SYNTHESIS OF THIOMETHYLATED CALIX[4]RESORCINARENE BASED ON FENNEL OIL VIA CHLOROMETHYLATION

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ABSTRACT

A research has been conducted to synthesize thiomethylated-C-4-methoxyphenylcalix[4]resorcinarene using fennel oil as a starting material. The synthesis was carried out in four steps i.e. (1) oxidation of anethole to yield p-anisaldehyde, (2) HCl-catalyzed condensation of p-anisaldehyde with resorcinol, (3) chloromethylation of C-4-methoxyphenylcalix[4]resorcinarene with paraformaldehyde and HCl in the presence of $ZnCl_2$ to yield tetrakis-chloromethyl-C-4-methoxyphenylcalix[4]resorcinarene, and (4) reaction of tetrakis-chloromethyl-C-4-methoxyphenylcalix[4]resorcinarene with thiourea followed by hydrolysis with sodium hydroxide solution to yield tetrakis-thiomethyl-C-4-methoxyphenylcalix[4]resorcinarene. The prepared compounds were characterized based on melting point, FT-IR, and NMR spectrometers. According to the analysis of ^{1}H-NMR spectrometer, C-4-methoxyphenylcalix[4]resorcinarene and tetrakis-chloromethyl-C-4-methoxyphenylcalix[4]resorcinarene were observed in the chair or flattened partial cone conformation, while tetrakis-thiomethyl-C-4-methoxyphenylcalix[4]resorcinarene tend to exist in the crown or cone conformation.

Keywords: *fennel oil, chloromethylation, tetrakis-thiomethyl-C-4-methoxyphenylcalix[4]resorcinarene, flattened partial cone, crown*

INTRODUCTION

Fennel oil is one of the essential oils that widely used in cosmetic and medicinal purposes. This essential oil is usually obtained through steam distillation towards leaves, seed, and other part of *Foeniculum vulgare* plant (*F. officinale, F. capillaceum* and *Anethum foeniculum*) from the *Umbelliferae (Apiaceae)* family. These plants commonly grow and are cultivated in Indonesia such as Boyolali, Kulon Progo, Cipanas, and Bintan. The main chemical components of Fennel essential oil include 2–6% volatile essential oils comprising of up to 50–70% of sweetish trans-anethole and up to 20% bitter and camphoraceous (+)-fenchone [1]. Unfortunately, the major part of this oil is exported directly as crude products which of course only with a relatively cheap price. Therefore, it should be very valuable if that readily available material could be transformed into other products having higher economic values such as supramolecule compound of calix[4]resorcinarene.

Calix[4]resorcinarenes are cyclic tetramer molecules, like crown ethers and cyclodextrins, made up of resorcinols linked by methylene bridges [2]. These compounds deliver a versatile molecular platform for the elaboration of more complicated host system by virtue of its conformational flexibility. They possessing eight hydroxyl groups at extra anular position, arranged in a unique geometry, that allows the molecule to be used as host for cations [3-8], anions [9-10] and organic neutral molecules [11-13]. Calix[4]resorcinarenes are well known prepared by acid-catalyzed condensation of resorcinol and various aliphatic [12,14-15] or aromatic aldehydes such as benzadehyde [14], 2-hydroxybenzaldehyde [16], and 4-phenoxybenzal dehyde [17], whose major structural feature is composed of four resorcinol units in a cyclic tetramer [18].

Based on the structure, properties, and such broad applications of these compounds the investigator to be interested in conducting exploration and synthesis of calix[4]resorcinarene derivatives from different types of aldehydes. In this publication, we describe the synthesis and conformational properties of resorcinarene compound from fennel oil-based materials which are available abundantly as renewable resources. Herein, we also investigate the thiomethylation of calix[4]resorcinarenes via chloro

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methylation toward electrophilic substitution at aromatic rings of resorcine residues.

EXPERIMENTAL SECTION

Materials

Acetic acid, sulphuric acid, dichloromethane, potassium permanganate, sodium bisulphite, sodium sulphate anhydrous, potassium carbonate anhydrous, resorcinol, ethanol absolute, fuming hydrochloric acid, aquadest, N,N-dimethylformamide (DMF), paraformaldehyde, zinc chloride, methanol, thiourea, and sodium hydroxide. All reagents in analytical grade were obtained from E Merck Co Inc. (Germany) and used without further purification. Anethole 90% was obtained from Schimmel & Co (Germany) and purified with fractional distillation technique.

