Jointly published by
Akadémiai Kiadó, Budapest
and Springer, Dordrecht

React.Kinet.Catal.Lett.
Vol. 88, No. 1, 165−173 (2006)
DOI:10.1556/RKCL.88.2006.1.22

RKCL4926

CARVONE EPOXIDATION BY SYSTEM "HYDROGEN PEROXIDE–$[Mn_2L_2O_3][PF_6]_2$ (L =1,4,7-TRIMETHYL-1,4,7-TRIAZACYCLONONANE)–CARBOXYLIC ACID": A COMBINATORIAL APPROACH TO THE PROCESS OPTIMIZATION**

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Received January 4, 2006; accepted January 16, 2006

Abstract

Epoxidation of natural terpene (+)-carvone by the system consisting of a catalyst, oxalic acid (co-catalyst) and H_2O_2 (70% aqueous solution; oxidant) was studied and factorial design methods were applied for the optimization of this reaction. A dinuclear manganese(IV) complex $[LMn(O)_3MnL](PF_6)_2$ (L = 1,4,7-trimethyl-1,4,7-triazacyclononane) was used as a catalyst, and acetonitrile was employed as a solvent. An analysis by methods of the complete 2^4 factorial design showed that an increase in the catalyst concentration gives a strong positive effect on the carvone conversion and selectivity. Hydrogen peroxide has a smaller positive effect on the conversion, but at high concentration, H_2O_2 leads to some decrease in the selectivity. An increase in the oxalic acid concentration has a beneficial effect on the conversion, but does not affect the selectivity.

Keywords: Epoxidation, homogeneous catalysis, hydrogen peroxide, manganese complexes, optimization

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**Part 7 of the series "Oxidations by the system hydrogen peroxide–$[Mn_2L_2O_3][PF_6]_2$ (L = 1,4,7-trimethyl-1,4,7-triazacyclononane)–carboxylic acid". For parts 1–6, see Refs [12–17], respectively. The present work was reported at the 13th International Congress on Catalysis, Paris, 2004 and published in a preliminary form: *Chemistry Preprint Archive,* Vol. 2004, Issue 2, p. 81–87 (2004)

0133-1736/2006/US$ 20.00.
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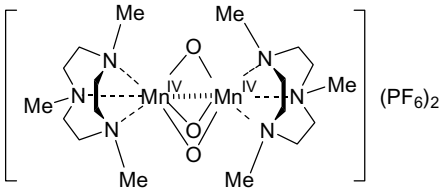
INTRODUCTION

Usually, slight changes in the preparative conditions of catalytic reactions have a dramatic effect on the resulting yield of a target product as well as on the selectivity [1–3]. In process optimization (that is, in a search of conditions for obtaining the highest possible yield or substrate conversion and selectivity), applications of various combinatorial methods are very useful [4–11]. For example, a general factorial design (see Ref. 4, p. 306–351) consists in that an investigator selects a fixed number of 'levels' for each of a number of variables (factors), then runs experiments with all possible combinations and measures a response (for example, the substrate conversion or/and selectivity). If each variable occurs only at two levels, such a version of the method is called a factorial design at two levels. In a catalytic reaction, we can choose couples of parameters for the concentrations of a substrate, oxidant, and catalyst, for the reaction temperature, etc. In the notation for the design matrix, 1 (or +) is used for the upper level of each factor and 0 (or –) for the corresponding lower level. In addition to the information about the effect of each variable on the response, the factorial design at two levels gives also information about the so-called interaction (that is, synergic or antagonistic) effects between two or more variables, which is impossible to obtain using the classical "one-factor-at-a-time" method. It is clear, however, that if we have many variables, it is necessary to carry out a huge number of experiments, and the method becomes non-productive. For example, if there are 7 variables, it should be necessary to perform $2^7 = 128$ experiments. Fortunately, there are statistically smart ways to select the experiments, building suitable fractions of the complete set. The application of the fractional design (see Ref. 4, p. 374–418) at two levels allows one to reduce the number of experiments. For example, by statistically choosing only $2^{4-1} = 8$ experiments from the complete set of $2^4 = 16$ runs, we can obtain almost the same amount of information.

Earlier, we have found that the system consisting of the dinuclear manganese(IV) complex $[LMn(O)_3MnL](PF_6)_2$ (L = 1,4,7-trimethyl-1,4,7-triazacyclononane; catalyst, complex **1**), carboxylic acid (co-catalyst, for example, acetic acid) and aqueous H_2O_2 efficiently oxidizes various organic compounds (alkanes, alcohols, sulphides, olefins) in acetonitrile at room temperature [12–22]. The kinetics and mechanisms of alkane hydroperoxidation [15,16] and olefin epoxidation [16] have been studied. Recently, we found [16] that oxalic acid is the most efficient co-catalyst in the hydrocarbon oxidations.

