C-BUTYLCALIX[4]RESORCINARENE OCTABENZOATE AND OCTASINNAMATE: THE SYNTHESIZED SUNSCREEN COMPOUNDS

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ABSTRACT

C-butylcalix[4]resorcinarene octabenzoate and octacinnamate have been synthesized and evaluated as absorbers for ultraviolet radiation. The C-butylcalix[4]resorcinarene (CBCR) was synthesized from resorcinol and pentanal using HCl as a catalyst in ethanol at 78 °C for 24 h to give CBCR 97% in yield. Synthesis of C-butylcalix[4]resorcinarene octabenzoate (CBCROB) and C-butylcalix[4]resorcinarene octacinnamate (CBCROC) were carried out via esterification of the CBCR with benzoyl chloride in pyridine at 60 °C for 2 h, producing CBCROB and CBCROC giving 46 and 66% yield, respectively. The chemical structure of all products was elucidated using FTIR and ¹H-NMR spectrometers. Furthermore, the sun protection factor (SPF) value and photostability of the synthesized compounds were determined based on UV-Vis spectrophotometer and lighting under UV lamp (intensity 0.27 mWcm⁻²) over various time of 15, 30, 60, 90, and 120 min. The UV spectroscopic result and calculation gave the SPF value of CBCR, CBCROB, and CBCROC at 50 ppm concentrations were 3.80, 1.78, and 380, respectively. Therefore, CBCROC could be used as a sunscreen compound, especially within the UV-B region.

Keywords: Sunscreen, Calix[4]resorcinarene, Benzoate, Cinnamate, SPF.

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INTRODUCTION

UV rays are a part of the sunlight (7%) as the greatest energy source for living organisms on Earth. The UV ray can also be used as phototherapy¹ and it can induce the skin to produce vitamin D3, as deficiency of vitamin D3 may increase the risk of several diseases, such as bone disease, cancer, and also heart disease.² However, UV also has adverse effects for living organisms such as erythema³, dark color skin⁴, melanoma⁵, accelerating skin aging⁶, and skin cancer.⁷

UV rays can be divided into three sections, i.e. UVA (315–400 nm), UVB (280–315 nm), and UVC (200–280 nm).⁸ UVA and UVB are harmful to the earth because they can penetrate the ozone atmosphere, but UVC cannot reach the Earth's surface if the ozone layer is safe.⁹ To decrease this harmfulness of the UVA and UVB, some researchers developing sunscreen compounds. In particular, sunscreens to absorb UV rays¹⁰ are xanthone¹¹, chalcone^{12,13}, lignin^{14,15}, and benzophenone.¹⁶ The compound with greater electron conjugation in its chemical structure is believed to have better UV-ray absorption ability.¹⁷

Calixarenes are stable macromolecules with unique geometry like flower vases or crowns. Besides this unique shape, the modified calixarenes usually have functional groups to be able to absorb UV rays (e.g. –OH, –COOH, and –NH2)¹⁸ and also great electron delocalization.^{19,20} Thus, the calixarenes have great potential to be applied as sunscreen. Furthermore, the calixarenes usually have a high molecular weight

preventing the sunscreen to be absorbed into the skin²¹ and give the molecules high chemical and thermal stability²² as well.

In this work, C-butylcalix[4]resorcinarene was synthesized from resorcinol and pentanal, and then it was modified using benzoyl chloride and cinnamoyl chloride to produce C-butylcalix[4] resorcinarene octabenzoate and C-butylcalix[4]resorcinarene octacinnamate, respectively. Afterward, these synthesized compounds were assayed as sunscreen candidates. The synthesized products are novel compounds and no one has ever published elsewhere.

EXPERIMENTAL

Materials and Instrumentations

Resorcinol, pentanal, benzoyl chloride, ethanol, ethyl acetate, pyridine, hydrochloric acid (37 wt%), and sodium sulfate anhydrous were obtained from Merck.

The apparatus used in characterizing the synthesized products were a melting point apparatus (Electrothermal 9100), an FTIR spectrometer (FTIR, Shimadzu Prestige 21), a ¹H-NMR (NMR, JEOL JSM6510LA 500 MHz), an LCMS (Waters Alliance), a UV-Vis spectrophotometer (Shimadzu UV spectrophotometer UV-1800), a UVB lamp, and a phototherapy controller.

