One-Pot Homogeneous and Heterogeneous Oxidation of Glycerol to Ketomalonic Acid Mediated by TEMPO

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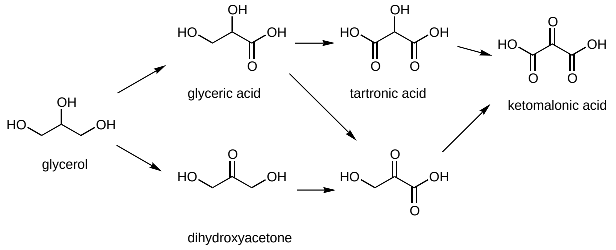
Abstract: Glycerol, an increasingly abundant by-product of biodiesel production, is selectively converted to ketomalonic acid in one pot at pH 10 using NaOCl as regenerating oxidant in water at 2 °C in the presence of catalytic Br^- along with the radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl). The reaction can also be conducted at completion over a sol-gel silica glass doped with the nitroxyl radical. Considering the stability and versatility of such doped glasses, these materials show real promise as reusable metal-free catalysts for the conversion of a readily available and renewable biofeedstock into a highly valued compound.

Keywords: glycerol; heterogeneous catalysis; oxidation; sodium hypochlorite; sol-gel catalyst; TEMPO

Introduction

The catalytic oxidation of alcohols to carbonyl compounds and to carboxylic acids is a highly active research field[1] due to the synthetic and commercial relevance of these compounds as fine chemicals and to the growing environmental and economic problems posed by traditional industrial oxidation processes using (*at best*) stoichiometric amounts of heavy metals or mineral acids.[2] The selective oxidation of carbohydrates, in particular, is a highly desirable conversion due to the number of useful substances that could be obtained from renewable and readily available feedstocks.[3]

Similarly, the selective oxidation of glycerol (1,2,3-propanetriol) is an important research goal due also to its increasing abundance as by-product in the biodiesel production (esterification of oil seeds triglycerides with methanol)[4a] that renders the production of glycerin independent of market demand.[4b] Clearly, an efficient oxidative route would open new markets for this abundant commodity due to the commercial importance of the obtainable oxygenated derivatives (Scheme 1).[5]



Scheme 1. Products obtainable from the selective oxidation of glycerol.

The oxidation of a primary alcohol group of glycerol, for instance, yields glyceric acid and, subsequently, tartronic acid, both commercially useful compounds obtained by glycerol oxidation with HNO_3;[6] on the other hand, the oxidation of a secondary hydroxy group of glycerol yields the important fine chemical dihydroxyacetone, while the oxidation of both primary *and* secondary alcohol groups affords the highly functionalised molecule ketomalonic (or mesoxalic) acid, a valuable compound with potential applications as an organic synthon[7] whose chlorophenylhydrazone was recently found to show relevant biological activity as an anti-HIV agent.[8]

Similarly to what happens with carbohydrates, however, the extensive functionalisation of the triol glycerol molecule with hydroxy groups of similar reactivity renders its selective conversion particularly difficult. Moreover, glycerol is easily converted to formaldehyde, formic acid and CO_2 and in some cases mass balances as low as 20% were observed[9] with good selectivities at high glycerol conversion difficult to achieve due to rapid overoxidation, and high selectivities becoming more difficult as the compounds become more oxidised.

Hence, for instance, the catalytic aerobic oxidation of glycerol in water over carbon-supported Pt at 50 °C yields glyceric acid with a maximum 70% yield obtained at pH 11;[5] while supported over CeO_2, Pt catalyses the oxidation of *both* primary alcohols giving tartronic acid in 40% yield.[10] Finally, at acidic pH a Pt/C catalyst promoted with bismuth favours the formation of dihydroxyacetone[11] with an optimised maximum 37% yield at 70% glycerol conversion.[5]

