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Preparation of natural α-tocopherol from non-α-tocopherols*

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Abstract: Non-α-tocopherols are hydroxymethylated and hydrogenated to produce α-tocopherol in one pot process by simultaneously reacting with paraformaldehyde and hydrogen in the presence of catalysts of benzenesulfonic acid and 5% Pd/C in an autoclave. Effects of various operation conditions have been studied. The preferable reaction conditions are: temperature 180 °C to 200 °C, pressure 5.0 MPa, acid concentration 0.5 g/100 ml ethanol, mass ratio of Pd/C to tocopherols 7.1 g/100 g, and reaction time 5.0 h. A product with α-tocopherol content of 80% was obtained by using a raw material with a total tocopherols content of 80.54%. The conversion of non-α-tocopherols is almost 100%, and the mole yield of α-tocopherol is more than 90%.

Key words: Tocopherol, Conversion, Hydroxymethylation, Hydrogenolysis
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INTRODUCTION

In nature, vitamin E occurs in eight different forms (α-, β-, γ- and δ-tocopherols and α-, β-, γ- and δ-tocotrienols) with varying biological activities. Tocopherols which possess three asymmetric carbon atoms have been intensively studied owing to their medical, biological, and physicochemical significance. α-tocopherol has the highest biological activity (Dutta-Roy, 1999; Kamal-Eldin and Appelqvist, 1996). The tocopherol molecule has three chiral centers in its phytyl tail (2, 4' and 8'), making a total of eight possible stereoisomeric forms. Natural α-tocopherol occurs as the 2R, 4'R, 8'R stereoisomer which has the highest biological activity whereas synthetic α-tocopherol is a mixture of eight stereoisomers. Therefore natural α-tocopherol is much more potent than synthetic α-tocopherol.

Since the non-α-tocopherols predominate in nature, many attempts have been made to convert them to the more biologically active α-tocopherol. The non-α-tocopherols differ from α-tocopherol only in that one or two methyl groups are missing from the 5 and/or 7 positions. Various methylation methods have been reported in the literature (Weisler and Chechak, 1949; Hickman and Weisler, 1949; Müller and Schneider, 2000; Baldwin *et al*., 1990; Lechtken *et al*., 1990; Brüggemann *et al*., 1999; Breuninger, 1999), e.g., chloromethylation, aminomethylation, hydroxymethylation, etc. However, they are all published in patents, not in papers. Therefore, they are not systematic. In this paper we reported the systematic results of the methylation method of hydroxymethylation and hydrogenolysis.

There are two steps in the methylation process.

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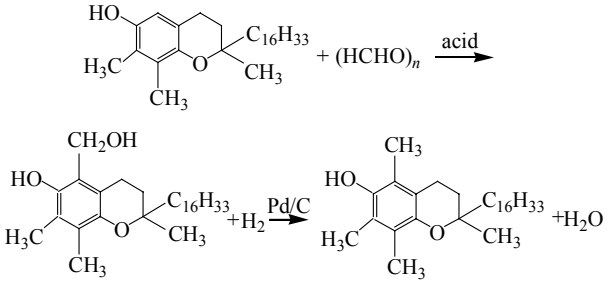
Firstly, non-α-tocopherols are hydroxymethylated by reacting with paraformaldehyde under acid catalysis. Secondly, the hydroxymethylated intermediates are hydrogenated by reacting with hydrogen under Pd/C catalysis. The reaction equations of γ-tocopherol, e.g., are as follows:



