

Sol-gel entrapped TEMPO for the selective oxidation of methyl α -D-glucopyranoside†

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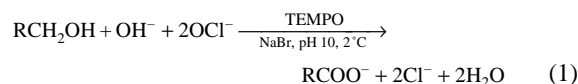
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The sol-gel entrapment of TEMPO within a silica matrix yields an efficient and recyclable catalytic system for the selective oxidation of methyl α -D-glucopyranoside (MGP) in water with NaOCl as primary oxidant, thus opening the way to the heterogeneous catalysis of the conversion of sugars into valuable uronates.

The selective oxidation of carbohydrate primary alcohols into carboxylic acids yields uronates, compounds with valuable biochemical properties.¹ Stable organic nitroxyl radicals belonging to the TEMPO family are excellent catalysts for this selective oxidation.² The radicals are soluble in H₂O (ca. 1% w/w) where, in the presence of alkaline (pH 9–10) NaOCl as primary oxidant along with a catalytic amount of bromide, they mediate the conversion of –CH₂OH groups into –COO[–] with complete selectivity for the primary alcohol groups:



A catalytic amount of bromide is added in order to increase the reaction rate upon fast formation of OBr[–] that in its turn generates *in situ* the catalytic oxidant, the oxoammonium salt TEMPO⁺.³ In this way the important detoxifying agent D-glucuronic acid,¹ previously produced enzymatically on a small scale,⁴ can now be easily obtained through the catalytic oxidation of D-methylglucose.

Apart from being clean and selective, reaction (1) is rapid and quantitative; its comparison with the heterogeneous oxidative dehydrogenation of methyl 4-O-methylglucose on Pt/C reveals the superiority of TEMPO mediated oxidation.⁵ Of relevance to this report is also the commercial production of ascorbic acid currently prepared either through the enzymatic oxidation of the –CH₂OH group in D-sorbose under cumbersome reaction conditions, or by the oxidation of sorbose primary alcohols with HNO₃.⁴

Clearly, considering the efficiency mentioned above and the commercial relevance of uronates, the immobilization of the nitroxyl radicals within a solid support would be a major advantage in the prolonged quest for heterogeneous catalysts for liquid-phase oxidations of sugars. An obvious prerequisite is that the catalytic material retains the activity of the radicals and is stable over prolonged time of use.

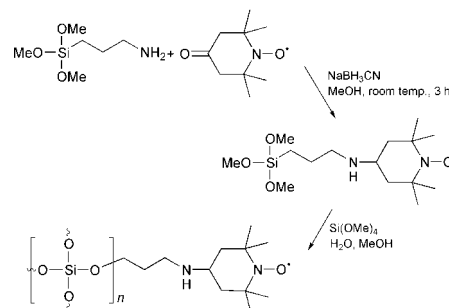
With these aims, several immobilization procedures have been reported in which the TEMPO moiety has been covalently linked either to organic polymers^{6,7} or to a functionalized aminopropyl silica.^{8,9} In all of the reported cases, the immobilization was carried out by heterogeneous reaction between a radical (or a precursor) functionalized in position 4 and a suitable function of the polymer. The catalytic organic polymers thus obtained were tested in the oxidation of organic alcohols and showed *lower* activity and stability of the radicals

under solution homogeneous reactions.^{6,7} On the other hand, TEMPO supported on aminopropyl-derivatized silica employed in the oxidation of various alcohols in a biphasic (H₂O–CH₂Cl₂) reaction system with NaOCl as co-oxidant, was found to be highly active, selective and recyclable.⁹ However, an attempt to use this anchored TEMPO with sacrificial NaOBr for the oxidation of anomerically protected D-glucose in water, resulted in rapid loss of activity upon 3 consecutive oxidative runs.⁹ Heeres *et al.* concluded that azeotropic distillation is the optimal method for the recovery of organic nitroxyl radicals in aqueous oxidations of carbohydrates.^{8b}

The sol-gel technology offers several advantages over the classical immobilization procedures employed in the preparation of heterogeneous catalysts.¹⁰ Depending on the needed utilization, sol-gel materials employed in catalysis are microporous (pore sizes < 15 Å) or mesoporous (20–100 Å); very often, provided that the reagents in solution have smaller size than the average pore diameter, these materials afford superior catalytic performances compared with similar heterogeneous catalysts prepared by classical impregnation or surface derivatization methods.¹¹ Inorganic sol-gel supports are indeed superior in their thermal stability, inertness towards and protectability of the entrapped molecules, and in their porosity and high surface areas (several hundreds of m² g^{–1}); moreover, the sol-gel doped materials show chromatographic properties, *i.e.* they *concentrate* the reagent at the surface enhancing (even by orders of magnitude) the chemical sensitivity and selectivity of the reactions with the dopant.¹⁰

Here we report that sol-gel silica organically modified with TEMPO (Scheme 1) is an effective, recyclable catalyst for the NaOBr oxidation of sugars into uronates.† The TEMPO moiety was tethered to (CH₃O)₃Si(CH₂)₃NH₂ by reductive amination of TEMPON (4-oxo-TEMPO). The reaction was followed by FTIR where the C=O peak at 1720 cm^{–1} decreased rapidly and the C=N peak increased at 1670 cm^{–1} showing clear evidence of CO amination. The C=N bond was thus reduced with NaBH₃CN and the radical monomer homogeneously entrapped within a silica matrix by the sol-gel process, *i.e.* by hydrolysis and co-polycondensation of the radical precursor with Si(OCH₃)₄ in aqueous methanol.

