The Modular Approach to Acetylenic Phthalocyanines and Phthalocyanine Analogues

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The need for new chromophores with intense absorptions at the far red end or the near infrared region of the electromagnetic spectrum is evident from recent developments in materials science and medicinal chemistry. This has prompted us to explore the potential of octaalkynyl-substituted phthalocyanines, tetrapyrazinoporphyrazines, and tetra-6,7-quinoxalinoporphyrazines. In order to assemble these chromophores efficiently and in a modular fashion, we have prepared two types of acetylenic building blocks – namely 3,4-dimethylenehexa-1,5-diynes and hexa-1,5-diyne-3,4-diones – and have successfully converted them into alkynyl-substituted benzenoid phthalonitriles, the former by means of cycloadditions with dicyanoacetylene, the latter through condensation reactions with vicinal diamines such as diaminomaleodinitrile and 4,5-diaminophthalonitrile. The dinitriles were cyclotetramerised to the corresponding octaalkynyl phthalocyanines and phthalocyanine analogues using magnesium butoxide in butanol. Core physical properties of the new chromophores, most notably their solubilities and absorptivities, are markedly influenced by the presence of the eight alkynyl substituents. Further fine-tuning of these characteristics by appropriate choice of terminal acetylene substituents is possible.

Introduction

The electromagnetic spectrum between the far red end of the visible spectrum and the near infrared (NIR) region below ca. 900 nm continues to be particularly valuable for applications in fields as diverse as those of materials science and biomedicine. While researchers active in the former area, for example, strive to develop new materials that can interact with the cheap and abundant gallium-arsenide laser diodes (CD players, laser printers etc.) that emit between 780−830 nm,[1,2] the interest of biomedical scientists in the NIR arises from the need to identify chromophores that emit or absorb in a region where biological tissue is relatively translucent. A particularly intriguing example for biomedical applications of NIR chromophores are the photosensitisers employed in so-called photodynamic tumour therapy (PDT).[3−10] The underlying principle of this innovative and microinvasive form of cancer treatment is based on local irradiation, by external light, of a photosensitiser embedded in the tumour tissue. The initial excitation of the chromophore is followed by energy transfer, via the sensitiser's excited triplet state, to molecular oxygen, resulting in the formation of reactive singlet oxygen. Alternatively, oxygen-containing radicals arising from electron transfer reactions may also be implicated. These reactive oxygen species will rapidly react with cellular components in their vicinity, inducing cell death and ultimately resulting in necrosis of the tumour. Photosensitisers currently employed in or undergoing testing for PDT applications are shown in Figure 1, together with their longest wavelength absorption maxima. At present, only Photofrin® (**1**),[11] a first generation PDT agent, is approved for medical use against certain types of cancer, whereas more recent sensitisers of the se-

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Rüdiger Faust, born in 1963 in Dortmund, completed his Diploma in Chemistry at the University of Dortmund in Germany. He then joined Prof. K. Peter C. Vollhardt as a postgraduate student at the University of California at Berkeley, USA, and was awarded a Doctorate of Philosophy in Chemistry from this university in 1993. He continued his scientific education as a postdoctoral fellow with Prof. François Diederich at the ETH Zürich, Switzerland, from which he moved on to a position as a Wissenschaftlicher Assistent at the Pharmaceutical Chemical Institute of the University of Heidelberg, Germany. In 1998 he accepted his current appointment as a Senior Lecturer in Chemistry at University College London, UK. Research in his group centres around new functional NIR chromophores, the construction of novel transition metal arrays, and the role of melatonin in sleep.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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cond generation, such as Foscan® (**2**),[12−14] the sulfonated aluminium phthalocyanine **3**[15] and the lutetium texaphyrin **4**,[16,17] are still being tested at various stages of clinical trials.

