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Bioinspired synthesis of pentalene-based chromophores from an oligoketone chain

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We report a bioinspired synthesis of 2,5-dihydropentalene-based chromophores from an aliphatic oligoketone bearing 1,3- and 1,4-diketone subunits. Unlike the natural polyketone sequence, fused five-membered rings were formed via an intramolecular aldol condensation. A subsequent Knoevenagel condensation reaction with malononitrile furnished a multiply cross-conjugated π-system with low-lying LUMO levels. Furthermore, pentalenes obtained from a non-conjugated aliphatic chain exhibited visible absorption and solid-state fluorescence.

The formation of polycyclic, π-conjugated compounds from polycarbonylated carbon chains is an important pathway in the polyketide synthesis.[1] This chemical transformation is of synthetic interest because π-conjugated carbon skeletons are prepared from aliphatic chains. A key step in this biological synthesis is an intramolecular aldol-type cyclization of polyketone chains, generated by condensation reactions between acetyl coenzyme A (CoA) and malonyl CoA.[2] As these polyketone precursors have repeating 1,3-diketone units, six-membered rings are preferentially generated and subsequently converted to benzene or benzoquinone-type π-conjugated systems via dehydration. Notably, the carbon frameworks of the final products were governed by the arrangement of carbonyl groups in the precursor chains.

We have recently synthesized bio-inspired polyketone chains bearing alternating 1,3- and 1,4-diketone subunits from 3,3-dimethylpentane-2,4-dione as the monomer.[3] In this sequence, six-membered ring formation is efficiently suppressed because no carbonyl groups are located at the 6-position relative to the α-carbons (Fig. 1). From polyketide synthesis in nature, we became interested in polycyclic, π-conjugated systems that can be generated from this new ketone sequence through polyketide-like intramolecular aldol condensation reactions. Herein, we report the formation of fused five-membered rings, 2,5-dihydropentalene-1,4-dione[4], from ketone chain **1** bearing alternating 1,3- and 1,4-diketone sequence. Despite the presence of quaternary carbons (dimethylmethylene units) in the precursor chain, a π-conjugated bicyclic system with six sp^2-hybridized carbon atoms was formed. A subsequent Knoevenagel condensation reaction with malononitrile resulted in the formation of multiply cross-conjugated, pentalene analogues with intramolecular charge-transfer bands and solid-state fluorescence emission in the visible region.

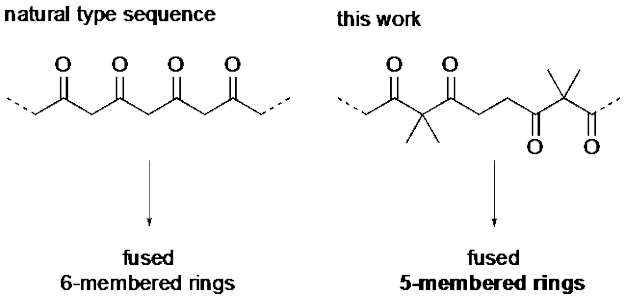

Fig. 1 Comparison of the natural ketone sequence with that reported in this work.

Aliphatic tetraketone **1** used in this work was synthesized from the oxidative homo-coupling reaction of the enol silyl ether of an acetylacetone derivative.[3] To examine the intramolecular cyclization of tetraketone **1**, we first conducted base-catalyzed aldol reaction conditions. When **1** was treated with potassium *t*-butoxide, a complex reaction mixture was obtained, presumably due to nonregioselective, intramolecular and intermolecular aldol reactions. Similar results were observed using other bases, such as sodium methoxide. In contrast, acid-catalyzed condensation reactions resulted in Paal-Knorr-type furan ring formation at the 1,4-diketone subunit, as previously reported.[3] Therefore, we further examined

