ELSEVIER

Journal of Molecular Catalysis B: Enzymatic 17 (2002) 257–259

JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC

www.elsevier.com/locate/molcatb

Chloroperoxidase-catalyzed cyclodimerization of methyl (2*E*)-2,4-pentadienoate: a [4 + 2] cycloaddition product

Despina J. Bougioukou, Ioulia Smonou*

Department of Chemistry, University of Crete, Iraklio 71409, Crete, Greece

Received 21 December 2001; accepted 11 March 2002

Dedicated to professor G.J. Karabatsos on his 70th birthday.

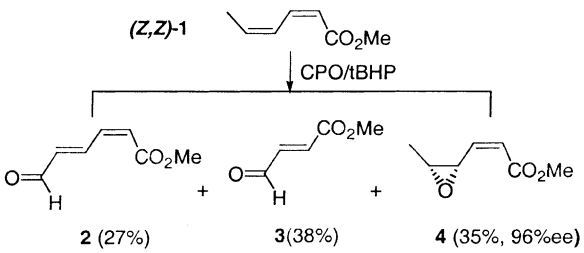
Abstract

The chloroperoxidase (CPO)-catalyzed oxidation of the methyl (2*E*)-2,4-pentadienoate gives the terminal double bond epoxide (25%) and a cyclodimerization compound (63%) as the major products. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Chloroperoxidase; Oxidation; Dienoic esters; Cyclodimerization; Epoxidation

Chloroperoxidase (CPO)-catalyzed oxidations [1–8] of a wide variety of simple and functionalized alkenes have been studied extensively in the last few years [9–16], with only two examples of conjugated dienes [17,18]. In our previous studies we have reported [19] the first examples of CPO-catalyzed oxidations of dienes conjugated to an ester group. We showed that the ratio of CPO-epoxidation to allylic oxidation depends on the stereochemistry at the C4–C5 double bond. When the C4–C5 double bond has the Z configuration, as in substrate **1**, enantioselective epoxidation competes well with allylic oxidation, forming the epoxide **4** with high enantiomeric purity (96% ee) and the allylic aldehyde **2** in comparable amounts, as shown in Scheme 1. Under aerobic conditions the C–C bond cleavage product **3** was formed in all cases, which was attributed to the formation of a radical cation intermediate [19].

In this short communication we report a new CPO-catalyzed oxidation of methyl (2*E*)-2,4-pentadienoate (**5**). The formation of a new dimerization product from [4 + 2] cycloaddition of substrate **5** and a possible mechanism for this unique transformation will be discussed.

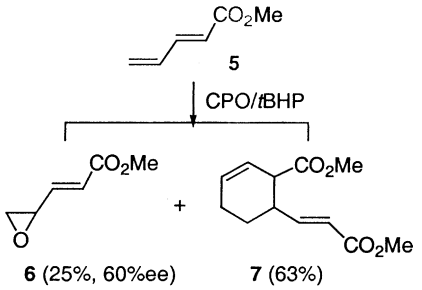


Scheme 1. CPO-catalyzed oxidation of methyl (2Z,4Z)-hexadienoate **1**.

The reaction of **5** with CPO using *tert*-butyl hydroperoxide (*t*BHP) as terminal oxidant [20,21] was accomplished under aerobic as well as unaerobic conditions with the same products being formed in both cases. The reaction was carried out in the absence of

* Corresponding author. Tel.: +30-810-393610; fax: +30-810-393601.
E-mail address: smonou@chemistry.uoc.gr (I. Smonou).

1381-1177/02/$ – see front matter
PII: S1381-1177(02)00042-5

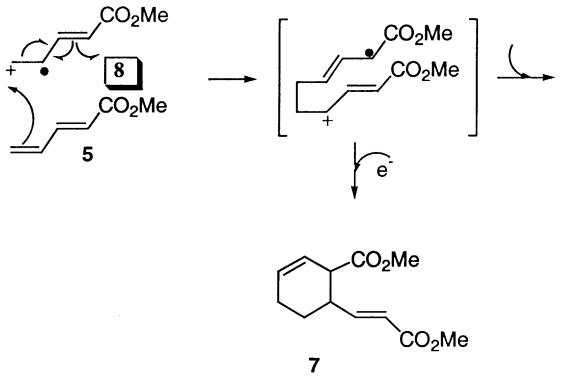


Scheme 2. CPO-catalyzed oxidation of **5**.

