行政院國家科學委員會專題研究計畫　成果報告

Calix[4]quinone monoketal 系列化合物的研究(2/2)

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計畫編號：NSC92-2113-M-034-004-
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計畫主持人：林立錦

計畫參與人員：王竹蓉、潘彥竹、張育強、廖亞龍

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行政院國家科學委員會補助專題研究計畫
■成果報告　□期中進度報告

Calix[4]quinone monoketal 系列化合物的研究 (2/2)

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一. 中文摘要

本計劃的主要目標，在於延續本研究室多年來從事國科會的研究成果，以合成出可供酵素模擬研究用之 calixarenes 衍生物。合成的方式則以二氧化氯氧化苯甲酸酯化的 calix[4]arenes 為基礎，並以僅上緣酮基可被保護之 calix[4]quinone monoketals 的中間衍生物為起始物，以合成出一系列之酚-甲醛環狀聚合物的衍生物。

Abstract:

The purpose of this proposal is to synthesize a series of calix[4]arene derivatives for the enzyme mimic studies. The synthetic route started with chlorine dioxide oxidization of calix[4]arene benzoates, and the calix[4]quinones were then protected by ketal moieties. The ketal formation step protected only the “upper rim” carbonyl group, and the protected calix[4]quinone monoketals was then served as a starting material for the various calix[4]arene derivatives.

二. 緣由與目的

Calixarenes，是一種酚-甲醛的環狀聚合物，[1] 因其含有分子內中空，故可以用於酵素模擬的研究。但實際上，這一方面的研究卻因為 calixarenes 本體合成上的問題，以致無法有系統且有效的合成出具有特定官能基化的 calixarenes, 進而使得整個酵素模擬的研究，無法得到更進一步的結果。

因此, 這一個計劃的主要目標便是在延續以往國科會研究之成果，進一步的希望發展出一種新的合成途徑，以引進新類型的 calixarenes 以供酵素模擬研究之用。

本實驗室在國科會補助的研究中發現，如果利用 chlorine dioxide (ClO_2) 的水溶液，可將 calix[4]arene benzoates 氧化成 calix[4]quinone benzoates, [2,3] 而這些 calix[4]quinones 上下緣的酮基(carbonyl groups)可在利用乙二醇進行縮酮保護時分別出，亦即在進行縮酮反應時，僅有立體障礙較小的上緣酮基會被形成縮

酮基，[2,3] 至於下緣之酮基則可能因為立體障礙的效應而保有 C=O 的原始形態。而這一類僅有上緣形成縮酮而被保護的中間化合物，calix[4]quinone monoketals，應有其合成上的特殊用途，而這一個兩年的研究計劃，便是以 calix[4]quinone monoketals 做為合成的起始物，以研究其合成其他 calix[4]arene 衍生物的可行性。

本實驗室在這一個兩年的計劃中提出，如對 calix[4]quinone monoketals 的下緣酮基進行親核基的加成，經水解並還原上緣之酮基，然後如再於酸催化下脫水，應可合成出一系列下緣取代之 *exo*-calix[4]arenes。同時，在這個計劃的方法中，如能以 Wolff-Kishner 的方式來還原下緣之酮基，則依相同的反應模式，理論上應可合成出僅含有上緣羥基之 *exo*-calix[4]arenes。這一類 *exo*-calix[4]arenes 因其羥基位於上緣，此和一般羥基位於下緣的 calix[4]arenes 有所不同，因此合成出這類新的 *exo*-calix[4]arenes 不但可供進行酵素模擬之研究，並可研究 *exo*-calix[4]arenes 和一般 calix[4]arenes 在組態上，因羥基位置的不同而可能造成之差異，而利用理論計算來研究此一組態的差異亦為本計劃之一個重點，亦即是利用實際合成出之產物，來檢驗與分子計算出的結果，並找尋兩者中間的關聯性。

三．結果與討論

本實驗室在多年國科會的補助下，研究各種 calix[4]arenes 衍生物的合成，經多年研究經驗的累積，本實驗室不但在對於 calix[4]arenes 的下緣進行官能基化已有完整之研究和成果，[4] 並且借由文獻上之報導，[5] 發展出一種將氧原子引進至 calix[4]arenes 上緣的方式。

本實驗室發現 calix[4]arene 的下緣羥基可在不同的反應條件之下，和苯甲酸醯氯 (benzoyl chloride) 進行不同程度的酯化反應；[4b] 而這些未完全酯化後的 calix[4]arenes 中，這些尚存有未酯化之自由的苯酚羥基可在二氧化氯的水溶液中氧化成 quinones 而形成所謂的 calix[4]quinones，此亦為另一類型的 calixarenes 衍生物。

本實驗室在多年前曾以合成含有對位羥基之 calix[4]arenes 的研究為目標。但在正式進行合成時，卻發現無法直接利用還原劑，將 calix[4]quinones 上下緣的酮基還原成羥基，亦即是無法以簡單的還原及水解來合成出含有對位羥基之 calix[4]arenes，所以必須要發展出新的合成途徑，才有機會製備出含有對位羥基之 calix[4]arenes 。

在進一步研究含有對位羥基之 calix[4]arenes 的合成中發現，如果將 calix[4]quinones 和乙二醇在利用酸催化進行縮酮的反應時，此一縮酮反應僅會進行部份的保護，亦即是生成僅有上緣之

酮基被保護的 calix[4]quinones, 而其下緣之酮基依然保有 C=O 的原始形態。

在本計劃中, 本實驗室認為如對這些僅上緣之酮基被保護的 calix[4]quinones, 進行下緣酮基的親核性加成反應, 然後再進行水解及還原, 則應可合成出僅上緣含有羥基的 *exo*-calix[4]arenes 之衍生物。相同的, 如對這些 calix[4]quinones 下緣的 C=O 官能基, 進行 Wolff-Kishner 的還原反應, 以還原下緣的酮基, 然後再進行水解及還原, 應可得到上緣含有羥基的 *exo*-calix[4]arenes。

但實際上, 當這些僅上緣之酮基被保護的 calix[4]quinones 進行 Wolff-Kishner 的還原反應, 以還原下緣的酮基時, 本實驗室卻發現下緣的酮基僅能被部份還原, 而形成含有羥基的 calix[4]arenes 之衍生物。而此一 Wolff-Kishner 的還原反應, 進一步的研究顯示, 對於所有之 calix[4]quinones 的衍生物, 均有相同的結果。由研究結果中發現, 如利用此一還原反應的特性, 則可將部份苯甲基化之 calix[4]quinones 在一步反應中, 直接得到上緣含有羥基的 calix[4]arenes。這一個結果將可對這些化合物的合成步驟, 由原來之六步驟簡化成為三步驟的合成, 研究之成果（如附件一）已於六月份發表於 Journal of Chinese Chemical Society。而另一以二醚化 calix[4]arenes 進行二氧化氯氧化, 而得其相對應之二醚化之 calix[4]diquinones 的研究成果已送交 Tetrahedron, 靜待審查報告（如附件二）。最後, 以 calix[4]quinines 為起始物, 以合成對位硝基苯偶氮化之 calix[4]arenes 的研究亦已完成, 供審查發表之草稿現正整理擬稿中。

