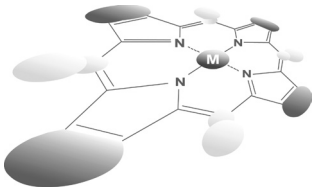
Journal of Porphyrins and Phthalocyanines
J. Porphyrins Phthalocyanines 2011; **15**: 865–870
DOI: 10.1142/S1088424611003744

Published at http://www.worldscinet.com/jpp/



Aryl nitroporphycenes and derivatives: first regioselective synthesis of dinitroporphycenes

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Dedicated to Professor Karl M. Kadish on the occasion of his 65th birthday

Received 29 April 2011
Accepted 19 May 2011

ABSTRACT: The nitration reaction of 2,7,12,17-tetraphenylporphycene has been studied. The use of $AgNO_3$ and a mixture of acetic acid and 1,2-dichloroethane as a mild nitrating system provides an optimized preparation of 9-nitro-2,7,12,17-tetraphenylporphycene and a regioselective synthesis of 9,20-dinitro-2,7,12,17-tetraphenylporphycene. While 25 min of reaction are needed to obtain the mononitrated compound, 4 h are necessary to yield a mixture of 9,20-dinitro and 9,19-dinitro 2,7,12,17-tetraphenylporphycene in a proportion of 3 to 1. From this mixture, the geometric isomers can be isolated by fractional crystallization. 9-Nitro-2,7,12,17-tetraphenylporphycene can be reduced to the corresponding amino derivative, which is the starting material to obtain 9-(glutaric methylesteramide)-2,7,12,17-tetraphenylporphycene, a versatile derivative useful for conjugation.

KEYWORDS: porphycenes, porphyrinoids, photosensitizers, aromaticity, nitration.

INTRODUCTION

Porphycene is the first and most stable constitutional isomer of porphyrin, prepared in 1986 by Vogel and coworkers [1]. These planar and aromatic macrocycles [2] are endowed with a unique set of physical and chemical properties that have attracted interest in many fields ranging from theoretical chemistry, material chemistry or biochemistry, and more specifically in photodynamic therapy (PDT).

In order to prepare porphycene derivatives amenable to be used in specific applications, two main strategies of derivatization have been devised: synthesis *de novo* (2,7,12,17-substituted porphycenes [3, 4], etioporphycenes [5], alkyl and aryl *meso* substituted porphycenes [6] and benzoporphycenes [7]) and direct functionalization of the macrocycle (hydroxylation, halogenation, nitration [8, 9] and sulfonylation [10, 11]).

From a practical point of view, the latter possibility emerges as the most straightforward route to prepare derivatives for conjugation to biological vectors. With this aim, the 9-amino and 9-hydroxy derivatives of some 2,7,12,17-alkyl substituted porphycenes have been prepared and coupled with carotenoids [12] and polymers [13]. It is noteworthy that 9-amino derivatives are prepared with higher yields than the 9-hydroxy counterparts, although their synthesis implies two steps: nitration and Zinin reduction to the amine. In general, this strategy combines experimental simplicity and economy without significantly eroding porphycene photophysical properties [8].

The incorporation of aromatic groups at positions 2,7,12,17 [14, 15] affects the optical properties of porphycene, leading to a dramatic bathochromic shift of the Q-bands. This enhanced absorption in the red region of the spectrum is of paramount importance in applications such as PDT, since the optimal optical window in biological tissue is located between 660–750 nm [16]. Therefore, the combination of aromatic substitution with the possibility of preparation of 9-amino conjugates would open the door for the design of new photosensitizers with

◊SPP full member in good standing

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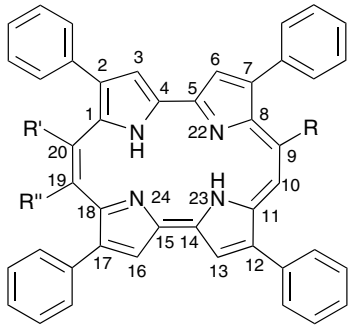


