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Review

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Has everything been done with phthalocyanines?

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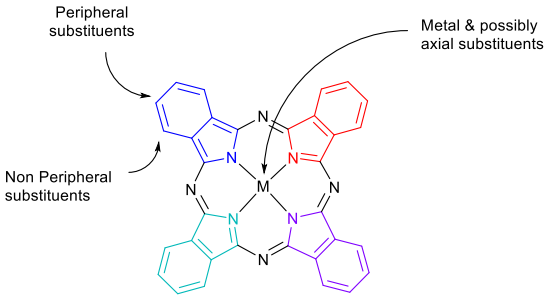
Abstract

Since their serendipitous discovery in 1928 and their first peer-reviewed description in 1934 in the Journal of the Chemical Society, phthalocyanines have proven to have suitable properties for a wide range of biomedical and technological applications. Their structural versatility is infinite, which does not mean that all new structures are innovative and of interest. While some are starting to think that everything interesting has been done, this mini-review aims at demonstrating that research on these very nice porphyrinoids still offers exciting research topics and promising developments while addressing regioisomerism, synthetic limitations, integration into nanotechnology and modern green chemistry aspects.



Keywords: Phthalocyanines; design; properties; applications

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1. Introduction

Phthalocyanines were first described in 1934 by R. P. Linstead in a paper entitled "*Phthalocyanines. I. A new type of synthetic coloring matters*"[1] and that was straight away published as the part I of a corpus of eight papers,[2-7] and in which the affiliation with the porphyrinoid family was immediately highlighted with the following sentence: "The central ring of this formula has a striking resemblance to that of the natural porphyrins" (Figure 1). Since then, in the last 94 years, phthalocyanines have proven to be powerful molecular materials in various biomedical and technological applications, either under their molecular form or combined with nanomaterials.[8-9] Incidentally, one may notice the second paragraph of this paper is a nice example of what would be considered nowadays as science fragmentation.

212. *Phthalocyanines. Part I. A New Type of Synthetic Colouring Matters.*

By R. P. Linstead.

This series of papers describes a new class of coloured organic compounds which comprises a parent substance, named *phthalocyanine* from its origin and deep blue colour, and a series of complex metallic derivatives which are of great beauty of appearance and unusual stability. The mode of formation and the reactions of these substances indicate that they are of a new structural type which may be exemplified by the formula (XIV) on p. 1035 of the parent substance.* The central ring of this formula has a striking resemblance to that of the natural porphyrins.

The present paper is concerned with the discovery and preliminary investigation of the first member of the class. This is followed by a description of preparative methods and properties (Parts II, III, and IV), molecular-weight determinations (Part V), and a general discussion of structure (Part VI).

The first phthalocyanine was discovered by chance in 1928 during the course of the industrial production of phthalimide in the Grangemouth works of Messrs. Scottish Dyes, Ltd. The process consists in passing ammonia into molten phthalic anhydride in iron vessels and it was found that during certain preparations traces of a dark blue substance were formed in the molten imide. This material was stable, crystalline, and contained iron which was not eliminated by treatment with concentrated sulphuric acid.† As it appeared that the substance might prove of academic interest, its study was taken up in 1929 through the kindness of Professor J. F. Thorpe, F.R.S., and the Research Committee of the Dyestuffs Group of Imperial Chemical Industries, Ltd.

This iron compound (crude *iron phthalocyanine*) was insoluble in the usual organic media and in water, dilute acids and alkalis. It could, therefore, easily be freed from simple impurities, but absolute purification was made difficult and it could not be determined whether the substance was a chemical individual or a mixture of compounds of a similar type. Preliminary experiments were carried out on the material purified as far as possible by suitable extraction. This product gave the mean analytical figures: C, 62·4; H, 2·9; N, 19·2; Fe, 12·6%, leaving a deficiency (? oxygen) of some 3%. No other elements could be detected. These values correspond to an atomic ratio of 4C : 1N, which indicates that two atoms of nitrogen are combined with a phthalic residue.

Figure 1. Reproduction of the first paragraphs of the first scientific peer-reviewed paper reporting on the existence of phthalocyanine.

As of May 2026, a Web of Science research with the keyword “phthalocyanin*” produces nearly 40,000 results, and a plateau can be seen in the last 15 years (Figure 2). The same search in SciFinder yields 119,382 results, 48k for articles and 68k for patents. This data can be a comment on the dynamism of the field or, on the contrary, be estimated to announce an upcoming decrease of interest.

