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Cu(II)-nitroxyl radicals as catalytic galactose oxidase mimics

Arné Dijksman, Isabel W. C. E. Arends and Roger A. Sheldon*
Laboratory for Biocatalysis and Organic Chemistry, Department of Biotechnology, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

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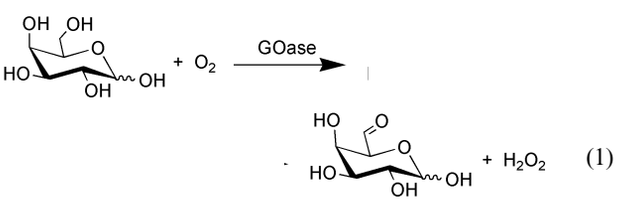
Results from Hammett correlation studies and primary kinetic isotope effects for the CuCl–TEMPO catalysed aerobic benzyl alcohol oxidations are inconsistent with an oxoammonium based mechanism. We postulate a copper-mediated dehydrogenation mechanism, in which TEMPO regenerates the active Cu(II)-species. This mechanism is analogous to that observed for Galactose Oxidase and mimics thereof.

Introduction

The selective oxidation of alcohols into their corresponding aldehydes and ketones is a pivotal reaction in organic synthesis.[1] Traditionally, alcohol oxidations are performed with stoichiometric amounts of inorganic oxidants, notably chromium(VI) reagents.[2] These – often hazardous or toxic – oxidising agents are not only relatively expensive, but they also generate copious amounts of heavy-metal waste. From both an economic and environmental point of view, the development of effective catalytic oxidation processes that simply use oxygen (or air) as the ultimate stoichiometric oxidant, *i.e.* a "green method" for converting alcohols to carbonyl compounds on an industrial scale, remains an important challenge.[3,4]

One approach to developing better catalysts is to mimic the enzymes that perform such transformations *in vivo*, notably alcohol dehydrogenases and oxidases. The advantage of the latter is that they have no stoichiometric cofactor requirement. Within the class of alcohol oxidases, galactose oxidase (GO) occupies a special position.[5] This mononuclear copper enzyme couples the oxidation of alcohols to aldehydes with the reduction of O_2 to H_2O_2 (eqn. 1) through an unusual Cu(II)-phenoxyl radical species in the active site.[6]



(1)

Recently several succesful biomimetic models of GO have been developed by the groups of Stack,[7,8] Wieghardt[9,10] and Fukuzumi.[11] For example, Stack's [Cu(II)BSP], where BSP is a salen-ligand with a binaphthyl backbone (Fig. 1), is able to catalyse the aerobic oxidation of activated (benzylic and allylic) alcohols.[7] The rate determining step of this system was suggested to involve inner sphere one-electron transfer from the alkoxide ligand to Cu(II) followed by hydrogen-transfer to the phenoxyl radical yielding Cu(I), phenol and carbonyl product. Similarly, Wieghardt *et al.* reported a dinuclear Cu(II)-phenoxyl complex which proved to be effective for the aerobic oxidation of non-activated (aliphatic) alcohols as well.[9]

Another system, which bears a superficial resemblance to the galactose oxidase, is the CuCl–TEMPO system first reported by Semmelhack and coworkers.[12–14] The combination of CuCl and the stable nitroxyl radical, TEMPO (2,2,6,6-tetramethylpiperidinyloxy) is able to catalyse the aerobic oxidation of alcohols to the corresponding carbonyl compounds. A mechanism was proposed[12] in which one-electron oxidation of TEMPO by Cu(II) afforded the oxoammonium cation (Fig. 2). The latter oxidizes the alcohol substrate and is itself reduced to the corresponding hydroxylamine, TEMPOH. Re-oxidation of the latter, presumably *via* TEMPO, completes the catalytic cycle.

More recently, another copper-dependent oxidase, laccase, in combination with TEMPO was shown to catalyse the aerobic oxidation of alcohols.[15,16] These reactions were assumed to involve an 'oxoammonium' mechanism,[16] analogous to the Semmelhack mechanism outlined above, rather than a copper-centred oxidation of the alcohol by analogy with the galactose oxidase.