1, TPPo, R, R', R'' = -H
2, 9-NTPPo, R = $-NO_2$, R', R'' = -H
3, 9,20-DNTPPo, R = R' = $-NO_2$, R'' = -H
4, 9,19-DNTPPo, R = R'' = $-NO_2$, R' = -H
5, 9-ATPPo, R = NH_2, R' = R'' = H
6, 9-EGlamTPPo, R = $-NHCO(CH_2)_3CO_2Me$ R'' = R' = -H

Chart 1. Chemical structure of 2,7,12,17-tetraphenylporphycene (TPPo), 9-nitro-, 9,20-dinitro, 9,19-dinitro-, 9-amino and 9-(glutaric methylesteramide)- 2,7,12,17-tetraphenylporphycenes

improved photophysical properties and selectivity. The main drawback of this scheme is the low yield that hampers the nitration of 2,7,12,17-tetraphenylporphycene (**1**) [17]. Considering this fact, we were prompted to study and optimize the preparation of 9-nitro-2,7,12,17-tetraphenylporphycene (**2**) with the goal of using this compound as a starting material to prepare amido conjugates [12].

EXPERIMENTAL

Chemicals

All solvents (1,2-dichloroethane (DCE), tetrahydrofuran, dichloromethane and cyclohexane) and starting materials for synthesis were purchased from Aldrich and were used as received. Spectroscopic grade chloroform was used as received. 2,7,12,17-Tetraphenylporphycene (TPPo) was synthesized as reported in the literature [14]. Purity of all compounds was checked by HPLC or tlc.

NMR spectroscopy

NMR spectra were recorded using a 400 MR spectrometer (^{1}H at 400 MHz and ^{13}C at 100.5 MHz). NMR spectra were recorded at 25 °C in deuterochloroform using tetramethylsilane as internal reference. NOESY1D experiments were recorded using a mixing time of 500 ms and a selective bandwidth of 10 Hz.

Synthesis

Preparation of 9-nitro-2,7,12,17-tetraphenylporphycene (2). To a solution of 92 mg (0.15 mmol) of 2,7,12,17-tetraphenylporphycene (**1**) in 35 mL of acetic acid and 35 mL of 1,2-dichloroethane, 2.4 g (14 mmol) of $AgNO_3$ were added. The resulting mixture was heated at 80 °C with stirring for 25 min. Then 50 mL of water were added and the mixture was extracted with dichloromethane. The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated. The residue was purified using silica gel column chromatography with a mixture of cyclohexane and dichloromethane (1:1) as eluent. Compound **2** was obtained in 90% yield (88 mg) as a dark green powder, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 10.34 (s, 1H, C(10)-H), 9.82 (d, 1H, ^3J = 11 Hz, C(19)-H), 9.74 (d, 1H, ^3J = 11 Hz, C(20)-H), 9.57–9.46 (4s, 4H, C(3,6,13,16)-H), 8.32–7.61 (m, 20H, 4 Ph), 3.45 (brs, 2H, NH).