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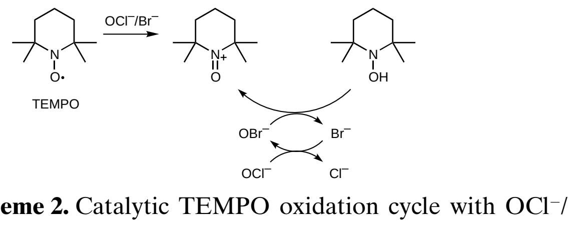
These differences in selectivity can be exploited to catalytically synthesise ketomalonic acid in a 2-step aerobic process with an overall 40% yield converting glycerol first to tartronic acid over a Pt/CeO_2 catalyst, and then tartronic acid to ketomalonic acid by replacing the first catalyst with PtBi/C;[10] interestingly, when a single *multifunctional* supported $BiPtPd/CeO_2$ catalyst is used either under basic[12a] or acidic[12b] conditions, glycerol is directly converted to poly(ketomalonate) in an elegant one-pot oxidative polymerisation process affording a high molecular weight polycarboxylate.

Oxidative dehydrogenations of alcohols over supported noble metal catalysts, however, generally suffer from the low stability of supported metals in the oxidative environment requiring high metal/substrate ratios, along with a thorough control of the reaction conditions to minimise the formation of undesired by-products which, nonetheless, are always present in the reaction mixture.[5,7,9–12]

On the other hand, stable organic nitroxyl radicals of the TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) family are increasingly used for the catalytic oxidation of alcohols to carbonyl (and carboxyl) compounds due to the pronounced selective activity and *versatility* of the actual oxidant species $TEMPO^+$, easily (re)generated *in situ* by a variety of primary oxidants under mild conditions either in water, in organic solvents or in biphasic systems.[13] A TEMPO-mediated process in water using bleach as primary oxidant, for example, is now commercially used for the synthesis of uronates in high yields starting from carbohydrates (Scheme 2),[14] which is based on the regioselectivity of the oxoammonium ion $TEMPO^+$ for the oxidation of primary *vs.* secondary alcohols in alkaline environment.

It is therefore somehow surprising that, in contrast to the number of studies on catalytic dehydrogenations over noble metals mentioned above, to the best of our knowledge no study reports on the employment of TEMPO in the oxidation of glycerol. This is even more surprising considering that the superiority of TEMPO over metal catalysis for sugar oxidations was reported,[15] and also that encapsulated sol-gel silica-entrapped TEMPO was recently found to be a reusable catalyst for the same conversion.[16]



Scheme 2. Catalytic TEMPO oxidation cycle with OCl^-/Br^- as terminal oxidant.

Now, we report that at pH 10 TEMPO is a selective and highly active catalyst for the homogeneous oxidation of glycerol in *one pot*, affording high yields of ketomalonic acid with $NaOCl/Br^-$ as regenerating oxidant. We also show that microporous sol-gel silica glasses doped with TEMPO are stable heterogeneous catalysts for the same conversion allowing easy catalyst separation from the reaction mixture and recycle.

Results and Discussion

Homogeneous Oxidation

The reaction started immediately after adding TEMPO to the reactants in solution with extremely fast generation of acid. No induction time typical of TEMPO-mediated sugar oxidations was observed (Figure 1):

$$RCH_2OH + 2\ OCl^- + OH^- \xrightarrow[\text{pH 10, 2 °C}]{\text{TEMPO, Br}^-} RCOO^- + 2\ H_2O + 2\ Cl^- \quad (1)$$

The ^{13}C NMR (Figure 2) and FT-IR spectra show evidence that the reaction product is the sodium salt of ketomalonic acid with the NMR signals of the carbonyl carbon resonating at 175 ppm and the carboxyl signal observed at 168 ppm; the infrared spectrum, in its turn, coincides with that of authentic sodium ketomalonate.

Consumption of 3 mmol of hydroxy groups per mmol substrate indicates complete oxidation of glycerol's alcoholic groups, with TEMPO being the actual oxidation mediator since when *no* TEMPO is added to the glycerol solution in the presence of NaOCl and Br^- at pH

