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ABSTRACT

The use of asymmetric phthalocyanines (Pcs) as platforms for the preparation of several asymmetric hexatriazolyl-monohydroxyphthalocyanines via copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction was investigated. Asymmetric Pcs **5a** and **5b** were prepared through statistical macrocyclization of phthalonitriles (Pns) **1a** and **2** to give PMB-protected **4a** and **4b** which afforded asymmetric Pcs **5a** and **5b** after acidic cleavage. The “ROMP-Capture-Release” method as a synthetic approach to prepare asymmetric Pc **5b** was also evaluated. TIPS-protection of the terminal alkynes was necessary to prevent cross-coupling during the ring-opening metathesis polymerization (ROMP) step. Zinc Pc **5b** was successfully used as a scaffold for functional modification under CuAAC conditions using several azides bearing hydrophobic, photo-crosslinkable, or electroactive moieties. Monitoring the CuAAC reaction by both UV/Vis and FT-IR spectroscopies provided insight into the role of azide equivalent, reaction time, and catalyst on reaction progress.

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1. Introduction

Pcs are 18 π -electron tetrapyrrolic macrocycles that have been applied in a number of advanced technologies including optical limiting devices,¹ photodynamic therapy (PDT),² organic field-effect transistors (OFETs),³ and organic photovoltaic (OPV) devices.⁴ Due to their physical and chemical properties,⁵ effort has been dedicated to the development of structurally diverse Pcs. Of particular interest is the development of asymmetrically substituted AB₃ Pcs⁶ which can possess improved photodynamic properties⁷ and unique second-order nonlinear optical effects.^{1d,8} Asymmetric AB₃ Pcs containing active functional groups in the odd quadrant such as hydroxy,⁹ amino,¹⁰ carboxylic acid,^{10a,11} isothiocyanate,¹² azide,¹³ and alkyne¹⁴ serve as building blocks in the design of Pc-based molecular systems.¹⁵ We have used asymmetric AB₃ Pcs as components of a model system to investigate charge capture at oxide interfaces from typical OPV donor materials.¹⁶

However, efficient production of Pc-based materials with structural diversity, including AB₃ asymmetry, still remains an open challenge, especially for Pcs with sensitive substituents that are not compatible with the conditions of cyclization of Pc precursors. The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction¹⁷ has proven useful for the synthesis of novel materials,¹⁸ and has been demonstrated by us¹⁹ and others²⁰ as appropriate for Pc/Nc modification. We have previously

demonstrated preparation of symmetric octaalkynyl Pcs as an effective platform for Pc chromophore modification through copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reactions.¹⁹ Herein we report the synthesis of asymmetric hexaalkynyl AB₃ Pcs **5a** and **5b** and subsequent post-cyclization modification with various azides to further demonstrate the utility of Pc modification through the CuAAC reaction.²¹

2. Results and Discussion

In seeking to use the CuAAC reaction as a means of increasing structural diversity in asymmetric Pc chromophores, we identified bis(alkynyl) Pn **1a**,^{19a} readily prepared from 4,5-bis(4'-hydroxyphenoxy)phthalonitrile and commercially available 1-hexyn-6-ol through a Mitsunobu reaction, as a suitable precursor. We have previously reported that macrocyclization of **1a** under basic Linstead conditions afforded octaalkynyl ZnPc **3b** which possesses good solubility in common organic solvents such as THF, DCM, acetone, and Et₂O.^{19a} Protection of the terminal alkyne moieties was not necessary during the macrocyclization reaction, providing a relatively simple way to incorporate acetylenic moieties into a Pc scaffold.

To use Pn **1a** in the preparation of asymmetric AB₃ Pcs, we needed to choose a strategy for asymmetric Pc synthesis. The preparation of asymmetrically substituted AB₃ Pcs can be achieved by solution phase statistical Linstead macrocyclization between two different phthalonitriles or diiminoisindolines.²² Ready availability of precursors makes the statistical macrocyclization often a more effective and direct than other

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Scheme 1. Synthesis of asymmetric Pc **5a** and **5b** by statistical macrocyclization followed by acidic cleavage.

approaches such as solid-phase synthetic methods²³ and the “sub-phthalocyanine” method.²⁴ The challenge of statistical macrocyclization is that it inherently yields a mixture of Pc products with minimal structural differences, making isolation of the desired Pcs often challenging.

However, we have recently reported statistical cyclization strategies but with modifications aimed at simplifying purification. We have described the synthesis of asymmetric AB₃ Pcs via: (1) statistical macrocyclization using 4-methoxybenzyl (PMB)-protected Pn^{16a} to yield asymmetric AB₃ Pcs with a unique phenolic quadrant that aids in isolation once deprotected; and (2) a ROMP-Capture-Release^{9b} strategy using a norbornyl-tagged Pn, again leading to an asymmetric AB₃ Pc with a phenolic unique quadrant. Both methods would potentially serve to produce asymmetric AB₃ Pcs with acetylenic moieties for post-synthetic modification by the CuAAC reaction.

Employing the former method, statistical macrocyclization of **1a** and 4-methoxybenzyl (PMB)-protected Pn **2**^{16a} (Pn **1a**:**2** = 3:1) in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a base and either LiBr or Zn(OAc)₂ as metal template provided a mixture of symmetric and asymmetric Pcs (Scheme 1). The crude mixture was chromatographed to remove DBU and excess metal salt from the Pc mixture. MALDI mass spectral analysis of the resultant Pc mixtures revealed the presence of PMB-protected A₃B (**4a/4b**) and symmetric A₄ (**3a/3b**) Pcs. Subjecting the mixtures to PMB deprotection conditions yielded a mixture of asymmetric free hydroxyl A₃B (**5a/5b**) and symmetric A₄ (**3a/3b**) Pcs. Due to the increased polarity afforded by the unique phenolic quadrant in the asymmetric Pcs, this mixture was easily separable by flash chromatography to provide the desired macrocycles **5a/5b** in overall yields of 20 and 22% from Pn **2**, respectively.

We also evaluated the latter method, our previously reported “ROMP-Capture-Release” strategy^{9b} to synthesize asymmetric hexaalkynyl Pc **5a**. This method employs solution phase crossover-Linstead cyclization of a norbornyl-tagged Pn (A) with a second Pn (B), followed by selective capture of asymmetric norbornyl-tagged AB₃ Pc under ROMP conditions and acidic cleavage of the target asymmetric Pc from the ROMP polymer. While this method was successfully developed for the synthesis of an asymmetric AB₃ Pc with alkyl substituents,^{9b} the concern of cross-coupling of free alkynes with the norbornyl tag during the ROMP process remained. Enyne metathesis²⁵ is well established to occur with ruthenium-based metathesis catalysts,²⁶ including the cross-metathesis of terminal alkynes with norbornene derivatives.²⁷ An unsuccessful attempt to ROMP a 7-oxanorbornene monomer with a pendant propargyl group was attributed to the competing enyne metathesis reaction.²⁸ If alkynes undergo ring-opening/ring-closing metathesis (ROM/RCM) with the norbornene moieties in the presence of Grubbs’ catalyst, a protecting strategy can be employed to prevent competing metathesis with the alkyne moiety.

To provide a comparison, preparation of two Pcs with free and protected alkyne peripheries was conducted (Scheme 2) by ROMP-Capture-Release through statistical macrocyclization of norbornyl-tagged Pc **6** with both acetylenic Pn **1a** and its TIPS-protected analog **1b**. When the mixture of Pcs **7a** and **8a** was subjected to the previously established ROMP conditions,^{9b} no polymer precipitate was observed. Modified conditions were also attempted, such as increasing the loading of crosslinker **9** and varying the reaction concentration and time, with similar negative results. Conversely, when the mixture of TIPS-protected Pcs **7b** and **8b** was subjected to the ROMP conditions in the presence of crosslinker **9** the corresponding cross-linked polymer was obtained after filtration and CH₂Cl₂ Soxhlet extraction (Scheme 3). Treatment of the resulting ROMP polymer **10** with 10% trifluoroacetic acid (TFA) in CH₂Cl₂ resulted in release of Pc **11**. Deprotection of Pc **11** using an excess of tetrabutylammonium fluoride (TBAF) afforded Pc **5a** in 7% overall yield from Pn **6**.

Despite the successful isolation of Pc **5a** via the ROMP-Capture-Release strategy, including successful prevention of

Scheme 2. Statistical macrocyclization of Pns **1a**, **1b**, and **6**.

