Design and synthesis of a sterically locked, highly distorted phthalocyanine and observation of all possible stereoisomers

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ABSTRACT: Disruption of the planarity of porphyrinoid cores has significant impact on both spectroscopic and solubility properties and is a useful tool in molecular design. Here we present the synthesis of a highly distorted phthalocyanine from a rigid, laterally extended phthalonitrile in which the extension is directed towards the core. This arrangement challenges macrocycle formation and aromatisation, such that forcing conditions and zinc templating are required. The phthalocyanine formed is a mixture of 4 isomers (2 of which are chiral, so 6 stereoisomers in total) and each of them are sterically locked. They can be distinguished by NMR spectroscopy, and careful separation and crystallisation allows the two most abundant isomers to be isolated. Crystal structures and the absorption spectra of these two isomers are reported.

KEYWORDS: Phthalocyanines, Distortion, Synthesis, Twisted Phthalocyanines, Crystal structures, Stereoisomers, Helical.

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INTRODUCTION

Phthalocyanine macrocycles are classically encountered as planar, aromatic systems [1]. Perturbation of macrocyclic planarity, however, can lead to significant modification of spectroscopic and other properties [2]. Non-planar analogues are less able to π-stack efficiently and solubility is therefore often enhanced. Bathochromic shifts are also commonly observed. Metal coordination can lead to distortion of the phthalocyanine/porphyrinoid core; in particular, large metals are unable to fit fully inside the ligand cavity. Distortion often results, but the degree of distortion is harder to predict and is influenced by the molecular and crystal structures [3]. This is widely observed and in simple systems the stability of the complexes is compromised by combination of poor fit and distortion. Sandwich complexes, on the other hand, provide a family of examples of stable systems in which the metal ions bridge two or three porphyrinoid macrocycles [4].

The alternative strategy to distort a phthalocyanine's preferred planarity is through the introduction of steric constraints by way of substitution. We and others have used this approach to prepare derivatives with improved solubility and processability (including liquid crystallinity) by synthetic introduction of flexible substituents at the non-peripheral (alpha-) positions on

phthalocyanines and naphthalocyanines [5]. Here the flexibility of the substituents allows minimal distortion of the core itself, and this presents few synthesis challenges (and modest impact on the core properties due to distortion). The design and synthesis of highly distorted systems, however, poses more significant challenges because introduction of bond-straining or sterically hindering substituents has both the potential to destabilise the molecule itself, and also to hinder the desired reaction sequence that builds up the monomer(s) chain, macrocyclization step, and aromatisation. Notable success in this area has been achieved in the synthesis of phthalocyanines bearing phenyl substituents on up to eight non-peripheral positions [6]. The octaphenyl phthalocyanine was isolated and shows bathochromic shift of its absorption. A crystal structure was obtained showing high distortion of the core and a "saddle" arrangement with alternating "up" and "down" isoindoline fragments [6a]. We have previously synthesised congested, fully conjugated "perylenophthalocyanines" [7] but their strong tendency towards aggregation prevented detailed characterisation.

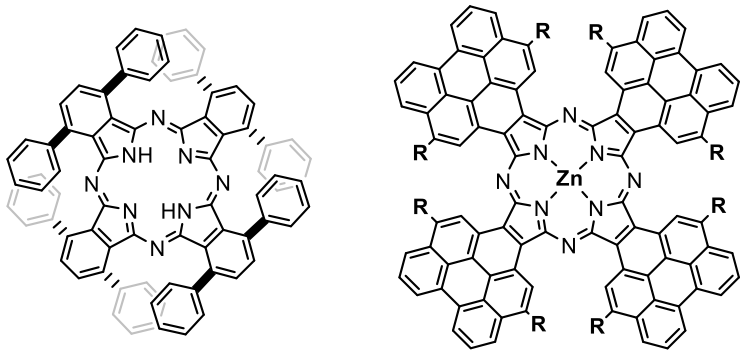


Figure 1. Octaphenyl phthalocyanine [6a] (saddle shape) and perylenophthalocyanine (R = alkyl) [7].