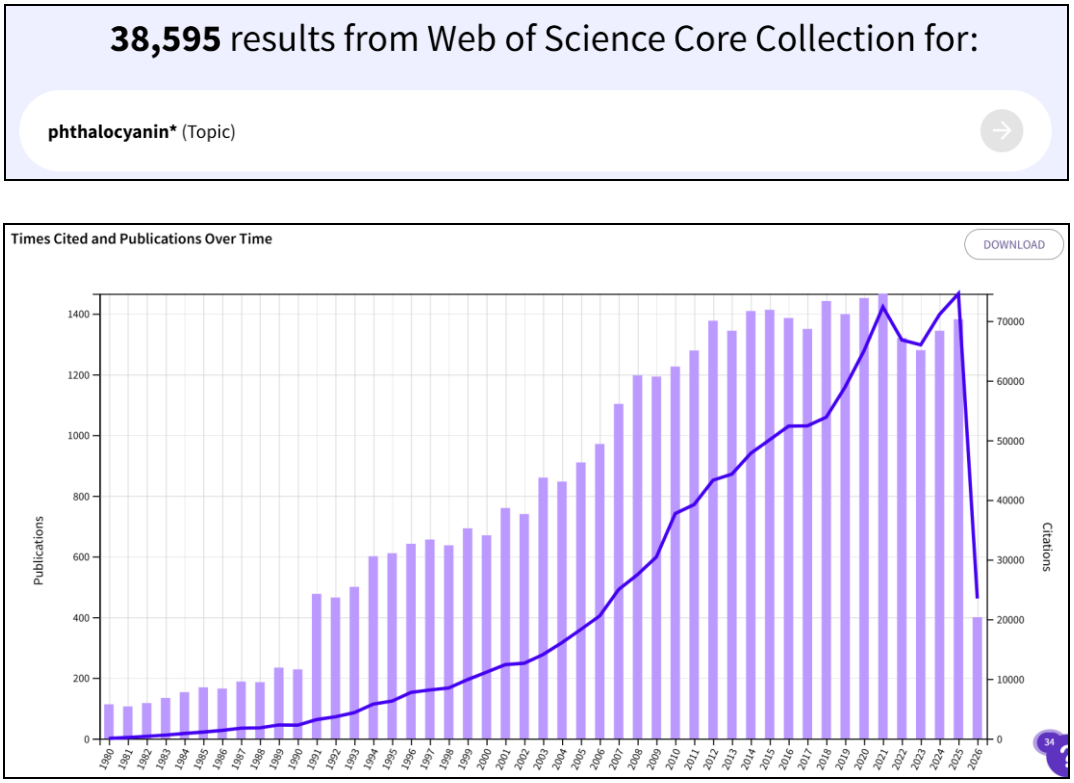


Figure 2. Screenshots of a Web of Science search made with the keyword “phthalocyanin*”

The structural versatility of phthalocyanines is nearly endless and undoubtedly contributes to maintaining the opportunity of publishing new compounds, new in the sense that they have not been described yet at the time of their publication, but not necessarily that they are bringing significant new knowledge.

In this context, and even if only sparse manner, it is sometimes said and heard that there is nothing really interesting to be done anymore with phthalocyanines. The line between what is new and what is interesting / innovative is a thin one, like in all fields of science. On our side, we do believe that many impactful outcomes based on phthalocyanines are still to be obtained and produced, and this will be discussed hereafter.

We do believe that the design and production of novel phthalocyanines with improved properties - rather than simply incremental design - can contribute to many fields. Besides this, the need for more selective synthetic pathways towards so far unavailable substitution patterns and with less environmental impact are another crucial research focuses of the field. This mini-review presents these current challenges in the field and clearly answers that there yes, are still many discoveries remaining to be done, should it be from the point of view of the synthetic methods and strategies, of the design of new derivatives, as well as on phthalocyanines’ implementation on crucial applications.

2. Phthalocyanines amongst other porphyrinoids

The main porphyrinoids are porphyrins. Together with their reduced analogues chlorins and bacteriochlorins, they are naturally occurring derivatives, unlike phthalocyanines that are entirely artificial (Figure 3). The family has other members, such as corroles[11-12] which are contracted tetrapyrroles whose corrin ring is the basis of cobalamin also known as vitamin B 12. Porphycenes are also artificial derivatives.[13] Bodipys, with their structure resembling a half-porphyrin, are referred to as porphyrins' little sister.[14]

Amongst this rich structural family, which prompted the existence of the whole Handbook of Porphyrin Science series,[15] the two intrinsic advantages of phthalocyanines over the other derivatives are their intense absorption usually centered around 700 nm but extendable to 800 nm and even 1 µm[16], as well as their robustness.

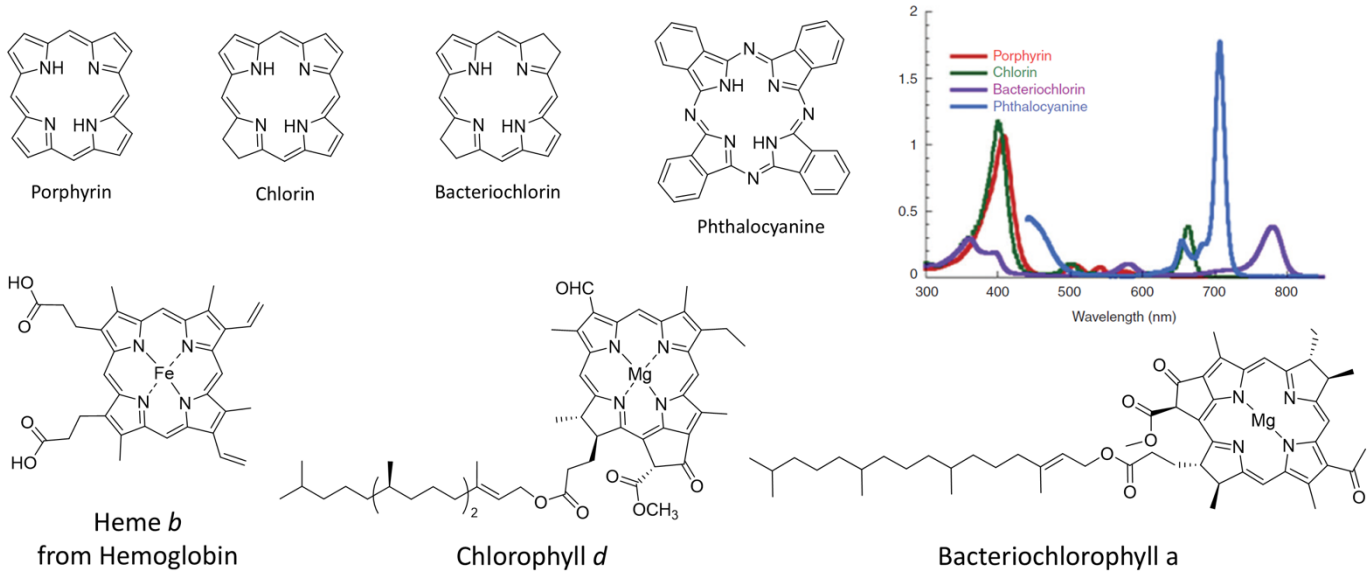


Figure 3. Structure of basic porphyrin, chlorin, bacteriochlorin and phthalocyanine, as well as natural porphyrin, chlorin and bacteriochlorin. Schematic and comparative electronic absorption spectra of porphyrin, chlorin, bacteriochlorin and phthalocyanine, reproduced from Ref 17 with permission.

