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Submission date: 12-May-2023 02:44AM (UTC-0500)
Submission ID: 2091163285
File name: prosiding.pdf (1.57M)
Word count: 2763
Character count: 15274

Synthesis and Antioxidant Activity of Calix[4]resorcinarene Derivatives Compounds

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Abstract. Synthesis of calix[4]resorcinarene derivatives and their activity as an antioxidant has been carried out. The calix[4]resorcinarene was synthesized through a condensation reaction of resorcinol, valeraldehyde, and benzaldehyde using HCl as a catalyst with ethanol as a solvent (73 °C, 24 h). Two synthesized products, C-butilcalix[4]resorcinarene and C-phenylcalix[4]resorcinarene were successfully prepared with 44.70% and 43.5% yield, respectively. Their chemical structure was elucidated by Fourier Transform Infrared (FTIR) and Proton Nuclear Magnetic Resonance (^{1}H-NMR) analysis. The antioxidant activity assay of these compounds was evaluated through an in vitro assay of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. The DPPH assay showed that the half-maximal inhibitory concentration (IC_{50}) values of C-butylcalix[4]resorcinarene and C-phenylcalix[4]resorcinarene were 6.28 ppm and 18.76 ppm, respectively. This finding demonstrates that both C-butylcalix[4]resorcinarene and C-phenylcalix[4]resorcinarene have very strong antioxidant properties.

Keywords: Antioxidant activity · C-butilcalix[4]resorcinarene · C-phenylcalix[4]resorcinarene · Synthesis

1 Introduction

The reactive nature of free radicals can cause various potential harm to biomolecules by damaging lipids, proteins, and DNA, as well as causing oxidative stress [1]. Oxidative stress can cause cell damage and disruption to the body [2]. The body has a mechanism to protect itself by neutralizing free radicals that are formed using the enzymes superoxide dismutase, catalase, and glutathione peroxidase. However, in certain circumstances, free radicals can exceed the body's defense system [3].

The accumulation of free radicals in the body can be prevented with antioxidant compounds that are able to neutralize, reduce, and inhibit the formation of new free radicals in the body [4]. Calixarene is a phenolic compound from resorcinol derivatives which are known as antioxidant agents and free radical scavengers. Calixarene has been widely known in the health sector as a sunscreen [5], anti-HIV and HCV [6], and anti-tumor [7]. One of the derivatives of calixarene, known to have antioxidant activity, is calix[4]resorcinarene [8].

S. Hadisaputra et al. (Eds.): NiTRIC 2022, AHCPS 4, pp. 75–82, 2023.
https://doi.org/10.2991/978-94-6463-130-2_9

Calix[4]resorsinarene compounds can be synthesized through a condensation reaction of resorcinol and aldehyde with an acid catalyst [9]. Modifying calix[4]resorcinarene is easy to do by substituting functional groups on both the upper and lower edges, depending on the compound required [10]. Calixarene compounds are cyclic oligomers with an aromatic ring of resorcinol connected by methine bridges and have geometric cavities [11]. The calix[4]resorcinarene structure can also be modified to have antioxidant properties [12].

The antioxidant activity test of a compound can be determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. It is a simple, fast, easy, and accurate colorimetric method for estimating antiradical activity [13]. This method shows the equivalent concentration parameter, which gives a 50% effect on antioxidant activity in the form of the inhibition concentration (IC) value [14]. The IC_{50} value range indicates the standard classification of antioxidant strength. A compound can be identified as a very strong ($IC_{50} < 50$), strong ($IC_{50} = 50–100$), moderate ($IC_{50} = 100–150$), or weak ($IC_{50} = 151–200$) antioxidant [15].

One of calix[4]resorcinarene derivatives, C-2-hydroxyphenylcalix[4]resorcinarene, has previously been successfully synthesized by Handayani, et al. [16]. Based on the DPPH method, this compound shows strong antioxidant activity with an IC_{50} value of 77.43 ppm. Another derivative, C-methoxyphenylcalix[4]resorcinarene, also exhibited strong antioxidant activity with an IC_{50} value of 79 ppm [17]. However, the antioxidant activities of both compounds are still weaker than that of vitamin C which has very strong antioxidant activity with an IC_{50} value of 20.95 ppm.

The derivative of calix[4]resorcinarene has the potential as an antioxidant. In this research, the synthesis of compounds derived from calix[4]resorcinarene has been carried out using resorcinol, valeraldehyde, and benzaldehyde by the Gutsche method. The synthesized compounds were then tested for their antioxidant activity using the DPPH method.

