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# Stepwise oxidation of 1,2-diols resulting from molecular oxygen activation by copper

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## Abstract

The oxidation of 1,2-diols through copper promoted activation of molecular oxygen was studied. The influence of the substituents and experimental conditions is discussed, and examples of catalytic applications are reported.

*Keywords:* Oxidation; Copper; Diol;  $\alpha$ -diketon;  $\alpha$ -hydroxyacid

## 1. Introduction

Environmental and economical constraints are incentives to develop synthetic methods using clean oxidants. The activation of dioxygen through copper compounds has attracted interest not only because of its synthetic applications [1] but also of its diffusion in biological systems. In such systems dioxygen is known to oxidize various substrates at high rates and with good selectivity [2]. In this connection the interest in modelling enzymatic oxidations has greatly increased in recent years, particularly for the galactose-oxidase enzyme in whose presence alcoholic groups are oxidized to aldehyde [3].

According to the literature copper and copper compounds represent an abiological alternative for the oxidation of alcohols by dioxygen [4].

However, in the case of diol oxidation, strong alkaline media [5] or strong acidic oxidants [6] are required in aqueous solution.

We recently reported that metal copper in pyridine promotes the facile activation of dioxygen [7] and this catalytic system allows the oxidation of ethane-1,2-diol under mild conditions [8]. It should be noted that the above reaction occurs through a two-step process where the formation of the hydroxyethanoate complex is followed by carbon–carbon scission, yielding a formate complex.

The present work extends the investigation to the oxidation of different substituted 1,2-diols and highlights how the structure of diols influences activity and selectivity.

## 2. Results and discussion

As already reported, ethane-1,2-diol is oxidized by oxygen under mild conditions (room

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Table 1  
Oxidation of 1,2 diols at 25°C<sup>a</sup>

Entry	R <sup>1</sup> and R <sup>2</sup>	Diol/Cu (mol)	t (h)	Conv. (%)	Products (Y%)
1	R <sup>1</sup> = R <sup>2</sup> = H	1	5	60	HOCH <sub>2</sub> COOH (60%) <sup>b</sup>
2	R <sup>1</sup> = R <sup>2</sup> = H	1	24	100	HCOOH (90%) <sup>b</sup>
3	R <sup>1</sup> = R <sup>2</sup> = H	10	24	20	HCOOH (20%) <sup>b</sup>
4	R <sup>1</sup> = Me R <sup>2</sup> = H	1	24	0	—
5	R <sup>1</sup> = R <sup>2</sup> = Me	1	24	0	—
6	R <sup>1</sup> , R <sup>2</sup> = (CH <sub>2</sub> ) <sub>4</sub>	1	24	0	—
7	R <sup>1</sup> = Ph R <sup>2</sup> = H	1	5	90	PhCH(OH)COOH (88%) PhCHO (< 1%) <sup>c</sup>
8	R <sup>1</sup> = Ph R <sup>2</sup> = H	1	24	100	PhCHO (10%) <sup>c</sup> , PhCOOH (60%) <sup>d</sup>
9	R <sup>1</sup> = Ph R <sup>2</sup> = H	10	24	25	PhCHO (5%) <sup>c</sup> , PhCOOH (20%) <sup>d</sup>
10	R <sup>1</sup> = R <sup>2</sup> = Ph	1	5	50	PhCOCOPh (18%), PhCOOH (32%) <sup>d</sup>
11	R <sup>1</sup> = R <sup>2</sup> = Ph	1	24	100	PhCOCOPh (34%), PhCOOH (48%) <sup>d</sup>
12	R <sup>1</sup> = R <sup>2</sup> = Ph	10	24	43	PhCOCOPh (40%), PhCHO (1%) <sup>c</sup>

<sup>a</sup> Substrate: 2 mmol; copper powder: 2 mmol; Pyridine: 5 ml; T = 25°C; p<sub>O<sub>2</sub></sub> = 310 kPa.

<sup>b</sup> Isolated as copper complex.







<sup>c</sup> Determined by HPLC and/or GC.