Instrumentation

In general, the melting points of compounds were determined on melting point electro thermal 9100 and are not corrected. Preparative TLC was carried out on 20x20x0.1 cm plates using Merck silica gel 7730 $60GF_{254}$. Compounds were detected by short and long wavelength ultraviolet light. FTIR spectra were taken on Shimadzu FTIR-Prestige-21. NMR spectra were recorded in the designated solvents on a JEOL 500 MHz or a Bruker AC300F 300 MHz spectrometer. Chemical shifts are reported as δ values in ppm relative to TMS as an internal standard.

Procedure

Oxidation of Anethole

A mixture of anethole (2.96 g; 20.0 mmol), aquadest (100 mL), acetic acid (2.0 mL), 50% of sulphuric acid (15.0 mL), tween 80 (0.1 g), and dichloromethane (100 mL) was stirred at room temperature followed by slowly addition (0.5 g per min) of potassium permanganate (9.80 g; 62.0 mmol). The mixture was then heating at steam bath for 15 min until become colorless. Sodium bisulphite (3.0 g; 20.8 mmol) was added to the stirred mixture at 10 °C for 10 min to change the unsoluble MnO_2 become Mn^{2+}. Organic phase was isolated and water fraction was than extracted with dichloromethane (2x30 mL). All Organic phases washed with water (2x60 mL), dried with Na_2SO_4 anhydrous, and evaporated to obtained colorless oily liquid in 73.24%; FTIR (neat) ν (cm^{-1}): 2806 and 2741 (C_{sp3}-H), 1682 (C=O aldehyde); ^{1}H-NMR (60 MHz, $CDCl_3$) δ (ppm): 9.9 (1H,*s*,CHO), 7.9 (2H,*d*,ArH), 7.0 (2H,*d*,ArH), 3.9 (3H,*s*,OCH_3).

Synthesis of C-4-methoxyphenylcalix[4]resorcinarene

Into a solution of resorcinol (0.55 g; 5 mmol) and *p*-anisaldehyde (0.83 g; 5 mmol) in 50 mL ethanol absolute was added 0.5 mL of fuming hydrochloric acid. The mixture was stirred an refluxed for 30 h until the spot of basic materials on TLC has been used up (TLC monitoring). The mixture was cooled and the product was filtered followed by washing with ethanol-aquadest (1:1) then dried to give the desired compound of C-4-methoxyphenylcalix[4]resorcinarene as a light purple crystal in 91.54%, mp 337-341 °C (dec); FTIR (KBr) ν (cm^{-1}): 3396 (OH group), 3001 (C_{sp2}-H), 1608 and 1510 (C=C aromatic), 2912-2839 (C_{sp3}-H aliphatic), 1430 (-CH methine bridge), 1370 (-CH_3); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 7.92 and 8.03 (8H,*s*,OH), 6.16-6.56 (24H,*m*,ArH), 5.53 and 5.68 (4H,*s*,Ar_2CHAr), 3.66 (12H,*s*,OCH_3).

Chloromethylation of C-4-methoxyphenylcalix[4] resorcinol

C-4-methoxyphenylcalix[4]resorcinarene (0,912 g; 1 mmol) was dissolved in 30 mL of dimethylformamide. To this stirred solution was added paraformaldehyde (0.14 g: 4.5 mmol), $ZnCl_2$ (1.36 g; 10 mmol), and 7 mL of hydrochloric acid fuming respectively. The mixture was then heated at mild reflux of 120 °C for 22 h to paid of the reaction followed by trituration with 50 mL of water at room temperature to yield crude product. The precipitate was filtered, washed twice with water (2x25 mL). The product of tetrakis-chloromethyl-C-4-methoxyphenylcalix[4]resorcinarene can be obtained by recrystallization with methanol : water (1:4) as a light brown powder in 83.45%; mp 322-324 °C; FTIR (KBr) ν (cm^{-1}): 3360 (OH group), 3101 (C_{sp2}-H), 1612 and 1512 (C=C aromatic), 1451 (-CH_2-),1373 (-CH_3); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 7.95-8.44 (8H,triple *s*,OH), 6.44-6.51 (16H,*d* of *d*,ArH), 6.11-6.30 (4H,*m*,ArH), 5.46-5.56 (4H,double *s*,Ar_2CHAr), 3.64 (12H,*m*,OCH_3), 2.54-2.88 (8H,triple *s*,$ArCH_2Cl$); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 165.86 (-C-OMe), 152.17 (-C-OH), 135.43, 128.78, 128.49, 126.96, 119.96, 111.43, (Ar), 60.52 (OCH_3), and 42.02 (Ar_2CHAr), 31.01 (Ar-CH_2-Cl).