We recently showed that a related Ru–TEMPO catalysed aerobic oxidation of alcohols does not involve an 'oxoammonium' mechanism.[17] Based on results of stoichiometric oxidations with TEMPO, kinetic isotope effects and Hammett correlation studies we proposed a hydridometal mechanism

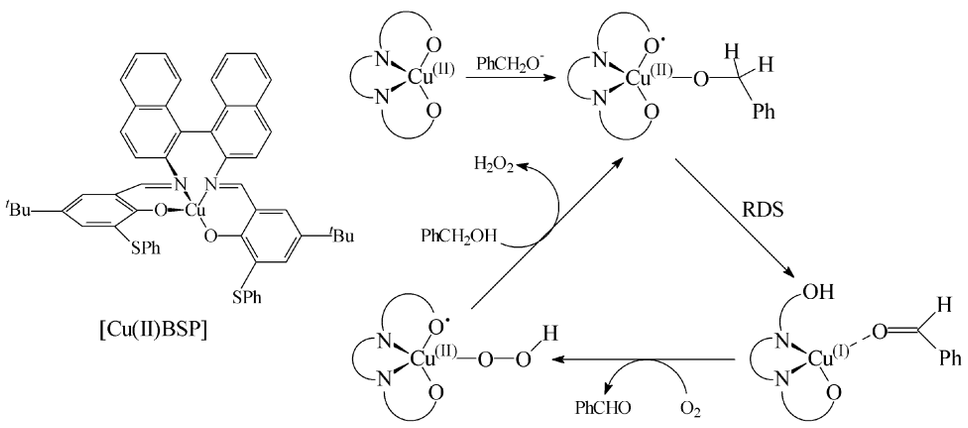


Fig. 1 [Cu(II)BSP]-catalysed aerobic oxidation of benzyl alcohol (adapted from ref. 7).

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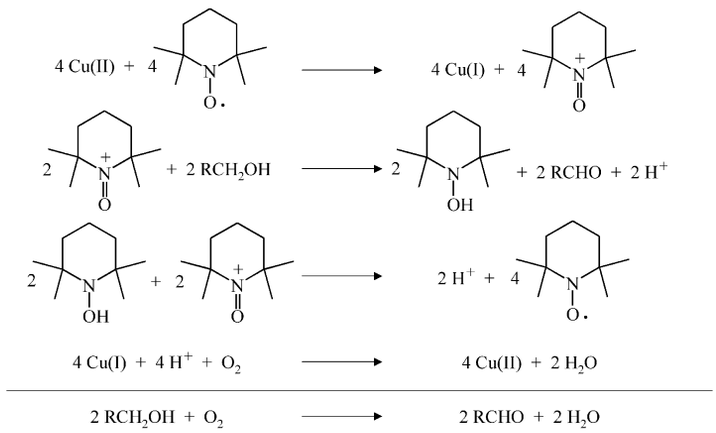


Fig. 2 Mechanism postulated by Semmelhack *et al*. in 1984[12] for the Cu–TEMPO catalysed oxidation of alcohols.

Table 1 CuCl–TEMPO catalysed aerobic oxidation of alcohols[a]

Alcohol[b]	Time/h	TON[c]
p-Methoxybenzyl alcohol	1	9.6
	24[d]	97
Benzyl alcohol	4[e]	18.8
Geraniol	1.75	9.2
Cinammyl alcohol	2.75	9.3

[a] Unless otherwise noted, according to the standard procedure: alcohol (10 mmol), CuCl (1 mmol), TEMPO (1 mmol), DMF (25 ml), 25 °C, O_2 atmosphere. Selectivity towards aldehyde >99%. [b] No reactivity was achieved for 1- and 2-octanol. [c] TON = turn over number (mmol of aldehyde per mmol of catalyst). [d] CuCl (0.1 mmol), TEMPO (0.1 mmol). [e] CuCl (0.5 mmol), TEMPO (0.5 mmol).

involving ruthenium-centred oxidative dehydrogenation of the alcohol affording a ruthenium hydride species. The function of the TEMPO is to facilitate the re-oxidation of this ruthenium hydride species. Based on these results we suspected that the Cu–TEMPO system may involve a copper-centred oxidation of the alcohol, as outlined in Fig. 3, rather than an 'oxoammonium' mechanism. Herein, we report the results of a detailed mechanistic investigation aimed at clarifying this dichotomy.