EXPERIMENTAL DETAILS

Apparatus

Fig.1 shows the flowsheet of the conversion process. The key element of the apparatus was a 500 ml autoclave with a stirrer. Reaction temperature and pressure were controlled and measured by temperature and pressure regulators. The operation protocol was as follows: mixed tocopherols, paraformaldehyde, benzenesulfonic acid, Pd/C and ethanol were placed in a 500 ml autoclave. After being closed, the autoclave was pressurized by using nitrogen to about 0.3 MPa to purge the air three times and then hydrogen was used to purge the nitrogen. Then it was pressurized by using hydrogen to about 3.0 MPa. While stirring, it was heated to 180 °C (the pressure rose accordingly to about 5.0 MPa due to ethanol vapor pressure). The mixture was stirred for 5.0 h at 180 °C, keeping the pressure in the range of 4.8 MPa to 5.2 MPa by hydrogen supplement. Then it was left to cool to room temperature. Hydrogen was released. The reaction mixture was separated from the catalyst by filtration and the filter cake was washed three times with n-hexane. The filtrate was extracted three times with n-hexane, and the n-hexane layer was washed three times with deionized water and dried with anhydrous sodium sulphate. The n-hexane was evaporated under vacuum and the product was analyzed by HPLC.

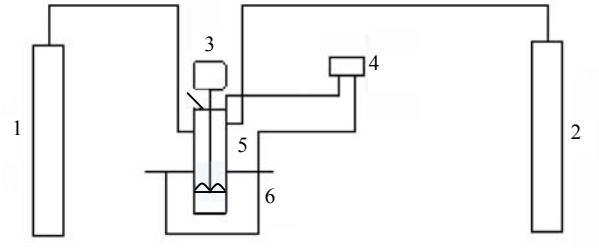


Fig.1 Flowsheet of the experimental apparatus
1: H_2 cylinder; 2: N_2 cylinder; 3: stirrer; 4: controller; 5: autoclave; 6: oil bath

Materials

Mixed tocopherols (δ-tocopherol 24.13%, β+γ-tocopherols 53.88%, α-tocopherol 2.53%; total tocophreols 80.54%), nitrogen (purity 99.9%); hydrogen (purity 99.9%), anhydrous ethanol (AR), n-hexane (AR), 5% Pd/C, paraformaldehyde (AR), and benzenesulfonic acid (AR).

RESULTS AND DISCUSSION

Three parameters were used to verify the process efficiency: conversion, mole yield and selectivity. Their expressions are as follows:

Conversion of non-α-tocopherols:

$$x=\frac{n-n'}{n}\times 100\%$$

Selectivity of α-tocopherol:

$$s=\frac{n''-n^0}{n-n'}\times 100\%$$

Mole yield of α-tocopherol:

$$y=\frac{n''-n^0}{n}\times 100\%=x\times s\times 100\%$$

where, n: total moles of non-α-tocopherols in raw material; n': total moles of non-α-tocopherols in product; n'': moles of α-tocopherol in product; n^0: moles of α-tocopherol in raw material.

Effect of temperature

The operation conditions were: mixed tocopherols 25.0 g, benzenesulfonic acid 1.0 g, Pd/C 1.3 g, paraformaldehyde 17.0 g, ethanol 200.0 ml,

pressure 5.0 MPa, reaction time 5.0 h. The temperature range 140 °C to 220 °C.

At all experimental conditions, the conversion of non-α-tocopherols was almost 100%, i.e., there were almost no β-, γ-, and δ-tocopherol remained in the products.

Fig.2 shows the results of temperature experiments. The temperature had a very significant role in the reaction. The content, mole yield, and selectivity of α-tocopherol increased sharply when the temperature rose from 140 °C to 180 °C. They maximized at temperature of 180 °C to 200 °C, but above 200 °C, declined slightly. Therefore, the preferable temperature was 180 °C to 200 °C.

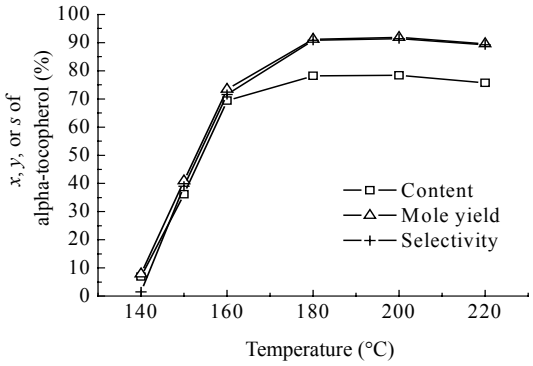


Fig.2 Effect of temperature on the content, mole yield, and selectivity of α-tocopherol

