

1,6-Disubstituted perylene bisimides: concise synthesis and characterization as near-infrared fluorescent dyes

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Abstract—Detailed studies on bromination and subsequent imidization of perylene bisanhydride were reported. 1,6,7,12-Tetrabromoperylene bisimide was obtained in an optimized high yield. In addition, 1,6-disubstituted regioisomer was separated for the first time in isomerically pure form, and the structure was confirmed by ¹H NMR, MS, element analysis, and photophysical measurements. By using a mixture of regioisomers 1,6- and 1,7-dibromo-perylene bisimide, 1,6-dipiperidinylperylene bisimides (1,6-Piper-Pery) were synthesized, purified, and their fluorescence were measured with a peak at 760 nm. These compounds can be used as stable near-infrared absorbing and fluorescent dyes.

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There has been intense interest in the preparation and study of near-infrared (NIR)-absorbing dyes as well as the applications with safe, noninvasive imaging/contrasting probes recently.^{1–3} The advantages of imaging in the NIR region (700–1100 nm) are numerous. Among them, the prominent one is the absence or significant reduction of background absorption, fluorescence, and light scattering along with the availability of low-cost sources of irradiation. However, problems have been encountered in the design and synthesis of NIR fluorescent dyes, such as aggregation, photostability, and low fluorescence quantum yields. Compared to chromophores absorbing in the visible region, there is a pressing need for the identification of newer, more effective dyes that absorb and emit in the NIR region. On the other hand, small Stokes shift and the aggregation formation for most common NIR dyes decrease the detection sensitivity to a great extent. Therefore, NIR dyes with a larger Stokes shift and nonaggregation trend are very promising for NIR fluorescence bioassays.

3,4:9,10-Perylenetetracarboxylic acid bisimides (PTCAIs) have been widely used in practical applications owing to their low light and thermal fading rates, high lumines-

cence efficiency, and optoelectronic properties.^{4–9} However, most of PTCAIs cannot absorb NIR light, even in the solid state (as pigments). Therefore, new NIR absorbing perylene, with excellent properties such as high photo- and thermal-stability as well as high luminescence quantum yield, has been strongly required. However, the chemical modification at imide groups in perylene bisimide does not significantly affect the optical and electronic properties of this chromophore because of nodes in the HOMO and LUMO orbitals at the imide nitrogen atoms.^{10,11} But, these properties could be drastically changed by functionalization of the perylene core with electron donor or acceptor groups. Such core-functionalized perylene bisimides are usually synthesized from the corresponding halogenated, in particular, brominated derivatives. Herein, we present our approach to incorporate an electron-rich amine with the π -system of the perylene chromophore. Such dyes have obvious bathochromic shift relative to the precursor due to the electron-donating ability of the amines.¹² On the other hand, incorporation of piperidinyl at the perylene backbone suppresses co-facial aggregation of parent perylene bisimide and enhances the solubility significantly.

In the patent,¹³ BASF disclosed a procedure for the bromination of perylene bisanhydride **1** and subsequent imidization of the brominated product. This patent presented a way to obtain pure 1,7-dibrominated perylene bisimides. But recently, Würthner et al. proved that the procedure was not true.¹⁴ The previously reported

Keywords: Near-infrared; 1,6-Dibromo-perylene bisimide; Bromination; Imidization; Absorption.