In this paper we report the first results on our efforts to prepare a phthalocyanine derivative from a (planar) C-shaped phthalonitrile in which the appended planar extensions and appended substituents are directed back towards the dinitrile (and therefore over the phthalocyanine core in the final macrocycle). In this design, the local (each isoindoline fragment) and macrocyclic aromaticity combine to favour planarity, but are prevented from doing so by steric factors, and rigidity in the system prevents any conformational interconversion.

EXPERIMENTAL

General methods

Reagents and solvents were purchased from commercial sources and used without further purification. Silica gel (Merck) 40-63 micron was used for column chromatography. NMR spectra were recorded either on a Bruker Ascend 500 instrument (^{1}H NMR at 500 MHz, ^{13}C NMR at 125.7 MHz) or an Ultrashield PlusTM 400 instrument (^{1}H NMR at 400 MHz) and the residual solvent peak was used as reference. A Shimadzu Biotech Axima spectrometer was used to record the MALDI-TOF MS analyses and matched to theoretical isotopic distribution patterns to confirm the assigned molecular ion. UV-vis spectra were measured in the stated solvents using a PerkinElmer Lambda 35 spectrophotometer. Fluorescence spectra were measured in the stated solvents using a PerkinElmer LS55 spectrophotometer. A PerkinElmer Spectrum BX FT-IR spectrometer was used to record the IR spectra. Melting points were measured using a Reichert Thermovar microscope with a thermopar based temperature control.

Synthesis of 4,5-bis(2-bromo-4-tert-butylphenoxy) phthalonitrile **1**

A mixture of 4,5-dichlorophthalonitrile (2 g, 10.1 mmol), 2-bromo-4-*t*-butylphenol (5.0 g, 21.8 mmol) and potassium carbonate (7 g, 5 eq.) in dry DMSO (35 ml) were heated at 90˚C under nitrogen. The reaction was monitored by removal of aliquots, addition to water to precipitate, and analysis of the solid by ^{1}H NMR spectroscopy until the reaction was complete (ca. 5 hrs). The reaction was then allowed to cool to rt and added to a water/ice mixture (200 ml) with stirring. The cream precipitate was collected by filtration, washed with water and left to dry in air to afford a quantitative yield of the title compound **1** (5.8 g, 100%). Mp. 203-204 ˚C. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.69 (d, 2H, *J* 2.3 Hz), 7.43 (dd, 2H, J_1 8.5 Hz, J_2 2.3 Hz), 7.12 (d, 2H, *J* 8.5 Hz), 6.96 (s, 2H), 1.37 (s, 18H) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz) 151.7, 150.95, 148.2, 131.7, 126.8, 122.1, 120.7, 115.29, 115.27, 110.3, 34.95, 31.4 ppm. MALDI m/z 500.1243 (50.0%, M-HBr) calculated for $C_{28}H_{25}BrN_2O_2$ m/z 500.1097. IR (neat) 2230 cm^{-1} (CN, weak). λ_{max} (DCM) 278 nm.

