Cyclization of citronellal to *p*-menthane-3,8-diols in water and carbon dioxide†

Haiyang Cheng,[a,b] Xiangchun Meng,[a] Ruixia Liu,[a,b] Yufen Hao,[a,b] Yanchun Yu,[a] Shuxia Cai[a] and Fengyu Zhao*[a]

Received 5th January 2009, Accepted 12th May 2009
First published as an Advance Article on the web 3rd June 2009
DOI: 10.1039/b823297k

A clean process has been developed for the synthesis of *p*-menthane-3,8-diols from cyclization of citronellal in CO_2–H_2O medium without any additives. With the addition of CO_2, the reaction rate could be enhanced about 6 times for the cyclization of citronellal in H_2O, because CO_2 dissolved into water and formed carbonic acid inducing an increase of the acidity. Although, the reaction conversion in CO_2–H_2O is slightly lower compared to that obtained with sulfuric acid as catalyst, CO_2–H_2O could replace the sulfuric acid at a relative higher reaction temperature. The reaction kinetics studies showed that the hydration of isopulegols to *p*-menthane-3,8-diols is a reversible reaction. The equilibrium constant and the maximum equilibrium yield obtained in CO_2–H_2O at a range of CO_2 pressures are similar to that with sulfuric acid catalyst.

Introduction

In the last two decades, many interests have been focused on CO_2 and H_2O as environmentally benign alternatives to conventional organic solvents. Both CO_2 and H_2O are non-toxic, non-flammable, abundant, cheap and easy to handle.[1] When water is compressed with CO_2, the acidity of the solution will increase in pH value by about 3 at a wide range of pressures and temperatures,[2,3] and the solution can be easily neutralized by depressurization.[4] In some cases, compressed CO_2 dissolved in water could replace the conventional hazardous acids such as HCl and H_2SO_4 to catalyze some chemical reactions without requiring post-reaction neutralization and salt disposal. The conventional acid-catalyzed reactions in water have been recently reported to be accelerated in the presence of CO_2 without addition of any acid catalysts.[5–13] Savage *et al.* reported that the addition of CO_2 could accelerate the dehydrations of cyclohexanol and 1,4-butanediol as well as the hydrolysis of dibenzyl ether in high-temperature water.[5–7] The same results have also been reported for the reactions of decarboxylation, hydrolysis, and diazotization.[10–13]

The present work has been undertaken to study the cyclization of citronellal to *p*-menthane-3,8-diols in the CO_2–H_2O system without any hazardous acids. *p*-Menthane-3,8-diols are composed of several stereo-isomers which have biological activities, *e.g.*, plant growth inhibition, allelopathic effect, and strong mosquito repellent activity.[14] The cyclization of citronellal in the CO_2–H_2O system has been compared to the reaction catalyzed with sulfuric acid.

Experimental

(*S*)-(−)-citronellal (Aldrich) and (±)-citronellal (Fluka) were used as received without further purification. Sulfuric acid and acetic acid are of analytical grade. The pH values of the reaction solution with acetic acid or sulfuric acid were adjusted to 3.20 at 25 °C. ZSM-5 catalyst, with a Si/Al ratio of 38, was purchased from the Catalytic Industry of Nankai University. Gases of CO_2 (99.999%) and N_2 (99.999%) (Changchun Xinxing Gas Company) were used as delivered. The reaction was carried out in a 50 ml Teflon-lined high-pressure stainless steel batch reactor. A desired amount of citronellal and deionized water were loaded into the reactor, and the reactor was sealed and flushed with N_2 and then heated up to the desired temperature. Then the CO_2 was compressed into the reactor using a high-pressure liquid pump and controlled by a back-pressure system. The reaction mixture was stirred continuously with a magnetic stirrer for a certain time. After the reaction, the liquid product was extracted with hexane and washed using deionized water. Then the mixture was dehydrated with anhydrous sodium sulfate and analyzed with a gas chromatograph (GC-Shimadzu-14C, FID, capillary column, Rtx-Wax 30 m × 0.25 mm × 0.25 µm) and the products were identified by gas chromatography/mass spectrometry (GC/MS, Agilent 5890).