Applications based on photoproperties are generally aiming at using dyes exhibiting strong absorption at red, far red or even near infrared wavelengths. This is especially important when these dyes are designed for photomedicine, in which case it is indeed very important to use wavelengths in the phototherapeutic window where endogenous chromophores do not absorb. For technological applications such as light harvesting, it is important to produce transparent materials with appropriate absorption at long wavelengths. In this respect, phthalocyanines are of immediate interest.

While it is not always true for biomedical applications, robustness is an essential criteria in technological applications, and phthalocyanines have a blatant superiority over their analogues.

However, a Web of Science search using keywords of applications and properties often using tetrapyrroles shows that porphyrins are much more often used than phthalocyanines (Table 1) despite their advantages. A likely explanation is their much more tedious synthesis and purification.

Table 1. Results obtained in Web of Science with search by keywords, combined with either Porphyrin* or Phthalocyanin* using AND as a Boolean operator.

	Porphyrin*	Phthalocyanine*	Por / Pc ratio
Applications			
"Photodynamic therapy"	7 020	4 758	1.5
"CO_2 reduction"	1 130	614	1.8
"Solar cell*"	3 466	2 832	1.1
Sensor	3 847	3 066	1.2
Biosensor	441	401	1.1
Catalysis	4 056	1 075	3.8
Battery	490	657	0.7
Properties			
"Liquid crystal"	266	349	0.8
"Energy transfer"	4 226	976	4.3
Fluorescence	10 873	4 009	2.7

3. The infinite structural versatility of phthalocyanines

Phthalocyanines are maybe the less well-known porphyrinoids, despite their outstanding properties rendering them extremely useful in many currently popular applications. They definitely have a bad reputation, especially regarding their alleged insolubility. Due to closer chemistry, synthetic pathways and the sue of similar precursors, researchers can more easily navigate between porphyrins, chlorins and bacteriochlorins, while phthalocyanine chemistry is entirely different. However, when given the opportunity to know how the bad reputation of phthalocyanines is exaggerated - yes they are soluble, yes we can functionalize them - researchers are usually appealed and willing to try using them.

On the other hand, phthalocyanines are often celebrated for properties that they don't really have, such as an absorption in the near-infrared when it is merely the red or the far-red, which is still immensely useful.

Structurally speaking, the most basic phthalocyanine is a tetrameric molecule composed of four isoindole subunits attached to each other by nitrogen atom. The whole macrocycle is entirely conjugated. In the sense that removing something from it would make it not a phthalocyanine anymore, the most basic and simple phthalocyanine structure is the 2HPc whose structure can be seen on Figure 4. The macrocycle can complex a metal, and substituents can be introduced on the peripheral and non-peripheral positions of each isoindole subunit, each having the same or different substituents. The substituents themselves, one each subunit, can be the same or not. This offers an endless variety of structures, thereby versatile ways to tailor their properties depending on the targeted applications.

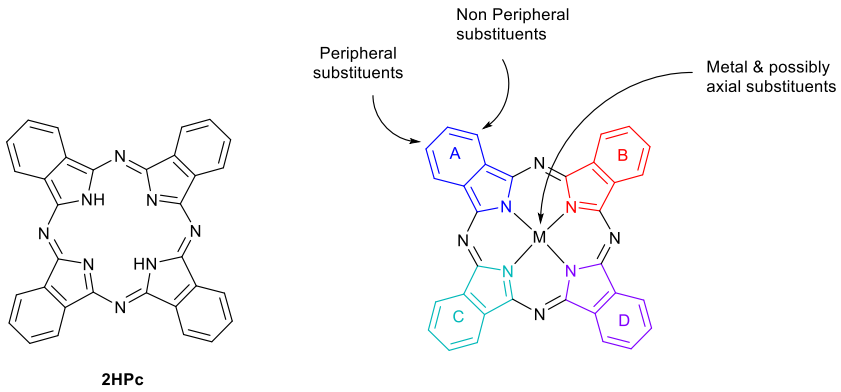


Figure 4. Structure of the simplest phthalocyanine **2HPc** (left) and possibilities for structural variations

Further variations are possible with more exotic structures, as shown in Figure 5.