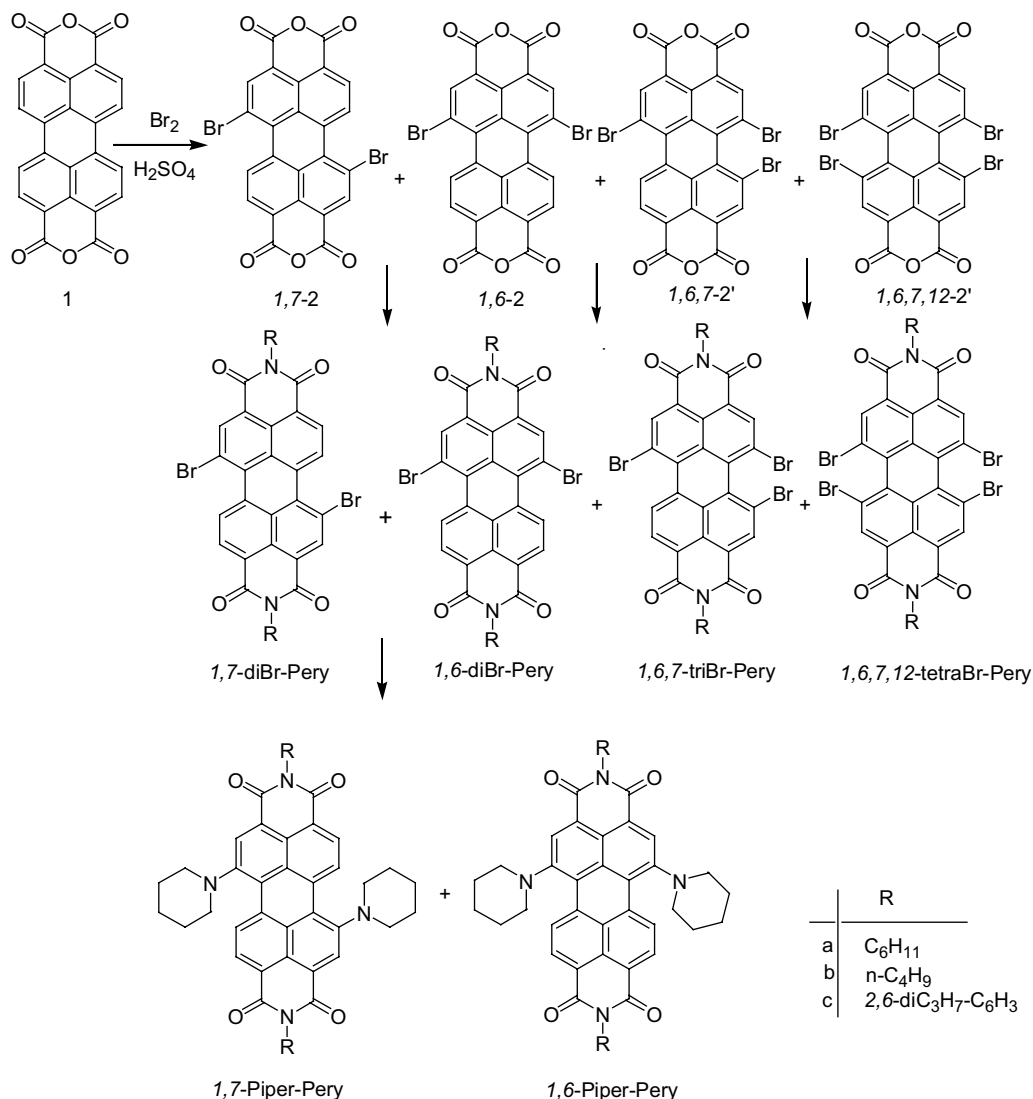
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difunctionalized perylene bisimides were apparently mixtures of 1,7- and 1,6-regioisomers rather than isomerically pure 1,7-dibrominated perylene bisimides. Würthner's group separated the pure 1,7-dibrominated compound with repetitive recrystallization, but they could not obtain the pure 1,6-regioisomer. The novelty in our strategy was that we developed a concise method not only to obtain pure 1,6-disubstituted compounds¹⁵ by nucleophilic replacement of bromine atoms but also to obtain the tetrabrominated perylene bisimides.