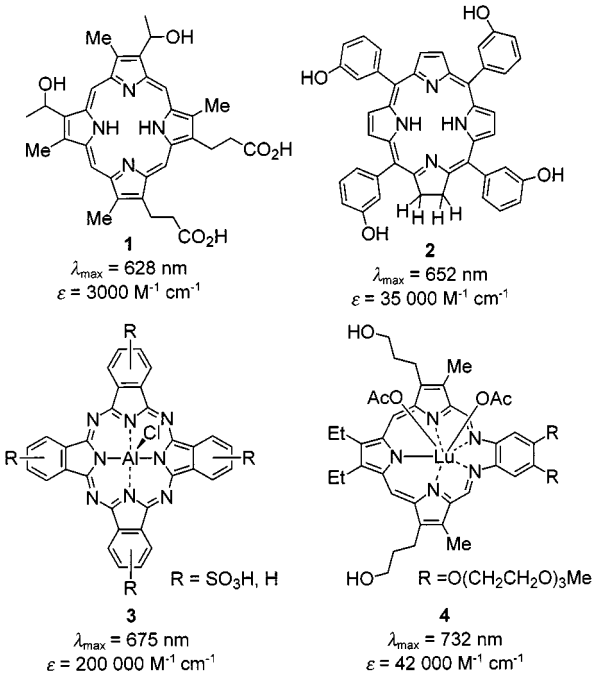


Figure 1. Photosensitisers currently in use in the photodynamic treatment of cancer

The common structural feature of the PDT agents depicted in Figure 1 is the porphine-related aza-macrocyclic core, which, in the cases of compounds **2**−**4**, has been modified variously by partial reduction (**2**), benzoannulation (**3**), or ring-expansion (**4**). One of the reasons for exploring such structural modifications lies in the need to improve upon the optical properties of Photofrin® (**1**), which shows only a low level of extinction (ca. 3000 $M^{-1}\cdot cm^{-1}$) at the relatively short wavelength of 624 nm and hence has a limited efficiency for acting as a photosensitiser in biomedical applications. The second generation PDT agents **2**−**4** address this problem and exhibit bathochromically and hyperchromically shifted longest wavelength absorptions that enhance the chromophore's accessibility to external light in cellular tissue.

We endeavour to contribute to this area of research by providing peripherally peralkynylated chromophores based on the phthalocyanine backbone, such as in **3**. The attachment of alkynyl groups at the periphery of a given chromophore is a convenient means to modulate some of the pertinent properties of the core structure. Thus, alkynyl substituents extend the chromophore's π-system by rigid two-carbon units, which can themselves be further functionalised at their termini with a variety of groups. In this way, the chromophores' absorptions can be bathochromically and hyperchromically shifted and the solubilities of the dyes easily fine-tuned to comply with the requirements of a given medium for a specific application.

The advantageous properties of acetylene substituents has not escaped the attention of researchers active in the field, and a variety of alkynylated phthalocyanines have recently been prepared. These include substituted mono-[18−20] and tetraalkynylphthalocyanines[21] (mostly as regioisomeric mixtures), octaalkynylphthalocyanines[22,23] and, most recently, phthalocyanino-fused dehydro[12]- and -[18]annulenes.[24,25]

A common method for achieving peripheral alkynylation of organic chromophores relies on sequential halogenation/transition metal-mediated CC-bond formation methods[26] on the preformed core structures, which, when applied to polyacetylenic phthalocyanines, may be prone to problems in terms of efficiency, regioselectivity and solubility of intermediates.[27] Retrosynthetic analysis of the phthalocyanines identifies 1,2-dicyanobenzene derivatives as direct precursors of the fully conjugated azamacrocycles[28] and suggests the introduction of the acetylene units at an early stage, preferably even prior to the formation of phthalonitriles from butadienoid substructures (Figure 2).