Preparation of 9,20-dinitro-2,7,12,17-tetraphenylporphycene (9,20-DNTPPo, 3) and of 9,19-dinitro-2,7,12,17-tetraphenylporphycene (9,19-DNTPPo, 4). To a solution of 50 mg (0.08 mmol) of 2,7,12,17-tetraphenylporphycene (**1**) in 15 mL of acetic acid and 15 mL of 1,2-dichloroethane, 1.3 g (7.7 mmol) of $AgNO_3$ were added. The resulting mixture was heated at 80 °C with stirring for 4 h. Then 50 mL of water were added and the mixture was extracted with dichloromethane. The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated. The residue was purified using silica gel column chromatography with cyclohexane and dichloromethane (1:1) as eluent. The second green fraction was recrystallized twice from a mixture of cyclohexane and dichloromethane yielding **3** (44%, 40 mg) as a dark green powder, mp > 300 °C. The resulting solution was evaporated and the solid was recrystallized from cyclohexane to render **4** as a dark green powder (18%, 13 mg), mp > 300 °C. **3.** ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 10.30 (s, 2H), 9.50 (s, 2H), 9.35 (s, 2H), 8.26 (d, 4H, *J* = 8 Hz), 7.97 (d, 4H, *J* = 8 Hz), 7.86 (t, 4H, *J* = 8 Hz), 7.76–7.61 (m, 8H), 4.31 (brs, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C, ppm 147.6, 144.6, 150.5, 139.9, 138.7, 137.3, 135.7, 135.6, 134.5, 131.3, 129.6, 129.4, 129.1, 128.9, 128.8, 128.5, 124.1, 112.4. IR (film, $CHCl_3$): ν, cm^{-1} 3400–3200 (st N–H), 3057, 3027 (as C–NO_2), 2924, 1531 (as C–NO_2), 1326 (st C–NO_2), 945, 843, 762, 699 (Ph). HRMS (HPLC-ESI-TOF): *m/z* calcd. for $C_{44}H_{29}N_6O_4$ 705.2245, found 705.2248. UV-vis: λ_{max}, nm (ε, $M^{-1}.cm^{-1}$) 679 (2.1×10^4), 629 (3.5×10^4), 600 (2.8×10^4), 413 (9.2×10^4). **4.** ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 10.23 (s, 2H), 9.43 (s, 2H), 9.30 (s, 2H), 8.26 (d, 4H, *J* = 8 Hz), 7.93 (d, 4H, *J* = 8 Hz), 7.86 (t, 4H, *J* = 8 Hz), 7.74 (t, 4H, *J* = 8 Hz), 7.76–7.61 (m, 8H), 4.31 (brs, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C, ppm 147.4, 144.4, 140.4, 139.7, 138.5, 137.1, 135.7, 135.4, 134.5, 131.4, 129.6, 129.3, 129.0, 128.9, 128.8, 128.4, 123.4, 112.3.

IR (KBr): ν, cm^{-1} 3400–3200 (st N–H), 3056, 3025, 1530 (as C–NO_2), 1327 (st C–NO_2), 945, 762, 697 (Ph). HRMS (ESI–TOF): *m/z* calcd. for $C_{44}H_{29}N_6O_4$ 705.2245, found 705.2230. UV-vis: λ_{max}, nm (ε, $M^{-1}.cm^{-1}$) 679 (2.1×10^4), 629 (3.2×10^4), 600 (2.5×10^4), 413 (8.3×10^4).

Preparation of 9-(glutaric methylesteramide)-2,7, 12,17-tetraphenylporphycene (9-EGlamTPPo, 6). A solution of 109 mg (0.17 mmol) of 9-amino-2,7,12,17-tetraphenylporphycene (prepared as described in the literature [17] and used without chromatographic purification) in 15 mL dry tetrahydrofuran and 15 mL dry pyridine was added at room temperature dropwise in 10 min by stirring a solution of 0.4 mL (2.89 mmol) glutaric methylester acid chloride in 10 mL of dry tetrahydrofuran. The solution was stirred for an additional hour at room temperature, diluted with tetrahydrofuran, cooled to 0 °C and treated with ice chilled water. The mixture was washed twice with 10% sulfuric acid, twice with water and once with 5% aqueous sodium hydrogen carbonate. After evaporation of the solvent of the separated organic layer, the residue was chromatographed with dichloromethane/ethyl acetate (20:1) on silica gel. Following evaporation of the solvent under vacuum and washing of the resulting solid with pentanes, 111 mg of the title compound were obtained in 93% yield as a dark blue powder, mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 10.24 (s, 1H), 9.77 (d, *J* = 12, 1H), 9.73 (d, *J* = 12, 1H), 9.59 (s, 1H), 9.55 (s, 1H), 9.50 (s, 1H), 9.39 (s, 1H), 8.68 (s, 1H), 8.41 (d, *J* = 8, 2H), 8.28 (t, *J* = 8, 4H), 7.96 (d, *J* = 8, 2H), 7.80 (m, 6H), 7.74 (m, 2H), 7.67 (m, 4H), 4.46 (brs, 1H), 4.04 (brs, 1H), 3.74 (s, 3H), 2.44 (s, 2H), 1.97 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C, ppm 173.6, 170.7, 144.9, 144.8, 144.16, 143.4, 141.8, 140.5, 140.4, 138.7, 137.6, 136.4, 136.3, 135.8, 134.4, 133.5, 133.4, 131.6, 131.4, 131.3, 130.1, 129.2, 129.1, 129.0, 127.9, 127.8, 126.5, 125.1, 123.8, 123.5, 123.3, 51.6, 35.6, 33.4, 20.3. HRMS (ESI–TOF): *m/z* calcd. for $C_{50}H_{40}N_5O_3$ 758.3126, found 758.3128.