四. 計劃結果自評

此一計劃由於數個未曾預期中之困難, 致使原計劃中之主要的產物, *exo*-calix[4]arenes, 無法順利合成出。但在合成過程中, 本實驗室藉由合成過程中, 發現 calix[4]quinone monoketals 的下緣的酮基, 因立體障礙的因素, 而使得在進行一些特定反應時, 其結果並不和期望中的產物一致。例如, 針對 calix[4]quinone monoketals 進行 Wolff-Kishner 的還原反應, 則其下緣的酮基僅會被部份還原而形成羥基, 且此一特性對 calix[4]quinones 的衍生物均有相同的結果。如利用此一特性, 則製備上緣含有羥基的 calix[4]arenes 之合成步驟, 可簡化為三個步驟的合成。

而針對其他可與酮基進行反應的反應試劑, 本實驗室發現 *p*-nitrophenylhydrazine 在乙醇的酸性溶液, 可和 calix[4]quinones 直接進行反應, 而得到對位硝基苯偶氮化之 calix[4]arenes。由這些研究成果中, 本實驗室已有效的發展出新類形之 calix[4]arens 的衍生物, 以供酵素模擬的研究之用。

五．參考文獻

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（附件一）

Calix[4]quinones III: The Synthesis of *p*-Hydroxycalix[4]arenes by Wolff-Kishner Reduction

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Abstract: The Wolff-Kishner reduction of the half-protected ketal calix[4]monoquinone **3** and its basic hydrolysis product **4** produced a partially reducing product **5.** When the same reduction conditions were applied to the calix[4]quinone benzoates **1** and **2,** the corresponding title compounds, *p*-hydroxycalix[4]arenes (**6** and **7**), were afforded in one-step.

Introduction

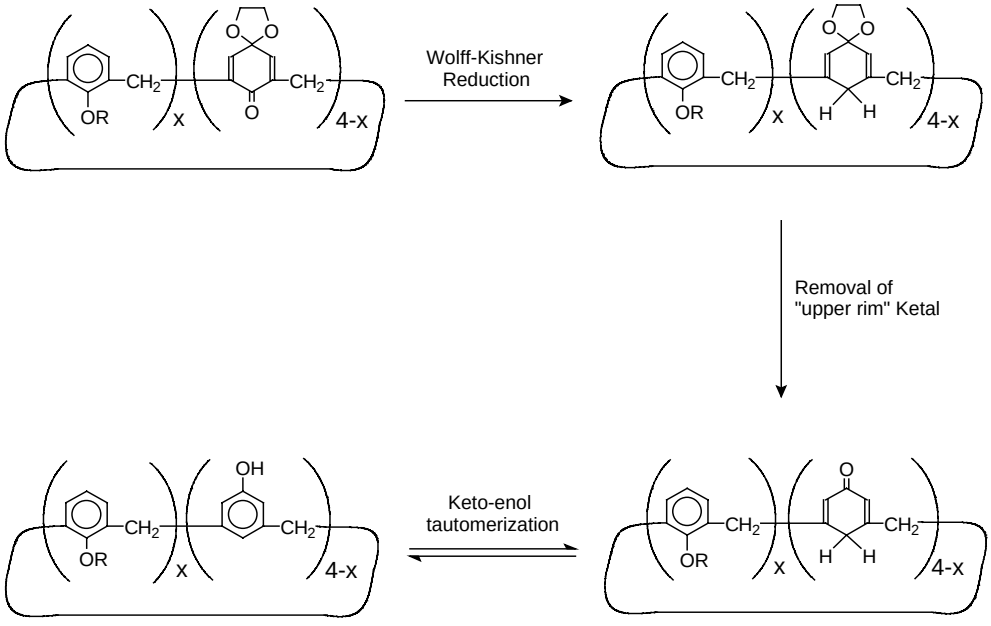
The calixarenes are divided into two sub-classes, *endo*-calixarenes and *exo*-calixarenes, based on the position of their phenolic hydroxy groups. The *endo*-calixarenes, which possess hydroxy groups on their "lower rim", are well demonstrated in the literature[1,2]; whereas, only a few research studies reported on the "upper rim" hydroxy containing *exo*-calixarenes[2-5].

It is well understood that, due to the strong *ortho*- and *para*- directing ability of the phenolic hydroxy group, the *exo*-calixarenes which had their phenolic hydroxy moieties *meta* to the methylene linkage were unable to be prepared in either a simple one-step condensation or in a stepwise condensation procedure[5]. However, we have demonstrated in our earlier work that an oxygen atom was able to introduce onto the calixarenes' *para*-position in

chlorine dioxide oxidation reaction, and the mono-substituted *p*-hydroxycalix[4]arenes was derived following a six-step conversion[6]. In this paper, we report that the transformation of calix[4]quinone benzoates to the partial *p*-hydroxy substituted calix[4]arenes can be simplified into a single step procedure by way of Wolff-Kishner reduction conditions.

Results and Discussion

In our earlier work[6], we established a six-step synthetic route for the mono-substituted *p*-hydroxycalix[4]arene. Unfortunately, due to the intramolecular Michael-addition, the *p*-1,3-dihydroxy-calix[4]arene could not be produced according to the same synthetic route[7]. During the course of the synthesis, we noted that the two carbonyl groups on the quinones moieties were differentiated, in which only the less hindered "upper rim" carbonyl groups were protected in the ketal formation step[6,7]. Therefore, it is reasonable to propose that the Wolff-Kishner reduction following by a removal of "upper rim" ketal protecting group may transform the calix[4]quinone monoketals into non-substituted *exo*-calix[4]arenes, as shown in scheme 1.