<sup>d</sup> Yields of isolated products.

temperature and 310 kPa) in the presence of metal copper and pyridine as the solvent [8]. In particular, metal copper slowly dissolves and the oxygen uptake leading to the copper oxoethanoate intermediate, or to the final formate

derivative, can be modulated by controlling the reaction time (5 h and 24 h, respectively) (Table 1, entries 1 and 2). In both cases high conversions (60–100%) of the diol are observed for a stoichiometric diol:copper ratio of 1: with an

Table 2  
Oxidation of 1,2 diols at 100°C<sup>a</sup>

entry	R <sup>1</sup> and R <sup>2</sup>	Diol/Cu (mol)	t (h)	Conv. %	Products (Y%)
1	R <sup>1</sup> =Me R <sup>2</sup> =H	1	5	47	MeCH(OH)COOH (47%) <sup>b</sup>
2	R <sup>1</sup> =Me R <sup>2</sup> =H	1	24	100	MeCH(OH)COOH (56%) <sup>b</sup>
3	R <sup>1</sup> =R <sup>2</sup> =Me	1	5	80	MeCOCOMe (47%), AcOH (33%) <sup>c</sup>
4	R <sup>1</sup> =R <sup>2</sup> =Me	1	24	100	MeCOCOMe (15%), AcOH (82%) <sup>c</sup>
5	R <sup>1</sup> =R <sup>2</sup> =Me	10	24	35	MeCOCOMe (35%), AcOH (<1%) <sup>c</sup>
6	R <sup>1</sup> , R <sup>2</sup> = (CH <sub>2</sub> ) <sub>4</sub> <sup>c</sup>	1	5	73	 (26%),  (32%) <sup>e</sup>
7	R <sup>1</sup> , R <sup>2</sup> = (CH <sub>2</sub> ) <sub>4</sub> <sup>d</sup>	1	24	95	 (30%),  (56%) <sup>e</sup>
8	R <sup>1</sup> , R <sup>2</sup> = (CH <sub>2</sub> ) <sub>4</sub> <sup>d</sup>	10	24	24	 (12%),  (10%) <sup>e</sup>
9	R <sup>1</sup> =R <sup>2</sup> =Ph	1	5	100	PhCOOH (64%) <sup>e</sup>
10	R <sup>1</sup> =R <sup>2</sup> =Ph	10	24	100	PhCHO (1%), PhCOCOPh (15%) <sup>c</sup> , PhCOOH (68%)

<sup>a</sup> Substrate: 2 mmol; copper powder: 2 mmol; Pyridine: 5 ml; T = 100°C; p<sub>O<sub>2</sub></sub> = 310 kPa.

<sup>b</sup> Determined by GC as methyl ester.

<sup>c</sup> Determined by GC.

<sup>d</sup> *trans*-isomer was used.

<sup>e</sup> Yields of isolated products.

excess of diol the conversion is limited by the copper amount (entry 3).

On reacting propane-1,2-diol under similar conditions, it can be observed that the methyl group inhibits the oxygen uptake at 25°C (entry 4). Moreover, the deactivating effect of the aliphatic substituents is also confirmed in the case of butane-2,3-diol and cyclohexane-1,2-diol (entries 5 and 6), both being almost inert.

However, diols bearing phenyl groups as substituents can be oxidized at room temperature. In fact both phenyl-1,2-ethanediol and 1,2-diphenyl-1,2-ethanediol are converted to different oxidation products. Conventional work-up followed by HPLC and/or GC techniques resulted in the yields reported in Table 1. As a comment on these results we can outline the following points:

(a) The oxidation of phenylethane-1,2-diol can be limited to mandelic acid (PhCH(OH)COOH) or extended to benzoic acid by controlling the reaction time, as in the case of ethane-1,2-diol. Benzaldehyde is observed as a transient intermediate.

(b) The symmetric 1,2-diphenyl-1,2-ethanediol allows the isolation of benzyl (PhCOCOPh) as a pure product, quite stable toward further oxidation.

(c) In the latter case we observed, after 24 h reaction time, a diol transformation of 4.3 mol of diol per mol of Cu, well exceeding the value observed for ethane-1,2-diol.

In order to obtain the oxidation of the less reactive diols we explored higher reaction temperatures. At 50°C only a trace amount of lactic acid was detected in the case of propane-1,2-diol whereas butane-2,3-diol and cyclohexane-1,2-diol were inert; however at 100°C all the above substrates reacted with dioxygen showing conversions from 35 to 100% (Table 2).