2 Method

2.1 Chemicals

The materials employed for this synthesis were resorcinol ($C_6H_4(OH)_2$), valeraldehyde ($C_5H_{10}O$), benzaldehyde (C_7H_6O), ethanol 98%, hydrochloric acid (HCl) 37%, and distilled water. The material used for the antioxidant test was 2,2-diphenyl-1-picrylhydrazyl (DPPH).

2.2 Synthesis of C-butylcalix[4]resorcinarene

The synthesis of C-butylcalix[4]resorcinarene was carried out by adding 2.2 g of 0.02 mol resorcinol, 2.12 mL of 0.02 mol valeraldehyde, and 55 mL of absolute ethanol into a three-neck flask equipped with reflux and stirring magnet. Then, 1 mL of 37% (v/v) HCl solution was added dropwise as a catalyst. The mixture was refluxed at 73 °C for 24 h and cooled to room temperature. After that, 30 mL of distilled water was added to the mixture until a precipitate was formed. The precipitate formed was filtered by vacuum and washed using ethanol:aquadest (1:1) until neutral. The synthesized product was dried in a vacuum desiccator and characterized by FTIR and ^{1}H-NMR.

2.3 Synthesis of C-phenylcalic[4]resorcinarene

The synthesis of C-phenylcalic[4]resorcinarene was carried out by adding 2.2 g of 0.02 mol resorcinol, 2 mL of 0.02 mol benzaldehyde, and 35 mL of absolute ethanol into a three-necked flask equipped with reflux and stirring magnet. Then, 1 mL of 37% (v/v) HCl was added dropwise. The mixture was stirred and heated at 70 °C for 24 h. After the reflux was complete, the mixture was cooled to room temperature. The solid formed was then filtered and washed with ethanol:aquadest (1:1) until neutral. The product was dried in a vacuum desiccator and characterized using FTIR and ^{1}H-NMR.

2.4 Antioxidant Activity Assay

The first step was the preparation of the calibration curve. A 100 ppm DPPH solution was prepared by placing 5 mg of DPPH powder inside a 50 mL round bottom flask and adding ethanol to the limit mark. The solution was diluted with various concentrations, 5, 10, 15, 20, and 25 ppm. The maximum wavelength was selected by measuring the absorbance of the solution using an interval of 400–700 nm and determining the wavelength with the highest absorbance value. The absorbance of each solution was then measured at the maximum wavelength to create a curve.

The second step was the sample preparation. As much as 2.5 mg of sample were dripped with 2–3 drops of DMSO and dissolved with 50 mL of ethanol to obtain a 50 ppm solution. The solution was diluted to obtain concentrations of 15, 20, and 25 ppm.

The last step was the antioxidant activity test. As much as 3 mL of each sample solution was placed in a test tube. Then, 2 mL of DPPH solution was added. After that, the mixture was incubated for 30 min. The incubated mixture was added to the cuvette. The absorbance was then measured using a UV-Vis spectrophotometer at 518 nm. The antioxidant activity of each test solution was determined by the equation:

$$A = \frac{A_0 - A_1}{A_0} \times 100\% \quad (1)$$

where:

A = %radical scavenging activity
A_0 = control absorbance
A_1 = sample absorbance.

The results of these calculations are entered into the regression equation with ln of the solution concentration as the abscissa (X axis) and the inhibition value (%) as the ordinate (Y axis). The curve is converted into linear regression so that the equation is obtained:

$$y = ax + b \quad (2)$$

where:

y = antioxidant activity
a = intercept
x = concentration of test solution
b = regression coefficient

Based on the linear regression equation, the calculation of the IC_{50} value is obtained using the equation:

$$IC_{50} = \text{anti } \ln(x) \tag{3}$$

3 Results and Discussion

The condensation reaction between resorcinol and valeraldehyde resulted in the synthesis of C-butylcalyx[4]resorcinarene. The condensation reaction used an HCl catalyst and ethanol as solvent. The synthesized product was washed using ethanol and distilled water to produce a pink solid with a 44.70% yield and a melting point of 322.6 °C. Meanwhile, the reaction between resorcinol and benzaldehyde successfully produced C-phenylcalix[4]resorcinarene. The product formed was a pale orange solid with a 43.5% yield and a melting point of 353 °C. The FTIR spectra of C-butylcalix[4]resorcinarene and C-phnylcalix[4]resorcinarene are shown in Fig. 1.