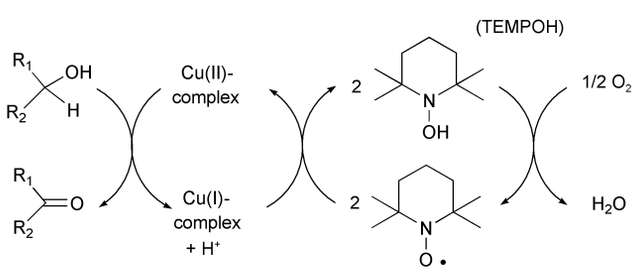


Fig. 3 Copper-centred mechanism for the Cu–TEMPO catalysed aerobic oxidation of alcohols.

Results and discussion

We first applied the Semmelhack procedure (CuCl–TEMPO in dimethylformamide at 25 °C) to the aerobic oxidation of a range of alcohol substrates. Benzylic and allylic alcohols underwent smooth oxidation under these conditions (Table 1). In contrast, simple aliphatic alcohols were unreactive. This is not consistent with an 'oxoammonium' mechanism since oxoammonium cations are known for their broad scope, including the facile oxidation of simple aliphatic alcohols.[18,19]

In the alternative mechanism, depicted in Fig. 3, a key step is the re-oxidation of Cu(I) to Cu(II) by TEMPO. In order to confirm the feasibility of this step we performed an experiment in which CuCl was allowed to react with one equivalent of TEMPO in DMF for 24 h, in an inert atmosphere at 25 °C. This resulted in the formation of a suspension of a yellow–orange compound. Evidence for the oxidation of Cu(I) to Cu(II) was provided by UV measurements (Fig. 4). In this case the experiments were performed with Cu(I) acetate in acetonitrile to avoid the precipitation of the putative Cu(II) complex observed in DMF. Under an inert atmosphere, addition of one equivalent of TEMPO resulted in a colour change from colourless (see spectrum Cu(I)(OAc) in Fig. 4) to green. The UV spectrum exhibited a maximum at *ca.* 670 nm (Fig. 4) consistent with the formation of Cu(II), as verified by reference samples of $Cu(OAc)_2$ in acetonitrile that exhibit the same absorption maximum.

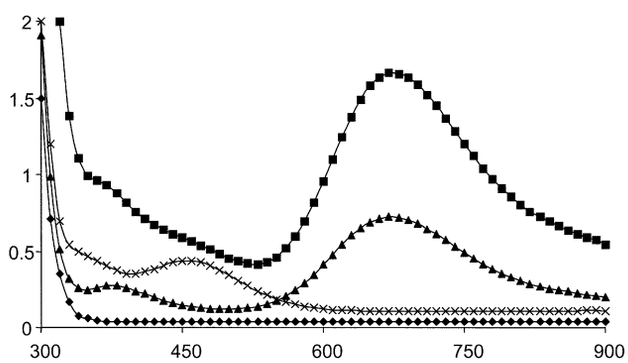
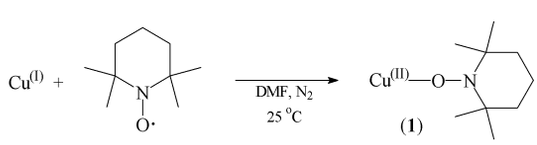


Fig. 4 UV spectra of 2 mM solutions of $Cu^{(I)}(OAc)$–TEMPO (■), $Cu^{(II)}(OAc)_2$ (▲), TEMPO (x) and $Cu^{(I)}OAc$ (◆) in acetonitrile under an inert atmosphere.

We suggest that the formation of a piperidinyloxy copper(II) complex (**I**), *via* one-electron oxidation of Cu(I) by TEMPO, as shown in eqn. 2, is consistent with the experimental observations.



A number of metal compounds are known to undergo one-electron oxidation by TEMPO, to afford piperidinyloxy complexes,[20–22] but this is the first example involving Cu(I) in this conversion.