In a 5 h experiment lactic acid was formed with excellent selectivity as a copper complex of undetermined composition from which the free acid could be obtained by acid hydrolysis (entry 1). However for a longer reaction time (24 h) increased conversion (100%) led to lower

selectivity owing to the formation of undetermined byproducts (entry 2).

The same trend was observed for butane-2,3-diol. Decreased selectivity in butane-2,3-dione was brought about by increasing the reaction time (entries 3 and 4), as evidenced by the large amount of acetic acid found in a 24 h experiment. In this case, a large excess of diol (diol/copper = 10) led to the formation of butane-2,3-dione with 100% selectivity at 35% conversion.

Experiments 3,4, and 5 (Table 2) confirm that the formation of butane-2,3-dione precedes carbon-carbon scission to acetic acid.

A behavior similar to butane-2,3-diol is shown also by a cyclic aliphatic diol, namely cyclohexane-1,2-diol (entries 6 and 7), where the vicinal dione was found as a stable intermediate. However, by using an excess of diol we were not able to accumulate the dione intermediate alone; cyclohexane-1,2-dione was present in 12% yield together with a similar amount of adipic acid (entry 8).

No aldehyde intermediates were detected in any of the experiments with aliphatic diols. On the contrary, in the case of aromatic substituted diols, owing to the relevant stability of benzaldehyde in the presence of reduced copper, it was possible to detect the benzaldehyde as an intermediate either during the oxidation of 1,2-diphenyl-1,2-ethanediol (Table 1, entry 12) or during the oxidation of phenyl-1,2-ethanediol (Table 1, entry 8).

Following the reaction of 1,2-diphenyl-1,2-ethanediol in the presence of a small amount of copper (substrate/copper ratio 10:1) at 25°C by GC and HPLC analyses, showed that benzyl (PhCOCOPh) was selectively produced up to 40% at 43% conversion since benzaldehyde appeared only after 24 h. Benzoic acid parallels benzaldehyde (Fig. 1).

When the diol was practically all converted (56 h) benzaldehyde was the predominant product (56%), followed by benzoic acid (27%) and benzyl (16%) (Fig. 1).

Thus, even under mild conditions the cop-

per/pyridine catalytic system is a useful tool for the oxidation of several diols with oxygen. A large spectrum of products can be obtained just by changing the reacting diol and, for a given substrate, the reaction time.

Therefore the possibility of obtaining, with high selectivity,  $\alpha$ -diketones (MeCOCOMe, PhCOCOPh) and  $\alpha$ -hydroxyacids (HOCH<sub>2</sub>COOH, MeCHOHCOOH) or to realize carbon–carbon bond cleavage at low temperature for aromatic diols and at moderate temperature for aliphatic diols is of synthetic interest.

This prompted us to make a comparison between metal copper and other different copper derivatives in the oxidation of diols; we there-