Scheme 3. ROMP-Capture-Release leading to asymmetric Pc **5a**.

alkyne metathesis, the lengthy reaction route involving the additional protection and deprotection resulted in low yields of the desired asymmetric Pc. This hampered straightforward scale-up to larger quantities of material. We relied on the statistical macrocyclization using 4-methoxybenzyl (PMB)-protected Pn for further preparation of **5a** and **5b**.

With Pcs **5a** and **5b** in hand, we examined modification of the periphery of the Pc chromophore with CuAAC chemistry. Although we had previous success with insertion of copper into non-metallated Pcs in the course of CuAAC reactions,¹⁹ we observed incomplete metal-insertion in the CuAAC reactions of Pc **5a** and azides, characterized by both MS-MALDI and UV/Vis. Samples isolated from these reactions contained a mixture of both Cu-metallated and metal-free Pc. Metallation of the modified Pc derivatives using various Cu(II) salts yielded insufficient intercalation as well.

We expected that Zn-metallated Pc **5b** would prevent the inherent Cu-insertion reaction in the modification of Pcs by CuAAC and therefore allow the use of less CuI. Conditions similar to those described in the previous literature were first applied to reactions with azides **12a-c**, CuI, and DIPEA in THF (Scheme 4).^{19b} Due to the poor solubility of **12d** in THF, the reaction towards **13d** was carried out in CHCl₃. Using a 10:1 ratio of azide to alkyne under these conditions, a reaction time at ambient temperature of sixteen hours was sufficient to provide hexatriazenyl Pcs **13a-d** in yields of 24-44% from Pc **5b**. Given that each reaction represented the successful completion of 6 parallel azide-alkyne coupling reactions, these isolated yields represent a range of 79-87% for the individual CuAAC reactions.

Pcs **13a-d** were characterized by mass spectrometry, combustion analysis and UV/Vis spectroscopy. UV/Vis spectroscopic data was consistent with the chromophoric structure of Pcs **13a-d** relative to precursor Pc **5b** (Figure 1). The

Scheme 4. Synthesis of Pc derivatives **13a-d** by CuAAC.

UV/Vis absorption spectra exhibited a singlet Q-band ca. 685 nm indicating the existence of metallated Pcs. Pc **13d** showed additional absorption peaks at 530 nm and 490 nm due to the incorporation of the perylene diimide (PDI) chromophores.

Observation of the CuAAC reactions indicated poor solubility of the Cu complex. We anticipated that further utilization of the CuAAC reaction on Pc **5b**, particularly from Pcs bound to solid support surfaces such as ITO and ZnO, would require fully

Figure 1. UV/Vis absorption of Pcs **5b** and **13a-d** in CHCl₃.

Figure 2. UV/Vis spectra of isolated products ($\sim 10 \mu\text{M}$ in CHCl_3) from the CuAAC reaction between **5b** and **12d** at different reaction times, normalized to the Pc Q-band. (a) CuI and (b) $\text{Cu}(\text{PPh}_3)_3\text{Br}$ were used as catalysts, respectively.

soluble Cu sources such as $\text{Cu}(\text{PPh}_3)_3\text{Br}$,^{19a} especially in flow-cell configurations.¹⁶ We carried out the CuAAC reaction of azide **12d** with both $\text{Cu}(\text{PPh}_3)_3\text{Br}$ and CuI and monitored both by UV/Vis characterization over approximately 60 hours (Figure 2). Due to the large excess of azide, the quenched reaction mixture at each time interval was subjected to flash column chromatography to isolate the mixture of Pc species. UV/Vis spectra were normalized to the absorbance of the Pc Q-band to illustrate the relative increase of the PDI chromophore absorption, indicative of the PDI to Pc ratio in the product mixture. The incorporation of the PDI chromophore during the reaction was qualitatively followed by monitoring the isolated products at 530 nm, an optical window of Pcs. Upon normalization at the Pc Q-band, the PDI absorbance arriving at a constant indicated that the CuAAC reaction had reached completion.

The ratio of PDI absorbance to Pc Q-band reached 2.68 and 2.66 for CuI and $\text{Cu}(\text{PPh}_3)_3\text{Br}$ catalyzed reactions, respectively. A plot of the PDI absorbance maxima vs. reaction time (Figure 3a) indicates that both reactions reached this level of completion after six hours under these reaction conditions. By visual inspection of the reaction mixture at various time points, we observed a clear progression of color as more PDIs are incorporated on the Pc periphery (Figure 3a, inset). Monitoring of the reaction by FT-IR also showed progress and confirmed completion by the disappearance of characteristic terminal alkyne absorptions of *sp*-hybridized C-H at 3291 cm^{-1} and the $\text{C}\equiv\text{C}$ at 2119 cm^{-1} (Figure S11).

The influence of azide equivalents on the modification of Pc **5b** was also studied in a similar fashion. Keeping all other reaction conditions constant (CuI, DIPEA, CHCl_3), variation of the azide equivalents (1, 3, 10 relative to alkyne residue) of **12d** was performed (Figure 3b). As expected, we observed that the reaction progress was expedited with increased azide loading, with ten equivalents showing a plateauing effect within six hours, while three equivalents of azide likely afforded the product with extended reaction times of longer than three days (Figure 3b). The use of equimolar amounts of azide to free alkyne yielded a PDI-Pc ratio of only 2.18, which is significantly lower than observed with ten equivalents of azide (vide supra).

Figure 3. (a) Maximum PDI absorbance normalized to Pc Q-band intensity as a function of reaction time with CuI or $\text{Cu}(\text{PPh}_3)_3\text{Br}$ as the catalyst. (Inset) Digital image of isolated Pc mixture ($\sim 100 \mu\text{M}$ in CHCl_3) at different reaction times: (left to right) 1 h, 2 h, 3 h, 6 h, 50 h, catalyzed by $\text{Cu}(\text{PPh}_3)_3\text{Br}$. (b) Normalized absorbance as a function of reaction time with 1, 3, 10 equivalents of azide **12d** relative to alkyne moiety in **5b**.

Thin films of Pcs **5b**, **13d**, and PDI azide **12d** were prepared to investigate the nature of the Pc in the condensed state. Spin-coated films on glass were fabricated from CHCl_3 solutions ($10 \mu\text{M}$). The resulting crack-free solid films were analyzed by UV/Vis spectroscopy (Figure 4). Comparison of the solution phase and condensed-phase spectra of Pc **5b** revealed a significant degree of aggregation in the thin film as evidenced by the hypsochromically shifted component of the Q band at ca. 640 nm. Similarly, the condensed phase UV-Vis spectrum of PDI azide **12d** indicates extensive aggregation of the PDI chromophores as evidenced by the greater intensity of the vibronic band at ca. 490 nm relative to the fundamental transition at ca. 550 nm.

Interestingly, the UV-Vis spectrum of **13d** reveals that while the PDI chromophores in this conjugate remain aggregated, again

Figure 4. Condensed-phase UV/Vis spectra of **5b**, **12d** and **13d** spin-coated on glass.

evidenced by the relative intensities of the bands at 490 and 550 nm, the Pc chromophores appear to be in primarily unaggregated form. This suggests that peripheral substitution with PDIs through CuAAC chemistry can provide sufficient hindrance to central Pc aggregation, presumably by steric interference. However, we have previously observed varying degrees of frustration of aggregation with varying substituents on the periphery of Pc chromophores,^{19b,29} and in the case of **13d**, frustration of aggregation of the Pc cannot be merely the result of steric interference of the PDI moieties alone. An analogous compound to **13d** with second generation benzyl arylene ether dendrons, much bulkier substituents, in the same position as the PDI moieties in **13d**, exhibited Pc aggregation in the condensed phase.^{19b} We postulate that the strong aggregation tendency of the PDI moieties, rather than their steric bulk alone, is a contributing factor to preventing Pc aggregation, perhaps by creating a tight shell around the Pc core of the compound.

3. Conclusions

The modification of Pc peripheral substituents with CuAAC chemistry was demonstrated on asymmetric Pc scaffold **5b**. Asymmetric Pc derivatives **13a-d** were constructed from Pc **5b** and azides **12a-d** under CuAAC conditions. The utility of using the CuAAC reaction as a means to introduce various substituents onto the periphery of the Pc chromophore holds much promise in the preparation of multifunctional Pc derivatives. Modification of the hydroxyl group in the unique quadrant of the Pc chromophore will be the subject of future research.