Synthesis of tetrakis-thiomethyl-C-4-methoxyphenylcalix[4]resorsinarene

Into a 100 mL two-necked round bottom flask, equipped with magnetic stirrer and reflux condenser was placed 1.446 g (1.5 mmol) of chloromethyl-C-4-methoxyphenylcalix[4]resorcinarene and 30 mL of dimethylformamide. The mixture was than stirred to get a perfect solution followed by carefully addition of thiourea (0.57 g; 7.5 mmol). A tube from the top of condenser was connected leading to an inverted funnel

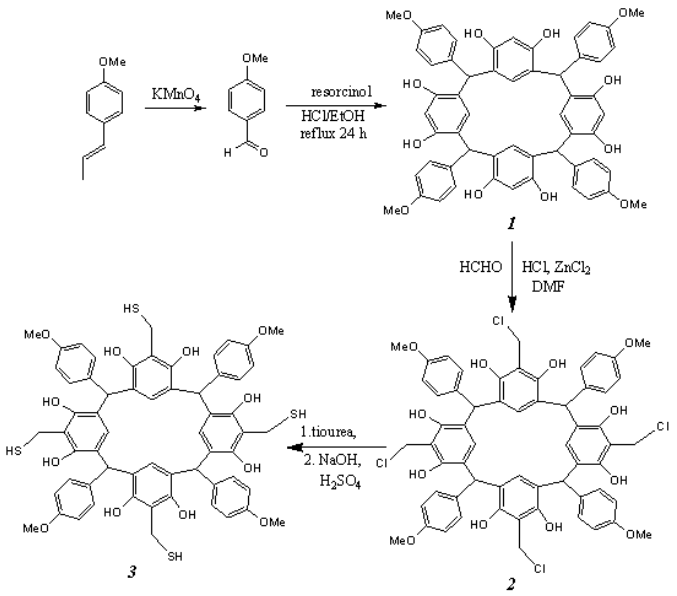


Fig 1. Synthesis of tetrakis-thiomethyl-C-4-methoxy phenylcalix[4]resorcinarene from anethole

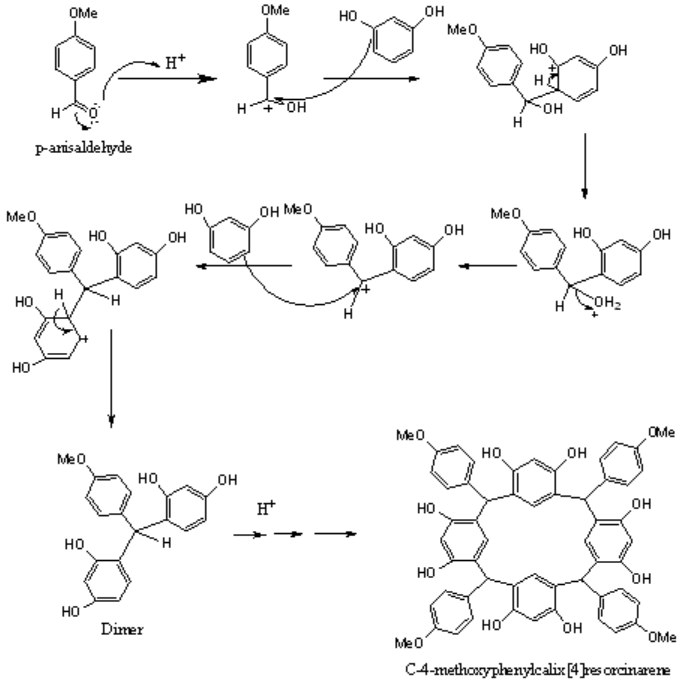


Fig 2. Reaction mechanism of synthesis of resorcinarene ***1*** from *p*-anisaldehyde

just immersed in potassium permanganate solution in order to prevent the escape of unpleasant odors. The mixture was stirred vigorously and heated under reflux for 5 h, the mixture become homogeneous after about 1 h and the additional heating ensure the completeness of the reaction. 2 g of NaOH was added to the mixture at room temperature followed by stirred and refluxed for a further 2 h. During this period the tiol separated since it was largely insoluble in the alkaline condition. The mixture was allowed to cool and residue was separated and acidified with 50 mL of sulphuric acid solution (10%). The product was filtered, washed twice with water and dried in vacuum to give an orange-brown powder in 78.85%; mp 300 °C; FTIR (KBr) ν (cm^{-1}): 3371 (OH group), 3063 (C_{sp2}-H), 1604 and 1512 (C=C aromatic), 2931 (C_{sp3}-H), 2568 (-SH), 1466 (-CH_2-), 1442 (Ar_2CHAr), 1381 (-CH_3); ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 7.95 (8H,*s*,OH), 6.54-6.59 (20H,broad *d*,ArH), 5.64 (4H,*s*,Ar_2CHAr), 3.69 (12H,*s*,OCH_3), 2.73 and 2.88 (8H,double *s*,$ArCH_2Cl$), 1.28 (-SH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 157.80 (-C-OMe), 152.64 (-C-OH), 134.00, 130.28, 129.85, 124.44, 123,53, 113.25 (Ar), 55.04 (OCH_3), and 31.17 (Ar_2CHAr), 8.34 (Ar-CH_2-SH).