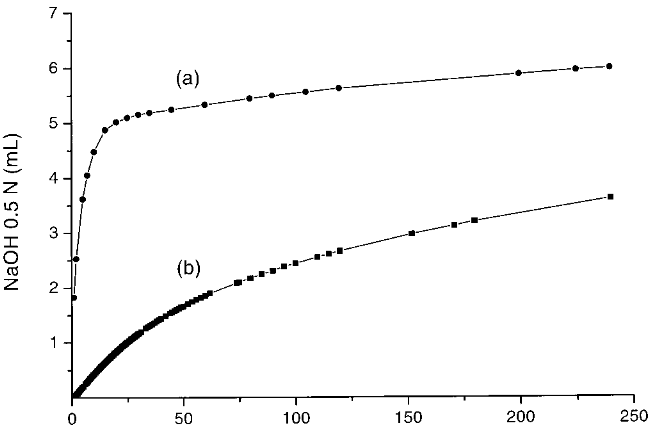


Figure 1. Kinetics of the NaOBr glycerol oxidation at 2 °C mediated by (a) homogeneous TEMPO and, (b) by sol-gel silica-entrapped TEMPO.

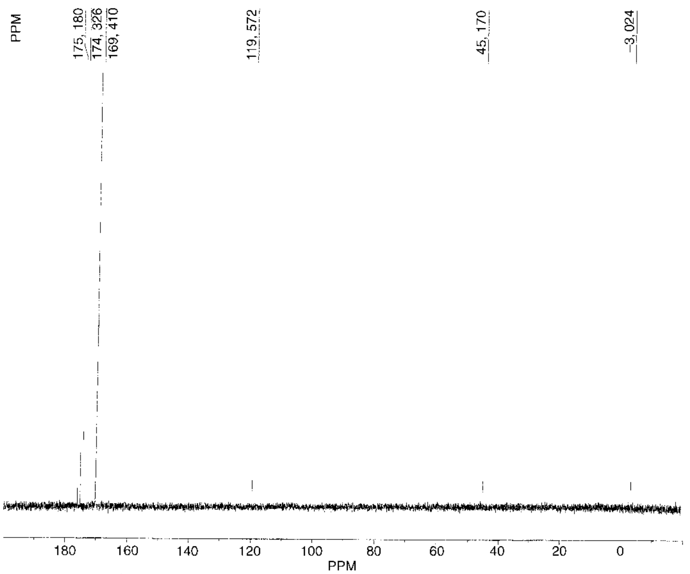


Figure 2. ^{13}C NMR spectrum of sodium mesoxalate obtained upon glycerol oxidation mediated by TEMPO.

10, the oxidation proceeds very slowly (0.130 mmol of OH^- consumed after 2 h) yielding low amounts of dihydroxyacetone and glyceric acid (5% and 2%, respectively) but *no* ketomalonic acid.

Upon the addition of 6.5% mol TEMPO, on the other hand, after 30 minutes only, most of the added glycerol substrate was directly converted to ketomalonic acid (average TOF ~70 h^{-1}), while the by-products tartronic acid (~0.6%, rt = 13.43 min) and dihydroxyacetone (~10%, rt = 24.35 min) also present in solution were progressively oxidised to ketomalonic acid until, after 3 h of reaction, a modest amount of dihydroxyacetone (~2%) was the sole by-product left in solution, with an overall 98% selectivity to ketomalonic acid at complete glycerol conversion.

The low temperature and the pH applied in the reaction minimise the oxidation of primary and secondary hydroxy groups by hypochlorite,[17] and it is TEMPO that mediates *also* the oxidation of the latter alcohol groups. Indeed, we attempted the oxidation of authentic tartronic acid under the same conditions as for glycerol oxidation and *no* formation of ketomalonate was observed until the addition of catalytic TEMPO (6.5 mol %), whereupon the oxidation of tartronic acid's H-C-OH function suddenly started with fast base consumption (due to consumption of hypochlorite in equilibrium with HOCl, Equations 2 and 3), eventually yielding quantitative conversion of tartronic to ketomalonic acid.

$$R^1R^2CHOH + OCl^- \xrightarrow[\text{pH 10, 2 °C}]{\text{TEMPO, Br}^-} R^1R^2CO + H_2O + Cl^- \quad (2)$$

$$OCl^- + H_2O \rightleftharpoons HOCl + OH^- \quad (3)$$

Finally, the pH of the oxidation had a crucial influence on the activity, which is typical of TEMPO mediated oxidations.[13] Hence, at pH 7 the reaction did *not* proceed while the reaction rate increased up to a maximum at pH 10, decreasing at more alkaline pH probably due to consumption of $TEMPO^+$ through basic dismutation.[18]

Heterogeneous Oxidation

Having recently introduced sol-gel silica glasses doped with TEMPO as recyclable catalysts for carbohydrate oxidation,[15] we attempted the oxidation of glycerol over such sol-gels using as catalyst a microporous xerogel prepared from a sol at pH 6 (SG-TEMPO, 300 μmol radical/g).