4. Experimental section

4.1. General aspects

All reactions were run under a nitrogen or argon atmosphere unless otherwise noted. All chemicals were purchased from commercial sources and used without further purification unless otherwise noted. Compounds **1a**,^{19a} **1b**,^{19a} **2**,^{16a} **6**,^{9b} **9**,³⁰ **12a-d**³¹ were prepared according to the literature. DMSO was dried over freshly activated 4 Å molecular sieves. Anhydrous CH₂Cl₂ was distilled from CaH₂ under argon. Anhydrous THF was distilled from sodium and benzophenone under argon. Anhydrous THF was distilled from sodium and benzophenone under argon. ¹H NMR spectra were recorded on a Bruker DRX-500 MHz or AVIII-400 MHz spectrometer with ¹³C operating frequencies of 125 MHz or 100 MHz. ¹H NMR spectra were obtained in CDCl₃ or CD₂Cl₂:DMSO-*d*₆ (95:5) and calibrated using residual CHCl₃ (δ = 7.26 ppm) or CHDCl₂ (δ = 5.32 ppm) as an internal reference. ¹³C NMR spectra were obtained in CDCl₃ or CD₂Cl₂:DMSO-*d*₆ (95:5) and calibrated using CDCl₃ (δ = 77.0 ppm) or CD₂Cl₂ (δ = 53.8 ppm) as an internal reference. UV/Vis spectroscopy was performed with a Shimadzu UV-2401PC spectrometer. Mass spectra were obtained at the Mass Spectrometry Facility, Department of Chemistry and Biochemistry, University of Arizona. Elemental analysis were obtained from NuMega Resonance Labs, Inc. Flash column chromatography and TLC were performed using silica gel 60 and Silica Gel 60 F₂₅₄ plates respectively.

4.2. Experimental procedures and spectroscopic data

4.2.1. 2,3,9,10,16,17-Hexa-(4'-(hex-5''-ynyloxy)phenoxy)-23-hydroxyphthalocyanine (5a) by statistical macrocyclization followed by acidic cleavage. A mixture of phthalonitrile **2** (0.9 g, 3 mmol), phthalonitrile **1a** (5.2 g, 10 mmol), DBU (2.0 g, 14 mmol) and LiBr (148 mg, 1.37 mmol) in 60 mL 1-pentanol were refluxed under Ar for 8 h. The reaction mixture was allowed to cool to RT and then poured into MeOH (150 mL). The precipitate was filtered, washed with MeOH, air dried and then

chromatographed (SiO₂, CH₂Cl₂: MeOH = 99:1). The green eluent was collected and concentrated under reduced pressure. A solution of the resultant green residue, TFA (5 mL) and CH₂Cl₂ (50 mL) was stirred at room temperature under Ar for 4h. The reaction mixture was washed with water (50 mL), aqueous NaHCO₃ (50 mL), and the organic layer was dried over MgSO₄, filtered, and evaporated. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂: MeOH = 99:1) to give 1.2 g of Pc **5a** (22% yield) as a green solid: ¹H NMR (500 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 9.85 (s, 1H), 8.30-7.90 (m, 8H), 7.44-7.26 (m, 13H), 7.06-6.93 (m, 12H), 4.06-3.99 (m, 12H), 2.38-2.29 (m, 12H), 2.11-2.07 (m, 6H), 2.01-1.95 (m, 12H), 1.85-1.77 (m, 12H); ¹³C NMR (125 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 160.6, 156.0, 155.9, 155.8, 155.4, 151.63, 151.55, 151.4, 151.1, 151.0, 150.9, 150.5, 150.4, 149.7, 137.3, 132.5, 1324, 131.7, 130.7, 130.4, 127.0, 124.2, 121.1, 121.0, 120.3, 120.2, 120.0, 119.5, 119.2, 116.0, 115.9, 115.8, 113.5, 113.4, 112.7, 112.5, 111.4, 111.1, 108.1, 84.52, 84.49, 68.96, 68.95, 68.91, 68.90, 68.5, 68.2, 30.0, 28.92, 28.88, 25.60, 25.56, 18.59, 18.55; MS (MALDI) calcd for C₁₀₄H₉₁N₈O₁₃ [M+H]⁺: m/z 1659.67, found 1659.72. Anal. calcd for C₁₀₄H₉₀N₈O₁₃: C, 75.25; H, 5.47; N, 6.75. Found: C, 75.00; H, 5.90; N, 6.44%

4.2.2. 2,3,9,10,16,17-Hexa-(4'-(hex-5''-ynyloxy)phenoxy)-23-hydroxyphthalocyanine (5a) by fluoride-deprotection of 11. A mixture of phthalonitrile **6** (400 mg, 1.12 mmol), phthalonitrile **1b** (3.5 g, 4.4 mmol), DBU (836 mg, 5.50 mmol) and LiBr (47 mg, 0.55 mmol) in 40 mL 1-pentanol was refluxed under Ar for 8 h. The reaction mixture was allowed to cool to room temperature, and poured into MeOH. The precipitate was filtered, washed with MeOH, air dried and chromatographed on silica gel, eluting with CH₂Cl₂: MeOH = 95:5. The green eluent was collected and concentrated in vacuum. The resultant green residue and cross-linker **9** (60 mg, 0.24 mmol) were dissolved in degassed CH₂Cl₂ (30 mL) under N₂. To this solution was added [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (Grubbs' 2nd generation catalyst, 60 mg, 72 μ mol), and the mixture was heated at 40 °C for 12 h. CH₂Cl₂ (3 mL), MeCN (1.5 mL), and ethyl vinyl ether (1.5 mL) were added sequentially. The mixture was heated at 40 °C for 1 h. The polymer was filtered and washed with CH₂Cl₂ (3×100 mL) and extracted with CH₂Cl₂ (Soxhlet) for 48 h. The resulting Pc polymer was rinsed out of the thimble with CH₂Cl₂ and concentrated to 20 mL. 2 mL trifluoroacetic acid was added to the suspension of polymer Pc, and the mixture was stirred at room temperature under Ar for 1 h. The reaction mixture was washed with water (20 mL), aqueous NaHCO₃ (20 mL), and the organic layer was dried over MgSO₄, filtered, and evaporated. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂: MeOH = 95:5) to give Pc **11** (0.26 g, 10% yield) as a green solid: ¹H NMR (500 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 9.96 (br s, 1H), 8.66 (br s, 1H), 8.48 (br s, 2H), 8.44 (br s, 1H), 8.36 (br s, 1H), 8.33 (br s, 1H), 8.27 (br s, 2H), 7.61 (d, J = 9 Hz, 1H), 7.38-7.34 (m, 4H), 7.28-7.25 (m, 8H), 7.05-7.03 (m, 4H), 6.99-6.94 (m, 8H), 4.06-3.99 (m, 12H), 2.47-2.40 (m, 12H), 2.08-2.01 (m, 12H), 1.87-1.79 (m, 12H), 1.13-1.09 (m, 126H); ¹³C NMR (125 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 160.8, 158.5, 156.1, 155.98, 155.90, 155.86, 155.6, 151.7, 151.64, 151.60, 151.4, 151.19, 151.16, 151.1, 150.74, 150.66, 150.2, 150.1, 149.9, 137.5, 132.8, 132.7, 132.2, 130.9, 130.7, 127.2, 124.4, 120.9, 120.9, 120.2, 120.1, 119.62, 119.58, 119.4, 116.12, 116.07, 115.95, 115.89, 115.6, 113.8, 113.7, 113.1, 112.9, 111.9, 111.5, 110.9, 109.13, 109.06, 108.3, 80.9, 80.80, 80.76, 68.4, 68.3, 29.0, 26.1, 26.0, 20.1, 20.0, 18.9, 18.8, 18.2, 12.21, 12.20, 12.0, 11.9, 11.7, 11.6, 11.5. To a solution of Pc **11** (170 mg, 0.0650 mmol) in 15 mL THF was added TBAF (0.7 mL, 1.0 M in THF, 0.7 mmol) in one portion. The reaction mixture was stirred at room temperature for 8h and the reaction was quenched by the addition of aqueous NH₄Cl. The aqueous layer was

extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2 , CH_2Cl_2 : MeOH = 99:1) to yield Pc **5a** (70 mg, 70%) as a green solid: ^1H NMR (500 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 9.91 (br s, 1H), 8.18-7.72 (m, 8H), 7.36-7.25 (m, 12H), 7.03-6.93 (m, 12H), 4.00 (br s, 12H), 2.33 (br s, 12H), 2.14-2.10 (m, 6H), 1.96 (m, 12H), 1.78 (m, 12H); ^{13}C NMR (125 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 160.5, 156.0, 155.83, 155.76, 155.71, 155.65, 155.42, 155.38, 151.7, 151.6, 151.5, 151.3, 151.0, 150.9, 150.8, 150.5, 150.4, 149.6, 149.5, 124.1, 121.2, 121.03, 120.98, 120.3, 120.1, 119.5, 119.0, 116.1, 115.9, 115.83, 115.76, 115.7, 113.4, 113.3, 112.6, 112.5, 111.3, 110.9, 107.9, 84.5, 69.1, 69.02, 68.97, 68.2, 68.1, 28.9, 28.8, 25.52, 25.49, 18.52, 18.48; MS (MALDI) calcd for $\text{C}_{104}\text{H}_{91}\text{N}_8\text{O}_{13}$ [M+H] $^+$: m/z 1659.67, found 1659.69. Anal. calcd for $\text{C}_{104}\text{H}_{90}\text{N}_8\text{O}_{13}$: C, 75.25; H, 5.47; N, 6.75. Found: C, 74.86; H, 5.87; N, 6.47%.

