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Synthesis of a Novel Calix[4]resorcinarene-Chitosan Hybrid

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ABSTRACT

Synthesis of a novel calix[4]resorcinarene-chitosan hybrid using vanillin as raw material has been conducted. The synthesis was carried out in four steps i.e. (1) allylation of vanillin, (2) HCl-catalyzed condensation allyl vanillin with resorcinol, (3) chloromethylation of C-4-allyloxy-3-methoxyphenylcalix[4] resorcinarene with paraformaldehyde and HCl in the presence of $ZnCl_2$ to yield tetrakis-chloromethyl-C-4-allyloxy-3 methoxyphenylcalix[4]resorcinarene, and (4) reaction of tetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix[4] resorcinarene with chitosan to yield calixarene-chitosan hybrid. Structure elucidation of products were performed using FT-IR, ^{1}H-NMR, ^{13}C-NMR, GC-MS, XRD, and SEM. The product of calixarene-chitosan hybrid was obtained as dark red solid with m.p. > 300 °C in 78% yield.

Keywords: Calixarene modification synthesis, Chitosan hybrid, Novel calix[4]resorsinarenes, Vanillin.

INTRODUCTION

Calixarene has attracted the attention of scientists since it was first introduced in 1978[1] because it can be utilized in various fields. Calixarene has been studied its use for various purposes, including: sunscreen,[2] extraction,[3] inhibitor of calcium carbonate[4,5] and calcium sulphate[6] scale formation, a stationary phase of HPLC,[7,8] drug delivery,[9] antioxidant and anti-toxoplasma,[10] dye fibers,[11] biosensors,[12] and adsorbent [13,14]. Calixarene is compound group of

synthetic oligomer containing aromatic ring in a cyclic sequence linked by a methylene group[1]. One derivate of this compound that has been studied is calix[4]resorcinarene[15-17]. Calix[4]resorcinarene (Fig. 1) consists of 4 units of resorcinol in the form of cyclic linked by a methylene bridge. It can be synthesized by reaction of resorcinol with an aldehyde under acidic conditions.

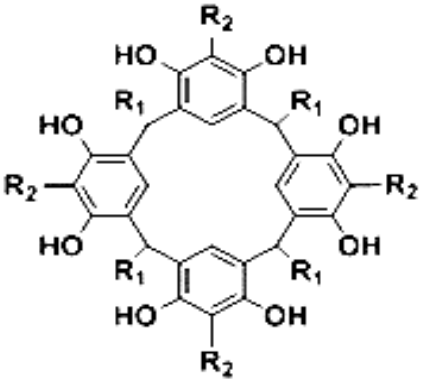


Fig. 1. Structure of calix[4]resorcinarene

A number of studies have shown that research developments of calixarene more focused on modifying the calixarene structure by adding a variety of new functional groups. Timmerman and his colleagues have been succes to synthesize and modify a wide variety of calix[4]resorcinarene by varying groups at R_1 and R_2[18]. Groups at R_1 can be varied by using aldehyde different as the reagent forming of calix[4]resorcinarene. While groups at R_2 can be varied via electrophilic substitution reaction of calix[4]resorcinarene. Because a position between OH in the aromatic ring of resorcinol has high electron density so it is very reactive to the presence of an electrophilic.[19]

In this research, the new calixarene produced was derived from reaction between resorcinol and vanillin as a source of aldehyde functional group. In addition, modification of calixarene structure was performed by reacting chitosan with calix[4]resorcinarene at R_2 position formed a calix[4]resorcinarene-chitosan hybrid. Anggraini has been successfully produced calix[4]resorcinarene-chitosan hybrid from chitosan and C-4-methoxycarbonilmethoxy-3-methoxyphenylcalix [4]resorcinarene through amide bond formation at R_1 group[20]. The product has sufficiently low yield, which is 28%. In this research, the hybrid was synthesized through bond formation of secondary amine between the amine group of chitosan with chloromethyl group of tetrakis-chloro methyl-C-4-alyloxy-3 methoxyphenylcalix[4]resorcinarene at R_2 group. Cl atom on the alkyl halide is better leaving group than $–OCH_3$ at the carbonyl group, so the hybrid formation reactions in this research would be easier to happen and has a high yield.

