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Bis-pyrene carbocations for chromogenic and fluorogenic dual-detection of fluoride anion in situ

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ABSTRACT

We have designed and synthesized a new carbocation precursor (carbinol) based on bis-pyrene derivative. The carbinol can be transformed to stable carbocations with quenched fluorescence and long wavelength absorption. The stable carbocations can be further used as fluoride anion detection in acidic environment, which show both chromogenic and fluorogenic responses in the presence of fluoride anion. UV–vis and fluorescence spectroscopy were utilized to monitor the changes during detection process. The responsive mechanism was studied by quantum chemical calculations and the results indicate that the carbocation mediated formation of C–F covalent bond leads to this dual responsive phenomenon. The bis-pyrene carbocations and corresponding F adduct was confirmed MALDI-TOF mass spectrum. The successful elucidation of this new mechanism opens a new avenue for carbocation-based sensor or biological labeling in the future.

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1. Introduction

Fluoride anion (F^-) detection has attracted growing attentions because of its pivotal importance in the fields of environmental science and food industry.[1] Appropriate amount of fluoride is often added to drinking water and toothpaste for its beneficial effects in dental and skeletal health.[2] However, chronic exposure to high levels of the fluoride leads to organ disorders, dental or even skeletal fluorosis.[3] To solve this problem, various receptor molecules responded to F^- have been reported.[2e,g,4–6] Different from other anions, fluoride anion shows small anionic diameter and strong electronegativity, and it still remains challenge for design and synthesis of the selective receptor for F^-.[1]

Over the past decades, extensive efforts have been devoted to develop new methods for selective detection of fluoride anions.[2e,g,4–6] Accordingly, various optically responsive molecules for fluoride have been explored mainly based on three molecular mechanisms, i.e., (i) hydrogen bonding formation between fluoride and NH hydrogen (amide, pyrrole, indole, urea, and thiourea).[2e,4] An optical-responsive chromophore covalently conjugate to a skeleton containing H-bond donor sites, and the resulting receptor can selectively bind with fluoride to give H···F^- type complex; (ii) fluoroborate complexation mechanism. For example, due to the intrinsic Lewis acidity, boron-centered receptors couple with fluorides to afford fluoroborate complex via donation of an electron pair of the fluoride anion into the p_z-orbital of the boron center;[2g,5] and (iii) fluoride mediated desilylation, i.e., Swager et al. developed a fluoride-triggered Si–O bond cleavage reaction for highly sensitive detection fluoride by fluorescence spectroscopy.[6]

Carbocations have been intensively investigated owing to its unique reaction selectivity and optically responsive properties.[7] Carbocations are able to synthesize and stabilize in the presence of acid. Many organic synthesis,[8] biosynthesis,[9] and pathogenic mechanism[10] involve carbocations as an intermediate of nucleophilic substitution reactions, such as *N*-heterocycles pharmaceuticals, terpenes, and DNA alkylation according to reports. Recently, carbocation has been utilized as a reaction-based probes and/or labelers,[11] in which the obviously colorimetric response of carbocation was observed by coupling the labeler with active amine or thiol residues of proteins.

Herein, we reported a new strategy for fluoride anion detection in acidic environment based on bis-pyrene carbocations, which exhibit both chromogenic and fluorogenic responses in the presence of fluoride. As depicted in Scheme 1, the solution of bis-pyrene carbocations **4** shows negligible fluorescence intensity due to intramolecular charge transfer (ICT).[7b,12] Upon the bis-pyrene carbocations are substituted by fluoride anion in acid environment, the color of the solution change from blue to transparent with remarkably enhanced fluorescence emission.

