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Crystal structure, optical properties and biological imaging of two curcumin derivatives

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ABSTRACT

Two new curcumin derivatives, 1,7-bis(4-ethyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione and 1,7-bis(4-butyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione, are conveniently synthesized. Single and two-photon fluorescence of two compounds have been investigated. The two-photon absorption cross-sections (σ) of the two compounds were calculated by quantum chemical method, which are as high as 386 and 418 $\times$ 10^{-50} cm^4 s $photon^{-1}$ in dimethyl formamide (DMF), as well as up to 475 and 563 $\times$ 10^{-50} cm^4 s $photon^{-1}$ in dichloromethane, respectively. Furthermore, cellular imaging results demonstrate that the as-prepared compounds have high photostability, strong fluorescence in the red region and are nontoxic up to 40 μmol/L, which are suitable for long-term and high-specificity immunofluorescent cellular labeling.

1. Introduction

Organic molecules with large two-photon absorption (TPA) cross-section (σ) have come to occupy a particularly practical position due to their applications in photodynamic cancer therapy [1,2], lighting devices [3,4], microscopy [5,6], luminescent probes for bio-analyses and live cell imaging and sensing [7–9]. Various design strategies have been put forward to synthesize organic molecules with large TPA cross-section, such as donor-π-bridge-donor(D-π-D)-type molecules, donor-π-bridge-acceptor(D-π-A)-type molecules, donor–acceptor–donor(D–A–D)-type molecules, polymers, multibranched molecules and metal complexes. Moreover, their structure–property relationships were also studied [10–13]. These investigated results demonstrate that D/A strength, π-conjugation length, and molecular symmetry are important factors responsible for the increasement of TPA cross-section.

For cell bioimagery application, it is necessary that TPA materials must be low toxic, long-term stable and remain highly fluorescent in strongly polar solvents. Most of TPA materials, however, are unstable, hydrophobic and their fluorescence quenches in polar solvents. Therefore, molecular designs of TPA materials possessing stable and strong fluorescence in polar solvents bring us a serious challenge in real biosystem research.

Curcumin is a natural pigment with low toxicity and good stability obtained from the rhizomes of turmeric (Curcuma longa Linn.), and it is a common ingredient used in spices, cosmetics, and traditional chinese medicines in Asian countries [14,15]. In addition, curcumin exhibits good optical and electrical properties owing to a highly π-electron delocalized system and symmetric structure [16–19]. Considering the above-mentioned factors and design strategies, in this article, we connect two types of electron-donating end groups, ethyl and butyl, to the 4,4′-positions of curcumin respectively, and then obtain two new donor-π-bridge-donor(D-π-D)-type curcumin derivatives **A** and **B** (Fig.1). It was expected to improve the fluorescence properties and increase TPA cross-section by means of such D-π-D-type molecular structures.

2. Experimental

2.1. General

Fourier transform infrared (FT-IR) spectra were recorded on SHIMADZU IR Prestige-21 spectrophotometer with samples prepared as KBr pellets. ^{1}H NMR spectra were recorded with Bruker AV400 NMR spectrometer. The mass spectra were obtained on FINNIGAN LCQ Advantage MAX LC/MS (Thermo Finnigan,

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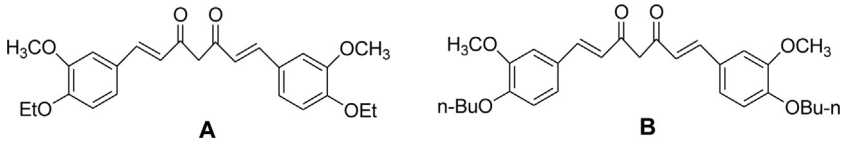

Fig. 1. The molecular structure of the curcumin derivatives **A** and **B**.

American). Elemental analyses were performed on Perkin–Elmer 240C analyzer. X-ray power diffraction (XRD) measurements were performed on Japan Rigaku DMax-γA rotation anode X-ray diffractometer equipped with graphite monochromatize Cu KR radiation ($\lambda = 0.71073$ Å) (shown in Table 1). Unit cell dimensions were obtained with least-square refinements, and all structures were solved by the direct method as SHELXL-97 [20]. The final refinement was performed by full-matrix least-square methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. Ultraviolet–visible (UV–vis) absorption spectra were obtained through SHIMADZU UV-3600 UV–vis–NIR spectrophotometer. Single-photon excited fluorescence (SPEF) spectra were recorded on PerkinElmer LS55 fluorescence spectrometer equipped with a 450 W Xe lamp. The two-photon emission fluorescence (TPEF) spectra were measured using a mode-locked Ti: sapphire laser(-Coherent Mira 900F) as pump source with a pulse width of 200 fs, a repetition rate of 76 MHz, and a single-scan streak camera (Hamamatsu, model: C5680-01) together with a monochrometer as the recorder. A Zeiss LSM510 two-photon microscope equipped with a 63× or 100× oil-immersion objective was used to obtain bright field transmission and two-photon images. The excitation light was provided by a mode-locked Ti: sapphire laser (Mai Tai, Spectra-Physics Inc., USA) tuned to 800 nm, and a broadband pass filter (450–600 nm) was used as emission filter. The microscope stage was outfitted with CTI-3700 incubator, which maintained samples at 37 °C and 5% CO_2.