In the present work, we investigated the epoxidation of a natural terpene (+)-carvone by the system 'catalyst **1**–oxalic acid–H_2O_2 (70% aqueous)' and performed factorial design methods for the optimization of this reaction. It is necessary to note that the epoxidation of terpenes is an important process from a practical viewpoint, because the products formed are valuable raw materials for



Complex **1**

the synthesis of fragrances and drugs [23]. Molecular oxygen, hydrogenperoxide and TBHP have been used as oxidizing reagent in the epoxidation of olefins, including terpenes (see reviews [24–26] and recent original papers [27–36]). Carvone was epoxidized with a good yield in the presence of a base in a two-phase system, following Inverse Phase Transfer Catalysis [37]. Alternatively, the epoxidation of carvone with hydrogen peroxide can be heterogeneously catalyzed at room temperature by a natural phosphate modified with sodium nitrate (the structure of the material was similar to that of fluoroapatite) with the conversion 98% after 24 h [38]. We believe that the epoxidation of carvone by the system 'catalyst **1**–oxalic acid–H_2O_2' has certain advantages in comparison with other methods (for example, described in [37, 38]), because in our case, the reaction occurs rapidly and requires very small amounts of the catalyst.

EXPERIMENTAL

For the synthesis and properties of catalyst **1**, see [39, 40]. Aqueous 70% solution of hydrogen peroxide (compound **2**; Peróxidos do Brasil), (+)-carvone (compound **3**; Fluka; content ≥ 99.0 %), and oxalic acid (compound **4**; Fluka) were used as received. The experiments on olefin oxidations were carried out in MeCN at 25°C in thermostated Pyrex cylindrical vessels (total volume 12 mL) with vigorous stirring. The total volume of the reaction solution was 5 mL. In a typical experiment, initially, a portion of the 70% aqueous solution of H_2O_2 was added to the solution of the catalyst, co-catalyst and carvone in acetonitrile. Nitromethane was used as an internal standard for quantification by gas chromatography (GC) (see below). After certain time intervals, samples (about 0.2 mL) were taken, the reaction was typically quenched by addition of solid MnO_2 to decompose an excess of hydrogen peroxide. The solutions were filtered and the concentrations of the carvone epoxide (compound **3a**) and initial carvone were determined by GC (an 'HP Series 6890' instrument; column Hewlett-Packard; the stationary phase was polyethyleneglycol: INNOWAX

with parameters 25 m × 0.2 mm × 0.4 μm; carrier gas was N_2 with column pressure of 15 psi). Authentic samples of **3** and **3a** were used to attribute the peaks in chromatograms (retention times were compared for different regimes of the GC-analysis).

The conversion (*Conv*, %), selectivity (*Sel*, %) and turnover numbers (*TON)* were determined after 10, 30 and 180 min using the following definitions:

Conv = 100 (initial concentration of **3** minus final concentration of **3**)/ (initial concentration of **3**)%, (1)

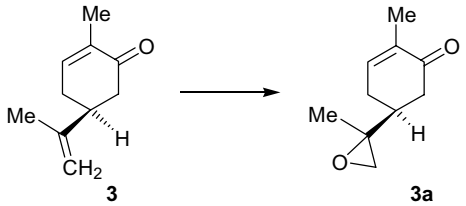
Sel = 100 (concentration of **3a**)/(initial concentration of **3** minus final concentration of **3**)%, (2)

TON = (moles of **3a** obtained)/(moles of **1**). (3)

The factorial design analysis was carried out in accordance with rules described in [4].

RESULTS AND DISCUSSION

We have found that stirring a solution of dinuclear manganese(IV) complex **1** (catalyst), aqueous 70% hydrogen peroxide (compound **2**), and (+)-carvone (compound **3**) in the presence of small amount of oxalic acid (co-catalyst, compound **4**) in acetonitrile at 25ºC leads to an efficient formation of the corresponding (+)-carvone epoxide (compound **3a**). The peaks of other detected products were negligible. Polymerization products have not been detected. It is important that only external epoxide with the epoxidized terminal double bond was detected in the reaction mixture. This is apparently due to a large steric hindrance in the interaction between the internal double bond of the substrate and a voluminous catalytically active species (containing bulky 1,4,7-trimethyl-1,4,7-triazacyclononane ligands). Since epoxide **3a** contains two chiral centers, the product obtained consisted of two diastereoisomers. Both diastereoisomers, however, gave one common peak in GC, and we did not follow the dependence of the ratio of these isomers on the reaction conditions.