Synthesis of phthalonitrile **2**

A mixture of 4,5-bis(2-bromo-4-tert-butylphenoxy) phthalonitrile **1** (1 g, 1.7 mmol), $Pd(OAc)_2$ (160 mg, 0.7 mmol), PPh_3 (800 mg, 3.1 mmol) and Cs_2CO_3 (1.5 g, 4.6 mmol) in toluene (40 ml) were brought to reflux under nitrogen. The progress of the reaction was followed by tlc (eluent DCM/Hexane 1:1) by monitoring the appearance of a fluorescent blue product. Upon completion (*ca*. 5 hrs) the reaction was allowed to cool to rt and then was filtered through Celite® (eluent: toluene). The solvent was then removed under vacuum and the residue chromatographed on silica (eluent: DCM/Hexane 1:1) to afford the title phthalonitrile **2** (470 mg, 65%). Mp. 298-299 ˚C. ^{1}H NMR ($CDCl_3$, 500 MHz) 8.52 (br s, 2H), 7.76 (dd, 2H, J_1 8.8 Hz, J_2 2 Hz), 7.69 (d, 2H, *J* 8.8 Hz), 1.48 (s, 18H) ppm. ^{13}C NMR ($CDCl_3$, 125.7MHz) 155.8, 148.8, 142.6, 128.45, 127.2, 121.1, 118.3, 115.0, 111.95, 103.0, 35.35, 31.9 ppm. MALDI m/z 420.1821 (100%) calculated for $C_{28}H_{24}N_2O_2$ m/z 420.1838. IR (neat) 2227 cm^{-1} (CN). λ_{max} (CH_2Cl_2) 291 nm. λ_{em} (CH_2Cl_2, λ_{ex} 290 nm) 395 nm.

Synthesis of phthalocyanines **3a-d**

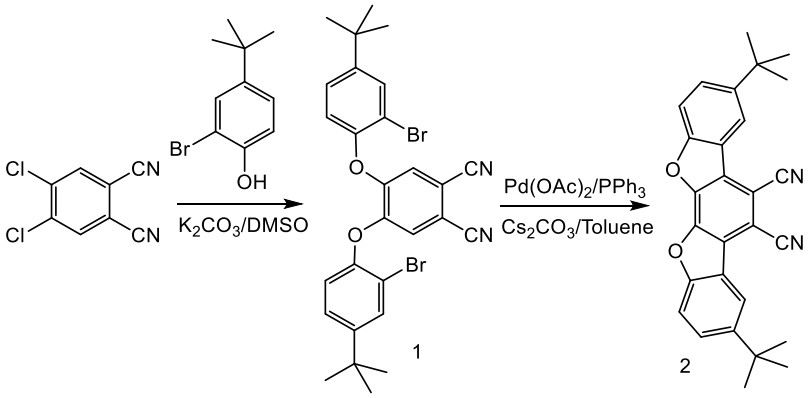
Phthalonitrile **2** (250 mg, 0.6 mmol) and $Zn(OAc)_2$ (70 mg, 0.4 mmol) were heated to reflux in 1-octanol (15 ml). DBU (0.5 ml, 3 mmol) was added to the orange solution which turned deep green immediately and the reaction was refluxed for 2 hrs in the dark. The solvent was removed. The residue was sonicated in methanol and the crude green solid filtered. This was passed through a plug of silica, eluent DCM/Hexane (1:1). The solvent was removed and the residue precipitated with methanol to yield a bright green powder containing all four isomers **3a-d** (see discussion) (39.5 mg, 15.1 %). MALDI m/z 1745.6555 calculated for $C_{112}H_{95}N_8O_8Zn$ (M+H) m/z 1745.6677. Tlc analysis (silica, eluent DCM/Hexane 1:2) indicated a mixture of isomers from which we were able to isolate the two main component green fractions by careful column chromatography (silica, eluent DCM/Hexane 1:2).

Phthalocyanine **3a** (14.5 mg). Crystals suitable for X-ray crystallography were grown from DCM/MeOH/EtOH.
Mp. >300˚C. ^{1}H NMR (CD_2Cl_2, 400 MHz) 10.21 (d, 8H, *J* 1.77 Hz), 7.87 (d, 8H, *J* 8.65 Hz), 7.71 (dd, 8H, J_1 8.68 Hz, J_2 1.9 Hz), 1.02 (s, 72H) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz) 156.2, 154.0, 147.3, 144.5, 127.3, 127.0, 124.5, 122.9, 121.1, 111.4, 34.85, 31.3 ppm. λ_{max} (ε x10^5) (CH_2Cl_2) 773 (1.66), 693 (0.42), 411 (0.66) nm.

