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Chiral resolution of R and S 1-phenylethanol on glassy carbon electrodes

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ABSTRACT

The electrochemical oxidation of the chiral alcohol 1-phenyl ethanol (1PE), on carbon electrodes, using TEMPO and an achiral (luitidine) and chiral ((−)-sparteine) base was reinvestigated in order to resolve conflicting reports in literature and to ascertain whether electrochemical chiral resolution is indeed possible with this system. Investigations using electrochemical and FTIR techniques reveal that chiral oxidation occurs due to modification of the working electrode material by the chiral base. This important observation has not been reported previously, in relation to the mechanism discussed here.

1. Introduction

The chiral alcohol, 1-phenyl ethanol (PE) is an important intermediate in many pharmaceutical syntheses, for example, enantiopure PE is used in lipase catalysed asymmetric transformations. There are several literature reports of the use of nitroxyl radicals as catalysts for alcohol oxidation [1,2]. TEMPO (2,2,6,6-tetramethyl-piperidinyloxy, Scheme 1) a redox active molecule is one of the favourite sources of the nitroxyl radical (Scheme 1a). The radical itself acts as a weak oxidant, but combined with a primary oxidant such as sodium hypochlorite, a cationic species forms (Scheme 1b) which is a much stronger oxidizing agent. After oxidation of the alcohol, the primary oxidant is also involved in regeneration of the TEMPO from its reduced hydroxylamine form (Scheme 1c) [1,3]. Redox catalysis of alcohols and amines using TEMPO has also been reported [4,5]. However, the mechanisms for the redox catalysis are not clear, and many conflicting reports exist [6,7,11]. There is consistency in all the reports that the TEMPO must first be oxidized to a TEMPO cation (Scheme 1b), which subsequently oxidizes the alcohol. The TEMPO/cation oxidation has a reversible oxidation potential at approximately +0.4 V vs Ag/AgNO$_3$ [8]. At constant TEMPO concentrations, the peak current should depend on alcohol concentration. A weak base such as 2,6-lutidine is also required to facilitate proton transfer. Discrepancy lies in the transition state formed during the alcohol oxidation, and in the mechanism of catalyst regeneration [9–11].

TEMPO itself is achiral, so no enantiomer resolution is expected. However, chiral TEMPO derivatives have been synthesized and used in enantiomer resolutions [2,8,9,12]. (6R,7S,10R)-4-oxo-2,2,7-trimethyl-10-isopropyl-1-azospiro[5.5]-undecane-N-oxyl was used as the chiral electro-catalyst for the amperometric determination and optical purity of (R)-1-PE in the presence of the (S)-form. However, chiral TEMPO derivatives are not readily available, and require a lengthy synthesis, and, moreover are prone to racemisation [2,10].

Instead of using a chiral electro-catalyst, PE has been resolved by using a chiral base such as (−)-sparteine. In a report [10], the surface of a graphite-felt electrode was modified with TEMPO, and the system was found to preferentially oxidize (S)-PE in the presence of the (R)-isomer. Choice of chiral base is important; (−)-strychnine was found to have lower (S)-enantioselectivity compared to (−)-sparteine. After 3 h electrolysis at controlled potential, under nitrogen, the unreacted alcohol was found to contain an impressive 99.6% ee of the (R)-isomer. The modified electrode plus chiral base system could also be applied to chiral resolutions of other secondary alcohols in which the alcohol containing carbon is also the chiral centre. However, these claims were irreproducible, Belgsir and Schafer [11] claim that the TEMPO cation causes oxidation of the (−)-sparteine to an iminium ion and the results reported by Kashwagi and co-workers were incorrect.

This work was carried out to investigate these controversies and to ascertain whether chiral resolution is indeed feasible with this system. Initial experiments were carried out using TEMPO oxidation in the presence of 2,6-lutidine (achiral proton abstractor) in order to resolve the controversy involving the mechanism of

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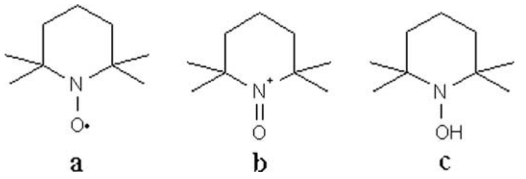


Scheme 1. (a) TEMPO; (b) oxidized form and (c) reduced form.

oxidation. A brief summary of this work is included as it relates to our primary aim of investigating chiral proton abstraction. Investigations of the effect of the electrode material on the oxidation of R and S PE using TEMPO and a chiral base (−)-sparteine was performed. The results indicate two parallel electrochemical reaction mechanisms occur depending on the potential window and base used. The most notable observation is the chiral abstraction of a proton is possible in presence of chiral base at higher potentials. FTIR and electrochemical studies lead us to believe this is due to chiral adsorption of the (−)-sparteine on the electrodes surface, a detail which has not been reported in the previous debates on the conflicting reaction mechanisms proposed for this system.

2. Experimental

2.1. Materials

2.1.1. Unless otherwise stated, all materials were obtained and used without further purification

TEMPO, 2,6-lutidine, sodium perchlorate ($NaClO_4$), (−)-sparteine were obtained from Sigma–Aldrich. Solutions containing TEMPO, were stored in at −5.0 °C, under nitrogen. Before use, the solutions were allowed to warm to room temperature. Racemic PE, acetophenone, S-PE, R-PE, were obtained from Fluka. Platinum (Pt) and glassy carbon (GC) working electrodes (WE), $Ag/AgNO_3$ non aqueous reference electrodes and Pt flag counter (auxiliary) electrodes were all obtained from BASi. Alumina slurry micro polish was obtained from Buehler.