4.2.3. Zinc 2,3,9,10,16,17-hexa(4'-(hex-5''-ynloxy)phenoxy)-23-hydroxyphthalocyanine (5b). A mixture of phthalonitrile **2** (0.1 g, 0.4 mmol), phthalonitrile **1** (0.6 g, 1 mmol), DBU (0.2 g, 1 mmol) and $\text{Zn}(\text{OAc})_2$ (140 mg, 0.765 mmol) in 60 mL 1-pentanol was refluxed under Ar for 8 h. The reaction mixture was allowed to cool to RT, and poured in MeOH (150 mL). The precipitate was filtered, washed with MeOH, air dried and then chromatographed (SiO_2 , CH_2Cl_2 : MeOH = 99:1). The green eluent was collected and concentrated under reduced pressure. A solution of the resultant green residue, TFA (2 mL) and CH_2Cl_2 (20 mL) was stirred at RT under Ar for 4h. The reaction mixture was washed with water (50 mL), aqueous NaHCO_3 (50 mL), and the organic layer was dried over MgSO_4 , filtered, and evaporated. The crude product was purified by column chromatography (SiO_2 , CH_2Cl_2 : MeOH = 99:1) to give Pc **5b** (0.13 g, 20% yield) as a green solid: ^1H NMR (500 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 9.77 (s, 1H), 8.80-8.40 (m, 8H), 7.51(d, J = 8 Hz, 1H), 7.36-7.35(m, 4H), 7.29-7.24 (m, 8H), 7.06-7.02(m, 4H), 6.98-6.95 (m, 8H), 4.07-4.00 (m, 12H), 2.35-2.30 (m, 12H), 2.08-2.06 (m, 6H), 2.00-1.91 (m, 12H), 1.81-1.73 (m, 12H); ^{13}C NMR (125 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 160.2, 156.0, 155.8, 155.60, 155.58, 155.52, 154.2, 153.3, 152.5, 151.8, 151.8, 151.64, 151.58, 151.2, 151.1, 151.0, 150.9, 150.5, 150.3, 149.9, 149.8141.0, 134.4, 134.3, 133.9, 130.7, 124.1, 120.8, 119.9, 119.8, 119.7, 119.6, 118.21, 116.0, 115.8, 113.74, 113.65, 113.5, 112.2, 112.0, 108.668.93, 68.87, 68.3, 68.23, 68.18, 30.0, 28.8, 25.5, 25.51, 25.47, 18.48, 18.45; MS (MALDI) calcd for $\text{C}_{104}\text{H}_{88}\text{N}_8\text{O}_{13}\text{Zn}$ [M] $^+$: m/z 1720.58, found 1659.72. Anal. calcd for $\text{C}_{104}\text{H}_{88}\text{N}_8\text{O}_{13}\text{Zn}$: C, 72.49; H, 5.15; N, 6.50. Found: C, 72.01; H, 5.60; N, 6.51%.

4.2.4. Zinc 2,3,9,10,16,17-Hexa(4'-(4''-(1'''-dodecyl-1 H-1''',2''',3'''-triazol-4'''-yl)-butoxy)phenoxy)-23-hydroxyphthalocyanine (13a). Asymmetric Pc **5b** (50 mg, 0.030 mmol) and **12a** (368 mg, 1.74 mmol) were dissolved in 20 mL dry THF before N,N-diisopropylethylamine (45 mg, 0.35 mmol) and CuI (13 mg, 0.070 mmol) were added to the solution. The mixture was degassed and backfilled with argon three times before stirring overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 followed by washing with 3x 100 mL 0.1 M EDTA, 3x 100 mL 1 M HCl, and 3x 100 mL brine. The organic layer was concentrated and the crude product was purified by column chromatography (SiO_2 , CH_2Cl_2 : MeOH = 95:5), followed by recrystallization (3x) from CH_2Cl_2 /MeOH to give Pc **13a** as a green solid (21 mg, 24%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{176}\text{H}_{238}\text{N}_{26}\text{O}_{13}\text{Zn}$ [M] $^+$: m/z 2987.81, found 2987.77. Anal. calcd for $\text{C}_{176}\text{H}_{238}\text{N}_{26}\text{O}_{13}\text{Zn}$: C, 70.67; H, 8.02; N, 12.17. Found: C, 70.49; H, 8.26; N, 11.83.

4.2.5. Zinc 2,3,9,10,16,17-Hexa(4'-(4''-(1'''-(3'''-phenylpropyl)-1 H-1''',2''',3'''-triazol-4'''-yl)butoxy) phenoxy)-23-hydroxyphthalocyanine (13b). Following the procedure for Pc **13a**, asymmetric Pc **5b** (50 mg, 0.030 mmol), **12b** (281 mg, 1.74 mmol), dry CHCl_3 (10 mL), N,N-diisopropylethylamine (113 mg, 0.876 mmol) and $\text{Cu}(\text{PPh}_3)_3\text{Br}$ (135 mg, 0.145 mmol) yielded Pc **13b** as a green solid (27 mg, 35%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{158}\text{H}_{154}\text{N}_{26}\text{O}_{13}\text{Zn}$ [M] $^+$: m/z 2687.15, found 2687.16. Anal. calcd for $\text{C}_{158}\text{H}_{154}\text{N}_{26}\text{O}_{13}\text{Zn}$: C, 70.53; H, 5.77; N, 13.54. Found: C, 70.47; H, 6.14; N, 13.19.

4.2.6. Zinc 2,3,9,10,16,17-Hexa(4'-(4''-(1'''-(3-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)-phenoxy) propyl)-1H-1,2,3-triazol-4-yl)-butoxy)phenoxy)-23-hydroxyphthalocyanine (13c). Following the procedure for Pc **13a**, asymmetric Pc **5b** (20 mg, 0.012 mmol), **12c** (200 mg, 0.726 mmol), dry CHCl_3 (20 mL), N,N-diisopropylethylamine (45 mg, 0.35 mmol) and $\text{Cu}(\text{PPh}_3)_3\text{Br}$ (54 mg, 0.058 mmol) yielded Pc **13c** as a green solid (17 mg, 44%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{188}\text{H}_{191}\text{N}_{26}\text{O}_{31}\text{Zn}$ [M+H] $^+$: m/z 3372.35, found 3372.12. Anal. calcd for $\text{C}_{188}\text{H}_{190}\text{N}_{26}\text{O}_{31}\text{Zn}$: C, 66.90; H, 5.67; N, 10.79. Found: C, 66.84; H, 5.90; N, 10.51.

4.2.7. Compound 13d. Following the procedure for Pc **13a**, a mixture of asymmetric Pc **5b** (21 mg, 0.012 mmol), **12d** (493 mg, 0.752 mmol), dry CHCl_3 (10 mL), N,N-diisopropylethylamine (50 mg, 0.39 mmol) and CuI (13 mg, 0.068 mmol) was stirred at room temperature overnight. After workup the crude solid was loaded to column chromatography and first flushed with 5% v/v ethyl acetate in CH_2Cl_2 until excess **12d** was completely removed from the column. Then the product was eluted with 5% v/v MeOH in CH_2Cl_2 followed by recrystallization from CHCl_3 /MeOH to give Pc **13d** as a dark purple solid (24 mg, 35%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{344}\text{H}_{335}\text{N}_{38}\text{O}_{37}\text{Zn}$ [M+H] $^+$: m/z 5653.48, found 5653.870. Anal. calcd for $\text{C}_{344}\text{H}_{334}\text{N}_{38}\text{O}_{37}\text{Zn}$: C, 73.02; H, 5.95; N, 9.41. Found: C, 73.02; H, 5.91; N, 9.08.