2.2. Preparation

The curcumin derivative **A** was prepared as follows: dimethylfomamide (20 mL) and curcumin (1.0 g, 2.7 mmol) were placed into a 50 mL flask. After the curcumin was completely dissolved, anhydrous potassium carbonate (1.2 g, 0.87 mmol) was added. The mixture was stirred at 40 °C, and then bromoethane (2 mL) was slowly added dropwise to the above solution. Then the reaction mixture was stirred for 5 h at 80 °C. After completion of the reaction (monitored by TLC), the mixture was dispersed and stirred in cold water (50 mL). The yellow solid was obtained by filtration. The product was purified by chromatography on a silica gel column with ethyl acetate/petroleum ether mixture (v/v: 2/3) as the eluent, then light yellow microcrystals were obtained, yield 54.4%. MS, *m*/*z* (%): 424.47 (M^+, 100). Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65; found: C, 70.58; H, 6.76.

The preparation of curcumin derivative **B**: curcumin (1.1 g, 3 mmol) was dissolved in methanol (30 mL), and anhydrous potassium carbonate (0.88 g, 6.4 mmol) and redistilled bromobutane (1.04 g, 6.2 mmol) were added into it. The reaction solution was refluxed for 4 h under vigorous stirring. After the mixture was cooled to room temperature, the reaction solution was added to 10 mL of water. The yellow solid was obtained by filtration. The product was purified by chromatography on a silica gel column with ethyl acetate/petroleum ether mixture (v/v: 1/3) as the eluent and then the target compound was obtained, yield: 47.2%. MS, *m*/*z* (%): 480.58 (M^+, 100). Anal. Calcd for $C_{29}H_{36}O_6$: C, 72.47; H, 7.55; found: C, 72.63; H, 7.74.

3. Results and discussion

3.1. Structural features

The single crystals of **A** and **B**, suitable for the X-ray analysis, were obtained by slow evaporation of ethyl acetate at room temperature several days later. The structures of **A** and **B** are shown in Fig. 2, which revealed that the molecular structures of **A** and **B** are similar and also symmetric to our satisfaction. Selected bond lengths (Å) and bond angles (°) listed in Table 2. For example, in the molecular structure of **A**, the least-square plane calculation shows that the dihedral angle between the two benzene rings is 8.2, indicating that they are nearly coplanar. The sum of the three C–C–C bond angles is 359.9°, which take carbon atom (C5) as center (C6–C5–C7, 118.7(3)°; C6–C5–C4, 118.5(3)°; C4–C5–C7, 122.7(3)°). This result demonstrates that the carbon atom (C7) is practically coplanar with the benzene ring. In addition, the bond lengths of C5–C7 (1.47.1(4)) and C8–C9 (1.455(7)) are longer than that of C7–C8 (1.320(4)) and O3–C9 (1.304(4)), or the bond lengths of C14–C13 (1.457(4)) and C12–C11 (1.449(4)) are longer than that of C12–C13 (1.338(4)) and O4–C11 (1.301(3)), which confirm the formation of π-conjugated system with the adjacent phenyl ring. It can be seen from Table 2 that all the bond lengths of C–C are located between the normal C=C double bond (1.32 Å) and C–C single bond (1.53 Å), which demonstrates that it is a π-electron highly delocalized system for the compound molecule **A**. That is necessary condition for the compound to bear a large TPA cross-section *σ* [21,22]. Furthermore, it can also be seen from Fig. 2 that the compound **A** exists in the enol form in solid state.

Table 1
Crystal data collection and structure refinement.

Compound	A	B
Formula	$C_{25}H_{28}O_6$	$C_{29}H_{36}O_6$
Formula weight	424.47	480.58
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)/n	P2(1)/c
Temperature/K	298(2)	298(2)
Radiation/Å (MoKa)	0.71069	0.71069
Absorption coefficient (mm^{-1})	0.086	0.083
a (Å)	22.689(5)	25.387(5)
b (Å)	4.913(5)	4.999(5)
c (Å)	23.224(5)	22.849(5)
β (°)	115.744(5)	114.022(5)
V/Å	2332(2)	2649(3)
Z	4	4
D (calc)/g cm^{-3}	1.209	1.205
F (000)	904	1032
θ (°)	1.05–25	0.88–25
Reflections/unique	15081/4099	17721/4637
R(int)	0.0461	0.0253
Data/restraints/parameters	40996/0/285	4637/0/321
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0503, wR2 = 0.1368	R1 = 0.0611, wR2 = 0.1701
Gof on F^2	1.001	1.028