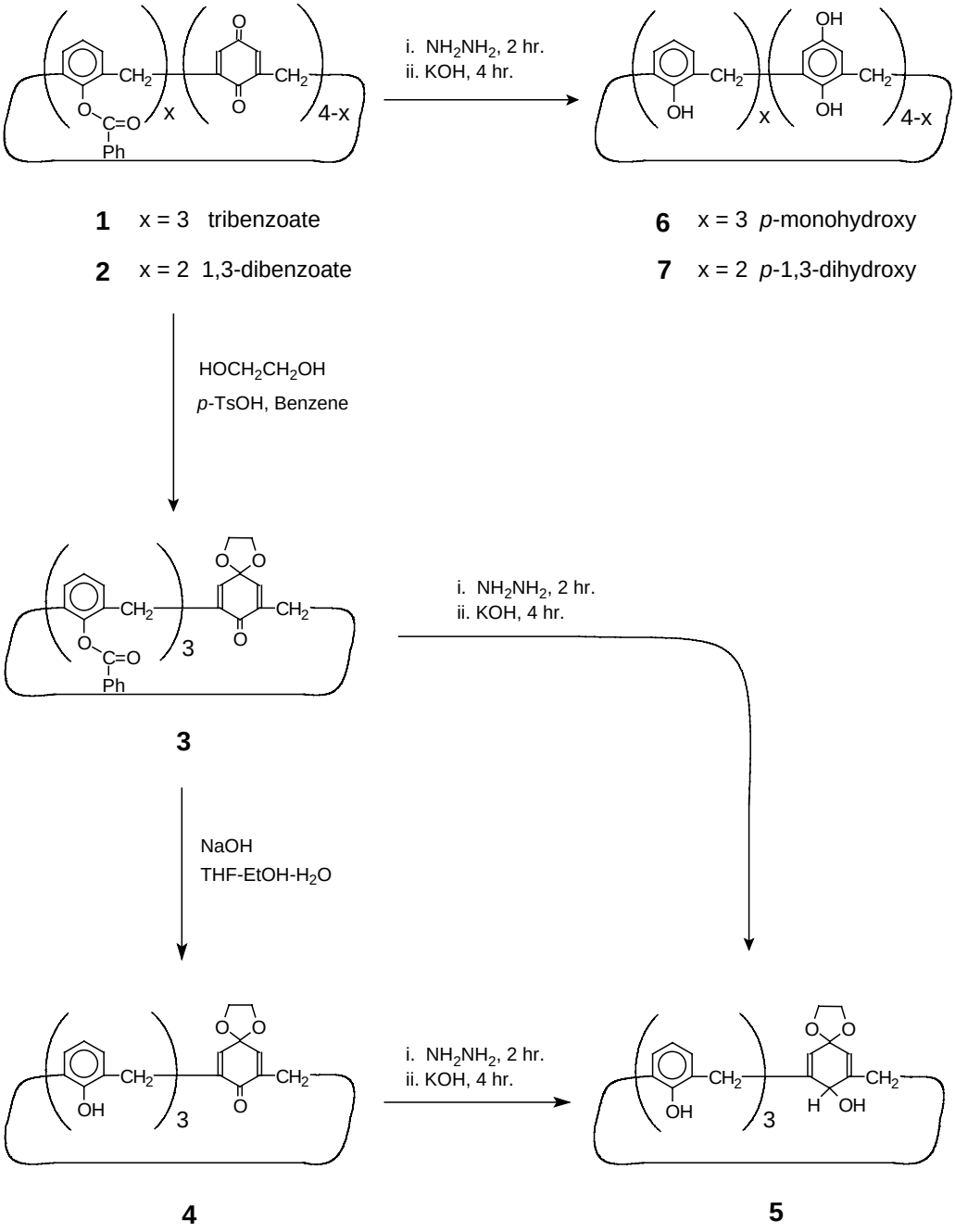


Scheme 1. A propose synthetic route for *exo*-calix[4]arenes

Partial reduced Calix[4]quinone 5. When the Wolff-Kishner reaction conditions were performed on monoketal **3**, a reddish solid material was attained after a chromatographic separation. All of the spectral data of this reddish solid material, instead of the expected totally reduced product, was shown to be a known partially reduced compound **5**. Compound **5**, which was prepared differently in our earlier work[6], was fully characterized and possessed a partially reduced "lower rim" tetrahedral carbinol structure. It is believed that the formation of the "lower rim" hydrazone moieties was hindered by the steric structure of monoketal **3**, and subsequently, the possibility of producing the totally reduced product as well as the *exo*-calix[4]arene in this Wolff-Kishner reduction condition was negated. However, the reaction conditions of hydrazine with strong base (which supplied the reducing power for the "lower rim" carbonyl groups) and the basic refluxing conditions (which removed all the benzoate moieties from the starting materials) provided the reaction conditions for the formation of the partially reduced compound **5**.

Upon examining the structure of compound **3**, we noted that either the structure of calix[4]arene itself or the three bulky benzoate groups could cause the failure of the "lower rim" hydrazones formation. In order to identify the origin of this failure, the basic hydrolysis compound **4** was chosen for the same reduction conditions. This resulted in a similar quantity of product **5** and indicated that the structure of calix[4]arene itself possessed a highly hindered "lower rim", and the tetrahedral carbon structure with larger substituents on the "lower rim" was not possible even in the intermediate stage.

***p*-Hydroxycalix[4]arenes 6 and 7.** On the Wolff-Kishner partial reduction of monoketal **3**, both the removal of the benzoate groups and the reduction of the "lower rim" carbonyl moieties were achieved in a simple one-step reaction. We speculated that the same reaction conditions may also transform the calix[4]monoquinone tribenzoate **1** into a partial



Scheme 2. The reaction paths of the calix[4]quinones

reduction with a benzoate removing product. When compound **1** was treated under Wolff-Kishner reaction conditions, a reddish solid material was produced as in previous cases. The spectral data indicated that the reddish solid product was the expected compound, *p*-monohydroxycalix[4]arene (**6**). The color of the product, which was not agreed with the

literature reported[5], was maintained through out the recrystallization process. However, the reddish color material possessed a very low R_f value, and a short column chromatography revealed the off-white appearance of the product **6**. In the original six-step synthetic route, $NaBH_4$ was applied to reduce calix[4]monoquinone to yield product **6** in the final stage, the same product was attained in higher yield when the Wolff-Kishner reduction reactions were employed instead. Nevertheless, the partially reduced Wolff-Kishner reaction conditions were able to modify and reduce the original synthetic route for *p*-monohydroxycalix[4]arene (**6**) to three-steps.

As mention earlier, calix[4]diquinone **2** underwent an intramolecular Michael-addition in basic conditions and the original six-step synthetic route for *p*-1,3-dihydroxycalix[4]arene (**7**) was disturbed. Therefore, the Wolff-Kishner reduced reaction conditions, which simultaneously removed the benzoate groups and reduced the "lower rim" carbonyl moieties in the calix[4]monoquinone case, were preformed on calix[4]diquinone **2** and were expected to generate the partially reduced product **7**. In the actual reduction reaction, a very fine pinkish powder was obtained during the worked-up procedure. Unlike its monohydroxy counterpart **6**, this pinkish solid was soluble in methanol and the recrystallization was achieved in acetone and *n*-hexane. The ^{1}H-NMR spectrum of this pinkish powder **7** displayed two broad singlets, which vanishing upon treating with D_2O, at 9.89 and 7.72 ppm at the ratio of 2:1, respectively. This spectral data indicated that a total of six phenolic hydroxy moieties were presented, and the four "lower rim" phenolic hydroxy groups were different from the other two "upper rim" hydroxy groups. With the support of other spectral data, the structure of pinkish powder **7** was assigned to be the title compound, *p*-1,3-dihydroxycalix[4]arene (**7**).

The same ^{1}H-NMR spectral feature was also observed in the *p*-monohydroxycalix[4]arene (**6**) case, in which two broad singlets at 10.09 and 4.40 ppm

with 4:1 integral ratio were displayed. This chemical shift could possibly indicate the overall strength of the calixarene's intramolecular hydrogen bond. We believe that these ^{1}H-NMR spectra would provide a valuable information for the structure of calix[4]arenes, if one could establish a correlation between the chemical shift and the distance between the phenolic hydroxy groups.

Acknowledgment

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Experimental[8]

Gerenal Procedure: A protion of 5 mL of hydrazine hydrate was added to a solution of 1.00 mmol of sample in 15 mL of diethylene glycol, and a solution of 2.30 g of KOH in 20 mL of ethylene glycol was then added. The reaction mixture was refluxed for 4 hours with a Dean-Stark trap to remove an excess hydrazine. The solution was cooled to room temperature, and a large excess of diluted HCl was added to induce a solid material. The purification procedure for individual product was described separately.

