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Synthesis of triazole- and pyridine-bridged porphyrin–chlorin and porphyrin dimers

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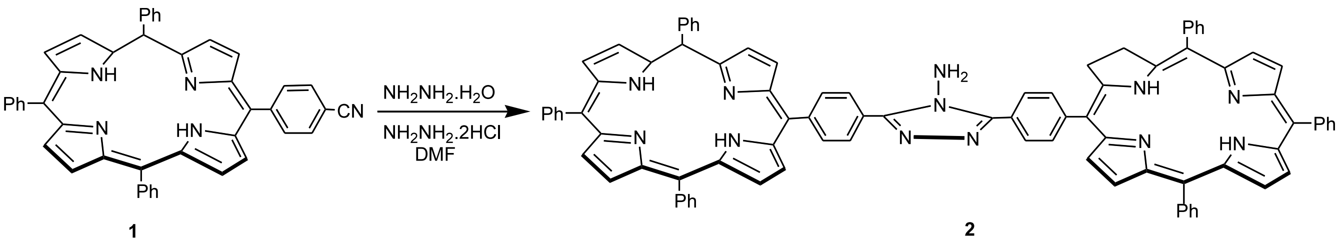
Abstract—The synthesis of 4-amino-1,2,4-triazole linked porphyrin–chlorin dimer and porphyrin dimer is described. New cationic porphyrin dimers were synthesized via the alkylation of the nitrogen atoms of 4,4′-bipyridine and 1,2-di-(4-pyridyl)ethene by *meso*-monobromomethylporphyrin. These cationic bisporphyrins can interact with DNA and have the ability to cleave it. © 2003 Elsevier Science Ltd. All rights reserved.

Porphyrins have been covalently linked to form dimers since 1977.[1] The nature and position of the linker have a strong influence on the overall properties of the porphyrin dimers, especially physical properties such as solubility and chemical or thermal stability. The placement and type of the linker may simply hold the porphyrins together or hold them in a rigid conformation or orientation. They can isolate each porphyrin from one another or conversely promote communication between the individual porphyrins.

A number of symmetrically 3,5-disubstituted 4-amino-1,2,4-triazoles had been prepared in excellent yields by the nucleophilic attack of hydrazine derivatives on the aromatic nitriles in the presence of hydrazine dihydrochloride or sulfate.[2] We followed the same route to get 3,5-bisporphyrinyl-4-amino-1,2,4-triazole. 5-(4′-Cyanophenyl)-10,15,20-tris-phenylporphyrin[3,4] was reacted with hydrazine hydrate in dimethylformamide (Scheme 1). The initial product is a 1,2-dihydro-1,2,4,5-tetrazine linked porphyrin with NH protons in ^{1}H NMR at 9.5 ppm.[2] Dihydrotetrazine rearranges to the corresponding 4-amino-1,2,4-triazol. The spectra showed a new Soret band in the form of a shoulder at 406 nm with increased intensity of the Q_y-band. After 24 hours, when no further changes were observed in the absorption spectra, the solvent was removed and the product was purified by preparative TLC. The ^{1}H NMR spectrum showed the appearance of the signals of a new methylene group at 4.1 ppm and two singlets at −1.36 and −1.46 ppm in addition to the porphyrin NH at −2.78 ppm. This indicates the presence of both a porphyrin and a chlorin system, and the presence of fourteen β-pyrrole protons in the range of 8.59–8.78 ppm suggests a dimer possessing an asymmetric structure. Under the reaction conditions, the β-reduction of porphyrin can be caused by hydrazine. To confirm this, tetraphenylporphyrin was subjected to the same reaction conditions and the reaction was followed by UV–vis. An increase with time of the Q_y-band intensity characteristic of a chlorin was observed without appearance of any characteristic bands of bacteriochlo-



Scheme 1. Synthetic route to dimer **2**.

Keywords: porphyrin dimer; chlorin; 1,2,4-triazole.