Addition of aqueous HCl (1 M) to the suspension of piperidinyloxy copper(II) in DMF afforded a yellow–green solution which was shown to contain Cu(II) and (by GC analysis) a 2 : 1 mixture of TEMPO and the corresponding amine TEMPH. We previously showed[17] that the corresponding hydroxylamine, TEMPOH, formed by protonation of the piperidinyloxy anion is unstable and, in an inert atmosphere,

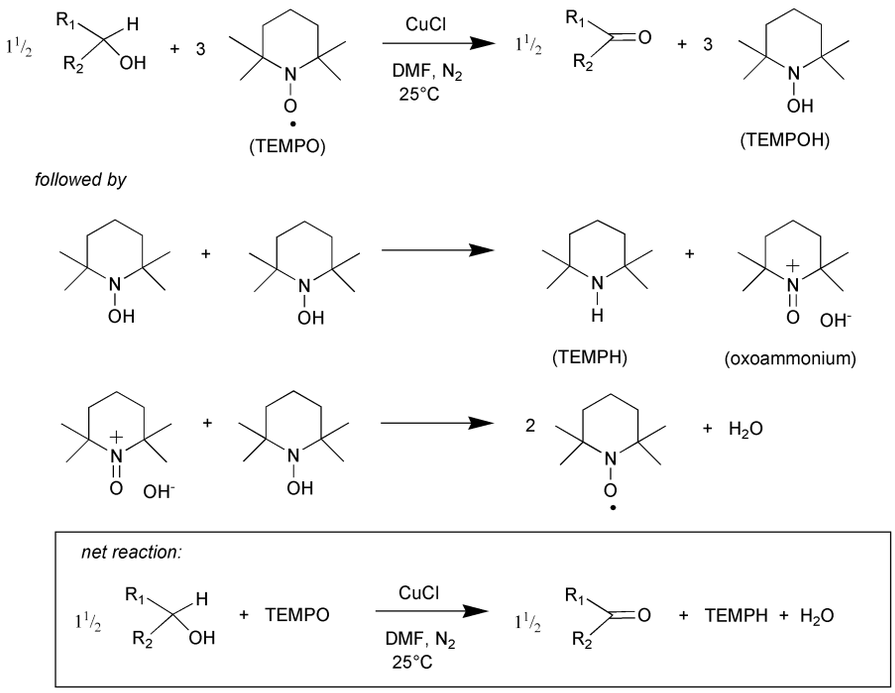


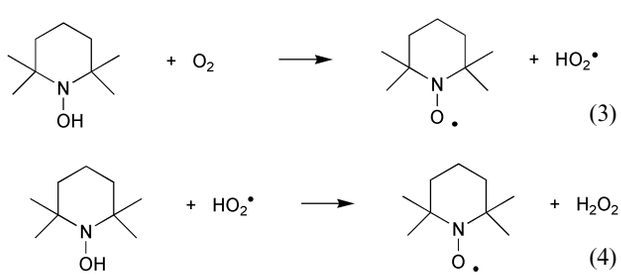
Fig. 5 CuCl-catalysed oxidation of alcohol under nitrogen using TEMPO as terminal oxidant.

spontaneously disproportionates to a 2 : 1 mixture of TEMPO and TEMPH (see Fig. 5). Indeed, attempts to prepare TEMPOH in an inert atmosphere always resulted in the formation of TEMPH.[23] The addition of one equivalent of benzyl alcohol to the yellow–orange suspension of piperidinyloxy copper(II) in DMF afforded a white precipitate of CuCl and a colourless supernatant, which was shown (by GC analysis) to contain one equivalent of benzaldehyde and one equivalent of TEMPH.

Having demonstrated the separate steps involved, we performed the copper-catalysed oxidation of benzyl alcohol in DMF, using TEMPO as the stoichiometric oxidant. After stirring for 24 h at room temperature, benzaldehyde and TEMPH were formed in a 3 : 2 molar ratio. These results can be rationalized on the basis of the reaction scheme shown in Fig. 5. Oxidation of the alcohol by TEMPO, catalysed by copper, affords the carbonyl compound and TEMPOH in a 1 : 2 molar ratio. The latter spontaneously disproportionates to a 2 : 1 mixture of TEMPO and TEMPH, resulting in the overall stoichiometry shown in Fig. 5.

