CHEMISTRY LETTERS, pp. 635 - 638, 1984. © The Chemical Society of Japan 1984

CUPRIC ION-CATALYZED DIOXYGENATION OF 1,2-CYCLOHEXANEDIONES. A NONENZYMATIC ANALOG FOR QUERCETINASE DIOXYGENATION

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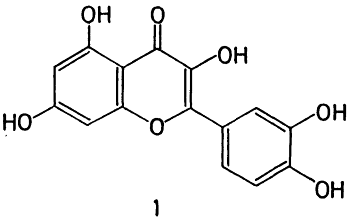
1,2-Cyclohexanediones were found to be dioxygenated by molecular oxygen with the aid of cupric ion to afford 1,5-keto acids and carbon monoxide. The reaction proceeds possibly via an endoperoxide intermediate. Methyl α-hydroxyadipates were also formed as byproducts. The mechanism of oxygenation is discussed.

Recently we have reported the base-catalyzed dioxygenation[1)] and the dye-sensitized photooxygenation[2)] of 1,2-cyclohexanediones **2**. The main feature of both reactions is the formation of 1,5-keto acid **3** accompanied by the evolution of carbon monoxide. Interestingly this has a resemblance to the biological dioxygenation of quercetin (**1**) to a depside and carbon monoxide by the action of quercetinase.[3)] This resemblance apparently originates from the common structure of enolized α-diketone. Since quercetinase is known to contain copper(II) in the active site,[3)] it is attractive to examine whether Cu(II) salts catalyze the dioxygenation of 1,2-cyclohexanediones **2** in a similar way.

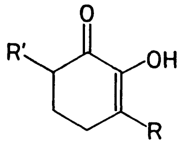
We have found that the cupric ion is a very efficient catalyst for the dioxygenation of **2** to **3** and carbon monoxide. Besides **3**, we have found methyl α-hydroxyadipate **4** among several products, which is presumably formed by methanol-trapping of an unstable endoperoxide **10** (Scheme 1).

Typically 2 mmol of the substrate[4)] was dissolved in 10 ml of methanol and the solution was stirred magnetically under oxygen (1 atm) after addition of 1 mmol of $CuCl_2 \cdot 2H_2O$. Absorption of oxygen and evolution of carbon monoxide were followed by both manometry and GC analysis. The methanol was removed under reduced pressure after the evolution of carbon monoxide was completed. Then dilute hydrochloric acid was added to the residue and the products were extracted with ether.

The results are shown in Table 1 and a tentative mechanism of the present dioxygenation is shown in Scheme 1.[5)] The formations of **3** and **4** are best understood in terms of the intermediacy of an unstable endoperoxide **10**.[6)] A similar reaction



1



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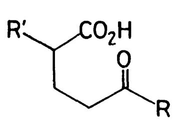

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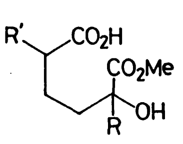

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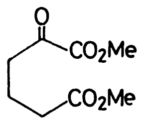
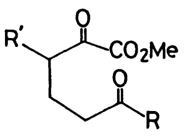