Results and discussion

It is known that *p*-menthane-3,8-diols are usually produced through acid-catalyzed cyclization of citronellal.[15] The cyclization of citronellal as shown in Scheme 1 involves the isomerization of citronellal firstly to isopulegols, and then isopulegols hydration to *p*-menthane-3,8-diols, as well as citronellal

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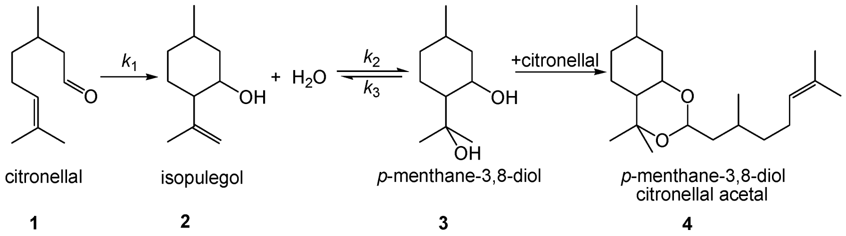
[a] *State Key Laboratory of Electroanalytical Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, P. R. China. E-mail: zhaofy@ciac.jl.cn; Fax: +86 431-8526-2410; Tel: +86 431-8526-2410*
[b] *Graduate School of Chinese Academy of Sciences, Beijing, 100049, P. R. China*

† Electronic supplementary information (ESI) available: Fig. S1 and S2. See DOI: 10.1039/b823297k



Scheme 1 The cyclization of citronellal to *p*-menthane-3,8-diols.

Table 1 Influence of CO_2 pressure on citronellal cyclization[a]

			Selectivity (%)		
Entry	CO_2/MPa	Conversion (%)	**2**	**3**	**4**
1	—	8	27	58	15
2	1	42	22	73	5
3	4	49	20	76	4
4	6.5	50	17	79	4
5	7	53	20	77	3
6	7.5	46	20	76	4
7	8	43	20	76	4
8[b]	—	16	24	70	6
9[b]	6	93	13	86	1
10[b]	7.5	97	12	85	3
11[b]	12	28	21	76	3

[a] Reaction conditions: (±)-citronellal: 1 mmol, water: 10 ml, *T*: 120 °C, *t*: 0.5 h. [b] (*S*)-(−)-citronellal: 1 mmol, water: 10 ml, *T*: 100 °C, *t*: 2 h.

Table 2 Results of citronellal cyclization at different temperatures

			Selectivity (%)		
Entry	*T*/°C	Conversion (%)	**2**	**3**	**4**
1	90	60	16	79	5
2	100	73	17	81	2
3	110	80	19	76	5
4	120	83	21	74	5
5	130	83	26	71	3

Reaction conditions: (±)-citronellal: 1 mmol, water: 10 ml, CO_2: 1 MPa, *t*: 2 h.

and *p*-menthane-3,8-diols condensation to *p*-menthane-3,8-diol citronellal acetals which was referred to the literature.[15]