MATERIALS AND METHODS

Materials and equipments

Chemicals used in this research were vanillin, resorcinol, allyl bromide, chitosan, paraformaldehyde, zinc chloride ($ZnCl_2$), Pb, ethanol, methanol, acetone, N,N-dimethyl formamide (DMF), dichloromethane, hydrochloric acid (HCl 37%), sodium sulfate (Na_2SO_4) anhydrate, ethyl acetate (EtOAc), and distilled water. All chemicals except distilled water were purchased from E. Merck KG. Distilled water was obtained from Laboratory of Fundamental Chemistry, University of Gadjah Mada.

Equipment used in this research were laboratory glassware, hot plate with magnetic stirrer, Büchner funnel, Buchi R-124 Rotary Vap System (Marshall Scientific), analytical mass balance (Mettler AT 200, Mettler Instrument Corp. Switzerland), infra-red spectrophotometer (IR, Shimadzu-Prestige 21, Japan), proton nuclear magnetic resonance spectrometer (^{1}H-NMR, JEOL JNM-MY60 and JEOL MY-500 MHz, USA), carbon nuclear magnetic resonance spectrometer (^{13}C-NMR, JEOL MY-500 MHz, USA), gas chromatography-mass spectrometer (GC-MS, Shimadzu QP-5000, Japan), X ray diffraction (XRD Shimadzu 6000, Japan) and scanning electron microscope (SEM, Jeol JSM T300, USA).

Procedures

As much as 15 mL of ethanol was added into 100 mL of three-necked-flask. Then, 0.38 g (16.40 mmol) of sodium metal was added and stirred until it was dissolved completely to produce sodium ethoxide. After that, 1.25 g (4.10 mmol) of vanillin was added and refluxed for 1 hour. Then, as much as 1.99 g (16.40 mmol) of allyl bromide was added portion by portion into the mixture of sodium ethoxide and vanillin. The mixture was then refluxed for 24 hours. The solution was evaporated, washed with 30 mL of NaOH 0.1 M and extracted with

20 mL of dichloromethane three times. The combined organic layer was washed with distilled water and dried with Na_2SO_4 anhydrate, filtered and evaporated. The product 1 was obtained as brown yellowish liquid in 72% yield; FT-IR (KBr) v (cm^{-1}): 1682 (C=O aldehyde), 1589 and 1512 (C=C aromatic), 1134 (C-O-C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 9.83 (1H,s,-HC=O), 7.40 (1H,d,ArH), 7.03 (1H,s,ArH), 6.97 (1H,d,ArH), 6.00 (1H,m,-CH=), 5.33 and 5.31 (2H,d of d, H_2C= allyl), 4.69 (2H,d,-CH_2- allyl), 3.92 (3H,s,-CH_3); ^{13}C-NMR (126 MHz, $CDCl_3$) δ(ppm): 191 (Ar-C=O), 154, 150, 130, 127, 112, 109 (Ar), 132 (-CH= allyl), 119 (H_2C= allyl), 70 (-CH_2- allyl), 56 (-CH_3); GC-MS: rt = 30 min, purity 87%, m/z 192 g/mol.

