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Author: Wen-Jing Hu Ming-Liang Ma Yahu A. Liu Jiu-Sheng Li Biao Jiang Ke Wen

PII: S1001-8417(15)00208-9
DOI: http://dx.doi.org/doi:10.1016/j.cclet.2015.05.017
Reference: CCLET 3321

To appear in: *Chinese Chemical Letters*

Received date: 31-3-2015
Revised date: 17-4-2015
Accepted date: 20-4-2015

Please cite this article as: W.-J. Hu, M.-L. Ma, Y.A. Liu, J.-S. Li, B. Jiang, K. Wen, Synthesis and structures of malonate derivative-calix[4]arene conjugates, *Chinese Chemical Letters* (2015), http://dx.doi.org/10.1016/j.cclet.2015.05.017

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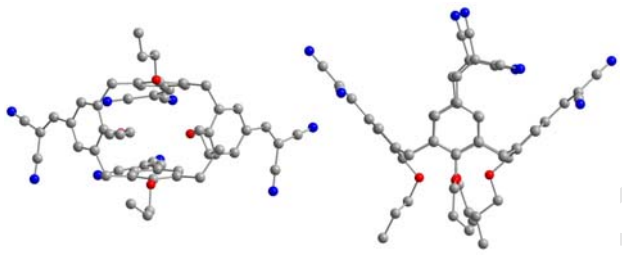
Graphical Abstract

Synthesis and structures of malonate derivative-calix[4]arene conjugates

Wen-Jing Hu [a], Ming-Liang Ma [b,*], Yahu A. Liu [c], Jiu-Sheng Li [a,*], Biao Jiang [a,*], Ke Wen [a,b,d*]

[a] *Shanghai Advanced Research Institute, Chinese Academy of Sciences, Shanghai 201210, China*
[b] *Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China*
[c] *Medicinal Chemistry, ChemBridge Research Laboratories Inc., San Diego, CA 92127, USA*
[d] *School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China*



A series of novel malonate derivatives-calix[4]arene conjugates were synthesized through Knoevenagel condensation reaction, and the structures of these functionalized calix[4]arenes have been determined.

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Original article

Synthesis and structures of malonate derivative-calix[4]arene conjugates

Wen-Jing Hu [a], Ming-Liang Ma [b,*], Yahu A. Liu [c], Jiu-Sheng Li [a], Biao Jiang [a], Ke Wen [a,b,d *]

[a] *Shanghai Advanced Research Institute, Chinese Academy of Sciences, Shanghai 201210, China*
[b] *Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China*
[c] *Medicinal Chemistry, ChemBridge Research Laboratories Inc., San Diego, CA 92127, USA*
[d] *School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China*

ARTICLE INFO

Article history:
Received 31 March 2015
Received in revised form 17 April 2015
Accepted 20 April 2015
Available online

Keywords:
Calix[4]arene
Malonate derivatives
Knoevenagel condensation reaction

ABSTRACT

A series of malonate derivatives-calix[4]arene conjugates were synthesized through Knoevenagel condensation reaction between formyl-tetrapropoxycalix[4]arene and malonate derivatives. The structures of the resulting malonate derivative functionalized calix[4]arenes were characterized by NMR spectroscopy, mass spectrometry and even single crystal X-ray diffraction analysis.

1. Introduction

Calix[n]arenes [1] are macrocyclic compounds with interesting conformational and cavity structures, and the easy functionalization of the rims (both upper and lower rims) of calix[n]arene skeletons makes them ideal candidates for many potential applications in supramolecular chemistry, such as host-guest chemistry [2], molecular encapsulation [3], and as scaffolds for the construction of multivalent ligands [4]. Calix[4]arene, the smallest member of the calix[n]arene family, can possess four different conformations and each of the four conformational structures can be geometrically locked. Thus, the spatial arrangement of the functional groups attached on the rims of calix[4]arenes could be controlled. The introduction of new functional groups into the calix[n]arene skeleton would certainly diversify its structural and functional properties and broaden its applications in the area of supramolecular chemistry.