Based on the FTIR spectra, The O-H functional group was observed as a broad signals at 3468 and 3487 cm^{-1} region for C-butylcalix[4]resorcinarene and C-phenylcalix[4]resorcinarene, respectively. The signals of aliphatic group appeared at a wave number of 1435 cm^{-1} for C-butylcalix[4]resorcinarene and 1427 cm^{-1} for C-phenylcalix[4]resorcinarene indicating the presence of C-H absorption or CH_2 bending vibrations. Those peaks are characteristic of calix[4]resorcinarene compounds indicating the presence of a methine bridge in the products. The C = C aromatic signals of C-butylcalix[4]resorcinarene and C-phenylcalix[4]resorcinarene appeared at 1611–1500 cm^{-1} and 1614–1512 cm^{-1}, respectively.

Further characterization using ^{1}H-NMR is shown in Fig. 2. Based on ^{1}H-NMR spectra, typical signals for both synthesis products, C-butylcalix[4]resorcinarene and C-phenylcalix[4]resorcinarene, appeared at δ_H 4.22–4.19 ppm (4H, *t*, J = 7.8 Hz) and δ_H 5.55–5.25 ppm, respectively, indicating the presence of a methine bridge. The signals for aromatic protons of the calyxarene skeleton were shown at the deshielding region (unprotected), δ_H 7.14 ppm (4H, *s*) and δ_H 6.13 ppm (4H, *s*) for C-butylcalix[4]resorcinarene and 6.61 ppm (*s*, 1H) for C-phenylcalix[4]resorcinarene. Singlet protons indicate that the benzene ring undergoes the substitution of a hydroxyl group. The proton signal at δ_H 8.8 ppm (8H, *s*) for C-buyilcalix[4]resorcinarene and δ_H 8.4 ppm (1H, *s*) and δ_H 8.5 ppm (2H, *s*) for C-phenylcalix[4]resorcinarene indicating the presence of a hydroxyl group (-OH) and therefore constructing resorcinol skeleton. Based on the FTIR and ^{1}H-NMR spectra analysis, both target compounds, C-butylcalix[4]resorcinarene and C-phenylcalix[4]resorcinarene, have been successfully synthesized.

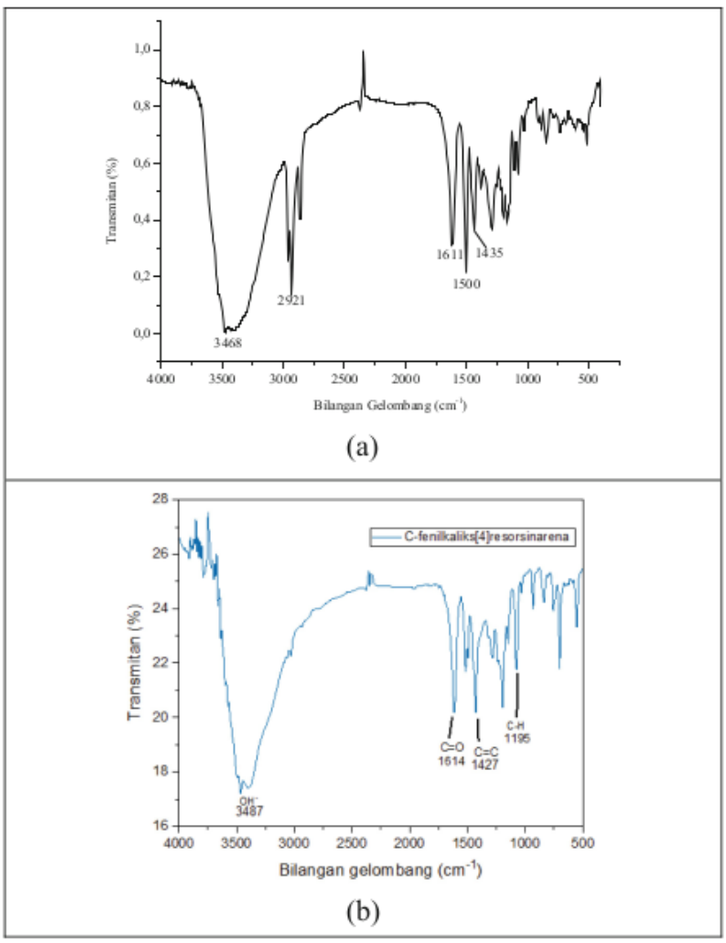

Fig. 1. FTIR spectra of (a) C-butylcalix[4]resorcinarene, and (b) C-phenylcalix[4]resorcinarene