The catalyst was then used in the oxidation of MGP to the corresponding uronic acid.† In each reaction run no other products apart from the uronate (whose content was also



Scheme 1

† Electronic Supplementary Information (ESI) available: details of the preparation of a typical catalyst and its use in the oxidation of MGP to the corresponding uronate. See <http://www.rsc.org/suppdata/cc/b0/b0030961/>

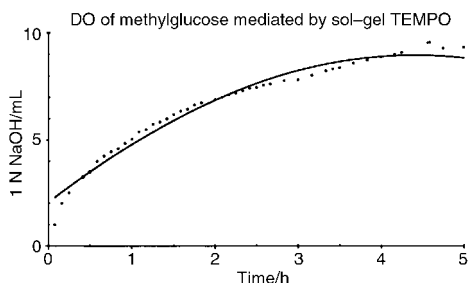


Fig. 1 The kinetics of the selective oxidation of MGP with NaOBr mediated by sol-gel entrapped TEMPO.

measured with the colorimetric test for uronic acids¹²) were detected in the reaction mixture and the catalyst retained its activity, as well as its shape and appearance, in the 4 consecutive reaction cycles in which it was tested affording at each run a high degree of oxidation (DO, ca. 95%); no leaching of entrapped radicals in solution was detected (with a spectroscopic limit of detection of 10 ppm). This is important since many heterogeneous oxidations can actually be promoted by catalyst leached in solution.¹³ Separating the catalyst from the reaction mixture shortly (30 min) after the beginning the oxidation, we tested the mother liquor and no extra formation of uronate was observed (Fig. 1).

According to the known stability of sol-gel materials mentioned above, we observed high activity of the material and *no* modification of the EPR spectrum of the doped glass before and after the oxidative runs (Fig. 2). Comparing the EPR spectra of sol-gel silica TEMPO and TEMPO impregnated on commercial silica, Lev *et al.* reported that sol-gel TEMPO yields absorption peaks similar to TEMPO dissolved in H₂O, *i.e.* considerably narrower than those shown by TEMPO impregnated on SiO₂; since the width of EPR absorption peaks is inversely proportional to the speed of rotational motion of the molecule containing unpaired electrons (spin label), this means that the molecular environment sensed by TEMPO within sol-gel hydrophilic cages closely resembles that sensed by *free* radicals in H₂O.¹⁴ With our organically modified silica (Ormosil), the radicals experience a situation in between these extremes, *i.e.* they are entrapped within sol-gel hydrophilic cages which resemble the aqueous medium *but* are limited in motion due to covalent linkage to the cage surface, resulting in EPR peaks of width comparable to impregnated TEMPO (Fig. 2). To explain the low activity and lack of recyclability of TEMPO linked to commercial aminopropyl silica (BioSil-NH₂),⁸ one should consider that surface derivatization requires the formation of a new covalent bond through a slow *heterogeneous* reaction and leaves the anchored molecule unprotected at the pore surface; the sol-gel entrapment, on the other hand, greatly protects the radical *within* the silica cage of the final xerogel starting from an *homogeneous* solution of the

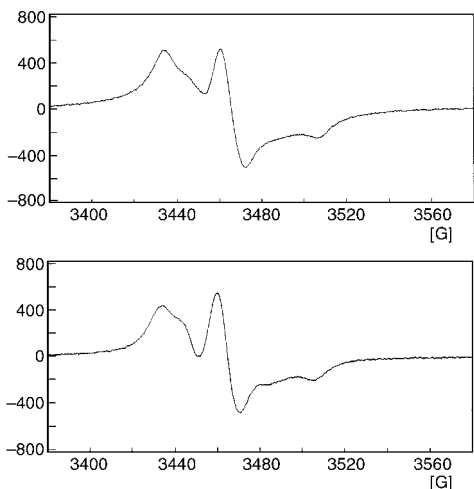


Fig. 2 The EPR spectrum of sol-gel entrapped TEMPO does not change before (a) and after (b) 4 consecutive reaction runs.

dopant species in the alcoholic solution of silicon alkoxide. Furthermore, within the sol-gel cage the entrapped radical senses a hydrophilic environment similar to that of polar aqueous solutions; these cages in fact contain all types (vicinal, geminal, isolated) of silanol groups as well as water and methanol molecules and it is in this inner surface that reactions take place due to the internal porosity and accessibility of the cages (380 m² g⁻¹ vs. few m² g⁻¹ of the outer surface regions of the gel).^{10,11} It may be assumed that the hydrophilic nature of the cage favours the diffusion of hydrophilic sugar molecules toward the active oxoammonium ion tethered at the surface of the cage. In fact, the origin of selectivity of sol-gel entrapped catalysts, which has also been observed in other cases,¹¹ has been attributed to two factors: the effect of the spatial confinement of the narrow pores, imposing a specific approach of the substrate to the catalysts and the participation of the intracage silanol groups in hindering free tumbling of the substrate molecule, directing specific orientational approach to the catalyst through the hydrogen bonds between the substrate and the pore-cage surface.

In conclusion, we found that sol-gel entrapped TEMPO is an efficient heterogeneous catalyst for the selective oxidation of D-methylglucose rapidly (turnover frequency ~ 5 h⁻¹) affording high yields of the uronate and retaining its activity and selectivity upon several consecutive reaction cycles. The rates are 15 times lower than an homogeneous reaction³ due to diffusional limitations imposed by the narrow pore network. A limitation, however, that is balanced by the advantages of the heterogenization. With the aim of practical, industrial application where continuous processes are often sought¹⁵ it should be kept in mind that fundamental properties of the sol-gel catalytic materials (including the form: monoliths, rods, granules, powders and films, surface area, hydrophobicity, *etc.*) can be *tailored*, varying parameters such as the ratio of metal to H₂O, the amount of alcohol employed as co-solvent, the nature of alkoxide, the pH, the temperature, the drying time and other important parameters. These and other aspects have been patented.¹⁶

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