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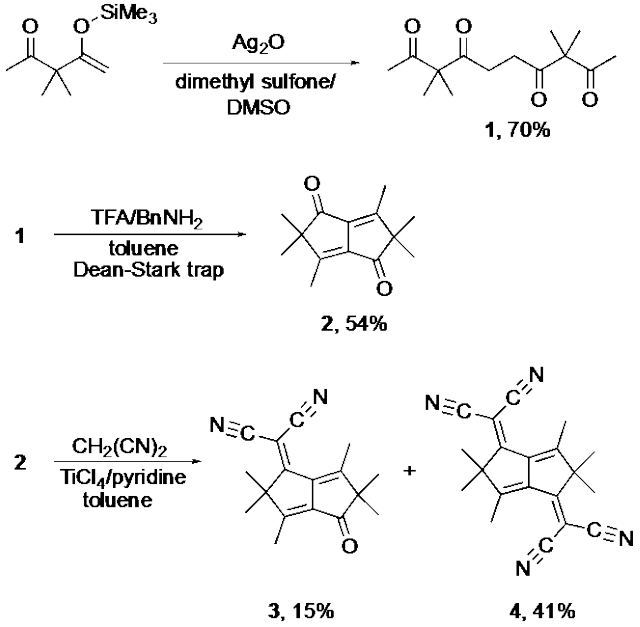
intramolecular cyclization using enamine-catalyzed mild pH conditions.



Scheme 1 Synthesis of pentalene-based electron acceptors.

When tetraketone **1** was refluxed under the weakly acidic conditions in the presence of benzylamine (1.0 equiv.) and trifluoroacetic acid (TFA, 1.2 equiv.), furan ring formation was almost completely suppressed, and doubly dehydrated product **2** was obtained as a colorless solid in 54% yield (Scheme 1). In the ^{1}H NMR spectrum, product **2** exhibited only two singlets at 2.08 and 1.19 ppm, which were assigned to methyl protons. The ^{13}C NMR spectrum also indicated the symmetric structure of **2**, showing two signals for sp^2-hybridized carbons at 149.6 and 137.5 ppm, and a carbonyl signal at 205.7 ppm.

Single crystal X-ray analysis showed that main product **2** contained a fused five-membered ring 3,3-dimethylpentane-2,4-dione skeleton with C_{2h} molecular symmetry (Fig. 2a). The pentalene skeleton was completely planar, and obvious bond length alternations were found in the dihydropentalene skeleton (see ESI). The structure of product **2** implied that intramolecular cyclization occurred twice, namely at the 2,6-positions and the 5,9-positions of tetraketone **1**. As no or trace product **2** was obtained when triethylamine or pyrrolidine were employed as base, pentalene **2** was considered to be produced via enamine intermediates formed at the internal carbonyl groups. The formation of pentalene skeleton **2** from **1** was reminiscent of naphthalene ring formation from polyketone chains bearing repeating 1,3-diketone units.[1] Critical differences in the final ring systems can be attributed to modulation of the sequence of carbonyl groups on the precursor chains.

Pentalene **2** has a unique cross-conjugated π-system[5] in which s-*cis* enone and s-*trans* diene conformations are both fixed by the bicyclic skeleton. To investigate this π-system as a chromophore, we expanded the conjugation of **2** at the remaining carbonyl groups through Knoevenagel condensation (Scheme 1). By heating a mixture of compound **2**, malononitrile, $TiCl_4$, and pyridine in toluene at 80 °C for 1 d,[6] mono- and bis-dicyanomethylene-substituted products **3** and **4** were formed as yellow solids in 15% and 41% yields, respectively. The Lewis acid ($TiCl_4$) was necessary to obtain bis-substituted **4** as the major product, while using a AcOH/$AcONH_4$ mixture[7] instead of $TiCl_4$/pyridine gave **3** as the major product in 28% yield along with **4** in 13% yield.