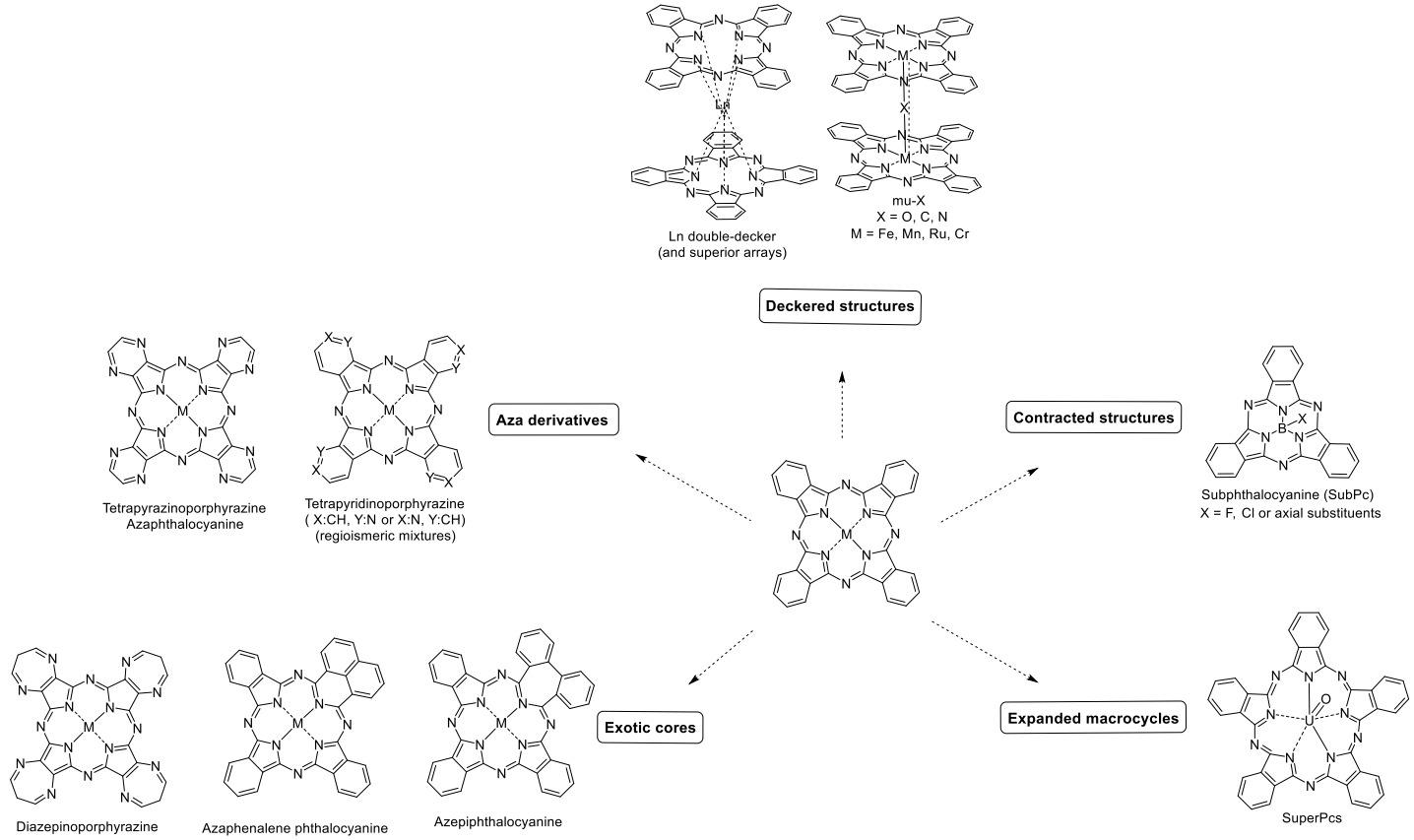


Figure 5. Phthalocyanine-based structures

Given that there are two peripheral positions and two non-peripheral positions on each isoindole subunit, phthalocyanines are often obtained as regioisomeric mixtures, with up to four different regioisomers (Figure 6). These regioisomers are actual constitutional isomers, but the term regioisomers is routinely used in the field. These regioisomers can have different properties as they are basically different molecules. In particular, they can have slightly different melting points, magnetic moments, polarity which makes them sometimes distinguishable chromatographically. The composition of a regioisomeric mixture is not always reproducible, which can cause issues when entering the process of drug approval. However, they are usually not separated and used as they are. Their separation involves indeed tedious, complex and chromatographic

operations. The determination of the structure of different regioisomers can be done by crystallographic means when single-crystals can be obtained, otherwise NMR analysis is a chosen method.

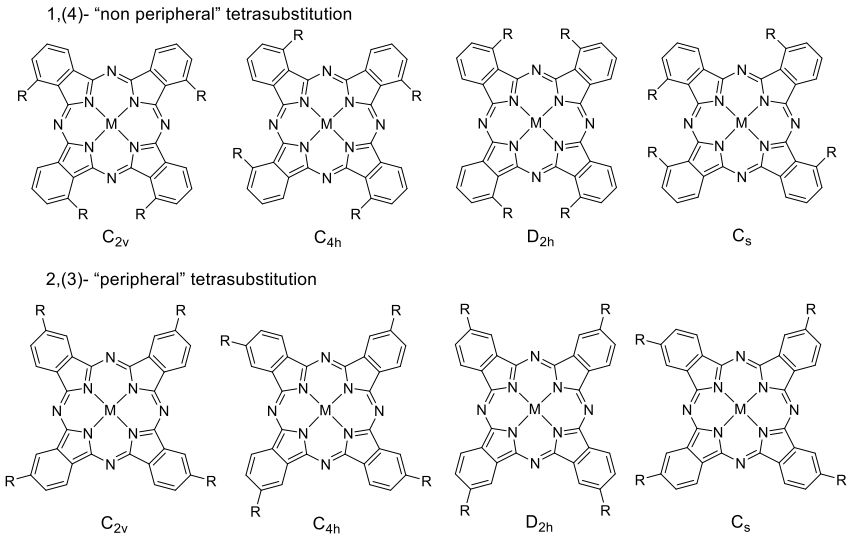


Figure 6. The four regioisomers of tetrasubstituted phthalocyanines

Only a few studies investigate the effect of this regioisomerism on phthalocyanine properties. As each regioisomer is basically a different molecule, they can be expected to have different physical properties. Given the sensitivity of liquid crystalline behaviour, a few works have been reported.[18-19] The magnetic properties of regioisomers of a cobalt phthalocyanine has also been shown to depend on the geometry of the molecules (Figure 7).[20]

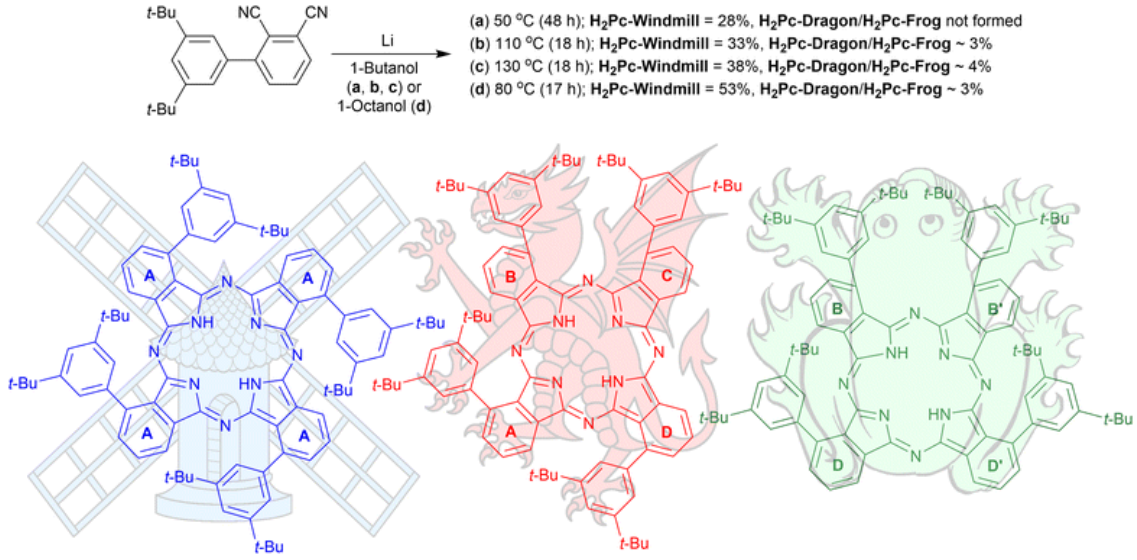


Figure 7. Structure of windmill, dragon, and frog-shaped regioisomers of a cobalt phthalocyanine with different magnetic behaviours. Reproduced from Ref 20 with permission.