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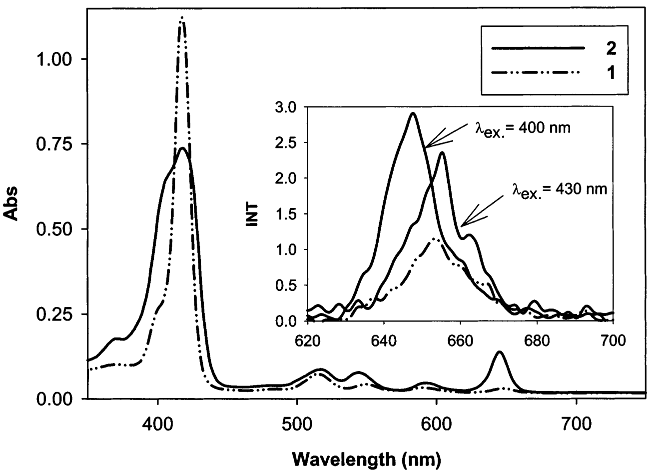

Figure 1. Absorption spectrum of dimer **2** and monocyanoporphyin **1** in CH_2Cl_2 at 5 μM. Inset: Fluorescence emission spectrum; excitation wavelength of **1** at 420 nm and of **2** at 400 nm and 430 nm, respectively.

rin or isobacteriochlorin.[5] Formation of a chlorin–chlorin dimer is excluded from ^1H NMR, that showed the presence of both inner NH protons of porphyrin and chlorin, and the smaller relative ratio of Q_y to the Soret band compared to that of the pure chlorin.[5]

These spectroscopic changes are in accord with the suggested structure **2** (Scheme 1), which shows that the 3,5-diphenyl-1,2,4-triazole bridge allows only an electrostatic interaction between the transition dipoles of the porphin moieties because of steric hindrance, which forces the 1,4-phenylene units out of coplanarity with the porphin rings and prevents efficient π-orbital overlap. This is reflected in the UV–vis spectrum and confirmed by the emission spectrum (Fig. 1). The fluorescence emission properties of dimer **2** showed a high intensity emission peak compared to **1**. Excitation of dimer **2** at 420 nm gave a fluorescence emission band at 652 nm, 5 nm blue-shifted compared to **1**, while excitation at 406 nm gave an additional shoulder at 643 nm. Excitation at 400 nm gave an emission at 646 nm, while excitation at 430 nm gave an emission at 655 nm. This can be attributed to the presence of two different chromophores, electronically isolated. The Lambert–Beer law is obeyed at low and high concentrations in dichloromethane and dichloromethane/pyridine (1%). The two solvents would be expected to have appreciably different effects on any conformational or dimerization process and this confirms that the changes in the dimer spectrum did not result from the aggregation of porphyrin monomers.

The aminotriazole-linked porphyrin **3** (Fig. 2) could be obtained when 3,5-(*p*-hydroxyphenyl)-4-amino-1,2,4-triazole[2] was first prepared and then used to link two