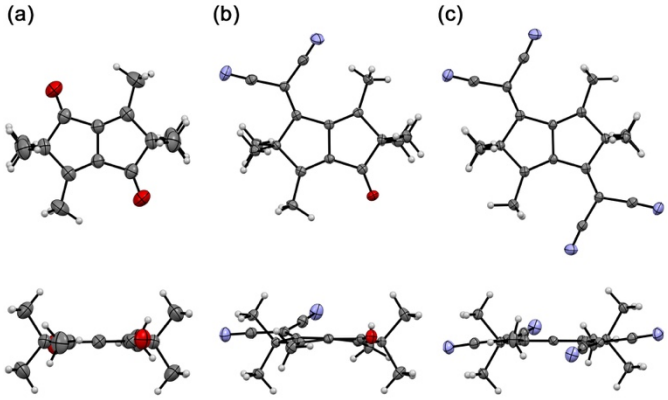


Fig. 2 X-ray crystal structures of pentalene analogues (a) **2**, (b) **3**, and (c) **4** (top: top view; bottom: side view). Thermal ellipsoids are drawn at the 50% probability level.

X-ray diffraction analysis confirmed that dicyanomethylene-substituted pentalene analogues **3** and **4** still had planar π-conjugated skeletons (Figs. 2b and 2c). The root-mean-square-deviations for all the sp^2-hybridized atoms in **3** and **4** were 0.207 Å and 0.122 Å, respectively. Although bond length alternation was also observed in **3** and **4** containing dicyanomethylene subunits, differences between the lengths of single and double bonds decreased with substitution (see ESI). Furthermore, the length of the central C7–C8 bond in the dihydropentalene core increased from 1.447(2) Å in **2** to 1.460(3) and 1.472(3) Å in **3** and **4**, respectively, upon substitution. These observations indicated the significant impacts of dicyanomethylene substituents on the π-electronic system of the pentalene cores.

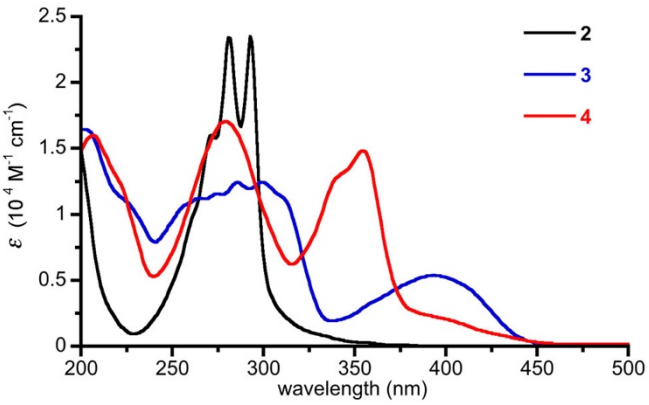


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Fig. 3 UV-Vis absorption spectra of pentalene analogues **2**-**4** in acetonitrile.

UV-Vis absorption spectra of compounds **2**–**4** in acetonitrile clearly showed the impact of dicyanomethylene subunits on the π-electronic system (Fig. 3). 2,5-Dihydropentalene-1,4-dione **2** exhibited intense absorption bands at 293 and 283 nm and some vibronic bands, reflecting the rigid structure. Mono-dicyanomethylene-substituted **3** showed dramatically different absorption bands, with a bathochromically shifted broad band at 394 nm and ill-defined bands at 250–320 nm. Symmetrically substituted **4** showed a split absorption band at 355 and 280 nm. The absorption edges of compounds **3** and **4** were both red shifted to the visible region (~450 nm) compared with that of **2** (~350 nm), indicating the effects of the elongation on π-conjugation.

Cyclic voltammetry (CV) showed the stabilization of LUMO levels of pentalene analogues upon substitution with dicyanomethylene groups (see ESI). The first reduction of dihydropentalenedione **2** was recorded at –2.35 V (vs ferrocene/ferrocenium ion) as a reversible wave in acetonitrile. Similar reduction waves were observed for **3** and **4** at –1.50 and –1.46 V, respectively. The positive shift in the first reduction potentials showed the electron-deficient nature of the dicyanomethylene groups attached to the π-conjugated system. Only compound **4** exhibited the second reduction, at –1.75 V, which was slightly negative shifted compared to those of the first reduction of compounds **3** and **4**. This suggested that the electrochemical reduction of **4** occurred mainly on the dicyanomethylene subunits that interact each other through the cross-conjugated system.