28-Hydro-25,26,27,28-tetrahydroxycalix[4]monoquinone-17-ethylene ketal (5). Method A: from 25,26,27-Tribenzoyloxy-28-calix[4]monoquinone-17-ethylene ketal (3). A deep red solid was collected from a sample of 0.80 g (1.00 mmol) of **3**. Chromatographic separation (eluent: EtOAc:*n*-hexane = 1:2) following by recrystallization from $CHCl_3$ and CH_3OH afforded 0.18g (37%) of deep red solid **8**: mp 300-302 ^oC (Lit.[6] 274-276 ^oC; after recrystallized from $CHCl_3$ and *n*-hexane); ^{1}H-NMR[9] ($CDCl_3$) δ 10.10 (s, 4H, ArO<u>H</u>), 7.01-7.06 (m, 6H, Ar<u>H</u>), 6.68-6.75 (m, 3H, Ar<u>H</u>), 6.60 (s, 2H, Ar<u>H</u>), 4.25 (bs, 4H, ArC<u>H</u>$_2$Ar), 3.90-3.93 (m, 2H, OC<u>H</u>$_2$-C), 3.81-3.86 (m, 2H, OC<u>H</u>$_2$-C), 3.51 (bs, 2H, ArC<u>H</u>$_2$Ar), 3.47 (bs, 2H, ArC<u>H</u>$_2$Ar); ^{13}C-NMR ($CDCl_3$) δ 153.0, 149.0, 148.6, 142.7, 139.7, 129.2, 129.0, 128.9, 128.8, 128.2, 127.9, 122.3, 122.1, 114.9, 69.5, 61.5, 32.0, 31.7; FAB-MS *m/z*: 484 (M^+). Anal. Calcd for $C_{30}H_{28}O_6$: C, 74.38; H, 5.79. Calcd for $C_{30}H_{28}O_6 \cdot 3/2H_2O$: C, 70.45; H,

6.07. Found: C, 70.70; H, 5.87.

Method B: from 25,26,27-Trihydroxy-28-calix[4]monoquinone-17-ethylene ketal (4). A deep red solid was collected from a sample of 0.48 g (1.00 mmol) of **4**. Chromatographic separation following by recrystallization from $CHCl_3$ and CH_3OH afforded 0.12g (25%) of deep red solid. The physical and the spectral properties of this product were identical to the product which produce in Method A.

5,25,26,27,28-Pentahydroxycalix[4]arene (6). Method A: from 25,26,27-Tribenzoyloxy-28-calix[4]monoquinone (1). A red solid was collected from a sample of 0.75 g (1.00 mmol) of **1**. A short column chromatographic separation (column height 10 cm; eluent: $CHCl_3$:*n*-hexane = 3:1) following by recrystallized from $CHCl_3$ and *n*-hexane afforded 0.24g (55%) of pale yellow solid **6**: mp 309-311 ^oC (Lit.[6] 310-312 ^oC); ^{1}H-NMR ($CDCl_3$) δ 10.09 (bs, 4H, ArO<u>H</u>), 7.00-7.06 (m, 6H, Ar<u>H</u>), 6.68-6.73 (m, 3H, Ar<u>H</u>), 6.50 (s, 2H, Ar<u>H</u>), 4.40 (bs, 1H, , ArO<u>H</u>), 4.22 (bs, 4H, ArC<u>H</u>$_2$Ar), 3.51 (bs, 2H, ArC<u>H</u>$_2$Ar) , 3.42 (bs, 2H, ArC<u>H</u>$_2$Ar); ^{13}C-NMR ($CDCl_3$) δ 149.8, 149.0, 148.7, 142.4, 129.3, 129.1, 129.0, 128.9, 128.2, 128.1, 128.0, 122.3, 122.1, 115.5, 31.8, 31.7; FAB-MS *m/z*: 440 (M^+). Anal. Calcd for $C_{28}H_{24}O_5$: C, 76.36; H, 5.45. Found: C, 74.30; H, 5.34.

Method B: from 25,26,27-trihydroxy-28-calix[4]monoquinone. A red solid was collected from a sample of 0.44 g (1.00 mmol) of 25,26,27-trihydroxy-28-calix[4]monoquinone. A short column chromatographic separation following by recrystallized from $CHCl_3$ and *n*-hexane afforded 0.41g (93%) of pale yellow solid **6**. This product is identical with product produced in method A.

5,17,25,26,27,28-Hexahydroxycalix[4]arene (7). A pink solid was collected from a sample of 0.66 g (1.00 mmol) of 25,27-dibenzoyloxy-26,28-calix[4]diquinone (**2**). The solid material was recrystallized from acetone and *n*-hexane to afford 0.23 g (50%) of pinkish powder: mp 222-224 ^oC; ^{1}H-NMR (acetone-D_6) δ 9.89 (bs, 4H, ArO<u>H</u>), 7.72 (bs, 2H, ArO<u>H</u>), 7.13-7.14 (d, *J* = 7.5Hz, 4H, *m*-Ar<u>H</u>), 6.69-6.72 (t, *J* = 7.5Hz, 2H, *p*-Ar<u>H</u>), 6.62 (s, 4H, Ar<u>H</u>), 3.50-4.10 (bs, 8H, ArC<u>H</u>$_2$Ar); ^{13}C-NMR (acetone-D_6) δ 152.4, 149.9, 141.8, 129.9, 129.7, 129.1, 122.5, 116.0, 31.7; FAB-MS *m/z*: 456 (M^+). Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.66; H, 5.30. Calcd for $C_{28}H_{24}O_6 \cdot 3/2H_2O$: C, 69.57; H, 5.59. Found: C, 69.57; H, 5.49.

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8. All reagents were obtained from Commercial Chemical Companies and used without further purification. Melting points were taken in capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) and are uncorrected. ^{1}H-NMR spectra are recorded on Burker DMX-300 WB and/or Burker DMX-500 SB spectrometer and chemical shifts are reported as δ values in ppm relative to TMS (δ=0.00) as an internal standard. FAB-MS spectra were taken on a JOEL JMS-HX 102 spectrometer and elemental analyses were taken on a Perkin-Elmer 240C analyzer. Chromatographic separations were performed with Merck silica gel (230-400 mesh ASTM) on columns of

25 mm diameter filled to height of 150 mm. TLC analyses were carried out on Merck aluminum back silica gel 60 F_{254} plates (absorbant thickness 0.2 mm).

9. In the ^{1}H-NMR spectrum of compound **5**, we were not able to assign the proton signal for the carbon-28's hydrogen which was located on tetrahedral carbinol carbon. It was speculated that a free rotation around the methylene linkage in calix[4]arene system constantly altered the magnetic environments for 28-hydro-, and therefore, a sharp proton signal for 28-hydro- was not observed.

（附件二）

Calix[4]quinones IV: The ClO_2 Oxidation of Calix[4]arene Dialkyl Ethers

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Abstract: Except for the special case of calix[4]arene diethyl ether **1**, the chlorine dioxide oxidation of dialkyl ethers **2-5** yielded only the corresponding calix[4]diquinone dialkyl ethers **8-11**. Chlorine dioxide oxidation of calix[4]arene diethyl ether **1** produced two isomeric products **6** and **7**, which were stable enough to be isolated by column chromatography. However, a slow conformational interconversion between isomeric pair **6** and **7** was observed at room temperature.

Introduction

Electron transport systems are the vital pathways for energy-producing mechanisms in all living cells, and the quinone and dihydroquinone (*p*-hydroxyphenol) pairs are the key moieties in coenzyme Q for the charge transport process. Based on these known principles, it is rational to propose that the calixquinone and *p*-hydroxycalixarene pair may serve as an enzyme model to probe the charge transport process.