Malonate is a naturally occurring substance possessing two carboxylate functions, and was used as a competitive inhibitor of the enzyme succinate dehydrogenase [5]. We envisioned that introduction of malonate derivatives to the calix[4]arene backbone would afford new calix[4]arene structures with malonate derivative-based interactive sites, and these malonate derivatives might be chemically transformed to variety of other functional groups, such as amino, amide, carboxyl and hydroxyl groups. These functional groups would broaden the application of calix[4]arene in the areas of molecular recognition and host-guest chemistry, or even find their practical use in biological and environmental fields [5,6]. However, research work toward these goals was almost absent in literature report [7]. Herein, we report the synthesis and structure characterization of six calix[4]arenes with their upper rims being functionalized by different number of malonate derivatives.

2. Experimental

Commercially available chemicals were used without further purification unless stated otherwise; compounds **1** and **2** were synthesized according to literatures [8-10]. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 500 spectrometer in $CDCl_3$ with TMS as the reference. Mass spectra were recorded on a microTOF QII mass spectrometer (Bruker Daltonics, Germany). Single crystal X-ray diffraction data were collected on a Bruker SMART APEX 2 X-ray diffractometer equipped with a normal focus Mo-target X-ray tube (λ = 0.71073 Å) and data reduction included absorption corrections by the multi-scan method. The structures were solved by direct methods and refined by full-matrix least-squares using SHELXS-97.

*2.1. Synthesis of symmetric substituted calix[4]arenes **3a-c***

*Corresponding authors.
E-mail addresses: wenk@sari.ac.cn (K. Wen), mlma@brain.ecnu.edu.cn (M.-L. Ma)

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To a round bottom flask containing a methanol solution (20 mL) of *tetra*-formyltetrapropoxycalix[4]arene **1** (70 mg, 0.1 mmol) and malononitrile (29 mg, 0.44 mmol) was added 0.05 mmol of piperidine and the mixture was heated to 50 °C. The formation of the product (**3a**) was monitored by TLC and the reaction was completed within 8 h. The crude mixture was concentrated under reduced pressure and the product was collected by a vacuum filtration. Alternatively, the product was purified *via* flash chromatography. Compounds **3b** and **3c** were synthesized in the similar procedure.

Compound **3a**: White solid (50 mg, yield: 55.7%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (s, 4H), 7.29 (s, 8H), 4.49 (d, 4H, J = 13.7 Hz), 3.97 (dd, 8H, J = 7.3, 7.6 Hz), 3.34 (d, 4H, J = 13.7 Hz), 1.94 (m, 8H), 1.04 (t, 12H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$,): δ 161.6, 158.8, 135.8, 131.7, 126.2, 113.6, 113.0, 80.6, 77.7, 30.7, 23.4, 10.2; HR-MS (ESI): *m/z* calcd. [M+Na$^+$] for $C_{56}H_{48}N_8O_4Na^+$: 919.3691; Found: 919.3674. Crystallographic data: [$C_{56}H_{48}N_8O_4$]; T = 173(2) K; M_r = 897.02; *Monoclinic*; space group *P2(1)/n*; a = 18.0374(6) Å; b = 14.0132(5) Å; c = 19.3730(7) Å; $a = \gamma$ = 90°; β = 90°; V = 4892.5(3) Å^3; Z = 4; ρ_{calcd} = 1.218 g/cm^3; crystal size = 0.34×0.27×0.20 mm; μ = 0.079 mm^{-1}; reflections collected 56035; unique reflections 8624; data/restraints/ parameters 8624/1/613; *GOF* on F^2 1.018; R_{int} for independent data 0.0429; final R_1 = 0.0584, wR_2 = 0.1443; R indices (all data) R_1 = 0.0824, wR_2 = 0.1636; largest diff. peak and hole: 0.705 and -0.556 e/Å^{-3}.

Compound **3b**: White solid (72 mg, yield: 62.0%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (s, 1H), 6.71 (s, 2H), 4.40 (d, 1H, J = 14.0 Hz), 3.85 (d, 2H, J = 8.0 Hz), 3.84 (s, 3H), 3.79 (s, 3H), 3.12 (d, 1H, J = 14.0 Hz), 1.86 (m, 2H), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 164.5, 159.1, 142.1, 135.2, 130.2, 126.9, 123.1, 52.6, 52.4, 31.0, 23.2, 10.2; HR-MS (ESI): *m/z* calcd. [M+Na$^+$] for $C_{64}H_{72}O_{20}Na^+$: 1183.4508; Found: 1183.4482.