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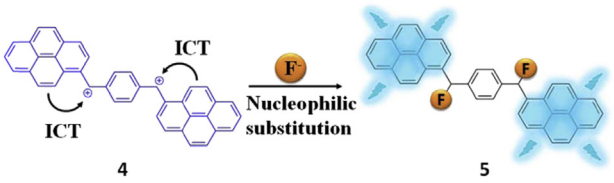
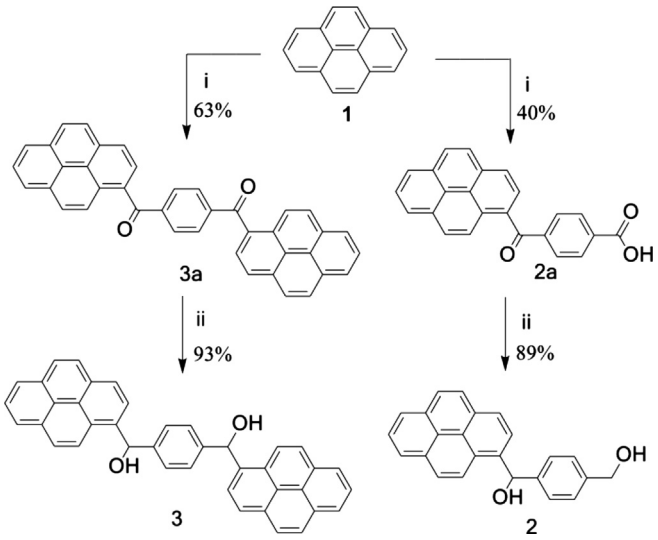


Scheme 1. A plausible mechanism of the detection of F^- by using stable bis-pyrene carbocations. The bis-pyrene carbocations **4** with quenched fluorescence due to intramolecular charge transfer (ICT) recovers its fluorescence upon coupling with fluoride through nucleophilic substitution.

2. Result and discussion

2.1. Synthesis of compounds 2 and 3

In this proof-of-concept study, a relatively stable carbocation with optical activity is required to monitor the reaction process by spectroscopy. Pyrene was chosen as fluorogenic group and delocalized π system to stabilize the carbocation (Scheme 2). The carbocation precursor **3** was synthesized from pyrene by Friedel–Crafts acylation and followed reduction. For the purpose of comparison, the mono-substituted pyrene **2** as a reference compound was prepared in a similar synthetic method. The full synthetic details were shown in Experimental part (Figs. S1–S12).



Scheme 2. Synthetic route of compounds **2** and **3**. Compound **2** is a mono-pyrene reference molecule. i, terephthaloyl chloride (1 equiv for **3a**, 0.5 equiv for **2a**), $AlCl_3$, CH_2Cl_2; ii, $NaBH_4$, ethanol.

2.2. Preparation and stability of carbocation 4

To obtain the carbocation **4**, compound **3** in chloroform was added with trifluoroacetic acid (TFA). This process could be monitored by UV–vis spectroscopy. Upon addition of TFA (from 100 to 600 μL, 6.5 M) into a solution of chloroform (2 mL) containing **3** ($c=5\times10^{-5}$ M), the absorption maxima of **3** at 330 and 347 nm decreased and two new peaks appeared at 440 and 645 nm, respectively. Accordingly, the color of the solution changed from colorless to deep blue as shown in Fig. 1(a). These results indicated the formation of bis-pyrene carbocations **4**.[13] Meanwhile, the formation of **4** was monitored by fluorescence spectroscopy. With addition of TFA from 2 to 200 μL (6.5 M) into a solution of chloroform (1 mL) containing **3** ($c=2\times10^{-6}$ M), the fluorescence intensity of **3** with emission peaks at 378, 398, and 423 nm was quenched and a new peak formed at about 445 nm (Fig. 1(b)). The quenched fluorescence upon formation of bis-pyrene carbocations **4** was directly visualized under the UV excitation ($\lambda_{ex}=365$ nm) (Fig. 1(b), inset). The corresponding NMR spectra are not available due to the low solubility of carbocations **4** in all tested solvents ($CHCl_3$+TFA, DMSO+TFA, and etc.).