To understand the absorption spectra and CV results of **2**–**4**, DFT calculations were performed at the B3LYP/6-31G(d) level (Fig. 4). The energy diagram of the frontier orbitals clearly showed that the LUMO level was effectively stabilized upon substitution with dicyanomethylene groups, while the HOMO levels were virtually intact. As predicted by the CV results, LUMOs of **3** and **4** were governed by the dicyanomethylene moieties. In compound **4**, the LUMO and LUMO+1 were almost degenerated, which agreed well with the observation of the second electrochemical reduction occurring at a potential close to that of the first reduction.

The theoretical HOMO–LUMO gaps for **2**–**4** were calculated to be 4.31, 3.45, and 3.28 eV, respectively, which matched well with the absorption edges observed in their UV-Vis absorption spectra. Time-dependent density functional theory (TD-DFT) calculations indicated that the absorption band observed at 293 nm was attributed to the HOMO–LUMO transition, which had a strong $\pi \rightarrow \pi^*$ transition character from the s-*trans* diene subunit in the pentalene skeleton. The broad absorption band at 394 nm of compound **3** was also assigned to the HOMO–LUMO transition, while the weak low-energy transition of **4** at around 400–450 nm was attributed to the transition from the HOMO to the degenerated LUMO+1. Although large orbital coefficients were observed for HOMOs on the diene of **3** and **4**, the LUMO of **3**, and the LUMO and LUMO+1 of **4** were dominated by the dicyanomethylene subunits. Therefore, weak and broad absorption bands observed in the 380–450 nm region for **3** and **4** were regarded as intramolecular charge-transfer bands.[8]

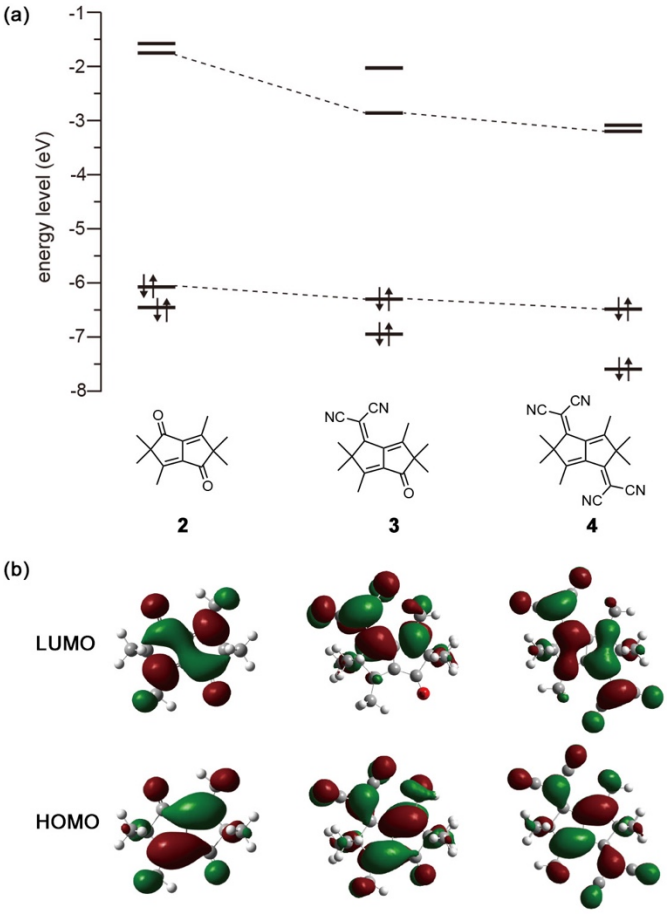

Fig. 4 (a) Energy levels and (b) orbital density diagrams of frontier orbitals of pentalene analogues **2**–**4** calculated at the B3LYP/6-31G(d) level.