In the literature, two groups of the calix[4]quinones derivatives, e.g. benzoated calix[4]quinones[1] and etherated calix[4]quinines,[2,3] were reported. The calix[4]quinone benzoates were synthesized by treating the corresponding calix[4]arene benzoates with chlorine dioxide at room temperature,[1] whereas, the oxidation of calix[4]arene ether derivatives occurred under more severe conditions.[3] Although, a milder chlorine dioxide oxidation condition for calix[4]arene ether derivatives was noted by Gutsche and his coworkers,[2] but eventually the oxidation reactions were performed on thallium tris-trifluroacetate in trifluroacetic acid.[3] In this paper, we report on the isolation of calix[4]quinone ether derivatives **6-11** from the chlorine dioxide oxidation of the corresponding calix[4]arene ethers **1-5**, and also describe the result of a slow conformational interconversion between isomeric pair **6** and **7**.

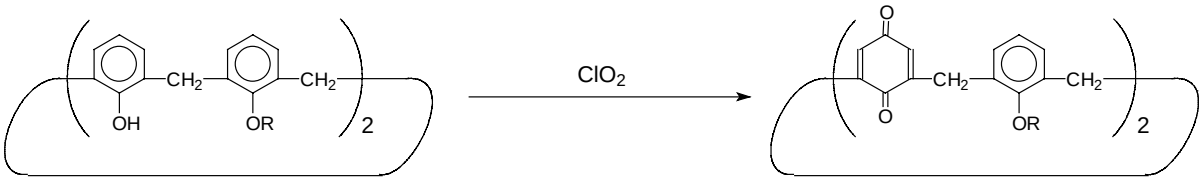
Results and Discussion

Calix[4]diquinone dialkyl ethers 6-11. In our earlier work, we have established a standard synthetic procedure for converting the benzoated calix[4]arenes to the corresponding benzoated calix[4]quinones. It would be supportive in calixarenes chemistry if the converting pathway for the calix[4]arene ethers to their corresponding calix[4]quinones can be established under the same milder reaction conditions.

Due to the conformational flexibility of the calix[4]arene dimethyl ether, five other common calix[4]arene dialkyl ethers **1-5** were prepared[4] for the study of the chlorine dioxide oxidation as shown on scheme 1. As in a standard procedure for the oxidation of calix[4]arene benzoated, the calix[4]arene dialkyl ether **1-5** were dissolved in acetonitrile and oxidized with a portion of yellow aqueous chlorine dioxide solution. The reaction mixture was stirred at room temperature, and the reaction was monitored by thin layer chromatography to determine the optimal reaction time for different calix[4]arene dialkyl

ethers. Unlike their benzoates counterparts[1], the oxidization of the calix[4]arene ether derivatives proceeded at various pace which ranged from 4 hours to 96 hours. Although the exact solubility of five dialkyl ethers **1-5** in acetonitrile was not measured, but the solubility, and hence the oxidation rate, seemed to be decreased as the sizes of the substitutent increased.

Large quantities of yellow solids were afforded for all five oxidative reactions after a standard worked up procedure. Except for calix[4]arene diethyl ether, all other oxidation cases produced only one major component. Unfortunately, a simple recrystallization method was not able to isolate the corresponding oxidative products, and therefore, the chromatographic separation was applied for all the oxidation reactions to isolate the corresponding products **6-11**.



1 R = $-CH_2CH_3$
2 $-CH_2CH_2CH_3$
3 $-CH_2CH_2CH_2CH_3$
4 $-CH_2CH{=}CH_2$
5 $-CH_2Ph$

6 + 7 R = $-CH_2CH_3$
8 $-CH_2CH_2CH_3$
9 $-CH_2CH_2CH_2CH_3$
10 $-CH_2CH{=}CH_2$
11 $-CH_2Ph$

In the chlorine dioxide oxidation conditions, only the free phenol moieties were oxidized into quinones and the alkylated phenol moieties were not affected. Therefore, the oxidated products **6-11** retained the structural C_{2v} symmetry, and the products were easy to identify by their ^{1}H-NMR spectrum. Of all the ^{1}H-NMR spectrum of products **6-11**, a singlet for quinone hydrogens appeared, whereas, the signals for the phenol moieties, which composed: one singlet for phenolic hydroxy hydrogens, one triplet for *para*-aromatic hydrogens, and one doublet for *meta*-aromatic hydrogens, vanished. The characteristic

signals of the different alkoxy groups, which were also not affected by the chlorine dioxide, were the labels for each oxidative product **6-11**.

Conformational interconversion of calix[4]diquinone diethyl ether isomeric pair 6 and 7. As mentioned previously, two major components were observed on the chlorine oxidation of calix[4]arene diethyl ether **1**. Using a TLC analysis, two colored fractions with very different R_f value (0.29 and 0.13) were displayed, and the corresponding products **6** and **7** were easily isolated by column chromatography. The first fraction, compound **6**, displayed a clean ^{1}H-NMR spectrum (Fig. 1) for the oxidated structure of calix[4]diquinone diethyl ether, and the FAB-MS confirmed the molecular weight of the diquinone structure. The second colored fraction, which took a longer period to elute, displayed an overlapping ^{1}H-NMR signal (Fig.2) with a contamination of the first colored fraction material. It was puzzling as a small amount of compound **6** always appeared on the ^{1}H-NMR spectrum even