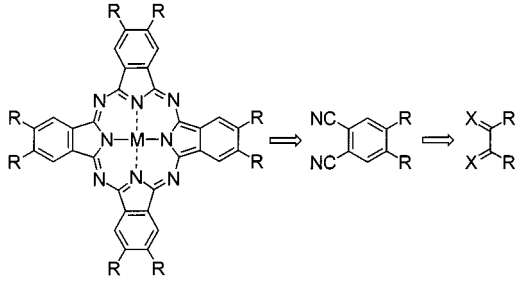


Figure 2. Retrosynthetic analysis of octasubstituted phthalocyanines

We have therefore devised a modular strategy for the production of acetylenic chromophores, starting from small, acetylene-bearing building blocks from which peripherally alkynylated phthalocyanine analogues may be constructed in a concise and flexible fashion. Key compounds in this design are the hexa-1,5-diyne-3,4-diones **5**[29] (Figure 3). These vicinal diones not only provide the basis for the syn-

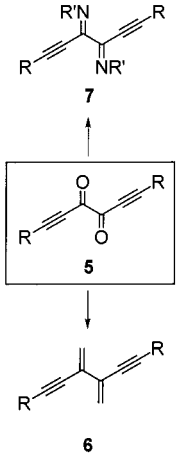


Figure 3. Acetylenic building blocks based on 3,4-difunctionalised hexa-1,5-diynes

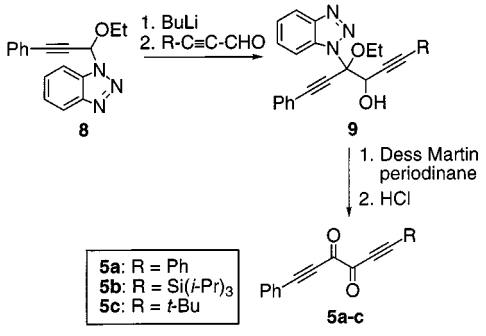
thesis of related building blocks such as the dialkynylbuta-1,3-dienes **6**[30] and the vicinal diimines **7**,[31] but also function as suitable starting materials for the preparation of azamacrocycles with phthalocyanine cores.

This contribution summarises our approach to two 3,4-difunctionalised hexa-1,5-diynes − namely the diketones **5** and the butadienes **6** − and describes their successful conversion into various phthalocyanine analogues. The positive influence of acetylene substitution on the optical and the solubility properties of the chromophores is highlighted.

Results and Discussion

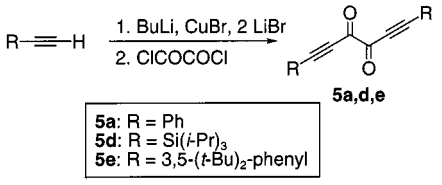
1. Synthesis of 3,4-Difunctionalised Hexa-1,5-diynes as Acetylenic Building Blocks

Prior to our work there was only one report about the preparation of an acetylenic 1,2-dione, namely that of dodeca-4,8-diyne-6,7-dione, from pentynyllithium and oxalyl chloride.[32] In our hands, this procedure was difficult to reproduce, giving rise to varying amounts of unstable product and, more importantly, was not generally applicable to other monosubstituted acetylenes. We therefore decided to explore more viable routes to the acetylenic vicinal diones and, after many ill-fated attempts, identified the 1*H*-benzotriazole method developed by Katritzky et al.[33] as a reliable entry to this class of compounds (Scheme 1).[29] The key to the success of this procedure is the ability of benzotriazole to engage in carbonyl protection and to form the mixed *N,O*-acetal **8**, which is able to stabilize an adjacent propargylic charge. The anion generated from **8** therefore reacts smoothly with acetylenic carbaldehydes to give the corresponding masked α-hydroxy ketones **9**.



Scheme 1. Synthesis of dialkynyl 1,2-diones using 1*H*-benzotriazole as an auxiliary

Much to our satisfaction, the dialkynyl 1,2-diones **5a−c** were obtained in multigram quantities after mild oxidation of **9** and acidic carbonyl deprotection.[29] Compounds **5a** and **5b** in particular proved to be stable to ambient conditions and so in principle are suitable for conversion into acetylenic NIR chromophores. However, the multistep nature of the benzotriazole-based approach to **5** presents a serious flaw in the modular build-up strategy for acetylenic phthalocyanine analogues, which aims to provide these compounds in as small a number of steps as possible. Reassured by this newly acquired knowledge of the stability of the dialkynyl 1,2-diones, we therefore returned to oxalyl chloride as an obvious choice through which to provide the vicinal dione substructure in **5**. Indeed, judicious choice of transition metal and auxiliary agents provided a much shorter route to the key building block **5**. Thus, in the presence of two equivalents of LiBr, copper acetylides (prepared in situ by transmetallation of lithium acetylides with CuBr) smoothly convert oxalyl chloride into the desired acetylenic 1,2-diones **5**, in yields usually between 50 and 80%, depending on the nature of the starting acetylene (Scheme 2).[34]