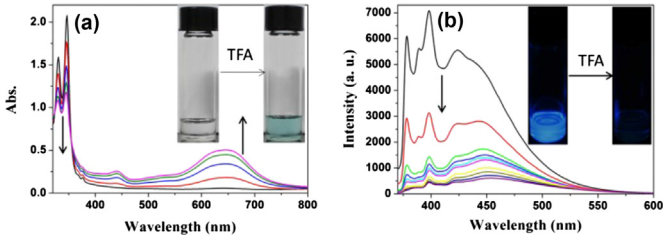


Fig. 1. Changes in UV–vis absorption (a) and fluorescence (b) of **3** upon gradual addition of TFA in chloroform. Inset: (a) photographs of **3** with visible color changes and (b) fluorescence changes (UV illumination) in chloroform.

To utilize the carbocations for fluoride detection, the carbocations should keep stable during employed. The large π-conjugated pyrene unit could effectively stabilize the carbocations.[14] Hence, the bis-pyrene carbocation **4** are stable and the carbocations disappeared in 15 h, which was characterized by the UV–vis spectroscopy through monitoring the characteristic absorption change of **4** at 645 nm. As shown in Fig. 2(b), the interval of each line was 150 min for **3**. The next titration process with anions usually takes 5 min. Hence, we assure that the carbocations of **3** were stable during next titration process. However, the carbocation of a reference compound **2** can only stabilize less than 2 h under the same condition (Fig. 2(a)), which was not stable enough for next titration. The results identified that the bis-pyrene carbocations **4** with two pyrene units could be more benefit for delocalization and stabilization of the positive charges of carbocations than one pyrene unit[14] (Fig. 2 and S13). The stable carbocations **4** were obtained by us for further experiments.

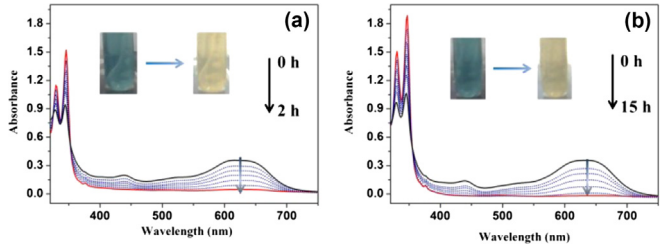


Fig. 2. Stability of compound **2** (a) and **3** (b) carbocations under ambient condition, indicating that the bis-pyrene can stabilize the carbocations.

2.3. Chromogenic and fluorogenic responses of carbocation 4

The fluorescence responses of **4** toward a series of anions (F^-, Cl^-, Br^-, I^-, CO_3^{2-}, $H_2PO_4^-$, OAc^-, SO_4^{2-}, and CN^- from their tetrabutyl ammonium salts) were tested. Upon addition of variable anions (10^{-5} M) into a $CHCl_3$ solution containing **4** ($c=3.3\times10^{-5}$ M), the peaks at 440 and 645 nm of **4** became weak or disappeared and some new peaks at 360 and 420 nm formed (Fig. S14), indicating the formation of **4** and anion complexes.[15] Furthermore, fluorescent titration experiments of **4** ($c=3.3\times10^{-5}$ M) with halide anions (from 0 to 10^{-4} M) in $CHCl_3$ were performed to observe the fluorescence intensity change. Upon addition of F^- into a solution of **4**, the fluorescence intensity of the **4**-F^- adduct was remarkably enhanced as the concentration of F^- was increased. The fluorescence emission maxima of the resulted **4**-F^- adduct formed at 380, 412, and

436 nm (Fig. 3(a)). In a sharp contrast, the fluorescence intensity of **4** kept increasing slightly or even quenched in the presence of Cl^-, Br^-, and I^- under the same condition owing to the heavy atom effect (Fig. 3(b)).[16] Other anions (CO_3^{2-}, $H_2PO_4^-$, OAc^-, SO_4^{2-}, and CN^-) were also investigated, no obvious fluorescence increases were observed (Fig. S15).

