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Synthesis of Phenylcalix[4]Resorcinarena Sulfonate and It's Aplication as An Antioxidant

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Abstract

Phenylcalix[4]resorcinarene sulfonate can be synthesized through two stages, namely the first stage, benzaldehyde and resorcinol condensation reactions in the presence of an acid catalyst (HCl) and ethanol solvent, the reaction is carried out for 24 hours. The second stage of the sulfonation reaction using concentrated sulfuric acid with catalyst Ag_2SO_4 against phenylcalix[4]resorcinarene compounds. The first condensation reaction results in the form of a yellowish solid with a yield of 82.81% and a melting point> 368.8 °C. The results of the sulphonation reaction of calix[4]recorinarene in the form of black solid with a yield of 75% and melting point above 300 °C. The reaction products were analyzed by infra red spectrophotometer (FT- IR), and ^{1}H NMR. The reaction product has a hydroxy phenol group which can be used as an antioxidant. The antioxidant activity test carried out by DPPH method on phenylcalixs[4] recorcinene sulfonate compounds and BHT (positive control) obtained ES_{50} (electron scavenging 50) with 248.18 ppm and 12.56 ppm respectively

1. Introduction

Calix[4]resorcinarene is an aromatic compound derived from resorcinol and aldehyde groups rich in electron conjugation [1]. Its hydrophobic cavity causes calix[4]resorcinarene to function as a host molecule inthe guest-host system. Caliks[4]resorcinarene has been widely used and among them are components ofsilver ion selective membrane electrodes [2], adsorbents [3], and NMR chiral solvent agents [4]. The increased utilization of calix[4]resorcinarene is done through the functionalization of it's active groups. The compound can undergo derivatization in the hydroxyl group, ortho position and lower group. Derivatization of the lower group can be done by reacting resorcinol with different aldehydes [5]. Aldehydes that have been used in the synthesis of calix[4]resorcinarene include benzaldehyde [6,7], 2-hidroxybenzaldehide[8],2-metoxy benzaldehyde [9],3-methoxybenzaldehyde, 4-hydroxybenzaldehyde, and 4-hydroxy-3-methoxybenzaldehyde [10]. Kaliks [4] resorcinarene produced from Sardjono (2007)[10] has very low watersolubility. One way to increase the solubility of compounds in water is to add highly polar groups such assulfonates. Sulfonation is a substitution reaction of H atoms in benzene by sulfonate groups. This reaction occurs when benzene is heated with concentrated sulfuric acid as a reagent. Sulfuric acid used generallycontains trioxide (oleum). Sulfonation of aromatic compounds is an electrophilic substitution, but it is areversible reaction. In the sulfonation process, it involves adding the $-SO_3H$ group to the aromatic ring. Apart from that, sulfonation of calix[4]resorcinarene has been widely carried out, one of which is tetra sulfonatomethylcalix[4]resorcinarene [11]. The resulting compound is very soluble in water and canform effective complexes with cations. Based on this background, sulfonation was carried out on C-phenylcalix[4]resorcinarene which will later have a structural prediction in Fig. 1 Because sulfonation itself is widely used for manufacturing drugs, the authors are interested in finding out the level of toxicity.

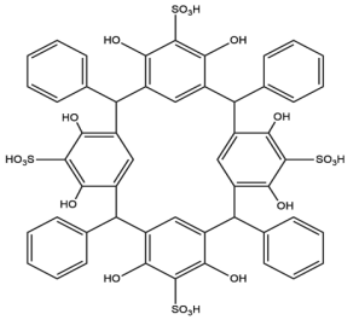


FIGURE 1 Structure of C-phenylcalix[4]resorcinarene sulfonate

The structure of calix[4]resorcinarene has the possibility to be modified so that it can be used asanti-radicals, antioxidants and sunscreen agents [12]. Research conducted by Handayani *et al*., (2016) [8,9] on the synthesis of 2-ethoxyphenylcalcally compound [4] resorcinarene showed strong antioxidantactivity with an ES_{50} value of 83.62 µg/mL, in other studies also showed a compound C-2-Hydroxyphenylcalix[4]resorcinarene and phenylcalix[4]resorcinarene have a strong antioxidant activity with an ES_{50} value of 77.43 µg/mL and 4.92 µg/mL. So it can be seen that compounds have potential asantioxidant. Antioxidant activity test can be done with the DPPH test (1,1-diphenyl-2-picrylhydrazyl). DPPH test is a simple colorimetric method in which the method can be done quickly and easily in estimatingantiradical activity, besides that the DPPH test is proven to be accurate, reliable, and practical [13]. Research on the antioxidant activity test of compounds synthesized C-phenylcalix[4]resorcinarene sulfonate it has not been reported. In this resaerch can synthesized of phenilcalix[4]resorcinarene and their application as antioxidant assay with DPPH methods.