Synthesis of CBCR

Resorcinol (5.50 g; 0.05 mol) was dissolved in 25 mL ethanol 97%. To the mixture, 1.5 mL HCl 37% was added and stirred until homogeneous. The mixture was cooled to 15 °C, and pentanal (4.30 g; 0.05 mol) was added and kept for 24 h. When the temperature system reached room temperature, the obtained solid was filtered and washed with distilled water until the pH of the filtrate was neutral. The product's melting point was determined by using melting point apparatus, while the chemical structure of the product was characterized by using FTIR and ¹H-NMR spectrometers.

Synthesis of CBCROB and CBCROC

CBCR (3.31 g; 4.60 mmol) was dissolved in 22.70 mL pyridine, followed with benzoyl chloride (10.34 mL; 73.60 mmol) addition, and the mixture was kept in an ice bath. Afterward, the mixture was stirred and heated at 60 °C for 2h. The mixture was left to reach room temperature and was acidified by HCl 10%. Furthermore, the sample was extracted using 10 mL ethyl acetate and saturated NaCl solution 1–2 mL (three times repetition), and was extracted with 10 mL of 10% NaOH solution and 10 mL distilled water, sequentially. The filtrate was dried by sodium sulfate anhydrous and then evaporated, giving the CBCROB. For the synthesis of CBCROC, the benzoyl chloride was replaced by cinnamoyl chloride (12.26 mL, 73.60 mmol). The desired compounds were characterized by using FTIR and ¹H-NMR spectrometers.

Detection Method

In Vitro Tests Using Spectroscopic Methods

The *in vitro* test using spectroscopy of the sample was conducted as reported by Walters *et al.*²³ The CBCR, CBCROB, and CBCROC compounds were weighed (1 mg), dissolved into 20 mL of ethyl acetate (solution concentration was 50 ppm). The absorbance of the test solution was measured by a UV-Vis spectrophotometer from 200 to 400 nm. Ethyl acetate was used as a blank solution. The compounds that have strong absorption in the UVB or UVA range area will be tested for their photostability.

Photostability Test

The photostability test of products was carried as reported by Chawla *et al.*²¹ CBCROC (0.40 mg) was transferred in 50 mL graduated cylinder, ethyl acetate was added up to fill up the cylinder, to obtain 8 ppm concentration. Each test solution was irradiated using UVB. 0.27 mWcm⁻² for various times (0, 15, 30, 60, 90, and 120 min). Following irradiation, the CBCROC solution absorbance was measured at its optimum wavelength using a UV-Vis spectrophotometer. Ethyl acetate was used as a blank. The compounds that displayed a significant increase of absorbance after irradiation with UVB were chosen as sunscreen candidates.

Scheme-1: The Synthetic Reaction of CBCR, CBCROB, and CBCROC

RESULTS AND DISCUSSION

Synthesized CBCR

The CBCR was obtained as a yellow solid (97%), melting point 340–345 °C. This high melting point can be explained by the presence of strong intermolecular hydrogen bonds between the –OH groups in the CBCR, as indicated by the FTIR and ¹H-NMR spectra. The FTIR spectra showed a strong broadened of O–H peak (3310 cm⁻¹). The C–H stretching and C–H bending appeared at 2932 and 1443 cm⁻¹, respectively, and also twin peaks at 1620 and 1504 cm⁻¹, indicating C=C absorption of aromatic rings. The absorption at 1296 cm⁻¹ is designated for the C–O group. This explanation of the CBCR FTIR spectra confirms the CBCR structure as well the ¹H-NMR spectrum that is presented in Fig.-1. It shows the proton resonance of –CH₃ (0.85 ppm), –CH₂ (1.30 and 2.02 ppm), –CH bridge of calix[4]resorcinarene (4.21 ppm), aromatic (6.17 and 7.14 ppm), and hydroxyl (8.88 ppm) of the CBCR.