Synthesis of C-4-allyloxy-3methoxyphenylcalix [4]resorcinarene (2)

In 100 mL three-necked flask equipped with water condenser, 0.87 g (4.54 mmol) of 4-allyloxy-3-methoxy benzaldehyde and 0.50 g (4.54 mmol) of resorcinol were dissolved in 20 mL of ethanol. Then, concentrated hydrochloric acid (0.5 mL) was added into the solution. The mixture was refluxed for 24 h and evaporated. The solid was washed using the mixture of distilled water and ethanol (1:1) and dried. The product 2 was obtained as a white solid with m.p. 235-236 °C in 64% yield; FT-IR (KBr) v (cm^{-1}): 3426 (OH), 1612 and 1512 (C=C aromatic), 1134 (C-O-C); ^{1}H-NMR (500 MHz, CD_3OD): 6.53 (1H,s,ArH), 6.47 (1H,d,ArH), 6.29 (1H,d,ArH), 6.25 (1H,s,ArH), 6.20 (1H, s, ArH), 5.61-5.77 (1H, m, -CH=), 5.21-5.39 (2H, d of d,H_2C=), 4.61 (1H, s,-CH methylene group), 4.54 (2H, d, -CH_2-), 3.57 (3H, s, -CH_3); ^{13}C-NMR (126 MHz, CD_3OD) δ(ppm): 154, 150, 147, 140, 132, 124, 122, 115, 114, 104 (Ar), 136 (-CH= allyl), 117 (H_2C= allyl), 71 (-CH_2- allyl), 56 (-CH_3), 43 (-CH methylene group).

Synthesis of tetrakis-chloromethyl-C-4-allyoxy-3-methoxyphenylcalix[4]resorcinarene (3)

Into 100 mL three-necked flask, C-4-allyloxy-3methoxyphenylcalix[4]resorcinarene (1.44 g, 1.27 mmol) was dissolved in 35 mL of DMF. Then, paraformaldehyde (0.23 g, 7.67 mmol), $ZnCl_2$ (1.50 g, 11 mmol) and concentrated hydrochloric acid (8 mL) were added to the solution, respectively. The mixture was heated at 120 °C for 22 hours. The trituration of the cool reaction mixture using distilled water was then carried out to give the precipitate. The formed solid was then filtered, washed with distilled water and dried in the oven. The dried solid was recrystallized with methanol-water. The product 3 was obtained as a light brown solid in 71% yield with m.p. > 250 °C (decomposed). FT-IR (KBr) v (cm^{-1}): 3426 (OH), 1605 and 1504 (C=C aromatic), 1450 (-CH_2-), 1080 (C-O-C); ^{1}H-NMR (500 MHz, CD_3OD): 8.51 (2H,s,OH), 6.17-6.56 (4H,s,ArH), 5.55-5.85 (1H,m,-CH=), 5.15-5.55 (2H,d of d,H_2C=), 4.85 (1H,s,-CH methylene bridge), 4.45 (2H,d,-CH_2-), 3.42 (3H,s,-CH_3), 3.10 (2H,s,-CH_2-Cl) ; ^{13}C-NMR (126 MHz, CD_3OD) δ(ppm): 153, 148, 145, 139, 135, 117, 115, 112, 113, 102 (Ar), 137 (-CH= allyl), 114 (H_2C= allyl), 69 (-CH_2- allyl), 55 (-CH_3), 40 (-CH methylene group), 34 (-CH_2-Cl).

Synthesis calix[4]resorcinarene-chitosan hybrid (4)

Mixture of chitosan (0.43 g, 2.40 mmol), tetrakis-chloromethyl-C-4-allyoxy-3-methoxyphenyl calix[4] resorcinarene (0.32 g, 0.24 mmol) and DMF (30 mL) in the 100 mL three-necked-flask was refluxed for 24 hours. Product was cooled, filtered and washed with distilled water until the solid was formed. The formed solid was filtered and dried. The product 4 was obtained as a dark red solid with m.p. > 250 °C (decomposed) in 78% yield. FT-IR (KBr) v (cm^{-1}): 3426 (OH), 1605 and 1512 (C=C aromatic), 1142 (C-O-C).