2. Methodology

2.1. Synthesis of C-phenylcalix[4]resorcinarena

Synthesis of C-phenylcalix[4]resorcinarene (CFKR) was carried out by dissolving as much as 1.60 grams of resorcinol in 50 mL of 95 % ethanol. Then added 1.59 grams of benzaldehyde into the mixture. After all dissolved as much as 1 mL concentrated HCl is added drop wise, the mixture is stirred and refluxed for 24 hours. The mixture is then cooled and filtered. The solid is washed with ethanol: water (1: 1) after it is dried.

2.2. Synthesis of C-phenylcalix[4]resorcinarene sulfonate[14]

A total of 5 mL of concentrated H_2SO_4 and 0.1 gram of Ag_2SO_4 as a catalyst were reacted in a three neck flask. Then 0.5 grams of CFKR are added little by little to the mixture and cooled at 0 °C. The mixture is then stirred using a stirrer for 2 hours. After that, the mixture is heated at 80 °C for 3 hours and allowed to sit in the room temperature. The process is followed by neutralization using 50% NaOH until the pH is neutral and solids are formed. The solid is filtered and dried in the oven. After drying, the solid is dissolved in methanol and the filtrate formed is evaporated to obtain the product. Product characterization was performed with FT-IR spectrophotometer and ^1H NMR spectrometer and melting point determination.

2.3. Antioxidant Activity Test

2.3.1 Preparation of DPPH solutions

DPPH compounds of 1.97 mg were weighed and dissolved with methanol p.a to 100 mL, so that a DPPH solution concentration of 0.05 mM was obtained. The solution is then closed using aluminum foil [9] (Handayani *et al*., 2016).

2.3.2 Preparation of test solutions

Five miligrams of C-phenylcalix[4]resorcinarene is weighed and put into a pumpkin the size of. Added 2-3 drops of DMSO and then dissolved in methanol up to 5 mL in volume to obtain a solutionconcentration of 1000 µg / mL. Then a variation of the concentration of the test solution was

made to obtain the concentration solution of the C-phenylcalix [4]resorcinarene of 100, 200, 300, 400, and 500 µg/mL [9].

2.3.3 Determination of the maximum wavelength of DPPH

Four mililiter of DPPH 0.05 mM was added with 1 mL of methanol and homogenized. Leave for 30 minutes in a dark room. Then the absorbance solution was measured using a UV-Vis spectrophotometer at a wavelength of 400-600 nm [8].

2.3.4 Determination of the operating time of the test solution

A total of 4 mL DPPH 0.05 mM and 1 mL of test solution added with a concentration of 100 µg / mL. The solution is then homogenized. After that, the absorbance of the solution is measured with a UV-Vis spectrophotometer at the maximum wavelength at 5 minute intervals until a stable absorbance is obtained. After measuring the absorbance in the test solution, the values obtained are used to calculate the % scavenging value. The value of % scavenging can be calculated using the formula :

$$\% \text{ scavenging} = \frac{\text{Absorbance of DPPH - Absorbance of sample}}{\text{Absorbance of DPPH}} \times 100\% \quad (1)$$

Linear regression y = ax + b is made through the curve of the relationship between concentration and % scavenging. Fifty % inhibitory value (ES_{50}) of antioxidant activity was calculated as a sample concentration that inhibited 50% activity on DPPH.

3. Results and Discussion

3.1 Synthesis of C-phenylcalix[4]resorcinarena (CFKR

CFKR synthesis is out by reacting resorcinol and benzaldehyde under acidic conditions obtained from concentrated HCl. HCl acts as a catalyst and protonates benzaldehyde so that it is easily attacked by resorcinol and undergoes aromatic electrophilic substitution [8,9]. Synthesis do for 24 hours at a temperature of 78 ℃. CFKR products are solids which are separate from the reaction mixture. This is because CFKR synthesis results have low solubility. Based on these data the physical characteristics of the CFKR are in the form of orange solids, yields 96.62% and melting points more than 300˚C.