Under the same conditions as for the homogeneous process, oxidation started immediately upon the addition of the solid catalyst as shown by rapid acid generation (Figure 1b). Again, glycerol was converted to ketomalonate with low amounts of dihydroxyacetone and tartronic acid produced as intermediate by-products even if, due to the diffusional limitations imposed by the narrow pore network (pores average size ~15 Å), the reaction rate was considerably lower (~ TOF 4 h^{-1}) than in the homogeneous conversion.

However, in each catalytic run mediated by the doped sol-gel no leaching of the encapsulated active species in solution was detected (elemental analysis of the reaction filtrate) and the reaction was heterogeneous in nature as proved by the lack of further reactivity of the reaction filtrate obtained upon separation of the catalyst shortly (30 min) after the beginning of reaction.

Catalyst Stability and Recyclability

Heterogeneous catalyst stability is truly measured by the *intermediate* yields after a given reaction time in consecutive reaction runs, since in case of absolute stability a constant yield in all subsequent runs should be expected.[1,19]

Reaction yields after 1 h of reactions presented in Figure 3 show indeed that SG-TEMPO is remarkably stable and this is in contrast to the low stability of silica-anchored TEMPO employed in water in the analogous oxidation of methyl-glucose with OCl^-/Br^-.[20]

To explain these differences in stability, it should be considered that in contrast to traditional surface derivatisation methods that leave the anchored nitroxyl radicals unprotected at the material surface, the sol-gel homogeneous encapsulation *isolates* the radicals within nanoporous sol-gel cages, that is within the hundreds of square metres per gram of internal surface area (430 m^2/g for SG-TEMPO) compared to the negligible amount of molecules entrapped at the outer reaches

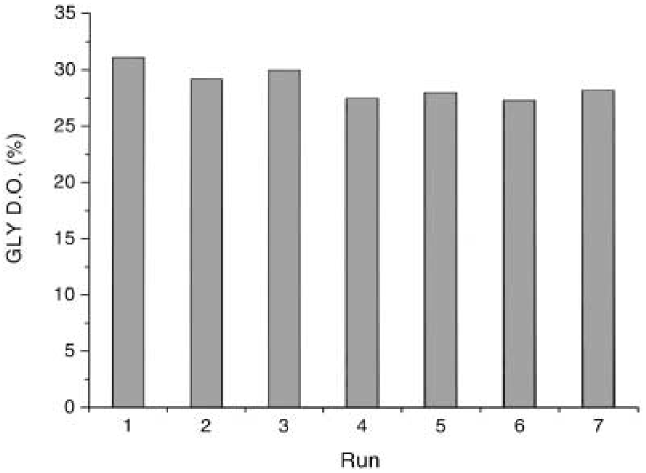


Figure 3. Degree of oxidation of glycerol (GLY D.O.) over SG-TEMPO with OCl^-/Br^- as primary oxidant after 1 h reaction time in consecutive reaction runs.

(1 – 2 m^2/g) of the particulate material.[21] And it is precisely this unique structural feature of sol-gels that protects the radicals from the *intramolecular* quenching of the molecules bound in proximity at the silica surface, that was recently found to be responsible for the continuous decrease in the activity of silica-anchored TEMPO in consecutive alcohol oxidation runs with OCl^-/Br^- as internal oxidant.[1]

To investigate thus the effect of reaction on the structure of the catalyst sol-gel cages, the EPR spectra of SG-TEMPO before and after oxidation were recorded (Figure 4).