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Cycloaddition

ABSTRACT

The use of asymmetric phthalocyanines (Pcs) as platforms for the preparation of several asymmetric hexatriazolyl-monohydroxyphthalocyanines via copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction was investigated. Asymmetric Pcs **5a** and **5b** were prepared through statistical macrocyclization of phthalonitriles (Pns) **1a** and **2** to give PMB-protected **4a** and **4b** which afforded asymmetric Pcs **5a** and **5b** after acidic cleavage. The “ROMP-Capture-Release” method as a synthetic approach to prepare asymmetric Pc **5b** was also evaluated. TIPS-protection of the terminal alkynes was necessary to prevent cross-coupling during the ring-opening metathesis polymerization (ROMP) step. Zinc Pc **5b** was successfully used as a scaffold for functional modification under CuAAC conditions using several azides bearing hydrophobic, photo-crosslinkable, or electroactive moieties. Monitoring the CuAAC reaction by both UV/Vis and FT-IR spectroscopies provided insight into the role of azide equivalent, reaction time, and catalyst on reaction progress.

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1. Introduction

Pcs are 18 π -electron tetrapyrrolic macrocycles that have been applied in a number of advanced technologies including optical limiting devices,¹ photodynamic therapy (PDT),² organic field-effect transistors (OFETs),³ and organic photovoltaic (OPV) devices.⁴ Due to their physical and chemical properties,⁵ effort has been dedicated to the development of structurally diverse Pcs. Of particular interest is the development of asymmetrically substituted AB₃ Pcs⁶ which can possess improved photodynamic properties⁷ and unique second-order nonlinear optical effects.^{1d,8} Asymmetric AB₃ Pcs containing active functional groups in the odd quadrant such as hydroxy,⁹ amino,¹⁰ carboxylic acid,^{10a,11} isothiocyanate,¹² azide,¹³ and alkyne¹⁴ serve as building blocks in the design of Pc-based molecular systems.¹⁵ We have used asymmetric AB₃ Pcs as components of a model system to investigate charge capture at oxide interfaces from typical OPV donor materials.¹⁶

However, efficient production of Pc-based materials with structural diversity, including AB₃ asymmetry, still remains an open challenge, especially for Pcs with sensitive substituents that are not compatible with the conditions of cyclization of Pc precursors. The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction¹⁷ has proven useful for the synthesis of novel materials,¹⁸ and has been demonstrated by us¹⁹ and others²⁰ as appropriate for Pc/Nc modification. We have previously

demonstrated preparation of symmetric octaalkynyl Pcs as an effective platform for Pc chromophore modification through copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reactions.¹⁹ Herein we report the synthesis of asymmetric hexaalkynyl AB₃ Pcs **5a** and **5b** and subsequent post-cyclization modification with various azides to further demonstrate the utility of Pc modification through the CuAAC reaction.²¹

2. Results and Discussion

In seeking to use the CuAAC reaction as a means of increasing structural diversity in asymmetric Pc chromophores, we identified bis(alkynyl) Pn **1a**,^{19a} readily prepared from 4,5-bis(4'-hydroxyphenoxy)phthalonitrile and commercially available 1-hexyn-6-ol through a Mitsunobu reaction, as a suitable precursor. We have previously reported that macrocyclization of **1a** under basic Linstead conditions afforded octaalkynyl ZnPc **3b** which possesses good solubility in common organic solvents such as THF, DCM, acetone, and Et₂O.^{19a} Protection of the terminal alkyne moieties was not necessary during the macrocyclization reaction, providing a relatively simple way to incorporate acetylenic moieties into a Pc scaffold.

To use Pn **1a** in the preparation of asymmetric AB₃ Pcs, we needed to choose a strategy for asymmetric Pc synthesis. The preparation of asymmetrically substituted AB₃ Pcs can be achieved by solution phase statistical Linstead macrocyclization between two different phthalonitriles or diiminoisindolines.²² Ready availability of precursors makes the statistical macrocyclization often a more effective and direct than other

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Scheme 1. Synthesis of asymmetric Pc **5a** and **5b** by statistical macrocyclization followed by acidic cleavage.

approaches such as solid-phase synthetic methods²³ and the “sub-phthalocyanine” method.²⁴ The challenge of statistical macrocyclization is that it inherently yields a mixture of Pc products with minimal structural differences, making isolation of the desired Pcs often challenging.

However, we have recently reported statistical cyclization strategies but with modifications aimed at simplifying purification. We have described the synthesis of asymmetric AB₃ Pcs via: (1) statistical macrocyclization using 4-methoxybenzyl (PMB)-protected Pn^{16a} to yield asymmetric AB₃ Pcs with a unique phenolic quadrant that aids in isolation once deprotected; and (2) a ROMP-Capture-Release^{9b} strategy using a norbornyl-tagged Pn, again leading to an asymmetric AB₃ Pc with a phenolic unique quadrant. Both methods would potentially serve to produce asymmetric AB₃ Pcs with acetylenic moieties for post-synthetic modification by the CuAAC reaction.

Employing the former method, statistical macrocyclization of **1a** and 4-methoxybenzyl (PMB)-protected Pn **2**^{16a} (Pn **1a**:**2** = 3:1) in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a base and either LiBr or Zn(OAc)₂ as metal template provided a mixture of symmetric and asymmetric Pcs (Scheme 1). The crude mixture was chromatographed to remove DBU and excess metal salt from the Pc mixture. MALDI mass spectral analysis of the resultant Pc mixtures revealed the presence of PMB-protected A₃B (**4a/4b**) and symmetric A₄ (**3a/3b**) Pcs. Subjecting the mixtures to PMB deprotection conditions yielded a mixture of asymmetric free hydroxyl A₃B (**5a/5b**) and symmetric A₄ (**3a/3b**) Pcs. Due to the increased polarity afforded by the unique phenolic quadrant in the asymmetric Pcs, this mixture was easily separable by flash chromatography to provide the desired macrocycles **5a/5b** in overall yields of 20 and 22% from Pn **2**, respectively.

We also evaluated the latter method, our previously reported “ROMP-Capture-Release” strategy^{9b} to synthesize asymmetric hexaalkynyl Pc **5a**. This method employs solution phase crossover-Linstead cyclization of a norbornyl-tagged Pn (A) with a second Pn (B), followed by selective capture of asymmetric norbornyl-tagged AB₃ Pc under ROMP conditions and acidic cleavage of the target asymmetric Pc from the ROMP polymer. While this method was successfully developed for the synthesis of an asymmetric AB₃ Pc with alkyl substituents,^{9b} the concern of cross-coupling of free alkynes with the norbornyl tag during the ROMP process remained. Enyne metathesis²⁵ is well established to occur with ruthenium-based metathesis catalysts,²⁶ including the cross-metathesis of terminal alkynes with norbornene derivatives.²⁷ An unsuccessful attempt to ROMP a 7-oxanorbornene monomer with a pendant propargyl group was attributed to the competing enyne metathesis reaction.²⁸ If alkynes undergo ring-opening/ring-closing metathesis (ROM/RCM) with the norbornene moieties in the presence of Grubbs’ catalyst, a protecting strategy can be employed to prevent competing metathesis with the alkyne moiety.

To provide a comparison, preparation of two Pcs with free and protected alkyne peripheries was conducted (Scheme 2) by ROMP-Capture-Release through statistical macrocyclization of norbornyl-tagged Pc **6** with both acetylenic Pn **1a** and its TIPS-protected analog **1b**. When the mixture of Pcs **7a** and **8a** was subjected to the previously established ROMP conditions,^{9b} no polymer precipitate was observed. Modified conditions were also attempted, such as increasing the loading of crosslinker **9** and varying the reaction concentration and time, with similar negative results. Conversely, when the mixture of TIPS-protected Pcs **7b** and **8b** was subjected to the ROMP conditions in the presence of crosslinker **9** the corresponding cross-linked polymer was obtained after filtration and CH₂Cl₂ Soxhlet extraction (Scheme 3). Treatment of the resulting ROMP polymer **10** with 10% trifluoroacetic acid (TFA) in CH₂Cl₂ resulted in release of Pc **11**. Deprotection of Pc **11** using an excess of tetrabutylammonium fluoride (TBAF) afforded Pc **5a** in 7% overall yield from Pn **6**.

Despite the successful isolation of Pc **5a** via the ROMP-Capture-Release strategy, including successful prevention of

Scheme 2. Statistical macrocyclization of Pns **1a**, **1b**, and **6**.

Scheme 3. ROMP-Capture-Release leading to asymmetric Pc **5a**.

alkyne metathesis, the lengthy reaction route involving the additional protection and deprotection resulted in low yields of the desired asymmetric Pc. This hampered straightforward scale-up to larger quantities of material. We relied on the statistical macrocyclization using 4-methoxybenzyl (PMB)-protected Pn for further preparation of **5a** and **5b**.