The synthesized CFKR was characterized using FTIR spectrophotometer to determine the fungsional groups contained in the CFKR. The FTIR spectrum of CFKR compounds can be seen in Fig. 2

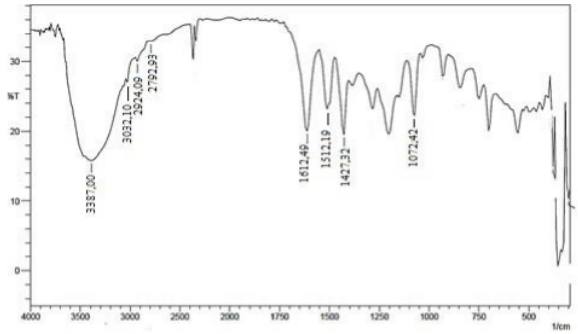
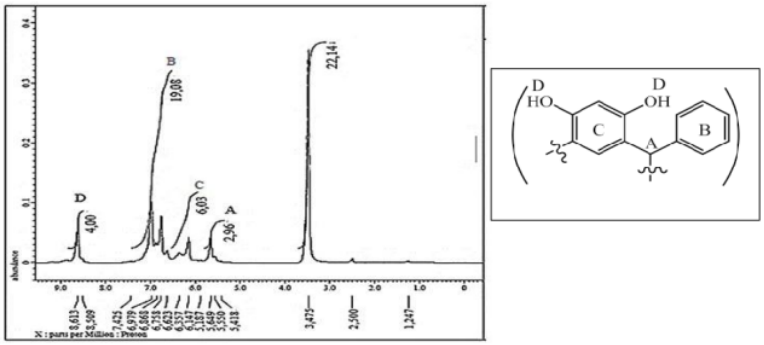


FIGURE 2 The FTIR spectrum of CFKR

Fig. 2 indicates the strong and wide absorption in the area of 3387 cm^{-1} shows the existence of vibrations from the O-H group. Absorption in the area of 2924 cm^{-1} and 2792 cm^{-1} is a stretch of C_{sp}^{3}-H. Strong

uptake was also found in the areas of 1612 cm^{-1} and 1512 cm^{-1} which was a stretch of C ^{2} indicating the presence of aromatic rings. A typical absorption with strong intensity in the area of 1472 cm^{-1} is a methylene bridge (C-H) indicating that cyclization has occurred.



(a) (b)

FIGURE 3 The ^{1}H-NMR spectrum of CFKR compounds.

Based on Fig. 3 there are several different signals including those in the δ H area of 5.619 ppm which are methylene bridges (C-H). Another signal is in the δ H area of 6.979 ppm which is an aromatic proton (Ar-H). In addition, there are also hydroxyl proton (-OH) signals in the δ H region of 8.613 ppm and 8.509 ppm. According to Utomo *et al*. (2011) [15] reactions that occur during the formation of CFKR are electrophilic substitution reactions. Resorcinol acts as nucleophilic and benzaldehyde as electrophilic. The acidic of concentrated HCl causes benzaldehyde to form its carbocation.

3.2 Synthesis of C-phenylcalix[4]resorcinarene sulfonate(CFKRS)

The results of sulfonation on CFKR can be seen from the change in color from orange to reddish orange. The sulfonation product is neutralized by the addition of 50% NaOH. The precipitate formed is a salt of reaction between strong acids and strong bases. CFKRS samples are found in the filtrate resulting from the neutralization process. The filtrate obtained is extracted using methanol, then evaporated to form solids and all the methanol has evaporated. This extraction is to separate the product from the remaining salt and dissolve it in water. The resulting solids are CFKRS products in the form of black solid powder, 75% yield, melting point of more than 400 ℃, and the compound decomposes at 300 ℃. The solubility test of CFKRS products in various solvents can be shown in Table1.