RESULTS AND DISCUSSION

Synthesis of calix[4]resorcinarene-chitosan hybrid compound was carried out in four steps i.e. allylation of vanillin, condensation allyl vanillin with resorcinol to yield 4-allyloxy-3-methoxyphenylcalix[4]resorsinarene, chloromethylation of C-4-allyloxy-3-methoxyphenylcalix[4], and reaction of tetrakis-chloro methyl-C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene with chitosan to yield calix[4]resorcinarene-chitosan hybrid. Synthesis scheme of calix[4]resorcinarene-chitosan hybrid was presented in Figure. 2.

Allylation of vanillin produce 4-allyloxy-3-methoxybenzaldehyde compound was performed by inserting Na into ethanol in a 100 mL three neck flask. The mixture was stirred until all the Na reacts generate sodium ethanolic. The sodium ethanolic is a strong base so it will take H^+ from the group

of phenol contained in vanillin (4-hydroxy-3-methoxy benzaldehyde) produced strong nucleophile. The nucleophile will attack the C atoms which charged positive partial binding Br in allyl bromide. This reaction is predicted through S_N2 mechanism. This is due to a nucleophile formed in this reaction is a strong nucleophile and alkyl halides involved in the reaction are primary alkyl halide which very open to attack by a nucleophile. Compound of 4-allyloxy-3-methoxybenzaldehyde was obtained as brown yellowish liquid in 72% yield. Then it was characterized with IR spectrometer, ^{1}H-NMR, ^{13}C-NMR and GC-MS. FT-IR spectra showed absorption of C=O aldehyde, C=C aromatic, and C-O-C groups. The most important information of the FT-IR spectra is the loss absorption of OH group at 3200-3400 cm^{-1}. This indicates that OH group at vanillin has been allylated.