The synthesis products, C-butylcalix[4]resorcinarene and C-phenylcalix [4]resorcinarene, had very strong antioxidant activities. The IC_{50} values of C-butylcalyx[4]resorcinarene and C-phenylcalyx[4]resorcinarene, were 6.28 and 18.76 ppm, respectively. The antioxidant activities of the synthesized compounds are stronger than that of vitamin C which has IC_{50} value of 20.95 ppm. The phenolic group can donate its hydrogen atom due to the high resonance stability. The C-butylcalix[4]resorcinarene possess potent antioxidant properties since it is a supramolecular compound. According to Lee, et al. 2020, supramolecular compounds such as calyxarene derivatives are promising for antioxidant development because they can modulate free radical reactions and ameliorate disorders associated with oxidative stress.

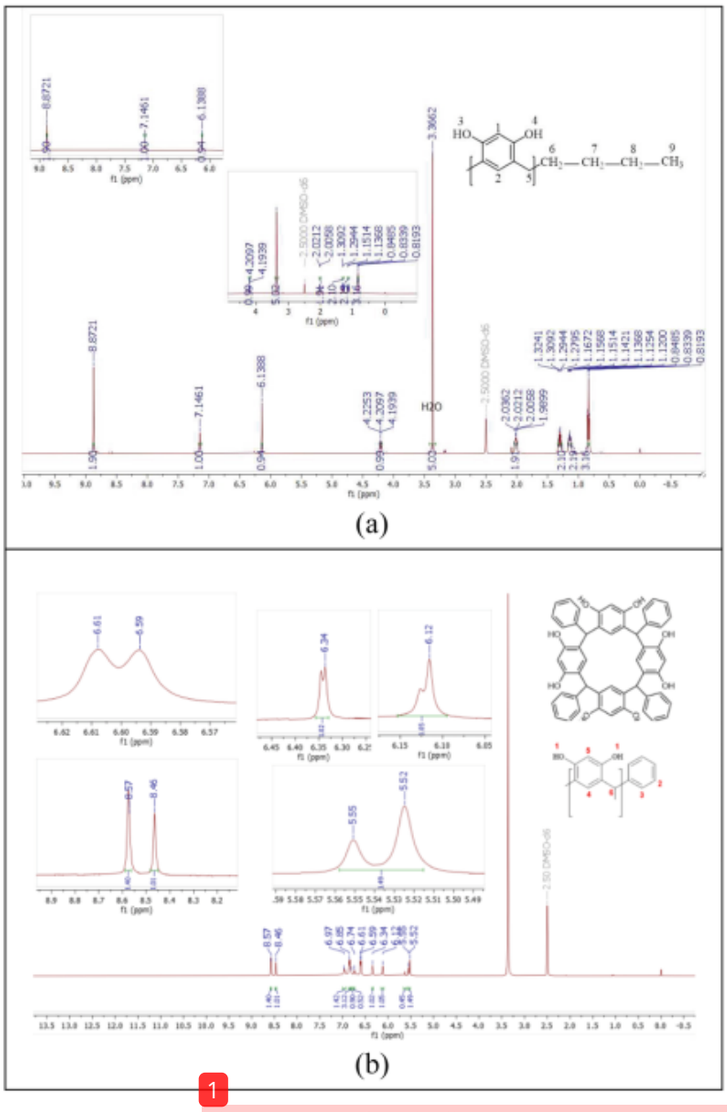

Fig. 2. ^{1}H-NMR spectra of (a) C-butylcalix[4]resorcinarene, and (b) C-phenylcalix[4]resorcinarene

4 Conclusions

The synthesis of calix[4]resorcinarene derivatives was successfully carried out using the Gutsche method to obtain two different products, C-butylcalyx[4]resorcinarene and C-phenylcalyx[4]resorcinarene, with yields of 44.70% and 43.5%, respectively. Based on antioxidant activity evaluation using the DPPH method, C-butylcalyx[4]resorcinarene and C-phenylcalyx[4]resorcinarene, had IC_{50} values of 6.28 and 18.76 ppm, respectively, indicating both are very strong antioxidant compounds.

Acknowledgement. The authors would like to express gratitude to the Staff and laboratory assistants of the Department of Chemistry, Faculty of Mathematics and Natural Sciences, University of Mataram, for assisting the research process and the Integrated Chemistry Laboratory of FMIPA-ITB for the measurement of NMR (Yana Maolana Syah).

Conflict of Interest. The authors declare that there are no conflicts of interest.

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