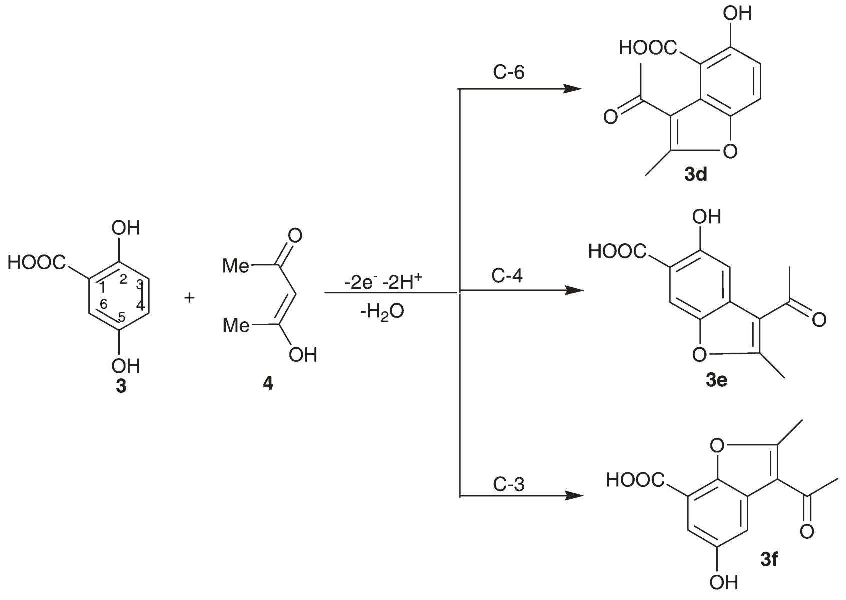
Reaction equipments are described in an earlier paper.[9b] All chemicals (dihydroxybenzoic acid and acetylacetone) were reagent-grade materials, and sodium acetate was of proanalysis grade. These chemicals were used without further purification.

Electroorganic synthesis of 1d–3d

In a typical procedure, 80 ml of sodium acetate solution (0.2 M) was pre-electrolyzed at the chosen potential (see Table 1), in an undivided cell; then 2 mmol of dihydroxybenzoic acid (**1–3**) and acetylacetone (**4**) (2 mmol) were added to the cell. The electrolysis was terminated when the decay of the current became more than 95%. The process was



Scheme 4



Scheme 5

interrupted during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, 20 ml 1 M hydrochloric acid was added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and washed with water. After washing, products were characterized by: IR, ^{1}H NMR, ^{13}C NMR and MS. The isolated yields of **1d–3d** after washing are reported in Table 1.

Characterization of compounds: 3-Acetyl-5,6-dihydroxy-2-methylbenzofuran (1d) ($C_{11}H_{10}O_4$): This compound was identified by comparison with an authentic sample (IR, ^{1}H NMR, ^{13}C NMR, MS, mp).[9b] **3-Acetyl-5,6-dihydroxy-2-methylbenzofuran-4-carboxylic acid (2d) ($C_{12}H_{10}O_6$)**: Mp 248–250 °C (dec.). $IR_{(KBr)}$: 3342, 1691, 1594, 1488, 1430, 1365, 1195, 1083, 906, 808, 595 cm^{-1}. ^{1}H NMR, δ (90 MHz DMSO d_6): 2.07 (s, 3 H), 2.45 (s, 3 H), 7.46 (s, 1 H), 10.45 (broad). ^{13}C NMR, δ (90 MHz DMSO d_6): 13.2, 31.5, 102.1, 107.1, 116.6, 124.2, 146.8, 153.4, 156.7, 157.8, 170.1, 196.6. MS: *m*/*z* (relative intensity); 250(20), 232(62), 206(50), 191(35), 175(17), 146(55), 118(22), 90(43), 69(100), 43(72). **3-Acetyl-5-hydroxy-2-methylbenzofuran-4-carboxylic acid (3d) ($C_{12}H_{10}O_5$)** Mp: 198–200 °C (dec.). $IR_{(KBr)}$: 3080, 1680, 1630, 1615, 1572, 1426, 1202, 1168, 1060, 977,835, 705 cm^{-1}. ^{1}H NMR, δ (500 MHz DMSO d_6): 2.29 (s, 3H), 2.39 (s, 3H), 6.84 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 11.0 (broad). ^{13}C NMR, δ (500 MHz DMSO d_6): 13.5, 32.0, 106.9, 114.2, 117.2, 120.9, 124.7, 147.2, 157.6, 158.0, 170.8, 197.2. MS: *m*/*z* (relative intensity); 234(46), 216(100), 201(25), 190(43), 175(80), 160(23), 146(18), 118(15), 89(20), 63(20), 43(69).

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Selection process of new solvents in temperature-dependent multi-component solvent systems and its application in isomerising hydroformylation

Arno Behr,* Guido Henze, Dietmar Obst and Barbara Turkowski

Received 8th June 2005, Accepted 20th June 2005
First published as an Advance Article on the web 15th July 2005
DOI: 10.1039/b508032k

The rhodium–BIPHEPHOS catalysed hydroformylation of *trans*-4-octene yields *n*-nonanal at high selectivity under mild reaction conditions. In this contribution a new method for an efficient product and catalyst separation in hydroformylation reactions is presented. By application of a temperature-dependent multi-component solvent (TMS) system, classical extraction process steps can be omitted and catalyst leaching reduced. The Hansen solubility parameter concept of solvent selection is presented to determine in general TMS systems for homogeneous catalysed reactions.

1. Introduction

Recently we reported the rhodium–BIPHEPHOS catalysed hydroformylation of *trans*-4-octene as a remarkably ecological and economical method for the synthesis of *n*-nonanal.[1] Considering the mild reaction conditions (1 MPa, 125 °C), high selectivity and improved utilisation of resources by use of olefin mixtures instead of α-olefins, this reaction is promising for an industrial application.

With an annual capacity of up to 9.3 million tons in 1998, hydroformylation is the most important homogeneous catalysed reaction.[2,3] It is carried out with cobalt or rhodium catalysis. Rhodium catalysts obtained greater importance due to milder reaction conditions in the hydroformylation and better *n*/*iso* ratios in product distribution. The high rhodium price[4] (between 20 and 75 € g^{-1} during the last five years) demands an efficient catalyst recycling. Along with the established Ruhrchemie/Rhône-Poulenc process we published another multiphase recycling concept based on temperature-dependent multi-component solvent (TMS) systems.[5]

The aim of these TMS systems is to combine a reaction procedure without any mass transport problems like in classical homogeneous single phase catalysis with an efficient catalyst recycling concept like in liquid–liquid two phase catalysis.

TMSs usually consist of three solvents with different degrees of polarity. Solvent 1 (S1) is polar in its nature and almost immiscible with the non-polar solvent 2 (S2). One of these components must be able to dissolve the catalyst, the other one has to be a suitable extraction agent for the reaction product. A third solvent (S3) with a polarity in between S1 and S2 serves as mediator for S1 and S2. Dependent on the composition, a mixture of S1, S2, and S3 is homogeneous or heterogeneous at a certain temperature. The extent of the heterogeneous sphere of the system — the so called miscibility gap — is temperature dependent: usually with rising temperature the miscibility gap decreases. By carrying out the reaction at a high reaction temperature in a single phase, and separating the catalyst phase from the product phase by phase split at a lower temperature this effect can be used for efficient catalyst recycling (Fig. 1).

This paper describes a method for efficient TMS determination which facilitates a reduction of rhodium and ligand leaching for the hydroformylation of *trans*-4-octene.

2. Results and discussion

2.1 Solvent selection

Recent investigations in single phase experiments showed that polar cyclic carbonates like propylene carbonate (Fig. 2) are suitable solvents for the rhodium–BIPHEPHOS catalyst system. In addition they have a selectivity increasing effect on the isomerising hydroformylation.[1]

As an extraction agent for the products, non-polar *n*-dodecane as well as a mixture of dodecane isomers revealed a high efficiency.

N-Octyl-2-pyrrolidone (NOP) (Fig. 3) has both a polar (nitrogen atom) and non-polar (alkyl chain) character and was used as mediator for the cyclic carbonates and the extraction

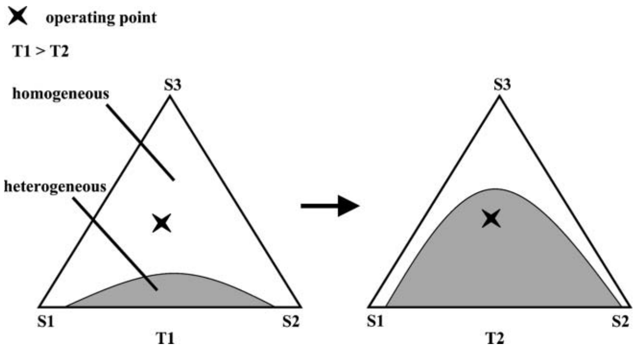

Fig. 1 General principle of temperature-dependent multi-component solvent systems (TMS).

Lehrstuhl für Technische Chemie A, Universität Dortmund, Emil-Figge-Str. 66, 44227 Dortmund, Germany. E-mail: behr@bci.uni-dortmund.de; Fax: +49-231-755-2311; Tel: +49-231-755-2310

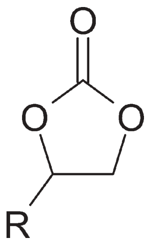

Fig. 2 Cyclic carbonate; R = H ethylene carbonate (EC), = CH_3 propylene carbonate (PC), = C_2H_5 butylene carbonate (BC).

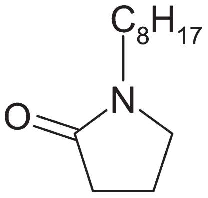

Fig. 3 *N*-Octyl-2-pyrrolidone (NOP).

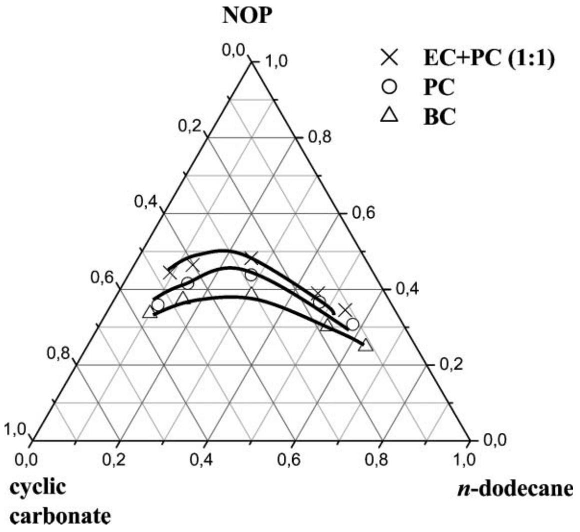

Fig. 4 Mixing behaviour of some cyclic carbonates (EC, PC, BC) with *n*-dodecane and *N*-octyl-2-pyrrolidone (NOP) at 25 °C.

agents. Fig. 4 shows the miscibility behaviour of some TMS systems dependent on the used cyclic carbonate. Obviously the miscibility gap increases with decreasing length of the carbonate's carbon chain.

Both the cyclic carbonates and NOP are able to dissolve the catalyst. It was observed that at the separation temperature NOP can be found in the product phase as well as in the catalyst phase which causes an undesirable catalyst leaching (Table 1). So it was necessary to determine a mediator with a similar property to NOP, but that can exclusively be found in the catalyst phase.

As a possibility for classifying the miscibility behaviour of solvents Hildebrand and Scott[6,7] developed the theory of the solubility parameter (δ). It is defined as the square root of the cohesive energy density:

$$\delta = \sqrt{\frac{E}{V}} \tag{1}$$

Table 1 Catalyst leaching dependence on cyclic carbonate; ethylene carbonate (EC), propylene carbonate (PC), butylene carbonate (BC), *N*-octyl-2-pyrrolidone (NOP)

Cyclic carbonate (wt%)	*n*-Dodecane (wt%)	NOP (wt%)	Rh leaching (%)	P leaching (%)
EC 50	12	38	90	60
EC 25 + PC 25	23	27	16	11
PC 50	23	27	2	2
BC 50	31	19	1	2

where E is the energy of vaporization of a pure solvent (reduced by the potential energy of an ideal gas) with molar volume V. The theory postulates that the more the two solvents are alike in their δ the sooner they are miscible.

Hansen[8,9] expanded this theory by dividing the cohesive forces of liquids into three components — dispersive (d), polar (p) and hydrogen bonding (h) forces — and defined the three component solubility parameter δ_0 as:

$$\delta_0 = \sqrt{\delta_d + \delta_p + \delta_h} \tag{2}$$

In this context we had to find a mediator with a Hansen solubility parameter (HSP, δ_0) closer to that of the catalyst solvent than to that of NOP. A detailed database can be found in the literature.[10–12]

As stated previously the main criteria in solvent selection for extraction purposes is the polarity. To prevent miscibility of the mediator with the product phase at separation temperature the mediator's polarity has to be preferably in the sphere of the cyclic carbonate.

Table 2 shows that with decreasing chain length of the *N* substituent of the pyrrolidone, the solubility parameter increases. In comparison to NOP *N*-methyl-2-pyrrolidone (NMP) is a common solvent in the chemical industry and therefore much cheaper. For this reason and because of the higher HSP NMP seems to be an interesting substitute for NOP. Fig. 5 shows the substitution effect of NMP in the phase diagram.

In general more NMP than NOP is needed to close the miscibility gap between the cyclic carbonate and the extraction agent *n*-dodecane. In addition a higher temperature dependency of the miscibility behaviour can be recognised by the use of NMP: at room temperature the NMP-TMS change from closed to open systems. This effect means an almost complete immiscibility of the mediator and the cyclic carbonate with the extraction agent at separation temperature. In this way the catalyst leaching into the product phase can be suppressed.

Table 2 Hansen solubility parameters of some solvents[5]

Solvent	δ_0 ($MPa^{0,5}$)	δ_d ($MPa^{0,5}$)	δ_p ($MPa^{0,5}$)	δ_h ($MPa^{0,5}$)
n-Dodecane	16.0	16.0	0.0	0.0
Ethylene carbonate	29.6	19.4	21.7	5.1
Propylene carbonate	27.3	20.0	18.0	4.1
N-Benzyl-2-pyrrolidone	20.0	18.2	6.1	5.6
N-*n*-Butyl-2-pyrrolidone	20.9	17.5	9.9	5.8
N-Methyl-2-pyrrolidone	22.9	18.0	12.3	7.2

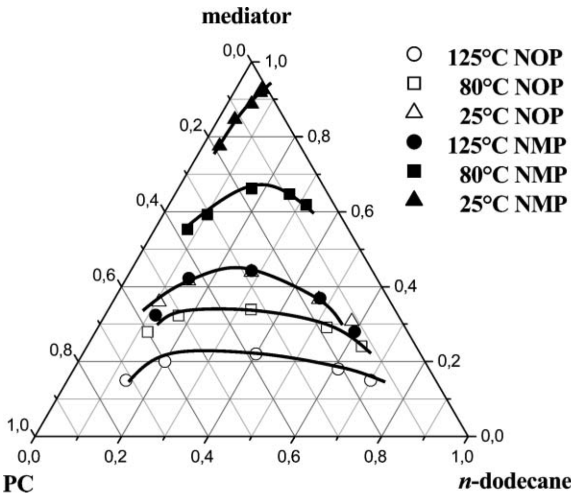

Fig. 5 Comparison of *N*-octyl-2-pyrrolidone (NOP) with *N*-methyl-2-pyrrolidone (NMP) as mediator for propylene carbonate (PC) and *n*-dodecane.

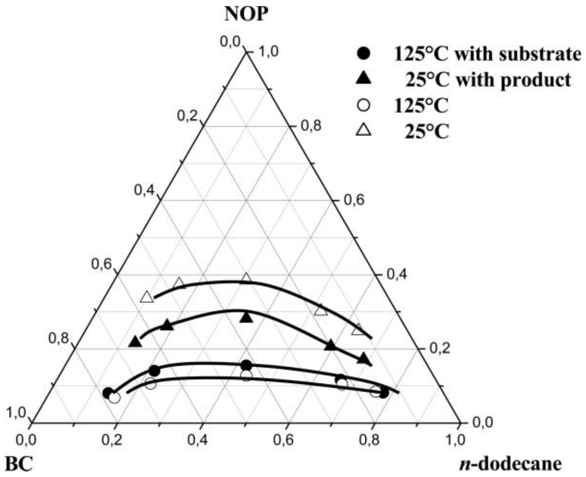

Fig. 6 Effect of *trans*-4-octene and nonanal on the mixing behaviour of TMS; addition of 15 wt% *trans*-4-octene at reaction temperature (125 °C) and 17 wt% nonanal at separating temperature (25 °C).

The determination of suitable operating points demands the consideration of the influence of the reaction's substrates and products. We ascertained that in this case the miscibility gap is increased by *trans*-4-octene at the reaction temperature and decreased by *n*-nonanal at the separating temperature which causes a diminution of the operating area. This effect is illustrated in Fig. 6.

2.2 Hydroformylation in TMS

In a first step we investigated hydroformylation at various compositions of the TMS propylene carbonate–*n*-dodecane–*N*-octyl-2-pyrrolidone (16 : 63 : 21, 24 : 50 : 26, 36 : 36 : 28, 50 : 23 : 27, 63 : 13 : 24 wt%). It was found that with increasing mass fraction of propylene carbonate the conversion of *trans*-4-octene can be increased from 92 to 98% while the selectivity regarding *n*-nonanal decreases from 81 to 72%. In the same way the rhodium loss is reduced from 21 to 1% and the loss of phosphorous from 15 to 7%.

The variation of the cyclic carbonate revealed that with increasing polarity (decrease in carbon chain length) the conversion regarding *trans*-4-octene is decreasing from 100 to 94% and the selectivity regarding *n*-nonanal is increasing from 76 to 86%. An explanation for the increasing catalyst leaching (from 1.2 to 89.5%) is again the increasing difference in HSP between the cyclic carbonates and the mediator (Table 3). The catalyst activity can be displayed by the turn over number (TON). For the catalyst system rhodium–BIPHEPHOS the TON is 194.

Comparable experiments with *N*-methyl-2-pyrrolidone as mediator produced similar results, but with a much lower catalyst leaching in between <0.1 and 0.3% for rhodium and 0.6 and 1.4% for phosphorous (Table 4).

Any influence of the mediator or the extraction agent on conversion or selectivity could not be observed.

Investigation of extraction behaviour revealed that the extraction efficiency (that is the amount of *n*-nonanal in grams per gram of extraction phase multiplied by 100) of *n*-dodecane and a mixture of dodecane isomers respectively is almost constant at 7 to 8.

Table 3 Hydroformylation of *trans*-4-octene in cyclic carbonate–*N*-octyl-2-pyrrolidone–*n*-dodecane, $T = 125$ °C, p(syngas, 1 : 1) = 1 MPa, t(reaction) = 4 h, m(solvents) = 30 g, $n([Rh(acac)(CO)_2]) = 10^{-4}$ mol, $n(\text{BIPHEPHOS}) = 5 \times 10^{-4}$ mol

Cyclic carbonate (wt%)	*n*-Dodecane (wt%)	NOP (wt%)	Conversion reg. *trans*-4-octene (%)	Selectivity reg. *n*-nonanal (%)	Rh leaching (%)	P leaching (%)
EC 50	12	38	94	86	89.5	60.3
EC 25 + PC 25	23	27	97	80	12.2	6.6
PC 50	23	27	98	79	2.5	2.1
BC 50	31	19	100	76	1.2	2.4

Table 4 Hydroformylation of *trans*-4-octene in cyclic carbonate–*N*-methyl-2-pyrrolidone–extraction agent (Do = dodecane/s), $T = 125$ °C, p(syngas, 1 : 1) = 1 MPa, t(reaction) = 4 h, m(solvents) = 30 g, $n([Rh(acac)(CO)_2]) = 10^{-4}$ mol, $n(\text{BIPHEPHOS}) = 5 \times 10^{-4}$ mol

Cyclic carbonate (wt%)	Extraction agent (wt%)	NMP (wt.%)	Conversion reg. *trans*-4-octene (%)	Selectivity reg. *n*-nonanal (%)	Rh leaching (%)	P leaching (%)
EC 18 + PC 18	*n*-Do 10	54	99	80	<0.1	0.6
PC 50	*iso*-Do 10	40	99	81	<0.1	0.5
BC 50	*n*-Do 23	27	100	76	0.3	1.4

2.3 Conclusions and outlook

The selective rhodium–BIPHEPHOS catalysed hydroformylation of *trans*-4-octene can be highly improved by carrying out the reaction in TMS at the same mild reaction conditions. In this way a separate extraction process step is obsolete. By the use of NMP as mediator, which affects the behaviour of an open system, an effective and clean catalyst recycle can be ensured. The concept of the Hansen solubility parameter proved to be a valuable general tool for TMS solvent selection.

Trans-4-octene can also be seen as a model substance for future hydroformylation of internally unsaturated fatty acid esters. That would mean the access of renewable resources for the synthesis of valuable *n*-aldehydes.[13]

3. Experimental

3.1 Reagents, catalyst and handling

Ethylene carbonate (99+%), propylene carbonate (99.5%), a technical mixture of dodecane isomers, *n*-dodecane (99%), *N*-methyl-2-pyrrolidone (99%) and *N*-octyl-2-pyrrolidone (98+%) were purchased from Acros Organics and used without further purification. Butylene carbonate (99%) was obtained from Huntsman, *trans*-4-octene (90+%) by Sigma-Aldrich and [Rh(acac)(CO)$_2$] (39.90wt.% Rh) by Umicore. The ligand BIPHEPHOS (2,2′-bis{[(2,2′-bisphenoxy)phosphino]-oxy-3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl) was synthesised according to ref. 14–16. Syngas (99.9%) was obtained by BASF, CDCl$_3$ (99.8% D) by Aldrich. All solvents were degassed and used saturated with argon. All reactions and handling were done under dry argon using standard Schlenk techniques.

3.2 Determination of temperature-dependent multi-component solvent (TMS) systems

All determination experiments for TMS were carried out by cloud titration. 1 g of a mixture of a cyclic carbonate and dodecane (5 : 1, 3 : 1, 1 : 1, 1 : 3, 1 : 5 wt. ratio) was transferred into a 5 ml centrifuge glass and warmed in a silicone oil bath under intense stirring. After having reached the desired temperature (125, 80, 25 °C) the mediator was added drop by drop using a syringe to the cloudy mixture until a homogeneous phase was formed. Each system was determined three times with an accuracy of ±0.5 weight percent and the average value was used.

3.3 Isomerising hydroformylation of *trans*-4-octene in temperature-dependent multi-component solvent (TMS) systems

All hydroformylation experiments were carried out in 70 ml laboratory reactors from Parr Instrument Company (USA). The reaction mixture was transferred into the reactor using standard Schlenk technique to prevent oxidation of the catalyst precursors as well as other deleterious reactions.

In a typical experiment 2.24 g (1.94×10^{-2} mol) *trans*-4-octene, 25.9 mg (1×10^{-4} mol) [Rh(acac)(CO$_2$)] and 393.3 mg (5×10^{-4} mol) BIPHEPHOS were dissolved in 30 g of a solvent mixture (cyclic carbonate, dodecane, mediator) and transferred into the evacuated stainless steel autoclave. After heating the vessel up to 125 °C it was pressurised with 1 MPa syngas (CO : H$_2$ = 1 : 1). The reaction time of 4 h was taken after accelerating the stirrer to 500 rpm. The reaction was ended by stopping the syngas influx, reducing the stirring velocity and rapidly cooling down to room temperature with an ice bath. After venting the syngas the reaction mixture was separated in a separating funnel. A sample of the catalyst phase and the product phase were taken and analysed by gas chromatography with *n*-heptane as internal standard and isopropanol as solvent. The catalyst leaching was analysed by ICP-spectrometry.

3.4 Analysis and product characterisation

Routine gas chromatographic analyses were done on a HP 6890 instrument (Hewlett-Packard GmbH, Waldbronn, Germany) equipped with a FI-detector and a HP-INNOWax capillary column (30 m, coating polyethylene glycol, diameter 0.25 mm, film thickness 0.25 μm) in connection with an autosampler. NMR spectra were recorded on a DRX 400 spectrometer (Bruker Instruments Inc., Billerica, MA, USA) using CDCl$_3$ as internal standard. Water contents were determined by Karl-Fischer titration on a 652-KF-Coulometer (Metrohm Herisau, Switzerland). Precious metal and phosphorous content were measured by inductively coupled plasma spectrometry with an IRIS Intrepid ICP spectrometer (Thermo Elemental). All reaction mixtures were analyzed by gas chromatography using calibration with pure compounds.