We previously showed that, in the presence of oxygen, TEMPOH is rapidly oxidized to TEMPO,[14] thus rendering the reaction catalytic in TEMPO. The facile conversion of TEMPOH into TEMPO in air contrasts with the observations of Neumann *et al.*[24] who studied the aerobic oxidation of alcohols catalysed by a combination of TEMPO and a heteropoly acid. They postulated that the oxidation of TEMPOH to TEMPO was the slower, rate-determining step. A similar hypothesis was made in a catalytic alcohol oxidation system consisting of a combination of Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates with TEMPO in acetic acid as the medium.[25] These apparently contradictory results can be rationalized on the basis of the pH-dependence of this reaction.[26] We confirmed this by generating TEMPOH in water, by ascorbic acid reduction of TEMPO. On addition of oxygen the orange colour of TEMPO reappeared instantaneously under basic conditions. In contrast, at acidic pH the solution remained colourless for more than an hour. Hence, we conclude that at basic pH aerobic reoxidation of TEMPOH to TEMPO is rapid while at acidic pH it is relatively slow and may be rate-determining, as proposed by Neumann *et al.*[24] At acidic pH the nitrogen of TEMPOH will be protonated making it less susceptible to oxidation.

The oxidation of TEMPOH by oxygen is expected to lead to the formation of hydrogen peroxide *via* the following steps:



However, we did not observe any hydrogen peroxide formation in our Cu–TEMPO catalysed oxidations. On the other hand, we showed, by deliberate addition of hydrogen peroxide during the reaction, that it is not stable under our reaction conditions, presumably owing to copper-catalysed decomposition.

Our results support the mechanism depicted in Fig. 3 in which a key step is the copper-centred dehydrogenation of the alcohol, rather than the previously proposed 'oxoammonium mechanism'.[12] The resulting Cu(I) is rapidly re-oxidized by TEMPO to afford Cu(II) and TEMPOH. The role of oxygen is to re-oxidize the TEMPOH to TEMPO. In separate experiments we showed that oxidation of Cu(I) by oxygen (in acetonitrile) is substantially slower than its oxidation by TEMPO.

Kinetic isotope effects and Hammett correlation studies

Additional evidence for a copper-centred dehydrogenation step was obtained from kinetic isotope effects and Hammett correlation studies. For studies of the kinetic isotope effects α-deutero-*p*-methylbenzyl alcohol was used as the substrate. In this case H/D competition is intramolecular and coordination of the substrate to the catalyst is not a complicating factor. The primary kinetic isotope effect (k_H/k_D) for the Cu/TEMPO catalysed aerobic oxidation of this alcohol at 25 °C was determined to be 5.42. This value indicates substantial C–H bond cleavage on progressing to the transition state and compares exceptionally well with isotope effects observed with other metal-centred dehydrogenations, including galactose oxidase and Stack's biomimetic copper complex (see Table 2). In contrast, a much smaller kinetic isotope effect was observed in the stoichiometric oxidation of the same alcohol with the TEMPO

Table 2 Kinetic isotope effects and Hammett ρ-values for the oxidation of benzyl alcohols

System	Kinetic isotope effect (k_H/k_D)[b]	Hammett ρ-value	Reference
CuCl–TEMPO–O_2	5.42	−0.16	
Oxoammonium chloride	1.7–2.3	−0.3	27
$RuCl_2(PPh_3)_3$–TEMPO–O_2	5.12	−0.58	17
CuCl–TEMPO–N_2[a]	5.77	—	
[Cu(II)BSP]–O_2	5.3	−0.14	7
Galactose oxidase	5.02	−0.09	28

[a] TEMPO is used as stoichiometric oxidant under an inert nitrogen atmosphere. [b] In all cases α-deutero, *p*-methyl benzyl alcohol was used for the determination of KIE.

oxoammonium cation[27] (see Table 2). The close similarity of kinetic isotope effect observed in the stoichiometric oxidation with TEMPO in an inert atmosphere *versus* that observed in the aerobic oxidation in the presence of Cu/TEMPO (k_H/k_D = 5.77 and 5.42, respectively) is consistent with the same mechanism being involved in both cases.

Next a series of substituted benzylic alcohols was oxidized using 1 mol% CuCl. The relative rates for *meta*- and *para*-substituted benzyl alcohols (see Fig. 6) can be readily fitted to the σ parameters. A Hammett ρ value of −0.16 was observed with Cu–TEMPO, which is different to that observed in stoichiometric oxidation with the oxoammonium cation ($\rho \sim -0.3$).[27] In both cases the negative value is consistent with electrons being withdrawn from the reactive centre in the transition state. The rather low ρ value suggests that a mechanism involving the formation of a cationic species, by oxidation of the α–C–H bond, can be excluded. Electron-donating substituents in the alcohol are however expected to favour hydrogen abstraction as was reported by Stack for the Cu(II)BSP complex.[7] The ρ value in this case was −0.14 which is also very small and very similar to the value obtained by us.