RESULT AND DISCUSSION

Synthesis of C-4-methoxyphenylcalix[4]resorcinarene (*1*) from fennel oil

Due to the existence of prophenyl group in anethole, this compound can be transformated to aromatic aldehyde of 4-methoxybenzaldehyde or *p*-anisaldehyde through oxidation with potassium permanganate as shown in Fig. 1. This oxidation reaction occurred in the presence of sulphuric acid at mild condition (30 °C) in order to prevent further oxidation that deliver undesired product i.e. carboxylic acid compound. This reaction well performed by using tween 80 as phase-transfer catalyst, so that MnO_4^- ion can effectively react with anethole in organic layer. The product of 4-methoxybenzaldehyde was obtained as colorless oily liquid in 73.24%.

It is commonly well known that a calixresorcinarene can be synthesized from an aliphatic or aromatic aldehyde. One example of this aromatic aldehyde usage for calixresorcinarene preparation i.e. benzaldehyde has been reported by Tunstad et al. [14]. According to the Tunstad and co-workers standard procedure, the condensation reaction between resorcinol and benzaldehyde need 10 mL of fuming hydrochloric acid to perform the reaction. In contrast, *p*-anisaldehyde only consumes 0.5 mL of fuming hydrochloric acid in the same reaction with resorcinol. Based on that phenomena, it can be inferred that condensation reaction of *p*-anisaldehyde – resorcinol more favorable than that of benzaldehyde – resorcinol. It most probably caused by the presence of new substituent of methoxy group that act as electron donating group.

The condensation reaction of 4-methoxybenzaldehyde with resorcinol occurred in the presence of hydrochloric acid fuming in absolute ethanol.