4. Synthetic considerations and limitations

The vast majority of phthalocyanines synthesized in the XXI[e] century have been obtained from phthalonitriles appropriately functionalized, while the first phthalocyanine reported in 1936 was the result of the cyclotetramerization of phthalic acid in the presence of ammonia. Post-cyclotetramerization reactions are useful to increase the access to diverse derivatives, either to add moieties[20] or simply to remove protecting groups[21].

Three main lines of research can be identified for improvement in the current state of the art:
- better synthetic access to asymmetric substitution patterns
- better access to regioisomerically pure derivatives that are currently obtained as mixtures
- reduction of the environmental impact of phthalocyanine syntheses.

4.1. Synthetic access to asymmetric substitution patterns

In the phthalocyanine community, the term asymmetric is routinely used to designate phthalocyanines having different substituents on one or more of their four isoindole subunits. Unlike its more general meaning in chemistry, it does not imply the presence of chiral elements.

Considering only cases of phthalocyanine compounds formed by a single macrocycle with four isoindole subunits - which is the immense majority of the cases, six substitution patterns are currently actually reported in the literature for such simple monomeric phthalocyanines. For those, the main ones are A4 and A3B. A few AABB[22] and ABAB[23] structures are reported as well as a single ABAC[24], and a handful of ABCD (Figure 8). Deckered complexes of lanthanides can be homoleptic or heteroleptic, homo- or heterometallic.[25] Each decker can be itself of symmetric type (A4) or asymmetric type, giving in the case of lanthanide double-deckers an A7B derivative.[26] Research on the synthesis of asymmetric substitution patterns is intensely active.[27-30]

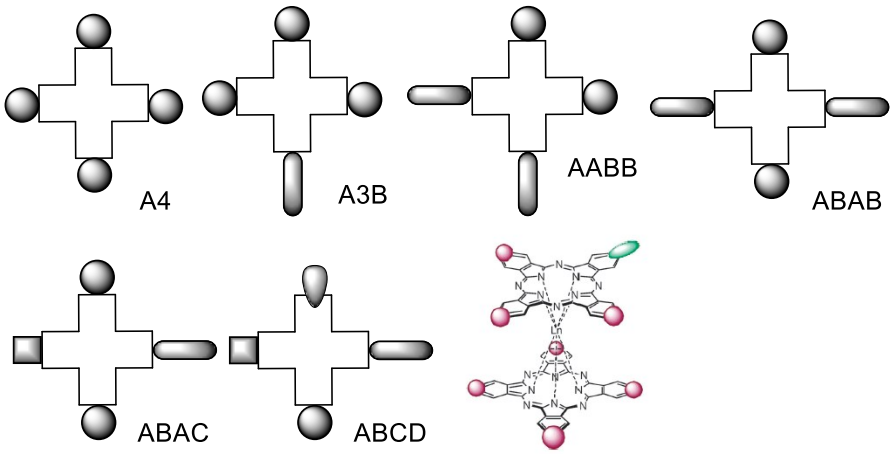


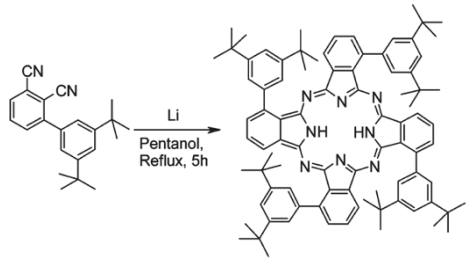
Figure 8. Schematic representation of the substitution patterns having actually been synthesized when this mini-review was written.

Two main strategies can usually be implemented when it comes to the preparation of asymmetric substitution patterns: either the use of selective methods involving the use of different precursors with specific reactivity, or a careful adjustment of the stoichiometry of the precursors. A3B derivatives can be obtained in satisfying yields using a mixture of two precursors of the same types, usually phthalonitrile, and using an excess of the A phthalonitriles - up to 10/1 - to favor the formation of the desired A3B and of the A4 only, preventing statistically the formation of undesired A2B2, AB3 and B4. Another method, which can be defined as selective, is based on first, the preparation of a boron

subphthalocyanine with all the A substituents, and its selective opening by a diiminoisoindoline bearing substituted B, as reported by Kobayashi in 1990.[31] ABAB derivatives can be selectively obtained by reacting a trichloroisoindoline bearing substituent A with a diiminoisoindoline bearing substituent B.[32,33] The same method to which a stoichiometric control of the use of two diiminoisoindolines bearing respectively substituents B and C has been applied to obtain an ABAC derivative.[24] The main limit is due to the very few substituents that can undergo the conditions necessary for the synthesis of the trichloroisoindoline which request the sue of PCl_5. ABCD phthalocyanine has been synthesized by making a chain of the A, B, C and D precursors, attached to each other by functionalized substituents. The intramolecular cyclotetramerization reaction has been performed on this linear tetrameric precursor.[34] Many researchers worldwide continue to work on the development of always more versatile, performant and universal methods to obtain more diverse substitution patterns more efficiently.