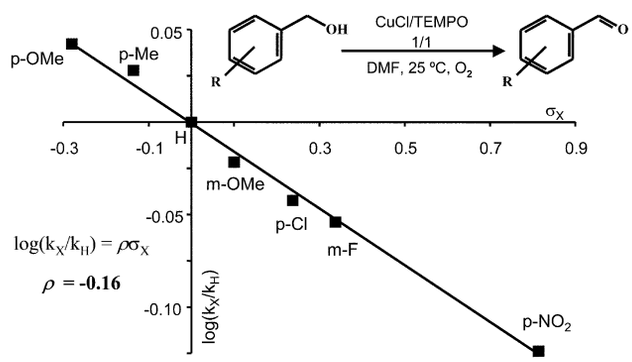


Fig. 6 Hammett plot for the Cu–TEMPO catalysed oxidation of substituted benzylic alcohols.

The similar primary kinetic isotope effects observed with the three copper systems is particularly striking and strongly suggests that the same (copper-centred) mechanism is involved in all three cases. By analogy with a Cu(II)-hydroxide system,[29] we assume that the first step in the dehydrogenation of benzyl alcohol is an alkoxy replacement, *i.e.* the piperidinyloxy ligand is replaced by a benzyloxy group yielding a copper(II)-alkoxide and TEMPOH. This also explains the fact that additional base is not required to achieve good activity, *i.e.* the piperidinyloxy ligand acts as a base and deprotonates the alcohol.

The abstraction of the β-hydrogen of the benzyloxy ligand yielding Cu(I) and benzaldehyde then probably involves – by analogy with the Cu(II)BSP complex – a reaction between the Cu(II)-benzyloxy compound and the copper ligated TEMPO (Fig. 7). Analogous to copper(II)-TEMPO complexes previously reported in the literature,[30] it is very likely that this involves η^2 coordination of TEMPO to Cu(II). As depicted in Fig. 7, the β-hydrogen of the alkoxide ligand is intramolecularly transferred to TEMPO generating a ketyl radical anion and

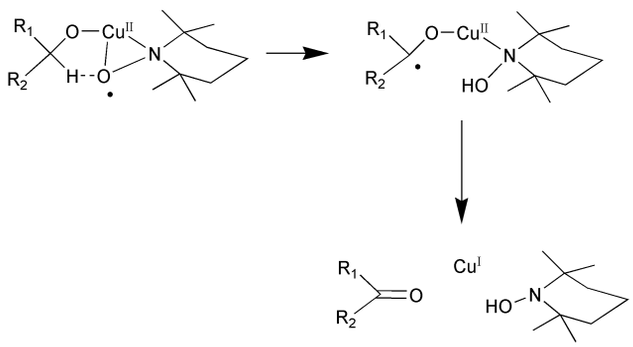


Fig. 7 Intramolecular transfer of β-hydrogen, followed by oxidative elimination.

TEMPOH. Subsequently, inner sphere one-electron transfer from the ketyl group to Cu(II) affords Cu(I) and the carbonyl product. This bears a close resemblance to the rate determining step in the [Cu(II)BSP] catalysed aerobic oxidation of (activated) alcohols (Fig. 1) reported by Stack and coworkers.[7]

The complete mechanism which we postulate for the CuCl–TEMPO catalysed aerobic oxidation of (activated) alcohols, and which summarizes all the results presented above is depicted in Fig. 8. The active Cu(II)-species is generated *via* a one-electron oxidation of Cu(I) by TEMPO. Alkoxy replacement, followed by coordination of a second molecule of TEMPO and intramolecular β-hydrogen abstraction affords the desired carbonyl compound, Cu(I) and TEMPOH. Finally TEMPO is regenerated by rapid air oxidation of TEMPOH.