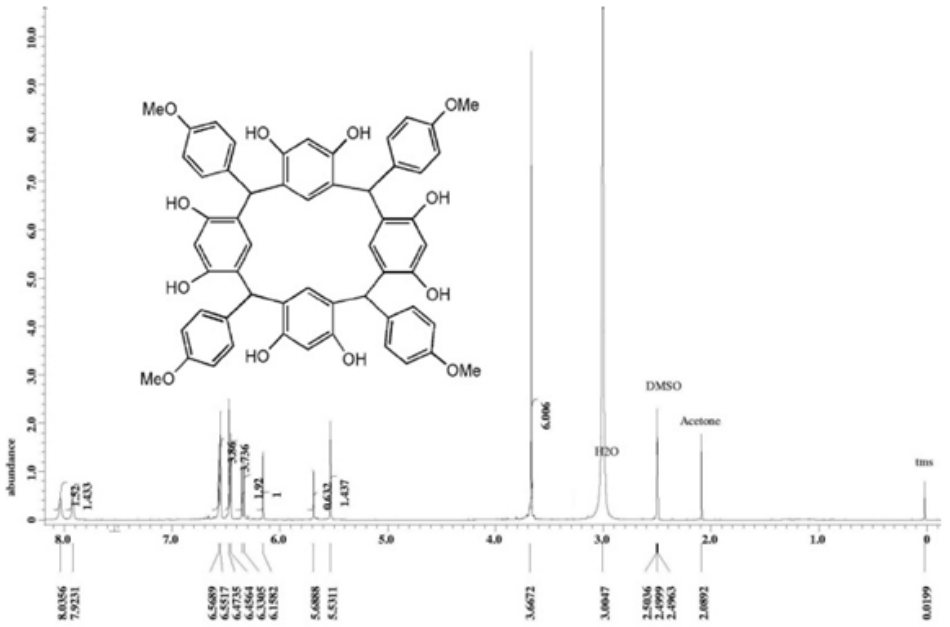


Fig 3. ^{1}H-NMR spectrum of resorcinarene ***1***

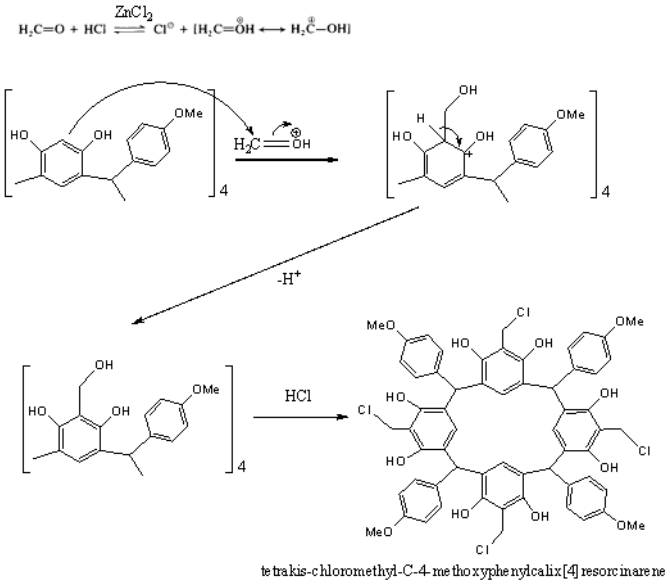


Fig 4. Chloromethylation of C-4-methoxyphenylcalix[4] resorcinarene

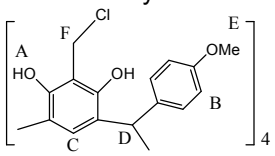
In this reaction, hydrochloric acid will protonize to the oxygen atom at aldehyde group of the *p*-anisaldehyde. It caused partial positive charge of carbonyl carbon atom at aldehyde group, thus, electrophilicity of the carbocation become increase.

On the other side, resorcinol has high electron density at the ortho and para position of two OH groups. As we now that the hydroxyl group is an electron-donating group that can releasing electron to the benzene ring. Therefore, the reactivity of benzene ring will increased through electrophilic substitution attack especially at the ortho-para position. Hydroxyl group is a powerful activating substituent, ortho-para director. It's mean that resorcinol has capability to act as a nucleophile by attacking the carbocation of aldehyde group of 4-methoxybenzaldehyde at ortho-para to the hydroxyl groups. The mechanism of this condensation and cyclization reaction was shown in Fig. 2.

The condensation reaction of *p*-anisaldehyde – resorcinol was performed under vigorous reflux in the presence of acid. The reaction process was observed and monitored by TLC with eluent of dichloro methane:ethyl acetat = 10:1. The product of this reaction is C-4-methoxyphenylcalix[4]resorcinarene **(*1*)** that obtained as a light purple crystal in 91.54% yield with melting point of 337–341 °C (decomposed). Structural determination of the product was made on the basis of FTIR and ^{1}H-NMR studies. The FTIR spectrum show many peaks of OH group, C-H aromatic, C=C aromatic, C_{sp3}-H aliphatic, methine bridge, and methyl group. The most important information from the FTIR spectrum is the absence of the aldehyde group signal at 1682 cm^{-1} for the starting material of *p*-anisaldehyde.

Based on the ^{1}H-NMR spectrum (Fig. 3) there are many different peaks, however, the product of resorcinarene ***1*** generally has 4 proton groups i.e. hydroxyl, aromatic, methine bridge, and methoxy protons. The first proton group was shown at two singlet signals at δ 8.0 and 7.9 ppm with equal amount of proton which correspond to hydroxyl proton. The appearance of this signal indicated that this hydroxyl

Table 1. [1]H-NMR data of Tetrakis-chloromethyl-C-4-methoxyphenylcalix[4]resorcinarene ***2***



Signal	δ (ppm)	Multiplicity	Integration	Proton (Hx)
1	7.95–8.44	three of singlet	8 H	A
2	6.44–6.51	doublet of doublet	16 H	B
3	6.11–6.30	doublet and singlet	4 H	C
4	5.46–5.56	double singlet	4 H	D
5	3.64	multipet	12 H	E
6	2.54–2.88	three of singlet	8 H	F