Acknowledgements

We thank the Bundesministerium für Bildung und Forschung (ConNeCat-project "smart solvents – smart ligands") and the Fonds der Chemischen Industrie for financial support. A scholarship of the "Konrad-Adenauer-Stiftung" (Guido Henze) is gratefully acknowledged.

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Poly(ethyleneglycol) (PEG): a versatile reaction medium in gaining access to 4′-(pyridyl)-terpyridines†

Christopher B. Smith,* Colin L. Raston* and Alexandre N. Sobolev

Received 27th May 2005, Accepted 20th June 2005
First published as an Advance Article on the web 12th July 2005
DOI: 10.1039/b507581p

A new paradigm for the synthesis of 4′-pyridyl terpyridines using poly(ethyleneglycol) (PEG) as a benign reaction medium is described, with the compounds readily accessible in high purity in *ca.* 4 hours using a 'one pot' procedure. This method requires no product purification and affords the desired compounds in reasonable yield without the formation of unwanted side products.

Introduction

Oligopyridines, particularly the terpyridines, are widely used as supramolecular tectons in molecular architectures,[1] as scaffolds in metallopolymers[2] and molecular devices[1,3] and are gaining promise in medicinal chemistry as possible anticancer and antimicrobial agents.[4] The methods for preparing the terpyridine ring system[5] include variations of the pioneering methods developed by Kröhnke[6] and Potts *et al.*,[7] and more recently synthetic methodologies based on Stille coupling reactions[8] and the use of solventless conditions.[9] The latter is suitable for preparing a 1,5-dione *via* sequential aldol condensation reaction (affording a chalcone) and a Michael addition reaction, as the precursor for ring closure and oxidation in forming the central pyridine ring.

All of the above methods of terpyridine formation suffer from significant drawbacks and limitations. The Kröhnke[6] and Potts *et al.*[7] methodologies often display moderate to low yields, utilise large volumes of volatile organic solvents, have low atom efficiency and often require extensive purification. In addition toxic and expensive organic solvents such as pyridine and halogens are used resulting in large volumes of halogenated waste. The use of organostannanes in Stille coupling reactions is also of a major concern due to their toxicity. Problems also exist with the solvent-based formation of the 1,5-diones, and in several cases, cyclohexanol side products are formed which introduces a tedious separation problem.[9,10] Although several classes of these compounds can be prepared in reasonable yield, the optimum conditions for their formation are still poorly understood.[10,11] The above drawbacks and limitations can be overcome using the aforementioned solventless conditions. This is a paradigm shift in the formation of terpyridyls, both in the context of green chemistry,[12] and the ease, generality and simplicity of the procedure. Waste generation and side products are largely avoided, and the chalcones and 1,5-diones can be formed in high yield and purity. Another advantage is that unsymmetrical terpyridyls and bipyridyls are accessible, simply by adding a different aryl ketone to the chalcone in the Michael addition step of the reaction prior to ring closure.[9] Nevertheless the solventless methodology is limited where highly exothermic and run away reactions prevail leading to competing reactions. This challenged us to devise a strategy to alleviate these problems, and keeping with our theme of green chemistry, we examined the potential for using alternative benign reaction media for the synthesis of terpyridyls.

Results and discussion

In gearing up for gaining access to a large library of terpyridines for medicinal applications of these compounds, and in other applications, we have devised a more versatile and convenient synthesis of such compounds, also applying the principles of 'green chemistry',[12] notably the use of poly(ethyleneglycol) (PEG), the results of which are reported herein. PEG is becoming prominent as a benign, alternative reaction medium in synthetic chemistry.[13] In general PEG is non-toxic, being used in food products and cosmetics, is potentially recyclable and is water-miscible which facilitates its removal from reaction products.[13]

Terpyridine **2**, an important synthon in supramolecular chemistry,[14] is accessible *via* a 1,5-dione **1**, through the traditional solvent-based approach, Scheme 1,[15] albeit often with a lack of reproducibility, low yield and the generation of side products. The 1,5-dione did not form under solventless conditions, the exothermic reaction of 2-acetylpyridine with 4-pyridinecarboxaldehyde and sodium hydroxide resulting in a black, tarry intractable residue. Slower addition of the base, or lowering of the temperature during grinding was to no avail, and this suggested the need for a reaction medium as a heat sink and to control chemical reactivity. For this purpose low molecular weight PEG300 proved a versatile medium.

In a typical experiment, formation of the 1,5-dione involved condensation of a 2 : 1 molar ratio of 2-acetylpyridine and 4-pyridinecarboxaldehyde. Addition of 2-acetylpyridine to a cooled (0 °C) suspension of crushed NaOH in PEG resulted in the formation of a yellow mixture presumably containing the enolate anion, and after 10 minutes the aldehyde was added. The reaction mixture was allowed to stand for 2 hours, with occasional manual stirring (*ca.* every 15 minutes) and during

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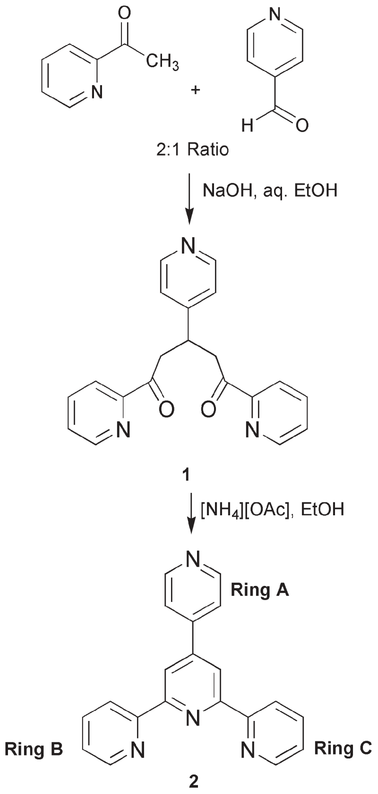
School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, Crawley, W.A. 6009, Australia.
E-mail: cbsmith@cyllene.uwa.edu.au; Fax: +61 86488 1005;
Tel: +61 86488 4422

† Electronic supplementary information (ESI) available: crystallographic details for compound **11**. See http://dx.doi.org/10.1039/b507581p



Scheme 1

this period the colour changed to deep red. Addition of water resulted in the formation of a sticky emulsion which solidified on standing overnight at 5 °C. Isolation of this material and washing with water and cold EtOH resulted in a white solid, the ^{1}H NMR spectrum being identical with the previously reported 1,5-dione **1** which can be readily converted to terpyridine **2**.[15]

However, isolation of the 1,5-dione intermediate can be avoided with the terpyridine accessible in 'one pot' whereby excess ammonium acetate is added after the 2 hours for the above reaction. On heating the mixture, the colour changes from red to brown and a fine solid precipitates. After 2 hours at 100 °C, the mixture was cooled and water added to remove PEG, affording a microcrystalline precipitate of pure **2** (^{1}H NMR spectroscopy and mass spectrometry). No side products, or unreacted intermediate products (chalcone or 1,5-dione) were present, which contrasts with the uncertainty in the traditional method. The yield (*ca.* 54%) is acceptable in the context of the short reaction times (4 hours compared to >24 hours for the traditional method) and the high purity of the end product which avoids the use of expensive, volatile organic solvents associated with labour intensive purification procedures. Prolonging the reaction time to >12 hours did not result in a significant increase in product yield.

Using our procedure, the eight isomeric 4′-pyridyl terpyridines **3–10** have been synthesised in high purity and in acceptable yields (Table 1). The first 2 hour stage can be undertaken at ambient temperature, but at 0 °C cleaner reaction products are obtained. At higher temperatures (50–70 °C) the formation of cyclohexanol products (the side products from traditional solvent-based syntheses) occurs. The use of concentrated aqueous NH_3 solution in place of ammonium acetate for the ring closure step has also been demonstrated for terpyridine **2**. This may enable easier recycling of the PEG medium as excess dissolved inorganic salts are then avoided.

Table 1 Yields of 4′-pyridyl terpyridines synthesised in PEG

Compound	Ring A	Ring B, C	Yield (%)
3	3-pyridyl	2-pyridyl	47
4	2-pyridyl	2-pyridyl	55
5	4-pyridyl	3-pyridyl	51
6	3-pyridyl	3-pyridyl	48
7	2-pyridyl	3-pyridyl	44
8	4-pyridyl	4-pyridyl	46
9	3-pyridyl	4-pyridyl	44
10	2-pyridyl	4-pyridyl	47

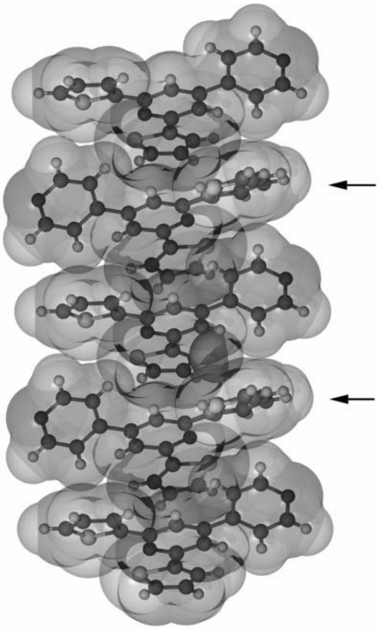


Fig. 1 The X-ray structure of **11** showing stacking of individual molecules. The disordered thiophenes are shown by the arrows.

We have also investigated the formation of pyridyls which contain other heterocyclic ring systems substituted at the 2, 4 and 6 positions. Particularly noteworthy is the synthesis of the hitherto unknown compound **11** in 32% yield and its structure authenticated using X-ray diffraction data, Fig. 1.‡ Remarkably the asymmetric unit is comprised of four unique molecules, arranged as pairs forming columns along the [010]

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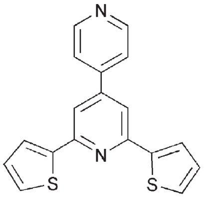
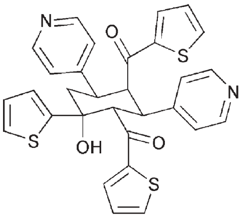
‡ Colourless crystals of **11** were deposited from a $CDCl_3$ solution. *Crystal data*: $C_{18}H_{12}N_2S_2$, $M = 320.42$, monoclinic, Pc (No. 7), $Z = 8$, $T = 153$ K, $a = 20.312(3)$, $b = 9.9902(15)$, $c = 15.927(2)$ Å, $\beta = 108.289(2)$ °, $U = 3068.7(8)$ Å^3; $D_c = 1.387$ g cm^{-3}; $\sin\theta/\lambda_{max} = 0.683$; N(unique) = 14336 (merged from 27936, $R_{int} = 0.0242$, $R_{sig} = 0.0411$), N_o ($I > 2\sigma(I)$) = 11766; $R = 0.0738$, $wR2 = 0.1835$ ($A,B = 0.114$, 1.4262), GoF = 1.029; $|\Delta\rho_{max}| = 1.2(1)$ e Å^{-3}. CCDC reference number 265089. See http://dx.doi.org/10.1039/b507581p for crystallographic data in CIF or other electronic format.

direction, with no unusual intermolecular contacts. One of each pair of molecules exhibits regular positioning of the S atoms in both thiophene rings such that the geometry of the S, N, S-heteroatomic set is defined as being in the *cis*,*cis*-conformation. The other molecule is interpreted as a mixture of S, N, S- *cis*/*trans* rotamers with one of the thiophene rings disordered over the two coplanar positions. As a consequence, the total composition of the asymmetric unit in the crystal can be best described as a 3 : 1 ratio of wholly *cis*, and *trans* molecules of **11**.



11



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The synthesis of **11** also shows temperature dependence: at ambient temperature almost none of the desired product is formed, with the major product being a cyclohexanol derivative, **12**, resulting from a further aldol condensation between the enolate and the dione.

Conclusions

We have demonstrated that PEG is a useful, alternative reaction medium for the synthesis of 4′-pyridyl terpyridines. In association with solventless strategies the scene is set for gaining access to a large library of 2,4,6-tris-aryl substituted pyridines. Current investigations are focusing on optimising the green chemistry metrics (PEG recycling) and fine-tuning the process for preparing pyridyls containing furan, thiophene and pyrrole ring systems which have potential applications in medicinal chemistry as new drugs[4] and as synthons in nanotechnology.

Experimental

General

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AX500 instrument. Samples were recorded in $CDCl_3$ solution in ppm (δ) and referenced to the internal $CHCl_3$ singlet at 7.26 ppm. Elemental analyses were performed at the Australian National University, Canberra. FAB mass spectrometry measurements were performed on a Waters Micromass Autospec Mass Spectrometer.

Synthesis

General experimental procedure: 2-acetylpyridine (10 g, 8.25 mmol) was added to a suspension of crushed NaOH (3.3 g, 8.25 mmol) in PEG300 (70 cm^3), and stirred at 0 °C for 10 minutes. 4-Pyridinecarboxaldehyde (4.42 g, 4.12 mmol) was then added by syringe and the suspension left standing at 0 °C for 2 h. Every 15 minutes the suspension was manually stirred with a spatula as the viscosity became too great for adequate mixing using a magnetic follower. After 2 h, NH_4OAc (20 g, excess) was added and the suspension heated at 100 °C for 2 h. During this time, the colour of the mixture changed from red to brown, and was accompanied by formation of a fine brown precipitate of the product. Water (150 cm^3) was then added and the precipitate of **2** isolated by filtration, washed with water (100 cm^3) and cold EtOH (20 cm^3). The product formed was pure by ^{1}H and ^{13}C NMR spectroscopy. Light brown microcrystals, yield 6.9 g, 54%. NMR and MS data as previously reported.[15] Compounds **3–11** were made using the above procedure by using the appropriate aryl aldehydes and ketones in place of 2-acetylpyridine and 4-pyridinecarboxaldehyde.

3: Grey microcrystalline solid, yield 47%.[16] δ_H (500 MHz, $CDCl_3$) 9.11 (dd, 1H, Ar), 8.72 (s, 2H, Ar), 8.71 (m, 2H, Ar), 8.69 (dd, 1H, Ar), 8.65 (m, 2H, Ar), 8.16 (m, 1H, Ar), 7.86 (dt, 2H, Ar), 7.42 (m, 1H, Ar), 7.34 (m, 2H, Ar). δ_C (125 MHz, $CDCl_3$) 156.13, 155.73, 149.92, 149.08, 148.24, 147.08, 136.93, 134.71, 134.23, 123.99, 123.64, 121.33, 118.74. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$. Elemental analysis calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05; found C, 77.35; H, 4.74; N,17.94%.

4: Beige solid, yield 55%.[17] δ_H (500 MHz, $CDCl_3$) 9.12 (s, 2H, Ar), 8.79 (m, 1H, Ar), 8.75 (m, 2H, Ar), 8.67 (d, 2H, Ar), 8.09 (d, 1H, Ar), 7.89 (dt, 2H, Ar), 7.83 (dt, 1H, Ar), 7.35 (m, 3H, Ar). δ_C (125 MHz, $CDCl_3$) 155.93, 155.89, 154.90, 149.97, 148.94, 148.66, 137.09, 136.88, 123.88, 123.74, 121.42, 121.31, 118.73. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$.

5: Beige powder, yield 51%. δ_H (500 MHz, $CDCl_3$) 9.38 (d, 2H, Ar), 8.82 (m, 2H, Ar), 8.72 (dd, 2H, Ar), 8.51 (dt, 2H, Ar), 7.96 (s, 2H, Ar), 7.65 (m, 2H, Ar), 7.48 (dd, 2H, Ar). δ_C (125 MHz, $CDCl_3$) 155.90, 150.84, 150.51, 148.37, 148.23, 145.65, 134.58, 134.20, 123.71, 121.57, 117.40. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$. Elemental analysis calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05; found: C, 77.52; H, 4.71; N, 18.05%.

6: Beige solid, yield 48%.[18] δ_H (500 MHz, $CDCl_3$) 9.38 (m, 2H, Ar), 9.01 (m, 1H, Ar), 8.76 (dd, 1H, Ar), 8.72 (dd, 2H, Ar), 8.51 (dt, 2H, Ar), 8.05 (dt, 1H, Ar), 7.95 (s, 2H, Ar), 7.50 (dd, 1H, Ar), 7.48 (dd, 2H, Ar). δ_C (125 MHz, $CDCl_3$) 155.78, 150.54, 150.44, 148.40, 148.22, 147.79, 134.56, 134.54, 134.31, 133.99, 123.95, 123.69, 117.58. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$.

7: White solid, yield 44%. δ_H (500 MHz, $CDCl_3$) 9.43 (m, 2H, Ar), 8.82 (m, 1H, Ar), 8.71 (dd, 2H, Ar), 8.57 (dt, 2H, Ar), 8.40 (s, 2H, Ar), 7.96 (d, 1H, Ar), 7.90 (dt, 1H, Ar), 7.49 (dd, 2H, Ar), 7.42 (m, 1H, Ar). δ_H (125 MHz, $CDCl_3$) 155.38, 154.29, 150.23, 149.84, 148.85, 148.09, 137.28, 134.86, 134.70, 124.22, 123.72, 121.04, 117.13. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$. Elemental analysis calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05; found: C, 77.40; H, 4.65; N, 18.02%.

8: Mauve powder, yield 46%.[19] δ_H (500 MHz, $CDCl_3$) 8.83 (m, 2H, Ar), 8.82 (m, 4H, Ar), 8.09 (m, 4H, Ar), 8.06 (s, 2H, Ar), 7.65 (m, 2H, Ar). δ_C (125 MHz, $CDCl_3$) 155.84, 150.91, 150.65, 148.54, 145.54, 145.39, 121.56, 121.17, 118.70. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$.

9: Mauve powder, yield 44%. δ_H (500 MHz, $CDCl_3$) 9.02 (m, 1H, Ar), 8.82 (m, 4H, Ar), 8.78 (dd, 1H, Ar), 8.09 (m, 4H, Ar), 8.05 (m, 1H, Ar), 8.04 (s, 2H, Ar), 7.52 (m, 1H, Ar). δ_H (125 MHz, $CDCl_3$) 155.67, 150.69, 150.60, 148.19, 148.07, 145.66, 134.54, 133.74, 123.98, 121.17, 118.85. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$. Elemental analysis calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05; found: C, 77.36; H, 4.75; N, 17.81%.

10: Beige solid, yield 47%. δ_H (500 MHz, $CDCl_3$) 8.82 (m, 1H, Ar), 8.79 (m, 4H, Ar), 8.48 (s, 2H, Ar), 8.13 (m, 4H, Ar), 7.96 (m, 1H, Ar), 7.90 (dt, 1H, Ar), 7.43 (m, 1H, Ar). δ_C (125 MHz, $CDCl_3$) 155.36, 153.98, 150.35, 150.30, 149.04, 146.08, 137.30, 124.36, 121.23, 121.00, 118.33. FAB MS: *m*/*z* (%) 311 (100) $[M+H]^+$.

11: Brown crystals, yield 32%. δ_H (500 MHz, $CDCl_3$) 8.77 (m, 2H, Ar), 7.71 (dd, 2H, Ar), 7.65 (s, 2H, Ar), 7.62 (m, 2H, Ar), 7.44 (dd, 2H, Ar), 7.14 (dd, 2H, Ar). δ_C (125 MHz, $CDCl_3$) 153.09, 150.14, 147.14, 146.43, 144.23, 128.33, 128.06, 125.23, 121.66, 114.50. FAB MS: *m*/*z* (%) 321 (100) $[M+H]^+$. Elemental analysis calcd for $C_{18}H_{12}N_2S_2$: C, 67.47; H, 3.77; N, 8.74; found: C, 67.60; H, 3.99; N, 8.75%.

Acknowledgements

We thank the Australian Research Council and the University of Western Australia for support. The award of a UWA Postdoctoral Research Fellowship to C. B. S. is gratefully acknowledged. We also thank Prof. Allan H. White (UWA) for the collection of X-ray data for compound **11**.

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A novel room temperature ionic liquid sol–gel matrix for amperometric biosensor application

Yang Liu,[a] Lihong Shi,[a] Meijia Wang,[a] Zhiying Li,[a] Hongtao Liu[a] and Jinghong Li*[ab]

Received 4th April 2005, Accepted 14th July 2005
First published as an Advance Article on the web 8th August 2005
DOI: 10.1039/b504689k

A novel type of ionic liquid (IL) sol–gel hybrid material was developed for amperometric biosensor application. This material was prepared by the hydrolysis of tetraethyl orthosilicate in a 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIM^+BF_4^-$) solution. The viscous IL prevented the cracking of the sol–gel derived glasses. Horseradish peroxidase (HRP) was immobilized in the hybrid material for the production of an amperometric hydrogen peroxide biosensor. The IL sol–gel enzyme electrodes retained the high activity of HRP and provided long-term stability of HRP in storage. The morphology of the matrix-containing enzyme was characterized by scanning electron microscopy. The characteristics of the biosensor were also investigated by cyclic voltammetry and chronoamperometry. In the presence of ferrocene as a mediator, the biosensor exhibited an excellent stability and sensitivity, and the linear calibration ranged from 0.02 to 0.26 mM with a detection of 1.1 μM. The apparent Michaelis–Menten constant of the immobilized HRP was 2.0 mM.

Introduction

The biosensor with electrochemical analysis is of great importance in chemical, biological, clinical and many other fields.[1–3] Though numerous other methods have been developed, such as spectrometry,[4,5] titrimetry[6] and chemiluminescene,[7,8] electrochemical analysis offers the most economic, simple and rapid procedure and has attracted much attention for the construction of biosensors, based on the immobilization of enzymes, with high selectivity and sensitivity. An important aspect for the application and development of biosensors is a stable and biocompatible matrix for the immobilization of the enzyme. The sol–gel matrix material has excellent properties of physical rigidity, chemical inertness, high photochemical and thermal stability and experiment-negligible swelling in aqueous and organic solvents and is particularly attractive for the fabrication of biosensors.[9]

Room temperature ionic liquids (ILs), which are relatively viscous liquids comprised entirely of ions at ambient temperature, are environmentally benign solvents, and have received much interest recently for their unique physicochemical properties, such as high thermal stability, negligible vapor pressure, relatively high ionic conductivity and good electrochemical stability. These properties have been explored for applications in electrochemistry,[10–13] organic synthesis,[14,15] inorganic synthesis[15–17] and liquid–liquid extraction processes.[18] ILs have also been used in analytic chemistry such as buffer additives in capillary electrophoresis,[19,20] stationary phases in gas–liquid chromatography[21,22] and sensitive materials.[23,24] On the other hand, ILs have also been widely applied in biocatalysis for their excellent biocompatibility and it has been reported that enzymes of widely diverging types can maintain their activities in ILs or aqueous biphasic IL systems, and the ILs improved reusability and stability of the enzymes.[25]

We have found that HRP immobilized in a 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIM^+BF_4^-$) RTIL-based sol–gel matrix has much higher activity than that in the sol–gel matrix without RTIL.[26] In this paper, we have attemped to develop a HRP-immobilized RTIL-based sol–gel matrix for the preparation of an electrochemical biosensor. The crack-free sol–gel matrix was obtained and characterized by scanning electron microscopy. HRP was selected as the model enzyme since it was inexpensive, stable and could catalyze the H_2O_2-dependent one electron oxidation. The characteristics of the IL enzyme electrode have been investigated. The resulting biosensor could provide a promising platform for the development of affinity supports and biosensors as well as in the application of ILs.