Effect of the acid concentration

The operation conditions were: mixed tocopherols 25.0 g, Pd/C 1.3 g, paraformaldehyde 17.0 g, ethanol 200.0 ml, temperature 180 °C, pressure 5.0 MPa, reaction time 5.0 h. Since the solvent used was 200.0 ml each time, the concentration depended on the mass of benzenesulfonic acid. The mass range of benzenesulfonic acid was from 0.4 g to 1.6 g, corresponding to concentration range of 0.2 g/100 ml to 0.8 g/100 ml.

At all experimental conditions, the conversion of non-α-tocopherols was almost 100%, i.e., there were almost no β-, γ-, and δ-tocopherol remained in the products.

The results are shown in Fig.3. The concentration of benzenesulfonic acid had no significant role in the conversion process in the experimental range. With the increase of the concentration from 0.2 g/100 ml to 0.5 g/100 ml, the content, mole yield, and selectivity of α-tocopherol increased slightly, but at concentration of 0.5 g/100 ml to 0.8 g/100 ml, they declined. Benzenesulfonic acid was the catalyst of hydroxymethylation in the first step. With the increase of its concentration, the rate of hydroxymethylation reaction rose. The hydroxymethylated intermediates were very reactive. If they did not convert to final product immediately, many side reactions would take place. But the mass of Pd/C, the catalyst of hydrogenolysis in the second step, remains the same. Thereby the rate of hydrogenolysis may be less than the rate of hydroxymethylation, which leads to the decline of the content, mole yield, and selectivity of α-tocopherol. So the preferable benzenesulfonic acid concentration was 0.5 g/100 ml ethanol.

Effect of the mass ratio of Pd/C on tocopherols

The operation conditions were: mixed tocopherols 25.0 g, benzenesulfonic acid 1.0 g, paraformaldehyde 17.0 g, ethanol 200.0 ml, temperature 180 °C, pressure 5.0 MPa, reaction time 5.0 h. Since the mass of raw material of mixed tocopherols was 25.0 g (total tocopherols content 80.54%), the mass ratio of Pd/C to tocopherols depended on the mass of Pd/C. The mass range of Pd/C was from 0.46 g to 1.426 g, corresponding to the mass ratio of 2.28 g/100 g to 7.08 g/100 g.

At all experimental conditions, the conversion of non-α-tocopherols was almost 100%, i.e., there were almost no β-, γ-, and δ-tocopherol remained in the products.

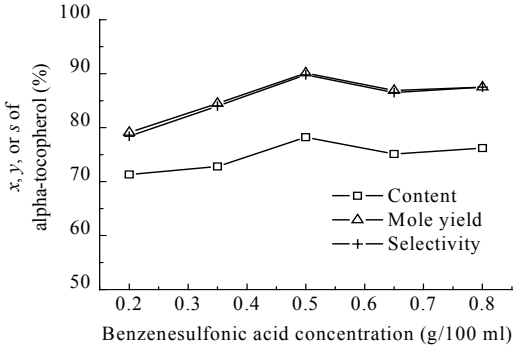


Fig.3 Effect of benzenesulfonic acid concentration on the content, mole yield, and selectivity of α-tocopherol

Fig.4 shows the change of the content, mole yield, and selectivity of α-tocopherol with the increase of the mass ratio. When the mass ratio increased, the content, mole yield, and selectivity rose steadily as well. So the preferable mass ratio was 7.1 g/100 g in the experimental range.