5a



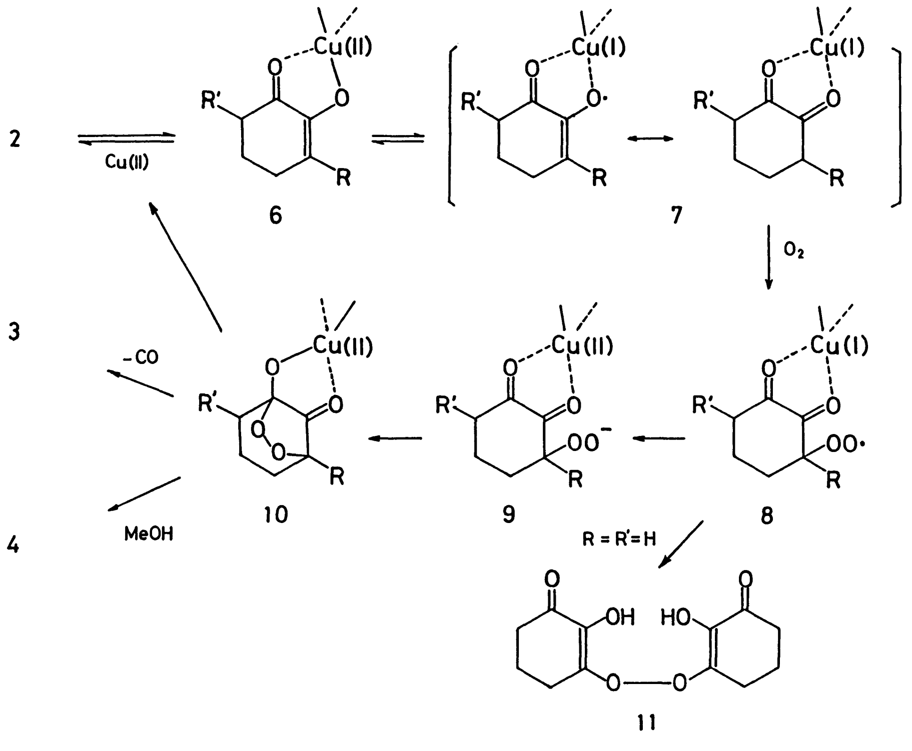
5b~d

	R	R'
a	H	H
b	Me	H
c	Me	i-Pr
d	i-Pr	Me

Table 1. $CuCl_2$-catalyzed Dioxygenation of 1,2-Cyclohexanediones in Methanol

Substrate			Reaction time*a)*	Product*b)* yield/%*c)*			Gas analysis %*d)*		
2	R	R'	h	3	4	5	O_2	CO	CO_2
a	H	H	5	8(5)*e)*	8(12)	3	82	34	4
b	Me	H	1	87(2)	2(3)	*f)*	115	97	0.6
c	Me	*i*-Pr	1	73(1)	8	9	78	76	0.8
d	*i*-Pr	Me	1	76(-)*f)*	*f)*	*f)*	71	68	0

a) The time required to complete the reaction at 25 °C. *b)* The products were identified by using ^1H and ^{13}C NMR spectra after isolation by HPLC or GLC. Satisfactory elemental analyses were obtained for new compounds. *c)* The values in parentheses are the yields for the products obtained as methyl ester. *d)* (moles of gas)/(moles of substrate)x100 for O_2 absorbed and CO and CO_2 evolved. *e)* The value involves a 6% yield of glutaric acid and a 3% yield of monomethyl glutarate. *f)* A trace amount of corresponding product was detected.



Scheme 1.

path to afford 3 and 4 has been proposed for the dye-sensitized photooxygenation.[2] Since 4 can be taken as a product formed from 10 by the nucleophilic attack of solvent methanol on the carbonyl carbon, the formation of 4 seems to be susceptible to steric crowding near the carbonyl group. The yields for 4a–d in Table 1 coincide with the reasoning. Similarly, nucleophilic attack of methanol on various intermediary carbonyl carbons may lead to methyl esters of 3 and 4 and α-keto methyl ester 5. However, details of the mechanisms, involving the formation of carbon dioxide, must await further investigation.

We have obtained some evidences[7] for the formation of Cu(II) complex 6, although its structure has not been determined.[8] The Cu(II) in 6 possibly abstracts one electron from the enolate anion to generate a radical species 7 which is oxygenated by molecular oxygen to a peroxy radical 8.[9] Support for the radical mechanism has been furnished by the isolation of a peroxide 11[10] for 2a, which is formed by a radical coupling of 8 with 7. Although one-electron transfer to Cu(II) is well-known,[11] for example, in the Cu(II)-catalyzed oxidations of α-hydroxy carbonyl compounds and ascorbic acid,[12] the Cu(II) takes ene diol anions as the ligand and molecular oxygen does not directly oxidize the substrate but reoxidizes Cu(I) to Cu(II). On the other hand, simple enolate anions of aldehydes or ketones, which do not form stable Cu(II) chelates, were reported to be dioxygenated at the enolate carbanion by Cu(II)-pyridine complex catalyst, where a one-electron transfer from the enolate oxyanion to Cu(II) takes place to generate a radical species.[13]

A brief survey of other substrates has shown that 1,2-cyclopentanediones were dioxygenated in a similar way but 3-hydroxy-2-methyl-4-pyron (maltol), which has the same 4-pyron structure of quercetin (1), was recovered intact. Quercetin (1) was also unreactive to molecular oxygen under the reaction conditions used.[14,15] The inertness appears strange since 1 forms a stable complex with Cu(II).[16]

Although further mechanistic studies are necessary to elucidate the present dioxygenation, it has become apparent that the reaction described here is a novel type of the Cu(II)-catalyzed dioxygenation by molecular oxygen to be of interest in connection with the quercetinase dioxygenation as well as organic syntheses.

This work was supported by a grant-in-aid for Special Project Research (No. 57102010) from the Ministry of Education, Science and Culture of Japan. Thanks are due to Prof. K. Kawazu, Department of Agricultural Chemistry, for the measurements of CI-MS spectra.