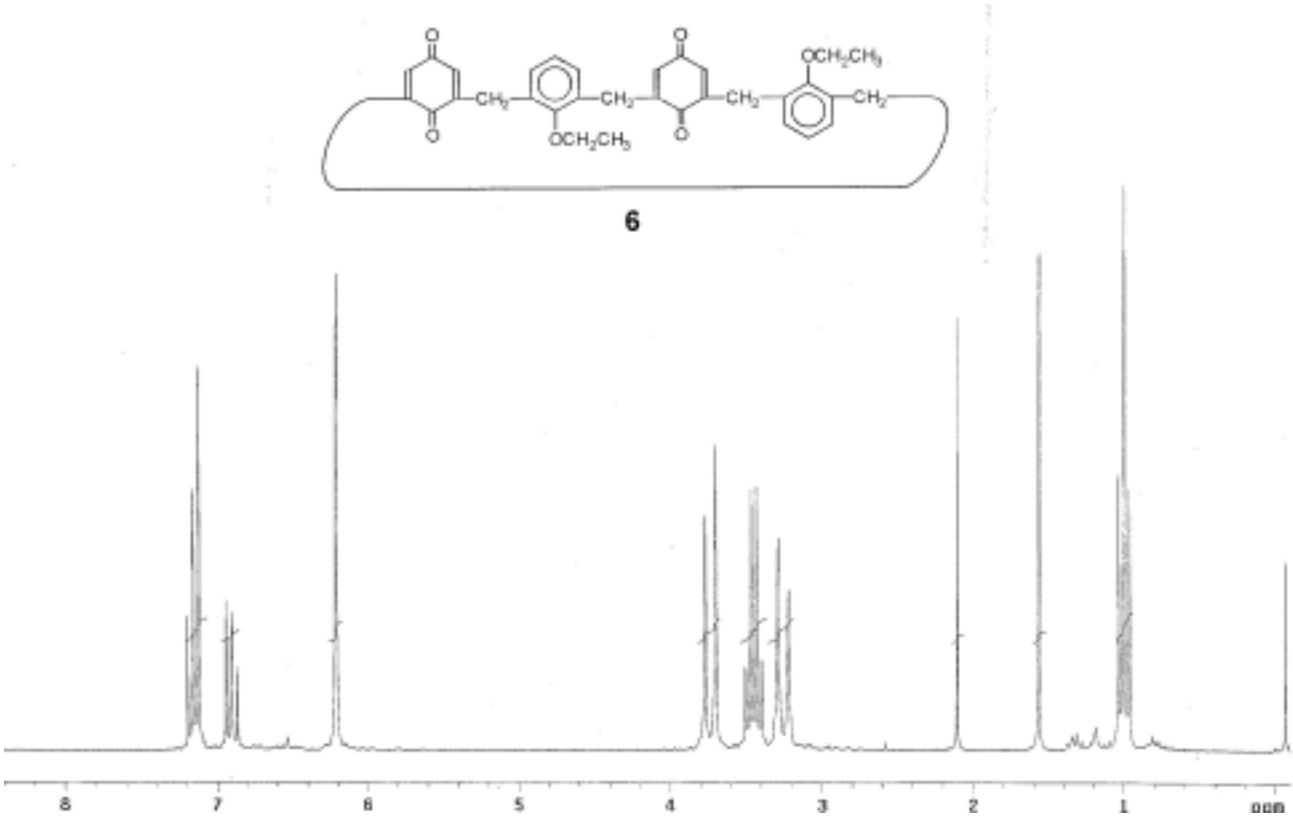


Fig. 1. 200 MHz ^{1}H-NMR spectrum of *anti*-25,27-diethoxy-26,28-calix[4]diquinone **(6).**

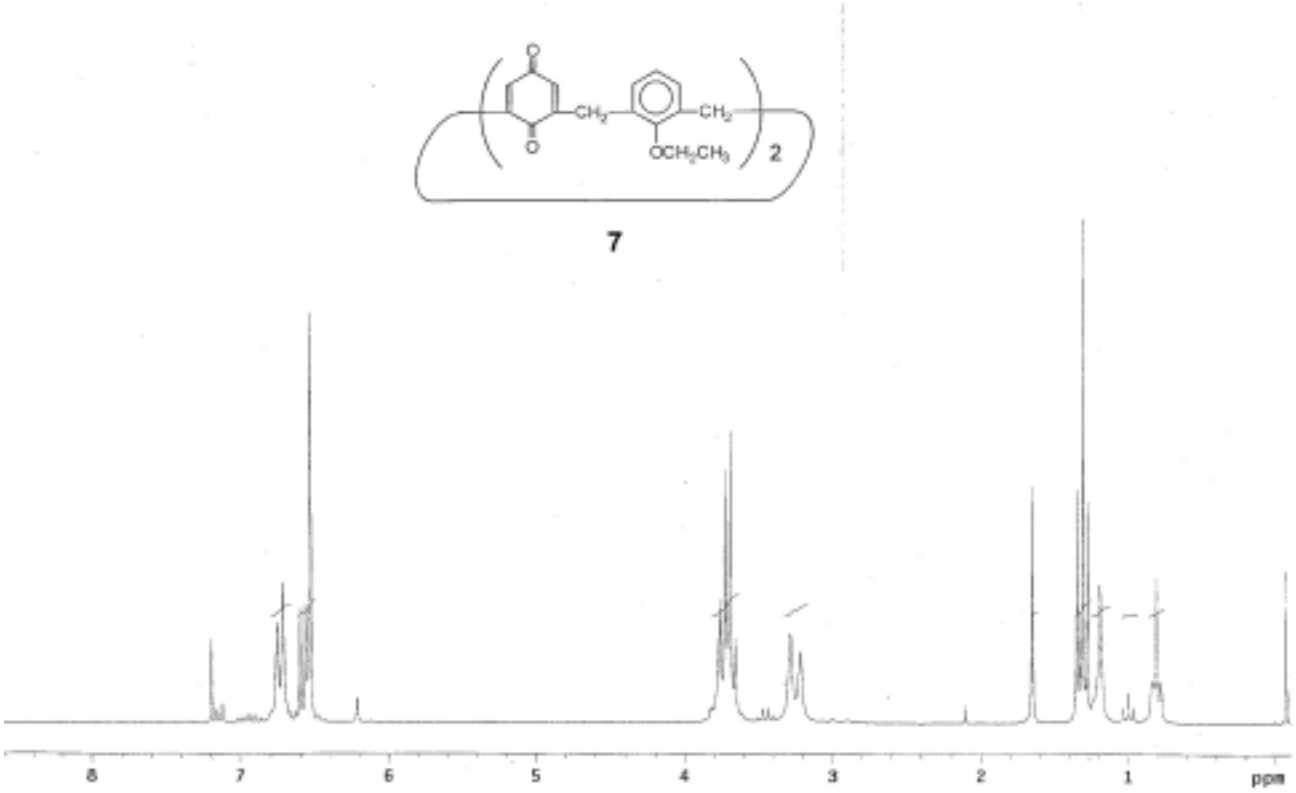


Fig. 2. 200 MHz ^{1}H-NMR spectrum of *syn*-25,27-diethoxy-26,28-calix[4]diquinone **(7).**

with a careful selection of the eluted fractions for the product **7**. The molecular weight determination and the ^{1}H-NMR spectral analysis indicated that the product **7** also possessed a molecular structure of calix[4]diquinone diethyl ether as the first colored fraction product **6**. The exact structures for each compound were determined by comparing the chemical shift of the quinone hydrogens' singlet. All other *syn*-1,3-dialkylated calix[4]quinones **8-11** displayed a singlet between δ 6.45-6.55 for the quinone hydrogens. Based on this observation, a singlet at δ 6.21 was the basis for assigning product **6** as the *anti*-isomer.

The *syn*-1,3-diethylated calix[4]arene (**1**) was not conformational mobiled,[5] but an oxidation process with a flexible intermediate was able to explain the formation of the *anti*- and *syn*-isomers (**6** and **7**). However, when products **6** and **7** were sent for a high field NMR spectrum,[6] after a long waiting, two identical ^{1}H-NMR spectra were obtained, as shown in

Figure 3. It was soon realized that the identical ^{1}H-NMR spectrum resulted from the conformational interconversion between the *anti*- and *syn*-isomers (**6** and **7**) at the ambient temperature, and the earlier flexible intermediate scheme for the formation of the isomeric pairs **6** and **7** was excluded. This "interconversion" phenomenon was also able to clarify the existence of the "contamination" during a long elution time for the second colored fraction **7**.