Results and discussion

Cyclic voltammetric behavior of IL enzyme electrode

Fig. 1 shows the cyclic voltammograms of the sensor in 0.05 M PBS (pH 7.0). In the absence of H_2O_2, the cyclic voltammogram showed a couple of well-defined oxidation and reduction peaks for ferrocene with the formed potential of 176 mV (Fig. 1a). The redox peak separation of ferrocene was 64 mV indicating a good one electron reversible process. When H_2O_2 was added, a typical electrocatalytic characterization appeared with a sharp increase of the reduction current and the oxidation current decreased nearly to zero (Fig. 1b). These phenomena indicated that ferrocene could effectively transfer electrons from the surface of the glass carbon electrode to the redox center of HRP immobilized in the IL silica gel. Based the integral charge of the CV, the surface coverage of ferrocene

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[a] *State Key Laboratory of Electroanalytical Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China. E-mail: jhli@mail.tsinghua.edu.cn; Fax: +86-10-62795290; Tel: +86-10-62795290*
[b] *Department of Chemistry, Tsinghua University, Beijing 100084, China*

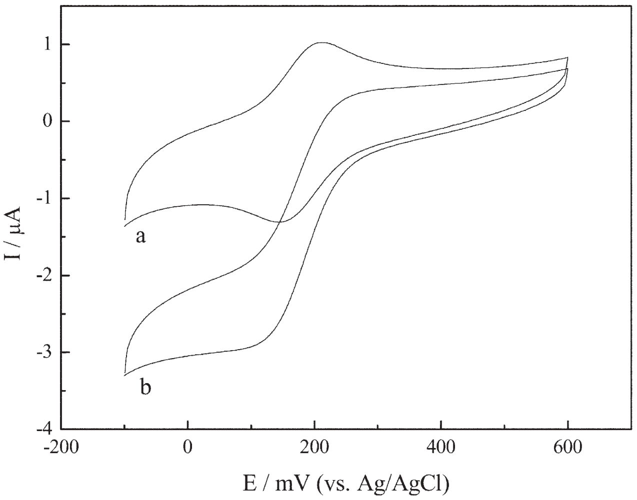
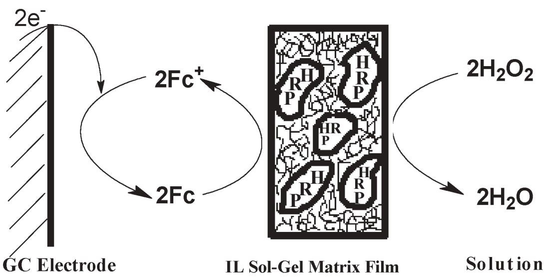


Fig. 1 Cyclic voltammograms of the IL enzyme electrode at a scan rate of 50 mV s^{-1} in 0.05 M PBS (pH 7.0) containing (a) 0, (b) 0.2 mM H_2O_2.

was calculated and was 7.2×10^{-11} mol cm^{-2}. Scheme 1 shows the mechanism of the determination of hydrogen peroxide using the IL enzyme electrode mediated with ferrocene.[27,28] The H_2O_2 in the bulk solution reached the HRP encapsulated in the IL sol–gel glasses through the pores in the matrix and HRP was oxidized to HRP(ox). Then, the HRP(ox) generated by the enzymatic reaction was reduced by ferrocene and HRP regenerated. Finally, the resulting ferrocerium ion (Fc^+) was reduced to ferrocene at the carbon glasses' electrode, producing the reduction current at the same time. After successive scanning, nearly no change was observed on the cyclic votammogram of ferrocene covered with the IL sol–gel matrix, demonstrating the good immobilization of ferrocene in the 3D network frame of the crack-free IL sol–gel matrix. On the other hand, cyclic voltammetry measurements were carried out both in air and N_2 conditions, and similar results were obtained. Therefore, the experiments were performed in air.

Optimization fabrication and operational parameters of the biosensor

Table 1 shows the optimization fabrication and operational parameters of the biosensor. The amount of acid and alcohol was chosen according to previous results, in which high activity of the HRP was obtained.[29] The $BMIM^+BF_4^-$ is a hydrophilic viscous liquid, and the amount of RTIL influences the quality of the enzyme electrode. Excessive amounts of IL could cause an instability of the matrix and the sol–gel matrix might crack if less IL is added. In our study, the ratio 2 : 1 (v/v) of TEOS to IL was chosen. Fig. 2 shows the morphology of the IL enzyme electrode characterized by SEM. The SEM image shows a network-like structure without cracks. The aggregations of the immobilized HRP molecules are distributed regularly and show an island-like structure. The structure facilitates the contact between substrate and the enzymes and results in a good response of the electrodes. The potential of 0 mV was selected as the applied potential for the largest amperometric response obtained at the potential and was expected to minimize possible interferences. On the other hand, the amperometric response of the biosensor was influenced by the pH value of the supporting electrolyte based on the activity change of HRP with different pH. The optimal pH was 7 which was similar to that reported previously for soluble HRP,[30] indicating that the IL sol–gel matrix did not alter the optimal pH value for catalytic behavior of HRP to H_2O_2.



Scheme 1 Mechanism of the determination of H_2O_2 using the IL enzyme electrode mediated with ferrocene. The Fc and Fc^+ were related to the reduced and oxidized form of ferrocene, respectively.

Table 1 Optimal fabrication and operational parameter of the biosensor

	Optimal parameters
The ratio of TEOS to RTIL (v/v)	2
Operating potential/mV *vs.* Ag/AgCl	0
pH of the buffer solution	7.0

Amperometric response of the IL enzyme electrode

Fig. 3A illustrates the typical current–time plot of the IL enzyme electrode on successive changes of aliquot H_2O_2. As the H_2O_2 was added to the stirring PBS solution, the biosensor responded rapidly to the substrate. The IL enzyme electrode could achieve 95% of the steady-state current within 10 s. The response of the IL enzyme electrode was faster than the previous result for HRP in a pure sol–gel matrix,[31] attributing to the uniform porous structure of the IL sol–gel matrix, which induced a fast mass transport barrier and resulted in a rapid diffusion of substrate from the bulk solution to enzyme. Fig. 3B shows the calibration curve of the biosensor. The reaction was first order with respect to the substrate

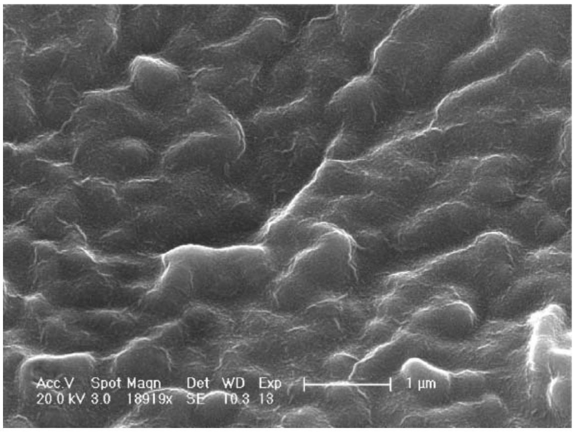


Fig. 2 Scanning electron micrographs of the IL sol–gel film doped with HRP.

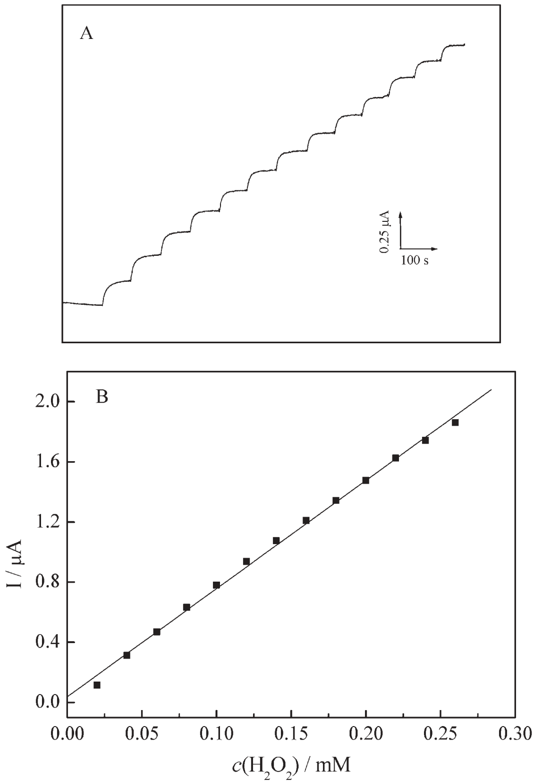


Fig. 3 Typical current–time response curves (A) and the resulting calibration plot (B) for the biosensor upon successive additions of 0.02 mM H_2O_2 into pH 7.0 PBS. Applied potential, 0 mV (*vs.* Ag/AgCl).

concentration when the substrate concentration was low. The linear response range of the sensor to H_2O_2 concentration was from 0.02–0.26 mM with a correlation coefficient of 0.9989. The detection limit of the biosensor was 1.1 μM at a signal-to noise ratio of 3. The apparent Michaelis–Menten constant (K_M^{app}), which gave an indication of the enzyme-substrate kinetics, was calculated to be 2 mM according to the Lineweaver–Burk equation.[32] The K_M^{app} value was smaller than that reported for HRP immobilized on the pure sol–gel matrix.[33] The smaller K_M^{app} value indicated the higher affinity of the IL enzyme electrode to H_2O_2. In addition, the sensitivity of the biosensor to H_2O_2 can also be calculated to be 7.2 μA mM^{-1}.

Reproducibility and stability of the H_2O_2 sensor

The repeatability of the current response of the IL enzyme electrode was examined at an H_2O_2 concentration of 0.2 mM. The relative standard deviation was 3.1% for ten successive assays, showing a fairly good repeatability owing to the good immobilization of ferrocene in the IL sol–gel matrix. The electrode-to-electrode reproducibility of six sensors, prepared under the same conditions independently, shows a good reproducibility with a relative standard deviation of 5.1%.

The IL enzyme electrode was dry stored at 4 °C when it was not in use. The sensor retained 95% of its initial current response after a 20 day storage. The biosensor did not lose its sensitivity in the period of the storage. Therefore, the IL sol–gel composite film is an efficient matrix to retain activity of HRP. The excellent stability of the biosensor can be attributed to three points as follows. On the one hand, as the enzyme was physically encapsulated in the IL sol–gel matrix, large quantities of hydroxyl groups existing in the sol–gel material can form a strong interaction between the enzyme and the matrix, maintaining the activity of the enzyme. On the other hand, the bottleneck effect of the silica sol–gel matrix can prevent the enzyme from leaking out of the thin film. Furthermore, for the existence of IL, improved enzyme stability was obtained as a result of alteration in the protein hydration level and structural compaction.[34]

The influence of chemical interferences was also evaluated in the PBS (pH 7.0) containing 0.02 mM H_2O_2 in the presence of ethanol, glucose, sucrose, oxalic acid, uric acid and ascorbic acid with the same concentration. It was found that ethanol, glucose, sucrose, oxalic acid and uric acid didn't cause any interference in the design concentration of H_2O_2. Ascorbic acid showed a slightly interference because it can reduce the oxidated ferrocene produced by the peroxidase reaction. The results were similar to those reported before.[31,33,35]

Conclusion

In this article, we have introduced a new type of amperometric biosensor based on a type of ionic liquid sol–gel material using the hydrolysis of tetraethyl orthosilicate in 1-butyl-3-methylimidazolium tetrafluoroborate solution. The novel material overcame the respective shortcomings of conventional silica sol for the existence of IL. A crack-free sol–gel matrix was obtained. The uniform porous structure of the IL sol–gel matrix resulted in a fast mass transport. On the other hand, the IL matrix provided a unique microenvironment around the enzyme, in which a high enzyme activity was retained, resulting in high sensitivity and excellent stability of the enzyme. The good properties of the IL sol–gel material implied that the matrix could not only be applied to HRP but also could be extended to other enzymes and bioactive molecules, providing a promising strategy for the development of biosensors.

Experimental details

Reagents

$BMIM^+BF_4^-$ was purchased from Solvent Innovation and was dried in vacuum at 60 °C for 24 h before use. Horseradish peroxidase (HRP, RZ ≈ 3.0, 250 U mg^{-1}) was purchased from BioBasic Incorporation. Tetraethyl orthosilicate (TEOS) was obtained from Sigma (⩾99%). Ferrocene (98%) was purchased from Aldrich. HCl, H_2O_2 (33%) and sodium phosphates were of chemical purity and purchased from Beijing Chemical Regent Corporation. β-D-glucose was from Shanghai Biochemical Reagent Corporation (Shanghai, China). Glucose stock solution was allowed to maturate at room temperature overnight before use. H_2O_2 was titrated by $KMnO_4$ before the activity assay. All other reagents and chemicals were used as received without further purification, and aqueous solutions were deionized water.

Preparation of IL–silica sol

The IL–silica sol was prepared by mixing 1 ml of $BMIM^+BF_4^-$, 2 ml of TEOS, 1 ml of H_2O and 0.05 ml of 0.1 M HCl in a beaker under magnetic stirring at room temperature. After 3 h, a homogenous clear sol was obtained and was subsequently stored at room temperature for about 1 h.

Preparation of the mediated IL–enzyme electrode

Glassy carbon electrodes with a diameter of 3 mm were polished with 1, 0.3, 0.05 μm alumina powder respectively before each experiment and rinsed with deionized water followed by sonicating in 1 : 1 nitric acid, acetone and deionized water successively. Then, the electrode was allowed to dry at room temperature.

For the preparation of the mediated HRP electrode, 10 μl of ferrocene ethanol solution (7.5 mg/1 ml) was dropped on the surface of a glassy carbon electrode and allowed to dry at room temperature. 1 mg of HRP was dissolved in 50 μl of 0.05 M phosphate buffer solution (PBS, pH 7.0) and 20 μl of the mixture was added to 20 μl of the IL silica sol. The above mixture was hand-mixed thoroughly and an homogenous solution was obtained. Then 10 μl of the new mixture was dropped on the surface of a glassy carbon electrode and allowed to dry at 4 °C for 24 h. Before the electrochemical measurements, the mediated IL enzyme electrodes were washed with PBS (pH 7.0). All the enzyme electrodes were washed thoroughly with PBS (pH 7.0) and stored at 4 °C in a dry state unless otherwise specified.

Apparatus and characterization

Cyclic voltammetric and amperometric experiments were carried out on a CHI 630A electrochemical station (CHI. Inc., USA) with a single-component cell. All the electrochemical experiments were performed with a conventional three-electrode system. The enzyme electrode was the working electrode and a Pt wire was used as the counter electrode. The Ag/AgCl (saturated KCl) electrode acted as the reference electrode. In the amperometric experiments, a magnetic stirring bar was used. The scanning electron micrograph (SEM) was made on a XL30 ESEM FEG SEM at an accelerating voltage of 20 kV by dropping the hybrid material onto a glass slice. All the experiments were conducted in ambient conditions.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (No. 20345002, No. 20125513, No. 20435010).

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Aluminium triisopropoxide: An inexpensive and easy-to-handle catalyst of the copolymerisation of cyclohexene oxide with CO_2

Thomas A. Zevaco,* Annette Janssen, Jakub Sypien and Eckhard Dinjus*

Received 7th April 2005, Accepted 21st June 2005
First published as an Advance Article on the web 12th July 2005
DOI: 10.1039/b504798f

Aluminium triisopropoxide, a versatile and cheap oligomeric Lewis acid catalyst, easily reacts with carbon dioxide to build complex oligomeric aluminium alkoxo-alkylcarbonato compounds. A first series of experiments with cyclohexene oxide and CO_2 showed that the catalyst is highly active in the copolymerisation with carbon dioxide and that a satisfactory carbon dioxide insertion takes place when the reaction is run at temperatures between 50 and 80 °C and pressures around 100 bar CO_2. High yields of polyether-carbonates can be obtained (up to 1000 g of copolymer per g aluminium) with molecular weight up to 11 000 g mol^{-1} and a better selectivity of the CO_2-insertion than other aluminium trialkoxides (carbonate to ether linkages ratio: 1 to 3). On the basis of ^{27}Al-NMR spectra it can be seen that the high reactivity of the catalyst is due to a rearrangement of the stable tetrameric aluminium isopropoxide in a more reactive oligomer and, most likely, during the copolymerisation, to a further fragmentation into reactive monomeric species.

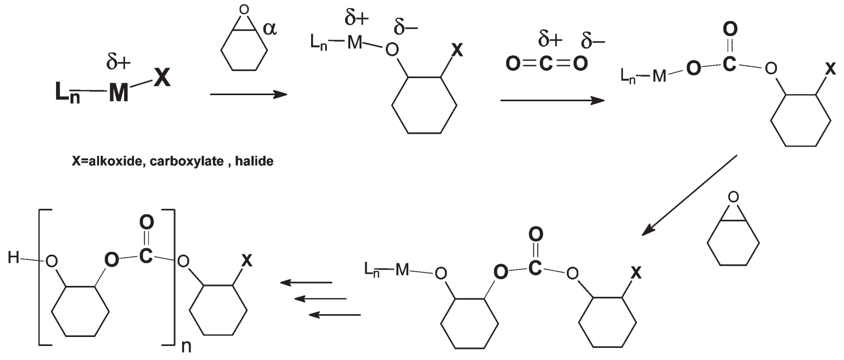
Introduction

Polycarbonates find an ever increasing use as engineering thermoplastics. With characteristics such as a high ductility, a very good transparency, a high heat and impact resistance as well as a high biocompatibility, polycarbonates are considered as specialty polymers and yield to technological applications in many different fields.[1] The usual industrial ways of synthesizing organic carbonates (polymeric and monomeric) involve the reaction between alcohols and reactive C_1-synthons such as phosgene or carbon monoxide.[2]

The problems encountered in the industry by the use of such toxic reagents could be overcome by the use of CO_2 as a C_1 building block. One more incentive is that the so-obtained aliphatic polycarbonates actually display promising characteristics such as a low toxicity and a good biodegradability making them interesting precursors for new materials and a useful complement to the usual polycarbonates.[3] Owing to the high thermodynamic stability of carbon dioxide, the use of catalysts and/or more reactive substrates is necessary. As a consequence the catalyzed insertion of CO_2 into a carbon–oxygen epoxidic bond yielding a carbonate is the topic of a regularly increasing number of publications with some remarkable reviews recently published.[4] Well documented studies of Sakakura *et al.*[5] (dialkyle carbonates), Aida and Inoue,[6] Beckman *et al.*,[7] Darensbourg *et al.*[8] and Coates *et al.*[9] (polycarbonates) indicate that especially molecular compounds based on tin, zinc and aluminium are promising candidates for new catalytic systems dealing with the activation of carbon dioxide. Recent works reported by the research groups of Holmes[10] and Lu[11] showed that chromium and cobalt are also able to successfully catalyze a copolymerisation of epoxides with CO_2.

Transition metal- and main group elements alkoxides are noteworthy candidates for new catalytic systems owing to the fact that a catalytic copolymerization of epoxides and CO_2 requires two complementary coordination sites at the active center (Scheme 1): An acidic site allowing the epoxide to coordinate (metallic core) and a nucleophilic site (oxygen of an alkoxide ligand) able to attack either the carbon atom of the

Forschungszentrum Karlsruhe GmbH, Institut für Technische Chemie-Chemisch-Physikalische Verfahren, Postfach 3640, 76021 Karlsruhe, Germany. E-mail: Thomas.zevaco@itc-cpv.fzk.de; Fax: 07247 82 2244



Scheme 1 Copolymerisation of cyclohexene oxide with carbon dioxide: the ideal case.

CO_2 molecule or an α-carbon atom of the epoxide and yield to the insertion of a new monomer into the reactive metal–oxygen bond consequently increasing the already-formed polycarbonate chain bound to the active center of the catalyst. Generally, the presence of ligands other than alkoxide such as *e.g.* chlorine or alkyle groups yields to a induction period before a copolymerisation reaction actually starts due to a lower reactivity of the metal-halide's respective metal–carbon bond relative to an epoxide insertion and the formation of the resulting reactive alkoxide.

Among the alkoxides tested as catalysts in the synthesis of polycarbonates from CO_2 and epoxides, zinc seems to be the best candidate (high selectivity of the CO_2-insertion, low toxicity). Aluminium alkoxides also displayed an interesting reactivity in respect to the investigated copolymerization. Firstly studied by Aida and Inoue[6] in the 80's, aluminium alkoxides were newly "rediscovered" by Beckman *et al.*[7] and Ree *et al.*[12] These catalytic systems are much more reactive than the zinc-based systems due to their high Lewis acidity. This is, considering the special case of a copolymerization reaction, a problematic issue yielding significant amounts of homopolymerization products in the final copolymers (polyether regions from a ring opening polymerization (ROP) of the epoxide). However these reports together with newly published works of Darensbourg and Billodeaux dealing with the use of aluminium-based salen complexes in copolymerization reactions[13] suggest that aluminium alkoxides have a rich chemistry with epoxides and carbon dioxide.

We focused on aluminium triisopropoxide which was widely applied in the ROP of cyclic anhydrides,[14] ε-caprolactone[15] and lactides[16] and as a catalyst of the Meerwein–Ponndorf–Verley reduction. Aluminium triisopropoxide is cheap, easy to synthesize and to handle and displays a promising reactivity with CO_2 alone affording complex isopropylcarbonato–isopropoxo compounds.[17] Surprisingly, to our knowledge, this bulk aluminium compound has not been systematically tested as a catalyst in copolymerization involving CO_2; we wanted to evaluate its reactivity and applicability in the copolymerization of cyclohexene oxide with carbon dioxide. This paper reports preliminary results on the copolymerization of cyclohexene oxide (CHO) with CO_2 initiated by aluminium triisopropoxide.

Results and discussion

In order to systematically evaluate the reactivity of alkoxides with CO_2 and a wide range of substrates, we developed a kind of "multi-reactor" system involving 4 high pressure reactors equipped with magnetically coupled stirring systems, electrical heating mantles and a computerized P,T-monitoring system. Aluminium triisopropoxide easily catalyses the reaction of cyclohexene oxide with carbon dioxide to form long-chained copolymers in high yields (up to 1000 g copolymer/g Al) with decent molecular weight distributions. A comprehensive list of copolymerization reactions of CHO with carbon dioxide run under different temperatures is presented in Table 1.

Influence of reaction parameters

A first catalytical screening showed that an optimum was found for temperatures between 50 and 80 °C and CO_2

Table 1 Effects of reaction parameters on the aluminium(III) isopropoxide-catalyzed copolymerization (catalyst to substrate molar ratio: 1 to 300)[a]

Entry		T/°C	P/bar	Time/h	Ether/carbonate; % CO_3	M_n	D: M_w/M_n	g polymer/g Al
1		50	83	18	3.6; 21.7	10 097	1.24	726
2		60	96	18	3.3; 23.2	10 390	1.40	725
3		70	114	18	3.2; 23.8	8645	1.23	1060
4		80	101	18	4.3; 18.9	5228	1.50	616
5		90	116	18	3.6; 21.7	4417	1.35	727
6		100	123	18	4.5; 18.2	1967	2.11	670
7		110	135	18	4.5; 18.2	2014	1.76	778
8		120	106	18	4.9; 16.9	1632	2.35	1050
9		90	92	4	5.0; 16.7	1336	2.8	1095
10		90	20	18	10; 9.1	15 000	2.0	579
11	35 g CO_2 10 mL CHO	90	100	18	3.9; 20.4	1612	6.4	218
12	15 mL CHO 5 mL CH_2Cl_2	90	108	18	2.0; 33.3	2189	1.78	238
13	10 mL CHO 10 mL CH_2Cl_2	90	72	18	2.5; 28.6	3691	1.37	105
14	5 mL CHO 15 mL CH_2Cl_2	90	102	18	No reaction; 0	—	—	—
15	10 mL CHO 10 mL Hexane	90	92	18	2.6; 28.5	6826	4.9	139
16	10 mL CHO 10 mL CH_3CN	90	90	18	4; 20	468	4.0	70
17	ref. 7*b* $ClAl(O\text{-}Cy)_2$	**60**	**80**	**24**	**12; 7.3**	**4531**	**2.6**	**340**
18	ref. 7*b* $(C_8H_{17}OCOCH{=}CHOCO)$ $AlCl(O\text{-}Cy)$	**62**	**80**	**24**	**11.7; 7.9**	**3274**	**4.1**	**150**

[a] Experimental conditions (otherwise stated) : CHO: 20 mL, 0.2 mol; CO_2: 24 g (±10%), 0.54 mol; $Al(OiPr)_3$, 135 mg: 0.66 mmol; pressure and temperature read after 4 h.

pressures between 80 and 110 bar with a substrate-to-catalyst molar ratio of 300 to 1 and a CO_2 to substrate molar ratio of *ca.* 2 to 1. This catalytic system appeared to give better results (better reactivity and reproducibility, narrower polydispersity indexes) than related systems reported by Beckman *et al.* which are based on the use of either pure aluminium alkoxides or mixed aluminium alkoxo-carboxylates (entry 17 and 18).[7b]

IR spectroscopy of the reaction mixture (thin film, KBr plates) allows a quick and easy confirmation of the carbon dioxide insertion in the epoxide and the nature of the so-formed carbonate (polycarb. at 1736 cm^{-1} *vs.* cyclic carb. at 1800–1820 cm^{-1}). We observed no formation of cyclic carbonate under the optimal experimental conditions. Operating at higher temperature (>150 °C) yields the formation of both *cis* and *trans* cyclic carbonate (1805 and 1820 cm^{-1} according to the literature[13,18]) as a result of a probable aluminium alkoxide-catalyzed "back-biting" degradation of the copolymer.