Besides analogous peak intensities (the spectra are qualitative, taken on powder samples packed in a glass tube for the analysis), the EPR signals show that upon reaction both the distance between the outer lines (related to the nitrogen hyperfine coupling constant of the interaction of the unpaired electron with the spin of ^{14}N nucleus)[22] and the line width (related to the probe rotation correlation times)[22] remain practically unvaried showing, respectively, no change in the *polarity* and in the *viscosity* sensed by the entrapped spin label chemically bound[16] to the sol-gel cage. This is likely due to the pronounced amount of bound water molecules within the cages of the original hydrophilic silica gel resulting in an high degree of hydrogen bonding between the Si-OH groups at the cage surface and said water molecules, which is unmodified upon reaction of the catalyst in aqueous bleach.

Evidence for a lack of degradation of the catalyst silica structure in the buffered alkaline reaction environment was obtained by FT-IR analysis of the catalyst prior to and after 7 oxidative runs with the broad signals overlapping in the 1085 – 1100 cm^{-1} region due to the Si-O-Si asymmetric stretching[23] showing that the silica polymeric backbone is unaffected by the prolonged use in the reaction system.

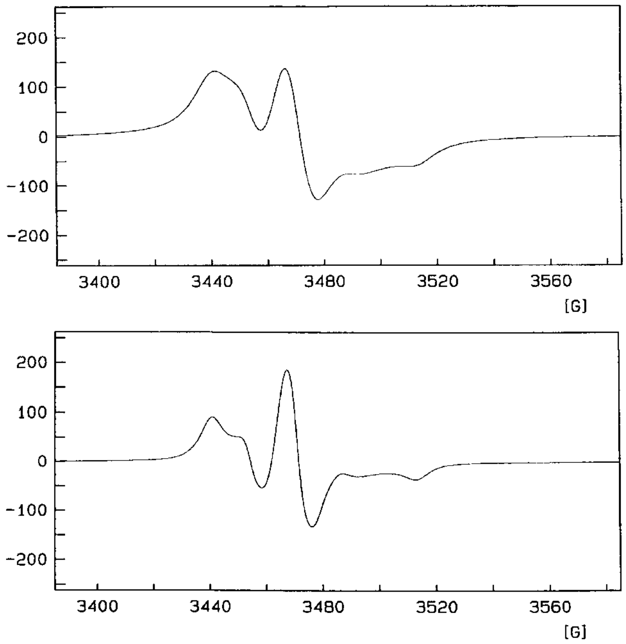


Figure 4. EPR spectra of the xerogel SG-TEMPO before (above) and after (below) reaction in aqueous bleach.

Finally, the catalyst morphology revealed by scanning electron microscopy (SEM) shows that the xerogel is essentially constituted of silica aggregates and magnification up to a 50,000 factor (Figure 5) reveals that in contrast to most powders the gel is *nanostructured* which – given that the surface geometry experienced by the approaching reactant molecules has a profound effect on the material reactivity,[24] and that the structural properties of sol-gels can be tailored to meet a vast range of requirements[25] – may be a relevant subject for further investigations aimed at optimisation of the materials catalytic performance.

Conclusions

In conclusion, we have discovered that TEMPO is an active and selective catalyst affording high yields of ketomalonic acid from glycerol by simply using NaOCl as primary oxidant under very mild conditions. Moreover, we show that sol-gel silica xerogels doped with the radical are recyclable heterogeneous catalysts for the same high-yield conversion while retaining their selective activity. Considering the enormous versatility of both technologies (the sol-gel process for the production of reactive materials[25] and TEMPO-mediated alcohol oxidations[13]) together with the usefulness of ketomalonic acid, these findings might open the way to an high value-added commercial conversion[26] of an increasingly abundant biomass product into a valuable fine chemical.