Synthesized CBCROB

The mole ratio between CBCR and the excess benzoyl chloride was 1:16. The reaction was carried out at 60 °C. These 8 hydrogen moieties of CBCR were able to be substituted by the benzoyl group originated from the benzoyl chloride. The CBCROB was formed as a brownish gel in 46% yield. The characteristic peaks of the CBCROB FTIR spectra: C=O ester (1736 cm⁻¹) and C–O ester (1265 cm⁻¹) indicated that the intended product has been successfully synthesized. The ¹H-NMR spectrum (CDCl₃ solvent) of the compound was displayed in Fig.-2. It showed the proton resonance of –CH₃ (0.84 ppm), –CH₂ (1.24 and

2.04 ppm), proton bridge calix[4]-resorcinarene (4.12 ppm), aromatic of benzoyl group (7.45 ppm), and aromatic benzene (7.24 and 8.65 ppm). This ^1H -NMR result proves that the CBCROB compound has been successfully synthesized.

Fig.-1: ^1H NMR (500 MHz) Spectra for CBCR in CD_3OD

Fig.-2: ^1H NMR (500 MHz) Spectra for CBCROB in CD_3OD

Synthesized CBCROC

The CBCROC was obtained as a solid yellow powder (66%), melting point 190–194 °C. The melting point of CBCROC was lower than that of the CBCR because the $-\text{OH}$ group of latter was replaced by a cinnamic group to form CBCROC. The CBCROC structure was again elucidated by FTIR and ^1H -NMR spectrometers. The FTIR spectra showed that the CBCROC has no $-\text{OH}$ moiety (3400 cm^{-1}) but $\text{C}=\text{O}$ (1728 cm^{-1}) and $\text{C}-\text{O}$ (1134 cm^{-1}) ester moieties instead, indicating the successful synthesis. The ^1H -NMR spectrum (CDCl_3 solvent) of the compound is depicted in Fig.-3, showing the proton resonance of $-\text{CH}_3$ (0.87 ppm), $-\text{CH}_2$ (1.35 and 2.00 ppm), proton bridge calix[4]-resorcinarene (4.43 ppm), $-\text{CH}=\text{CH}-$ (6.56 ppm) aromatic of the benzoyl group (7.31 ppm), and the aromatic benzene (7.14 and 7.59 ppm). This chemical structure elucidation reveals that the CBCROB compound has been successfully synthesized.

UV Absorption Tests

The UV spectra of the three synthesized compounds: CBCR, CBCROB, and CBCROC, are summarized in Table-1. It showed that these three compounds absorb in the UVB region spectrum; the CBCROB and the CBCROC absorb in the UVC region as well. The CBCROC indicates much higher SPF values as compared to that of CBCR and CBCROB because the CBCROC chemical structure has greater electron resonance

that decreases the band gap between HOMO and LUMO, resulting in the increase of absorbed UV intensity and also SPF values. We suggest that CBCROC is the best sunscreen candidate amongst the three synthesized products.

Fig.-3: ^1H NMR (500 MHz) Spectra for CBCROC in CD_3OD

Table-1: Ultraviolet Absorption Spectra and the Respective Sun Protection Factor (SPF)

Name of Compound	Maximum Wavelength Absorption (nm)			SPF
	UVC	UVB	UVA	
CBCR	-	286	-	3,80
CBCROB	255	280	-	1,78
CBCROC	275	285	-	380

Photostability Tests

The CBCROC stability test was carried out under irradiation of the UVB spectrum towards CBCROC over various times, and the absorbance (Fig.-4) was compared to that of the cinnamon tetrapropoxycalix[4]arene (Fig.-5). This result showed that CBCROC has lower photostability than that of the cinnamon tetrapropoxycalix[4]arene, due to ester moiety that is not stable towards the light. However, it has a higher absorbance as compared with the cinnamoyltetra-propoxycalix[4]arena, meaning that the CBCROC is potential as a sunscreen active compound.

Fig.-4: Spectra Photostability CBCROC

Fig.-5: Spectra Photostability, cinnamon tetrapropoxycalix[4]arene

CONCLUSION

CBCR compound has been synthesized and gives 97% in yield, while the synthesis of CBCROB and CBCROC compounds from this synthesized CBCR give 46 and 66% in yield, respectively. The SPF value of 50 ppm of CBCR, CBCROC, and CBCROB were 1.78; 3.80 and 380, respectively. The SPF value of CBCROB was greatest compared to CBCR and CBCROC, thus CBCROB compound was the best candidate as sunscreen, in spite of the relatively low photostability.

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