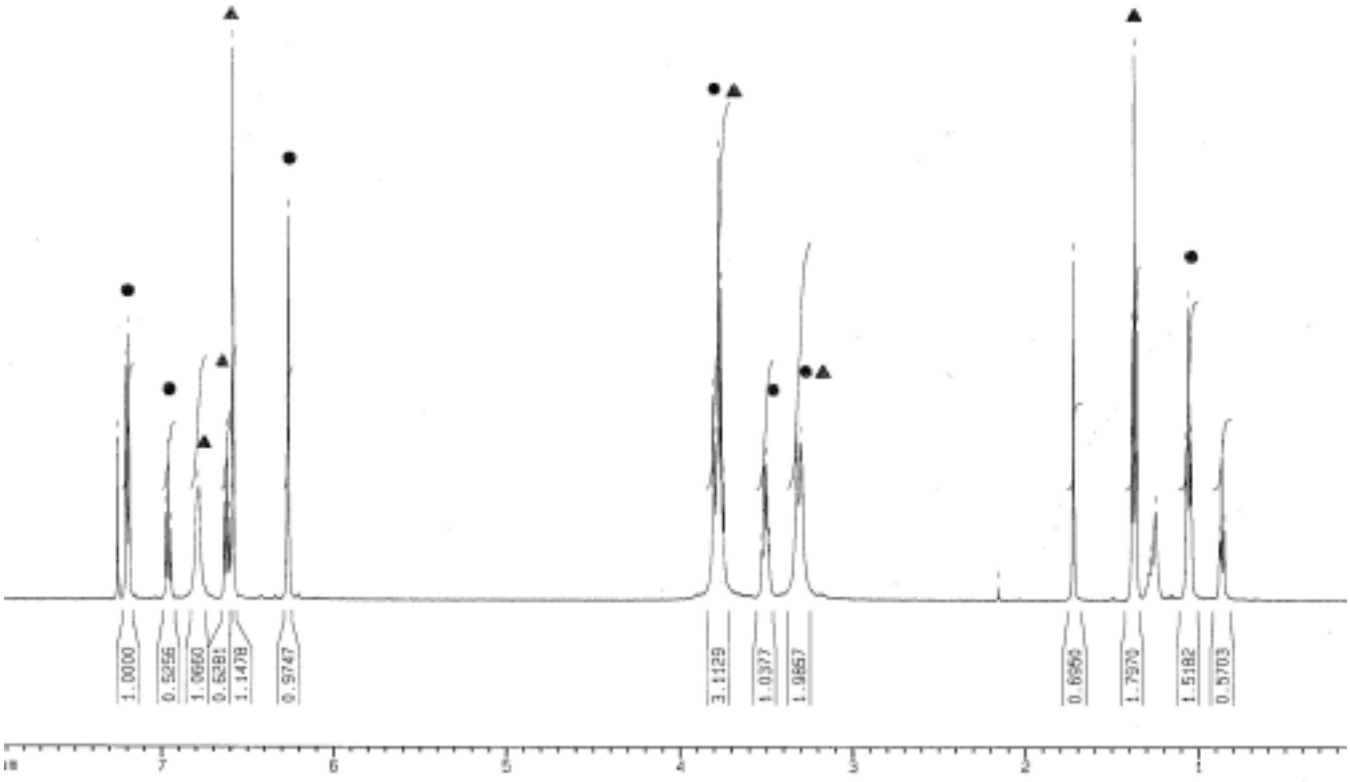


Fig. 2. 500 MHz ^{1}H-NMR spectrum of a mixture of calix[4]diquinones **6 (●)** and **7 (▲).**

It was known that the conformational interconversion arose from the "through-the-annulus-rotation" in the calix[4]arene system, and the rotation could be suppressed by introducing an ethoxy or other larger alkoxy moieties in the "lower rim".[5] A simple structure analysis indicated that the oxidation on the diethylated calix[4]arene **1** would not only reduce the size of the "lower rim" substitutents but also remove the "lower rim"

hydrogen bond. The result created a suitable space for the ethoxy moieties to slowly rotate through the "lower rim" annulus, and produced two stable isomers **6** and **7**. Both isomers were stable enough to be isolated from the reaction mixture, but the slow "through-the-annulus-rotation" of the ethoxy moieties would enable the two isomers to convert to one another. The rate of the interconversion between two isomers **6** and **7** was in the order of days, and a kinetic study to determine an exact rotation rate and the free energy barrier is still under investigation.

Experimental[7]

General Procedure: A slurry of 5 mmol of calix[4]arene dialkyl ethers **1-5**[4] was dissolved in 150 mL of CH_3CN, and a portion of 100 mL of aqueous ClO_2 solution[8] was then added. The reaction mixture was stirred at room temperature for a specific time, and the organic solvent was removed to leave a yellow and/or orange solid. The solid materials were collected and the purification procedures for the individual product were described separately.

***anti*-25,27-Diethoxy-26,28-calix[4]diquinone (6) and *syn*-25,27-diethoxy-26,28-calix[4]diquinone (7).** The reaction mixture was stirred at room temperature for 6 hours, and a yellow solid was collected from a sample of 2.40 g (5.00 mmol) of **1**. Chromatographic separation (eluent: EtOAc:*n*-hexane = 1:4) of the first colored fraction (R_f= 0.29), which was recrystallized from $CHCl_3$ and CH_3OH, afforded 0.69g (18.5%) of oxidized product **6** as yellow crystals: mp 125-127 ^oC; ^1H-NMR ($CDCl_3$) δ7.13-7.16 (d, *J*= 7.4Hz, 4H, Ar<u>H</u>), 6.87-6.95 (t, *J*= 7.5Hz, 2H, Ar<u>H</u>), 6.21 (s, 4H, quinone-<u>H</u>), 3.70-3.77 (d, *J*= 13.4Hz, 4H, ArC<u>H</u>$_2$Ar), 3.40-3.50 (q, *J*= 7.1Hz, 4H, ArOC<u>H</u>$_2$$CH_3$), 3.22-3.29 (d, *J*= 13.4Hz, 4H, ArC<u>H</u>$_2$Ar), 0.97-1.04 (t, *J*= 7.1Hz, 6H, $ArOCH_2C$<u>H</u>$_3$); FAB-MS *m/z*: 509 (M^++1). Anal.[9] Calcd for $C_{32}H_{28}O_6$: C, 75.59; H, 5.51; for $C_{32}H_{28}O_6 \cdot$ 1/4$CHCl_3$: C, 71.94; H, 5.25. Found: C, 71.84; H, 5.13.

A second colored fraction (R_f= 0.13), which was also recrystallized from $CHCl_3$ and CH_3OH, yielded 0.86 g (42.5%) of yellow crystals **7**: mp 125-127 ^oC; ^1H-NMR ($CDCl_3$)

δ6.72-6.76 (d, *J*= 7.6Hz, 4H, ArH), 6.54-6.60 (m, 6H, ArH and quinone-H), 3.66-3.76 (m, 8H, $ArCH_2Ar$ and $ArOCH_2CH_3$), 3.22-3.29 (d, *J*= 13.2Hz, 4H, $ArCH_2Ar$), 1.28-1.35 (t, *J*= 7.0Hz, 6H, $ArOCH_2CH_3$); FAB-MS *m/z*: 510 (M^++2). Anal. Calcd for $C_{32}H_{28}O_6$: C, 75.59; H, 5.51; for $C_{32}H_{28}O_6 \cdot H_2O$: C, 73.00; H, 5.70. Found: C, 73.03; H, 5.79.

25,27-Dipropoxy-26,28-calix[4]diquinone (8) The reaction mixture was stirred at room temperature for 36 hours, and a yellow solid was collected from a sample of 2.54 g (5.00 mmol) of **2**. Chromatographic separation (eluent: EtOAc:*n*-hexane = 1:4) following by recrystallization from $CHCl_3$ and CH_3OH afforded 1.16g (43%) of orange color crystals **8**: mp 178-180 °C; ^{1}H-NMR ($CDCl_3$) δ6.76 (bs, 4H, ArH), 6.57-6.61 (m, 6H, ArH and quinone-H), 3.78 (bs, 4H, $ArCH_2Ar$), 3.60-3.63 (t, *J*= 7.4Hz, 4H, $ArOCH_2CH_2CH_3$), 3.26-3.30 (bd, 4H, $ArCH_2Ar$), 1.75-1.82 (m, 4H, $ArOCH_2CH_2CH_3$), 0.96-0.99 (t, *J*= 7.4Hz, 6H, $ArOCH_2CH_2CH_3$); ^{13}C-NMR ($CDCl_3$) δ 188.3, 186.0, 156.4, 148.0, 132.0, 129.9, 129.5, 123.3, 76.3, 31.6, 23.6, 10.6; FAB-MS *m/z*: 537 (M^++1). Anal. Calcd for $C_{34}H_{32}O_6$: C, 76.12; H, 5.97. Found: C, 75.94; H, 5.83.