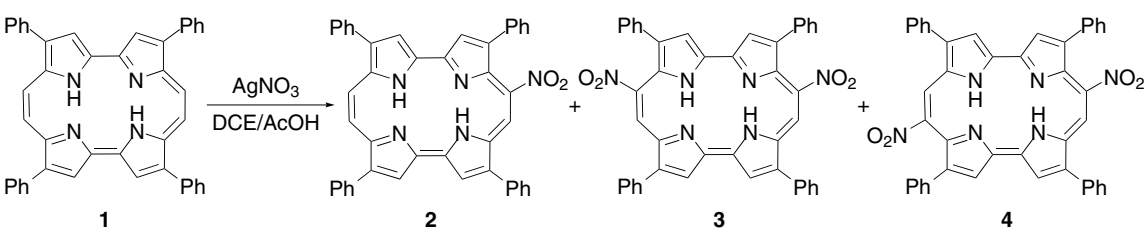
RESULTS AND DISCUSSION

Synthesis

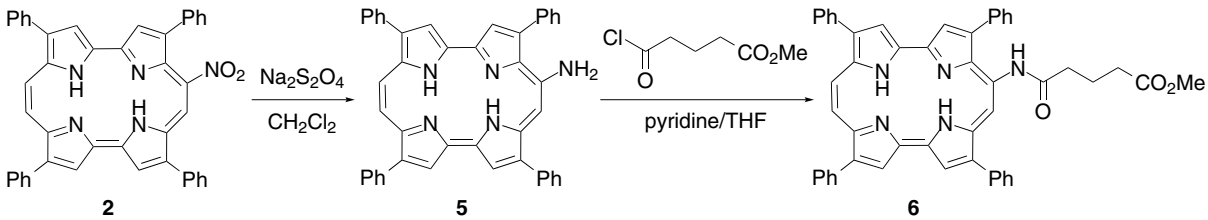
Among other methods, functionalization of porphyrinoids can be conveniently accomplished by electrophilic or nucleophilic substitutions [18, 19]. Alternatively, the use of palladium cross-coupling reactions has gained popularity in order to introduce substituents into the peripheral positions for instance in porphyrins and chlorins [20]. However, electrophilic substitution still plays a central role since halogenated and nitrated derivatives provide the starting materials for other functionalization and conjugation reactions. Particularly, electrophilic substitutions on porphyrins are well known whether the electrophile attacks on a *meso*-position [21–23] or in the pyrrole position [24]. Recently, the group of Paolesse has studied in detail the regioselective nitration of β-pyrrolic positions of corroles [25–27].

It is noteworthy that electrophilic substitution in porphycenes has been closely examined. The first examples were reported in the early patents by Vogel, where bromination and nitration of porphycenes were disclosed along with the mono hydroxylation of the *meso*-position 9 [8]. According to the regioselectivity of the substitution, it is possible to distinguish two kind of electrophiles: electrophiles that attack on pyrroles (positions 3,6,13,16) and electrophiles that attack on the *meso*-positions (positions 9,10,19,20). Typical reagents that react with the beta position of pyrroles are sulfonyl chloride and bromine [8, 10]. These reactions, usually, give mixtures of polysubstituted isomers that must be purified. Interestingly, while halogens and sulfonyl groups substitute pyrrolic positions 3,6,13,16, the nitration of porphycenes renders only the mono 9-nitro derivative [8, 17].