Scheme 2. Synthesis of dialkynyl 1,2-diones from oxalyl chloride

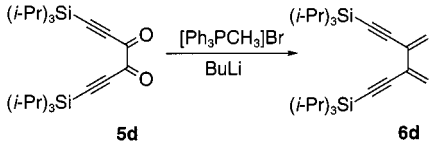
The copper-mediated alkynylation of oxalyl chloride has proved itself as a method of broad generality that tolerates various acetylene terminal groups. To date we have thus been able to prepare over twelve different silyl- and aryl-terminated derivatives of **5** and are now in a position to address a range of different solubility requirements in our pursuit of acetylenic NIR chromophores (vide infra). Limitations in the stability of **5** are encountered when the reactive ynone moieties are not sufficiently shielded (e.g. in the presence of the relatively small terminal *tert*-butyl and trimethylsilyl substituents) or when the aryl substituent carries strongly electron-withdrawing groups such as 4-nitro, 4-carboxyalkyl, 3,5-dicarboxyalkyl etc.

The one-step procedure depicted in Scheme 2 also allows for the preparation of differently terminated dialkynyl 1,2-diones by the simultaneous addition of two different acetylides to oxalyl chloride and subsequent chromatographic separation of the products. While the benzotriazole-mediated route to dialkynyl-1,2-diones was therefore crucial for the successful start of this project, the ease and the generality of the oxalyl chloride alkynylation method has clearly superseded this multistep procedure.

With the acetylenic diones **5** in hand, their synthetic potential for the construction of various *N*-heterocycles[34] and the vicinal diimines **7**[31,35,36] was readily explored. In the context of the preparation of acetylenic phthalocyanine analogues, we were particularly interested in the conversion of **5** into the 3,4-dimethylene-hexa-1,5-diynes **6**. The first members of this class of cross-conjugated hydrocarbons had previously been obtained by Hopf and co-workers,[37,38] who also investigated the behaviour of these dienes in [4+2] cycloaddition reactions. However, the nickel-mediated alkynylation of 2,3-dichlorobuta-1,3-diene that was used for the construction of **6** did not provide triisopropylsilyl- or aryl-terminated congeners of **6**. In the light of the stabilising properties of bulky silyl groups[39] on one hand, and the

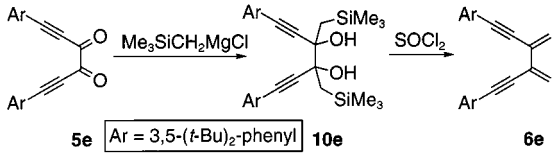
variable functionalization opportunities of aryl groups on the other, we set out to fill this void and tried to obtain the corresponding derivatives of **6** from the diacetylenic 1,2-diones **5**.[30]

Gratifyingly, the triisopropylsilyl-protected dialkynyl-1,2-dione **5d** was readily diolefinated to **6d**, by use of standard Wittig conditions with methylenetriphenylphosphorane at −78 °C (Scheme 3). The yield of this transformation, at 19%, is certainly not optimal, but is acceptable in view of the similar results obtained in the analogous Wittig reaction behaviour of the simpler dione benzil.[40,41] Unfortunately, the aryl-terminated dione derivatives **5a** and **5e** could not be converted into the corresponding butadienes in this fashion and only decomposition products were obtained.