The quantification of the CO_2 insertion (*i.e.* the ether- to carbonate-linkage ratio) in the final products can be easily performed *via* ^{1}H-NMR spectroscopy and directly taken from the integration's ratio between methine protons of the oxycarbonyloxy(1,2-cyclohexene) units (4.7 ppm) and the oxy(1,2-cyclohexene) units (3.4 ppm); the rest of the aliphatic backbone producing broad signals in the range of 1.2–2.2 ppm. The isolated copolymers generally contain more ether linkages than carbonate linkages (approx. in a 3 to 1 ratio *i.e.* 25% carbonate in the copolymer, in the best cases). The molecular weights of the isolated copolymers (number average, M_n, and weight average, M_w) and the related polydispersities, were obtained *via* gel permeation chromatography (see Experimental for more details). The molecular weights of the isolated copolymers range from 1600 to 10000 g mol^{-1} and significantly depend on the reaction temperature: higher working temperature yielding shorter copolymer chains (entries 1–8). This evolution has to be compared with the evolution of the CO_2-incorporation into the copolymer which worsens with raising working temperature. It can be seen from Table 1 that, under the chosen experimental conditions, the best CO_2-insertion is achieved at *ca.* 115 bar and 70 °C (entry 5).

Running the copolymerization at lower CO_2 pressure and temperatures affords principally poly(ether-carbonates) with a significant lower carbonate percentage in the final copolymer (entry 10) and high molecular weights (M_n up to 15 000 g mol^{-1}, M_w/M_n ranging from 1.3 to 1.9). Shorter reaction times, others parameters kept constant, yields short copolymers and low carbonate fractions (entry 9), suggesting that the catalyst acts, at the beginning of the reaction, more like a homopolymerisation catalyst. In order to increase the CO_2-uptake in the polymer, we ran a couple of tests at higher pressure (entry 11). Unfortunately operating at higher carbon dioxide pressures afforded short copolymers, in low yields, and did not allow a better CO_2-incorporation into the copolymer. This poor CO_2-insertion into the copolymer despite the higher CO_2 concentration in the reaction mixture might be explained by a lower reactivity of the formed aluminium carbonato species which cannot coordinate the epoxide and further prolong the copolymer chains. The issue of the solubility in a CO_2-rich phase of the active aluminium catalyst bearing the growing copolymer chains has also to be assessed in more detail.

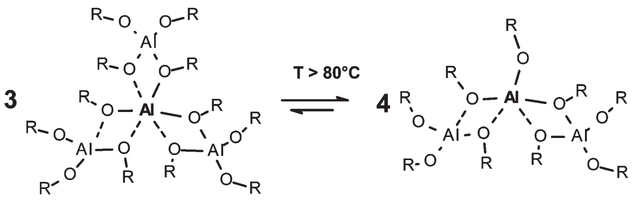
Another approach was found in order to better the CO_2 insertion. Diluting the reaction mixture with additional solvents in order to increase the local CO_2 concentration at the aluminium center and hence decrease the formation of polyether regions in the copolymer actually yields a better CO_2 incorporation into the polymer. The tests run with CH_2Cl_2 as a solvent (up to 15 mL) gave the best results. With 5 mL dichloromethane we could isolate copolymers with 33% carbonate linkages, although significantly shorter that the copolymer obtained with pure CHO (entries 12–14). Likewise, hexane and acetonitrile yield copolymers, although in poor yields and with broad molecular weight distributions (entries 15 and 16). Using a coordinating solvent like *e.g.* acetonitrile, also known to dissolve larger amounts of carbon dioxide, didn't improve the formation of poly(cyclohexene carbonate) (entry 16), the coordination sites of the catalyst being probably partially blocked by acetonitrile molecules.

This sort of optimal "Reaction Window" found during the screening tests is most likely explained by two concomitant facts: on the one hand, according to the work of Beckman *et al.* dealing with the *P*,*T*-phase behavior of cyclohexene oxide/carbon dioxide mixtures,[19] we have to operate from *ca.* 60 bar and 90 °C upward to get a CO_2-rich epoxide phase and eventually a one-phase regime of the reaction and, on the other hand, the tetrameric aluminium triisopropoxide is known to undergo at *ca.* 80 °C a rearrangement of its structure to a more reactive trimeric oligomer[20] (Scheme 2).

The versatility of the coordination geometry of aluminium isopropoxide was already reported in depth in the literature dealing with ring opening homopolymerization.[15,16] Hence working in the optimal *P*,*T*-domain allows the trimeric reactive catalyst to meet both reaction partners: epoxide and carbon dioxide and probably to further disaggregate into even more reactive monomeric species.

^{27}Al-NMR spectroscopy study

Such a rearrangement of the oligomeric aluminium isopropoxide was confirmed using ^{27}Al-NMR spectroscopy which, thanks to its high sensitivity, allows an easy and rapid assessment of the coordination geometry of the aluminium atom(s) involved in the copolymerization. The ^{27}Al-NMR spectra recorded using a sapphire high pressure NMR-tube and small amount of toluene D_8 showed the presence of several aluminium centers involved in the reaction, presenting a more complex situation than reported by Beckman *et al.*[7b] in the case of the chloro-aluminium cyclohexanoxide, ClAl(O-Cy)$_2$,



Scheme 2 Oligomeric nature of the aluminium(III) isopropoxide in the solid state and in non-coordinating solvents.

where the reacting species appears to have a high degree of symmetry and to be partly hexacoordinated.

The initial ^{27}Al-NMR spectrum of aluminium triisopropoxide recorded at RT dissolved in CHO exhibits the two expected signals in an intensity ratio of *ca.* 1 to 3 (Fig. 1a, one sharp signal at 1 ppm ($w_{1/2}$ 80 Hz) assigned to the central octahedrically coordinated aluminium atom of the tetramer and a broad signal ($w_{1/2}$ 1500 Hz) found at *ca.* 58 ppm attributed to the three terminal tetrahedrally coordinated aluminium atoms[21]). After being submitted to CO_2 pressure (60 bar, sample-shaker 15 min) and then heated at 80 °C, two relevant features could be noticed in the NMR spectra: the rapid decrease of the sharp signal of the octahedrally coordinated central atom of the tetrameric $Al(OiPr)_3$ and the appearance of two new signals at higher field in the ^{27}Al-NMR spectrum (Fig. 1).

We could also observe a rapid thickening of the reaction mixture due to the formation of the copolymer which eventually yields a solid. The recorded ^{27}Al spectra remained unchanged afterwards, the catalyst being embedded in a copolymer matrix.

In Fig. 1b, two broad signals at 64.8 ppm and 2.15 ppm which can be quite easily attributed to tetrahedral and octahedral aluminium atoms, account for aluminium alkoxo species carrying growing copolymer chains. Two new broad signals appearing at −10.6 and −14.6 ppm can be tentatively attributed to new aluminium alkylcarbonate species also supporting copolymer chains and exhibiting trigonal bipyramidal and octahedral coordination geometries. Owing to the lack of comprehensive NMR data concerning aluminium alkoxo-alkylcarbonates or aluminium oxo-alkylcarbonates, it is not easy to unequivocally attribute those new signals. A relevant example of an upfield shift in the negative region of the ^{27}Al spectra for octahedral Al compounds was reported in the literature dealing with the complexation of aluminium(III) by phosphinate ions, $(H_2O)_4Al(H_2P{=}O(OR))$.[22] In our case, the proposed structures assume the intramolecular complexation of aluminium atoms by the carboxylic oxygen atom from the oxycarbonyloxy(1,2-cyclohexene) repeating units (Scheme 3).

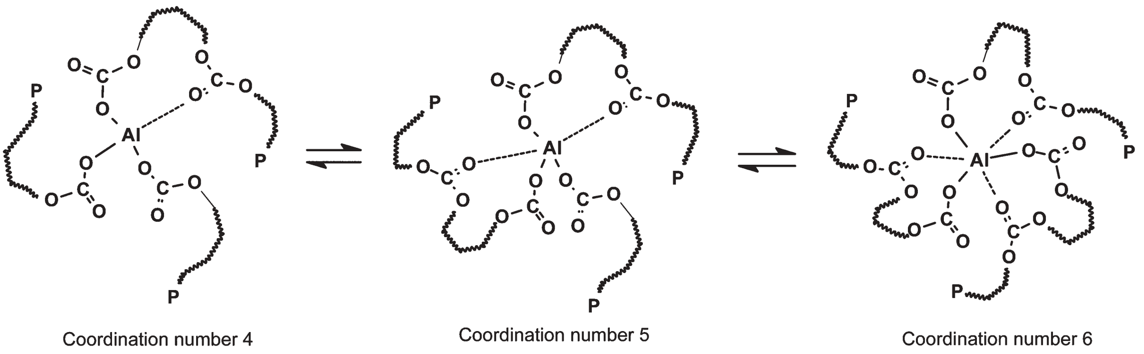
The intramolecular coordinative interactions between aluminium and growing copolymers more likely implies the carbonate groups than the ether linkage of the poly(ether-carbonate) due to the bulkiness of the 1,2-cyclohexylene fragment. ^{27}Al-NMR studies reported by Jerome and coworkers which deal with aluminium isopropoxide catalyzed ROP of lactide[16] and caprolactone[15] showed some similarities with the considered copolymerization reaction. Unfortunately ^{13}C high pressure NMR studies concomitantly run with the ^{27}Al-NMR studies didn't deliver enough information (partly due to the low sensitivity of ^{13}C and the thickening of the solution) to give more details on the structure of the active sites involved in the catalysis.

^{13}C-NMR spectroscopy study

Standard ^{13}C-NMR spectroscopy of the final products logically confirmed the CO_2 incorporation into the polymer: The isolated polyether-carbonates display one signal at *ca.* 155 ppm in benzene D_6 (resp. 154 ppm in $CDCl_3$) in the carbonate region of the spectrum (Fig. 2).

Additionally the ^{13}C-NMR spectroscopy allows the investigation of the stereochemistry of the incorporation of the cyclohexene oxide monomer into the polymer backbone. Cyclohexene oxide being a meso compound, its controlled opening can yield either isotactic or syndiotactic polymers. Dealing with the formation of pure poly(cyclohexene carbonate), the research groups of Nozaki[23] and Coates[24] proposed a new interpretation of the ^{13}C-NMR spectra of poly(cyclohexene carbonates) and could precisely attribute the different ^{13}C-signals to different carbonate fragments' geometries and so easily access the tacticity of a given copolymer: the ^{13}C-NMR signal for the carbonate carbons of isotactic fragments is observed at 153.7 ppm whereas the signals for carbonate carbons of syndiotactic fragments are observed at higher field between 153.3 and 153.1 ppm. In our case, the ^{13}C-NMR analysis of the purified copolymers (see Fig. 2b) showed a broad single signal (0.2 ppm, *ca.* 20 Hz) at *ca.* 154 ppm in the carbonate region of the spectrum.

Comparing the NMR spectra of a purified poly(ether-carbonate) with the models reported by Nozaki and coworkers[22b] seems to indicate that the copolymers isolated in our studies displayed an isotactic structure. Unfortunately it is not easy to ascertain the stereochemistry of the reaction as easily as in the case of a complete CO_2 insertion yielding pure poly(cyclohexene carbonate). This broad signal results most likely from the superposition of different discrete carbonate signals. We propose that the carbonate signal at *ca.* 154 ppm is the sum of different signals of carbonate fragments separated



Coordination number 4

Coordination number 5

Coordination number 6

Scheme 3 Proposed structures for the new aluminium species (high field, ^{27}Al-NMR) formed during the copolymerization reaction.

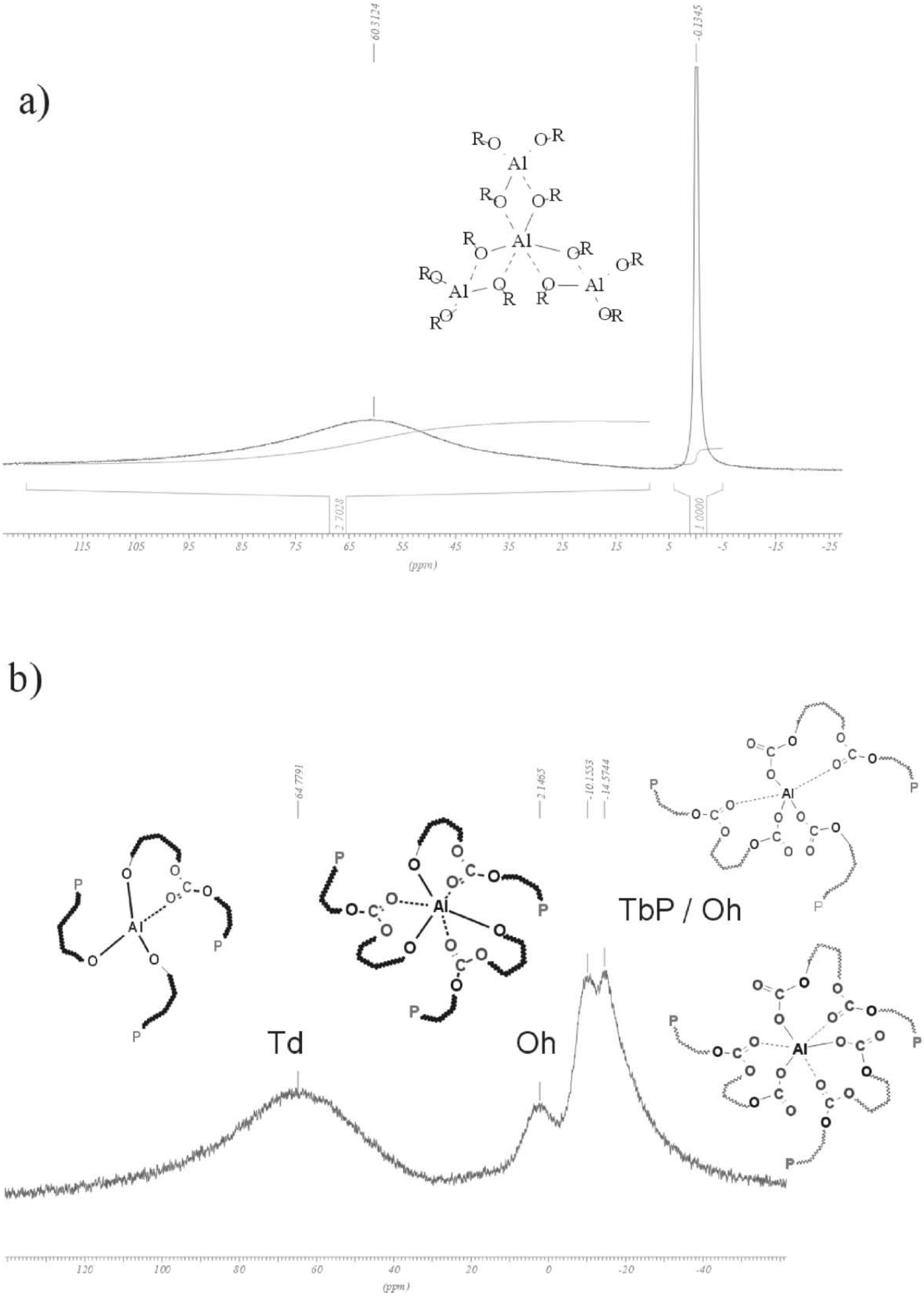


Fig. 1 ^{27}Al-NMR spectra of aluminium tri-isopropoxide (a) in solution (CHO/toluene D_8) under argon; (b) in solution (CHO/toluene D_8) under CO_2 atmosphere at *ca.* 80 °C.

by pure polyether regions as it can be expected for a statistical copolymer. The lack of selectivity "copolymerization *vs.* homopolymerization" already reported for other aluminium alkoxides[7] is due to the "fragmentation" of the initial aluminium catalyst. The aluminium triisopropoxide oligomers are too labile to allow an efficient control of the reaction of

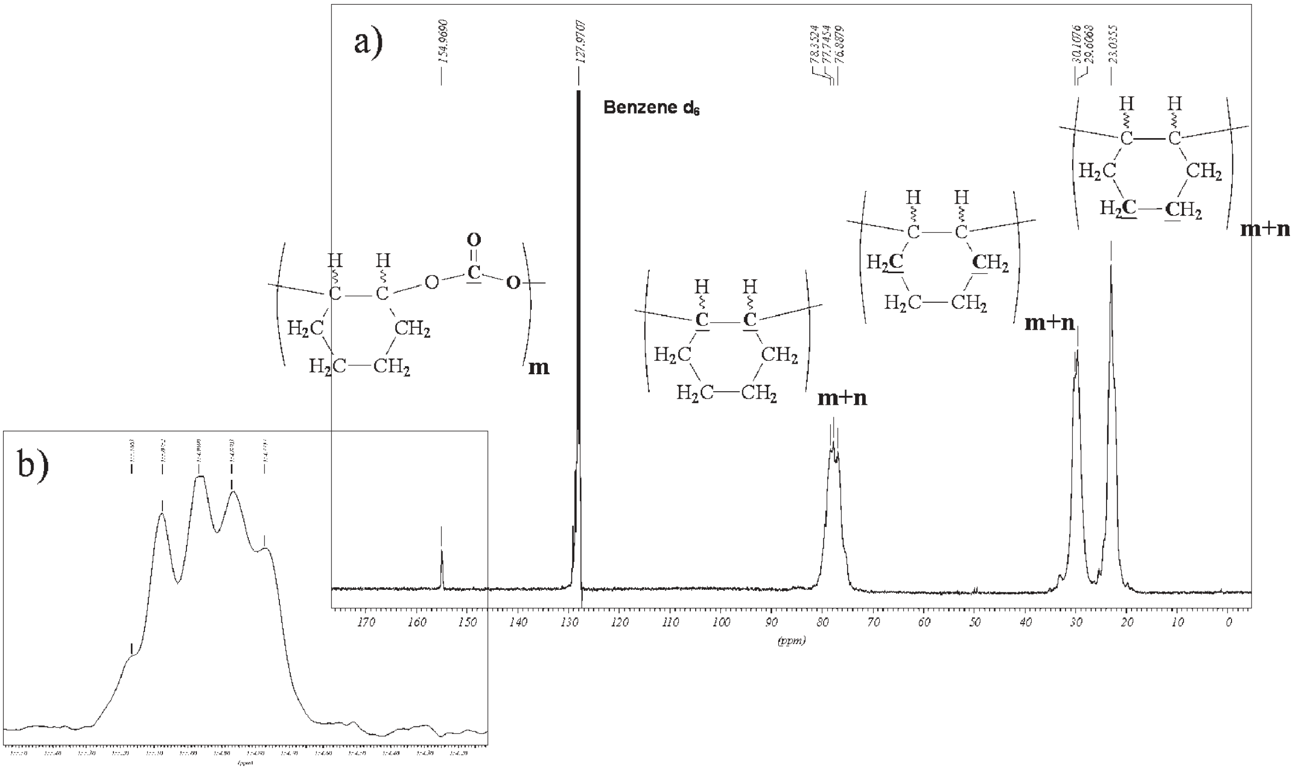


Fig. 2 (a) ^{13}C-NMR spectrum (solution, benzene D_6) of a poly(ether-carbonate) obtained from the copolymerisation of CHO with CO_2; (b) enlargement of the carbonate region of the ^{13}C-NMR spectrum.

CO_2 with epoxides. More work is actually in progress to optimize the reaction (*e.g.* repress the formation of alkoxide oligomers) and spectroscopically characterize the nature of some intermediates. The dependence of the carbon dioxide insertion on the nature of different co-catalysts is also under further study.

Conclusions

We have demonstrated in this contribution that the cheapest aluminium alkoxide, aluminium triisopropoxide, can be used to effectively catalyze the copolymerization of cyclohexene oxide with carbon dioxide to produce high yields of poly(ether-carbonates) with no traces of monomeric cyclohexene carbonate. This investigation showed that we can use a cheap and non-toxic alkoxide to produce high amounts of poly(ether-carbonates) in reasonable time for further applied studies (derivatization of the copolymers, miscibility with other polymers, *etc.*). The reactivity and selectivity can be, to a certain extent, tuned through an appropriate temperature and solvent choice. This system, although not considerably better in term of selectivity of the carbon dioxide insertion than other reported aluminium alkoxide-based catalytic systems, stands out for its unique synthetic simplicity.

Experimental

Commercially available Al(III)isopropoxide (Aldrich) was reagent grade and, after a NMR-control, used without further purification. Cyclohexene oxide ((Aldrich) was distilled under vacuum over CaH_2. CH_2Cl_2 and MeOH were dried by standard methods and store under argon. Carbon dioxide (Messer Griesheim, purity 99.9990%) was used without further purification. NMR deuteriated solvents (chemotrade) were degassed, dried over molecular sieves Linde 4 Å and stored under argon.

Analyses

The NMR spectra of the catalysts and copolymer solutions in C_6D_6, $CDCl_3$ or toluene D_8 were recorded with a Varian Inova 400 spectrophotometer (^{1}H 399.81 MHz, ^{13}C: 100.54 MHz). TMS was used as internal standard (^{13}C, ^{1}H) with different deuteriated solvents. The chemical shifts δ (in ppm) are then given relative to the residual signal of the solvent for all these runs. The ^{27}Al-NMR (104.207 MHz) spectra of the aluminium catalysts as solutions in toluene D_8 were obtained at the following operating conditions: sweep width (25 kHz, non-decoupling mode, relaxation delay 0.4 s, pulse width 8.7 µs and number of scans 3000). The FIDs were processed using an exponential multiplication. For all measurements the chemical shifts were reported relative to a saturated solution of aluminium nitrate $Al(NO_3)_3$ in D_2O used as a standard. High-pressure NMR experiments were run in a 5 mm HP NMR sapphire tube fitted with titanium-based alloy valves (90% Ti, 6% Al, 4% V).[25] Infrared spectra (KBr pellets and thin films between KBr plates) were recorded on a BIORAD 175C FT-IR spectrometer in the range of 4000–400 cm^{-1}. Molecular weights and MWD of the polymers were measured using a Merck gel permeation chromatograph (Lichograph

Gradient pump L-6200 with thermostat, LaChrom RI detector L-7490), equipped with a pre-column and 2 different columns (PSS SDV 5 m 1000 Å and 100 Å). THF was used as eluent, and calibration was performed using polystyrene standards.

General procedure for autoclave experiments

We developed a kind of ''multi-reactor'' system involving 4 high pressure reactors equipped with magnetically coupled stirring systems and electrical heating mantles (magnetic stirrer + aluminium block + thermoelement). Temperature and pressure were monitored *via* a digital multimeter (HP 34970A) connected to a personal computer.

The copolymerization was typically conducted in 70 mL stainless steel (SS316) autoclaves equipped with standard Swagelock fittings and a separate loop made of stainless steel tubing which can be operated independently of the main reactor body. Because of the general moisture sensitivity of metal alkoxides and in order to get reproducible results, the reactors were heated at 100 °C and purged with argon prior to use. Cyclohexene oxide (5–20 mL) was transferred (with or without co-solvent) into the autoclave, the reactor was then pressurized with CO_2 (60 bar) for a few minutes under stirring and afterwards weighed, the procedure was repeated until the desired CHO/CO_2 molar fraction was reached (10–35 g CO_2). Owing to the high Lewis acidity of aluminium isopropoxide and thus its ability to also catalyze a homopolymerization of the epoxide, the catalyst was firstly dissolved under argon into *ca.* 1 ml toluene (or CH_2Cl_2) introduced into the separate loop and was then, establishing the communication with the epoxide/CO_2 mixture in the autoclave, allowed to diffuse into the reaction mixture through gravity. This procedure though time-consuming was necessary to get reproducible results and clearly evaluate the reactivity of the catalyst in pure copolymerization reactions. In order to evaluate the practicality of this ''catalyst-in-the-loop'' method, we firstly run a couple of copolymerization reactions in a stainless steel autoclave fitted with Borosilicate windows (MPI für Kohlenforschung, Mülheim, SS-316, 220 mL, max 220 °C–200 bar) and could see that the forming copolymer under the chosen experimental condition remained a thick solution at the bottom of the reactor. Slowly decompressing the autoclave yields the poly(ether-carbonate) as a white foam which can be easily dissolved in CH_2Cl_2.