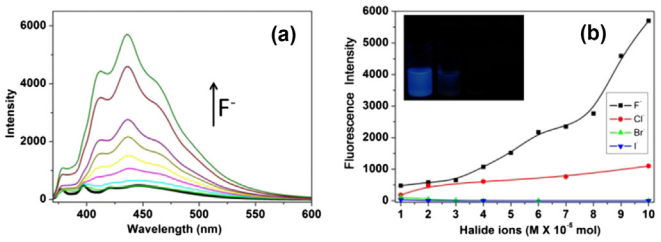


Fig. 3. (a) The fluorescent spectral change of carbocations **4** (3.3×10^{-5} M) in chloroform with addition of F^- (from 0 to 10^{-4} M), (b) fluorescence intensity of **4** in chloroform upon addition of halide ions (from 0 to 10^{-4} M) inset: photos were taken under UV illumination (from left to right, F^-, Cl^-, Br^-, I^-).

An important aspect of F^- sensors is their ability to detect F^- anions selectively over other competing anions. The competition experiments were carried out in the presence of F^- (10^{-4} M) mixed with 10^{-4} M of another anion (Fig. 4). As shown in Fig. 4, no significant interference in detection of F^- was observed in the presence of many competitive anions except for Br^- and I^- due to the strong owing to the heavy atom effect.[16] This demonstrates the exceptional selectivity of **4** for F^-. The fluorescent titration profile of **4** with F^- (Fig. S16) demonstrated that the detection limit of F^- is 3.0×10^{-5} M under the experimental conditions used here. The fast chromogenic and fluorogenic responses of carbocation 4 to fluoride anions could be used as fluoride anion detection in situ.

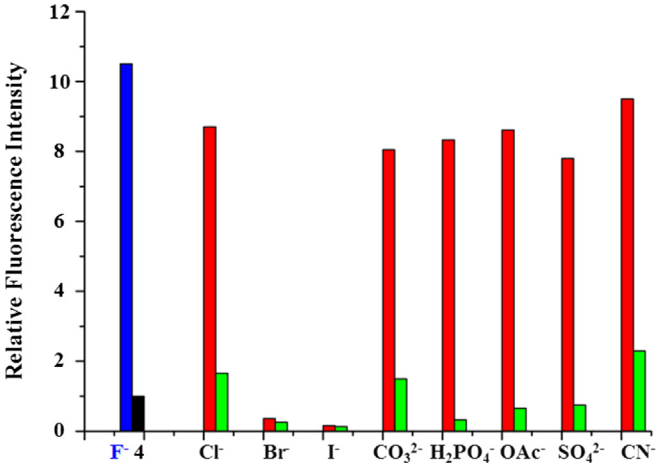


Fig. 4. Fluorescence response of **4** (2.0×10^{-5} M) in $CHCl_3$ to 10^{-4} M of various tested anions (green bar) and to the mixture of 10^{-4} M of anions with F^- anion (10^{-4} M, red bar). Blue bar=**4**+F^-, black bar=**4**. λ_{ex}=350 nm.

Given the fact that the complexation between **4** and F^- is not reversible, we deduce that the significant spectral response of **4** towards F^- is not attributed to the electrostatic interaction but the formation of new compound **5** through nucleophilic substitution reactions between F^- and **4**. The proposed mechanism was further confirmed by MALDI-TOF, which was carried out right after the titration of F^- to carbocation **4** and validated the formation of **5** (Fig. 5). It is reasonable that due to the order of nucleophilicities of halide anions in protic solvents is $F^->>Cl^->Br^->I^-$ and reversed leaving capability,[17] the F^- is regarded as the strongest nucleophile among halide anions and prefers the formation of C–F bond.[8b,18] The MALDI-TOF mass spectrum was utilized for monitoring the mixture of **4** and other halide anions (Cl^-, Br^-, I^-), there are no molecular ion peak of C–X adduct were found.