Compound **3c**: White solid (70 mg, yield: 68.3%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (s, 4H), 7.36 (s, 8H), 4.47 (d, J = 13.8 Hz, 4H), 3.94 (dd, J_1 = 7.3 Hz, J_2 = 7.4 Hz, 8H), 3.87 (s, 12H), 3.32 (d, J = 13.6 Hz, 4H), 1.91 (m, 8H), 1.02 (t, J = 7.4 Hz, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 163.2, 160.8, 154.4, 135.6, 132.1, 126.5, 115.8, 100.4, 77.3, 53.0, 30.8, 23.4, 10.2; HR-MS (ESI): *m/z* calcd [M+H$^+$] for $C_{60}H_{61}N_4O_{12}$: 1029.4286; Found: 1029.4468.

2.2. Synthesis of asymmetric substituted calix[4]arene ***4a-c***

To a round bottom flask containing a methanol solution (20 mL) of *tri*-formyl-tetrapropoxycalix[4]arene **2** (810 mg, 1.2 mmol) and malononitrile (262 mg, 3.96 mmol) was added 0.4 mmol of piperidine and the mixture was heated to 50 °C. The formation of the product (**4a**) was monitored by TLC and the reaction was completed within 8 h. The crude mixture was concentrated under reduced pressure and the product was collected by a vacuum filtration. Alternatively, the product was purified *via* flash chromatography. Compounds **4b** and **4c** were obtained similarly.

Compound **4a**: White solid, yield: 60% (591 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 2H), 7.54 (d, 2H, J = 1.8 Hz), 7.47 (d, 2H, J = 1.7 Hz), 7.24 (s, 1H), 6.90 (s, 2H), 6.35 (m, 3H), 4.46 (dd, 4H, J = 13.9, 13.8 Hz), 4.10 (m, 2H), 3.99 (m, 2H), 3.87 (t, 2H, J = 7.1 Hz), 3.74 (t, 2H, J = 7.2 Hz), 3.29 (dd, 4H, J = 14.7, 14.4 Hz), 1.89 (m, 8H), 1.06 (m, 6H), 0.96 (t, 6H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9, 161.4, 159.1, 158.8, 155.7, 137.7, 136.6, 135.4, 133.0, 132.7, 131.4, 131.2, 128.2, 126.0, 125.8, 122.5, 114.0, 113.1, 112.8, 80.1, 79.7, 77.6, 77.4, 77.2, 30.9, 30.8, 23.4, 23.3, 10.5, 10.4, 10.0; HR-MS (ESI): *m/z* calcd. [M+Na$^+$] for $C_{52}H_{48}N_6O_4Na^+$: 843.3630; Found: 843.3692.

Compound **4b**: White solid, yield: 72.5% (887 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (s, 2H), 7.32 (s, 1H), 6.86 (s, 2H), 6.82 (s, 2H), 6.64 (dd, 1H, J = 8.3, 11.7 Hz), 6.50 (s, 2H), 6.37 (d, 2H, J = 7.0 Hz), 4.39 (d, 4H, J = 13.7 Hz), 3.85 (m, 8H), 3.79 (m, 18H), 3.11 (t, 4H, J = 14.5 Hz), 1.85 (m, 8H), 1.00 (m, 6H), 0.93 (t, 6H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 167.3, 164.9, 164.7, 159.8, 142.7, 142.6, 136.5, 135.6, 134.9, 133.8, 130.8, 130.3, 130.1, 128.1, 126.7, 126.6, 122.9, 122.5, 76.9, 76.8, 52.7, 52.6, 52.5, 52.4, 31.0, 23.3, 23.2, 10.4, 10.3, 10.1; HR-MS (ESI): *m/z* calcd. [M+Na$^+$] for $C_{58}H_{66}O_{16}Na^+$: 1041.4243; Found: 1041.4262.

Compound **4c**: White solid, yield: 68.3% (754 mg,). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.89 (s, 2H), 7.37 (s, 2H), 7.34 (s, 2H), 7.28 (s, 2H), 6.59 (d, 2H, J = 7.4 Hz), 6.52 (d, 1H, J = 7.7 Hz), 4.46 (dd, 4H, J = 13.8, 13.7 Hz), 3.92 (m, 14H), 3.83 (d, 3H, J = 7.6 Hz), 3.28 (dd, 4H, J = 13.8, 13.7 Hz), 1.91 (m, 8H), 1.01 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6, 163.4, 161.5, 161.0, 156.1, 155.1, 154.7, 136.7, 135.7, 134.0, 132.4, 132.2, 131.7, 128.6, 126.4, 126.0, 122.7, 115.9, 99.8, 77.2, 76.9, 53.2, 53.1, 30.9, 30.8, 23.4, 23.4, 10.3, 10.2; HR-MS (ESI): *m/z* calcd. [M+Cl$^-$] for $C_{55}H_{57}N_3O_{10}Cl^-$: 954.3727; Found: 954.3582.