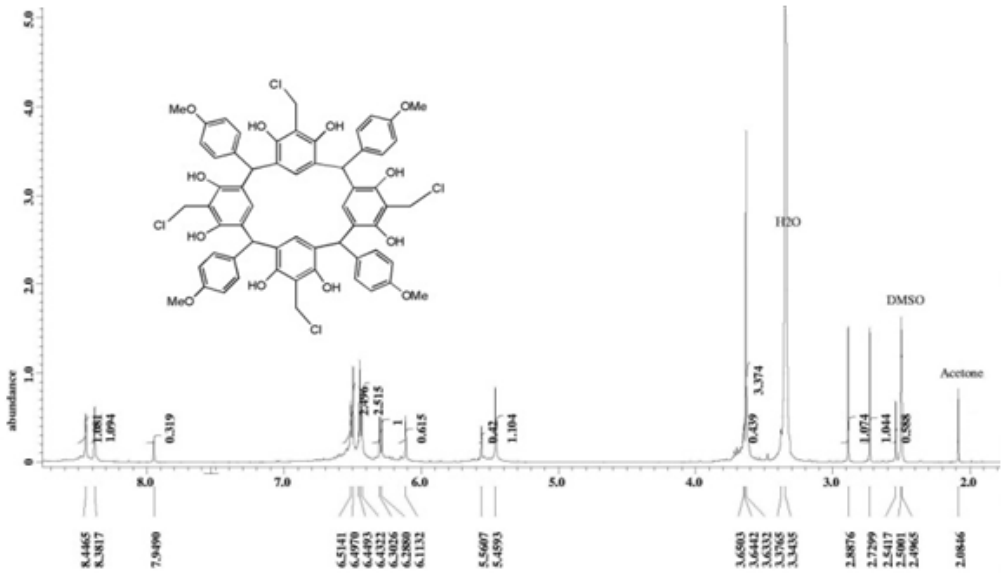


Figure 5. [1]H-NMR spectrum of resorcinarene ***2***

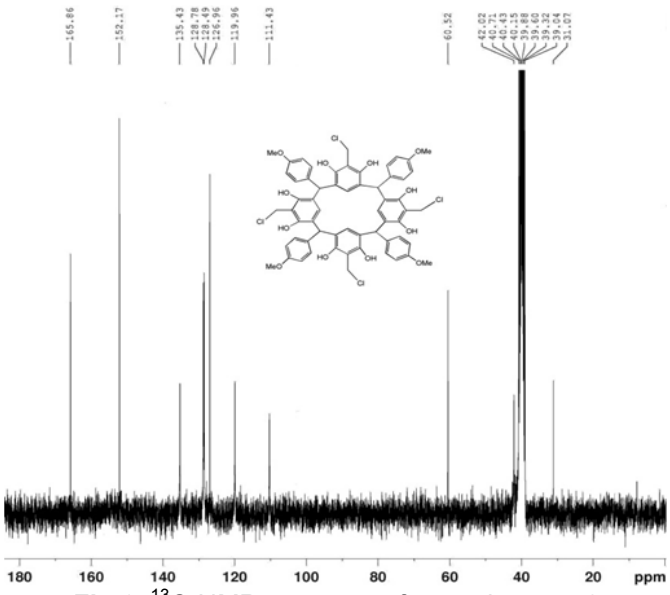


Fig 6. [13]C-NMR spectrum of resorcinarene ***2***

proton are divided into two different chemical environment, 4 hydroxyl protons have different orientation with the other.

The multiple peaks at δ 6.2 – 6.5 ppm refer to 24 proton resonances at aryl groups (Ar-H) which consist of 16 protons of *p*-anisaldehyde residue at δ 6.46 – 6.56 ppm with doublet of doublet signals and 8 protons of resorcin residue at δ 6.16 – 6.33 ppm with appearances of doublet and singlet signals. Furthermore, two singlet peaks at chemical shift of 5.53 and 5.68 ppm with total integration of 4 protons indicated to uneighbor protons of methine bridge. While the singlet signals at δ 3.67 ppm with the highest intensity for approximately of 12 protons correspond to protons of methoxy groups.

Synthesis of Tetrakis-chloromethyl-C-4-methoxy phenylcalix[4]resorcinarene (*2*)

C-4-methoxyphenylcalix[4]resorcinarene has several active sides toward further modification especially