In this work, the cyclization of citronellal in pressurized CO_2–H_2O medium in the absence of additives has been studied. The influence of CO_2 pressure was examined and the results are shown in Table 1. When (±)-citronellal was used, both the conversion and the selectivity to *p*-menthane-3,8-diols were improved in the presence of CO_2, and the conversion increased with increasing CO_2 pressure, it increased to a maximum value of 53% at 7.0 MPa CO_2 (entry 5), which is about 6 times higher than that (8%) obtained in the absence of CO_2 (entry 1). The changes of conversion with CO_2 pressure may depend on the solubility of CO_2 and the acidity in the reaction solution. As reported in the literature, the solubility of CO_2 in the reaction solution increases with CO_2 pressure resulting in the solution acidity noticeably increasing,[2,3,6,8] the pH value changes from 6.8 to 3.24 when CO_2 pressure increases from 0 to 7.0 MPa, then it changes very little with pressure further increasing, it changes from 3.24 to 3.20 when CO_2 pressure was increased from 7.0 MPa to 8.0 MPa.[3] The selectivity to the desired product of *p*-menthane-3,8-diols was larger in the CO_2–H_2O system than that in the pure water, and it did not change much with CO_2 pressure. When (*S*)-(−)-citronellal was used the conversion also increased with increasing CO_2 pressure. It increased to 93% and 97% at 6.0 and 7.5 MPa CO_2, respectively (entries 9 and 10), which are more than 6 times higher than that in the absence of CO_2 (entry 8). While, at 12.0 MPa CO_2, the conversion decreased largely due to the extraction of citronellal into CO_2 phase and the dilution effect (entry 11), because that the solubility of citronellal in CO_2 phase increased with increasing CO_2 pressure, especially at pressures above 7 MPa (critical pressure) from the solubility measurement as described in the literature,[16] it was 6.25 mmol L^{-1} at 8.5 MPa CO_2, and increased to 25 mmol L^{-1} at 11.2 MPa CO_2 (see Fig S1, ESI†).

The solubility of CO_2 and solution acidity increases with CO_2 pressure up to 7 MPa, so that the following reactions were carried out at a CO_2 pressure of 1 MPa. The effects of temperature are shown in Table 2. The conversion increased from 60% to 83% when the reaction temperature was enhanced from 90 °C to 120 °C (entries 1 and 4), then it almost did not change at a higher temperature of 130 °C. The selectivity to *p*-menthane-3,8-diols presented a maximum of 81% at 100 °C (entry 2), then it decreased at higher temperatures. Both temperature and acidity of the system are important factors influencing the cyclization of citronellal. Higher temperature and higher acidity favor the present reaction, but the acidity of the system becomes weaker at higher temperatures due to the solubility of CO_2 in the aqueous phase decreasing under constant pressure.[2] So that, the reaction conversion increases and then changes slightly with increased temperature. The higher selectivity to *p*-menthane-3,8-diols was obtained at lower temperature due to the forward reaction of isopulegols hydration to *p*-menthane-3,8-diols is an exothermic reaction as discussed later.

The cyclization of citronellal in the CO_2–H_2O system was compared with the results in the presence of conventional liquid acids and solid acid catalyst, the results are presented in Table 3. Under the same temperature, sulfuric acid is more effective for the cyclization of citronellal than acetic acid and 7 MPa CO_2–H_2O system, and the selectivity to *p*-menthane-3,8-diols is also the highest with sulfuric acid (entries 1–3), in which the pH value changed slightly (from 3.20 to 3.43) during the reaction. While, the conversion and selectivity in CO_2–H_2O system were 73% and 81%, respectively. Those are higher than the values of 48% and 73% obtained over the ZSM-5 catalyst (entries 4 and 5). Furthermore, the conversion over ZSM-5 catalyst was increased to 78% (entry 6) in the presence of CO_2 due to the acidity of the reaction solution being increased.

Table 3 The cyclization of citronellal to *p*-menthane-3,8-diols in the presence of different acid catalysts

					Selectivity (%)		
Entry	Catalyst	CO_2/MPa	*T*/°C	Conv. (%)	**2**	**3**	**4**
1	—	7	60	35	17	72	11
2	CH_3COOH	—	60	52	13	78	9
3	H_2SO_4	—	60	72	14	82	4
4	ZSM-5 (0.01 g)	—	100	48	21	73	6
5	—	1	100	73	17	81	2
6	ZSM-5 (0.01 g)	1	100	78	21	75	4

Reaction conditions: (±)-citronellal: 1 mmol, water: 10 ml, *t*: 2 h.