References

1) M. Utaka, S. Matsushita, H. Yamasaki, and A. Takeda, Tetrahedron Lett., 21, 1063 (1980).

2) M. Utaka, M. Nakatani, and A. Takeda, Tetrahedron Lett., 24, 803 (1983). See also: H. H. Wasserman and J. E. Pickett, J. Am. Chem. Soc., 104, 4695 (1982).

3) For reviews, see: W. H. Vanneste and A. Zuberbühler, "Molecular Mechanism of Oxygen Activation," ed by O. Hayaishi, Academic Press, New York (1974), Chap. 9; T. Matsuura, Tetrahedron, 33, 2869 (1977).

4) Prepared conveniently according to the method described in M. Utaka, S. Matsushita, and A. Takeda, Chem. Lett., 1980, 779.

5) We have also obtained the following results for **2b** (2 mmol) in methanol (10 ml): $CuCl_2 \cdot 2H_2O$ (0.02 mmol), 25 °C, 6.5 h, **3b** 69%, **4b** 6%; $CuCl_2 \cdot 2H_2O$ (1 mmol), 0 °C, 7 h, **3b** 73%, **4b** 14%; $Cu(OAc)_2 \cdot 2H_2O$ (1 mmol), 25 °C, 4 h, **3b** 79%, **4b** 10%.

6) It is worth noting that **10** corresponds to the postulated intermediate for the enzyme reaction.[3)]

7) Release of hydrogen ion by addition of $CuCl_2$ (1 mmol) to **2b** (2 mmol) in methanol (10 ml) acidified the solution (apparent pH 2) which was neutralized with aq NaOH (2 mmol). UV_{max} (MeOH): **2b**, 271 nm (ε 10300); **2b** with $CuCl_2 \cdot 2H_2O$ (2:1), 270 (6710), 331 (4450).

8) To our best knowledge, the Cu(II) complex with 1,2-cyclohexanedionato ligands has never been reported, although bis(1,2-cyclohexanedionato)Co(II) was prepared and its analysis was given. See: R. H. Toeniskoetter and S. Solomon, J. Inorg. Chem., **30**, 2189 (1968).

9) We have found that the base-catalyzed oxygenation of **2b** using 4 mol equiv of MeONa in methanol was very slow and not completed within 17 h, about one third of the starting **2b** being recovered. This fact indicates that the role of Cu(II) is not merely to generate an enolate anion. On the other hand, under a nitrogen atmosphere in the presence of Cu(II), **2a** was converted to 2-methoxy-2-cyclohexen-1-one (20%) and intractable materials with recovery of **2a** (30%), while **2b** was mostly recovered intact along with trace amounts of methoxy-containing products. Thus oxygen is essential for the formation of **3** and **4**.

10) **11** (obtained in 5% yield): mp 73–76 °C; IR (neat) 3280, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (m, 2H), 2.58 (t, 2H), 2.76 (t, 2H), 6.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9 (t), 32.5 (t), 35.3 (t), 128.4 (s), 144.3 (s), 192.6 (s); MS (CI, NH_3) 255 ($M + H^+$), 272 ($M + NH_4^+$). Elemental analysis gave a satisfactory result. Reflux in KI–AcOH–i-PrOH, positive. Reduction of **11** with sodium borohydride gave 1,2,3-trihydroxycyclohexane in about 90% yield.

11) For a review, see: R. A. Sheldon and J. K. Kochi, "Metal-Catalyzed Oxidations of Organic Compounds," Academic Press, New York (1981), Chap. 12.

12) For a review, see: W. G. Nigh, "Oxidation in Organic Chemistry, Part B," ed by W. S. Trahanovsky, Academic Press, New York (1973), Chap. 1.

13) H. C. Volger and W. Blackman, Recl. Trav. Chim. Pay-Bas, **84**, 1233 (1965); W. Brackman and H. C. Volger, ibid., **85**, 446 (1966).

14) In ethanol (50 ml), **1** (1 mmol) was dissolved with $CuCl_2 \cdot 2H_2O$ (0.5 mmol) at 27 °C. The homogeneous solution was stirred under oxygen for 10 h.

15) It was reported that oxygenation of 3-hydroxyflavones was catalyzed by $CuCl_2$ in DMF. See: A. Nishinaga, T. Tojo, and T. Matsuura, J. Chem. Soc., Chem. Commun., **1974**, 896. However, according to the private communication from Prof. Nishinaga, he needed an excess of the substrate to carry out the oxygenation.

16) E. Makasheva and M. T. Golovkina, Zh. Obshch. Khim., **43**, 1640 (1973); K. Takamura and M. Ito, Pharm. Bull., **25**, 3218 (1977).

(Received December 22, 1983)