25,27-Dibutoxy-26,28-calix[4]diquinone (9). The reaction mixture was stirred at room temperature for 72 hours, and an orange solid was collected from a sample of 2.68 g (5.00 mmol) of **3**. Chromatographic separation (eluent: EtOAc:*n*-hexane = 1:4) following by recrystallization from $CHCl_3$ and CH_3OH afforded 1.37 g (48.5%) of orange color crystals **9**: mp 76-78 °C; ^{1}H-NMR ($CDCl_3$) δ6.76 (bs, 4H, ArH), 6.57-6.61 (m, 6H, ArH and quinone-H), 3.79 (bs, 4H, $ArCH_2Ar$), 3.64-3.67 (t, *J*= 7.0Hz, 4H, $ArOCH_2CH_2CH_2CH_3$), 3.29-3.30 (bd, 4H, $ArCH_2Ar$), 1.72-1.77 (m, 4H, $ArOCH_2CH_2CH_2CH_3$), 1.38-1.45 (m, 4H, $ArOCH_2CH_2CH_2CH_3$), 0.92-0.95 (t, *J*= 7.4Hz, 6H, $ArOCH_2CH_2CH_2CH_3$); ^{13}C-NMR ($CDCl_3$) δ 188.2, 185.9, 156.6, 148.0, 132.0, 129.9, 129.5, 123.3, 74.6, 32.4, 31.7, 19.3, 13.9; FAB-MS *m/z*: 566 (M^++2). Anal. Calcd for $C_{36}H_{36}O_6$: C, 76.60; H, 6.38; for $C_{36}H_{36}O_6 \cdot 1/3H_2O$: C, 75.79; H, 6.32. Found: C, 75.72; H, 6.32.

25,27-Dibenzyloxy-26,28-calix[4]diquinone (10). The reaction mixture was stirred at room temperature for 96 hours, and a yellow solid was collected from a sample of 3.02 g (5.00 mmol) of **4**. Chromatographic separation (eluent: EtOAc:*n*-hexane = 1:4)

following by recrystallization from $CHCl_3$ and CH_3OH afforded 1.96 g (62%) of yellow crystals **10**: mp 234-235 ^oC; ^1H-NMR ($CDCl_3$) δ7.33-7.34 (m, 6H, Ar'H), 7.26-7.28 (m, 4H, Ar'H), 6.77 (bs, 4H, ArH), 6.62-6.65 (t, *J*= 7.5Hz, 2H, ArH), 6.44 (s, 4H, quinone-H), 4.77 (s, 4H, OCH_2Ar'), 3.63 (bd, 4H, $ArCH_2Ar$), 3.14 (bs, 4H, $ArCH_2Ar$); ^{13}C-NMR ($CDCl_3$) δ 188.1, 185.9, 155.8, 147.8, 136.6, 132.1, 130.2, 129.6, 128.6, 128.5, 128.3, 128.2, 123.6, 76.3, 31.7, 31.5; FAB-MS *m/z*: 634 (M^++2). Anal. Calcd for $C_{42}H_{32}O_6$: C, 79.75; H, 5.06; for $C_{42}H_{32}O_6 \cdot 1/2H_2O$: C, 78.63; H, 5.15. Found: C, 78.69; H, 4.81.

The yellow crude product can also be purified by recrystallized four times from $CHCl_3$ and CH_3OH to afford 1.35 g (42.5%) of the yellow powder **10**. The physical and the spectral properties of this yellow powder were identical to the product which was purified from the chromatographic method.

25,27-Diallyloxy-26,28-calix[4]diquinone (11). The reaction mixture was stirred at room temperature for 4 hours, and an orange solid was collected from a sample of 2.52 g (5.00 mmol) of **5**. Chromatographic separation (eluent: EtOAc:*n*-hexane = 1:4) following by recrystallization from $CHCl_3$ and CH_3OH afforded 1.82 g (67.5%) of orange color crystals **11**: mp 186-188 ^oC; ^1H-NMR ($CDCl_3$) δ6.82-6.83 (bd, 4H, ArH), 6.63-6.66 (t, *J*= 7.6Hz, 2H, ArH), 6.55 (s, 4H, quinone-H), 5.99-6.07 (m, 2H, $ArOCH_2CH=CH_2$), 5.30-5.34 (dd, *J*= 17.1, 1.3Hz, 2H, $ArOCH_2CH=CH_2$), 5.23-5.25 (dd, *J*= 10.4, 0.9Hz, 2H, $ArOCH_2CH=CH_2$), 4.22-4.23 (d, *J*= 5.5Hz, 4H, $ArOCH_2CH=CH_2$), 3.69 (bs, 4H, $ArCH_2Ar$), 3.33-3.34 (bd, 4H, $ArCH_2Ar$); ^{13}C-NMR ($CDCl_3$) δ 188.2, 186.1, 156.0, 147.6, 133.4, 132.2, 130.1, 130.0, 123.6, 118.0, 74.6, 32.2; FAB-MS *m/z*: 533 (M^++1). Anal. Calcd for $C_{34}H_{28}O_6$: C, 76.69; H, 5.26. Found: C, 76.62; H, 5.04.

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6. We thank Ms. S.-L. Huang of NSC Instrumental Center in Taipei for taking all the high field NMR measurements.

7. All reagents were obtained from Commercial Chemical Companies and used without further purification. Melting points were taken in capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) and are uncorrected. ^{1}H-NMR spectra are recorded on JOEL DMX-200 WB and/or Burker DMX-500 SB spectrometer and chemical shifts are reported as δ values in ppm. FAB-MS spectra were taken on a JOEL JMS-HX 102 spectrometer and elemental analyses were taken on a Perkin-Elmer 240C analyzer. Chromatographic separations were performed with Merck silica gel (230-400 mesh ASTM) on columns of 25 mm diameter filled to height of 150 mm. TLC analyses were carried out on Macherey-Nagel aluminum back silica gel 60 F_{254} plates (absorbant thickness 0.2 mm).

8. Aqueous chlorine dioxide solution was prepared by mixing equal volume of sodium chlorite solution ($NaClO_2 \cdot 2H_2O$, 31.60 g, 0.25 mol in 500 mL of deionized water) and

sodium persulfate solution ($Na_2S_2O_8$, 29.70 g, 0.25 mol in 500 mL of deionized water). The solution was then stored in a brown bottle at 0 ^oC prior being used.

9. All the new compounds, which were submitted to Elemental Analysis (EA), were dried at 120 ^oC under vacuum for 48 hours prior to the analysis. If the analysis value was different from the calculated value, the sample was dried at 140 ^oC under vacuum for 48 hours prior to another analysis. The drying period will be increase further, if the sample still received a different EA value from the theoretical value. The procedure was continued until a constant EA value was attained.