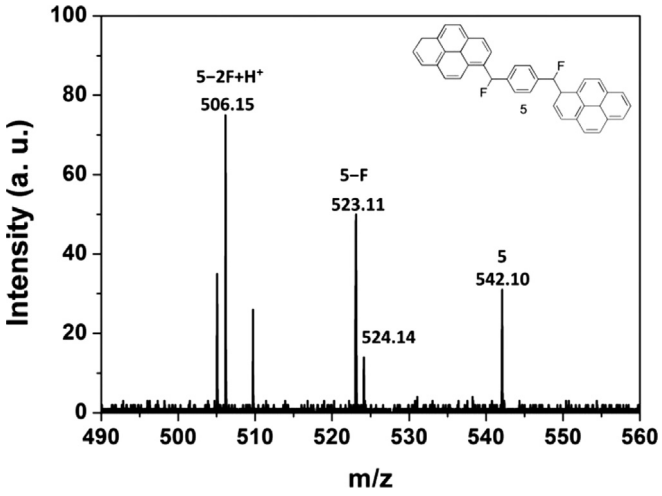


Fig. 5. MALDI-TOF mass spectrum of **5**.

2.4. Quantum chemistry stimulations

To investigate fluorogenic response in the presence of fluoride, we performed quantum chemical calculations of **3**, **4**, and **5** using density function theory (DFT)[19] and time-dependent density function theory (TD-DFT)[20] at the B3LYP/6-31G(d) level of the Gaussian09 program. Meanwhile, in order to be consistent with the experimental measurements, the emission properties have been performed in chloroform using the well-known polarized continuum model (PCM) approximation, which is adequate for the fluorescence spectrum.[21]

As displayed in Fig. 6, the optimized structure of the lowest singlet excited state (S_1) has a dihedral angle about 166.1° between the pyrene and terephthaloyl moieties for bis-pyrene carbocations **4**, however, the dihedral angles of compounds **3** and **5** are 72.6° and 88.3°, respectively. Furthermore, the frontier molecular orbitals (FMOs), which strongly affect the photophysical properties were simulated in detail. The electron densities in the lowest unoccupied molecular orbitals (LUMOs) and the highest occupied molecular orbitals (HOMOs) are dominantly delocalized on pyrene moieties in **3** and **5**, whereas relevant LUMOs and H-7 for bis-pyrene carbocations **4** are mainly delocalized over the pyrene and terephthaloyl moieties (Fig. 7).

On the basis of the optimized S_1 structures, the emission wavelengths, emission energies, transition nature, and oscillator strength (f) were calculated by TD-B3LYP method. As shown in Table 1, strong emission wavelengths are predicted at 387 nm (f=0.0843) and 376 nm (f=1.1769) for **3**, in good agreement with experimental values, these bands are ascribed to LUMO→HOMO (72%) and L+1→H-1 (71%) transitions, respectively, and described as $\pi^*\rightarrow\pi$ character of the pyrene moieties. However, the calculated weak emission wavelengths of **4** are 393 nm, 369 nm, respectively, and a new peak formed at about 449 nm (f=0.0579), this new emission originates from L+1 to H-7 [$\pi^*\rightarrow\pi$ character of the pyrene and terephthaloyl moieties]. For **5**, the experimental emission spectrum presents two major bands, centered around 412 nm and

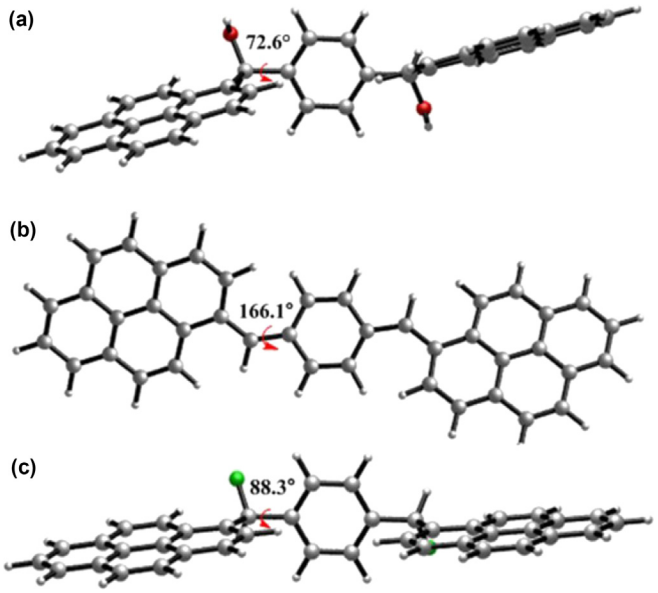


Fig. 6. Optimized structures of **3** (a), **4** (b), and **5** (c) in the lowest singlet excited states (S_1) at TD-B3LYP/6-31G (d) level.