3 **3a**

Because terpene epoxides are very valuable compounds for fragrance and drug industry, we decided to optimize this process in order to obtain the highest carvone conversion (equation 1) and selectivity (equation 2). Applying the

method of the 'factorial design at two levels 2^4', we varied four possible factors between two levels. These factors were the concentrations of compounds (reactants) **1**, **2**, **3** and **4**, while all other conditions were fixed. The response parameters (*Conv*, *Sel* and *TON*) were determined after 10, 30 and 180 min for all possible combinations.

Table 1

Factors and levels (concentrations) used in the carvone epoxidation

Reactant	Factor No.	Concentration (M)	
		Lower level (–)	Upper level (+)
Complex **1**	**1**	5.0×10^{-5}	10.0×10^{-5}
H_2O_2	**2**	0.65	0.87
Carvone	**3**	0.25	0.50
Oxalic acid	**4**	0.025	0.050

Table 2

Carvone epoxidation at various concentrations of reactants

Run	Factor				Response (after 10, 30 and 180 min)											
					Conv. (%)			*Sel. (%)*			*Mass balance (%)*			*TON*		
	1	**2**	**3**	**4**	10	30	180	10	30	180	10	30	180	10	30	180
1	–	–	–	–	29	51	84	72	66	93	92	83	94	1071	1721	3968
2	+	–	–	–	58	89	100	97	93	60	104	99	84	1556	2250	2139
3	+	+	–	–	50	96	100	72	78	27	89	84	51	1997	4099	2587
4	+	+	+	–	30	48	99	61	83	71	90	94	79	1009	2120	3993
5	+	+	+	+	59	84	100	72	67	60	85	75	71	4539	6001	7186
6	–	+	+	+	27	48	86	41	48	67	85	76	74	1224	2472	6142
7	–	–	+	+	38	45	82	90	68	84	99	88	90	3722	3341	7373
8	–	–	–	+	48	54	100	60	84	73	83	95	84	803	1237	2115
9	–	+	–	–	19	49	100	76	92	61	97	99	73	812	2444	3710
10	–	–	+	–		39			100			105			4421	
11	–	+	+	–	26	44	82	36	50	62	83	79	70	964	2363	5332
12	+	–	–	+	73	89	99	67	86	27	78	93	45	1312	2094	1140
13	–	–	+	+	38	45	82	90	68	84	99	88	90	3722	3341	7373
14	–	+	–	+	46	80	99	76	81	56	92	89	70	1950	3505	6546
15	+	–	+	–	30	43	88	75	99	72	94	102	79	1241	2306	3402
16	+	+	–	+	43	92	100	94	90	24	101	96	58	1123	2238	1467

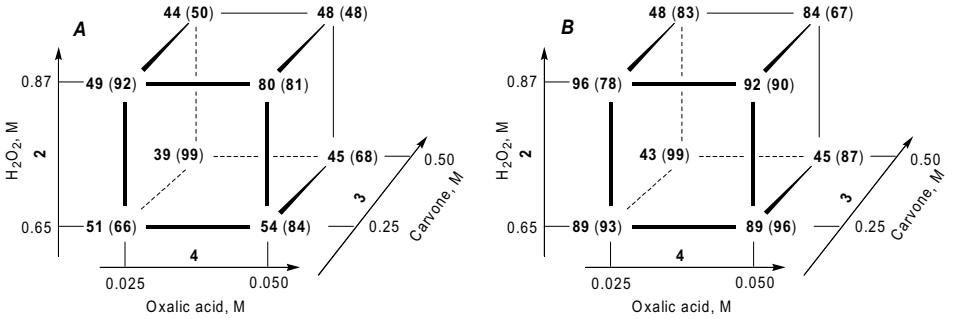


Fig. 1. Carvone (compound **3**) epoxidation with the '**1**–**2**–**4**' system at two various concentrations of the reactants for [**1**] = 5×10^{-5} (graph *A*) and 10×10^{-5} (graph *B*) M. Conversion of **3** and (in parentheses) epoxide selectivity are given in bold (30 min)

The concentrations of the components corresponding to the upper and lower levels are summarized in Table 1. As the upper-level concentrations, we used the concentrations of the components close to their maximal possible solubility in the reaction solution. The lower-level concentrations were two times lower for **1**, **3** and **4**, and 1.3 times lower for **2**. All primary experimental data are presented in Table 2.