With Pcs **5a** and **5b** in hand, we examined modification of the periphery of the Pc chromophore with CuAAC chemistry. Although we had previous success with insertion of copper into non-metallated Pcs in the course of CuAAC reactions,¹⁹ we observed incomplete metal-insertion in the CuAAC reactions of Pc **5a** and azides, characterized by both MS-MALDI and UV/Vis. Samples isolated from these reactions contained a mixture of both Cu-metallated and metal-free Pc. Metallation of the modified Pc derivatives using various Cu(II) salts yielded insufficient intercalation as well.

We expected that Zn-metallated Pc **5b** would prevent the inherent Cu-insertion reaction in the modification of Pcs by CuAAC and therefore allow the use of less CuI. Conditions similar to those described in the previous literature were first applied to reactions with azides **12a-c**, CuI, and DIPEA in THF (Scheme 4).^{19b} Due to the poor solubility of **12d** in THF, the reaction towards **13d** was carried out in CHCl_3 . Using a 10:1 ratio of azide to alkyne under these conditions, a reaction time at ambient temperature of sixteen hours was sufficient to provide hexatriazeryl Pcs **13a-d** in yields of 24-44% from Pc **5b**. Given that each reaction represented the successful completion of 6 parallel azide-alkyne coupling reactions, these isolated yields represent a range of 79-87% for the individual CuAAC reactions.

Pcs **13a-d** were characterized by mass spectrometry, combustion analysis and UV/Vis spectroscopy. UV/Vis spectroscopic data was consistent with the chromophoric structure of Pcs **13a-d** relative to precursor Pc **5b** (Figure 1). The

Scheme 4. Synthesis of Pc derivatives **13a-d** by CuAAC.

Figure 2. UV/Vis spectra of isolated products ($\sim 10 \mu\text{M}$ in CHCl_3) from the CuAAC reaction between **5b** and **12d** at different reaction times, normalized to the Pc Q-band. (a) CuI and (b) $\text{Cu}(\text{PPh}_3)_3\text{Br}$ were used as catalysts, respectively.

UV/Vis absorption spectra exhibited a singlet Q-band ca. 685 nm indicating the existence of metallated Pcs. Pc **13d** showed additional absorption peaks at 530 nm and 490 nm due to the incorporation of the perylene diimide (PDI) chromophores.

Observation of the CuAAC reactions indicated poor solubility of the Cu complex. We anticipated that further utilization of the CuAAC reaction on Pc **5b**, particularly from Pcs bound to solid support surfaces such as ITO and ZnO, would require fully soluble Cu sources such as $\text{Cu}(\text{PPh}_3)_3\text{Br}$,^{19a} especially in flow-cell configurations.¹⁶ We carried out the CuAAC reaction of azide **12d** with both $\text{Cu}(\text{PPh}_3)_3\text{Br}$ and CuI and monitored both by UV/Vis characterization over approximately 60 hours (Figure 2). Due to the large excess of azide, the quenched reaction mixture at each time interval was subjected to flash column chromatography to isolate the mixture of Pc species. UV/Vis spectra were normalized to the absorbance of the Pc Q-band to illustrate the relative increase of the PDI chromophore absorption, indicative of the PDI to Pc ratio in the product mixture. The incorporation of the PDI chromophore during the reaction was qualitatively followed by monitoring the isolated products at 530 nm, an optical window of Pcs. Upon normalization at the Pc Q-band, the PDI absorbance arriving at a constant indicated that the CuAAC reaction had reached completion.

The ratio of PDI absorbance to Pc Q-band reached 2.68 and 2.66 for CuI and $\text{Cu}(\text{PPh}_3)_3\text{Br}$ catalyzed reactions, respectively. A plot of the PDI absorbance maxima vs. reaction time (Figure 3a) indicates that both reactions reached this level of completion after six hours under these reaction conditions. By visual inspection of the reaction mixture at various time points, we observed a clear progression of color as more PDIs are incorporated on the Pc periphery (Figure 3a, inset). Monitoring of the reaction by FT-IR also showed progress and confirmed completion by the disappearance of characteristic terminal alkyne absorptions of *sp*-hybridized C-H at 3291 cm^{-1} and the $\text{C}\equiv\text{C}$ at 2119 cm^{-1} (Figure S11).

The ~~impact-influence~~ of azide equivalents on the modification of Pc **5b** was also studied in a similar fashion. Keeping all other reaction conditions constant (CuI, DIPEA, CHCl_3), variation of the azide equivalents (1, 3, 10 relative to alkyne residue) of **12d**

Figure 3. (a) Maximum PDI absorbance normalized to Pc Q-band intensity as a function of reaction time with CuI or $\text{Cu}(\text{PPh}_3)_3\text{Br}$ as the catalyst. (Inset) Digital image of isolated Pc mixture ($\sim 100 \mu\text{M}$ in CHCl_3) at different reaction times: (left to right) 1 h, 2 h, 3 h, 6 h, 50 h, catalyzed by $\text{Cu}(\text{PPh}_3)_3\text{Br}$. (b) Normalized absorbance as a function of reaction time with 1, 3, 10 equivalents of azide **12d** relative to alkyne moiety in **5b**.

was performed (Figure 3b). As expected, we observed that the reaction progress was expedited with increased azide loading, with ten equivalents showing a plateauing effect within six hours, while three equivalents of azide likely afforded the product with extended reaction times of longer than three days (Figure 3b). The use of equimolar amounts of azide to free alkyne yielded a PDI-Pc ratio of only 2.18, which is significantly lower than observed with ten equivalents of azide (vide supra).

Thin films of Pcs **5b**, **13d**, and PDI azide **12d** were prepared to investigate the nature of the Pc in the condensed state. Spin-coated films on glass were fabricated from CHCl_3 solutions ($10 \mu\text{M}$). The resulting crack-free solid films were analyzed by UV/Vis spectroscopy (Figure 4). Comparison of the solution phase and condensed-phase spectra of Pc **5b** revealed a significant degree of aggregation in the thin film as evidenced by

Figure 4. Condensed-phase UV/Vis spectra of **5b**, **12d** and **13d** spin-coated on glass.

the hypsochromically shifted component of the Q band at ca. 640 nm. Similarly, the condensed phase UV-Vis spectrum of PDI azide **12d** indicates extensive aggregation of the PDI chromophores as evidenced by the greater intensity of the vibronic band at ca. 490 nm relative to the fundamental transition at ca. 550 nm.

Interestingly, the UV-Vis spectrum of **13d** reveals that while the PDI chromophores in this conjugate remain aggregated, again evidenced by the relative intensities of the bands at 490 and 550 nm, the Pc chromophores appear to be in primarily unaggregated form. This suggests that peripheral substitution with PDIs through CuAAC chemistry can provide sufficient hindrance to central Pc aggregation, presumably by steric interference. However, we have previously observed varying degrees of frustration of aggregation with varying substituents on the periphery of Pc chromophores,^{19b,29} and in the case of **13d**, frustration of aggregation of the Pc cannot be merely the result of steric interference of the PDI moieties alone. An analogous compound to **13d** with second generation benzyl arylene ether dendrons, much bulkier substituents, in the same position as the PDI moieties in **13d**, exhibited Pc aggregation in the condensed phase.^{19b} We postulate that the strong aggregation tendency of the PDI moieties, rather than their steric bulk alone, is a contributing factor to preventing Pc aggregation, perhaps by creating a tight shell around the Pc core of the compound.

3. Conclusions

The modification of Pc peripheral substituents with CuAAC chemistry was demonstrated on asymmetric Pc scaffold **5b**. Asymmetric Pc derivatives **13a-d** were constructed from Pc **5b** and azides **12a-d** under CuAAC conditions. The utility of using the CuAAC reaction as a means to introduce various substituents onto the periphery of the Pc chromophore holds much promise in the preparation of multifunctional Pc derivatives. Modification of the hydroxyl group in the unique quadrant of the Pc chromophore will be the subject of future research.