Phthalocyanine **3b** (4.5 mg). Crystals suitable for X-ray crystallography were grown from $CHCl_3$/MeOH.
Mp. >300˚C. ^{1}H NMR (CD_2Cl_2, 500MHz) 10.17 (s, 2H), 10.08 (s, 2H), 9.79 (d, 4H, *J* 8.2 Hz), 1.08 (s, 18H), 1.02 (s, 18H), 0.89 (s, 18H), 0.74 (s, 18H) ppm. λ_{max} (CH_2Cl_2, ε x10^5) 755 (1.12), 675 (0.33), 403 (0.42) nm

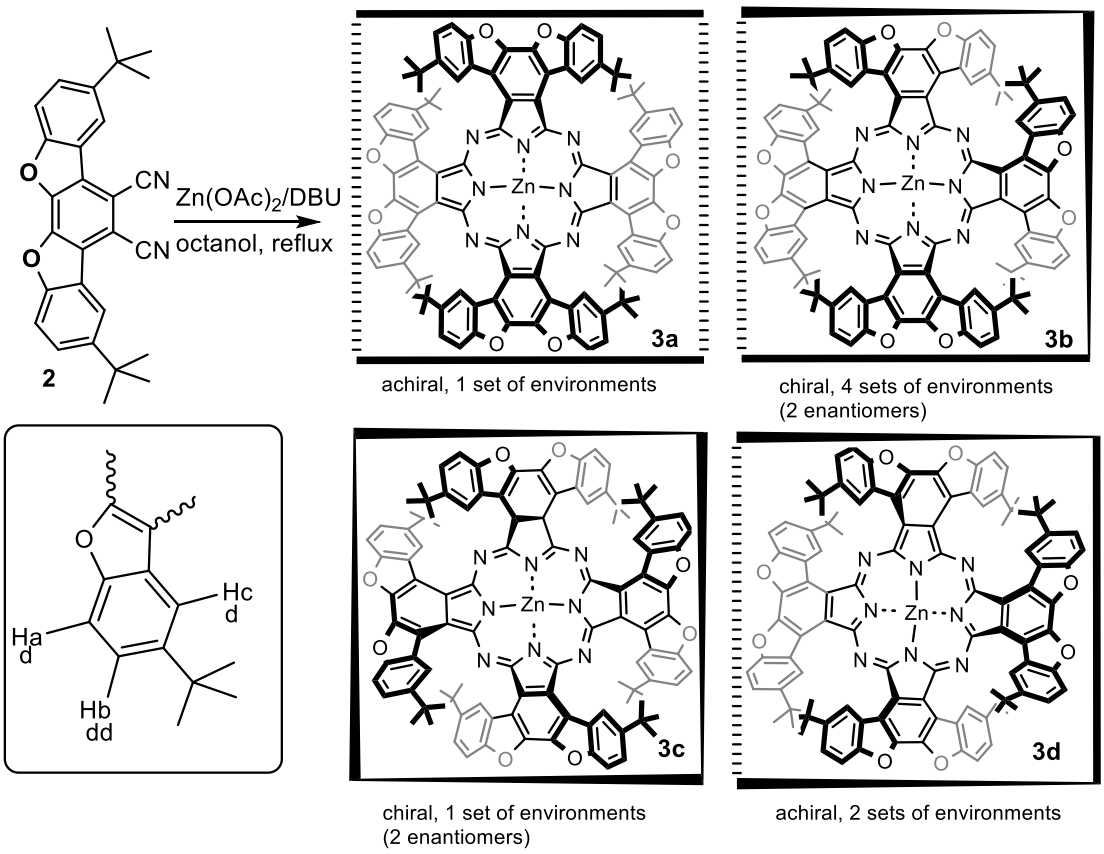
RESULTS AND DISCUSSION

The designed C-shaped planar phthalonitrile and its synthesis is shown in scheme 1, and it exploits sequential double nucleophilic aromatic substitution (diphenyl ether synthesis) and C-H activation cross-couplings related to the protocol reported by Furuyama *et al.* [8]. 4,5-Dichlorophthalonitrile was reacted with 2-bromo-4-*t*-butylphenol in the presence of potassium carbonate as base, smoothly yielding the product of double chloride displacement, phthalonitrile **1**. Double C-H activation cross-coupling was achieved by treating phthalonitrile **1** with palladium catalyst and caesium carbonate in refluxing toluene. The resulting (planar) phthalonitrile **2** shows distinctive blue fluorescence and the reaction is therefore easily monitored to completion.