Table 1. Solubility test of 0.05 g CFKRS in 1 mL ofsolvent

No	Solvent	Solubility
1	Water	Partialy Soluble
2	DMSO	Soluble
3	Methanol	Soluble
4	Ethanol	Insoluble
5	Acetone	Insoluble
6	n-Hexane	Insoluble
7	Chloroform	Insoluble

Sulfonation reaction is an alternating reaction that cannot occur at room temperature [16]. A decrease in temperature until it reaches 0 ˚C causes the equilibrium reaction to shift to the right isothermic so that the amount of SO_3, H_3O +, and HSO_4^- is greater. The equilibrium reaction can be seen in equation :

$$2H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO^-_4 \quad (2)$$

Sulfonation is also an electrophilic substitution reaction that occurs in two stages, namely electrophilic attack and proton release [16]. SO_3 which is formed from the decomposition of H_2SO_4 acts as an electrophile that attacks the ortho CFKR position which is the most reactive position [17]. CFKR will react with SO_3, H_3O^+, and HSO_4^- to obtain CFKRS. The reaction that occurs is unstable and can form its original material so the temperature is raised to 80 ˚C in order to obtain a more stable product. Whereas SO_3 which does not react with CFKR will form sulfuric acid again.

Thin layer chromatography (TLC) was carried out to monitor the course of the reaction, so that an optimal product was obtained. The eluent used was ethyl acetate: ethanol (1: 1) and formed 1 stain when the sample was eluted with an Rf value of 0.75 green when illuminated by a 366 nm UV lamp and brown when illuminated by a UV lamp at 254 nm .

The FTIR spectrum of CFKRS compounds shows different functional groups when compared to the FTIR spectrum of CFKR compounds. This is due to the sulfonation reaction that occurs with the CFKR compound being the CFKRS compound. The analysis shows that the sulfonate group has entered the ring and the sulfonation reaction has taken place. Strong absorption was found in the 1118 cm^{-1} region by the - SO_3H group. Strong and wide absorption at 3448 cm^{-1} is the vibration of the -OH group. In addition, there is also absorption which shows the presence of aromatic rings in the area of 1604 cm^{-1}. The spectrum of FTIR analysis results on CFKRS compounds can be seen in Fig. 4

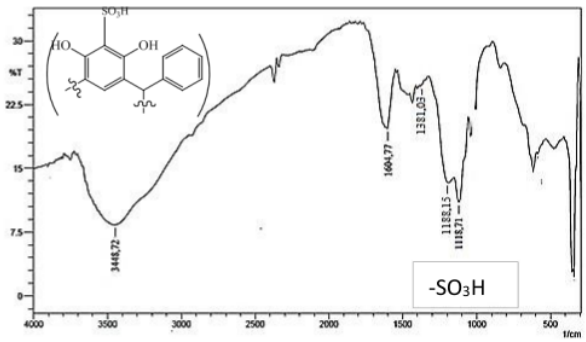


FIGURE 4 FTIR spectrum of CFKRS compounds

The ^{1}H-NMR spectrum of the CFKRS compound showed the presence of several signals. These signals are hydroxyl (-OH), aromatic ring (Ar-H), methylene bridge (C-H), and -SO_3H signal. The presence of hydroxyl groups (-OH) appears in the area of 59 H 8.059 ppm. In addition, aromatic protons (Ar-H) are indicated in the δ H area of 7.667 ppm – 7.721 ppm which shows greater chemical shift. The signal peak in the32Hareaof6.321ppmindicatesthepresenceofamethylenebridge(C-H) and the proton signal of ¬SO_3H is indicated in the δH areaof1,913 ppm. H_2O content will increase with an increase in the amount

of sulfonic acid [18]. The presence of sulfonate groups causes the aromatic protons to shift. ^{1}H-NMR spectrum of CFKRS compounds can be seen in Fig. 5.

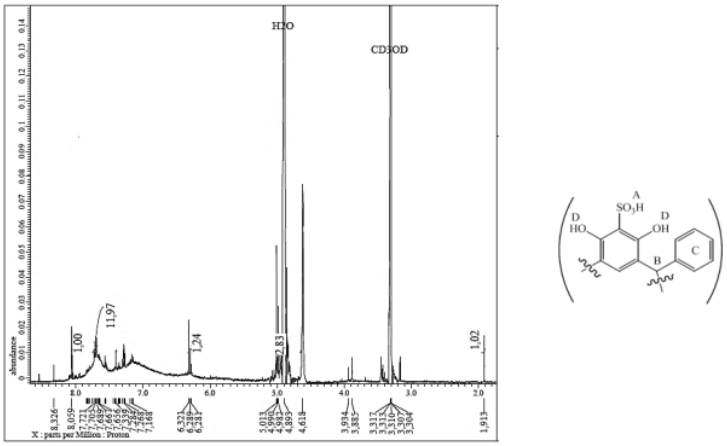


FIGURE 5 CFKRS 1H-NMR spectrum

Based on the structural analysis of FTIR and ^{1}HNMR it can be concluded that the CFKRS product has been formed. This is also supported by the results of the solubility test, which is the starting material CFKR which is insoluble in water into a partially soluble product in water.