Electrochemical measurements using CV and square wave voltammetry (SQW) were performed using a PARC, Model 263, potentiostat in a Faraday cage under nitrogen.

2.2. Investigation of the TEMPO and base catalysed electro-oxidation of 1-phenylethanol

An acetonitrile solution containing a $NaClO_4$ (0.1 mol dm^{-3}) supporting electrolyte was used as the solvent for all solutions described in this section. Solutions containing 0.1 mmol dm^{-3} TEMPO were prepared and characterized by CV at varying scan rates. PE concentrations (1 mmol dm^{-3}, 15 mmol dm^{-3}, 20 mmol dm^{-3} and 100 mmol dm^{-3}) was added to the TEMPO solution and characterized by CV (at 25 mV/s). Following this, the effect of the achiral base 2,6–luitidine was investigated in solutions containing TEMPO and various 2,6-lutidine/PE concentrations in a 2:1 ratio (PE concentrations of 1 mM, 10 mM, 15 mM, 20 mM, 30 mM and 50 mM) were prepared and characterized by CV (at 25 mV/s and 2 mV/s). The auxiliary electrode was a platinum flag, the WE was a GC, and the reference electrode was a $Ag/AgNO_3$ electrode.

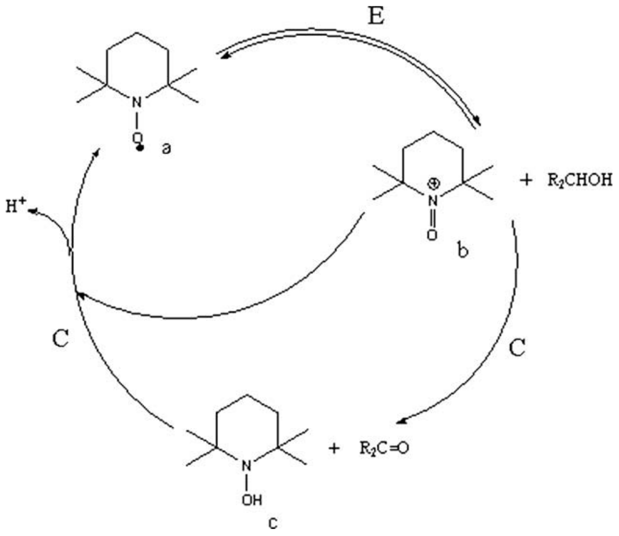
The experiments using the chiral base (−)sparteine were performed with GC as WE. The solutions used were; $NaClO_4$ (0.2 mol dm^{-3}), and TEMPO (0.15 mmol dm^{-3}); $NaClO_4$ (0.2 mol dm^{-3}), TEMPO (0.15 mmol dm^{-3}) and (−)-sparteine (0.02 mol dm^{-3}) and TEMPO (0.15 mmol dm^{-3}), (−)-sparteine (0.02 mol dm^{-3}), $NaClO_4$ (0.2 mol dm^{-3}) and S- or R-PE (0.01 mol dm^{-3}).

To investigate the adsorption effects of the analytes on GC WE electrodes, FTIR experiments were carried out using a Thermo Nicolet Nexus FTIR spectrophotometer. ATR effect and atmospheric contributions from carbon dioxide were corrected by the Omnic software. The electrochemical experiments were performed by performing repetitive CVs in the following solutions in acetonitrile: $NaClO_4$ (0.2 mol dm^{-3}) + TEMPO (0.15 mmol dm^{-3}), $NaClO_4$ (0.2 mol dm^{-3}) + sparteine (0.02 mol dm^{-3}), $NaClO_4$ (0.2 mol dm^{-3}) + phenylethanol (0.01 mol dm^{-3}), and $NaClO_4$ (0.2 mol dm^{-3}) + TEMPO (0.15 mmol dm^{-3}) + sparteine (0.02 mol dm^{-3}) + phenylethanol (0.01 mol dm^{-3}) at 100 mV/s.

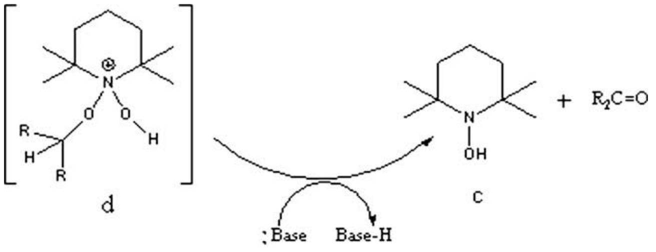
3. Results and discussions

3.1. Achiral oxidation of PE with TEMPO and 2,6-lutidine as proton abstractor

Initially, experiments described by Kashiwagi and co-workers [12] were replicated using 2,6-lutidine as proton abstractor, sodium perchlorate as electrolyte, and acetonitrile as solvent. The expected mechanism [13] for this system (Schemes 2ai and 2aii) was reported to proceed by the reversible oxidation of the radical (a) at the electrode surface (an electrochemical step E). The TEMPO cation (b) formed is a good oxidizing agent, and should oxidize most primary and secondary alcohols (a chemical step, C), via a rather dubious intermediate step (2aii). According to Le Chatelier's principle, removal of the cation will shift the equilibrium, causing oxidation of more TEMPO and resulting in a higher peak current. If this



Scheme 2ai. Literature proposed electrocatalytic oxidation of alcohols with TEMPO. This is an ECC mechanism, where E represents an electrochemical step and C represents a chemical step. The letters represent – (a) TEMPO; (b) TEMPO cation and (c) hydroxylamine.



Scheme 2aii. Literature suggested intermediate (d) formed during the chemical step reacting with the proton abstractor to form a carbonyl compound and hydroxylamine (c).