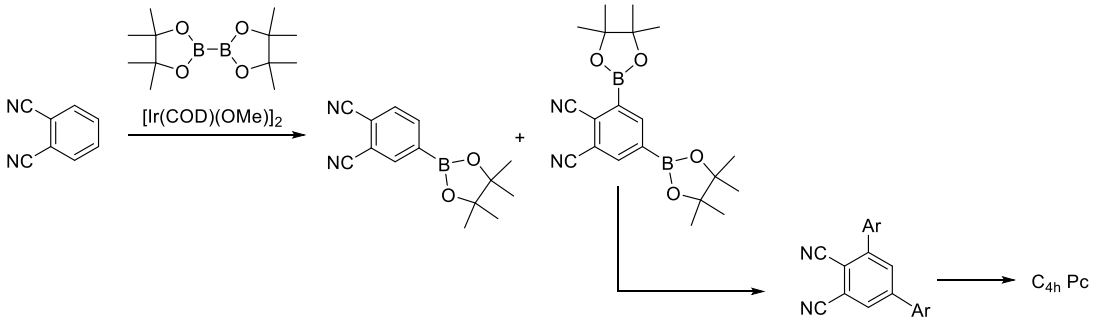
4.2. Better access to regioisomerically pure derivatives.

The only reported way to obtain tetrasubstituted phthalocyanines as a single isomer is by using bulky substituents in non-peripheral position. The use of bulky 3,5-di-tert-butylphenyl substituent at the non-peripheral position by Efimov in 2010 allowed to obtain a single regioisomer in quite satisfying yield (23%, Scheme 1).[35] Quite obviously, bulky substituents in peripheral positions do not prevent the formation of regioisomers as they do not have the capacity to pre-orient the orientation of the four phthalonitriles undergoing the cyclotetramerization.[36]



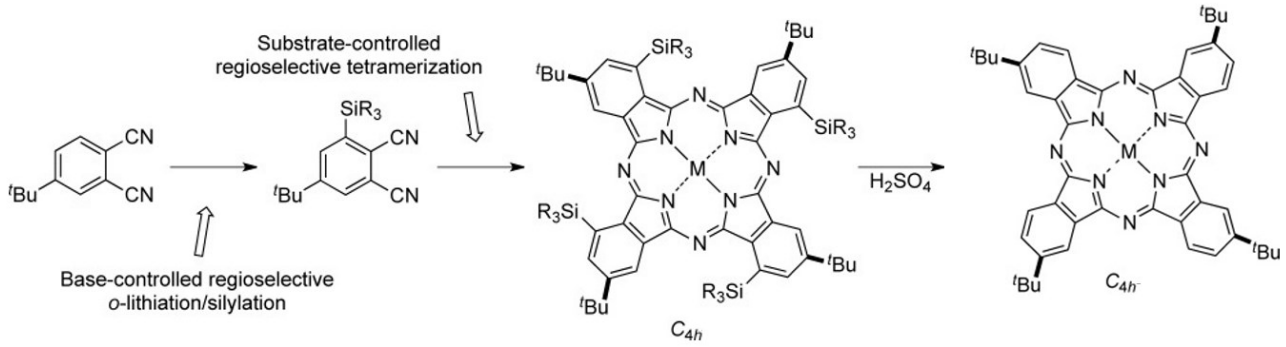
Scheme 1. Preparation only one regioisomer of a tetrasubstituted phthalocyanine by using a bulky 3,5-di-tert-butylphenyl substituent in non-peripheral position

Other efforts aiming at increasing the access to more phthalonitriles with bulky substituents in the 3-position have been developed, based on Suzuki couplings that have proven to be a powerful synthetic tool when the bis-borylation of phthalonitrile became a key strategy to access 3,5-bis-arylphthalonitriles with bulky aryl substituents yielding only C_{4h} octaarylphthalocyanines (Scheme 2).[37]



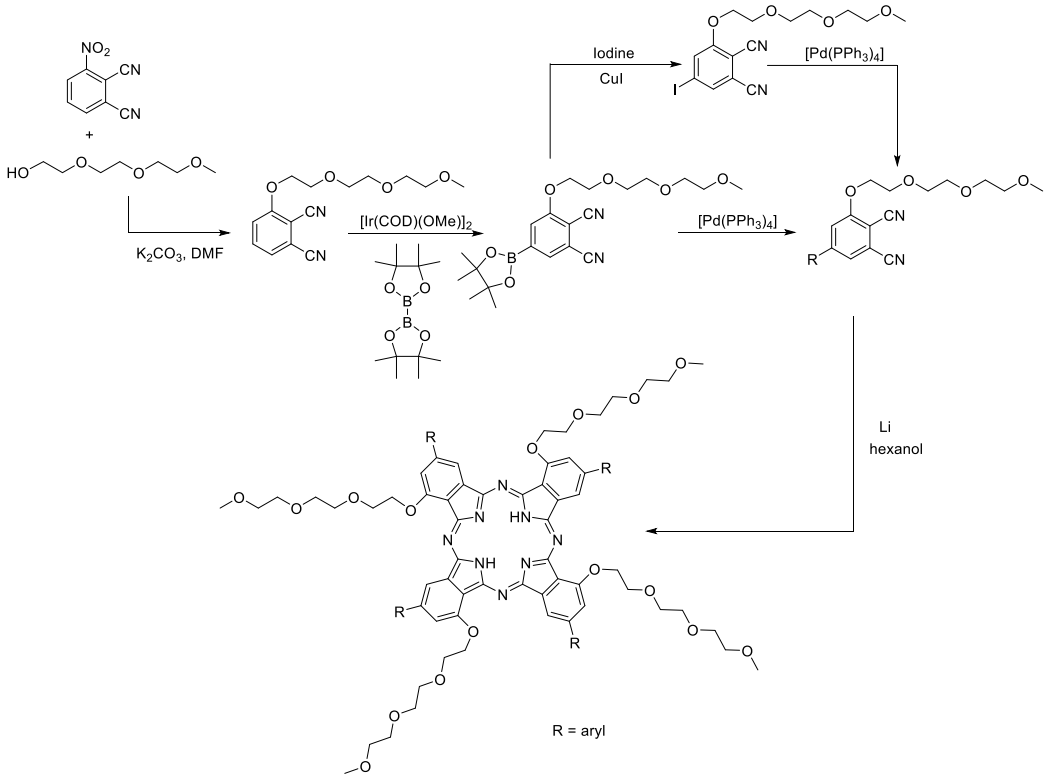
Scheme 2. Synthesis of 3,5-bis-arylphthalonitriles to produce C_{4h} octaarylphthalocyanines

Bulky groups may be introduced in a clever and transitory way with the same purpose (Scheme 3).[38] The base-controlled o-lithiation and silylation of 4-tert-butylphthalonitrile gave, after cyclotetramerization, a single C4h regioisomer which could be converted into the corresponding tetra-*tert*-butyl phthalocyanine after deprotection of the silyl groups with an acid treatment.