Scheme 1. The synthesis of C-shaped phthalonitrile **2**.

Unsurprisingly, phthalocyanine formation from phthalonitrile **2** proved to be more challenging than simple phthalocyanine synthesis. Reaction of **2** in refluxing pentanol with either lithium metal (LiOPe) or DBU gave no evidence of phthalocyanine formation, even after prolonged reaction time. Magnesium templating, which has proved very effective in our challenging macrocyclisations to give porphyrin-phthalocyanine hydrids [9] also failed. Phthalocyanine formation was eventually achieved using forcing conditions and zinc as template. Consequently, treatment of phthalonitrile **2** with zinc acetate in refluxing octanol produced an orange solution. Addition of DBU caused immediate production of a green solution, and reflux was continued for 2 h. Workup and separation by column chromatography allowed isolation of a bright green solid that was identified to be the phthalocyanines **3** by MALDI-TOF MS. ^{1}H NMR spectroscopy, however, revealed a complex series of peaks that clearly indicated that the isolated product was, in fact, a mixture of 4 isomers. The hindrance posed by the isoindoline substituents will prevent neighbours from locating on the same face of the phthalocyanine's (twisted) core. Based on this safe assumption, four general arrangements (isomers) are possible, **3a-d**, and they are shown in scheme 2. The nature of the phthalonitrile/phthalocyanine substituent makes interpretation of ^{1}H NMR spectra straightforward, with each unique unit presenting three clearly coupled aromatic signals and a t-butyl singlet (Scheme 2 inset). As mentioned, there are theoretically four possible isomeric arrangements, **3a-d**, and they would present these components in 1 (**3a** and **3c**), 2 (**3b**) and 4 (**3d**) theoretically different environment(s), also indicated in scheme 2. Structures **3b** and **3c** are helically chiral and would be present as pairs of enantiomers.



Scheme 2. Synthesis of twisted phthalocyanines **3**; all possible isomers **3a-d** are shown. Inset: the three distinctive signals expected for each unique aryl fragment.

The ^{1}H NMR spectrum for the as-isolated mixture of isomers is shown in Figure 2, with an expansion of the region showing protons Hc (identified by the small *meta*-coupling to Ha). All four isomers **3a-d** can be identified, and the peaks are labeled to show the isomer that they represent. Two isomers are expected to show a single set of resonances (**3a** and **3c**). The most abundant isomer was assumed to be the saddle configuration (as found for octaphenyl phthalocyanine [6]). Integration of the signals shows the ratio of isomers **3a**:**3b**:**3c**:**3d** to be 15:20:1:1, although this ratio was found to vary across experiments.