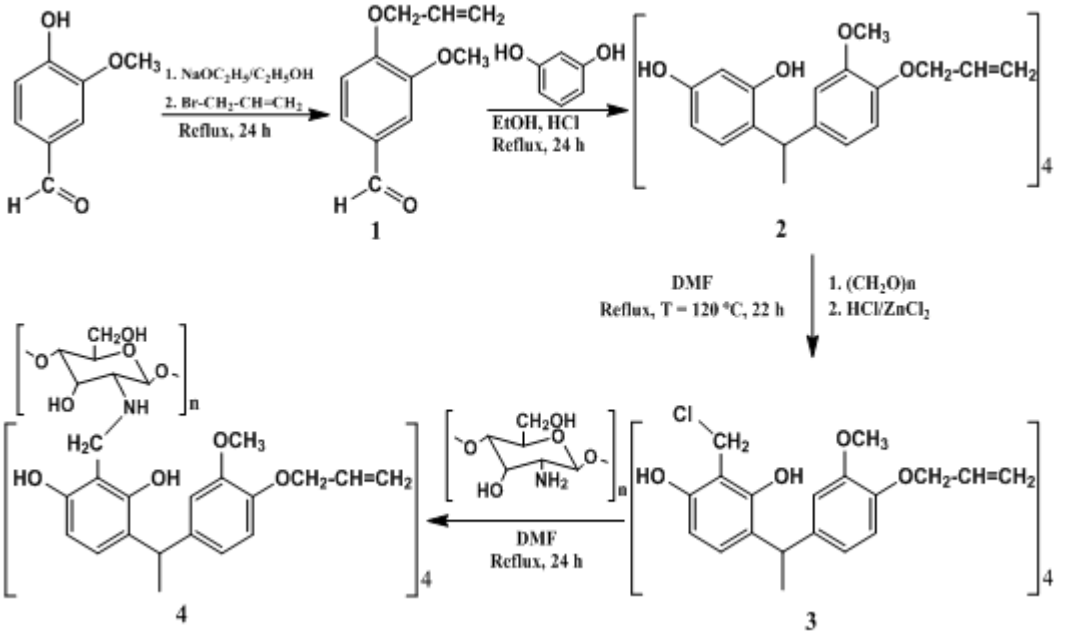


Fig. 2. Synthesis scheme of calix[4]resorcinarene-chitosan hybrid from vanillin

Based on ^{1}H-NMR spectra, there are nine hydrogens are in a different environments. Singlet signal at 9.83 ppm showed one proton aldehyde group. Three signals at 7.40 ppm (duplet), 7.03 ppm (singlet) and 6.97 ppm (duplet) showed protons aromatic group. Multiplet signal at 6.00 ppm shift shows 1 proton -CH = the allyl group. Two protons of H_2C = were shown at 5.33 ppm (duplet of duplet) and 5.31 ppm (duplet of duplet). Two protons of -CH_2- the allyl group were shown by duplet signal at 4.69 ppm and three protons of -CH_3 were shown by shift at 3.92 ppm. Characterization of vanillin allylation product was resumed with ^{13}C-NMR spectrometer. Spectra of ^{13}C-NMR showed that the compound of 1 contained 11 C atoms in different environments. C atom of carbonyl was shown by signal at 191 ppm. Six C atoms of aromatic group were shown by signal at 154, 150, 130, 127, 112 and 109 ppm. Three C atoms of allyl (-<u>C</u>H=, H_2<u>C</u>=, -<u>C</u>H_2-) were shown by signal at 132, 119 and 70 ppm. One C atom of methoxy was shown by at 56 ppm. The last characterization product of vanillin allylation was performed using GC-MS. The use of GC-MS aimed to determine purity and confirmed the relative molecular mass of product. Based on data from GC-MS, product has 87% purity, 192 g/mol molecular weight and 30 min. retention time.

Synthesis of C-4-allyloxy-3methoxypheny lcalix[4]resorcinarene compound was conducted by reacting resorcinol and 4-allyloxy-3-methoxy benzaldehyde results of previous phase synthesis using HCl for catalyst in ethanol. The mixture was refluxed at 78 °C for 24 hours. Formation of C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene was preceded by protonation of the carbonyl group

4-allyloxy-3-methoxy benzaldehyde to form carbonyl group which is positively charged. The existence of positive charge causes double bond of carbonyl group conjugated to the oxygen atom. It causes carbon atom of the carbonyl group to be positively charged. Then carbon atom which positively charged will be attacked by a double bond of carbon atom number 4 on the benzene ring of resorcinol. A second carbocation formed again after releasing a water molecule. The next step was cyclization through attack of second carbocation by electron double bond of carbon atom number 4 on the benzene ring of resorcinol. This happened repeatedly until formed calix[4]resorcinarene. Compound of C-4-allyloxy 3-methoxy phenylcalix [4]resorcinarene was obtained as a as a white solid with m.p. 235-236 °C in 64% yield. Furthermore, to ensure that the compound of 2 has formed, structure elucidation was conducted by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectrometry.

Based on the data from FT-IR spectra, it was obtained information that the compound C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene which was synthesized containing OH groups. This was shown by absorption band at 3426 cm^{-1}. Absorption bands at 1512 and 1612 cm^{-1} indicate the presence of C=C aromatic groups. The presence of ether groups (C-O-C) was shown by an absorption band at 1134 cm^{-1}. Absorption band at 1682 cm^{-1} shows the aldehyde carbonyl group (C=O) in 4-allyloxy-3-methoxybenzaldehyde as the reactants have been lost. This indicates that the formation of bonds between carbon atom number 4 and 6 in resorcinol with carbon atom atom of carbonyl at the 4-allyloxy-3-methoxybenzaldehyde formed methylene bridge.