Scheme 3. Diolefination of dialkynyl 1,2-diones by means of a Wittig reaction

After numerous attempts to circumvent this problem, we finally found that the Peterson olefination[42] smoothly converted the acetylenic ketone **5e** into the corresponding vicinal diol **10e** (Scheme 4). Although it was not possible to achieve a formal twofold hydroxymethylsilane elimination to generate the butadiene substructure of **6** from the isolated diols, the direct conversion of **5e** to **6e** without prior isolation of the intermediate diols **10e** was successful when thionyl chloride was used to assist in the elimination. Not surprisingly, hydrocarbons **6d** and **6e** proved to be rather sensitive towards heat, light and air, and readily polymerised and turned deep yellow when exposed to ambient conditions over prolonged periods.



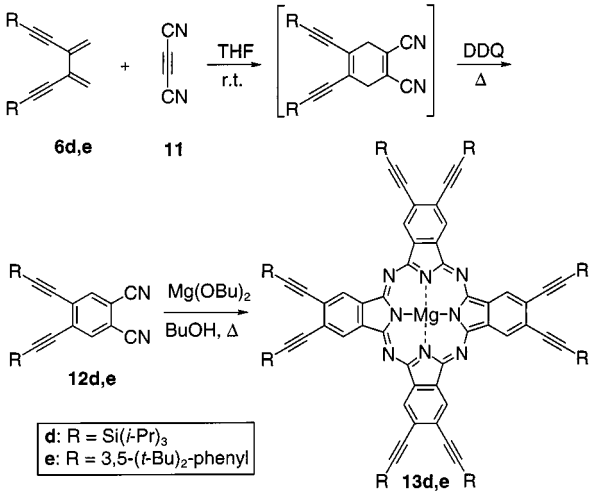
Scheme 4. Diolefination of dialkynyl 1,2-diones by means of a Peterson olefination

The successful synthesis of new members of the 3,4-dimethylenehexa-1,5-diynes **6** provides the second acetylenic building block from which we plan to construct phthalonitrile derivatives. The stage is therefore set to explore the suitability of the hexadiynes in the assembly of acetylenic analogues of the phthalocyanines.

2. The Synthesis of Acetylenic Phthalocyanine Analogues

As mentioned in the Introduction, the immediate precursors to the phthalocyanines are phthalonitrile (1,2-dicyanobenzene) derivatives, from which the target compounds can be derived by base-induced cyclotetramerisation.[28] In order to attach peripheral alkynyl groups onto the aza-macrocycles using our modular building block approach, one is therefore faced with the task of converting the hexa-1,5-diynes **5** and **6** into acetylenic benzenoid dinitriles. Given the nature of the 3,4-substituents of **5** and **6**, two principle routes towards achieving this goal emerge. On the one hand, the dimethylene derivatives **6** can be envisioned as engaging in [4+2] cycloadditions with dicyanoacetylene, whereas on the other hand, the acetylenic diketones **5** would be expected to engage in condensation reactions with vicinal diamines such as diaminomaleodinitrile or diaminophthalonitrile. Both routes have been explored successfully.

The behaviour of selected derivatives of the cross-conjugated dimethylenehexadiynes **6** in [4+2] cycloadditions has previously been investigated by Hopf and co-workers,[38] and the compounds were generally found to react quite readily with various dienophiles. Unfortunately, the derivatives **6d** and **6e** prepared by us turned out to be much less reactive than initially expected. To make matters worse, thermal activation to induce the [4+2] cycloaddition turned out to be counterproductive, owing to the lability of **6d** and **6e** at elevated temperatures. We presume that the bulky acetylene substituents on the dialkynylbutadienes render the adoption by the butadiene substructure of an *s-cis* conformation more difficult and promote alternative radical pathways or polymerisation. These caveats notwithstanding, **6d** and **6e** do react at room temperature with one of the most reactive dienophiles known: namely dicyanoacetylene **11**[43,44] (Scheme 5).