After the reaction time the autoclaves were cooled down to RT (water bath) and the carbon dioxide slowly vented, under stirring, in a fume hood. After opening the remaining solid/syrupy solution was dissolved in dichloromethane and the aluminium catalyst was then hydrolyzed with 10% HCl aqueous solution (50–100 ml) and separated from the copolymers *via* a separating funnel. The organic extracts were washed two times with saturated $NaHCO_3$ and dried with $MgSO_4$. The short-chained copolymers were then separated from the long-chained ones *via* repeatedly dissolving in CH_2Cl_2 and consecutive precipitation in methanol. The white amorphous solids which have at the end of the purification process a talcum-like appearance are easily soluble in $CHCl_3$, benzene, toluene and are insoluble in acetone or water.

Acknowledgements

The authors are thankful for financial support from the program ''Sustainability and Technology'' of the Helmholtz Association of National Research Centres. This work was also partially supported by the German Federal Ministry of Education and Research within the context of a ''Sonderforschungsbereich'' with the University of Heidelberg (SFB 623).

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Metal-coated nanoscale TiO_2 catalysts for enhanced CO_2 photoreduction

Pankaj Pathak, Mohammed J. Meziani, Linette Castillo and Ya-Ping Sun*

Received 19th May 2005, Accepted 14th July 2005
First published as an Advance Article on the web 5th August 2005
DOI: 10.1039/b507103h

Nanoscale TiO_2 particles embedded in the hydrophilic cavities of Nafion membrane films were coated with silver for significantly improved photoconversion of CO_2. The primary product from the photocatalytic reduction became methanol, with the overall conversion efficiency higher than that without the silver coating. These catalytic films are also stable chemically and photochemically, reusable in repeated reactions. The results from the characterization of the nanoparticles and the use of films with different silver loadings are presented and discussed.

Metal-coated semiconductor nanoparticles have attracted much attention for various applications, especially in heterogeneous photocatalysis relevant to the solar energy conversion and environmental cleanup.[1–3] For example, noble metals such as silver, gold, copper, platinum, and palladium were deposited onto a TiO_2 surface for improved photocatalytic activities,[4,5] in particular with evaluations in the photochemical production of hydrogen and photoreductive conversion of CO_2.[6–8] These composite photocatalysts have been based primarily on the metal coating of colloidal semiconductors.[9,10] However, a widely acknowledged issue with the colloidal particles is their significant aggregation in suspension, which not only reduces the active surface area but also compromises the desired photoreaction conditions due to severe light scattering effect of the aggregates.[10,11] Several strategies for addressing the issue have been explored in the preparation of photocatalysts based on metal-coated nanoscale semiconductors.[12–16] Anpo *et al.* hosted TiO_2 in zeolite cavities for subsequent platinum coating,[13] while Lianos *et al.* prepared TiO_2 nanoparticle films ($\sim$15 nm) on a glass substrate *via* the sol–gel method, followed by the photodeposition of silver nanoparticles (35–60 nm).[14] Separately, Wu *et al.* applied an improved sol–gel method to the preparation of nanoscale copper-loaded titania, in which the copper precursor was added during the hydrolysis and polycondensation.[16] These methods required high-temperature calcination to increase the crystallinity of the nanoparticles, which was generally accompanied by significant agglomeration of the nanoparticles. The agglomeration resulted in metal-coated catalyst particles of various sizes and shapes, but also negatively affected their photocatalytic activities.[17,18]

We recently used commercially available perfluorinated ionomer membrane Nafion films, or more specifically the hydrophilic structural cavities in the membrane films, to host TiO_2 nanoparticles and demonstrated the superior performance of these optically transparent catalytic films in the photoreduction of CO_2.[19] We have taken advantage of the homogeneous particle dispersion in the films to photochemically coat the TiO_2 nanoparticles with nanoscale silver. These films containing the silver-TiO_2 composite nanoparticles remained optically transparent, serving as improved photocatalysts for the CO_2 photoconversion.

The procedure for the preparation of TiO_2 in nanoscale cavities of Nafion membrane has been reported previously.[20,21] Briefly, cleaned Nafion-117 membrane films (Du Pont Co.) were soaked in a solution of $Ti(OC_3H_7)_4$ in isopropanol (0.5 M) for 48 h. Upon repeated washing and rinsing with isopropanol and acetone, the films were immersed in boiling water for the hydrolysis of $Ti(OC_3H_7)_4$ to form TiO_2 nanoparticles in the membrane structure.[20] A typical UV/vis absorption spectrum of the TiO_2-loaded Nafion films is shown in Fig. 1. The onset for the band-gap transition is at $\sim$380 nm. The X-ray powder diffraction result is consistent with nanoparticles of anatase TiO_2. According to the TEM imaging (cross-sectional slices of the films from microtomy),[20,21] the embedded TiO_2 nanoparticles in different films have similar average sizes, generally about 4 nm in diameter, with size distribution standard derivations around 0.5 nm. The TiO_2 loadings in the films are

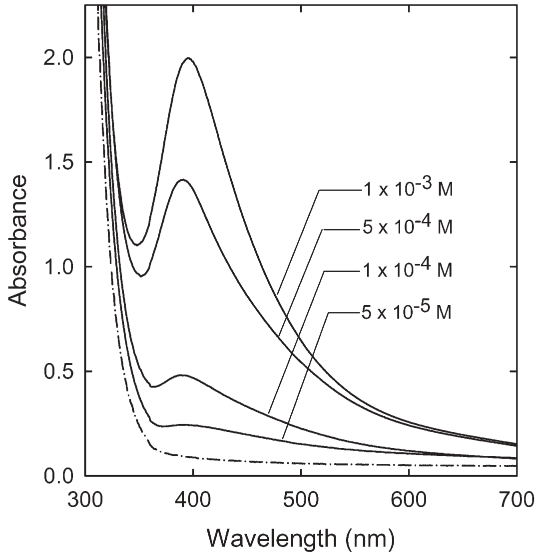


Fig. 1 UV/vis absorption spectra of Nafion membrane films containing TiO_2 without (-··-) and with (—) silver coating. The corresponding silver salt solution concentrations used for the coating are as marked.

Department of Chemistry and Laboratory for Emerging Materials and Technology, Clemson University, Clemson, South Carolina, 29634-0973, USA

also similar, ~10 wt% (1.3 mmol-TiO_2/g-Nafion) estimated gravimetrically and confirmed by UV/vis absorption results.

The TiO_2 nanoparticles embedded in Nafion membrane films were coated with silver metal *via* photolysis.[14] In a typical experiment, a piece of the film containing TiO_2 nanoparticles was soaked in an aqueous $AgNO_3$ solution with known concentration for 30 min. The film surface was washed carefully with water and then dried, followed by photoirradiation with a xenon arc source for 20 min. After thoroughly cleaning with water (to remove any residual silver salt), the film was brownish, consistent with the presence of nanoscale silver (plasmon absorption), but remained optically transparent. The amount of silver deposition was dependent on the concentration of the $AgNO_3$ solution used for soaking the film. As shown in Fig. 1, the plasmon absorption of nanoscale silver in the films after photolysis increases with the soaking $AgNO_3$ solution concentration. However, the presence of TiO_2 nanoparticles was necessary (acting as photosensitizer) for the silver photoreduction in Nafion membrane cavities. No photodeposition of silver was observed in the $AgNO_3$-soaked film without TiO_2 nanoparticles because of no direct light absorption by the silver cation. Thus, the nanoscale silver (made evident by the significant plasmon absorption) was associated with the embedded TiO_2 nanoparticles in Nafion membrane films, as confirmed by scanning transmission electron microscopy (STEM, Hitachi HD-2000) analyses.

The specimens for STEM imaging were ultra-thin slices (<100 nm in thickness and 0.2 mm^2 in area) from cross-sectionally cutting the films in microtomy. Since the high-resolution TEM characterization of embedded TiO_2 nanoparticles and their distribution was available before the silver coating,[19,20] the focus of the STEM analysis was on the coated silver by taking advantage of the Z-contrast imaging mode. Shown in Fig. 2 are essentially distributions of silver in the films. The objects of 6–7 nm are likely TiO_2 nanoparticles well-coated with silver, thus larger than the average size of as-prepared TiO_2 nanoparticles, while the smaller ones are due to silver on partially coated TiO_2 nanoparticles. The silver distributions in the two specimens shown in Fig. 2 reflect the silver loadings in their respective Nafion membrane films. In addition, the association of silver with TiO_2 at the nanoscale was confirmed by the energy dispersive X-ray (EDX) analysis of randomly selected regions in the image, all of which indicated the substantial presence of Ti together with Ag.

The photocatalytic activities of the silver-coated TiO_2 nanoparticles embedded in Nafion membrane films were evaluated in the photoreduction of CO_2. Illustrated in Scheme 1 is the configuration of the catalyst films in the high-pressure optical cell of the reaction setup. In a typical experiment, the cell was purged with CO_2 gas for 30 min before it was filled with liquid CO_2 to a pressure of 2000 psi, followed by photoirradiation with a xenon arc source (990 W) through a water filter for 5 h. Immediately after the depressurization, water (2 mL) was added to the cell.[19] The resulting aqueous solution contained methanol as the major reaction product according to HPLC and ^{1}H NMR analyses. This was different from the result from the use of TiO_2 nanoparticles without silver coating in the same configuration, in which the major product was formic acid.[19] The silver coating of TiO_2 nanoparticles also significantly increased the efficiency of CO_2 photoreduction, as compared in Fig. 3. The enhancement may be attributed primarily to an improved separation of the photoinduced charge carriers.[22] The noble metal reduces the recombination rate by acting as a sink for the photogenerated electrons, while holes remain on the TiO_2 surface.[23,24]

A significant advantage with the catalytic films is that they can be stacked conveniently (Scheme 1) to increase the quantity of photocatalysts in the reaction. As shown in

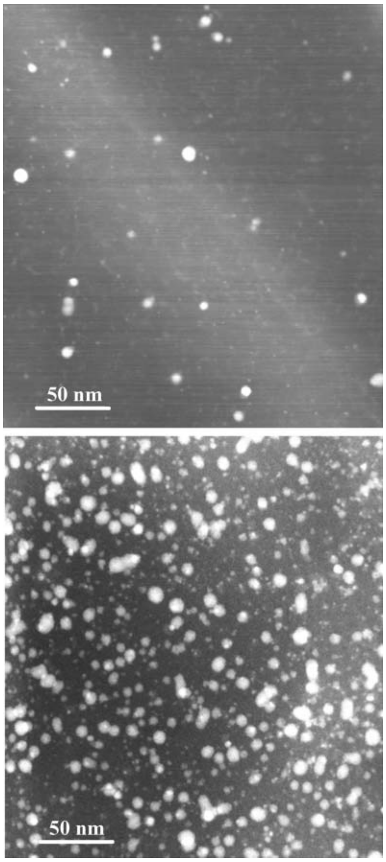
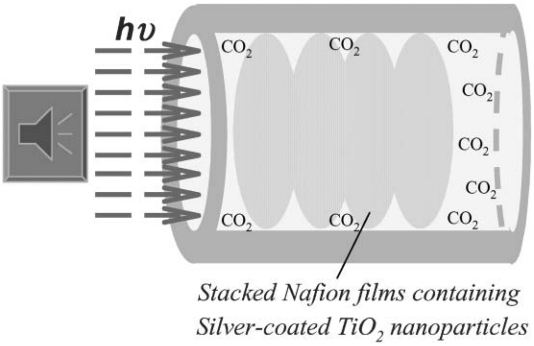


Fig. 2 STEM images (Z-contrast mode) for a cross-sectional view of the silver distribution in Nafion membrane films containing silver-coated TiO_2 nanoparticles of lower (top) and higher (bottom) silver loadings.



Scheme 1 Experimental setup for the photoreduction of liquid CO_2 with Nafion films containing silver coated TiO_2 nanoparticles as photocatalyst.

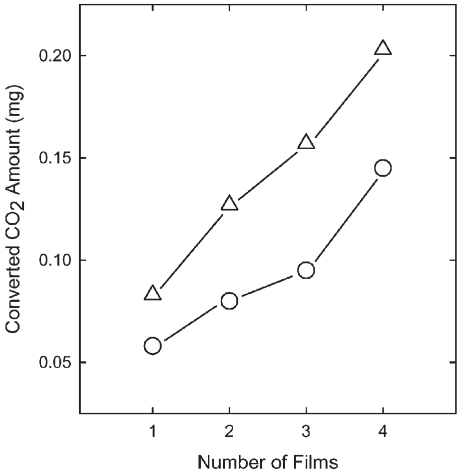


Fig. 3 The photoconversion of CO_2 as a function of the number of stacked catalytic films with (△) and without (○) the silver coating of the embedded TiO_2 nanoparticles.

Fig. 3, the use of 4 stacked films tripled the photoconversion of CO_2 in comparison with that of one film under the same reaction conditions. A longer irradiation time also increased the photocatalytic conversion of CO_2. For example, with the use of 4 stacked films, the irradiation for 20 h resulted in a total conversion of ~0.4 mg CO_2, which is significantly higher than that achieved with similar films without silver coating of the embedded TiO_2 nanoparticles under comparable experimental conditions.[19]

The silver coating enhances the photocatalytic activities of TiO_2 nanoparticles, but the nanoscale silver alone is hardly a potent catalyst for the photoreduction of CO_2. In fact, the use of Nafion membrane films containing only silver nanoparticles (synthesized *via* chemical reduction of silver salt),[21] under the same photocatalytic reaction conditions resulted in only trace amount of CO_2 conversion, namely that the presence of TiO_2 nanoparticles is necessary for the photoreduction. For silver-coated TiO_2 nanoparticles, an increase in silver loading initially benefitted the photoconversion of CO_2, but then became a hindrance (Table 1). The latter may be attributed in part to the absorption by the silver coating, which serves as an inner filter that decreases the light harvesting by the TiO_2 nanoparticles.

Another major advantage with the nanoscale photocatalysts embedded in Nafion membrane films is their photostability. The films exhibited no deterioration in photocatalytic activities over an extended photoirradiation time (at least 50 h). They were also reusable multiple times in repeated photoreduction reactions of CO_2. For example, after a piece of Nafion film containing the silver-coated TiO_2 nanoparticles was used in a photoreduction experiment, it was washed thoroughly with deionized water and then reused in the second photoreduction under the same experimental conditions. The product yields obtained in the two experiments were hardly distinguishable. The reusing of the film was repeated again, and the photoreduction results remained similar. This is different from that with the use of colloidal photocatalysts, for which significant deterioration in their photocatalytic activities is well-documented in the literature.[11]

Table 1 Photocatalytic conversion of CO_2 with different film catalysts[a]

$AgNO_3$ solution conc./mM[b]	HCOOH/mg	CH_3OH/mg	Converted CO_2/mg
0.05	0.016	0.032	0.059
0.1	0.020	0.051	0.089
0.5	0.031	0.071	0.13
1	0.017	0.044	0.077

[a] Two stacked Nafion films containing TiO_2 nanoparticles with different silver loading. [b] Used for loading silver in the coating of TiO_2 in Nafion membrane *via* photolysis.

Even the silver deposition on TiO_2 nanoparticles is reversible. The silver coating may be removed from the TiO_2 nanoparticles in Nafion membrane films by immersing the films in a concentrated nitric acid solution, in which the TiO_2 nanoparticles and Nafion films remain stable. The removal of silver turned the films colorless. Then, TiO_2 nanoparticles in the same films could be coated with silver again *via* photolysis, and the characterization of the resulting films yielded similar results. The photocatalytic activities for the CO_2 conversion were also comparable with those of the original Nafion films with silver-coated TiO_2 nanoparticles. The reversibility may find many other applications beyond photocatalysis, such as the recovery of silver from wastes and other samples.[25,26]

In summary, the TiO_2 nanoparticles embedded in Nafion membrane films could be coated with silver without changing the particle dispersion and the optical transparency of the catalytic films. The silver coating resulted in significant improvements in the photocatalytic conversion of CO_2, with methanol becoming the primary reduction product. These films are also stable chemically and photochemically, reusable in repeated photocatalytic reactions. The same coating method may be used in the preparation of other metal-coated semiconductor nanoparticles homogeneously dispersed in optically transparent ionomer membrane films for photocatalysis applications.

Acknowledgements

Financial support from the DOE (DE-FG02-00ER45859) and the Center for Advanced Engineering Fibers and Films (NSF-ERC at Clemson University) is gratefully acknowledged. L.C. was a participant of the Summer Undergraduate Research Program sponsored jointly by NSF and Clemson University.

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Stability and activity of immobilised penicillin G amidase in ionic liquids at controlled a_w

Alessandra Basso, Sara Cantone, Paolo Linda and Cynthia Ebert*

Received 4th May 2005, Accepted 21st June 2005
First published as an Advance Article on the web 19th July 2005
DOI: 10.1039/b506230f

Despite the great interest in ionic liquids as novel solvents for biocatalysis, there is still no clear idea of their influence on the stability and the activity of enzymes. Here we analysed the activity and stability of PGA in six different ionic liquids, having different cations ([bmim] and [omim]) and anions ($CH_3OSO_3^-$, PF_6^- and BF_4^-). To be active in ionic liquids, PGA-450 requires an acceptable hydration ($a_w > 0.60$), as in organic solvents. PGA is highly stable in [bmim][PF_6] and [bmim][BF_4], and catalytic activity, assayed by studying the synthesis of the amide of L-phenylglycine methyl ester with methyl phenylacetate, in these ILS is comparable to that obtained in toluene.

Introduction

Twenty years have passed since the pioneering work of Klibanov on the activity of enzymes in non-aqueous media.[1] It is now accepted that performing reactions in organic solvents offers undoubted advantages over aqueous media, mainly in reactions that are thermodynamically unfavoured.[2,3]

The advantages given by the use of enzymes in organic solvents can also be achieved in ILs, and the use of room-temperature ionic liquids (RTILs) can be a good strategy to couple the advantages of biocatalysis in non-aqueous media to the increasing demand for clean technologies. The application of ionic liquids, as novel solvents or co-solvents for organic catalysis[4,5] or biocatalytic transformations, has attracted considerable interest and many reviews on the subject are available.[6–9] In addition, the increasing number of examples of successful applications of product extraction with supercritical fluids from ionic liquids offer the possibility to recycle both biocatalyst and IL, thus allowing the design of environmentally friendly integrated biocatalysis/separation processes.[10–13]

Numerous examples of biocatalysed processes in ILs presenting 1,3-dialkylimidazolium or N-alkylpyridinium cations together with a non-coordinating anion have been reported. Lipases and esterases,[14–22] proteases (α-chymotrypsin, thermolysin or subtilisin),[20,23–25] and recently also epoxide hydrolases,[26] peroxidases,[27] alcohol dehydrogenases[28] or cutinases[19] were demonstrated to be active in ILs, showing comparable or higher activity than in organic solvent.

Despite the growing number of examples of biocatalysed applications in ILs, the understanding and study of the influence of the properties of ILs on the enzymes has lagged behind. It is really important to develop a rational approach towards the use of ILs in order to exploit them as novel solvents also in industrial processes. Most IL properties such as polarity, hydrophobicity and solvent miscibility can be tuned through appropriate modification of the cation and anion.[29]

Penicillin G amidase is one of the most widely used enzymes for the industrial production of β-lactam antibiotics. In recent years, it has been demonstrated that PGA is highly active in apolar organic solvents, catalysing resolution and protection of L-amino acids and amines,[30–34] and, more recently, also the protection of D-amino acids.[35] This biocatalyst, which offers highly attractive opportunities in amine resolution, has a great potential in ILs, since these alternative solvents offer a highly solvating, yet non-coordinating medium in which a large number of organic and inorganic solutes can be dissolved.[36]

Results and discussion

In the present work we have evaluated the activity and stability of immobilised penicillin G amidase (PGA-450) in 1-alkyl-3-methylimidazolium ILs. In order to tune the properties of the ionic liquids, two different cations, 1-butyl-3-methylimidazolium and 1-octyl-3-methyl-imidazolium, were combined with inorganic (PF_6^- and BF_4^-) and organic ($CH_3OSO_3^-$) anions so that six different ionic liquids were synthesised according to reported procedures (Scheme 1).[20]

The characterisation by NMR spectroscopy, compared to reported data,[37] confirmed the formation of the desired compounds.

After the chemical synthesis, the water content (determined by Karl Fischer titration) and the water activity (a_w, measured in a sealed vessel) of the ILs were determined (see Table 1).

As previously reported, the anion greatly influences the water miscibility and the maximum amount of retained water. Literature data show that both [$C_n$mim][PF_6] and [omim][BF_4] are only partially water miscible (see footnote† for details about water miscibility),[29,38,39] while [$C_n$mim][CH_3OSO_3] and [bmim][BF_4] are all water soluble.

Laboratory of Applied and Computational Biocatalysis, Dipartimento di Scienze Farmaceutiche, Università degli Studi, Piazzale Europa 1, 34127 Trieste, Italy. E-mail: ebert@units.it; Fax: +39 04052572; Tel: +39 0405583110

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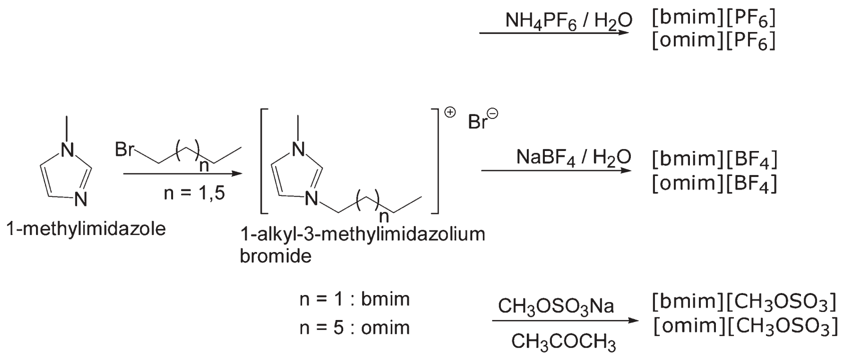
† Water is only partially miscible in [bmim][PF_6] and [omim][PF_6]: 11700 and 6666 ppm respectively.[29] Holbrey and Seddon reported that for [$C_n$mim][BF_4], those with $n < 6$ are water soluble, although to varying degrees: water is partially miscible in [omim][BF_4]: 110000 ppm.[46]



Scheme 1 Synthesis of ILs.

Table 1 Characterisation of ILs and their effect on enzyme stability

		a_w [b]			
Ionic liquid	Water content [a] (%)	IL	IL/PGA-450	IL/PGA-450 (H_20, %)	$k_{in}{}^c/h^{-1}$
[bmim][PF_6]	1.5	0.30	0.62	0.66 (1)	$<10^{-5}$
[omim][PF_6]	0.3	0.30	0.76	0.80 (1)	0.35
[bmim][BF_4]	0.3	0.17	0.40	0.70 (10)	$<10^{-5}$
[omim][BF_4]	2.0	0.21	0.53	0.76 (5)	0.0065
[bmim][CH_3OSO_3]	11.4	0.19	0.40	0.71 (20)	0.13
[omim][CH_3OSO_3]	7.3	0.20	0.44	0.78 (20)	0.41

[a] Water content was determined by Karl Fischer titration. [b] Water activity was measured using a hygrometer (DARAI, Trieste) after 24 h equilibration. Conditions: T = 30 °C, 1 mL of pure IL, with the addition of 100 mg of wet PGA-450 (containing 35 μL water) and additional water, which is indicated in parentheses. [c] Inactivation constants were determined by suspending the enzymatic preparation in pure IL and measuring the residual activity through the NIPAB assay.

However, for any given solvent, there will be a characteristic relationship between water activity (a_w) and water concentration. Water activity depends on the specific interactions between solvent and water molecules, and in solvents that solubilize water these interactions are favorable, resulting in low values of a_w. In poor solvents, at a given molar fraction of water, a_w is much larger.[40]

ILs with the more hydrophobic [PF_6] as anion, have the higher a_w (0.30), while tetrafluoroborates and methylsulfates show lower and similar a_w, despite differences in the water content.

It is widely reported that the activity of enzymes as amidases, glycosidases and proteases in non-aqueous media, organic solvents or ionic liquids, strongly depends on the water activity (a_w) of the system.

We have previously demonstrated that, in dichloromethane or toluene, immobilised PGA is active at a_w above 0.5, showing a maximum of activity at a value of about 0.8.[31]

From data in Table 1 it clearly appears that the ionic liquids, as obtained, could not be directly used for PGA biocatalysis, since they are not sufficiently hydrated (in all cases a_w is lower than 0.3).