Further characterization by ^{1}H-NMR spectrometer was obtained information that there are at least 10 types of protons that can be identified in different environments in the C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene synthesized. Singlet proton at 3.57 ppm shows proton at methoxy group (-OCH_3). Singlet proton at 4.54 ppm shows proton of -CH_2- allyl group. Singlet protons at 4.61 ppm shows proton of methylene bridge. Protons at 5.21-5.39 ppm with the appearance duplet of duplet indicated proton of =CH_2 allyl group. Protons at 5.61-5.77 ppm with the appearance multiplet show proton of -CH= allyl group. Protons at 6.20 and 6.53 ppm with the appearance show proton of resorcinol aromatic ring. Protons at 6.25, 6.29, and 6.47 ppm with the appearance singlet, duplet, and duplet respectively show protons of allyl vanillin aromatic ring.

Further characterization using ^{13}C-NMR spectrometer shows that all of the carbons appear in the appropriate area. The carbon of methylene bridge appears at 43 ppm, the carbon of methoxy seems at 56 ppm, the carbons of allyl are indicated at 71, 117, and 136 ppm. The carbons for aromatic benzene ring which come from vanillin can be identified at 114, 115, 122, 140, 147, and 150 ppm. While, the carbons of aromatic benzene ring from resorcinol can be seen at 104, 124, 132, and 154 ppm. The data of carbon shift of C-4-allyloxy-3-methoxyphenilcalix[4]resorcinarene compound have a shift similar to the shift shown in chem draw software. Based on data from FT-IR, ^{1}H-NMR and ^{13}C-NMR spectrometer can be concluded that the C-4-allyloxy-3-methoxyphenilcalix[4]resorcinarene has been formed.

Tetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene was produced through two reaction stages. The first stage is an electrophilic substitution reaction, while the second stage is a nucleophilic substitution reaction with zinc chloride as a catalyst in both reactions. Tetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix[4] resorcinarene was synthesized by reacting C-4-allyloxy-3-methoxyphenylcalix [4]resorcinarene with paraformaldehyde, zinc chloride and concentrated hydrochloric acid in N,N-dimethylformamide. The compound of Tetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix[4] resorcinarene was obtained as a light brown solid in 71% yield with m.p. > 250 °C (decomposed). Increasing of melting point of compound 3 compared to compound 2 was predicted by increasing of polarity due to the inclusion chloromethyl and increasing of relative molecular mass from 1137 g mol^{-1} to 1331 g mol^{-1}. Furthermore compound 3 was characterized by IR, ^{1}H-NMR, and ^{13}C-NMR spectrometer.

Based on identify of IR spectra performed, it was obtained information the OH group absorption that appeared in the 3426 cm^{-1}. The absorbance of C=C aromatic group existed at 1504 and 1605 cm^{-1}.

The absorbance of C-O-C group was displayed at 1142 cm^{-1}. The absorbance of $–CH_2–$ at 1450 cm^{-1} indicated that chloromethylation reaction of C-4-allyloxy-3-methoxyphenylcalix[4] resorcinarena have done successfully. Further characterization of chloromethylation product was done by ^{1}H-NMR and ^{13}C-NMR spectrometer.

From the result of ^{1}H-NMR, least 8 protons were in a different environments. Success of chloromethylation reaction was shown by presence of chemical shift at 3.10 ppm in the form singlet proton which indicates proton of chloromethyl group. This is similar to the result proton chloromethyl of tetrakis-chloromethyl-C-4methoxyphenylcalix [4]resorcinarene which was synthesized by Utomo, *et al.,* (2011)[20]. The next characterization using ^{13}C-NMR showed that all of the carbons appear in the appropriate area with the chloromethyl carbon at 34 ppm[19]. The methylene bridge carbon identified at 40 ppm, the methoxy carbon existed at 55 ppm, and the carbons of allyl group appeared at 69, 115, and 137 ppm. The carbons of resorcinol aromatic ring appeared at 102, 103, 135, and 153 ppm. While carbons of vanillin aromatic ring appeared at 112, 114, 117, 139, 145, and 148 ppm. Based on FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra can be stated that the compound of tetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene has been formed.