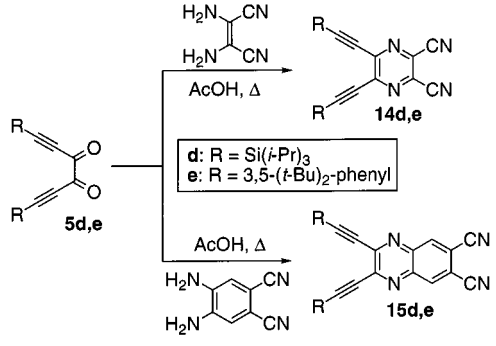
Scheme 5. Diels−Alder approach to octaalkynyl phthalocyanines

The resulting cyclohexadiene adducts are not normally isolated, but rather are aromatised directly to the 4,5-dialkynylphthalonitriles **12d** and **12e** by treatment of the reaction mixture with DDQ in toluene. The synthetic sequence towards the octaalkynylphthalocyanines **13** was completed by treating **12d** and **12e** individually with magnesium butoxide in refluxing butanol (Scheme 5). The good solubility in common organic solvents of the deep green, crystalline chromophores thus obtained permitted convenient purifica-

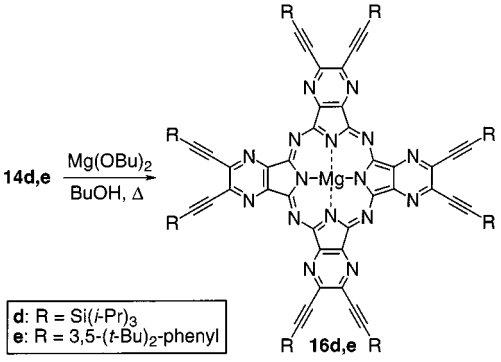
tion of the octaalkynylphthalocyanines with standard chromatographic techniques on silica gel. Analytically pure samples were readily obtained using gel permeation chromatography. Furthermore, the bulky substituents at the periphery of **13d** and **13e** efficiently prevented the aggregation of the chromophores in solution, and hence **13d** and **13e** represent some of the few examples for which ^{1}H and ^{13}C NMR spectroscopic data are available.[30]

It should be pointed out that the building block approach to the octaalkynylphthalocyanines **13** compares favourably with a more traditional halogenation/palladium-mediated alkynylation procedure described for related compounds by Leznoff et al.[22,23] The preparation of **13** only takes four steps from oxalyl chloride and avoids problems associated with the formation of regioisomeric mixtures of intermediates.

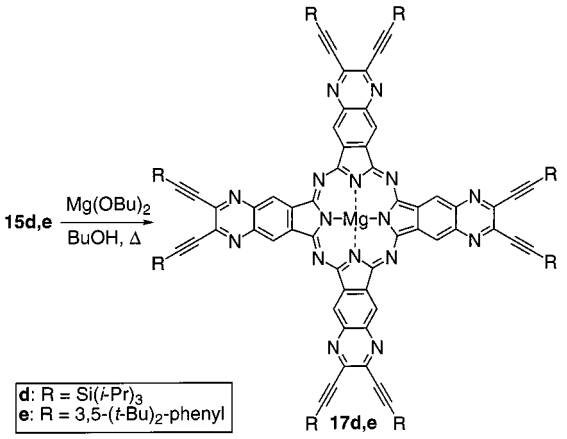
A similar level of brevity and unambiguity is observed when the dialkynyl 1,2-diones **5** are converted into acetylenic phthalocyanine analogues. The diketones **5d** and **5e**, for example, react smoothly with commercially available diaminomaleodinitrile to give the dicyanodiethynylpyrazines **14d** and **14e** (Scheme 6).[27] Similarly, condensation of **5d** and **5e** with 4,5-diaminophthalonitrile, available in three steps from phenylenediamine,[45] produces the 2,3-dialkynylquinoxaline-6,7-dinitriles **15d** and **15e** (Scheme 6).[28] Base-induced cyclotetramerisation of the aromatic dinitriles **14** and **15** with magnesium butoxide in refluxing butanol generates the peripherally peralkynylated phthalocyanine or naphthalocyanine analogues: namely the tetrapyrazinoporphyrazines **16d** and **16e**[46] (Scheme 7) and tetra-6,7-quinoxalinoporphyrazines **17d** and **17e**[47] (Scheme 8), respectively.