Scheme 3. Use of bulky silyl moieties to form a single C4h regioisomer. Adapted from ref 38.

Synthetic conditions are also known to play an important role in the regioisomer that is obtained. Temperature has especially proven to play a critical role, with very nice bifunctional phthalocyanines being obtained as a single isomer in a one-week reaction at 45 °C, whereas higher temperatures yield regioisomeric mixtures (Scheme 4).[39,40]



Scheme 4. Synthesis of octa substituted phthalocyanine as a single regioisomer. Adapted from ref 39

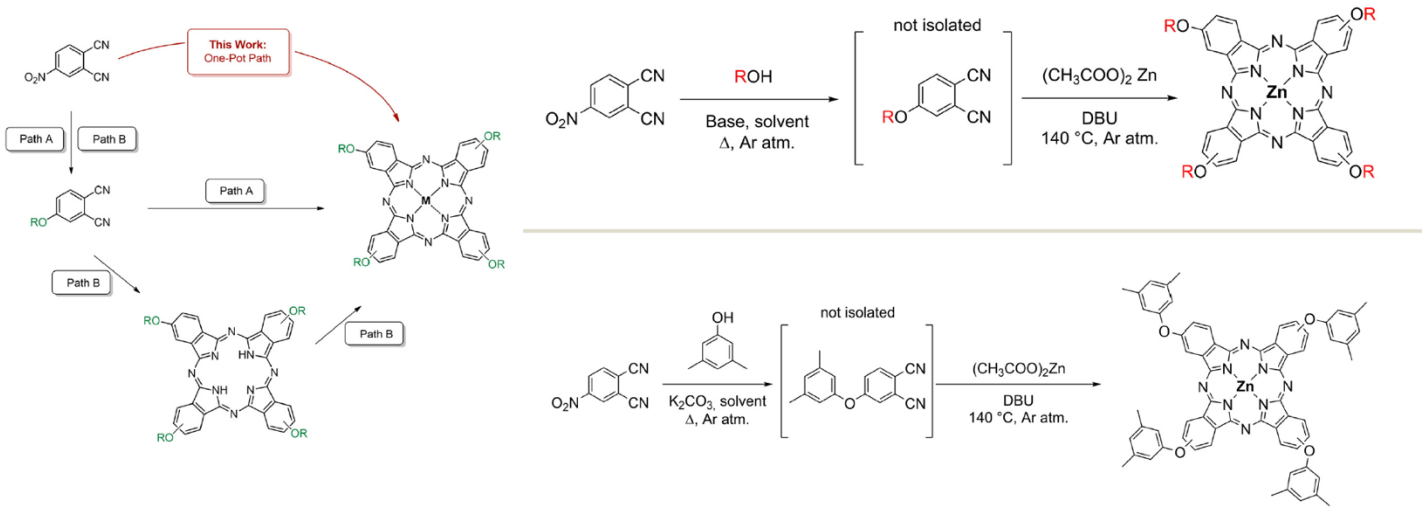
The strategies have proven to be effective but have some limitations. The first and main one is that it is limited to phthalocyanines with non-peripheral substitution. The second one is that really bulky substituents are needed, which limits the versatility of the structures possibly obtained.

4.3. Reduction of the environmental impact of phthalocyanine syntheses.

Very interesting efforts are being conducted to improve the environmental friendliness of phthalocyanine synthesis. The main leverages would be the reaction temperature and the use of solvents.

Solid-state synthesis has therefore prompted a lot of efforts, in particular with a very detailed investigation and systematic screening of solid-state reaction parameters, either performed by ball-milling and aging, and studying also the role of several parameters such as temperature, presence of a template, taking the conversion of *t*Bu phthalonitrile to tetra-*t*Bu phthalocyanine as the reaction model. Dimethylaminoethanol (DMAE) was used in equimolar amounts, acting as a base rather than a solvent.[41] Related works on a different range of solvent has also been conducted.[42]

Achieving in a one-pot sequence the substitution of the nitro function on nitro-phthalonitrile and the cyclotetramerization via tandem SNAr-cyclotetramerization is a way to limit the amount of solvent during the reaction and for the purification steps. This has been achieved to produce tetra-alkoxy substituted metalated phthalocyanines (Scheme 5).[43] Such derivatives are usually obtained by the metalation of the already formed free-base phthalocyanine, itself obtained from the corresponding substituted phthalonitrile. Such phthalonitriles are obtained from alcohols that are also suitable solvents for the cyclotetramerization reactions. It could therefore act as the solvent, unless a non-hydroxylated solvent is used. This proved to be a successful strategy with various alcohols and phenols. The same method was also successfully applied to octa-aryloxy substituted phthalocyanines, but starting from 4,5-dichlorophthalonitriles.



Scheme 5. The one-pot preparation of tetra-alkoxy substituted metalated phthalocyanines starting from nitrophthalonitrile. Adapted from ref 43.