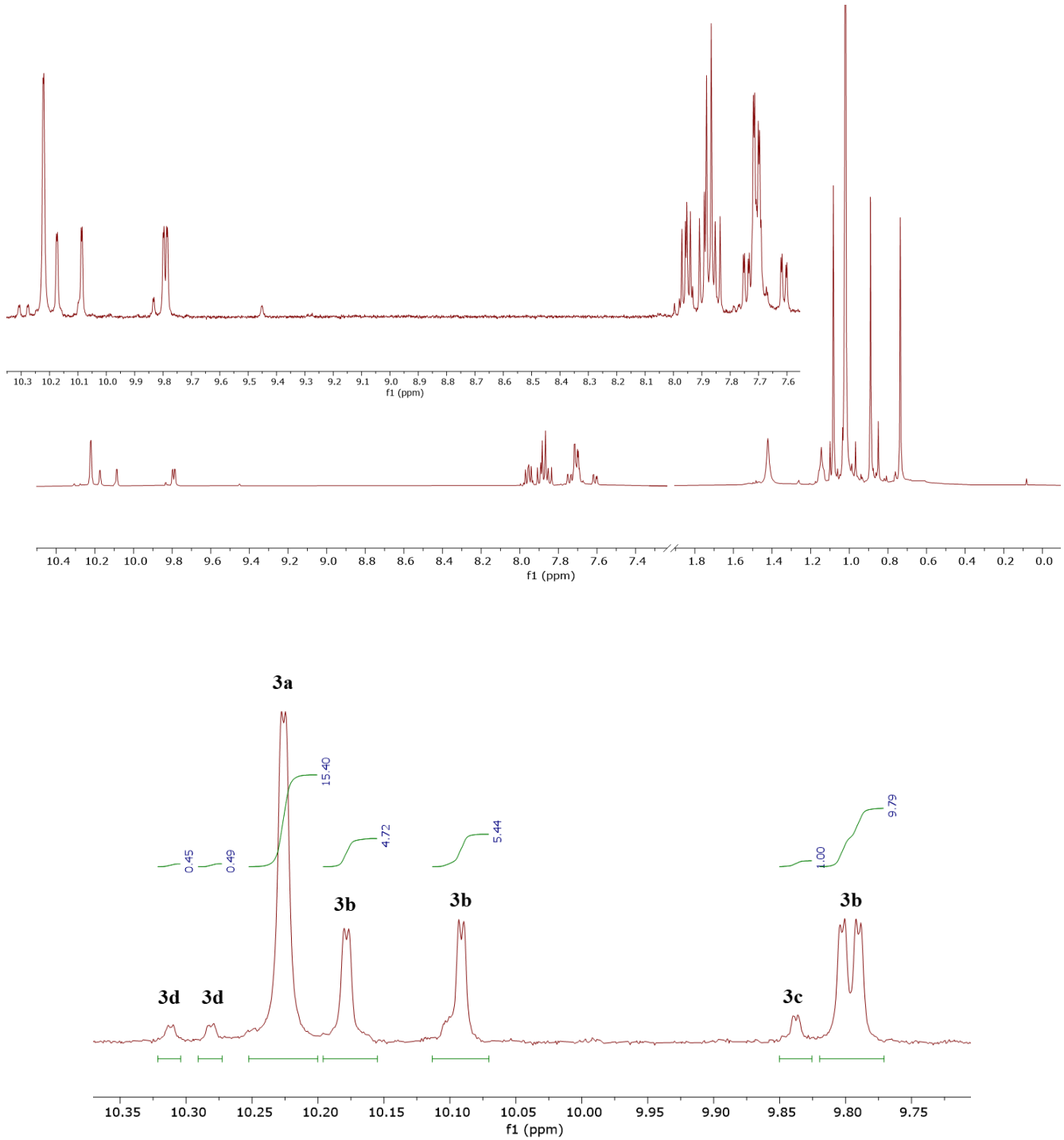


Figure 2. The [1]H NMR spectrum for the as-isolated isomeric mixture of twisted phthalocyanines showing the presence of all four isomers **3a-d** in ratio 15:20:1:1; top, full spectrum and aromatic region; bottom, expanded region for Hc signals.

The identification of all four possible isomers prompted further investigation and attempts to separate the mixture. Eventually, through careful chromatographic separation and recrystallisation, the two most abundant isomers were isolated. In accordance with our expectations following [1]H NMR analysis, the two most abundant isomers are saddle isomer **3a** and chiral isomer **3b**. Saddle isomer **3a** is expected and, as previously mentioned, its formation is consistent with the observations for octaphenyl phthalocyanine. Crystals suitable for X-ray crystallography were grown and the solved structure is shown in figure 3 (top), along with the aromatic section of the [1]H NMR spectrum for this pure isomer. The deviation from planarity is