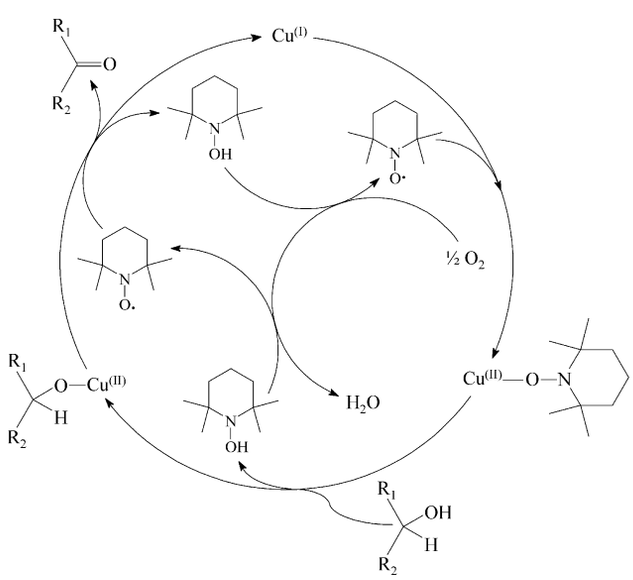


Fig. 8 Postulated mechanism for the CuCl–TEMPO catalysed aerobic oxidation of (activated) alcohols.

In conclusion, we have shown that the Cu–TEMPO catalysed aerobic oxidation of alcohols involves a copper-centred oxidation which bears a close resemblance to the accepted

mechanism for analogous oxidations mediated by galactose oxidase and mimics thereof. Further investigations are currently underway that are aimed at improving the activity of the Cu(I)–TEMPO system in order to broaden the scope to unactivated primary and secondary alcohols.

Experimental

General

The solvents (p.a.) were used as received. TEMPO free radical and copper(I) chloride were purchased from the Aldrich Chemical Co. and used without further purification. Oxoammonium chloride was prepared analogous to a literature procedure.[8] CuOAc was prepared according to literature:[31] Under an inert nitrogen atmosphere, $Cu(OAc)_2$ (4.0 mmol) was dissolved in degassed acetonitrile (40 ml). An excess of copper powder (10.0 mmol) was added to the green–blue Cu(II)-solution and the resulting suspension was stirred for 48 hours. After filtration a colorless Cu(I) acetate solution was obtained.

GC-analyses were done using a CP-WAX 52 CB column (50 m × 0.53 mm).

CuCl–TEMPO catalysed aerobic oxidation of benzyl alcohol

Benzyl alcohol (10.0 mmol; 1.08 g), hexadecane (internal standard; 2.0 mmol; 0.46 g), CuCl (1.0 mmol; 99 mg) and TEMPO (1.0 mmol; 156 mg) were dissolved in DMF (25 ml) and stirred (1000 rpm) under an oxygen atmosphere for 24 hours. Benzyl alcohol conversion and benzaldehyde selectivity were determined using GC-analysis.

Stoichiometric reaction of octan-2-ol and oxoammonium chloride

Octan-2-ol (5.0 mmol; 0.54 g), hexadecane (internal standard; 1.0 mmol; 0.23 g) and oxoammonium chloride (5.5 mmol; 1.05 g) were dissolved in DMF (12.5 ml) and stirred (1000 rpm) for 24 hours. Octan-2-ol conversion and octan-2-one selectivity were determined using GC-analysis.

Synthesis of α-deutero-*p*-methylbenzyl alcohol

α-Deutero-*p*-methylbenzyl alcohol was synthesised according to a literature procedure.[32] ^{1}H-NMR (400 MHz, $CDCl_3$, TMS) δ 7.25 (d, 2H, $^3J_{HH}$ = 8.0 Hz, $2H^{ortho}$), 7.16 (d, 2H, $^3J_{HH}$ = 7.8 Hz, $2H^{meta}$), 4.60 (s, 1H, C*H*DOH), 2.35 (s, 3H, CH_3), 1.69 (d, 1H, $^3J_{HH}$ = 5.1 Hz, O*H*); ^{13}C-NMR (100 MHz, $CDCl_3$, TMS) δ 137.8 (C^{ipso}), 137.4 (C^{para}), 129.2 ($2C^{meta}$), 127.2 ($2C^{ortho}$), 64.9 (t, $^1J_{CD}$ = 21.8 Hz, CHDOH), 21.2 (CH_3); *m*/*z* = 124 (17), 123 (M^+, 92), 122 (25), 108 (100), 106 (33), 94 (50), 93 (31), 92 (32), 91 (48), 80 (71), 78 (52), 77 (36), 65 (28).