Since the brominated perylene bisanhydrides based on the BASF's patent are insoluble in common organic solvents, they could not be purified by general means, and the crude product mixture was used for the subsequent imidization with cyclohexylamine (Scheme 1). The imidization afforded a mixture of 1,7- and 1,6-dibromoperylene bisimides (1,7-diBr-Pery and 1,6-diBr-Pery) and tribrominated bisimide (1,6,7-triBr-Pery). We then changed the reaction condition by: (a) increasing the reagent amount including bromine and sulfuric acid;

(b) elevating the reaction temperature from 85 °C to 110 °C; and (c) prolonging reaction time from 20 h to 48 h. Bromine could easily escape from the flask during the reaction process. The addition of excess bromine could make up the deficiency. More sulfuric acid could promote the solubility of perylene bisanhydride. The higher temperature and extended reaction time were in favor of the nucleophilic replacement reaction for bromine atoms positioned at the perylene core. All these above-mentioned changes caused the reduction of the content of 1,6- and 1,7-dibrominated compounds and the increase of the mole ratio of 1,6,7-tri- and 1,6,7,12-tetrabrominated products and, finally, resulted in the formation of tetrabrominated perylene bisimide (1,6,7,12-tetraBr-Pery) (yield: 20.8%, Table 1).

The product mixture obtained (after incorporating piperidinyl group to a mixture of 1,7-diBr-Pery and 1,6-diBr-Pery) was separated by column chromatography on silica gel by elution with CH₂Cl₂:CCl₄ (v/v, 1:2) to obtain the minor component dibrominated bisimide (synthetic



Scheme 1. Regioisomeric products formed in the bromination and subsequent imidization and introduction of piperidinyl at 1,6- and 1,7-position of perylene bisanhydride **1**.

Table 1. Comparison of the bromination reaction for perylene dianhydride **1** between BASF's patent and modified process in this work

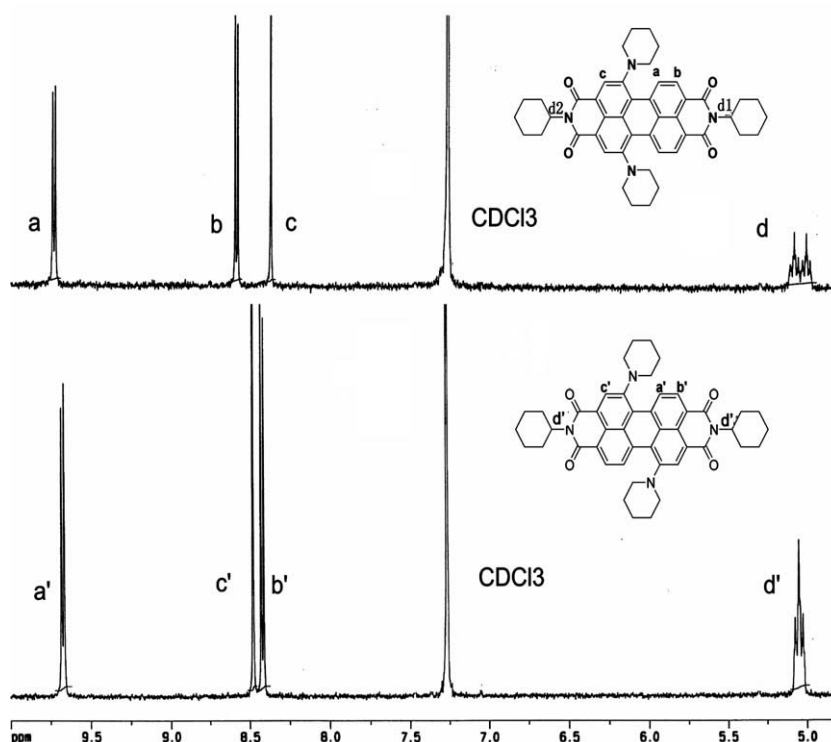
Reaction product	Yield in Ref. 13 (%)	Yield in this work (%)
1,6-DiBr-Pery and 1,7-DiBr-Pery	38.7	11
1,6,7-TriBr-Pery	1	12.4
1,6,7,12-TetraBr-Pery	0	20.8