The nitration reaction of the 2,7,12,17-tetraphenylporphycene with $AgNO_3$ as mild nitrating reagent yields a mixture of the 9-nitroTPPo in a modest yield (20%) along with different polynitrated porphycenes, in a very low rate [17]. In order to optimize the formation of 9-NTPPo (**2**) different solvents and temperature conditions have been tested. Gratifyingly, when 1,2-dichloroethane was used as a solvent at 80 °C the nitration was found to proceed smoothly. The reaction rate of nitration is quite slow, however, the addition of an excess of $AgNO_3$ completes the transformation in 25 min. It was observed that longer reaction times produced increasing quantities of the polynitrated mixture of porphycenes (Scheme 1). Surprisingly, ^{1}H NMR analysis of this mixture revealed the presence of only two sets of signals with a ratio of 3 to 1, tentatively ascribed to two different dinitrated porphycenes **3** and **4**. With the aim to gain insight into the composition of this mixture, the reaction conditions of the nitration of **1** were adjusted to maximize the amount of dinitroporphycenes produced. It was found that 4 h were necessary to yield the mixture of the geometric isomers



Scheme 1. Synthesis of 9-nitro-, 9,20-dinitro and 9,19-dinitro-TPPo



Scheme 2. Synthesis of 9-(glutaric methylesteramide)-2,7,12,17-tetraphenylporphycene

almost quantitatively along with traces of the 9-NTPPo and little amounts of a complex mixture of uninvestigated green colored porphycenes. NMR analysis of the mixture allowed confirming the *prima facie* evidence that the compounds present in the mixture were two unprecedented *meso* dinitrated porphycenes, namely the 9,20-dinitro-2,7,12,17-tetraphenylporphycene (**3**, 9,20-DNTPPo) and the 9,19-dinitro-2,7,12,17-tetraphenylporphycene (**4**, 9,19 DNTPPo) (cf. NMR spectroscopy). Column chromatography was unsuccessful to separate the isomers. Fortunately, recrystallization of the mixture from cyclohexane/dichloromethane provided pure isomer **3**. Evaporation of the solvents and recrystallization of the residue with cyclohexane allowed the isolation of the counterpart isomer **4**.

It is not clear whether the nitration takes place *via* a polar or a radical complex mechanism. However, we postulate that Ag^+ plays an important role in the process. According to Olah [28, 29], the nitration with $AgNO_3$ would start with the formation of a $AgNO_3$ complex with the non-bonding pairs of electrons of one of the pyrrolic nitrogens. This complexation would enable the preferential nitration at the proximal *meso*-position. Another question is the origin of the regioselectivity observed between positions 19 and 20 in porphycenes **3** and **4**. We hypothesize that taking into account our mechanism proposal it is plausible that tautomerism of **2** could explain the ratio of geometric isomers. However, at this stage more research is still needed since other rationales cannot be ruled out.

Thanks to the optimization of the synthesis of 9-nitro-2,7,12,17-tetraphenylporphycene (**2**) it is possible to synthetize this porphycene in a preparative scale to be transformed into 9-amino-2,7,12,17-tetraphenylporphycene (**5**). The amino derivative **5** is an ideal starting material for conjugation since it allows taking advantage of the well-known chemistry of the amides. As a proof of concept, the synthesis of the versatile 9-(glutaric methylesteramide)-2,7,12,17-tetraphenylporphycene (9-EGlamTPPo, **6**) was proposed (Scheme 2).

The synthesis of **6** consisted of the reduction of the nitro group to the amine with $Na_2S_2O_4$ as reductant under basic conditions (Zinin reduction) and amide coupling with the corresponding acid chloride. The Zinin reduction was performed as previously described without any further purification in order to avoid losses of the product during chromatography [17]. It must be pointed out that the progress of the reaction must be followed by tlc to minimize overreduction. The crude amino derivative **5** is obtained nearly quantitatively and pure enough to be coupled with acid chloride in the presence of pyridine to yield the 9-(glutaric methylesteramide)-2,7,12,17-tetraphenylporphycene in 93% yield.