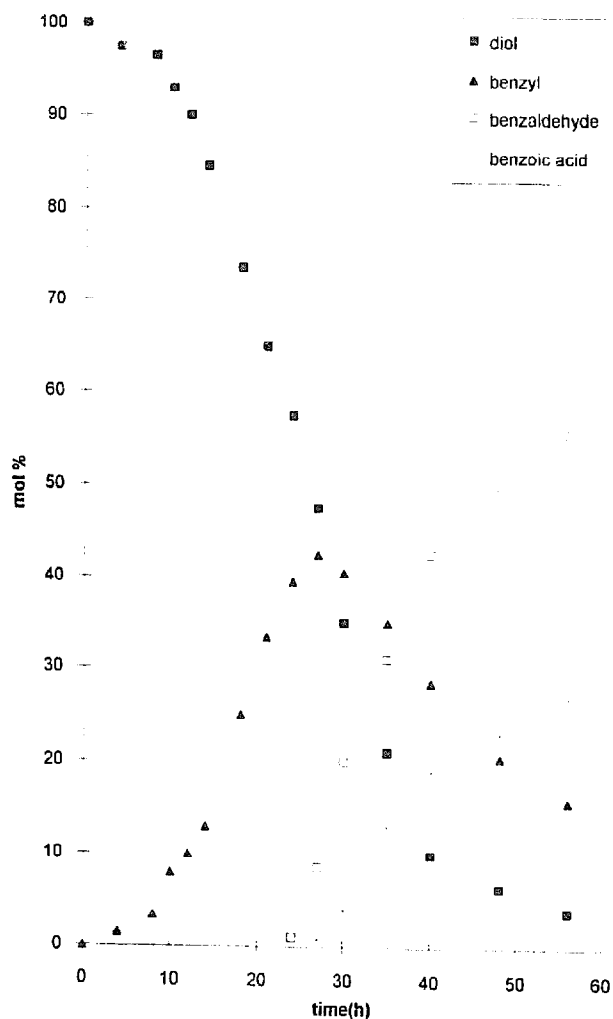


Fig. 1. Oxidation of 1,2-diphenyl-1,2-ethanediol in the presence of Cu(0).

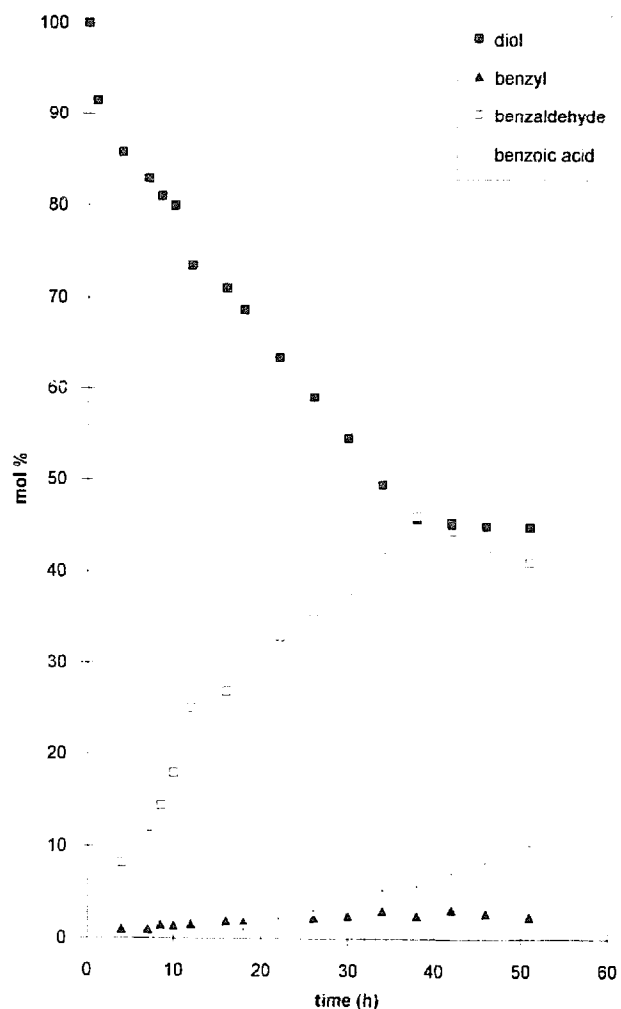


Fig. 2. Oxidation of 1,2-diphenyl-1,2-ethanediol in the presence of CuCl.

fore carried out a few experiments using CuCl and CuCl<sub>2</sub> as catalyst.

The CuCl–pyridine system tested at 25°C in the oxidation of 1,2-diphenyl-1,2-ethanediol showed an activity similar to Cu metal but a quite different selectivity. In fact benzaldehyde was formed even at the beginning of the reaction, along with benzyl, whereas benzoic acid appeared after a longer reaction time (Fig. 2).

Under identical conditions, CuCl<sub>2</sub> showed no catalytic activity (time tested 24 h).

Although to our knowledge no other works dealing with copper promoted oxidation of diols has been published, we can note that the oxidation of benzoin with CuCl/Py/O<sub>2</sub> and CuCl<sub>2</sub>/Py/O<sub>2</sub> systems have already been dis-

cussed [9]. According to Kinoshita, these systems at 60°C are both able to oxidize benzoin but Cu(I) produces almost exclusively benzoic acid whereas Cu(II) doesn't cleave the C–C bond and benzyl is obtained.

In our experiments by reacting 1,2-diphenyl-1,2-ethanediol under milder conditions (25°C) we were unable to detect benzoin as an intermediate either with Cu or CuCl catalyst. In both cases, however, we noted the presence of benzaldehyde that precedes the formation of benzoic acid.