severe (*ca*. 20º between pairs of benzofuran rings), although shallower than non-peripherally substituted octaphenyl- [6] and octaisopentyl [2] phthalocyanines. Unambiguous observation of the other isomers is, however, much more remarkable. Figure 3 (bottom) shows the ^{1}H NMR spectrum of isomer **3b** (containing a trace of **3c**), clearly showing the different environments for both 4 x H_c and 4 x t-butyl. Crystals for this sample were also grown. The X-ray crystallographic data, although complicated by disordered solvent molecules, unambiguously confirm the isolated isomer as **3b**. UV spectra are bathochromically shifted compared to typical phthalocyanines, as expected for the combination of π-extension and twist. The fundamental difference in the cores of the two isomers, however, is reflected in their respective absorption spectra (Figure 4). The spectral shape is essentially identical for each isomer, but the main Q-band of **3a** is bathochromically shifted by ~18 nm compared to **3b**. Visually the two samples have subtly different colour but neither show any fluorescence.

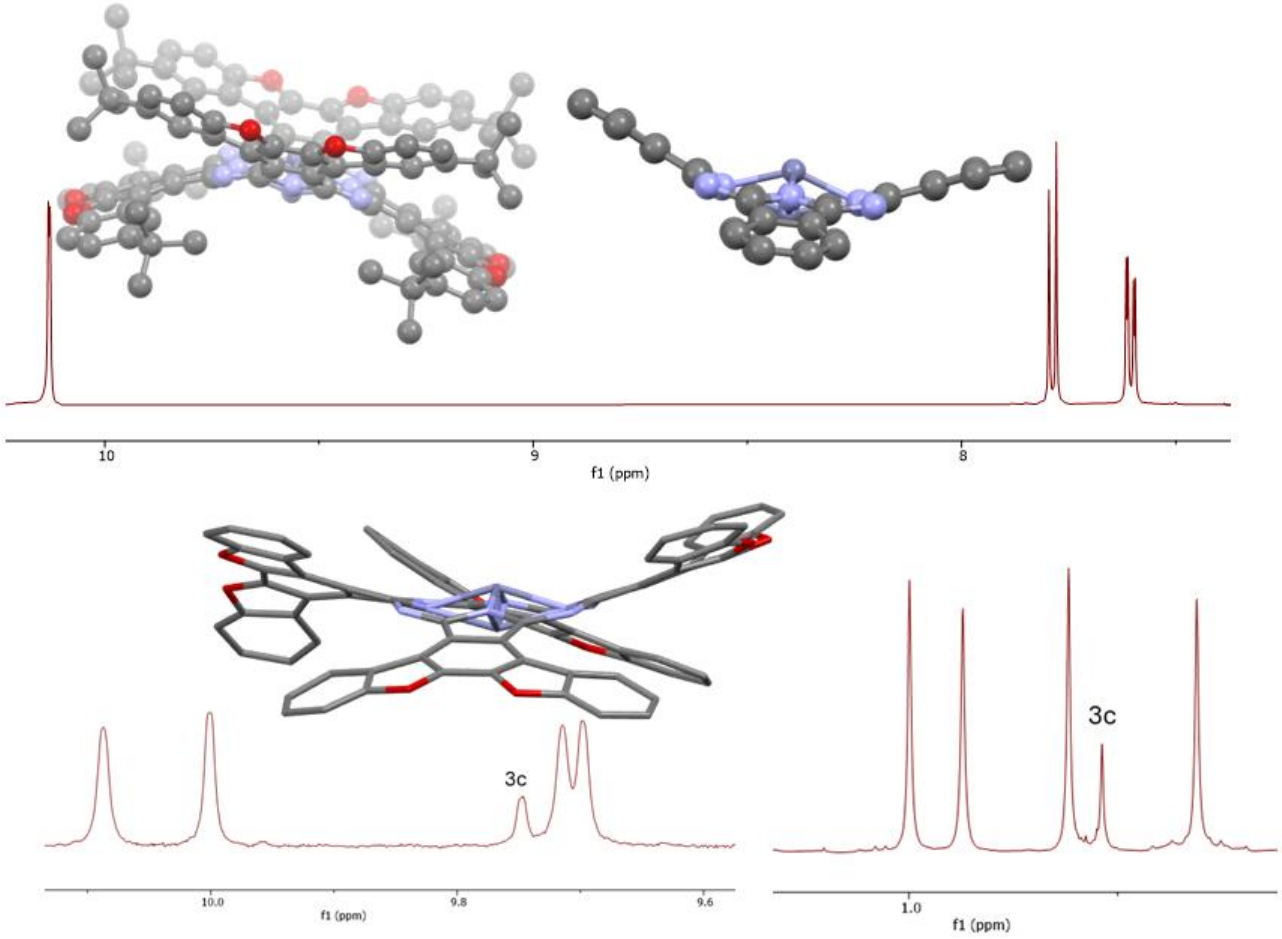


Figure 3. Top: the ^{1}H NMR spectrum for pure phthalocyanine isomer **3a** and its crystal structure (top left, hydrogens not shown; top right, phthalocyanine core only). Bottom: the ^{1}H NMR spectrum for phthalocyanine isomer **3b** and its crystal structure (*t*-Bu groups hidden for clarity).

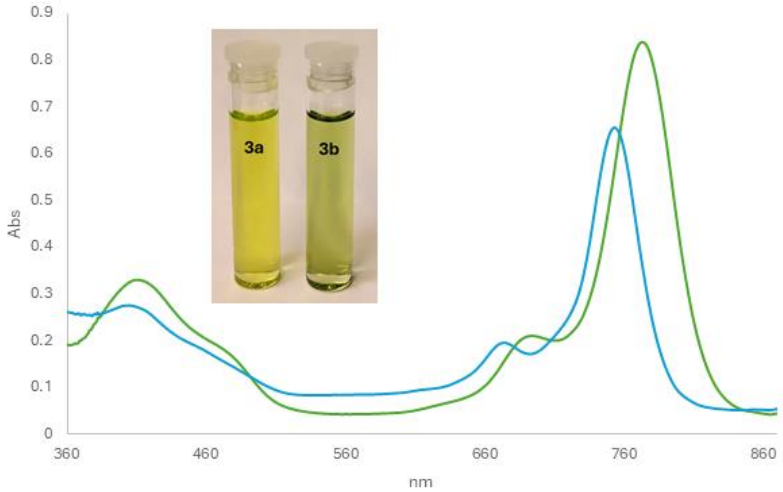


Figure 4. UV-Vis spectra for isomers **3a** (green) and **3b** (blue)