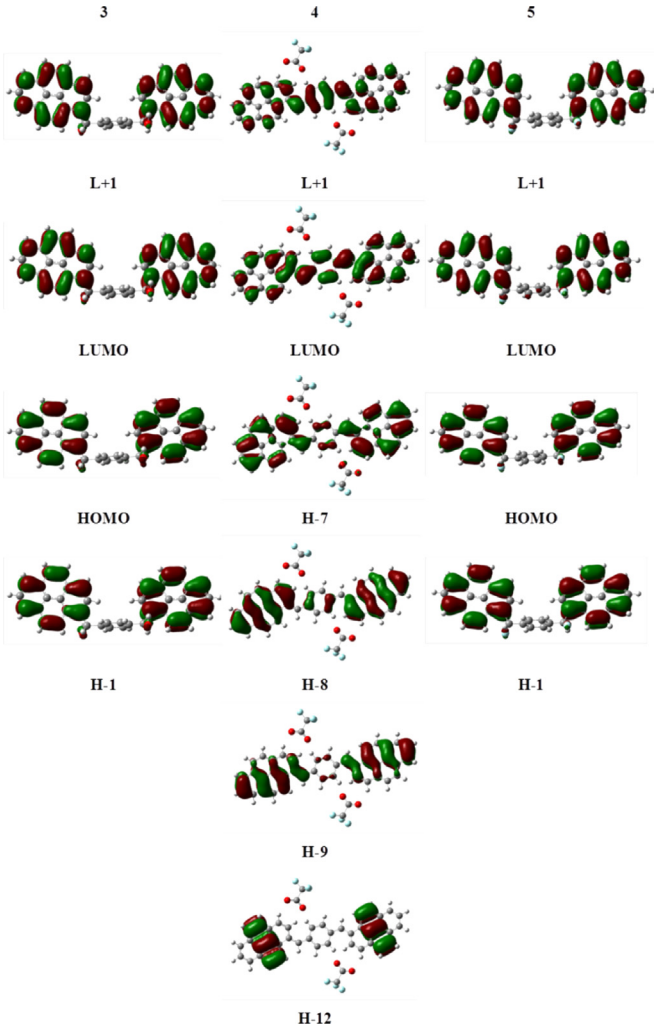


Fig. 7. Contour plots of LUMOs and HOMOs in the first excited states for **3**, **4**, and **5** in detail.

Table 1
The fluorescence emission wavelength (λ_{em}), corresponding transition contribution, and oscillator strength (f) of **3**, **4**, and **5**

	E (eV)	λ_{em} (nm) in chloroform	f	Major transition		Expt. (nm) in chloroform
3	3.20	387	0.0843	LUMO→HOMO	72%	398
				L+1→H-1	27%	
	3.30	376	1.1769	L+1→H-1	71%	378
				LUMO→HOMO	26%	
4	2.76	449	0.0579	L+1→H-7	75%	445
				LUMO→H-11	18%	
	3.16	393	0.0088	L+1→H-8	90%	398
	3.36	369	0.0137	L+1→H-9	86%	378
5	3.19	388	0.0989	LUMO→HOMO	74%	412
				L+1→H-1	26%	
	3.30	376	1.1610	L+1→H-1	73%	380
				LUMO→HOMO	24%	

380 nm, TD-B3LYP method also predicts two strong emission bands at 388 nm (f=0.0989) and 376 nm (f=1.1610), which have the same character as **3**. These results are in good agreement with experimental values (fluorescence response) and prove the mechanism of the fluoride anions detection.