section). Their structures were characterized by ^1H NMR, MS, element analysis, and their photophysical properties (note: in current work, we synthesized six analogous compounds 1,6-Piper-Pery-a, 1,6-Piper-Pery-b, and 1,6-Piper-Pery-c with corresponding 1,7-Piper-Pery-a, 1,7-Piper-Pery-b, and 1,7-Piper-Pery-c, and only 1,6-Piper-Pery-a and 1,7-Piper-Pery-a were chosen to be discussed, whose characters were resembled by other compounds).

As the ^1H NMR spectra (Fig. 1) revealed, three sets of signals with the same integration including two doublets (protons: a or a', b or b') and one singlet (protons: c or c') were observed in the region of 8.3–9.8 ppm, indicating that there were three different kinds of protons at the perylene core. This was in agreement with the structure of 1,6-Piper-Pery-a and 1,7-Piper-Pery-a. In the region around 5.0 ppm, a multiplet signal appeared (protons: d or d'), which was assigned to the proton neighboring to the imide nitrogen atom in cyclohexyl group (signed as H_{d} , H_{d1} , and H_{d2}). For 1,7-Piper-Pery-a, the signal was only a common multiplet, but for 1,6-Piper-Pery-

a, the signal split into double multiplets. Comparing the chemical structures between 1,6-Piper-Pery-a and 1,7-Piper-Pery-a (Scheme 1), we can clearly find that the chemical environment for the respective protons neighboring to the imide nitrogen atom in cyclohexyl group are different, that is, in 1,7-Piper-Pery-a, the chemical environment for the two protons H_{d} is the same, so their chemical shifts are positioned at the same area. But in 1,6-Piper-Pery-a, the chemical environment changed, which results in the split of the H_{d} signal as H_{d1} and H_{d2} .

This assignment can be further confirmed by the photophysical properties of 1,6-Piper-Pery-a and 1,7-Piper-Pery-a. By comparing the chemical structures of 1,6-Piper-Pery-a and 1,7-Piper-Pery-a, the latter possesses strong electron push–pull ability. The 1,7-isomer has two electron donors (piperidine substituents) on the same side of the perylene imide ring (i.e., opposite against the imide ring), which has stronger electron push ability (from two donors) into the perylene imide (one-side) molecule, where imide functionality acts as an electron acceptor. The different location of electron donors mainly changes the HOMO energy level of the molecule and the 1,7-isomer has a higher HOMO level than 1,6-isomer. The LUMO remains mostly the same in two isomers because the imide functionality is the same for both isomers. In other words, 1,7-isomer has a more polar electronic structure than 1,6-isomer. This is consistent with the similar fluorescence wavelength but different absorption wavelength of two disubstituted isomers (note: in fact, the maximal absorption of 1,7-Piper-Pery-a red shifted 32 nm compared with that of 1,6-Piper-Pery-a, as shown in Fig. 2).

**Figure 1.** ^1H NMR (500 MHz, CDCl_3) partial spectra of regioisomerically pure perylene bisimides 1,7-Piper-Pery-a and 1,6-Piper-Pery-a.