The enzymatic preparation used in the present study is a covalently immobilised form of penicillin G amidase (PGA-450) that is supplied in a wet form (it contains 35% water). Thus, when PGA-450 was suspended in the ionic liquids, the a_w of the overall system increased. Since the hydrophobic character of the ionic liquid is mainly determined by the anion,[29] PGA-450 gives the highest values of a_w (0.62 and 0.76) when suspended in [bmim][PF_6] and [omim][PF_6]. The cation influences the a_w of the system, but to a minor extent. ILs with [omim] as the cation give, as expected, higher values of a_w if compared to the analogous ILs with [bmim].

As a consequence, we added the necessary amount of water to the systems formed by PGA-450 in ILs in order to obtain a_w compatible with enzyme activity: in [bmim][PF_6] and [omim][PF_6] the addition of 1% water was sufficient, whereas for the more hydrophilic ILs, [bmim][BF_4] and [omim][BF_4], the addition of 10% and 5% water, respectively, was necessary to obtain a_w of 0.70–0.76. Both [$C_n$mim][CH_3OSO_3] required the addition of 20% water to obtain values of a_w compatible with enzyme activity (Fig. 1). Our data are in agreement with results obtained by Kragl and co-workers, who reported that

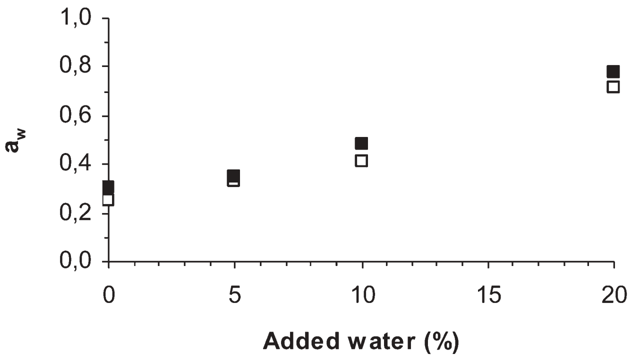


Fig. 1 Variation, upon addition of water, of the a_w of the system formed by PGA-450 suspended in [bmim][CH_3OSO_3] (empty squares) and [omim][CH_3OSO_3] (black squares). Conditions: 1 mL IL, 100 mg PGA-450, system equilibrated for 24 h at 30 °C.

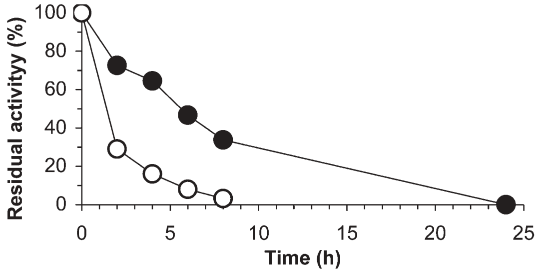


Fig. 2 Stability (activity over time) of PGA-450 suspended in [bmim][CH_3OSO_3] (black circles) and [omim][CH_3OSO_3] (empty circles).

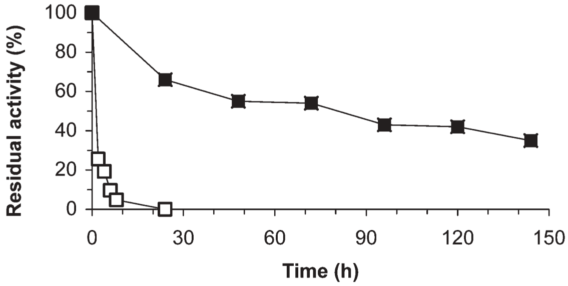


Fig. 3 Stability (activity over time) of PGA-450 suspended in [omim][BF_4] (black squares) and [omim][PF_6] (empty squares).

ILs with an alkyl sulfate as the anion required percentages of water of up to 50% to obtain a water activity of about 0.8.[41,42]

Stability of PGA in ILs

The effect of ILs on the stability of immobilised PGA was assayed by suspending the enzyme in ILs, and determining the activity over time. After being suspended in ILs, the enzyme was washed with buffer and the residual activity was determined by the standard NIPAB assay.[43]

PGA-450 is a highly stable preparation and, when suspended in toluene or buffer, it fully maintains its original activity for up to several weeks. Results reported in Table 1 show that PGA-450 suspended in [bmim][CH_3OSO_3] or [omim][CH_3OSO_3] completely lost its activity in a few hours (see Fig. 2). The stability of the biocatalyst was also assayed in the presence of additional water (20% added water) and the inactivation constants were found comparable. The inactivation of the biocatalyst in these ILs presumably depends on unfavourable interactions of methyl sulfate anion with PGA. Detrimental effects of alkyl sulfates are already reported in the literature.[21,41,42]

The cation exerts a strong effect on the denaturation of PGA-450, since the enzyme is more stable when suspended in the ILs with [bmim] as cation. PGA suspended in [bmim][PF_6] or [bmim][BF_4], maintained its activity after one week of exposure, showing a stability similar to that observed in organic solvent (toluene) or Kpi buffer. The [omim] cation causes a gradual loss in activity of the enzyme suspended in [omim][PF_6] or [omim][BF_4] (Fig. 3). This effect was more evident in the more hydrophobic [omim][PF_6], with an inactivation constant that was almost fifty times higher than the k_{in} observed for [omim][BF_4].

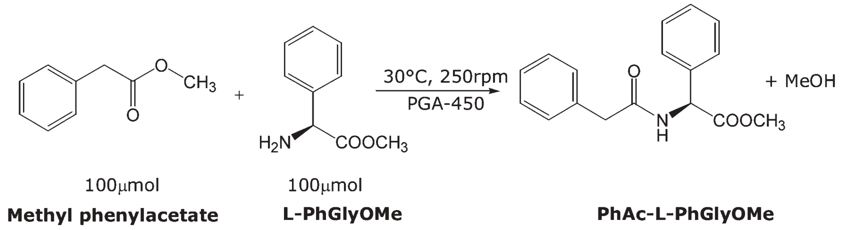
In contrast to the behaviour in organic solvents, where the enzyme stability increases at high values of log*P*, the stability in ILs seems to be due to a fine balance between the hydrophobicity and the hydrophilicity of the cation and anion.

Recently it has been suggested that the enzymatic activity of lipase CALB in ionic liquids results from a fine balance of hydrogen bond-accepting and donating properties, that maintain structural integrity of the α-helices and β-sheets and prevent the protein unfolding.[22] Furthermore, other factors, such as free volume contributions, ionic interactions and confinement effects, may also contribute to protein stabilization,[43] and spectroscopic studies of stability of α-chymotrypsin confirm that the enzyme stabilization is associated with structural changes of the protein.[24] These studies regard the enzyme in the native form, while PGA-450 is immobilized. We are currently investigating the possibility of applying alternative techniques suitable for studying insoluble enzymes.

Catalytic activity of PGA in ILs

The catalytic activity of PGA-450 was assayed in ILs by studying the synthesis of the amide of L-phenylglycine methyl ester with methyl phenylacetate working at equimolar concentrations of reagents (Scheme 2).

The results are reported in Table 2, together with the data obtained in toluene. In order to perform the reactions at comparable a_w values, water was added to the ILs as shown in Table 1. No addition of water was necessary to PGA-450 suspended in toluene (the ratio of biocatalyst in solvent was maintained at 10% w/v), since, in these conditions, the water retained by the enzymatic preparation is sufficient to guarantee optimal a_w for synthetic PGA activity ($a_w \sim 0.8$).[31] The synthesis of the amide in [bmim][PF_6] and [bmim][BF_4]—where PGA-450 is fully stable—was efficient as in toluene (complete synthesis without any side reaction or hydrolysis of reagents or product), using the same amount of catalytic units. The reactions carried out in toluene and [bmim][PF_6] were



Scheme 2 PGA catalysed synthesis of PhAc-L-PhGlyOMe in ILs and toluene.

Table 2 Viscosity data and synthetic activity of PGA-450 in ILs and organic solvent (toluene)

Solvent	Viscosity (cP, 30 °C)	Initial rate/μmol min^{-1}
Toluene	0.590[45]	1.244
[bmim][PF_6]	204[29]	1.027
[bmim][BF_4]	91[29]	0.813

Conditions: 1mL solvent, 100 μmol of PhAcOMe and L-PhGlyOMe, 30 °C in blood rotator. Before the addition of reagents 1% and 10% water was added to [bmim][PF_6] and [bmim][BF_4] respectively.

complete in three hours, whereas reactions performed in [bmim][BF_4] were complete after 24 hours.

From results reported in Table 2, it is remarkable to observe that, despite the high viscosity of both ILs that critically affects mass transfer, the initial rates determined in [bmim][PF_6] and [bmim][BF_4] were similar to that measured in toluene.

The synthetic activity was also assayed in the other ionic liquids. Figs. 4 and 5 show the yields achievable in [omim][PF_6] and [omim][BF_4] at different a_w values. At high values of a_w the initial rate of the reaction increases, and prevails on the inactivation effect of the ILs.

The inactivation rate of PGA-450 caused by [omim][BF_4] is lower than the rate observed for [omim][PF_6], so that, at $a_w = 0.76$, complete conversion can be achieved thanks to favourable kinetics. Nevertheless, a small decrease in the a_w of the system reduces the synthetic rate in [omim][BF_4], causing the reaction to stop at 80% ($a_w = 0.70$); at $a_w = 0.53$ the yield is only 20%. In [omim][PF_6], at $a_w = 0.76$ or 0.80, yields of 15% or 60% were obtained respectively.

[bmim][CH_3OSO_3] and [omim][CH_3OSO_3] require an addition of 20% water to reach optimal a_w values, thus obtaining systems that are more similar to co-solvent aqueous mixtures. PGA-450 is highly stable in apolar solvents,[31] but, as with many other enzymes, it suffers the presence of polar co-solvents. When suspended in ILs–water mixtures the activity of PGA-450 decreased rapidly and no synthetic activity was observed.

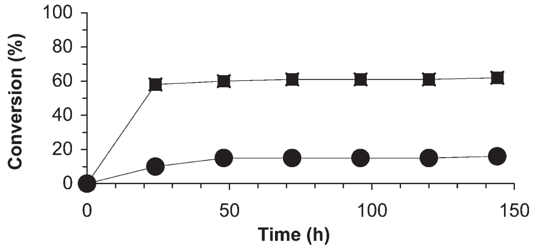


Fig. 4 Synthesis of PhAc-L-PhGlyOMe in [omim][PF_6]. Conditions: T = 30 °C, 1 mL IL, 100 mg PGA-450, 0 μL H_2O, $a_w = 0.76$ (black circles), 10 μL H_2O, $a_w = 0.80$ (black squares).

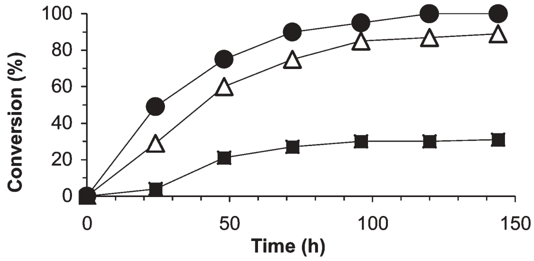


Fig. 5 Synthesis of PhAc-L-PhGlyOMe in [omim][BF_4]. Conditions: T = 30 °C, 1 mL IL, 100 mg PGA-450, 0 μL H_2O, $a_w = 0.53$ (black squares), 30 μL H_2O, $a_w = 0.70$ (empty triangles), 50 μL H_2O, $a_w = 0.76$ (black circles).

Conclusions

Here we report on a study of activity and stability of immobilised penicillin G amidase (PGA-450) in different ionic liquids. The study was conducted in ionic liquids with 1-alkyl-3-methylimidazolium cations, looking at the effect of both the anion and the alkyl chain of the cation on the activity, and most importantly, on the stability of the enzyme. The stronger effect on the stability of the biocatalyst is given by the anion. PGA is fully stable in [bmim][PF_6] and [bmim][BF_4] and shows good synthetic activity in these ionic liquids. The initial rates of synthetic reactions performed in these ILs and in toluene are of the same order of magnitude. The reactions were performed in ILs at equimolar concentrations of reactants, without any observed side hydrolysis.

Similarly to its behaviour in hydrophobic organic solvents, PGA in ILs requires an optimal hydration (a_w of about 0.80). This value was obtained by adding between 1% and 20% water, depending on the nature of the ILs.

ILs with methylsulfate as the anion require more than 20% added water to achieve an a_w value compatible with enzyme activity. However, even at optimal hydration of the enzyme, no synthetic activity was observed due to the strong denaturising effect of such ILs.

In conclusion, despite the high viscosity of these media, the synthesis catalysed by PGA is highly efficient in ionic liquids, thus achieving a promising basis for the development of environmentally benign methodology. We believe that a rational screening among ILs could lead to their successful application in the resolution of racemic compounds, in particular for the production of enantiomerically pure or enriched amines.

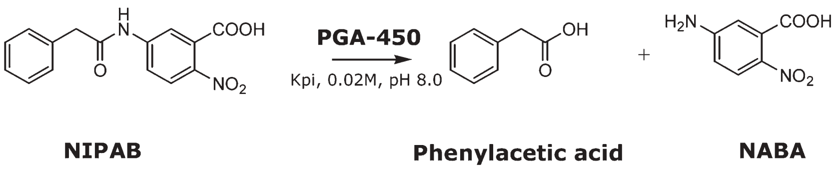
Experimental

Materials

All chemicals, 1-methylimidazole, 1-bromobutane, 1-bromooctane, ammonium hexafluorophosphate, sodium tetrafluoroborate, sodium methylsulfate, 5-amino-2-nitrobenzoic acid (NABA), cinnamyl alcohol, methyl phenylacetate (PhAcOMe), L-phenylglycine methyl ester hydrochloride (L-PhGlyOMe·HCl) and phenylacetyl chloride were obtained from Sigma-Aldrich–Fluka or Lancaster and were used without further purification.

Toluene (RUDI PONT) used in enzymatic reactions was previously dried over molecular sieves (4 Å). Ethyl acetate and acetone were from Sigma-Aldrich. Ultrapure water (18.2 Ω cm^{-1}) was obtained with MilliQ Plus (Millipore) and was used for HPLC mobile phases preparation and in the enzymatic reactions.

PGA-450 (35% water content), kindly donated by Roche, consists of penicillin G amidase from *Escherichia coli*



Scheme 3 Activity assay of PGA by hydrolysis of the chromogenic NIPAB substrate to phenylacetic acid and NABA.

covalently immobilised on a polymer, the chemical structure of which is not disclosed by the supplier.

Synthesis of NIPAB [2-nitro-5-(phenylacetylamino) benzoic acid]

5-Amino-2-nitrobenzoic acid (NABA, 0.05 mol, 9.1 g) was combined in a flask with 2,6-lutidine (0.1 mol, 10.7 g) in CH_2Cl_2 and maintained in an ice bath. Phenylacetyl chloride (0.075 mol, 22.5 g) was added dropwise and the mixture was maintained under stirring overnight. The organic phase was washed with HCl 0.1 M, NaOH 0.1 N and H_2O, then the organic solvent was dried on $MgSO_4$ and removed under reduced pressure. 6.37 g of brown crystals were obtained (70% yield). NIPAB was characterised by ^1H NMR and ^{13}C NMR and data compared to literature.[44]

Preparation of free L-PhGlyOMe from the corresponding hydrochloride salt

Equimolar amounts (0.005 mol) of L-PhGlyOMe·HCl and $NaHCO_3 \cdot 10H_2O$ were suspended in CH_2Cl_2 and the mixture was stirred for 30 min at 30 °C, then filtered. CH_2Cl_2 was removed under reduced pressure. 0.7 g of yellow oil was obtained (85% yield). L-PhGlyOMe was characterised by ^1H NMR and ^{13}C NMR and data compared to literature.[34]

Water content

The water content of each preparation was determined by Karl Fischer titrations.

Water activity

The water activity a_w of ILs, of ILs with PGA-450 and of ILs with PGA-450 and added water (Table 1) was measured using a hygrometer Darai (Trieste, Italy). Measurements were carried out by sealing the sensor into the open end of 5 mL glasses vials, thermostatted at 30 °C, until constant reading. All samples were previously equilibrated for 24 h.

Enzyme stability in ionic liquids

20 mg of PGA-450 were added to 1 mL of ILs. Samples were mixed in an orbital shaker at 25 °C and 180 rpm, then filtered (0.45 μm) and washed with Kpi buffer (KH_2PO_4, 0.02 M, pH 8.0).

2 mL Kpi buffer and 1 mL of NIPAB solution (0.015 M in KH_2PO_4) were added to the enzyme and samples were mixed for 10 minutes at 180 rpm in an orbital shaker (Scheme 3).

Samples were then filtered (0.45 μm) and analysed with a UV-spectrophotometer (Perkin Elmer Lambda 20). The conversion of NIPAB to NABA was detected at 405 nm ($\varepsilon_{405} = 9090$). One unit of activity was defined as the amount of enzyme required to produce 1 μmol of NABA at 25 °C.

Synthetic activity in ionic liquids

PGA-450 (100 mg), ionic liquid (1 mL) and water (where indicated) were mixed in a 5 mL glass vial. Reactions were started upon addition of 100 μmol of both L-PheGlyOMe (16.5 μL) and PhAcOMe (14.4 μL). Reactions were incubated in a thermostatted orbital shaker, at 30 °C.

Samples of 100 μL from the reaction were dissolved in 900 μL of MeCN and were analysed by HPLC (HPLC Gilson-351 equipped with a C-18 Supelco column, flow 1 mL min^{-1}, elution isocratic: MeCN : H_2O = 40 : 60, 0.02% trifluoroacetic acid).

The formation of the product was evaluated by using an internal standard (cinnamyl alcohol).

Acknowledgements

Thanks are due to M.I.U.R. (Rome, Italy) for financial support to P. L. We thank Prof. L. Gardossi for fruitful discussions.

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$ZrOCl_2·8H_2O$ catalysts for the esterification of long chain aliphatic carboxylic acids and alcohols. The enhancement of catalytic performance by supporting on ordered mesoporous silica

Kshudiram Mantri, Kenichi Komura and Yoshihiro Sugi*

Received 29th March 2005, Accepted 14th July 2005
First published as an Advance Article on the web 3rd August 2005
DOI: 10.1039/b504369g

$ZrOCl_2·8H_2O$ is an efficient catalyst for the esterification of long chain carboxylic acids with long chain primary and secondary alcohols. Supporting $ZrOCl_2·8H_2O$ on ordered mesoporous silica enhances the catalytic activity of the esterification. The esters of C_{10}–C_{18} normal acid and alcohol are obtained in high yield by supported $ZrOCl_2·8H_2O$ on MCM-41 although the yield of the esters decreases with the chain length of acids and alcohols. The esterification of less reactive branched acids and secondary alcohols gives excellent to good yield of the corresponding esters over supported catalysts. Zirconium cation cluster $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ is suggested as the catalytic active species. The enhancement of catalytic performance by supporting on MCM-41 is due to increased contact between substrate and catalyst because the cation cluster is highly dispersed over MCM-41 with high surface area. The hydrophobic properties of mesoporous silica accelerate the removal of water during the esterification by controlling hydrated water in the cluster. The catalyst is recyclable without significant loss of activity.

1. Introduction

Fatty (aliphatic) acid esters are used as raw materials for emulsifiers or as oiling agents for foods, spin finishes and textiles; lubricants for plastics; paint and ink additives and for mechanical processing; personal care emollients; surfactants and base materials for perfumes; Japanese candles, *etc.*[1] They are also used as solvents, co-solvents, and oil carriers in the agricultural industry.[1] They are produced conventionally by the esterification of acids and alcohols using a mineral acid, such as concentrated sulfuric acid, as the catalyst.[2,3] These catalysts suffer from inherent problems of corrosiveness, high susceptibility to water, difficulty in catalyst recovery, environmental hazards, waste control, *etc*. It is therefore important to replace these hazardous and polluting acids with environmentally friendly catalysts, which are active under mild conditions, and which can be easily recovered and reused.

Homogeneous acids (*viz.* mineral acids) and Lewis acids are well known catalysts in esterification.[4–9] However, large amounts of catalyst and large excesses of either carboxylic acids or alcohols are essential to achieve high yields of esters by these methods.[4] It is not of practical interest to use large amounts of catalyst and condensing reagents to promote green chemistry.

In recent decades much work has been done to find heterogeneous acid catalysts; however, the success of the catalysis was limited to esters less than C_{10} in either carboxylic acids or alcohols. Some of examples of solid catalysts for the esterification of long chain aliphatic acids with methanol are tungsten oxide supported on zirconia,[10] Ti^{4+}-modified montmorillonite,[11] and Fe^{3+}-modified montmorillonite.[12] Recently, functional organic sulfonic acids on mesoporous silicas were proposed for the esterification of long chain aliphatic acids with methanol[13,14] and with glycerine.[15–18]

Much recent research has investigated homogeneous and heterogeneous catalysts in the esterification of carboxylic acids with equal amount of alcohols.[19–30] However recent research by Yamamoto *et al.* reports the direct ester condensation of equimolar carboxylic acids and alcohols using Hf(IV) and Zr(IV) chlorides.[25–28] Bartoli *et al.* described $Zn(ClO_4)_2·6H_2O$ catalyzed condensation of nearly equimolar amount of acids and alcohols without solvent.[29] These catalysts are easy to recycle and reuse because the metal salts spontaneously separate from the product solution after esterification.

However, no promising method has previously been identified to combine long chain acids and long chain alcohols. This situation prompted us to examine a "green" synthesis of esters with long chain carboxylic acids and alcohols, which have carbon numbers higher than 10. In our preliminary communication, we described the efficient catalytic performance of $ZrOCl_2·8H_2O$ in the esterification of long chain carboxylic acids and alcohols.[30] However, $ZrOCl_2·8H_2O$ was less active for the esterification of branched acids and alcohols.

Our aim has been to improve the catalytic performance of $ZrOCl_2·8H_2O$ in esterification. In this paper, we describe a novel enhancement of catalytic performance of $ZrOCl_2·8H_2O$ by supporting on ordered mesoporous silica, such as MCM-41, in the esterification of long chain aliphatic acids and alcohols.

Department of Materials Science and Technology, Faculty of Engineering, Gifu University, Gifu 501-1193, Japan.
E-mail: sugi@apchem.gifu-u.ac.jp; Fax: +81 58 293 2653;
Tel: +81 58 293 2597

2. Experimental

2.1. Chemicals

Stearic acid (1-octadecanoic acid), palmitic acid (1-hexadecanoic acid), myristic acid (1-tetradecanoic acid), lauric acid (1-dodecanoic acid), capric acid (1-decanoic acid), isostearic acid (2-heptylundecanoic acid), stearyl alcohol (1-octadecanol), cetyl alcohol (1-hexadecanol), myristyl alcohol (1-tetradecanol), lauryl alcohol (1-dodecanol), capryl alcohol (1-decanol), 2-tetradecanol, 2-dodecanol, and 2-decanol were purchased from Tokyo Kasei Kogyo Co. Ltd., Japan. Oleic acid (*Z*-9-octadecenoic acid), elaidic acid (*E*-9-octadecenoic acid), and linoleic acid (*Z,Z*-9,12-octadecandienoic acid) were purchased from Sigma-Aldrich Inc. 2-Hexadecanol was supplied by Acros Organics. *m*-Xylene, mesitylene, and tetralin were purchased from Nacalai Tesque, Japan. Diethylbenzene (*o*- : *m*- : *p*- = 5 : 66 : 29; average ethyl number in benzene ring = 2.014) was supplied from Nippon Steel Chemicals Ltd. All chemicals were used without further purification.

2.2. Catalysts

$ZrOCl_2 \cdot 8H_2O$ was purchased from Kanto Chemical Co. Inc., Japan. Ordered mesoporous silica, MCM-41, FSM-16, and SBA-15 silica was synthesized as per the procedure reported in the literature.[31–33] The supported $ZrOCl_2 \cdot 8H_2O$ catalysts were prepared by impregnation on ordered mesoporous silica such as MCM-41, FSM-16, SBA-15, amorphous silica, alumina, zirconia, and activated charcoal from ethanol solution according to the following procedure: the support (1 g) was dispersed in a 10 ml ethanol solution with a specified quantity of $ZrOCl_2 \cdot 8H_2O$, and stirred for 6 h at room temperature. Solvent was evaporated *in vacuo* to dryness at 30 °C, and the catalysts were also dried *in vacuo* at 110 °C for 4 h. The catalyst was abbreviated as $ZrOCl_2$(20)/MCM-41, where the value in parenthesis is wt% loading $ZrOCl_2$ on MCM-41.