3. Conclusion

We demonstrated a new molecular mechanism for in situ fluoride anion detection in acidic environment based on stable π-conjugated carbocations. First, we have designed and synthesized a new bis-pyrene based carbocation precursor, which could form stable carbocations with weak fluorescence and long wavelength absorption. The carbocations show both chromogenic and fluorogenic responses in the presence of fluoride anion. We proposed that the carbocations react with fluoride anion to form C–F covalent bond, which leads to this dual responsive phenomenon. The responsive mechanism was supported by quantum chemical calculations and the MALDI-TOF spectrum. The successful elucidation of this new mechanism opens new avenue for carbocation-based sensor or biological labeling in the future.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercially available sources and used without further purification. All the reactions were performed under an inert atmosphere of nitrogen. ^{1}H NMR spectra were recorded on an Advance Bruker 400M spectrometer in deuterated chloroform. Chemical shifts are quoted in parts per million (ppm) and referenced to tetramethylsilane. The ^{13}C NMR spectra were recorded at 100 MHz on the same spectrometer in deuterated chloroform. Chemical shifts were defined relative to the ^{13}C resonance shift of chloroform (77.0 ppm). Microflex LRF MALDI-TOF was used to determine the molecular mass. Elemental analyses were performed on a Flash EA 1112 analyzer. The UV absorption was determined with a PE Lambda 650 UV–vis spectrometer. Fluorescence spectrum was recorded on F-280 spectrometer from Tianjin Gangdong Sci&Tech. Development. Co., Ltd.

4.2. Friedel–Crafts acylation procedure for compound 3a

Pyrene **1** (2.02 g, 10.00 mmol) and *p*-phthanoyl chloride (1.01 g, 5.00 mmol) were dissolved in dichloromethane (50 mL), the mixture was cooled to 0 °C. After the portionwise addition of $AlCl_3$ (2.00 g, 15.00 mmol), the mixture was allowed to react overnight at room temperature, then poured into ice-water and the resulting

mixture was stirred until the color of the organic phase turned from black to yellow. The aqueous phase was extracted with dichloromethane, the combined organic phases were dried with $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography (elute CH_2Cl_2/PE=4:1), and compound **3a** was obtained (1.62 g, 63%). Mp>300 °C. IR (KBr, cm^{-1}) 3084, 3040, 1643, 1595, 1509, 1390, 1250, 1203, 1065, 935, 870, 844, 832, 806, 710. ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 8.40 (d, J=9.6 Hz, 2H), 8.27 (t, J=8.8 Hz, 4H), 8.22–8.06 (m, 12H), 7.94 (d, J=8.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 197.74, 142.28, 134.10, 133.59, 132.15, 131.20, 130.68, 130.50, 130.07, 129.56, 129.34, 127.41, 127.21, 126.57, 126.36, 126.19, 124.92, 124.60, 124.41, 123.80. MALDI-TOF: calcd for $C_{40}H_{22}O_2$ 534.16, found 534.30. Elemental analysis: calcd (%) for $C_{40}H_{22}O_2$: C, 89.87; H, 4.15. Found: C, 89.88; H, 4.18.