3. Results and discussion

As shown in Scheme 1, tetra-formyltetrapropoxycalix[4]arene (**1**) and tri-formyltetrapropoxycalix[4]arene (**2**) were obtained according to literature procedures [8-10]. The malonate derivatives-calix[4]arene conjugates (**3a-3c** and **4a-4c**) were synthesized through Knoevenagel condensation reaction between formyl-tetrapropoxycalix[4]arenes (**1** and **2**) and malonate derivatives in the presence of piperidine in methanol at 50 °C in 8h (Scheme 2). Symmetrically substituted calix[4]arenes **3a-3c** were obtained in the yields of 55.7%, 62% and 68.3%, respectively. While asymmetrically substituted calix[4]arenes **4a-4c** were obtained in the yields of 60%, 72.5% and 68.3%, respectively.

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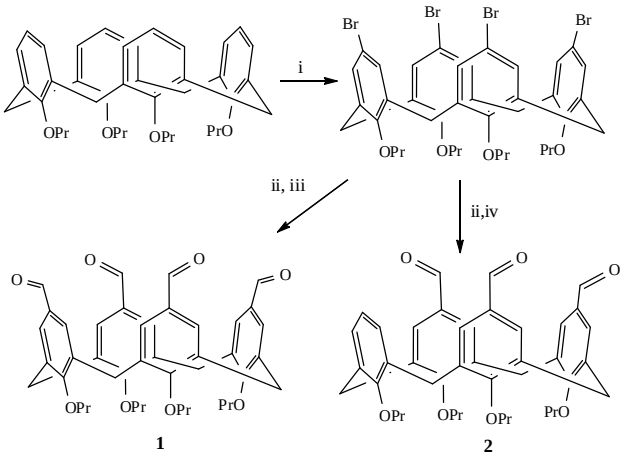
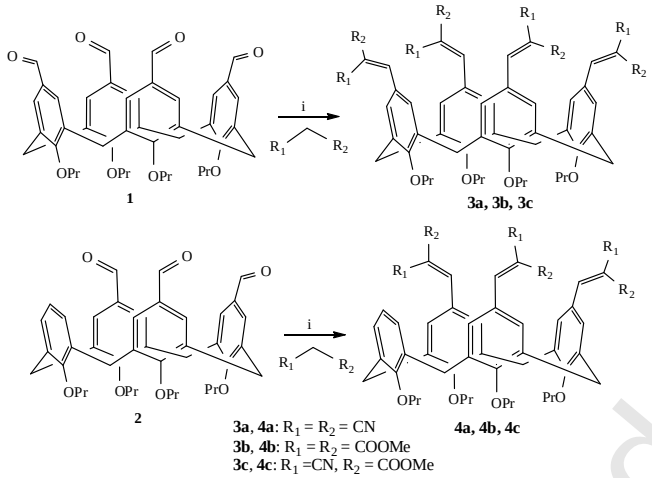


Scheme 1. Synthesis of compound **1** and **2.** Conditions: (i) NBS, acetone, r.t.; (ii) *n*-BuLi, THF, -78 °C; (iii) excessive dry DMF, HCl; (iv) 3eq. dry DMF, HCl.



Scheme 2. Synthesis of symmetric and asymmetric substituted calix[4]arene **3a-3c** and **4a-4c**. Conditions: (i) piperidine, methanol, 50 °C.

The ^{1}H NMR, ^{13}C NMR and mass spectra of **3a-3c** and **4a-4c** are consistent with the assigned structures. In the ^{1}H NMR spectrum of symmetric **3a**, aromatic hydrogens display two singlets at 7.48 and 7.29 ppm, and the bridging methylene protons split into doublets at 4.49 and 3.34 ppm. While the ^{1}H NMR spectrum of asymmetric **4a** is more complex than that of the symmetric **3a**, the aromatic hydrogens of asymmetric **4a** exhibit several singlets, doublets and even multiplets, and the resonance of its bridging methylene protons shows two triplets, as shown in Fig. 1. Similar phenomenon in the ^{1}H NMR spectra of **3b-3c**, as well as **4b-4c** was observed (see Supporting information).