2.3. Esterification

The esterification was carried out in a single-necked, round-bottomed flask (100 ml) equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted with a reflux condenser. An equimolar mixture of substrates (long chain primary acids and alcohol) (6 mmol) and catalyst ($ZrOCl_2$/MCM-41: 0.115 g; $ZrOCl_2 \cdot 8H_2O$: 0.12 mmol) in 40 ml of solvent (benzene, toluene, *m*-xylene, mesitylene, diethylbenzene and tetralin) were charged into the round-bottomed flask. The mixture was heated to reflux temperature and water generated by the reaction removed. After 12 or 24 h, the temperature of the resulting reaction mixture was cooled to ambient temperature, and the catalyst was separated from the reaction mixture by filtration. GC analysis determined the conversion and product yield. Product purification was achieved by column chromatography using silica gel (70–230 mesh) eluted by 10% ethyl acetate in hexane.

The products were analysed by GC (Shimadzu Gas Chromatograph 14A, Ultra-1 (25 m × 0.3 mm) capillary column) equipped with FID. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Varian Inova 400 spectrometer. Elemental analyses of all esters were carried out at the Center for Organic Elemental Microanalysis, Kyoto University.

Analytical data of typical esters are listed below, and others are listed.[30]

2-Dodecyl isostearate. IR (neat): 1737 cm^{-1}. ^1H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (br tr, 9H), 1.27 (br s, 40H), 1.38–1.42 (br m, 4H), 1.56–1.64 (br m, 4H), 2.28–2.34 (m, 1H), 4.04–4.08 (tr, *J* = 6.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.07, 22.64, 22.68, 25.94, 27.47, 28.73, 29.18, 29.25, 29.31, 29.52, 29.53, 29.55, 29.58, 31.82, 31.89, 32.58, 45.86, 64.11, 176.65. Elemental analysis: Calcd for $C_{30}H_{60}O_2$: C, 79.58; H, 13.36. Found: C, 79.56; H, 13.38.

2-Tetradecyl isostearate. IR (neat): 1735 cm^{-1}. ^1H-NMR (400 MHz, $CDCl_3$): δ = 0.87–0.88 (br tr, 9H), 1.27 (br s, 44H), 1.40–1.44 (br m, 4H), 1.56–1.65 (br m, 4H), 2.27–2.34 (m, 1H), 4.04–4.08 (tr, *J* = 6.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.03, 22.60, 22.68, 25.94, 27.46, 28.70, 29.17, 29.27, 29.32, 29.51, 29.53, 29.56, 29.57, 31.81, 31.88, 32.57, 45.88, 64.10, 176.70. Elemental analysis: Calcd for $C_{32}H_{64}O_2$: C, 79.93; H, 13.42. Found: C, 79.95; H, 13.45.

2-Hexadecyl isostearate. IR (neat): 1728 cm^{-1}. ^1H-NMR (400 MHz, $CDCl_3$): δ = 0.86–0.89 (br tr, 9H), 1.26 (br s, 48H), 1.39–1.43 (br m, 4H), 1.57–1.66 (br m, 4H), 2.27–2.36 (m, 1H), 4.05–4.07 (tr, *J* = 6.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.07, 22.61, 22.67, 25.95, 27.47, 28.72, 29.17, 29.28, 29.31, 29.51, 29.53, 29.55, 29.57, 31.81, 31.87, 32.57, 45.86, 64.10, 176.69. Elemental analysis: Calcd for $C_{34}H_{68}O_2$: C, 80.24; H, 13.47. Found: C, 80.28; H, 13.50.

2-Decyl oleate. IR (neat): 1739 cm^{-1}. ^1H-NMR (400 MHz, $CDCl_3$): δ = 0.87–0.90 (br m, 9H), 1.23–1.30 (br s, 32H), 1.45–1.48 (br m, 4H), 1.55–1.62 (br m, 4H), 2.22–2.33 (m, 2H), 4.85–4.91 (m, 1H), 5.31–5.35 (br m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.07, 22.67, 25.00, 25.93, 27.14, 28.65, 29.09, 29.12, 29.25, 29.31, 29.51, 29.59, 29.65, 29.68, 31.90, 34.36, 64.35, 129.70, 129.94, 173.86. Elemental analysis: Calcd for $C_{28}H_{54}O_2$: C, 79.55; H, 12.88. Found: C, 79.32; H, 12.64.

2.4. Recycling and reuse of the catalysts

Recycling and reuse of the catalysts was examined by esterification of palmitic acid with cetyl alcohol using $ZrOCl_2$(20)/MCM-41. Catalyst recovery was achieved by the following procedure: the catalyst was separated by filtration from the reaction mixture, washed with warm mesitylene, and dried at 100 °C for 6 h. The same amount of substrate was used for each fresh catalyst reuse.

3. Results and discussion

Table 1 summarizes catalytic performances of some zirconium salts in the esterification of palmitic acid with cetyl alcohol at boiling points of mesitylene (162 °C) for 24 h. Water was removed azeotropically from boiling mesitylene. Zirconyl salts, such as chloride, nitrate, sulfate, and acetate, are highly efficient catalysts for the esterification, and gave almost the same level of yield of cetyl palmitate. These results show that

Table 1 Effects of type of zirconium salts on the esterification of palmitic acid with cetyl alcohol[a]

Entry	Zirconium salt	Yield (%)
1	None	12.8
2	$ZrCl_4$	86.2
3	$ZrOCl_2 \cdot 8H_2O$	86.2
4	$ZrO(NO_3)_2 \cdot 2H_2O$	92.5
5	$ZrO(SO_4) \cdot 4H_2O$	84.3
6	$ZrO(CH_3COO)_2$	88.0

[a] Reaction conditions: substrate: palmitic acid, 6 mmol, cetyl alcohol, 6 mmol; solvent: mesitylene, 40 ml; catalyst: 0.12 mmol as Zr salts; reaction temperature, 162 °C; reaction time 24 h.

catalytic activity of these zirconyl salts is due to the zirconyl moiety and not to the anion moiety. The esterification was slow in the absence of the catalyst: only 13% of conversion was obtained under typical reaction conditions.

$ZrCl_4$, originally proposed by Yamamoto *et al.*,[25–28] has high activity for the esterification. $ZrOCl_2 \cdot 8H_2O$ has similar catalytic performance to $ZrCl_4$. These results show that $ZrOCl_2 \cdot 8H_2O$ is active for the catalysis because $ZrCl_4$ is hydrolyzed to $ZrOCl_2 \cdot 8H_2O$ under the reaction conditions. From these results, we chose $ZrOCl_2 \cdot 8H_2O$ as the standard catalyst for further investigation.

Table 2 shows the effects of supports on yield of cetyl palmitate for the esterification of palmitic acid with cetyl alcohol at 162 °C for 12 h. Supporting $ZrOCl_2 \cdot 8H_2O$ on solid materials with large surface area enhanced the catalytic activity of the esterification. Among them, ordered mesoporous silicas (*viz.*, MCM-41, FSM-16 and SBA-15) showed higher activity, and MCM-41 gave the best result: the reaction was completed within half the time compared to unsupported $ZrOCl_2 \cdot 8H_2O$ under the same conditions. Other supports (*viz.*, activated charcoal, SiO_2 and ZrO_2) also promoted the esterification; however, these were less effective than MCM-41. Al_2O_3 and ZrO_2 made almost no enhancement in the esterification. We suggest that the high activity of mesoporous silica is due to its hydrophobic character which stabilizes the catalytic species and accelerates the removal of water. We chose MCM-41 mesoporous silica as a standard support for further investigation.

Table 3 summarizes the effects of loading $ZrOCl_2 \cdot 8H_2O$ on MCM-41 in the esterification of palmitic acid with cetyl alcohol at 162 °C for 12 h. Loading was changed by altering the amount of MCM-41 at constant amounts of $ZrOCl_2 \cdot 8H_2O$. The catalytic activity increased with high loading even with the same quantity of $ZrOCl_2 \cdot 8H_2O$, the esterification was almost completed by loading more than 30 wt% $ZrOCl_2$ on MCM-41. From these results, we chose 20 wt% of $ZrOCl_2$ as a standard loading amount for further investigation.

Table 2 Effects of support of $ZrOCl_2 \cdot 8H_2O$ on the esterification of palmitic acid with cetyl alcohol[a]

Entry	Support	Yield (%)
1	None	59.3
2	MCM-41	89.3
3	FSM-16	85.0
4	SBA-15	87.2
5	Amorphous SiO_2	71.2
6	Al_2O_3	62.0
7	ZrO_2	62.5
8	Activated charcoal	77.5

[a] Reaction conditions: substrate: palmitic acid, 6 mmol, cetyl alcohol, 6 mmol; solvent: mesitylene, 40 ml; catalyst: $ZrOCl_2 \cdot 8H_2O$, 0.12 mmol; reaction temperature, 162 °C; reaction time 12 h.

Table 3 Effects of loading of $ZrOCl_2 \cdot 8H_2O$ on MCM-41 on the esterification of palmitic acid with cetyl alcohol[a]

Entry	Loading (wt%)[b]	Yield (%)
1	—[c]	2.5
2	5	27.5
3	10	70.8
4	20	89.3
5	30	95.6
6	40	99.5

[a] Reaction conditions: substrate: palmitic acid, 6 mmol, cetyl alcohol, 6 mmol; solvent: mesitylene, 40 ml; $ZrOCl_2 \cdot 8H_2O$ 0.12 mmol (MCM-41 0.05–0.44 g); temperature, 162 °C; reaction time 12 h. [b] Loading amount was based on $ZrOCl_2$. [c] MCM-41 0.55 g.

Fig. 1 shows the effects of variable amounts of $ZrOCl_2 \cdot 8H_2O$ on the yield of cetyl palmitate at the initial stages for unsupported and supported catalysts. The yield of the ester, *i.e.*, catalytic activity increased as the amounts of $ZrOCl_2 \cdot 8H_2O$ increased for both unsupported and supported catalysts. However, supported catalysts have higher catalytic activity than unsupported catalysts even in small amounts; and the activity saturated as amounts increased. The saturated activity level of the supported catalyst was higher than that of the unsupported catalyst. These results show that supporting $ZrOCl_2 \cdot 8H_2O$ on the MCM-41 enhanced the catalytic activity in the esterification.

Table 4 summarizes the effects of reaction temperature obtained by changing the boiling temperature of the solvents. The yield of cetyl palmitate increased at higher temperatures with and without $ZrOCl_2 \cdot 8H_2O$ catalyst. Moreover, both the supported and unsupported catalyst enhanced the esterification. Particularly, the catalytic activity of $ZrOCl_2 \cdot 8H_2O$ was improved by supporting on MCM-41, and reasonable results were obtained using a lower boiling solvent such as *m*-xylene.

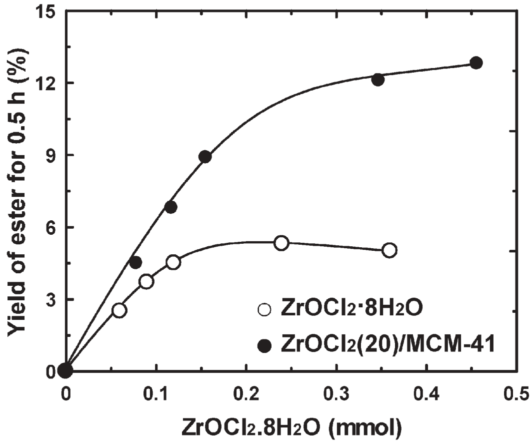

Fig. 1 Effects of amounts of $ZrOCl_2 \cdot 8H_2O$ on initial rate of the esterification of palmitic acid with cetyl alcohol. Reaction conditions: substrate: acid, 6 mmol, alcohol, 6 mmol; solvent: mesitylene, 40 ml; $ZrOCl_2$: 0–0.155 mmol; reaction temperature, 162 °C; reaction time 30 min.

Table 4 Effects of reaction temperature on the esterification of palmitic acid with cetyl alcohol over MCM-41 supported $ZrOCl_2 \cdot 8H_2O$ catalyst[a]

			Yield (%)		
Entry	Solvent	Reaction temperature/°C	Unsupported[b]	Supported[c]	Without catalyst[b]
1	Benzene	80	4.3	—	—
2	Toluene	110	11.8	26.4	—
3	*m*-Xylene	140	48.6	65.8	1.8
4	Mesitylene	162	86.2	89.3	12.8
5	Diethylbenzenes	182	99.6	100	18.5
6	Tetralin	207	100	—	28.9

[a] Reaction conditions: substrate: palmitic acid, 6 mmol, cetyl alcohol, 6 mmol; catalyst: $ZrOCl_2 \cdot 8H_2O$, 0.12 mmol. $ZrOCl_2$(20)/MCM-41, 0.115 g; solvent: 40 ml. [b] reaction time, 24 h. [c] reaction time, 12 h.

From these results, we chose mesitylene as solvent for the reaction at 162 °C under azeotropic removal of water for further investigation.

Fig. 2 shows reaction times for the esterification of palmitic acid with cetyl alcohol over $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41 catalysts. The catalytic activity was greatly enhanced by supporting $ZrOCl_2 \cdot 8H_2O$ on MCM-41. After 12 h reaction time, the conversion of palmitic acid was about 90% with $ZrOCl_2$(20)/MCM-41; however, unsupported $ZrOCl_2 \cdot 8H_2O$ catalysts gave only about 60% conversion although the reaction did progress at a slower rate even after 12 h. No coke formation was observed after the reaction, and catalysts were white colored.

Table 5 summarizes the esterification of normal aliphatic carboxylic acids and primary alcohols of different chain lengths (C_{10} to C_{18}) with $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41 catalysts at reflux temperature using mesitylene as solvent. The reaction periods for unsupported and supported catalysts were 24 h and 12 h, respectively. MCM-41 supported $ZrOCl_2 \cdot 8H_2O$ catalysts showed much higher activity than the unsupported $ZrOCl_2 \cdot 8H_2O$. The yield of palmitate decreased with increasing chain length of alcohols for the esterification with palmitic acid for both the catalysts. Complete conversion of palmitic acid was observed in the case of reaction with myristyl alcohol. The yield of the esters with palmitic acid decreased with chain length of alcohols in the following order: $C_{10} > C_{12} > C_{14} > C_{16} > C_{18}$ (Table 5, entries 1–5). Similarly, the yield of the esters with cetyl alcohol decreased with increasing chain length of carboxylic acids in the following order: $C_{10} \approx C_{12} > C_{14} > C_{16} > C_{18}$ (Table 5, entries 6–10).

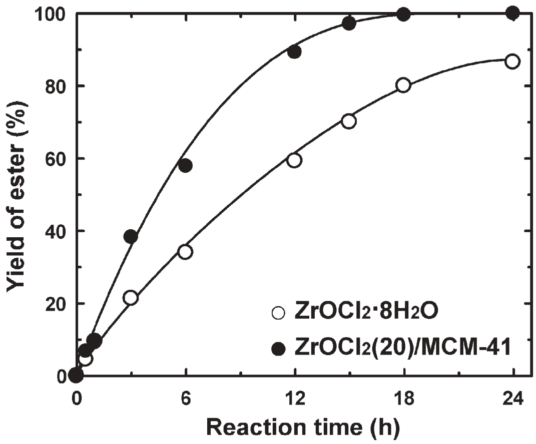

Fig. 2 Reaction time for the esterification of palmitic acid and cetyl alcohol. Reaction conditions: substrate: acid, 6 mmol, alcohol, 6 mmol; solvent: mesitylene, 40 ml; $ZrOCl_2 \cdot 8H_2O$, 39 mg (12 mmol); $ZrOCl_2$(20)/MCM-41, 0.117 g; reaction temperature, 162 °C.

Table 5 The esterification of normal acid with primary alcohol with different carbon chain length over $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41catalysts[a]

			Yield (%)	
Entry	Acid	Alcohol	Unsupported[b]	Supported[c]
1	Palmitic acid	Capryl alcohol	>99.9	>99.9
2	Palmitic acid	Lauryl alcohol	>99.9	>99.9
3	Palmitic acid	Myristyl alcohol	90.5	92.5
4	Palmitic acid	Cetyl alcohol	86.2	89.3
5	Palmitic acid	Stearyl alcohol	85.3	88.5
6	Capric acid	Cetyl alcohol	>99.9	>99.9
7	Lauric acid	Cetyl alcohol	99.9	>99.9
8	Myristic acid	Cetyl alcohol	99.5	94.5
9	Palmitic acid	Cetyl alcohol	86.2	89.3
10	Stearic acid	Cetyl alcohol	83.3	87.8

[a] Reaction conditions: substrate: acid, 6 mmol, alcohol, 6 mmol; solvent: mesitylene, 40 ml; $ZrOCl_2$(20)/MCM-41, 0.115 g ($ZrOCl_2 \cdot 8H_2O$, 0.12 mmol); reaction temperature, 162 °C. [b] Reaction time, 24 h. [c] Reaction time, 12 h.

Table 6 shows the esterification of palmitic acid with secondary alcohols and of isostearic acid (2-heptylundecanoic

Table 6 The esterification of normal acid with secondary alcohols, branched acid with primary alcohols, and branched acid with secondary alcohols[a]

			Yield (%)	
Entry	Acid	Alcohols	Unsupported	Supported
1	Palmitic acid	2-Decanol	70.8	>99.9
2	Palmitic acid	2-Dodecanol	60.2	99.3
3	Palmitic acid	2-Tetradecanol	41.2	75.8
4	Palmitic acid	2-Hexadecanol	33.1	70.1
5	Isostearic acid	Capryl alcohol	42.4	>99.9
6	Isostearic acid	Lauryl alcohol	35.2	99.2
7	Isostearic acid	Myristyl alcohol	33.5	96.1
8	Isostearic acid	Cetyl alcohol	30.7	84.4
9	Isostearic acid	Stearyl alcohol	28.5	67.8
10	Isostearic acid	2-Decanol	7.1	30.2
11	Isostearic acid	2-Dodecanol	5.1	28.8
12	Isostearic acid	2-Tetradecanol	6.2	23.5
13	Isostearic acid	2-Hexadecanol	No reaction[b]	21.6

[a] Reaction conditions: substrate: acid, 6 mmol, alcohol, 6 mmol; solvent: mesitylene, 40 ml; $ZrOCl_2$(20)/MCM-41, 0.115 g ($ZrOCl_2 \cdot 8H_2O$, 0.12 mmol); reaction temperature, 162 °C; reaction time, 24 h. [b] Substrate to $ZrOCl_2 \cdot 8H_2O$ molar ratio: 10.

acid) with primary and secondary alcohols in the presence of $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41 catalysts. The rates of these esterification reactions with unsupported $ZrOCl_2 \cdot 8H_2O$ catalysts were much slower than in the case of normal acids and primary alcohols. However, the catalytic activity increased by supporting $ZrOCl_2 \cdot 8H_2O$ on MCM-41 although the yield of the palmitates decreased gradually with increasing chain length of secondary alcohols (Table 6, entries 1–4). The esterification of isostearic acid with primary alcohols gave corresponding isostearates in moderate to low yield (Table 6, entries 5–9) in the presence of $ZrOCl_2 \cdot 8H_2O$. The MCM-41 supported $ZrOCl_2 \cdot 8H_2O$ shows much higher activity, and gave corresponding isostearates in excellent to good yield although the gradual decrease of the yield was observed with increasing chain length of alcohols. The esterification of isostearic acid with secondary alcohols over $ZrOCl_2 \cdot 8H_2O$ catalysts was much slower than the others, and the yield of the corresponding esters were very low. However, MCM-41 supported $ZrOCl_2 \cdot 8H_2O$ showed much higher activities (Table 6, entries 10–13) although the yields of the esters were 20–30%.

To achieve better yields of the esters from less reactive isostearic acid and secondary alcohols, we varied the reaction parameters such as acid/alcohol ratios, catalyst amount, reaction temperature and reaction time as shown in Table 7. It can be observed that the conversion of 2-decanol was increased by increasing the catalyst amount (Table 7, entries 1 and 2) (other reaction conditions were kept constant); the increase is, however, not high even at doubling of the catalyst concentration. The reactions in higher boiling solvents (Table 7, entries 3 and 4) increased the conversion of 2-decanol. The best yield of 2-decyl isostearate was obtained by increasing the amount of catalyst and by prolonging the reaction time. The conversion rate to bulky esters in reasonable yields was also increased by increasing acid/alcohol ratio (Table 7, entries 2, 7 and 11), and increasing reaction time (Table 7, entries 2, 5 and 6).

Table 7 Effects of reaction variables on the esterification of 2-decanol with isostearic acid over $ZrOCl_2$(20)/MCM-41 catalyst[a]

Entry	Solvent	Reaction time h	Acid/alcohol ratio	Catalyst amount g	Yield (%)
1	Mesitylene	24	1.0	0.155	30.2
2	Mesitylene	24	1.0	0.310	43.2
3	Diethylbenzene	24	1.0	0.310	59.5
4	Decalin	24	1.0	0.310	63.8
5	Mesitylene	48	1.0	0.310	74.8
6	Mesitylene	72	1.0	0.310	95.0
7	Mesitylene	24	1.5	0.155	40.9
8	Mesitylene	48	1.5	0.155	67.0
9	Mesitylene	24	1.5	0.310	62.2
10	Mesitylene	48	1.5	0.310	87.6
11	Mesitylene	24	2.0	0.310	88.5

[a] Reaction conditions: substrate: 2-decanol, 6 mmol; isostearic acid, 6–12 mmol; mesitylene, 40 ml; catalyst: $ZrOCl_2$(20)/MCM-41, 0.115 g; temperature: 162–190 °C.

Table 8 The recycle and reuse of $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41 catalyst in the esterification of palmitic acid with cetyl alcohol[a]

Entry	Fresh/recycled catalysts	Yield (%)	
		$ZrOCl_2 \cdot 8H_2O$[b]	$ZrOCl_2$(20)/MCM-41[c]
1	Fresh	86.2	89.3
2	First recycle	84.5	88.0
3	Second recycle	84.3	88.5
4	Third recycle	84.8	88.6
5	Fourth recycle	84.2	89.0

[a] Reaction conditions: substrate: palmitic acid, 6 mmol, cetyl alcohol, 6 mmol; catalyst: $ZrOCl_2 \cdot 8H_2O$, 0.12 mmol. $ZrOCl_2$(20)/MCM-41, 0.115 g; solvent: 40 ml mesitylene; reaction temperature, 162 °C. [b] Reaction time, 24 h. [c] Reaction time, 12 h.

The recyclability of $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41 catalysts for the esterification of palmitic acid with cetyl alcohol is shown in Table 8. A slight decrease in the yield of cetyl palmitate was observed in the second recycle for unsupported and supported $ZrOCl_2 \cdot 8H_2O$; however, there was no further decrease during the third and fourth recycle of the catalysts. $ZrOCl_2$(20)/MCM-41 catalysts maintained higher activity than unsupported $ZrOCl_2 \cdot 8H_2O$ during the recycling. Unsupported $ZrOCl_2 \cdot 8H_2O$ catalysts were recovered as white paste after the reaction, and white dry solid was separated from the reaction mixtures for supported $ZrOCl_2 \cdot 8H_2O$ catalysts. These results show that there is no coke-formation during the catalysis.

The esterification of unsaturated aliphatic acids such as oleic, elaidic, and linoleic acids with cetyl alcohol are shown in Table 9. The complete conversion with very high yield of the ester was achieved in the esterification of oleic and elaidic acids with cetyl alcohol over $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41 catalysts in 24 h and 12 h reactions, respectively; however, linoleic acid gave the ester in lower yield for both catalysts. The activity was increased by supporting $ZrOCl_2 \cdot 8H_2O$ on MCM-41 for the esterification. The ester of oleic acid with 2-decanol was also obtained in almost quantitative yield over supported catalyst. These esterification reactions occurred without isomerization at the double bond retaining their configuration.