4. Experimental section

4.1. General aspects

All reactions were run under a nitrogen or argon atmosphere unless otherwise noted. All chemicals were purchased from commercial sources and used without further purification unless otherwise noted. Compounds **1a**,^{19a} **1b**,^{19a} **2**,^{16a} **6**,^{9b} **9**,³⁰ **12a-d**³¹ were prepared according to the literature. DMSO was dried over freshly activated 4 Å molecular sieves. Anhydrous CH₂Cl₂ was distilled from CaH₂ under argon. Anhydrous THF was distilled from sodium and benzophenone under argon. Anhydrous THF was distilled from sodium and benzophenone under argon. ¹H NMR spectra were recorded on a Bruker DRX-500 MHz or AVIII-400 MHz spectrometer with ¹³C operating frequencies of 125 MHz or 100 MHz. ¹H NMR spectra were obtained in CDCl₃ or CD₂Cl₂:DMSO-*d*₆ (95:5) and calibrated using residual CHCl₃ (δ = 7.26 ppm) or CHDCl₂ (δ = 5.32 ppm) as an internal reference. ¹³C NMR spectra were obtained in CDCl₃ or CD₂Cl₂:DMSO-*d*₆ (95:5) and calibrated using CDCl₃ (δ = 77.0 ppm) or CD₂Cl₂ (δ = 53.8 ppm) as an internal reference. UV/Vis spectroscopy was performed with a Shimadzu UV-2401PC spectrometer. Mass spectra were obtained at the Mass Spectrometry Facility, Department of Chemistry and Biochemistry, University of Arizona. Elemental analysis were obtained from NuMega Resonance Labs, Inc. Flash column chromatography and TLC were performed using silica gel 60 and Silica Gel 60 F₂₅₄ plates respectively.

4.2. Experimental procedures and spectroscopic data

4.2.1. 2,3,9,10,16,17-Hexa-(4'-(hex-5''-ynyloxy)phenoxy)-23-hydroxyphthalocyanine (**5a**) by statistical macrocyclization followed by acidic cleavage. A mixture of phthalonitrile **2** (0.9 g, 3 mmol), phthalonitrile **1a** (5.2 g, 10 mmol), DBU (2.0 g, 14 mmol) and LiBr (148 mg, 1.37 mmol) in 60 mL 1-pentanol were refluxed under Ar for 8 h. The reaction mixture was allowed to cool to RT and then poured into MeOH (150 mL). The precipitate was filtered, washed with MeOH, air dried and then chromatographed (SiO₂, CH₂Cl₂: MeOH = 99:1). The green eluent was collected and concentrated under reduced pressure. A solution of the resultant green residue, TFA (5 mL) and CH₂Cl₂ (50 mL) was stirred at room temperature under Ar for 4h. The reaction mixture was washed with water (50 mL), aqueous NaHCO₃ (50 mL), and the organic layer was dried over MgSO₄, filtered, and evaporated. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂: MeOH = 99:1) to give 1.2 g of Pc **5a** (22% yield) as a green solid: ¹H NMR (500 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 9.85 (s, 1H), 8.30-7.90 (m, 8H), 7.44 (s, 1H), 7.42-7.26 (m, 12H), 7.06-6.93 (m, 12H), 4.06-3.99 (m, 12H), 2.38-2.29 (m, 12H), 2.11-2.07 (m, 6H), 2.01-1.95 (m, 12H), 1.85-1.77 (m, 12H); ¹³C NMR (125 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 160.6, 156.0, 155.9, 155.8, 155.4, 151.63, 151.55, 151.4, 151.1, 151.0, 150.9, 150.5, 150.4, 149.7, 137.3, 132.5, 1324, 131.7, 130.7, 130.4, 127.0, 124.2, 121.1, 121.0, 120.3, 120.2, 120.0, 119.5, 119.2, 116.0, 115.9, 115.8, 113.5, 113.4, 112.7, 112.5, 111.4, 111.1, 108.1, 84.52, 84.49, 68.96, 68.95, 68.91, 68.90, 68.5, 68.2, 30.0, 28.92, 28.88, 25.60, 25.56, 18.59, 18.55; MS (MALDI) calcd for C₁₀₄H₉₁N₈O₁₃ [M+H]⁺: m/z 1659.67, found 1659.72. Anal. calcd for C₁₀₄H₉₀N₈O₁₃: C, 75.25; H, 5.47; N, 6.75. Found: C, 75.00; H, 5.90; N, 6.44%

4.2.2. 2,3,9,10,16,17-Hexa-(4'-(hex-5''-ynyloxy)phenoxy)-23-hydroxyphthalocyanine (**5a**) by fluoride-deprotection of **11**. A mixture of phthalonitrile **6** (400 mg, 1.12 mmol), phthalonitrile **1b** (3.5 g, 4.4 mmol), DBU (836 mg, 5.50 mmol) and LiBr (47 mg, 0.55 mmol) in 40 mL 1-pentanol was refluxed under Ar for 8 h. The reaction mixture was allowed to cool to room temperature, and poured into MeOH. The precipitate was filtered, washed with MeOH, air dried and chromatographed on silica gel, eluting with CH₂Cl₂: MeOH = 95:5. The green eluent was collected and concentrated in vacuum. The resultant green residue and cross-linker **9** (60 mg, 0.24 mmol) were dissolved in degassed CH₂Cl₂ (30 mL) under N₂. To this solution was added [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethyl-ene)(tricyclohexylphosphine)ruthenium (Grubbs' 2nd generation catalyst, 60 mg, 72 μ mol), and the mixture was heated at 40 °C for 12 h. CH₂Cl₂ (3 mL), MeCN (1.5 mL), and ethyl vinyl ether (1.5 mL) were added sequentially. The mixture was heated at 40 °C for 1 h. The polymer was filtered and washed with CH₂Cl₂ (3×100 mL) and extracted with CH₂Cl₂ (Soxhlet) for 48 h. The resulting Pc polymer was rinsed out of the thimble with CH₂Cl₂ and concentrated to 20 mL. 2 mL trifluoroacetic acid was added to the suspension of polymer Pc, and the mixture was stirred at room temperature under Ar for 1 h. The reaction mixture was washed with water (20 mL), aqueous NaHCO₃ (20 mL), and the organic layer was dried over MgSO₄, filtered, and evaporated. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂: MeOH = 95:5) to give Pc **11** (0.26 g, 10% yield) as a green solid: ¹H NMR (500 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 9.96 (br s, 1H), 8.66 (br s, 1H), 8.48 (br s, 2H), 8.44 (br s, 1H), 8.36 (br s, 1H), 8.33 (br s, 1H), 8.27 (br s, 2H), 7.61 (d, J = 9 Hz, 1H), 7.38-7.34 (m, 4H), 7.28-7.25 (m, 8H), 7.05-7.03 (m, 4H), 6.99-6.94 (m, 8H), 4.06-3.99 (m, 12H), 2.47-2.40 (m, 12H), 2.08-2.01 (m, 12H), 1.87-1.79 (m, 12H), 1.13-1.09 (m, 126H); ¹³C NMR (125 MHz, CD₂Cl₂:DMSO-*d*₆ = 95:5) δ (ppm) 160.8, 158.5, 156.1, 155.98, 155.90, 155.86, 155.6, 151.7, 151.64, 151.60, 151.4, 151.19, 151.16, 151.1, 150.74, 150.66, 150.2,

150.1, 149.9, 137.5, 132.8, 132.7, 132.2, 130.9, 130.7, 127.2, 124.4, 120.9, 120.9, 120.2, 120.1, 119.62, 119.58, 119.4, 116.12, 116.07, 115.95, 115.89, 115.6, 113.8, 113.7, 113.1, 112.9, 111.9, 111.5, 110.9, 109.13, 109.06, 108.3, 80.9, 80.80, 80.76, 68.4, 68.3, 29.0, 26.1, 26.0, 20.1, 20.0, 18.9, 18.8, 18.2, 12.21, 12.20, 12.0, 11.9, 11.7, 11.6, 11.5. To a solution of Pc **11** (170 mg, 0.0650 mmol) in 15 mL THF was added TBAF (0.7 mL, 1.0 M in THF, 0.7 mmol) in one portion. The reaction mixture was stirred at room temperature for 8 h and the reaction was quenched by the addition of aqueous NH_4Cl . The aqueous layer was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2 , CH_2Cl_2 : MeOH = 99:1) to yield Pc **5a** (70 mg, 70%) as a green solid: ^1H NMR (500 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 9.91 (br s, 1H), 8.18–7.72 (m, 8H), 7.36–7.25 (m, 12H), 7.03–6.93 (m, 12H), 4.00 (br s, 12H), 2.33 (br s, 12H), 2.14–2.10 (m, 6H), 1.96 (m, 12H), 1.78 (m, 12H); ^{13}C NMR (125 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 160.5, 156.0, 155.83, 155.76, 155.71, 155.65, 155.42, 155.38, 151.7, 151.6, 151.5, 151.3, 151.0, 150.9, 150.8, 150.5, 150.4, 149.6, 149.5, 124.1, 121.2, 121.03, 120.98, 120.3, 120.1, 119.5, 119.0, 116.1, 115.9, 115.83, 115.76, 115.7, 113.4, 113.3, 112.6, 112.5, 111.3, 110.9, 107.9, 84.5, 69.1, 69.02, 68.97, 68.2, 68.1, 28.9, 28.8, 25.52, 25.49, 18.52, 18.48; MS (MALDI) calcd for $\text{C}_{104}\text{H}_{91}\text{N}_8\text{O}_{13}$ $[\text{M}+\text{H}]^+$: m/z 1659.67, found 1659.69. Anal. calcd for $\text{C}_{104}\text{H}_{90}\text{N}_8\text{O}_{13}$: C, 75.25; H, 5.47; N, 6.75. Found: C, 74.86; H, 5.87; N, 6.47%