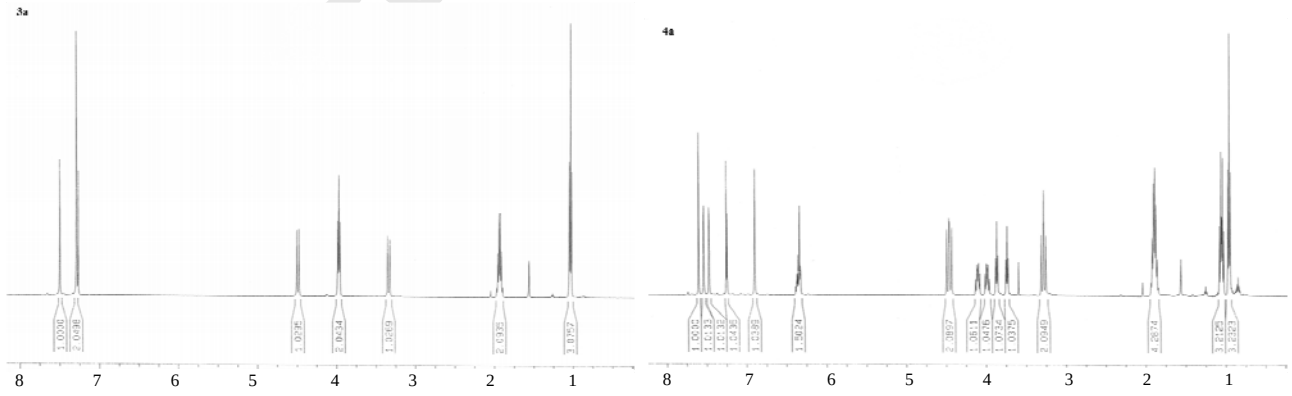


Fig. 1. ^{1}H NMR of compound **3a** and **4a**.

The structure of **3a** was unambiguously established by single crystal X-ray diffraction analysis. Single crystals of **3a** have been obtained in mixed solvent of ethyl acetate and petroleum ether. As shown in Fig. 2, calix[4]arene **3a** adopts a typical, pinched cone conformation with dihedral angles between the opposing phenoxy rings of 16.4 ° and 86.6 °, respectively, and the centroid-to-centroid distances between the two pairs of opposing phenyl planes are 4.876 Å and 7.555 Å, respectively. The cyano groups in each malononitrile function are conjugated to the connected benzene ring and only slightly twisted away from the phenyl planes. The

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distances between the central carbon atoms of the two pairs of face-to face oriented malononitrile functions are 3.858 Å and 12.911 Å, respectively. No guest molecule was found being included in the narrow void space.

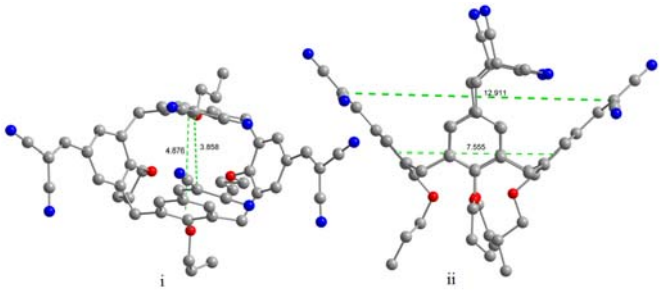

Fig. 2. X-ray crystal structures of **3a**: top view (i), side view (ii). Color code: N (blue), O (red), C (gray).

4. Conclusion

In summary, series of malonate derivatives functionalized calix[4]arenes were synthesized by Knoevenagel condensation of formyl-tetrapropoxycalix[4]arene with corresponding malonate derivatives (malononitrile, methyl 2-cyanoacetate and dimethyl malonate) in good yields. Single crystal X-ray study of malononitrile derived calix[4]arene revealed a pinched cone conformational structure. No guest molecules were found to be included in its narrow cavity. The cyano and ester groups in these calix[4]arene structures might be further transformed to other functional groups, such as amino, amide, carboxyl and hydroxyl groups, which could diversify the structures and functions of the calix[4]arene analogous for potential use in molecular recognition and other related research fields. Research works in these directions are ongoing in our laboratory.

Acknowledgment

Financial support from the National Natural Science Foundation of China (No. 21371177) is acknowledged.

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