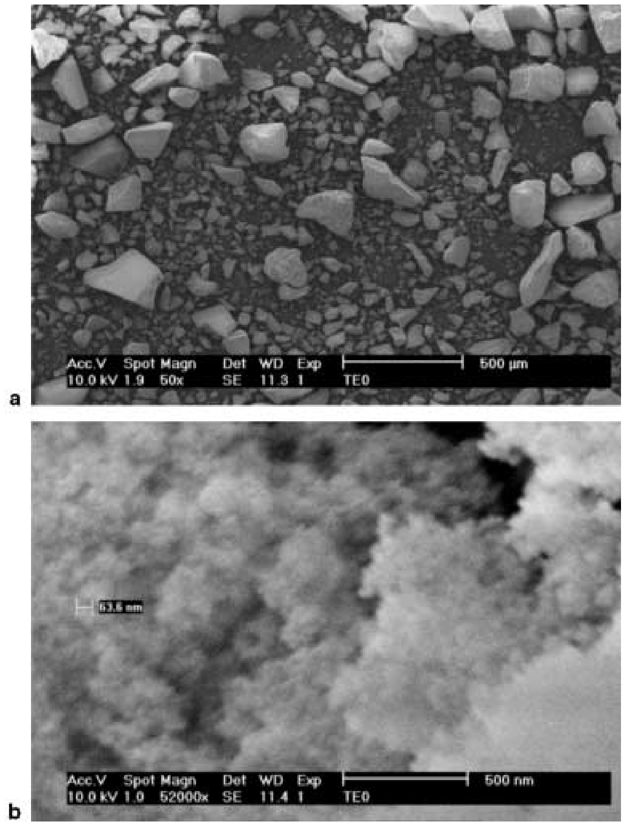


Figure 5. SEM photographs of the SG-TEMPO xerogel at 500 (**a**) and 50,000 (**b**) magnifications.

Experimental Section

Materials and Reagents

Aqueous sodium hypochlorite (13% w/w, 1.2 g mL^{-1}) was obtained by Fluka (Buchs, Switzerland). Glycerol (99.9% purity) and all other chemicals were obtained by Aldrich (St. Louis, MO, USA) and used without further purification. The preparation of the catalytic xerogel (SG-TEMPO, obtained by a sol precursor with molar ratio $Si{:}H_2O{:}MeOH = 1{:}8{:}5$) through reductive amination of 4-oxo-TEMPO with 3-aminopropyltrimethoxysilane followed by sol-gel hydrolysis and co-polycondensation with $Si(OMe)_4$ was reported elsewhere.[16]

General Oxidation Procedures

A solution of glycerol (62.5 µL, 1 mmol) and NaBr (6.78 mg, 6.6% mol) in 25 mL of distilled water immersed in an ice-bath was added with NaOCl (2.80 mL, 6 mmol) in 20% molar excess with respect to the amount needed for conversion of glycerol primary and secondary alcohols to carboxyl and carbonyl groups, respectively. The pH was adjusted to 10 and kept at this value throughout the oxidation by the addition of 0.5 M NaOH, controlled by a pH stat. The reaction started immediately after adding TEMPO (10.36 mg, 65 µmol; or, in equivalence, 220 mg of SG-TEMPO), and the oxidation was followed by the consumption of NaOH as a function of time and by withdrawing samples (quenching the excess bleach with ethanol). When the reaction was complete (no more acid formation), the reaction product was precipitated with cold ethanol (50 mL, – 20 °C), filtered and extensively washed with EtOH (80%, v/v), prior to drying at 40 °C and analysis of the resulting white powder by NMR and FT-IR. In the heterogeneous oxidation, after reaction was complete the reaction mixture was filtered and the powdered solid catalyst recovered, washed with water and EtOH, air-dried and reused as such in a consecutive reaction run.

General Methods

Acid formation was monitored by an automatic titrator (Mettler-Toledo DL50) and the reaction products detected at 215 nm. The HPLC column system (Alltech IOA 1000 for organic acids) was connected in series with a UV-Vis detector (Shimadzu) using 0.005 M H_2SO_4 as mobile phase. Yields were calculated by the calibration curves obtained using authentic reagents and by the isolated product. The NMR spectra in D_2O were recorded on a Bruker spectrometer working at a proton resonating frequency of 250 MHz; the EPR experiment was conducted on a Bruker spectrometer working at medium frequency (50 kHz) and low amplitude (0.504 G) modulation. The FT-IR spectra were obtained on a Bruker Vector 22 spectrometer from samples dispersed in KBr, and the SEM photographs taken with a Philips XL 30 ESEM scanning electron microscope. Textural N_2-BET values of the sol-gel were obtained on a Carlo Erba 1900 Sorptomatic surface analyzer for powders.

Acknowledgements

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