The amount of water being used showed a large influence on the reaction conversion also, the conversion increased from 21.6% to 75% with an increasing volume of water from 2 ml to 15 ml, and it changed little with further increases in water volume. While, the selectivities to *p*-menthane-3,8-diols were above 70% and it presented a maximum value of 80.9% in 10 ml water. In the present reaction system, the reactant is not soluble to water, so the reaction is a biphasic system that occurs on the interphase of water and reactant. With increases in the volume of water, the interface area will increase so that the reactant can be well dispersed and form an emulsion, which may explain the conversion increase with increasing water content. This could be demonstrated by varying the agitation speed (see Fig. S2. ESI†), the reaction rate increased with enhancing the stirring speed initially, suggesting the reaction is not homogeneous but heterogeneous (biphasic). Under the reaction stirring speed of 1200 r min^{-1} the diffusion effect could be ignored.

Table 4 shows the conversion and product selectivities of citronellal cyclization in the presence of 1 MPa CO_2. The results presented that with increasing of conversion, the selectivity to isopulegols decreased but the selectivity to *p*-menthane-3,8-diols increased initially (entries 1 and 2), and then both of the selectivities kept a constant with a further increasing of the conversion (entry 3–6). It indicates that the reaction from isopulegols to *p*-menthane-3,8-diols is a reversible reaction, this will be discussed later in detail.

Table 4 Conversion and product selectivities of cyclization of citronellal at 120 °C

			Selectivity (%)		
Entry	*t*/min	Conversion (%)	**2**	**3**	**4**
1	15	14	32	56	12
2	30	42	22	73	5
3	45	57	19	74	7
4	60	66	19	74	7
5	90	81	18	73	9
6	120	84	19	73	8

Reaction conditions: (±)-citronellal: 1 mmol, water: 10 ml, CO_2: 1 MPa.

As shown in Scheme 1 the cyclization of citronellal to *p*-menthane-3,8-diols mainly contain two reaction steps, namely isomerization of citronellal at first to isopulegols, and then isopulegols hydration to *p*-menthane-3,8-diols. In the cyclization of citronellal in the CO_2–H_2O system without addition of any acid catalyst citronellal could be converted near completely under the reaction conditions used, but an intermediate of isopulegols was produced around a constant content after reaction for 45 min, and it did not decrease with extension of the reaction time. So that the second step of isopulegols hydration to *p*-menthane-3,8-diols is supposed as a reversible reaction, and the equilibrium constant and the maximum (equilibrium) yield of *p*-menthane-3,8-diols were estimated under the different reaction conditions. Fig. 1 shows the molar fraction *versus* reaction time profiles. According to the data in Fig. 1 the reaction rate constant k_1 was calculated followed pseudo-first order kinetics, with the initial linearity for the expression $k_1 = 1/t \times \ln(1/(1-x_t))$ (x_t : citronellal conversion at *t*). Fig. 2 shows that the first step followed exactly first order kinetics and the reaction rate constant k_1 were calculated and listed in Table 5. The higher reaction rates were obtained at higher reaction temperatures (entries 1 and 4) and higher CO_2 pressures (entries 2 and 3) in the CO_2–H_2O system without addition of any acid catalyst. However, for the isomerization of citronellal to isopulegols at a similar pH value the reaction rate in the presence of 1 MPa CO_2 was lower than that in the addition of sulfuric acid as catalyst (entries 4 and 5).

For second step of isopulegols hydration to *p*-menthane-3,8-diols, a reversible reaction performed in a constant volume batch reactor, the following kinetic equations were applied to calculate the equilibrium constant *K*:

$$K = K_2/K_3 = Y_3/Y_2 \tag{1}$$

where K, k_2, k_3, Y_2 and Y_3 represent the equilibrium constant, forward and reverse rate constants of isopulegols hydration to *p*-menthane-3,8-diols, the yield of isopulegols and *p*-menthane-3,8-diols, respectively.