4.2.3. Zinc 2,3,9,10,16,17-hexa(4'-(hex-5''-ynyloxy)phenoxy)-23-hydroxyphthalocyanine (5b). A mixture of phthalonitrile **2** (0.1 g, 0.4 mmol), phthalonitrile **1** (0.6 g, 1 mmol), DBU (0.2 g, 1 mmol) and $\text{Zn}(\text{OAc})_2$ (140 mg, 0.765 mmol) in 60 mL 1-pentanol was refluxed under Ar for 8 h. The reaction mixture was allowed to cool to RT, and poured in MeOH (150 mL). The precipitate was filtered, washed with MeOH, air dried and then chromatographed (SiO_2 , CH_2Cl_2 : MeOH = 99:1). The green eluent was collected and concentrated under reduced pressure. A solution of the resultant green residue, TFA (2 mL) and CH_2Cl_2 (20 mL) was stirred at RT under Ar for 4 h. The reaction mixture was washed with water (50 mL), aqueous NaHCO_3 (50 mL), and the organic layer was dried over MgSO_4 , filtered, and evaporated. The crude product was purified by column chromatography (SiO_2 , CH_2Cl_2 : MeOH = 99:1) to give Pc **5b** (0.13 g, 20% yield) as a green solid: ^1H NMR (500 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 9.77 (s, 1H), 8.80–8.40 (m, 8H), 7.51(d, J = 8 Hz, 1H), 7.36–7.35(m, 4H), 7.29–7.24 (m, 8H), 7.06–7.02(m, 4H), 6.98–6.95 (m, 8H), 4.07–4.00 (m, 12H), 2.35–2.30 (m, 12H), 2.08–2.06 (m, 6H), 2.00–1.91 (m, 12H), 1.81–1.73 (m, 12H); ^{13}C NMR (125 MHz, CD_2Cl_2 :DMSO- d_6 = 95:5) δ (ppm) 160.2, 156.0, 155.8, 155.60, 155.58, 155.52, 154.2, 153.3, 152.5, 151.8, 151.8, 151.64, 151.58, 151.2, 151.1, 151.0, 150.9, 150.5, 150.3, 149.9, 149.8141.0, 134.4, 134.3, 133.9, 130.7, 124.1, 120.8, 119.9, 119.8, 119.7, 119.6, 118.21, 116.0, 115.8, 113.74, 113.65, 113.5, 112.2, 112.0, 108.668.93, 68.87, 68.3, 68.23, 68.18, 30.0, 28.8, 25.5, 25.51, 25.47, 18.48, 18.45; MS (MALDI) calcd for $\text{C}_{104}\text{H}_{88}\text{N}_8\text{O}_{13}\text{Zn}$ $[\text{M}]^+$: m/z 1720.58, found 1659.72. Anal. calcd for $\text{C}_{104}\text{H}_{88}\text{N}_8\text{O}_{13}\text{Zn}$: C, 72.49; H, 5.15; N, 6.50. Found: C, 72.01; H, 5.60; N, 6.51%

4.2.4. Zinc 2,3,9,10,16,17-Hexa(4'-(4''-(1'''-dodecyl-1 H-1''',2''',3'''-triazol-4'''-yl)-butoxy)phenoxy)-23-hydroxyphthalocyanine (13a). Asymmetric Pc **5b** (50 mg, 0.030 mmol) and **12a** (368 mg, 1.74 mmol) were dissolved in 20 mL dry THF before N,N-diisopropylethylamine (45 mg, 0.35 mmol) and CuI (13 mg, 0.070 mmol) were added to the solution. The mixture was degassed and backfilled with argon three times before stirring overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 followed by washing with 3x 100 mL 0.1 M EDTA, 3x 100 mL 1 M HCl, and 3x 100 mL brine. The organic layer

was concentrated and the crude product was purified by column chromatography (SiO_2 , CH_2Cl_2 : MeOH = 95:5), followed by recrystallization (3x) from CH_2Cl_2 /MeOH to give Pc **13a** as a green solid (21 mg, 24%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{176}\text{H}_{238}\text{N}_{26}\text{O}_{13}\text{Zn}$ $[\text{M}]^+$: m/z 2987.81, found 2987.77. Anal. calcd for $\text{C}_{176}\text{H}_{238}\text{N}_{26}\text{O}_{13}\text{Zn}$: C, 70.67; H, 8.02; N, 12.17. Found: C, 70.49; H, 8.26; N, 11.83.

4.2.5. Zinc 2,3,9,10,16,17-Hexa(4'-(4''-(1'''-(3'''-phenylpropyl)-1 H-1''',2''',3'''-triazol-4'''-yl)butoxy) phenoxy)-23-hydroxyphthalocyanine (13b). Following the procedure for Pc **13a**, asymmetric Pc **5b** (50 mg, 0.030 mmol), **12b** (281 mg, 1.74 mmol), dry CHCl_3 (10 mL), N,N-diisopropylethylamine (113 mg, 0.876 mmol) and $\text{Cu}(\text{PPh}_3)_3\text{Br}$ (135 mg, 0.145 mmol) yielded Pc **13b** as a green solid (27 mg, 35%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{158}\text{H}_{154}\text{N}_{26}\text{O}_{13}\text{Zn}$ $[\text{M}]^+$: m/z 2687.15, found 2687.16. Anal. calcd for $\text{C}_{158}\text{H}_{154}\text{N}_{26}\text{O}_{13}\text{Zn}$: C, 70.53; H, 5.77; N, 13.54. Found: C, 70.47; H, 6.14; N, 13.19.

4.2.6. Zinc 2,3,9,10,16,17-Hexa(4'-(4''-(1'''-(3-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)-phenoxy) propyl)-1H-1,2,3-triazol-4-yl)-butoxy)phenoxy)-23-hydroxyphthalocyanine (13c). Following the procedure for Pc **13a**, asymmetric Pc **5b** (20 mg, 0.012 mmol), **12c** (200 mg, 0.726 mmol), dry CHCl_3 (20 mL), N,N-diisopropylethylamine (45 mg, 0.35 mmol) and $\text{Cu}(\text{PPh}_3)_3\text{Br}$ (54 mg, 0.058 mmol) yielded Pc **13c** as a green solid (17 mg, 44%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{188}\text{H}_{191}\text{N}_{26}\text{O}_{31}\text{Zn}$ $[\text{M}+\text{H}]^+$: m/z 3372.35, found 3372.12. Anal. calcd for $\text{C}_{188}\text{H}_{190}\text{N}_{26}\text{O}_{31}\text{Zn}$: C, 66.90; H, 5.67; N, 10.79. Found: C, 66.84; H, 5.90; N, 10.51.

4.2.7. Compound 13d. Following the procedure for Pc **13a**, a mixture of asymmetric Pc **5b** (21 mg, 0.012 mmol), **12d** (493 mg, 0.752 mmol), dry CHCl_3 (10 mL), N,N-diisopropylethylamine (50 mg, 0.39 mmol) and CuI (13 mg, 0.068 mmol) was stirred at room temperature overnight. After workup the crude solid was loaded to column chromatography and first flushed with 5% v/v ethyl acetate in CH_2Cl_2 until excess **12d** was completely removed from the column. Then the product was eluted with 5% v/v MeOH in CH_2Cl_2 followed by recrystallization from CHCl_3 /MeOH to give Pc **13d** as a dark purple solid (24 mg, 35%): ^1H NMR (see Supplementary data); MS (MALDI) calcd for $\text{C}_{344}\text{H}_{335}\text{N}_{38}\text{O}_{37}\text{Zn}$ $[\text{M}+\text{H}]^+$: m/z 5653.48, found 5653.870. Anal. calcd for $\text{C}_{344}\text{H}_{334}\text{N}_{38}\text{O}_{37}\text{Zn}$: C, 73.02; H, 5.95; N, 9.41. Found: C, 73.02; H, 5.91; N, 9.08.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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