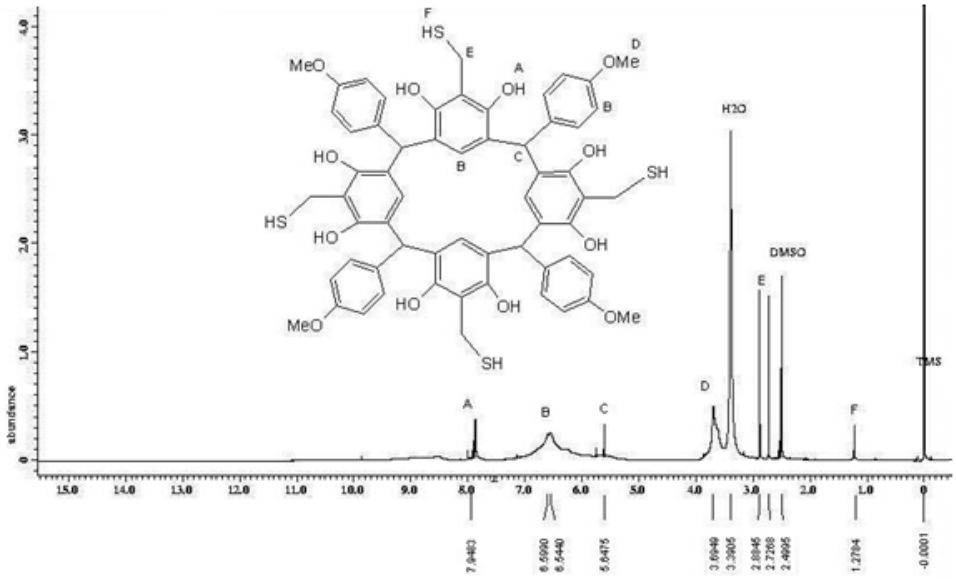


Fig 7. ^{1}H-NMR spectrum of resorcinarene ***3***

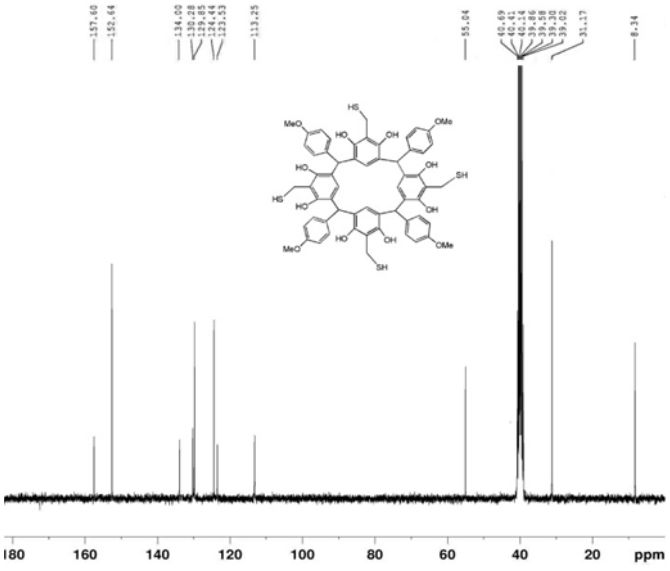


Fig 8. ^{13}C-NMR spectrum of resorcinarene ***3***

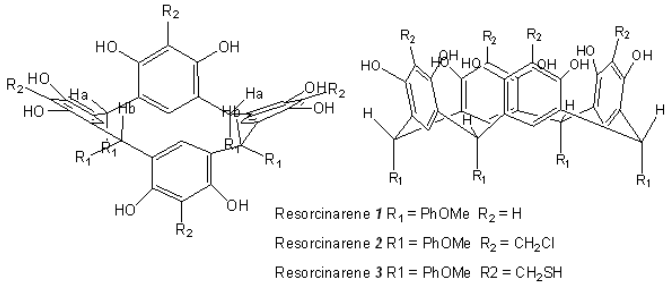


Fig 9. Resorcinarenes conformers

for electrophilic substitution at aromatic rings. In this stage of synthesis, ortho positions between two hydroxyl groups at resorcine residues of resorcinarene ***1*** are the most reactive side toward electrophilic attack. This phenomena is affected by the existence of two electron donating groups (-OH) that increased electron density at aromatic rings especially at ortho position. The synthesis of chloromethyl-C-4-methoxyphenyl calix[4] resorcinarene was performed under mild reflux (120 °C) of the mixture of C-4-methoxyphenyl calix[4] resorcinarene, paraformaldehyde, HCl, and $ZnCl_2$ in dimethylformamide.

Chloromethylation (Fig. 4) is the substitution reaction in which hydrogen atoms at resorcine residue of resorcinarene ***1*** are replaced by chloromethyl groups ($-CH_2Cl$). The original classical reaction consists essentially of the interaction of formaldehyde and hydrogen chloride in the presence of a catalyst such as zinc chloride or aluminium chloride with an aromatic compound. The reaction is similar in some aspects to that of Friedel-Craft reaction wherein hydroxymethyl cation acts as the electrophilic species. This species reacted with aromatic ring of resorcine residue to give the benzylic alcohol which was then converted into the chloromethyl derivative by hydrogen chloride.

This type of reaction was also reported by Almi and co-workers [19]. They used another calixarene compound namely 25,26,27,28-tetrahydroxycalix[4] arene. Treatment of the calix[4]arene with octyl chloromethyl ether and $SnCl_2$ affords an 80% yield of *p*-chloromethylcalix[4]arene. In comparation with our procedure, there are some differences appear especially on resources of electrophile species. Chloromethylation of *p*-H calix[4]arene used cation species of octyloxymethyl, meanwhile in this research we used hydroxymethyl cation. This conditions are affected by some factors: 1. *p*-H calix[4]arene is soluble

in common non polar organic solvent such as chloroform, whereas C-4-methoxyphenylcalix[4]resorcin arene only dissolves in hot DMF; 2. Octyl chloromethyl ether prefer exist in non polar media, but HCl and formaldehyde are polar compounds.