4.3. Reduction with $NaBH_4$ for compound 3

Compound **3a** (0.53 g, 1.00 mmol) and $NaBH_4$ (0.15 g, 4 mmol) was dissolved in ethanol (30 mL), the mixture was stirred at room temperature until the compound **3a** reacted completely about 3 h. Then the 1 M HCl was added until the pH value reached 7. The solvent was evaporated and the residue was washed with deionized water. The compound **3** was purified by column chromatography (elute CH_2Cl_2, 0.50 g, 93%). Mp>300 °C. IR (KBr, cm^{-1}) 3410, 3046, 2919, 1434, 1384, 1362, 1254, 1108, 1026, 953, 926, 785, 705. ^1H NMR (DMSO-d_6, 400 MHz) (δ, ppm) 8.46 (dd, J=11.2, 1.7 Hz, 2H), 8.28–8.21 (m, 8H), 8.16–8.08 (m, 6H), 8.03 (t, J=7.6 Hz, 2H), 7.38 (s, 4H), 6.70 (d, J=4.2 Hz, 2H), 6.23 (d, J=4.2 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm) 143.75, 138.97, 130.79, 130.09, 131.20, 129.85, 127.39, 127.11, 127.08, 126.91, 126.54, 126.12, 125.13, 124.94, 124.91, 124.80, 124.02, 123.97, 123.67, 71.30. MALDI-TOF: calcd for $C_{40}H_{26}O_2$ 538.19, found 538.00. Elemental analysis: calcd (%) for $C_{40}H_{26}O_2$: C, 89.19; H, 4.87. Found: C, 89.22; H, 4.82.

4.4. Friedel–Crafts acylation procedure for compound 2a

Pyrene **1** (2.02 g, 10.00 mmol) and *p*-phthanoyl chloride (2.03 g, 10.00 mmol) were dissolved in dichloromethane (100 mL), the mixture was cooled to 0 °C. After the portionwise addition of $AlCl_3$ (1.33 g, 10.00 mmol), the mixture was allowed to room temperature for 10 min, then poured into ice-water and the resulting mixture was stirred until the color of the organic phase turned from black to yellow. The aqueous phase was extracted with dichloromethane, the combined organic phases were dried with $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography, and compound **2a** was obtained (1.41 g, 40%). Mp: 192 °C. IR (KBr, cm^{-1}) 3437, 3044, 1773, 1653, 1595, 1507, 1263, 1202, 1065, 938, 876, 847, 837, 814, 693. ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 8.44 (d, J=9.2 Hz, 1H), 8.28 (t, J=8.0 Hz, 2H), 8.24–8.04 (m, 8H), 7.99 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 197.96, 168.87, 145.23, 137.21, 134.77, 132.42, 132.25, 132.21, 132.06, 131.77, 131.57, 131.50, 131.10, 130.73, 130.49, 128.49, 128.07, 127.57, 127.46, 127.26, 125.82, 125.32, 125.22, 124.70. MALDI-TOF: calcd for $C_{24}H_{14}O_3$ 350.09, found $(M+H)^+$ 350.88. Elemental analysis: calcd (%) for $C_{24}H_{14}O_3$: C, 82.27; H, 4.03. Found: C, 82.31; H, 4.02.

4.5. Reduction with $NaBH_4$ for compound 2

Compound **2a** (0.35 g, 1.00 mmol) and $NaBH_4$ (0.15 g, 4 mmol) was dissolved in ethanol (30 mL), the mixture was stirred at room temperature until the compound **2a** reacted completely about 3 h. Then the 1 M HCl was added until the pH value reached 7. The solvent was evaporated and the residue was washed with deionized water. The pure compound **2** was obtained by column chromatography (0.30 g, 89%). Mp: 140 °C. IR (KBr, cm^{-1}) 3423, 3261, 3041, 2921, 2869, 1417, 1383, 1209, 1062, 1028, 1016, 843, 758, 717. ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 8.31 (d, J=9.6 Hz, 1H), 8.21–8.15 (m, 4H), 8.06–7.98 (m, 4H), 7.44 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 6.87 (s, 1H), 4.66 (s, 2H), 2.53 (s, 1H), 1.62 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 143.14, 140.23, 138.53, 131.33, 131.07, 130.61, 128.07, 127.86, 127.52, 127.45, 127.22, 127.21, 126.03, 125.40, 125.34, 125.23, 125.06, 124.92, 124.81, 124.77, 124.70, 123.03, 73.42, 65.10. MALDI-TOF: calcd for $C_{24}H_{18}O_2$ 338.13, found 338.02. Elemental analysis: calcd (%) for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.16; H, 5.29.

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Supplementary data

This material contains the details of ^1H and ^{13}C NMR, MALDI-TOF-MS spectra, and UV–vis and fluorescence spectra. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.044.

References and notes

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