Determination of intramolecular kinetic isotope effect

α-Deutero-*p*-methylbenzyl alcohol (5.0 mmol; 615 mg), CuCl (0.5 mmol; 49.5 mg) and TEMPO (0.5 mmol; 78 mg) were dissolved in DMF (25 ml) and stirred (1000 rpm) under an oxygen atmosphere for 24 hours. The resulting reaction-mixture was analysed by GC and the oxidation products, α-deutero-*p*-methylbenzaldehyde and *p*-methylbenzaldehyde, were isolated using Kugelrohr distillation. The intramolecular kinetic isotope effect was determined by ^{1}H NMR.

***p*-Methylbenzaldehyde.** ^{1}H-NMR (300 MHz, $CDCl_3$, TMS) δ 9.95 (s, 1H, C*H*O), 7.75 (d, 2H, $^3J_{HH}$ = 7.8 Hz, $2H^{ortho}$), 7.31 (d, 2H, $^3J_{HH}$ = 7.8 Hz, $2H^{meta}$), 2.42 (s, 3H, CH_3).

α-Deutero-*p*-methylbenzaldehyde. ^{1}H-NMR (300 MHz, $CDCl_3$, TMS) δ 7.75 (d, 2H, $^3J_{HH}$ = 7.8 Hz, $2H^{ortho}$), 7.31 (d, 2H, $^3J_{HH}$ = 7.8 Hz, $2H^{meta}$), 2.42 (s, 3H, CH_3).

Hammett plot studies

Substituted benzylic alcohol (5 mmol), 0.05 mmol CuCl and 0.05 mmol TEMPO were reacted in 12.5 ml DMF at 25°C under an oxygen atmosphere. The $\log(k_x/k_H)$ values for these substituted benzylic alcohols were determined from the initial reaction rate (below 10% conversion) in separate experiments. Reactions were followed by GC relative to internal standard (hexadecane); selectivities to aldehyde were >99% in all cases. Under these conditions (only 1 mol% Cu) conversions obtained after 24 h range from 54% for *p*-NO_2 to 76% for *p*-OMe substituted benzylic alcohols.

Stoichiometric reaction of benzyl alcohol with TEMPO

Benzyl alcohol (1.0 mmol; 108 mg), CuCl (0.1 mmol; 10 mg) and TEMPO (2.0 mmol; 312 mg) were dissolved in DMF (5 ml) and stirred under an inert nitrogen atmosphere at room temperature for 24 hours. After this period, substrate (benzyl alcohol and TEMPO) conversion and product (benzaldehyde and TEMPH) selectivity were determined using GC-analysis.

Stoichiometric reaction of CuCl with TEMPO (followed by addition of HCl)

CuCl (3.0 mmol; 297 mg) was added to a solution of TEMPO (3.0 mmol; 468 mg) in DMF (30 ml) and stirred under an inert nitrogen atmosphere for 24 hours. The resulting yellow–orange suspension was treated with an aqueous hydrogen chloride solution (4 ml; 1.0 M), yielding a clear yellow–green solution. The colour-change is due to the formation of $CuCl_2$ which indeed gives a yellow–green solution upon dissolving it in DMF. The product-distribution (TEMPO–TEMPH) was determined using GC-analysis.

Stoichiometric reaction of CuCl with TEMPO (followed by addition of benzyl alcohol)

CuCl (3.0 mmol; 297 mg) was added to a solution of TEMPO (3.0 mmol; 468 mg) in DMF (30 ml) and stirred under an inert nitrogen atmosphere for 24 hours. The resulting yellow–orange suspension was treated with benzyl alcohol (5.0 mmol; 540 mg), yielding a colourless solution and a white precipitate (CuCl). The product-distribution (benzaldehyde–TEMPH) was determined using GC-analysis.

H_2O_2 stability studies

Benzyl alcohol (10 mmol), 0.1 mmol CuCl, and 0.1 mmol TEMPO were mixed in 25 ml DMF. Addition of 4 mmol H_2O_2 followed after 1.5 h, upon which some gas formation was observed. Iodometric titration of H_2O_2 after 24 h revealed that <5% of hydrogen peroxide was left. Direct mixing of H_2O_2 and CuCl resulted in rapid gas formation and therefore a high catalase activity.

Acknowledgements

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