Noting that:

$$1 - Y_1 - 2Y_4 = Y_2 + Y_3 \tag{2}$$

Table 5 Kinetic parameters estimated for citronellal cyclization at different reaction conditions

Entry	Citronellal/mmol	CO_2/MPa	pH value	H_2O/ml	*T*/°C	$k_1 \times 10^2$/h^{-1a}	*K*	$Y_{3,\,EQ}$ (%)
1	1	1	3.64–4.00	10	120	118.7 ± 4.7	3.96	69
2	2	1	3.64^b	10	60	8.0 ± 0.3	7.32	81
3	2	7	3.24^b	10	60	10.3 ± 0.4	7.29	81
4	1	1	3.64^b	10	60	14.5 ± 0.6	7.28	81
5^c	1	—	3.20	10	60	62.1 ± 4.6	7.34	81

[a] The observed rate constants k_1 were determined according Fig. 2. [b] Ref. 3. [c] Sulfuric acid was used as catalyst.

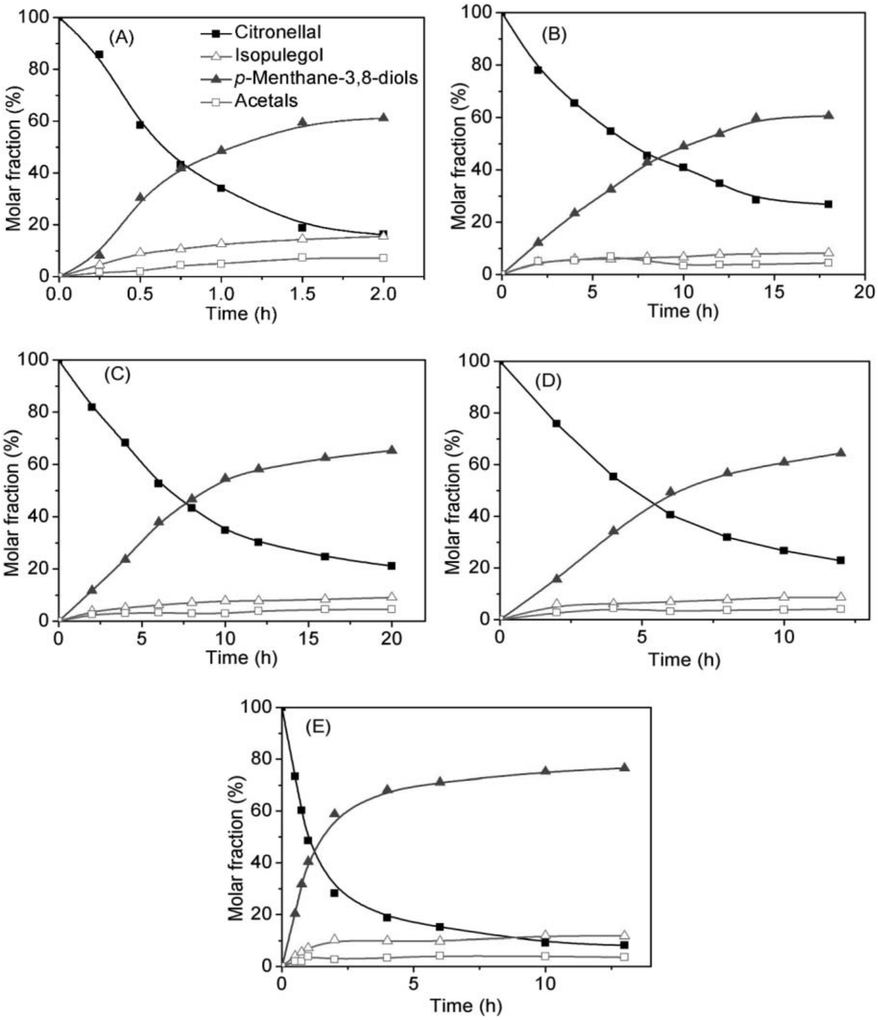


Fig. 1 Molar fraction *versus* time profiles on cyclization of citronellal. Reaction conditions: (A) (±)-citronellal: 1 mmol, water: 10 ml, CO_2: 1 MPa, *T*: 120 °C. (B) (±)-citronellal: 2 mmol, water: 10 ml, CO_2: 1 MPa, T: 60 °C. (C) (±)-citronellal: 2 mmol, water: 10 ml, CO_2: 7 MPa, T: 60 °C. (D) (±)-citronellal: 1 mmol, water: 10 ml, CO_2: 1 MPa, *T*: 60 °C. (E) (±)-citronellal: 1 mmol, water: 10 ml, *T*: 60 °C, In the case of sulfuric acid was used as catalyst, the pH value of the solution was 3.20.