Scheme 6. Preparation of acetylenic pyrazinoid dinitriles



Scheme 7. Synthesis of octaalkynyl tetrapyrazinoporphyrazines



Scheme 8. Synthesis of octaalkynyl tetra-6,7-quinoxalinoporphyrazines

Once more, two facts are worth pointing out. Firstly, both chromophore types **16** and **17** greatly benefit from the terminal alkyne substituents, which enhance the compounds' solubilities and prevent their aggregation in common (aprotic) organic solvents, thereby facilitating the isolation and the purification of the material by chromatographic methods. Secondly, the advantages of achieving peripheral alkynyl substitution of the chromophores become apparent when the brevity of the syntheses of **16** and **17** is considered. Both preparations require only three steps, starting from oxalyl chloride, and are flexible with respect to the terminal alkyne substituents and the central metal ion. These facts are of particular interest for the 6,7-quinoxalinoporphyrazines **17**, a new class of phthalocyanine-based chromophores that can be viewed as octaaza analogues of the naphthalocyanines. Previously, solubility-enhancing naphthalocyanine substituents were predominantly introduced either at the metal centre[48] or in the bay regions of the aromatic macrocycle,[49] where steric interactions between the appending groups impose some degree of nonplanarity. A substitution pattern such as in **17** is rare[50,51] but preferable, since it does not interfere with the symmetry of the chromophore and does not depend on the nature of the central metal ion. It is, however, notoriously difficult to achieve, due to regioselectivity problems encountered in the preparation of the appropriate 2,3-dicyanonaphthalene precursors. The modular approach to compounds such as **17** circumvents these difficulties.

3. Electron Absorption Spectra of Acetylenic Phthalocyanine Analogues

With a convenient methodology for the implementation of peripheral alkynyl substitution of phthalocyanine and some of its analogues at hand, the optical properties of these molecules were of considerable interest. In particular, we were hoping that the acetylene substitution would provide chromophores with absorptions bathochromically and hyperchromically shifted with respect to non-acetylenic derivatives. As will become clear from a close inspection of Figures 4 and 5, all of these expectations were indeed met.

Figure 4 depicts the UV/Vis/NIR spectra, in THF at room temperature, of the octaalkynylmagnesium phthalocyanines **13d** and **13e** and the peralkynylated magnesium tetrapyrazinoporphyrazines **16d** and **16e**, respectively. It is well known that aza-substitution within the phthalocyanine macrocycle results in absorptions at wavelengths lower than those in the unperturbed parent systems.[52] It therefore comes as no surprise that compounds **16** show an intense longest wavelength absorption around 670 nm (ε ca. 300000 $M^{-1}\cdot cm^{-1}$), while the phthalocyanines **13** display sharp bands at the far red end of the visible spectrum around 720 nm (ε ca. 400000 $M^{-1}\cdot cm^{-1}$). Both of these so-called *Q*-bands are significantly red-shifted with respect to those of non-acetylenic model compounds. For example, the octabutylmagnesium tetrapyrazinoporphyrazine **18** has a longest wavelength absorption at 634 nm.[46] Similarly, the corresponding *Q*-band of unsubstituted magnesium phthalocyanine appears at 670 nm.[53] It therefore appears that octaalkynyl-substitution induces a bathochromic shift between 4 and 6 nm per CC triple bond in each of the chromophores.

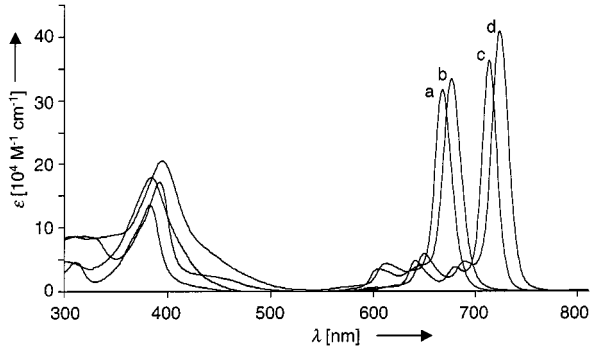
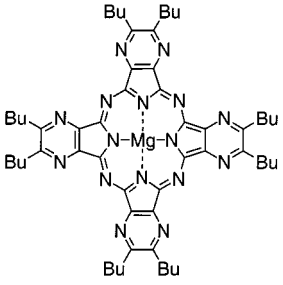