The product of chloromethyl-C-4-methoxy phenylcalix[4]resorcinarene was obtained as a light brown powder in 83.45% yield with melting point of 322–324 °C. The FTIR spectrum of this compound show many peaks consist of OH group, C-H aromatic, C=C aromatic, methylene, and methyl group. In the ^{1}H-NMR spectrum (Fig. 5) of chloromethyl-C-4-methoxyphenyl calix[4]resorcinarene displayed six band groups that already intrepreted in Table 1. The clear evidence for the chloromethyl product was given by ^{13}C-NMR spectrum (Fig.6) in which the typical singlet signal corresponding to chloromethyl carbon (Ar-$\underline{C}H_2$-Cl) appeared at 31.01 ppm.

Synthesis Tetrakis-thiomethyl-C-4-methoxyphenyl calix[4]resorcinarene (*3*)

The embroidering of calixarenes via functionalization has been further expanded by a *p*-chloromethylation route. Generally, the chloromethylation is only the beginning step on making the calixarene derivatives. For examples, the reaction of *p*-chlorometyhl-calix[4]arene with triethylphosphite produced *p*-diethylphosphorylmethylcalix[4]arene. This compound can be hydrolyzed to yield *p*-phosphatemethylcalix[4]arena [22].

In this research, four chloromethyl groups of ***2*** was transformed into methylthiol groups. The reaction was performed under reflux for 5 h of ***2*** with thiourea. This interaction produced an intermediate compound of *S*-alkylisothiouronium salt that can be further hydrolyzed with sodium hydroxide to yield tetrakis-thiomethyl-C-4-methoxyphenylcalix[4]resorcinarene (***3***) as shown in Fig. 1. The thiol compound was recovered after neutralization with sulphuric acid solution and was obtained as orange-brown powder with the melting point of 300 °C in 78.85 % yield.

In this stage of functionalization at the extraannular positions of calix[4]resorcinarene involve nucleophilic substitution reaction between thiourea and chloromethyl groups to afford tetrakis-thiomethyl-C-4-methoxyphenyl calix[4]resorcinarene. The most important signal correspond to the thiol group was showed by S-H stretching absorption in the wave number of 2568 cm^{-1}. This S-H stretching band is characteristically weak due to the hydrogen bonding of S-H groups much weaker than that of O-H and N-H groups. Clear evidence for the thiol product was also given by ^{1}H-NMR spectrum in which the typical singlet signal of thiol proton (-SH) appeared at 1.28 ppm (Fig. 7). The compound ***3*** was indicated in ^{13}C-NMR spectrum too that show 11 peaks correspond to 11 different type of carbon resonance (Fig. 8).

Conformational properties of the resorcinarene products

As mentioned by some articles [20-22], calixresorcinarene compounds are conformationally flexible. There are four probability stereoisomer that could theoretically be formed i.e. *ccc (cone), ctt (partial cone), tct (1,3-alternate), and cct (1,2-alternate)* based on the position of both resorcine ring and substituent at methine bridge. In the most cases, only two diastereoisomers were obtained, those are cone and partial cone conformers. According to the result of ^{1}H-NMR spectrometer analysis (Fig. 3, 5, and 7), it could be determined the conformation of each resorcinarene. Proton NMR spectrum will generally be a better conformational probe than the ^{13}C-NMR spectrum, because each of the two conformers displays a distinctively different pattern especially at methine protons. The ^{1}H-NMR spectra of resorcinarene ***1*** and ***2*** (Fig. 3 and 5) in DMSO-d_6 recorded at ambient temperature shows two singlet peaks for methine protons at δ 5.53 and 5.68 ppm, H*a* and H*b* resonance. This phenomena indicated that protons at methine bridge are decided in two direction namely equatorial (H*a*) and axial (H*b*). Therefore, both of them exist in partial cone (*cct*) or chair (C_{2h}) conformation. On the other hand, the presence of a singlet peak at 5.64 ppm for methine protons of resorcinarene ***3*** indicates that the compound ***3*** exhibit in crown (C_{4v}) or cone conformer (Fig.9). This formation influenced by the presence of thiol groups that causing intermolecular hydrogen bonding with OH groups at resorcine residues

CONCLUSION

Tetrakis-thiomethyl-C-4-methoxyphenylcalix[4]re sorcinarene (***3***) has been synthesized via chloromethylation of C-4-methoxyphenylcalix[4]resorcin arene (***1***) followed by nucleophilic substitution with thiourea and hydrolysis with sodium hydroxide. Due to the presence of electron-donating hydroxyl groups, the 2-position of resorcinol is susceptible to electrophilic aromatic substitution, namely chloromethylation. The synthesis of calix[4]resorcinarene ***1, 2*** and ***3*** was conducted using fennel oil as the source of aromatic aldehyde through HCl-catalyzed condensation with resorcinol. Based on the analysis of ^{1}H-NMR spectrometer resorcinarene ***1*** and ***2*** exhibit in the chair or flattened partial cone, while resorcinarene ***3*** tend to exist in the crown or cone conformation.

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