Chromophores **3** and **4** were virtually nonfluorescent in solution, but emitted blue and green fluorescence upon irradiation with UV light in the solid state (Fig. 5). The solid-state fluorescence spectrum of **3** showed a broad emission at 472 nm as a mirror image of the lowest energy absorption band. The absolute fluorescence quantum yield of **3** was determined to be 0.044. Compound **4** exhibited a red-shifted emission at 534 nm with a quantum yield of 0.077, reflecting its expanded π-conjugation. Similar fluorescence emissions were also observed for **3** and **4** in frozen dichloromethane solution (ESI). As the rotation of C=C double bonds in the excited state is known as a major fluorescence quenching path for similar dicyanomethylene substituted π-conjugated compounds[9], these results indicated that such bond rotation in the excited state is effectively inhibited in the solid state. In fact, the crystal structures of **3** and **4** showed tight packing of the chromophores. Furthermore, bulky dimethylmethylene groups in **3** and **4** played an important role in blocking π–π interactions in the crystalline state, which is also a possible pathway for quenching fluorescence emission.[10]

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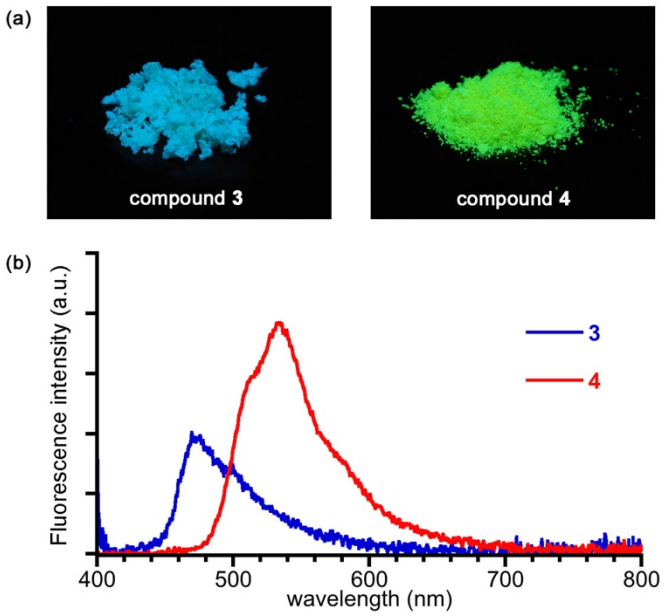

Fig. 5 (a) Photographs of solid compounds **3** and **4** under UV irradiation (365 nm) and (b) solid-state fluorescence spectra for **3** and **4** (excitation wavelengths: 395 and 355 nm, respectively).

In summary, we have synthesized 2,5-dihydropentalene-based, cross-conjugated chromophores from oligoketone chain **2** which was designed from polyketone precursors in polyketide synthesis. Unlike the natural ketone sequence, which often gives six-membered rings, the alternating 1,3- and 1,4-diketone chain furnished a fused five-membered ring system. Dicyanomethylene-substituted pentalene analogues **3** and **4** showed bathochromically shifted absorption bands, low-lying LUMOs, and solid-state visible-light emission derived from their unique π-conjugation. Notably, these chromophores were synthesized from a nonconjugated, aliphatic ketone chain containing two quaternary carbons (dimethylmethylene units) using only dehydrative condensation reactions. As longer oligoketone chains with the same 1,3- and 1,4-diketone sequence can also be synthesized using recently developed synthetic protocols[3], more elaborate, large π-conjugated systems could be generated using the current strategy.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