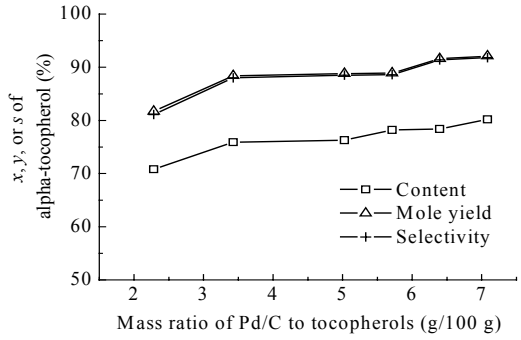


Fig.4 Effect of mass ratio of Pd/C to tocopherols on the content, mole yield, and selectivity of α-tocopherol

Effect of reaction time

The operation conditions were: mixed tocopherols 25.0 g, paraformaldehyde 17.0 g, benzenesulfonic acid 1.0 g, Pd/C 1.3 g, ethanol 200.0 ml, temperature 180 °C, pressure 5.0 MPa. The reaction time was from 1.0 h to 7.0 h.

At all experimental conditions, the conversion of non-α-tocopherols was almost 100%, i.e., there were almost no β-, γ-, and δ-tocopherol remained in the products.

The results are shown in Fig.5. From 1.0 h to 5.0 h, the content, mole yield, and selectivity of α-tocopherol rose rapidly; but beyond 5.0 h they declined. α-tocopherol might be unstable under the reaction conditions, and side reactions would take place which lead to the decline of the content, mole yield, and selectivity. Therefore the preferable reaction time was 5.0 h.

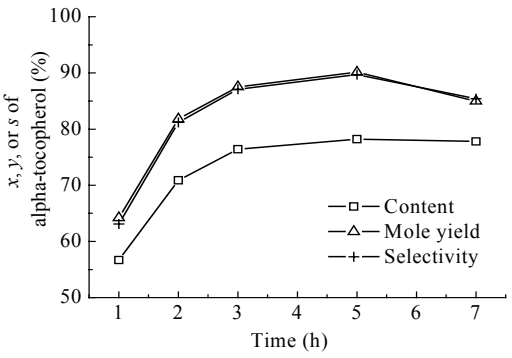


Fig.5 Effect of reaction time on the content, mole yield, and selectivity of α-tocopherol

CONCLUSION

Natural non-α-tocopherols were simultaneously hydroxymethylated and hydrogenated in an autoclave to α-tocopherol in the presence of catalysts of benzenesulfonic acid and 5% Pd/C. The preferable reaction conditions were: temperature 180 °C to 200 °C, pressure 5.0 MPa, acid concentration 0.5 g/100 ml ethanol, mass ratio of Pd/C to tocopherols 7.1 g/100 g, reaction time 5.0 h. Under the above conditions, a product with α-tocopherol content of 80% was obtained by using raw material with total tocopherols content of 80.54%. The conversion of non-α-tocopherols was almost 100%, and the mole yield of α-tocopherol was more than 90%. There were almost no β-, γ-, and δ-tocopherol remained in the product.

References

Baldwin, W.S., Willging, S.M., Siegel, B.M., 1990. Production of D-alpha-Tocopherol from Natural Plant Sources. US 4,977,282.

Breuninger, M., 1999. Process for Permethylating non-α-Tocopherols to Produce α-Tocopherol. US 5,932,748.

Brüggemann, K., Herguijuela, J.R., Netscher, T., Riegl, J., 1999. Hydroxymethylation of Tocopherols. US 5,892,058.

Dutta-Roy, A.K., 1999. Molecular mechanism of cellular uptake and intracellular translocation of α-tocopherol: role of tocopherol-binding proteins. *Food and Chemical Toxicology*, **37**:967-971.

Hickman, K.C.D., Weisler, L., 1949. Vitamin E Preparation. US 2,486,540.

Kamal-Eldin, A., Appelqvist, L., 1996. The chemistry and antioxidant properties of tocopherols and tocotrienols. *Lipids*, **31**(7):671-701.

Lechtken, P., Hoercher, U., Jessel, B., 1990. Preparation of D-α-Tocopherol from Natural Intermediates. US 4,925,960.

Müller, R.K., Schneider, H., 2000. Aminomethylation of Tocopherols. US 6,066,731.

Weisler, L., Chechak, A.J., 1949. Simultaneous Haloalkylation and Reduction of Organic Compounds. US 2,486,542.