Synthesis of calix[4]resorcinarene-chitosan hybrid was conducted by reactingtetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix [4]resorcinarene with chitosan using N,N-dimethyl formamide solvent. The use of chitosan excessive number of moles was expected that all Cl atoms of chloromethyl group substituted by an amine group of chitosan. Synthesis reaction of calix[4]resorcinarene-chitosan was predicted through S_N1 mechanism. It is due to carbocation formed in this reaction will be stabilized by conjugation of electrons from the aromatic ring and solvation by the N, N-dimethylformamide solvent which is polar. Moreover, NH_2 nucleophile of chitosan was steric condition. Initially, C-4-allyloxy-3-methoxyphenyl calix[4]resorcinarene releases Cl^- ion forming carbocation then the cation will be attacked by amine group of chitosan to form a hybrid product. Calix[4]resorcinarene-chitosan hybrid was obtained as dark red solid with m.p > 300 °C (decomposed) in 78% yield. Furthermore, it was characterized by FT-IR spectrometer, XRD, and SEM. ^{1}H-NMR and ^{13}C-NMR spectrometer was not used for the characterization of hybrid product because of it was not soluble in solvents commonly used in ^{1}H-NMR and ^{13}C-NMR spectrometer.

Based on FT-IR spectrometer, it was gained OH group absorbance at 3426 cm^{-1}. Absorbance of C=C aromatic appeared at 1512 and 1605 cm^{-1}. Absorbance of C-O-C group arised at 1142 cm^{-1}. The data was supported by data from XRD and SEM to compare hybrid with calixarene and chitosan constituent. Based on X-ray diffraction pattern in Fig. 3, it was found information that calix[4]resorcinaren-chitosan hybrid and chitosan have a semi-crystalline form. Tetrakis-chloromethyl-C-4-allyloxy-3methoxycalix [4]resorcinarene has amorphous form. From Fig. 3 also show that calix[4]resorcinarene-chitosan decreased crystallinity caused by destruction of hydrogen bonds from amine groups of chitosan. Kumirska *et al.,* reported that destruction of hydrogen bonds in chitosan will decrease crystallinity of compounds [21].

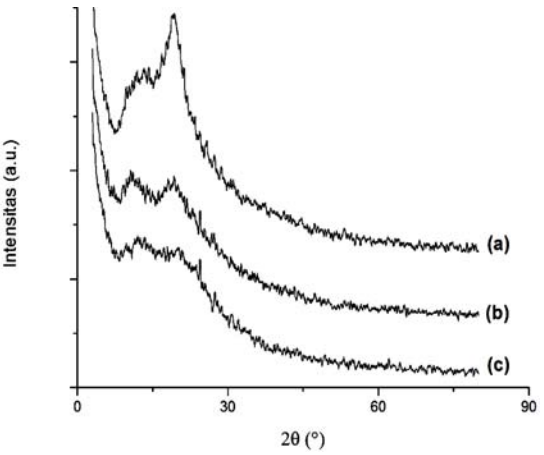
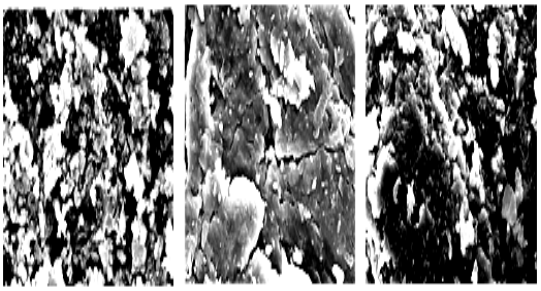


Fig. 3. X-ray diffraction pattern (a) chitosan, (b) calix[4]resorcinarene-chitosan hybrid, and (c) tetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene

SEM analysis was carried out to see the surface profile difference of calix[4]resorcinarene-chitosan with chitosan and calixarene constituent. Result of SEM analysis was presented in Fig. 4. From this Fig, it can be seen that there was a difference between surface profile of calix[4] resorcinarene-chitosan with chitosan and calixarene constituent. In addition, result of SEM image analysis shows that tetrakis-chloromethyl-C-4-allyloxy-3-methoxyphenylcalix[4]resorcinarene has been distributed or bound to chitosan. Based on results of FT-IR spectrometer, XRD and SEM analysis were predicted that calix[4]resorcinarene-chitosan hybrid have been formed. Mechanism of hybrid formation was presented in Figure. 5.