Figure 4. UV/Vis/NIR spectra of **16d** (a), **16e** (b), **13d** (c), and **13e** (d) in THF at 298 K



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It is also evident from inspection of Figure 4 that the longest wavelength absorptions of both chromophore systems are amenable to fine-tuning by simple variation of the terminal acetylene substituents. Hence, arylethynyl groups such as in **13e** and **16e** result in *Q*-bands that are bathochromically shifted by ca. 10 nm with respect to those of the silyl derivatives **13d** and **16d**. The chromophores' π-systems are therefore further extended not only by alkynyl substitution, but also by appropriate choice of alkyne terminus.

The UV/Vis/NIR spectra of magnesium tetra-6,7-quinoxalinoporphyrazine **17d** and the non-acetylenic derivative **19**, prepared analogously from hexacosane-13,14-dione, is shown in Figure 5.[10] Quite clearly, the longest wavelength absorption of **17d** is beyond the range of the visible spectrum and extends with intense absorptions (ε ca. 500000 $M^{-1}\cdot cm^{-1}$) into the near infrared. Again, the *Q*-band of the acetylenic representative **17d** (λ_{max} = 770 nm) is bathochromically shifted with respect to that of non-acetylenic **19** (λ_{max} = 735 nm) by a magnitude amounting to ca. 4 nm per alkyne unit. However, and unlike the smaller acetylenic homologues **13** and **16**, the chromophore of **17** cannot be further extended by the attachment of aryl groups on the termini of the acetylenes. Hence, the *Q*-band of **17e** (λ_{max} = 770 nm) is almost identical in position and shape to that of **17d**.

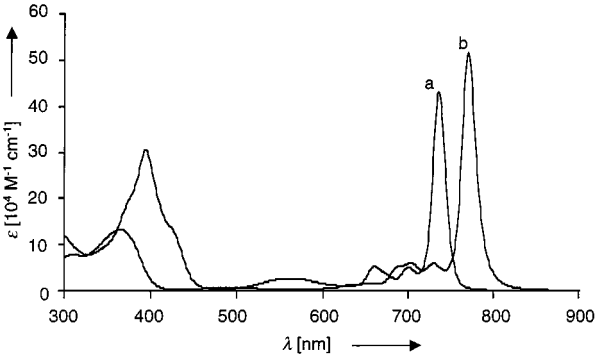
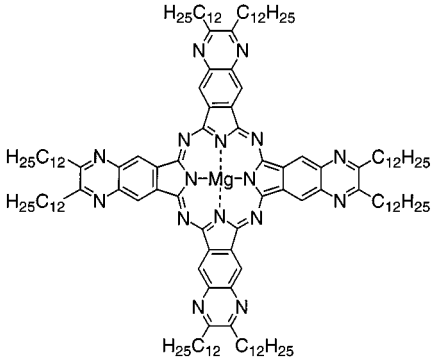


Figure 5. UV/Vis/NIR spectra of **17d** (**b**) and **19** (**a**) in THF at 298 K



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Another remarkable feature of the electron absorption spectrum of **17d** is the broad window of virtually no absorptivity between the high-energy band around 390 nm and the *Q*-band at 770 nm. In addition to the areas mentioned in the introduction, this may also suggest that compounds such as **17** may function as efficient markers for monitoring industrial processes or in analytical applications.

Conclusion

The short and efficient syntheses of the hexa-1,5-diyne building blocks provides a rapid and flexible route to peripherally alkynylated phthalocyanines and their octaaza

analogues. All of the chromophores are characterised by bathochromically shifted, intense absorptions in the far red of the visible spectrum or beyond. As such, these compounds are promising candidates for a variety of applications, among them the photodynamic treatment of cancer. To this end we are currently exploring hydrophilic variants of these chromophores and are evaluating their suitability as singlet oxygen sensitisers.

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