Green Chemistry Metrics, and, amongst them, the E-factor, are useful tools to quantify the environmental impact of a reaction. The E-factor is the ratio of the mass of waste generated per mass of product obtained and takes into account all chemical species part of a reaction, including byproducts, unreacted substrates, non-recyclable solvents, catalysts. It has been used to analyze a large series of cyclotetramerization, in what is a crucial step to better define future objectives and survey the possible strategies.[44]

5. Tailoring of phthalocyanine properties

Properties that can be exhibited by phthalocyanines are the basis for the use in biomedical and technological applications. They can be modulated by the metalation and substitution pattern which as structural parameters, and depend also on external factors, such as the concentration, temperature, solvent, association with other materials (polymers,[45] carbon nanomaterials such as graphene or carbon nanotubes[46]), presence of biomarkers,[47-48] etc. While the effect of structural factors on fundamental properties, especially optical, are quite well-known,[49-51] tailoring precisely their properties in actual applications remains to be deeply explored given the quantity of parameters, as for example in this recent work investigating the structural factors governing the photodynamic activity of phthalocyanines,[52] their sensing properties,[53-54] their performance as photosensitizers in Perovskite Solar Cells,[55] as molecular catalysts[56] or energy producing materials.[57] Using phthalocyanines as bricks of MOFs or COFs has opened new avenues to further modulation of their properties and use in various applications.[58]

Conclusions

Fundamental and technological research on phthalocyanines or implying phthalocyanines has produced an enormous corpus of knowledge and an even larger number of publications and patents. Some are therefore considering that a peak has passed and that everything worth has already been done. As passionate phthalocyanine chemists, we do believe that phthalocyanines have outstanding potential, and that many discoveries are yet to come. Phthalocyanines have indeed properties that are crucially needed in biomedical and technological applications, and able to improve nanotechnology. Yet better, more specific, more efficient synthetic pathways remain to be discovered and optimized. Our answer to the somehow provocative title of this mini-review is definitely that no, not everything has been done with phthalocyanines, and that many discoveries remain to be done in this exciting field, should it be from the point of view of the synthetic methods and strategies, of the design of new derivatives, as well as on their implementation on crucial applications.

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Authors' Biographies

Fabienne Dumoulin, PhD, FRSC, studied first biology, graduated in biochemistry then completed her PhD with a European Label in organic chemistry in Lyon, France in 2002, settled in Türkiye in 2005 and is a faculty of the Department of Biomedical Engineering of Acıbadem University since 2020. She works on the design and synthesis of tetrapyrrolic derivatives, mainly phthalocyanines for photodynamic therapy, authored so far 100+ research articles, three book chapters and supervised a dozen of Master and PhD students. She has been elected four times officer of the executive committee of the European Society for Photobiology, is an associate editor and editorial board member for RSC Advances, associate editor Journal of Porphyrins and Phthalocyanines, co-edited the book series "Porphyrin Science by Women" (January 2021) and strongly advocates for the recognition of women in STEM.

Dr. Atefeh Emami is a Postdoctoral Researcher at Acıbadem Mehmet Ali Aydınlar University, Türkiye. She received her Ph.D. in Organic Chemistry from Iran University of Science and Technology in 2018. Her doctoral research focused on catalysts in organic chemistry, graphene-based nanomaterials, polymers, and the synthesis of organic compounds. Currently, her postdoctoral research interest focuses on phthalocyanines and their applications in photodynamic therapy.

Derya Topkaya Taşkıran is a Professor of Organic Chemistry at Dokuz Eylül University, Türkiye. She received her B.Sc. in Chemistry from Ondokuz Mayıs University (2002), followed by an M.Sc. (2005) and Ph.D. (2010) from Dokuz Eylül University. Her research focuses on synthetic organic chemistry, particularly the design and synthesis of porphyrin and phthalocyanine derivatives for applications in photodynamic therapy, medicinal chemistry, and sensor technologies. She also works on sustainable chemistry, utilizing natural waste materials for nanomaterial production in environmental remediation. She has led several TÜBİTAK research projects and supervises graduate students in functional organic materials.

Dilara Sipahioğlu received her B. Sc. (2020) an M. Sc. (2023) in Chemistry from Koç University. During her master's studies, she focused on near-infrared absorbing gold-gold sulfide nanoparticles as multifunctional agents for Photodynamic Therapy (PDT), photothermal therapy (PTT), and nitric oxide (NO) gas therapy. She is currently pursuing her Ph.D. in Biomedical Engineering at Acıbadem Mehmet Ali Aydınlar University under the supervision of Prof. Dr. Fabienne Dumoulin. Her doctoral research focuses on the synthesis and nanoformulation of phthalocyanine-based photosensitizers for photodynamic therapy.

Emel Önal is an Assistant Professor at Doğuş University, Türkiye. She received her PhD in Chemistry through a joint program at Université Claude Bernard Lyon 1 (France) and Gebze Technical University (Türkiye) in 2014. Her research focuses on porphyrinoid and graphene-based nanomaterials for health, sensors, and energy with applications in photodynamic and sono-photodynamic therapy, antimicrobial systems, and advanced functional materials.

Gülçin EKİNEKER, received her B.Sc. degree in Chemistry from Selçuk University in 2007. She completed her M.Sc. (2010) and Ph.D. (2017) studies in Chemistry at Gebze Technical University with the support of The Scientific and Technological Research Council of Türkiye (TÜBİTAK) 2210 and 2211 National Scholarship Programs. Between 2020 and 2022, she conducted postdoctoral research under the TÜBİTAK 2218 Fellowship Program. She joined Trakya University in 2022 and has been serving as an Assistant Professor since 2026. Her research focuses on the synthesis of phthalocyanines, particularly in photodynamic therapy (PDT) and sterilization applications.

Zeynep Ulupınar Uman graduated with a degree in Biology with Honors in 2010 and received his master's degree in the same department in 2012. She is currently Ph.D. candidate in Biomedical engineering at the Acıbadem Mehmet Ali Aydınlar University under the supervision of Prof. Dr. Fabienne Dumoulin. Her research has focuses on porphyrinoid-based photosensitizing polymeric scaffolds for photodynamic applications.

Sinem Tuncel Kostakoğlu was born in 1981 in Istanbul and received her MSc and PhD in Chemistry at Gebze Technical University. Since 2025 she has been at Acibadem University where she currently is a Professor in the Department of Chemistry. Her research interests focus on developing functional materials based on photo-active phthalocyanines, porphyrins, BODIPYs mainly for photodynamic therapy and sensors.

Prof. Dr. Ümit İşci is an expert in the design and synthesis of phthalocyanines and his research focus mainly on their use as catalysts (oxidation catalysts or CO_2 reduction) He is also interested in the use of these fascinating molecules for sensing, light harvesting and environmental applications. He has authored so far 50+ publications in peer-reviewed journals and is leading several international worldwide collaborations.