Table 3

Effects of factors (variables) on the conversion and selectivity in the factorial design of the carvone epoxidation (after 3 h)

Effect	2^4 complete design		2^{4-1} fractional design	
	Conv. (%)	*Sel.* (%)	*Conv.* (%)	*Sel.* (%)
Average	62±3	79±4	66±3	74±4
1	22±6	14±8	23±6	16±8
2	11±6	–10±8	19±6	–11±8
3	–25±6	–11±8	–25±6	–7±8
4	10±6	–4±8	16±6	
1 × **3**	–11±6	8±8		
2 × **3**	2±6	–13±8		

Figure 1 and Table 3 show the results of the complete 2^4 factorial design. In order to simplify the situation, we statistically chose $2^{4-1} = 8$ experiments that gave almost the same amount of information (Table 3). The analysis of the complete 2^4 factorial design showed that an increase in the catalyst concentration gives a strong positive effect (22%) on the carvone conversion as well as on the selectivity (14%). Hydrogen peroxide has a smaller positive effect on the conversion (11%), but at high H_2O_2 concentration, some decrease in the selectivity (–10%) can be noticed. An increase in the oxalic acid concentration has a beneficial effect on the conversion (10%) but does not affect the selectivity. By analyzing the results of the complete factorial design of the conversion parameter, we were able to evaluate a second order interaction (–11%) between the catalyst and carvone (**1** × **3**) (Fig. 2).

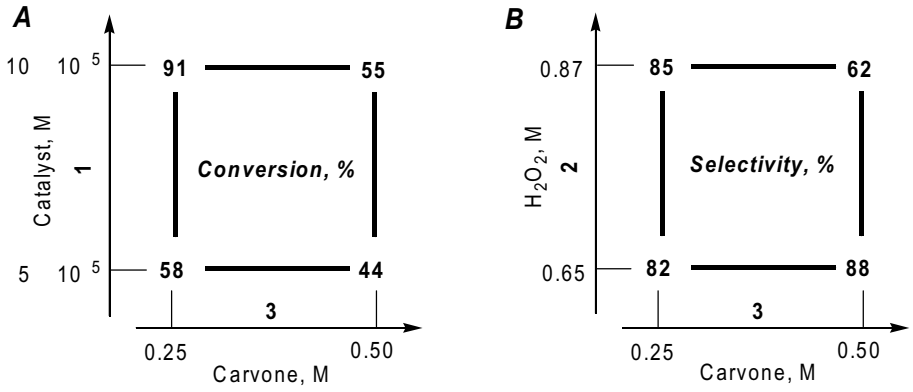


Fig. 2. Carvone (compound **3**) epoxidation with the '**1**–**2**–**4**' system at two various concentrations of the reactants. Carvone conversion (graph *A*) and selectivity (graph *B*) parameters are given in bold (30 min)

An increase in the catalyst concentration has a more pronounced effect on the conversion if carvone is used in low concentration. We also obtained that the **2** × **3** interaction has a negative effect (–13%) on the selectivity. This means that using high concentrations of both carvone and H_2O_2, we will obtain the epoxide with relatively low selectivity.

Using lower concentrations of carvone and oxalic acid (Table 2, run 1; *i.e.* $[\mathbf{1}]_0 = 5.0\times10^{-5}$ M; $[\mathbf{2}]_0 = 0.65$ M; $[\mathbf{3}]_0 = 0.25$ M; $[\mathbf{4}]_0 = 0.025$ M; $[\mathbf{1}]_0:[\mathbf{2}]_0:[\mathbf{3}]_0:[\mathbf{4}]_0 = 1:13000:5000:500$), the highest selectivity (93%) was attained at the expense of the TON (only 3968). It means that under conditions of run 1, the highest possible yield of epoxide **3a** will be obtained, but in this case, the required amount of the catalyst per one gram of the product will be approximately 2 times larger.

In conclusion, this study allowed us to optimize the reaction conditions in order to obtain the carvone epoxide with a highest possible selectivity (84%) and with a highest TON (up to 7373) at high conversion (82%) of carvone. This result was obtained (Table 2, run 7) under the following conditions: time 180 min; initial concentrations $[\mathbf{1}]_0 = 5.0 \times 10^{-5}$ M; $[\mathbf{2}]_0 = 0.65$ M; $[\mathbf{3}]_0 = 0.50$ M; $[\mathbf{4}]_0 = 0.05$ M. These concentrations correspond to the following ratio: $[\mathbf{1}]_0:[\mathbf{2}]_0:[\mathbf{3}]_0:[\mathbf{4}]_0 = 1:13000:10000:1000$.

Acknowledgements. The authors thank the State of São Paulo Research Foundation (Fundação de Amparo a Pesquisa do Estado de São Paulo, FAPESP) and the Brazilian National Council on Scientific and Technological Development (Conselho Nacional de Desenvolvimento Cientifico e Tecnológico, CNPq, Brazil) for support. G.B. Shul'pin expresses his gratitude to the FAPESP (grant No. 2002/08495-4), the CNPq (grant No. 300601/01-8) and the Faculdade de Química, Pontifícia Universidade Católica de Campinas for making it possible for him to stay at this University as an invited Professor and to perform a part of the present work. This work was supported by the grant from the Section of Chemistry and Material Science of the Russian Academy of Sciences (Program "A theoretical and experimental study of chemical bonds and mechanisms of main chemical processes").

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