§ Crystallographic data for compound **2**: $C_{14}H_{18}O_2$, M = 218.28, crystal size: 0.25 × 0.16 × 0.11 mm^3, monoclinic, space group $P2_1/c$, a = 8.8275(7) Å, b = 6.0025(5) Å, c = 12.1333(9) Å, β = 103.211(7)°, V = 625.89(9) Å^3, Z = 4, T = 123(2) K, μ = 0.076 mm^{-1}, D_{calc} = 1.158 g/cm^3, 2.370° ≤ θ ≤ 27.477°, 1133 unique reflections out of 1432 with $I > 2\sigma(I)$, GOF = 1.068, R_1 = 0.0519 and wR_2 = 0.1387 for all data, CCDC 1829371.
§§ Crystallographic data for compound **3**: $C_{17}H_{18}N_2O$, M = 265.13, crystal size: 0.29 × 0.18 × 0.09 mm^3, orthorhombic, space group $Pna2_1$, a = 12.1379(9) Å, b = 7.1688(5) Å, c = 16.6494 (10) Å, V = 1448.73(17) Å^3, Z = 4, T = 123(2) K, μ = 0.077 mm^{-1}, D_{calc} = 1.221 g/cm^3, 2.447° ≤ θ ≤ 27.449°, 2949 unique reflections out of 3297 with I > 2σ (I), GOF = 1.035, R_1 = 0.0335 and wR_2 = 0.0776 for all data, CCDC 1829372.
† Crystallographic data for compound **4**: $C_{20}H_{18}N_4$, M = 313.15, crystal size: 0.17 × 0.16 × 0.06 mm^3, monoclinic, space group $P2_1/n$, a = 9.8253(8) Å, b = 6.7180 (5) Å, c = 13.1473 (12) Å, β = 110.128 (8)°, V = 814.81(12) Å^3, Z = 4, T = 123(2) K, μ = 0.078 mm^{-1}, D_{calc} = 1.281 g/cm^3, 2.256 ° ≤ θ ≤ 27.457°, 1411 unique reflections out of 1859 with $I > 2\sigma(I)$, GOF = 1.024, R_1 = 0.0478 and wR_2 = 0.1202 for all data, CCDC 1829373.

1 C. Hertweck, *Angew. Chem. Int. Ed.*, 2009, **48**, 4688-4716.
2 J. Staunton and K. J. Weissman, *Nat. Prod. Rep.*, 2001, **18**, 380-416.
3 M. Uesaka, Y. Saito, S. Yoshioka, Y. Domoto, M. Fujita and Y. Inokuma, *Communications Chemistry* in press (DOI: 10.1038/s42004-018-0021-3).
4 For reviews of pentalene system: (a) O. T. Summerscales and F. G. N. Cloke, *Coord. Chem. Rev.*, 2006, **250**, 1122-1140; (b) F. G. N. Cloke, J. C. Green, A. F.R. Kilpatrick and D. O'Hare, *Coord. Chem. Rev.*, 2017, **344**, 238-262.
5 (a) N. F. Phelan, *J. Chem. Educ.*, 1968, **45**, 633-637; (b) A. J. Zucchero, P. L. Mcgrier and U. H. F. Bunz, *Acc. Chem. Res.*, 2010, **43**, 397-408; (c) M. Gholami and R. R. Tykwinski, *Chem. Rev.*, 2006, **106**, 4997-5027.
6 F. Bureš, W. B. Schweizer, C. Boudon, J.-P. Gisselbrecht, M. Gross and F. Diederich, *Eur. J. Org. Chem.*, 2008, **6**, 994-1004.
7 A. R. Longstreet, D. Rivalti and D. T. McQuade, *J. Org. Chem.*, 2015, **80**, 8583-8596.
8 (a) S. Yoshida, M. Fujii, Y. Aso, T. Otsubo and F. Ogura, *J. Org. Chem.*, 1994, **59**, 3077-3081; (b) A. J. Moore, A. Chesney, M. R. Bryce, A. S. Batsanov, J. F. Kelly, J. A. K. Howard, I. F. Perepichka, D. F. Perepichka, G. Meshulam, G. Berkovic, Z. Kotler, R. Mazor and V. Khodorkovsky, *Eur. J. Org. Chem.*, 2001, **14**, 2671-2687.
9 (a) M. S. A. Abdel-Mottaleb, R. O. Loutfy and R. Lapouyade, *J. Photochem. Photobiol. A: Chem.*, 1989, **48**, 87-93; (b) T. Suhina, S. Amirjalayer, B. Mennucci, S. Woutersen, M. Hilbers, D. Bonn and A. M. Brouwer, *J. Phys. Chem. Lett.*, 2016, **7**, 4285-4290; (c) A.-Y. Jee, E. Bae and M. Lee, *J. Phys. Chem. B*, 2009, **113**, 16508-16512.
10 D. Zhao and T. M. Swager, *Macromolecules*, 2005, **38**, 9377-9384.

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