light, in a phosphate buffer (100 mM, pH 6) by using 0.4 mmoles of substrate, 1000 U of commercially available CPO and two equivalent of 70% *t*BHP, which was added in two aliquots to a total volume of 5 ml. The reaction was monitored by gas chromatography, the products were separated by flash column chromatography (SiO_2, 10–30% Et_2O in pentane) and were identified by 500 MHz ^{1}H NMR and GC–MS. The product yields are reported after completion of the reaction in 6 h and are shown in Scheme 2. In a control experiment the racemic mixture of epoxide **6** was prepared separately by mCPBA epoxidation [22–24] of dienoic ester **5**. The ee value for epoxide **6** was determined by gas chromatography with a chiral column (HP-Chiral 20% permethylated β-cyclodextrin, 30 m × 0.25 mm). In the absence of enzyme, substrate **5** remains stable under the reaction conditions.

The epoxide **6**[1], whose absolute configuration we have not determined, was formed with moderate enantioselectivity (60% ee), which is analogous to the selectivity observed previously in the case of the CPO-oxidation of styrene (49% ee) [4]. It is well established that with terminal alkenes there is a decrease in enantioselectivity with this enzyme [4,16]. Although the dienoic ester **5** is a terminal alkene, it does not deactivate this enzyme as do simple terminal alkenes, because the terminal double bond of **5** is conjugated with a second double bond. Only butadiene [17] and para-substituted styrenes [25], which are also conjugated, have been proven to be accepted by this enzyme as substrates.

[1] ^{1}H NMR (500 MHz, $CDCl_3$) of **6**: δ_H (ppm) 2.74 (m, 1H); 3.08 (dd, 1H, $J_1 = 5.5$ Hz, $J_2 = 4.4$ Hz); 3.48 (m, 1H); 3.77 (s, 3H); 6.20 (d, 1H, $J = 15.7$ Hz); 6.66 (dd, 1H, $J_1 = 15.7$ Hz, $J_2 = 7.3$ Hz).



Scheme 3.

The dimer **7**, whose structure was established by ^{1}H NMR and MS[2] , was the main product of the reaction (63% yield) and may be considered as a [4 + 2] cycloaddition product. Although it is well known that CPO can catalyze classical peroxidase reactions (oxidative dehydrogenation reactions), such as the oxidation of phenols to form oligomers [25–28], this is the first example, as far as we know from the literature, of a dimerization reaction mediated by CPO with a non aromatic system.

A reasonable explanation for the formation of the products involves the intermediacy of the radical cation **8**, Scheme 3, in analogy to the corresponding intermediate which we proposed in order to explain the formation of partially isomerized products and C–C bond cleavage products in our previous studies with the four isomers of methyl (2,4)-hexadienoates. The difference in behavior in terms of product formation between substrate **5** and the methyl 2,4-hexadienoates is probably due to steric interactions in the transition states that lead to the cycloaddition products. Such interactions will be more severe in the 2,4-hexadienoate cases and make the cycloaddition product paths less competitive with those leading to the other products. The radical cation **8** may be formed either through

[2] ^{1}H NMR (500 MHz, $CDCl_3$) of **7**: δ_H (ppm) 1.84–2.1 (br, 4H, CH_2); 2.86 (m, 1H, proton γ to ester group); 3.3 (m, 1H, proton alpha to ester group); 3.68 (s, 3H); 3.74 (s, 3H); 5.82 (d, 1H, $J = 10$ Hz, vinyl proton of the cyclohexene moiety); 5.92 (m, 2H, one vinyl proton alpha to ester function and one vinyl proton of cyclohexene moiety); 7.03 (dd, 1H, $J_1 = 15.7$ Hz, $J_2 = 8.1$ Hz, vinyl proton beta to ester group). GC–MS gave the peak $M_r^+ = 224$.

direct electron transfer from the substrate to compound I (oxoiron(IV) π-radical cation), or through electron transfer from an enzymatically derived *tert*-BuOO or *tert*-BuO radicals, which are established intermediates during CPO-catalyzed reactions [29,30].