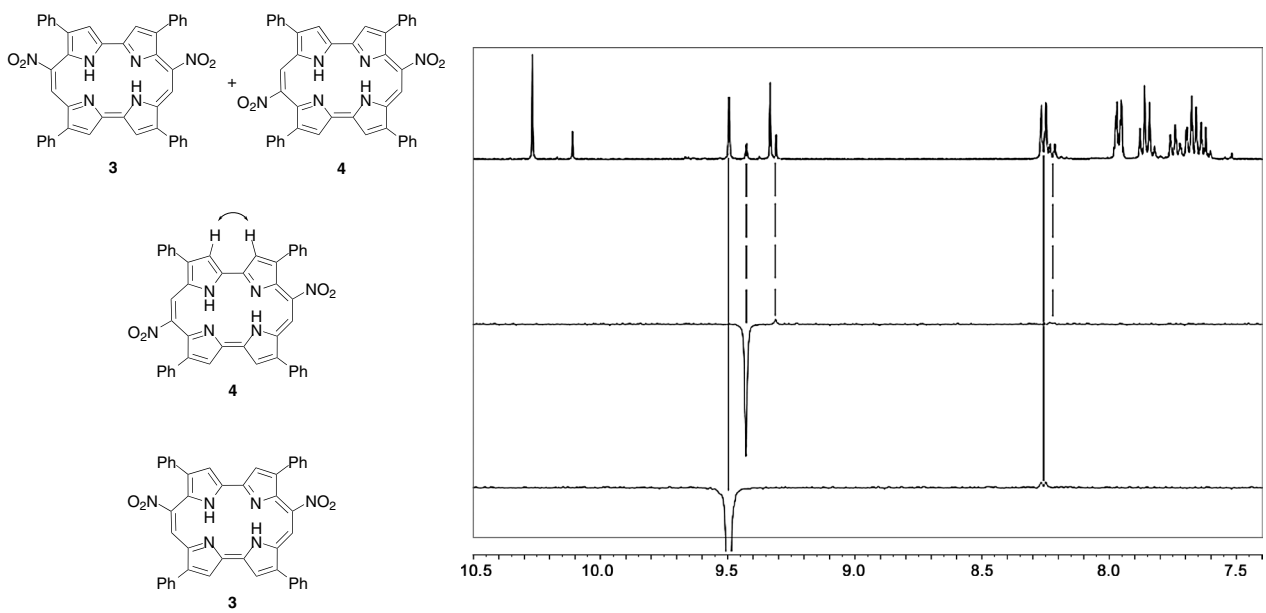


Fig. 1. ^{1}H NMR of the mixture and NOESY1D of 9,20-nitro-, and 9,19-nitro-TPPo

NMR spectroscopy

Identification of both isomers from each other was carried out by means of monodimensional transient NOE experiments (NOESY1D). Due to the different geometry of these compounds, signals at δ_H = 9.3–9.5 ppm (CH of pyrrole rings) come from fairly different pairs of protons. Thus, both methynes of vicinal pyrrole rings of isomer **3** contribute to the same signal, while in isomer **4** each of these protons contributes to a different signal, so a NOE between the corresponding pair of signals is only expected in the second case.

Two NOE experiments were recorded on the original mixture of both isomers, selecting signals at δ_H = 9.50 (major isomer) and at δ_H = 9.43 (minor isomer) (Fig. 1). No enhancement of the signal at δ_H = 9.35 was observed in the first experiment, while the signal at δ_H = 9.30 was enhanced in the second. This result unambiguously identifies the minor isomer as isomer **4**, and thus the major isomer must be isomer **3**.

CONCLUSION

Optimization of the synthesis of 9-nitro-2,7,12,17-tetraphenylporphycene (**2**) by using an excess of $AgNO_3$ and 1,2-dichloroethane as solvent has been accomplished. This new procedure allows obtaining 9-(glutaric methylesteramide)-2,7,12,17-tetraphenylporphycene (**6**) in two steps in a preparative scale. An increase in the time of the nitration reaction of 2,7,12,17-tetraphenylporphycene (**1**) proceeds with the regioselective formation of two dinitro isomers: 20,9-nitro-2,7,12,17-tetraphenylporphycene (**3**) and 19,9-nitro-2,7,12,17-tetraphenylporphycene (**4**) in a ratio of 3 to 1. These geometric isomers were isolated by fractional crystallization and their structure confirmed by NMR. Dinitro porphycenes **3** and **4** could be synthetically useful allowing, in principle, the attachment of two different groups in order to provide specific properties to the macrocycle such as water solubility for potential PDT studies.

Acknowledgements

Fellowships by the IQS grants (GA and MCL) are acknowledged. We would like to thank Dr. Magda Faiges for her assistance in UV-vis spectroscopy.

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