(a) (b) (c)

Fig. 4. SEM image of (a) tetrakis-chloromethyl-C-4-allyloxy-3-methoxy phenylcalix[4]resorcinarene, (b) chitosan, and (c) calix[4] resorcinarene chitosan hybrid

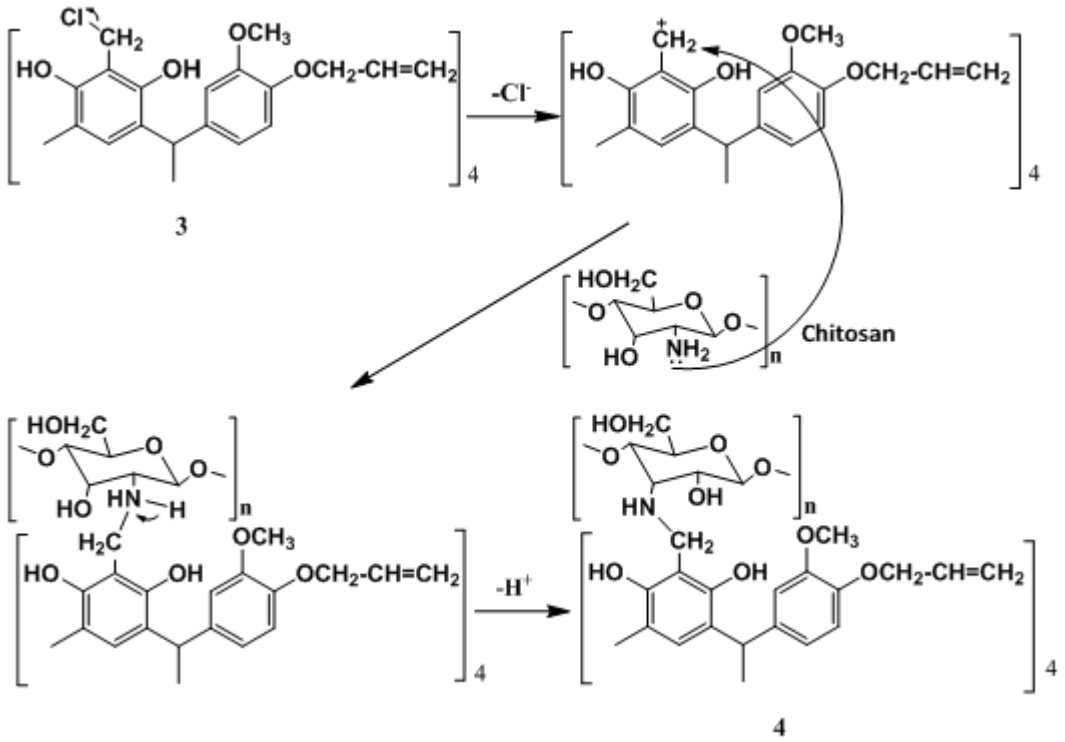


Fig. 5. Reaction mechanism of calix[4]resorcinarene-chitosan hybrid formation

CONCLUSIONS

Calix[4]resorcinarene-chitosan hybrid (4) has been synthesized through vanillin allylation, aromatic electrophilic substitution followed by cyclization, chloromethylation, and unimolecular nucleophilic substitution as well as characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, XRD and SEM. Product was obtained as dark red solid with m.p. > 300 °C in 78% yield.

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