In conclusion, we have designed and synthesized a C-shaped, benzofuran-fused phthalonitrile and cyclized it to form the corresponding phthalocyanine which cannot adopt a planar core or interconvert its stereoisomers. Remarkably, all four possible isomers are observed and the two most abundant have been isolated. The first is the expected achiral saddle arrangement (*up-down-up-down* arrangement of alternating isoindoline units), with *ca*. 20° angle between neighbouring isoindolines. The second most abundant isomer is much more surprising, and the isoindoline fragments are arranged *up-down-twisted-twisted*, and to the best of our knowledge this is the first time such a phthalocyanine stereoisomer (itself formed as an enantiomeric pair) has been observed and isolated. Neither the isomeric mixture nor the isolated isomers **3a** and **3b** show any fluorescence, but the absorption spectrum of **3a** is bathochromically shifted compared to **3b** (by 18 nm for the main Q-band).

Acknowledgements

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Supporting information

Crystallographic data have been deposited at the Cambridge Data Centre (CCDC) under deposition Nos. CCDC 2425513 [**3a**] and CCDC 2425514 [**3b**]. Copies can be obtained on request, free of charge, *via* www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44 1223-336-033 or email: deposit@ccdc.cam.ac.uk). Details on the structures, plus additional images can be found in the supporting information document.

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