3.3 Antioxidant ActivityTest

3.3.1 Determination of maximum wavelength

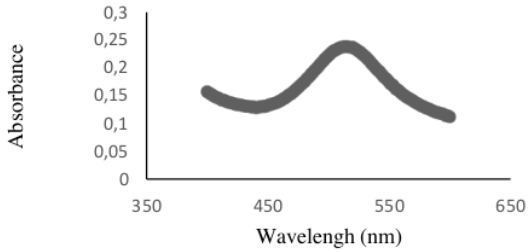


FIGURE 6 Graph determining of optimum wavelengh of DPPH

The maximum wavelength of DPPH is determined to determine the wavelength at which the compound to be measured gives the most optimum absorbance. The maximum wavelength of DPPH is 515 nm with an absorbance value of 0.2831.

3.3.2 Determination of operatingtime

Determination of rainy operating time to find out the most appropriate time when the compounds produced by sinesis reduce DPPH free radicals. Operating time is characterized by perfect reaction when

there is no longer a decrease and increase in absorbance [19]. The results of determining the operating time of the synthesis product are 55-65 minutes (Fig. 7).

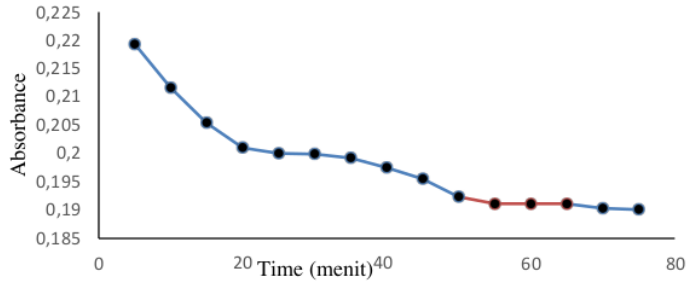


FIGURE 7 Graph of determining operating time

3.3.3 Determination of antioxidant activity tests

Determination of antioxidant activity with DPPH radicals aims to determine the ability of synthesizedproducts to scavenging radical compounds or their ability as antioxidant compounds. BHT (Butylatedhydroxy toluene) was used in this study as a comparison. The parameter used to determine the ability ofcompounds as antioxidants is ES_{50} (electron scavenging). The antioxidant activity of BHT compounds canbe observed in Fig. 8.

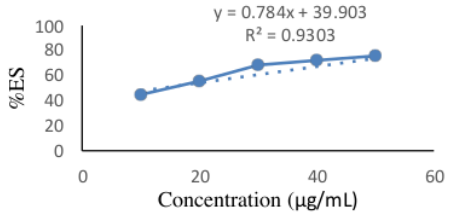


FIGURE 8 Curve concentration of BHT vs % ES

The measurement results of BHT antioxidant activity have a linear regression equation y = 0.784x + 39.903, so the ES50 value was 12.88 µg / mL.Equation of linear regression between% ES and CFKRS concentration (Figure 3.9). The results of the C-phenylcalix[4]resorcinarene obtained a linear regression equation of y = 0.1259x + 18.753, so the ES_{50} value was 248.18 µg / mL and displayed weak antioxidant activity.

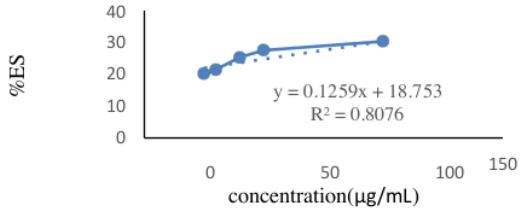


FIGURE 9 Curve concentration of phenylcalix[4]resorcinarene sulfonate vs % ES

Conclusion

CFKRS compounds can be synthezied through two reaction stages sicyclization and sulfonation. The result of CFKRS are in form black solids, yield of 75% and a melting point > 400^{o}C. The result of the DPPH method antioxidant activity test showed that the CFKRS and BHT have an ES_{50} value 248.18 μg/ml and 12.88 μg/ml.

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