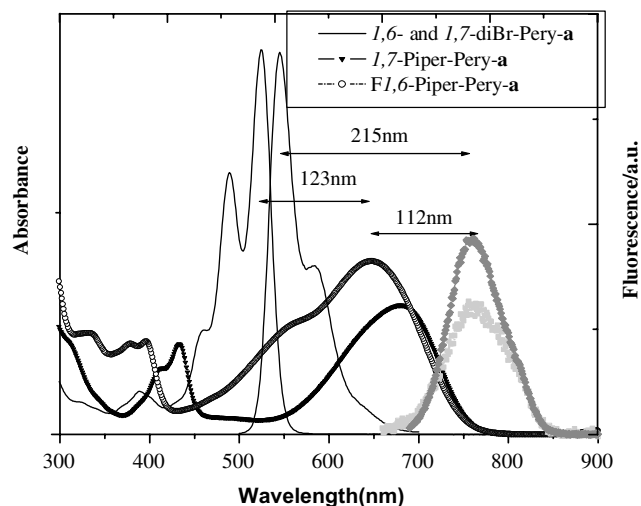


Figure 2. Absorption and fluorescence spectra of a mixture of 1,6- and 1,7-diBr-Pery-a (excited at 510 nm), 1,7-Piper-Pery-a and 1,6-Piper-Pery-a (excited at 645 nm) in CH_2Cl_2 solution (10^{-5} M).

As shown in Figure 2, the dyes meet the necessary requirements of a NIR chromophore: (1) peak fluorescence at 700–900 nm (fluorescence quantum yield Φ_f : 1,6-Piper-Pery-a: 0.25; 1,7-Piper-Pery-a: 0.2. The fluorescence quantum yields were determined by the optically dilute method with fluorescein ($\Phi_f = 0.92$ in 1 N NaOH aqueous solution) and cresyl violet ($\Phi_f = 0.54$ in methanol) as reference); (2) large Stokes shift (112 nm for 1,6-Piper-Pery-a, and by comparison with the absorption and fluorescence spectra of its precursor 1,6- and 1,7-diBr-Pery-a, the bathochromic shifts are 123 and 215 nm, respectively); and (3) high chemical stability and photostability, as well as a convenient commercially viable synthesis in useful quantities. Additionally, the sharp fluorescence of the dye is insensitive to solvent polarity.

In conclusion, based on the modification of the synthesis, we firstly obtained tetrabrominated perylene bisimide 1,6,7,12-tetraBr-Pery, and after incorporating piperidinyl group to the mixture of dibrominated perylene bisimides, the regioisomeric pure 1,6-Piper-Pery-a was firstly separated and confirmed by ^1H NMR, MS, and element analysis. By incorporating the electron donating amines into the perylene core, the π -system of push-pull aromatic of the perylene molecules is extended, resulting in the bathochromic shifts of their absorption and emission, which make these compounds promising near-infrared absorbing and fluorescent dyes candidates. Efforts are currently underway to develop nonsymmetrically substituted, water-soluble versions to allow conjugation for biosensing experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [10.1016/j.tetlet.2005.04.137](https://doi.org/10.1016/j.tetlet.2005.04.137). The experimental details and synthetic data are available in Supplementary data.

Acknowledgements

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15. Synthesis and confirmation data for 1,6-Piper-Pery-a, and for other series of compounds, the data are appended in

the Supplementary data. A mixture of 100 mg of 1,6-diBr-Pery-**a** and 1,7-diBr-Pery-**a** was dissolved in 15 ml piperidine. The solution was heated at 60 °C under dry nitrogen for 48 h with stirring. Excess piperidine was removed on a rotary evaporator and the residue was column chromatographed on silica with 1:2 CH₂Cl₂:CCl₄ (v/v, R_f = 0.46) to afford 13 mg deep blue product (first band, 12.9%). (Note: 1,7-diBr-Pery-**a** was collected as the

second band showing deep green color, R_f = 0.38, 56 mg, yield: 55.4%.) Mp >300 °C. ¹H NMR (CDCl₃, ppm): δ = 1.2–2.0 (m, 28H), 2.57 (m, 4H), 2.75 (m, 4H), 3.37 (m, 4H), 5.02 (m, 1H), 5.08 (m, 1H), 8.37 (s, 2H), 8.58 (d, J = 8.28 Hz, 2H), 9.74 (d, J = 8.27 Hz, 2H). MS (ESI): 721.3 [M⁺] (100%). Elemental analysis: Calcd for C₄₆H₄₈N₄O₄: C, 76.64; H, 6.71; N, 7.77. Found C, 76.72; H, 6.64; N, 7.69.