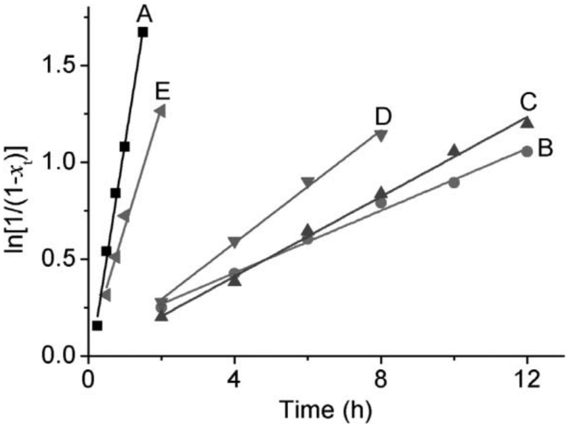


Fig. 2 Plot of $\ln[1/(1\text{-}x_t)]$ against reaction time for the data in Fig. 1.

where Y_1 and Y_4 represent the residual citronellal and the yield of *p*-menthane-3,8-diol citronellal acetal, respectively.

The maximum equilibrium yield of *p*-menthane-3,8-diols $Y_{3,\mathrm{EQ}}$ could be calculated by combining eqn (1) and (2).

$$Y_{3,\mathrm{EQ}} = K\,(1 - Y_1 - 2Y_4)/\,(1 + K) \qquad (3)$$

In the case of citronellal being converted completely, Y_1 equals to zero, Y_4 equals to the selectivity of *p*-menthane-3,8-diol citronellal acetal which was about 7% at 120 °C and 4% at 60 °C. Then the equilibrium constant *K* and the maximum equilibrium yield $Y_{3,\mathrm{EQ}}$ were calculated according to the data in Fig. 1, the results are listed in Table 5. The equilibrium constant *K* is 3.96 at a reaction temperature of 120 °C, but it increased to 7.28 at 60 °C in the presence of 1 MPa CO_2, indicating that lower reaction temperature favored the forward reaction with the equilibrium yields of *p*-menthane-3,8-diols around 81% at 60 °C, which is higher than the result at 120 °C (entries 1 and 4), namely the forward reaction from isopulegols to *p*-menthane-3,8-diols is an exothermic reaction. Moreover, the similar values of equilibrium constant *K* and yield of *p*-menthane-3,8-diols were obtained in the presence of sulfuric acid as a catalyst (entries 5) or at the CO_2 pressure of 1 MPa and 7 MPa at

60 °C (entries 2–4). Based on the above results, the CO_2–H_2O system was efficient for catalyzing the present cyclization of citronellal to *p*-menthane-3,8-diols without addition of any additives.

Conclusions

The cyclization of citronellal to *p*-menthane-3,8-diols could proceed in CO_2–H_2O medium successfully in the absence of any additives. The CO_2 pressure and temperature are the key factors affecting reaction rate and selectivity. The reaction rate in water has been enhanced largely in the presence of CO_2 for the formation of carbonic acid. Kinetic analysis indicates the hydration of isopulegols to *p*-menthane-3,8-diols is a reversible reaction. Compared to sulfuric acid catalyst, the CO_2–H_2O system is an environmentally friendly and easy to operate process for the cyclization of citronellal to *p*-menthane-3,8-diols.

Acknowledgements

The authors gratefully acknowledge the financial support from the NSFC 20573104 and the One Hundred Talent Program of CAS.

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