The observed different selectivity between metal copper and CuCl could be ascribed at least to two different factors: one is the slowly dissolution of metal copper in pyridine which means, at the beginning of the reaction, a defect of copper in solution comparing to diol; the second is the difference between the active species derived from the interaction of CuCl/O<sub>2</sub>/Py [10] and Cu(0)/O<sub>2</sub>/Py [7].

### 3. Experimental

#### 3.1. Materials

Diols, pyridine and standards were of the highest purity grade from Fluka and were used without any further purification. Gaseous oxygen from SIAD was 99.99% pure. Metal copper was 99.99% and its granulometry 200–315 nm.

#### 3.2. Oxidation procedures

Reactions were carried out at the appropriate temperature in a thermostated glass reactor (25 cm<sup>3</sup>) provided with an electronically controlled magnetic stirrer connected to a large reservoir (5,000 cm<sup>3</sup>) containing oxygen at 310 KPa.

##### 3.2.1. diol / copper = 1

In samples containing copper (2 mmol), the substrate (2 mmol) dissolved in 5 ml of pyridine was used. The mixture was stirred for 5 or 24 h at the appropriate temperature.

Reactions were then worked up evaporating pyridine under vacuum and, in the cases of phenyl derivatives, products were extracted in AcOEt/3% HCl/H<sub>2</sub>O. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. Products were purified by flash chromatography using AcOEt/hexane as eluent. Yields are reported in the tables.

##### 3.2.2. diol / copper = 10

Catalytic experiments for 1-phenyl- and 1,2-diphenyl-1,2-ethanediol, cyclohexane-1,2-diol and 2,3-butanediol were performed using the above reported oxidation procedure, but with a diol/copper ratio of 10.

In the case of 2,3-butanediol the reaction products were directly analyzed by GC, whereas for 1-phenyl- and 1,2-diphenyl-1,2-ethanediol, and cyclohexane-1,2-diol oxidations, after GC analysis, the solutions were evaporated to dryness. The oily residues were then purified by flash chromatography using ethyl acetate/*n*-hexane as eluent.

##### 3.2.3. oxidation of 1,2-diphenyl-1,2-ethanediol with different copper compounds

The substrate (50 mmol) was dissolved in pyridine (125 ml) and copper, or CuCl or CuCl<sub>2</sub> (5 mmol) was added. The mixture was stirred at 25°C under 310 kPa pressure of oxygen. Samples (1 ml) were taken up every 2 h and analyzed by both GC and HPLC methods, as reported in Section 3.3.

#### 3.3. Analyses of products

Samples were analyzed by both GC and HPLC techniques.

HPLC analyses were performed on a Varian 9010 equipped with a Varian 9050 UV detector (254 nm) using a Merck Lichrospher 100 RP18 (5 μm) column, 1 ml/min flow and MeCN (A)/HCOONH<sub>4</sub> 0.2% (B) as eluent. The gradient used for the analyses was as follows:

A/B = 2/98 for 5 min, then a linear gradient for 15 min to A/B = 1/1.

GC analyses for aliphatic diols were performed on a HP5890 equipped with a TC detector and capillary column Supelcowax 10 (15 m), 0.25  $\mu\text{m}$  film thickness (oven 110°C, 4 psi, i.p. 250°C, TCD 280°C). For 1-phenyl-, and 1,2-diphenyl-1,2-ethanediol analyses were performed on the same instrument but with a Spb1 capillary column (15 m) (i.p. 210°C, TCD 280°C, 3 psi, with a programmed temperature as follows: 90°C for 1 min, gradient of 25°/min until the temperature reaches 280°C).

(a) The oxidations of diols were followed by direct GC analyses using the internal standard method, except for propane-1,2-diol where the transformation into methyl was necessary.

*Methyl esters:* 1 ml of the solution was dried under vacuum and the residue was dissolved in 2 ml of MeOH and 1 ml of  $\text{BF}_3$  10% in MeOH. After 10 min at 80°C the reaction products were analyzed.

(b) The oxidations of 1-phenyl-, and 1,2-diphenyl-1,2-ethanediol were followed also by HPLC; 50  $\mu\text{l}$  of the solution was dried under vacuum and the residue was dissolved in 1 ml of MeCN/HCl 3% (2:1 v/v). Crystals of  $\text{HCOONH}_4$  were added before analyzing the sample.

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