Acknowledgements

We thank Professor G.J. Karabatsos for his valuable comments. This work was supported by the graduate program ΕΠΕΑΕΚ.

References

[1] P.D. Shaw, L.P. Hager, J. Biol. Chem. 236 (1961) 1626.
[2] L.P. Hager, D.R. Morris, F.S. Brown, H. Eberwein, J. Biol. Chem. 241 (1966) 1769.
[3] J.A. Thomas, D.R. Morris, L.P. Hager, J. Biol. Chem. 245 (1970) 3129.
[4] A. Zaks, D.R. Dodds, J. Am. Chem. Soc. 117 (1995) 10419.
[5] M.P.J. van Deurzen, F. van Rantwijk, R.A. Sheldon, Tetrahedron 53 (1997) 13183.
[6] S. Colonna, C. Gaggero, C. Richelmi, P. Pasta, TIBTECH 17 (1999) 163.
[7] V.P. Miller, R.A. Tschirret-Guth, P.R. Ortiz de Montellano, Arch. Biochem. Biophys. 319 (1995) 333.
[8] S.R. Blanke, L.P. Hager, J. Biol. Chem. 263 (1988) 18739.
[9] W. Adam, M. Lazarus, C.R. Saha-Möller, O. Weichold, U. Hoch, D. Häring, P. Schreier, Biotransformations with peroxidases in Biotransformations, in: K. Faber (Ed.), Springer, Berlin, 1999, pp. 73–108.
[10] P.R. Ortiz de Montellano, Y.S. Choe, G. DePillis, C.E. Catalano, J. Biol. Chem. 262 (1987) 11641.
[11] J. Geigert, T.D. Lee, D.J. Dalietos, D.S. Hirano, S.L. Neidelman, Biochem. Biophys. Res. Commun. 136 (1986) 778.
[12] E.J. Alain, L.P. Hager, L. Deng, E.N. Jacobsen, J. Am. Chem. Soc. 115 (1993) 4415.
[13] F.J. Lakner, K.P. Cain, L.P. Hager, J. Am. Chem. Soc. 119 (1997) 443.
[14] A.F. Dexter, F.J. Lakner, R.A. Campbell, L.P. Hager, J. Am. Chem. Soc. 117 (1995) 6412.
[15] F.J. Lakner, L.P. Hager, Tetrahedron: Asymmetry 8 (1997) 3547.
[16] F. van Rantwijk, R.A. Sheldon, Curr. Opin. Biotech. 11 (2000) 554.
[17] A.A. Elfarra, R.J. Duescher, C.M. Pasch, Arch. Biochem. Biophys. 286 (1991) 244.
[18] C. Sanfilippo, A. Patti, G. Nicolosi, Tetrahedron: Asymmetry 11 (2000) 3269.
[19] D.J. Bougioukou, I. Smonou, Tetrahedron Lett. 43 (2002) 339.
[20] M.P.J. van Deurzen, K. Seelbach, F. van Rantwijk, U. Kragl, R.A. Sheldon, Biocatal. Biotransform. 15 (1997) 1.
[21] M.K. Manoj, L.P. Hager, Biochim. Biophys. Acta 1547 (2001) 408.
[22] D. Bur, M. Nikles, U. Séquin, M. Neuburger, M. Zehnder, Helv. Chim. Acta 76 (1993) 1863.
[23] A.S.-Y. Lee, F.-Y. Su, Y.-C. Liao, Tetrahedron Lett. 40 (1999) 1323.
[24] H. Akita, C. Saotome, M. Ono, Tetrahedron: Asymmetry 7 (1996) 2595.
[25] P.R.O. Montellano, L.A. Grab, Biochemistry 26 (1987) 5310.
[26] S. Poli, M. Gullotti, C. Selvaggini, T. Beringhelli, Biochemistry 33 (1994) 6377.
[27] H. Uyama, C. Lohavisavapanich, R. Ikeda, S. Kobayashi, Macromolecules 31 (1998) 554.
[28] D. Teixeira, T. Lalot, M. Brigodiot, E. Marechal, Macromolecules 32 (1999) 70.
[29] W. Chamulitrat, N. Takahashi, R.P. Mason, J. Biol. Chem. 264 (1989) 7889.
[30] Z. Alfassi, Peroxyl Radicals, Wiley, New York, 1997, p. 198.