Zirconium cation cluster $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ was suggested as the active catalytic species for the esterification with $ZrOCl_2 \cdot 8H_2O$ by Yamamoto *et al.*[28] The cationic cluster complexes from zirconyl salts are considered to be the active species for our supported catalysts although we do not have decisive evidence. The enhancement of catalytic activity of the MCM-41 supported catalyst is due to its easy contact with substrate and catalyst because the cation cluster is highly dispersed on MCM-41 with a high surface area. We also

Table 9 The esterification of unsaturated aliphatic acids with cetyl alcohol over $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2$(20)/MCM-41 catalysts[a]

Entry	Acid	Alcohol	Yield (%)	
			Unsupported[b]	Supported[c]
1	Oleic acid (*cis*)	Cetyl alcohol	>99.9	97.8
2	Elaidic acid (*trans*)	Cetyl alcohol	>99.9	99.4
3	Linoleic acid	Cetyl alcohol	70.1	62.5
4	Oleic acid (*cis*)	2-Decanol	50.3	58.3(98.0[b])

[a] Reaction conditions: substrate: acid, 2 mmol, alcohol, 2 mmol; solvent: mesitylene, 30 ml; $ZrOCl_2$(20)/MCM-41, 0.052 g ($ZrOCl_2 \cdot 8H_2O$, 0.04 mmol); reaction temperature, 162 °C. [b] Reaction time, 24 h. [c] Reaction time, 12 h.

suggest that the hydrophobic properties of mesoporous silica accelerate the removal of water during esterification by controlling hydrated water in the cluster. There have been similar discussions on the acceleration of the esterification with acid catalysts under hydrophobic environments by organic modified mesoporous silicas[13–18] or O/W micelles with surfactants.[20]

4. Conclusion

$ZrOCl_2 \cdot 8H_2O$ is an efficient catalyst for the esterification of long chain carboxylic acids with long chain aliphatic primary and secondary alcohols. Supporting $ZrOCl_2 \cdot 8H_2O$ on ordered mesoporous silica enhances the catalytic activity in the esterification. The esters of C_{10}–C_{18} normal acids and alcohols are obtained in high yield although the yield of the esters decreases with chain length for unsupported $ZrOCl_2 \cdot 8H_2O$. The esterification of less reactive branched acids and secondary alcohols gives excellent to good yield of the corresponding esters by supported $ZrOCl_2 \cdot 8H_2O$ on MCM-41. The type of supports influences the catalytic performance of $ZrOCl_2 \cdot 8H_2O$. Enhancement of catalytic activity of $ZrOCl_2 \cdot 8H_2O$ by mesoporous and amorphous silicas and actived charcoal with hydrophobic properties is much higher than that of alumina and zirconia. Zirconyl salts such as nitrate, sulfate, and acetate show similar levels of catalytic activity in esterification. The catalyst is recyclable without significant loss of activity.

Further aspects of the catalysis, especially the catalytic active species are under investigation and will be published in the near future.

Acknowledgements

A part of this work was financially supported by a Grant-in Aid for Scientific Research (B) 16310056, the Japan Society for the Promotion of Science (JSPS). K. Mantri is also grateful to JSPS for a postdoctoral fellowship.

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A solvent-free synthesis of α,α′-bis(substituted benzylidene) cycloalkanones catalyzed by lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ under microwave irradiation†

Lijun Zhang,[ab] Shaowu Wang,*[bc] Enhong Sheng[b] and Shuangliu Zhou[b]

Received 7th April 2005, Accepted 29th June 2005
First published as an Advance Article on the web 28th July 2005
DOI: 10.1039/b504890g

Under solvent-free and microwave irradiation conditions, the corresponding *E*,*E*′-α,α′-bis(substituted benzylidene) cycloalkanones were prepared in high yields by the cross-aldol reactions of cyclopentanone or cyclohexanone with aromatic aldehydes catalyzed by the lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$. The reactions produce the products in relatively low yields and require a long time when they were performed in various solvents without microwave irradiation. Thus, the procedure provides a simple and a green synthetic methodology.

Introduction

Recently, there has been a significant research effort to establish lanthanide(III) compounds as catalysts for various organic transformations. Lanthanide catalysts are active in two fields of application. One involves organolanthanide compounds such as the metallocenes, which can work as catalysts for the transformation of olefins, dienes, and alkynes.[1–7] However, the metallocenes are difficult to prepare. The other one covers lanthanide alkoxides, triflates, and halogenides, which were used as Lewis acid catalyzed organic reactions,[8] such as the Aldol reaction,[9] Michael reaction,[10] Diels–Alder reaction,[11] Meerwein–Ponndorf–Verley reduction[12] and hydrocyanation.[13] In contrast to these well-established catalysts, the reports on the catalytic activity of homoleptic bis(trimethylsilyl) amido of Group 3 metals $Ln[N(SiMe_3)_2]_3$ (Ln = Y, lanthanide), which can either be prepared from a simple one-step synthesis in very high yields or be purchased commercially from a chemical company, are very limited. Berberich and Roesky have reported that the lanthanide amides $Ln[N(SiMe_3)_2]_3$ are very efficient active catalysts for the Tishchenko reaction[14] and also that the lanthanide amides $Ln[N(SiMe_3)_2]_3$ are good catalysts for intramolecular alkene hydroaminations,[15] hydrosilylation[16] and the ring-opening polymerization of ε-caprolactone and δ-valerolactone.[17] Our group has reported that lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ can act as highly efficient catalysts for the stereoregularity of PolyMMA.[18] These compounds are distinguished by a number of practical advantages, such as the ease of accessibility, inexpensive metals, and a high durability of the catalysts. These advantages led us to explore their further applications for catalysts.

As useful precursors to potentially bioactive pyrimidine derivatives, α,α′-bis(substituted benzylidene) cycloalkanones have attracted considerable attention for many years.[19] Usually, the preparation of the compounds can be realized through the cross-aldol reaction of benzaldehydes with cycloalkanones catalyzed by many catalysts such as traditional acid or base, $FeCl_3$,[20] Cp_2TiPh_2,[21] BMPTO,[22] SmI_3 in ionic liquids.[23] The reaction catalyzed by those catalysts gives the products either in low yields or requires a long reaction time or with a very expensive catalyst. In this paper we prepare α,α′-bis(substituted benzylidene) cycloalkanones (**1a–2e**) through reaction of aromatic aldehydes and cycloalkanones catalyzed by lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ under microwave irradiation and solvent-free conditions (Scheme 1).

Microwave irradiation has been established as a useful energy source in synthetic reactions. The decomposition of the reagents or products can be avoided by the rapid heating induced by the microwave irradiation, while reactions are clean, and yields are in many cases higher than those obtained by typical methods.[24] It has been found that the microwave technique can not only save reaction time, but can also provide synergy with solvent-free conditions.[25] For these reasons, we have tried the method for the preparation of the title compounds.[26]

Results and discussion

To select the favorable reaction conditions, reactions of benzaldehyde (2 mmol) with cyclohexanone (1 mmol) catalyzed by the lanthanide amide $[(Me_3Si)_2N]_3Y(\mu\text{-}Cl)Li(THF)_3$ were performed under different conditions. At first, different solvents such as hexane, toluene, diethyl ether and THF were used to initiate the reactions (Table 1). It is found that THF was the most suitable solvent for the reaction. The reaction was quite sensitive to temperature changes *e.g.* at −20 °C for 1 day the yield was only 50% increasing to 68% at 60 °C. From Table 1, we can see that the mole ratio of the catalyst to benzaldehyde has little influence on the yields. For example,

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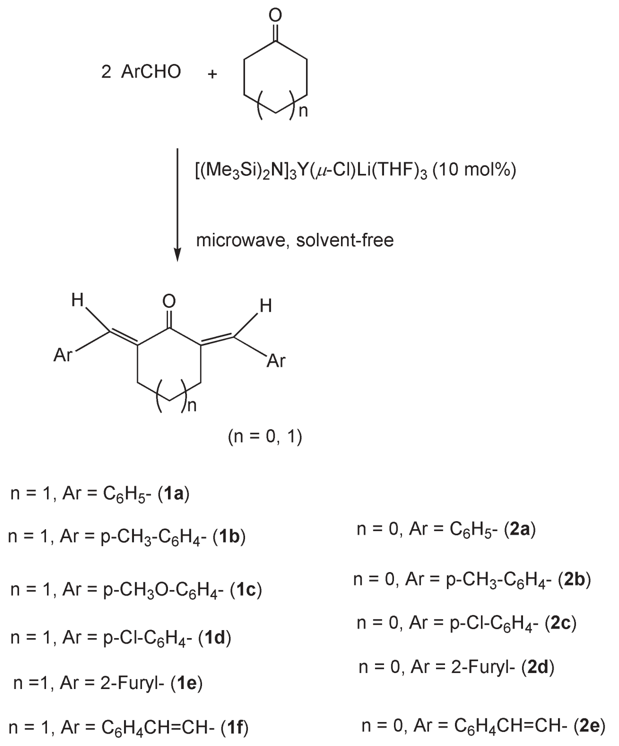
[a] *Department of Chemistry, University of Science and Technology of China, 230026 Hefei, Anhui, China*
[b] *Institute of Organic Chemistry, School of Chemistry and Materials Science, Anhui Normal University, 241000 Wuhu, Anhui, China*
[c] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China. E-mail: swwang@mail.ahnu.edu.cn; Fax: +86-553-3883517; Tel: +86-553-3869310*

† CCDC reference number 268269. See http://dx.doi.org/10.1039/b504890g for crystallographic data in CIF or other electronic format.



Scheme 1 The cross-condensation aldol reaction of aldehydes with cycloalkanones catalyzed by 10 mol% of ([(Me$_3$Si)$_2$N]$_3$)Y(μ-Cl)Li(THF)$_3$ under microwave irradiation and solvent-free conditions.

Table 1 Conditions and yields of the reaction

T/°C	Solvent	Catalyst (%)[a]	Yield (%)[b]
−20	THF	10	50
0	THF	10	60
20	THF	10	65
60	THF	10	68
60	n-Hexane	10	40
60	Toluene	10	56
30	Et$_2$O	10	58
30	CH$_2$Cl$_2$	10	28
60	THF	5	50
60	THF	20	68
60	THF	50	70
60	THF	100	70

[a] Catalyst to cyclohexanone mole ratio. [b] Isolated yield after purification by preparative TLC. [c] Condition: 2 mmol benzyldehyde reacted with 1 mmol cyclohexanone; catalyst: [(Me$_3$Si)$_2$N]$_3$Y(μ-Cl)Li(THF)$_3$; time: 24 h.

the yields only changed from 68% to 70% when the catalyst to cyclohexanone mole ratio was changed from 10% to 100%. The influence of cyclohexanone to benzaldehyde mole ratio on the reaction was also investigated. When the cyclohexanone to benzaldehyde mole ratio was changed from 1 : 2 to 1 : 3 or even more, the main product of all reactions was α,α′-bis(substituted benzylidene) cyclohexanone. When the cyclohexanone to benzaldehyde mole ratio was 5 : 1, the expected product of α-benzylidene cyclohexanone was not obtained. Instead, the main product was α,α′-bis(benzylidene) cyclohexanone. Considering that the lanthanide amides [(Me$_3$Si)$_2$N]$_3$Ln(μ-Cl)Li(THF)$_3$ can be easily dissolved in the cycloalkanone and the cross-aldol rection favoured high temperature, we then tried to use solvent-free conditions under microwave irradiation (Table 2).

Table 2 Results for the catalytic reaction under solvent-free and microwave irradiation

Entry	N	Ar	Power/W	Time/min	Yield (%)[a]
1	1	C$_6$H$_5$	450	9	84 (**1a**) 68 (**1a**)[b]
2	1	p-CH$_3$C$_6$H$_4$	450	9	85 (**1b**)
3	1	p-CH$_3$OC$_6$H$_4$	450	9	88 (**1c**)
4	1	p-ClC$_6$H$_4$	450	9	85 (**1d**)
5	1	2-Furyl	300	1.5	94 (**1e**)
6	1	C$_6$H$_5$CH=CH	450	3	80 (**1f**)
7	0	C$_6$H$_5$	300	6	91 (**2a**)
8	0	p-CH$_3$C$_6$H$_4$	300	6	91 (**2b**)
9	0	p-ClC$_6$H$_4$	300	6	85 (**2c**)
10	0	2-Furyl	150	1	85 (**2d**)
11	0	C$_6$H$_5$CH=CH	300	1	82 (**2e**)

[a] Isolated yield catalyzed by 10 mol% of [(Me$_3$Si)$_2$N]$_3$Y(μ-Cl)Li(THF)$_3$. [b] Isolated yield catalyzed by 10 mol% of [(Me$_3$Si)$_2$N]$_3$Y. [c] Conditions: 2 mmol aldehyde reacted with 1 mmol cycloalkanone under microwave irradiation by cycles.

Table 3 The influence of the lanthanide metal on the reaction

Ln	Y	La	Pr	Sm	Eu	Dy	Ho	Tm	Yb
Yield (%)[a]	84	84	68	89	77	64	75	69	89

[a] Isolated yield. [b] Conditions: 2 mmol benzyaldehyde reacted with 1 mmol cyclohexanone; catalyst: 10 mol% of [(Me$_3$Si)$_2$N]$_3$Ln(μ-Cl)Li(THF)$_3$; microwave irradiation (450 W) and solvent-free conditions for 9 min.

When cyclohexanone was changed to cyclopentanone, similarly good results were obtained (Scheme 1, Table 2). The crystal structure of compound **1d** was determined; X-ray analysis reveals that the product is the E,E'-α,α′-bis(p-chlorobenzylidene) cyclohexanone.‡ As shown in Table 2, where the R group is either electron-donating or moderately electron-withdrawing, such as halides, the yields are satisfactory. However, when the aldehyde was p-nitrobenzaldehyde, the corresponding product can not be isolated. The reason remains unclear. The influence of the rare earth metal on the product yields was also investigated. From Table 3 it was found that [(Me$_3$Si)$_2$N]$_3$Yb(μ-Cl)Li(THF)$_3$ is the most efficient catalyst, while the catalytic activity of [(Me$_3$Si)$_2$N]$_3$Dy(μ-Cl)Li(THF)$_3$ is low. The results are in accordance with the Lewis acidity of the Ln^{3+} cations.[27] It can be seen from Table 4 that the synthetic methodology under the microwave irradiation and solvent-free conditions has the advantages of high yields and short time.

To investigate the influence of the Li+ cation on the reaction, the reaction of benzaldehyde (2 mmol) with cyclohexanone (1 mmol) catalyzed by the yttrium amide Y[N(SiMe$_3$)$_2$]$_3$ (10 mol%) instead of [(Me$_3$Si)$_2$N]$_3$Y(μ-Cl)Li(THF)$_3$ under

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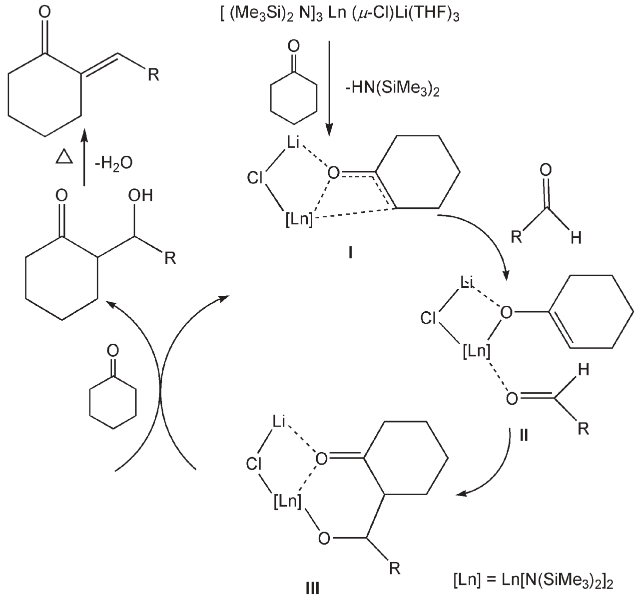
‡ Crystal data for **1d**: C$_{20}$H$_{16}$Cl$_2$O, M = 343.23, monoclinic, space group $P2(1)/n$, a = 10.0665(4), b = 16.6372(7), c = 10.5634(3) Å, α = 90°, β = 107.793(2)°, γ = 90°, V = 1684.52(11) Å^3, F(000) = 712, Z = 4, μ = 0.387 mm^{-1}, 5278/2916 independent reflections [Rint = 0.0302] for 2.37 < θ < 25.04°, R indices: $R1$ = 0.0707, $wR2$ = 0.1275 [$I > 2\sigma(I)$]. Intensities were measured to $\theta_{\max}$ 25.04° on a Siemens CCD area detector at 293(2) K with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97) and refined against F^2 by full-matrix least-squares using SHELXS-97.

Table 4 Comparison between the solvent free/under microwave methodology and conventional synthesis

Compound	Time^{a}min	Yield (%)^a	Time^{b}h	Yield (%)^b
1a	9	84	24	68
1b	9	85	24	68
1c	9	88	24	65
1d	9	85	24	69
1f	1.5	94	18	78
1g	3	80	18	72
2a	6	91	24	79
2b	6	91	24	80
2c	6	85	24	76
2d	1	85	18	78
2e	1	82	18	76

[a] 2 mmol aldehyde reacted with 1 mmol cycloalkanone under microwave irradiation by cycles without solvent. [b] 2 mmol aldehyde reacted with 1 mmol cycloalkanone in THF at 60 °C; catalyst: 10 mol% of $[(Me_3Si)_2N]_3Y(\mu\text{-Cl})Li(THF)_3$; yield: Isolated yield.

microwave irradiation and solvent-free conditions was performed, and the yield was only 68% (Table 2). However, under the same conditions, the yield of the product, when $[(Me_3Si)_2N]_3Y(\mu\text{-Cl})Li(THF)_3$ was the catalyst, was 84%. So it can be seen that the catalytic activity of yttrium amide $[(Me_3Si)_2N]_3Y(\mu\text{-Cl})Li(THF)_3$ is higher than that of the yttrium amide complex $Y[N(SiMe_3)_2]_3$. On the basis of the above described facts and the previously proposed mechanism,[28] the following catalytic cycle for the cross-condensation aldol reaction of aromatic aldehydes with unmodified cycloalkanones was proposed (Scheme 2). The mechanism of the aldol condensation reaction was thought to involve the cooperation of the Ln^{3+} cation and Li^+ cation. First the cycloalkanone could coordinate to the lanthanide metal and lithium metal of the catalyst, then it can be deprotonated by $–N(TMS)_2$ at the α-position to generate the intermediate (**I**) (Scheme 2). The priority of the ketone for the coordination to the lanthanide center metal over that of the aldehyde can be explained by the possible capability of the ketone to form a stable complex with Lewis acids of a lanthanide ion,[28] while at the same time the coordination of oxygen atom of aldehyde to lanthanide metal gives intermediate (**II**). The latter could then react with the metal enolate to afford the intermediate (**III**). Then the intermediate (**III**) would be protonated by cycloketone to produce the α-hydroxy ketone which could be easily condensed to give the desired product, and the intermediate (**I**) regenerated.



Scheme 2 Proposed catalytic cycle for the cross-aldol reaction of aldehydes with cycloalkanones catalyzed by $[(Me_3Si)_2N_3Ln(\mu\text{-Cl})Li(THF)_3$.

Conclusion

In summary, under microwave irradiation and solvent-free conditions, lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ can act as highly efficient catalysts for the cross-aldol condensation of benzaldehydes and cycloketones producing the corresponding *E,E*′-α,α′-bis(substituted benzylidene) cycloalkanones in high yields. The procedure has the advantages of short reaction time, inexpensive and easy availability of the catalysts, easy work-up and is environmentally benign. It is the first time that microwave irradiation and solvent-free synthesis have been used to deal with the air- and water-sensitive lanthanide complexes. Further investigations on the use of lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ as catalysts in organic synthesis are in progress.

Experimental

General

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker Advance 300 instrument in $CDCl_3$ solutions using TMS as internal standard. Chemical shifts (δ) are reported in ppm. IR spectra were obtained with a Perkin-Elmer 983 FT-IR spectrometer. Mass spectra were performed on Micromass GCT-MS. Microwave assisted organic reactions were performed in Sanyo EM-202ES1 (domestic, 80 W–700 W). All aldehydes, cycloalkanones and solution are pre-dried, redistilled or recrystallized before use. The lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ were synthesized according to the literature.[18]

General procedures

The typical reaction procedure for the cross-aldol condensation reaction of aldehydes with cycloalkanones catalyzed by lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ was as follows: To a mixture of cycloalkanone (1 mmol) with lanthanide amide $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ (0.1 mmol) in Schlenk flask connected to the Schlenk line, aldehyde (2 mmol) was added. Then, the glassware flask with a Teflon stopper was put into the microwave oven (150 W–450 W) in an alumina bath for 1–9 min, leaving the mixture at room temperature to solidify. The dilute hydrochloric acid (0.1 M, 1 mL) was then added, the mixture was extracted with diethyl ether, dried with anhydrous $MgSO_4$, the solvents were evaporated under vacuum almost to dryness. The *E,E*′-α,α′-bis(substituted benzylidene)cycloalkanones produced as pale yellow needles by recrystallization of the crude material from a mixed solvent of diethyl ether and hexane.

1a: mp 115–116 °C (Lit.[29] 115–116 °C); IR (KBr) 1664 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.80 (s, 2H), 7.34–7.48 (m, 10H), 2.92–2.96 (t, 4H), 1.76–1.84 (p, 2H); MS (EI) *m*/*z* 274.13 (M).

1b: mp 172–173 °C (Lit.[29] 172–173 °C); IR (KBr) 1662 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.79 (s, 2H), 7.16–7.41 (m, 8H), 2.92–2.96 (t, 4H), 2.40 (s, 6H), 1.78–1.82 (p, 2 H); MS (EI) *m*/*z* 302.17 (M).

1c: mp 203–204 °C (Lit.[29] 205 °C); IR (KBr) 1666 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.79 (s, 2H), 6.92–7.46 (m, 8H), 3.84 (s, 6 H), 2.90–2.94 (t, 4H), 1.78–1.82 (p, 2 H); MS (EI) *m*/*z* 334.16 (M).

1d: mp 108–110 °C (Lit.[29] 108–110 °C); IR (KBr) 1686 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.74 (s, 2H), 7.31–7.50 (m, 8H), 2.89–2.92 (t, 4H), 1.77–1.86 (p, 2H); MS (EI) *m*/*z* 342.05 (M).

1e: mp 142–143 °C (Lit.[29] 145 °C); IR (KBr) 1644 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.57 (s, 2H), 6.67–6.68 (d, 2H), 6.53 (s, 2H), 3.01–3.04 (t, 4 H), 1.88–1.94 (p, 2 H); MS (EI) *m*/*z* 254.03 (M).

1f: mp 179–180 °C (Lit.[29] 179–180 °C); IR (KBr) 1655 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 6.94–7.51(m, 16H), 2.78–2.82 (t, 4H), 1.86–1.90 (p, 2H); MS (EI) *m*/*z* 326.07 (M).

2a: mp 116–117 °C (Lit.[29] 116–117 °C); IR (KBr) 1685 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.28–7.62 (m, 12H), 3.13 (s, 2H), 3.01–3.04 (t, 4H); MS (EI) *m*/*z* 260.12 (M).

2b: mp 183–184° C (Lit.[29] 183–184 °C); IR (KBr) 1686 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.57 (s, 2H), 7.23–7.51 (m, 4H), 3.0 (s, 4 H), 2.39 (s, 6 H); MS (EI) *m*/*z* 288.15 (M).

2c: mp 223–224° C (Lit.[29] 224–225 °C); IR (KBr) 1687 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.33–7.47 (m, 10H), 3.02 (s, 4 H); MS (EI) *m*/*z* 329.03 (M).

2d: mp 161–162 °C (Lit.[29] 162 °C); IR (KBr) 1688 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 7.59 (s, 2H), 7.35 (s, 2H), 6.53–6.71 (m, 4H), 3.08 (s, 4 H); MS (EI) *m*/*z* 240.08(M).

2e: mp 215–216 °C (Lit.[29] 215–216 °C); IR (KBr) 1672 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR 6.97–7.56 (m, 16H), 2.92 (s, 4 H); MS (EI) *m*/*z* 312.16 (M).

Acknowledgements

The work was supported by the National Natural Science Foundation of China (20472001), the Program for the NCET (NCET-04-0590), the Excellent Young Scholars Foundation of Anhui province (04046079), a grant from the Anhui Education Department (2005hbz06) and Anhui Normal University. We are grateful to Prof. Jiping Hu and Prof. Qin Meng for their assistance in running NMR and IR spectra.

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CHI Cambridge Healthtech Institute
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