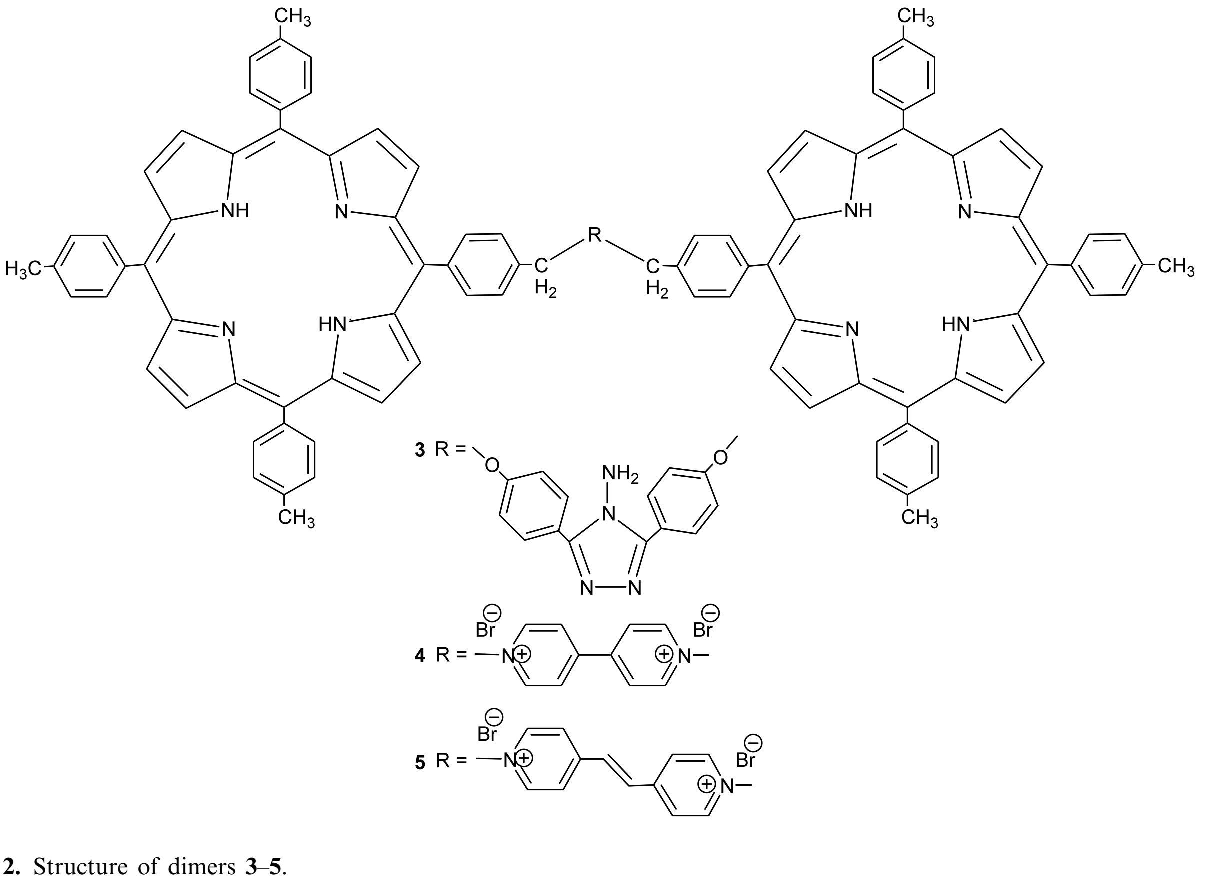

Figure 2. Structure of dimers **3**–**5**.

units of monobromomethylporphyrin.[3,4] The optical spectra of **3** did not show any change compared to the monomeric form, except that a slight fluorescence quenching was observed.

Cationic porphyrins have attracted considerable attention because of their remarkable ability to form complexes with nucleic acids and to cleave them.[6] A molecule composed of two bipyridine and bipyridylethene-linked porphyrins was prepared by the alkylation of the bidentate nucleophiles 4,4′-bipyridine and 1,2-di-(4-pyridyl)ethene with monobromomethylporphyrin, and afforded dicationic dimers **4** and **5**. The optical spectra of **4** and **5** did not show any change compared to the monomer.

Addition of *E. coli* plasmid DNA at pH 7.4 to a solution of **4** or **5** caused a small red shift ($\Delta\lambda = 2$ and 3 nm, respectively) and an hypochromicity (ca. 10%) of the Soret band. These spectroscopic variations strongly indicate that cationic porphyrins **4** and **5** interact with DNA.[7] This was confirmed by resonance light scattering (RLS) experiments, which showed an increased scattering following addition of DNA.

The DNA-photocleavage activity by cationic porphyrins **4** and **5** was examined using supercoiled double-stranded *E. coli* plasmid DNA. A mixture of the cationic porphyrin (0.5 μM) and the plasmid DNA (50 μM, [porphyrin]/[DNA base pair] = 0.01) in air-saturated buffer (PBS, pH 7.4) was illuminated in a fluorescence spectrophotometer at 430 nm for 2 min. After illumination, conversion of super-coiled DNA (form I) to nicked circular DNA (form II) was visualized by agarose gel electrophoresis at 110 V and subsequent ethidium bromide staining (stain XL1-blue).[8] Treatment with porphyrin **4** resulted in form II DNA while porphyrin **5** had no cleavage effect on DNA.

All the synthesized dimers **2**–**5** possess spectroscopic data in accord with the assigned structures.[9]

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4. Porphyrin monomers: 5-(4′-cyanophenyl)-10,15,20-tris-(4′-tolyl)porphyrin **1** was prepared according to Lindsey[3] (25%) and chromatographed on a silica gel column (CH_2Cl_2, $R_f = 0.58$). ^1H NMR ($CDCl_3$): δ −2.68 (s, 2H, NH), 7.83–8.38 (m, 19H, H_{arom}), 8.95 (d, 8H, β-pyrrole); MS (DCI): *m*/*z* 640 (M+H, 50%), 639 (M, 100%). 5-(4′-Acetoxylphenyl)-10,15,20-tris-(4′-tolyl)porphyrin was prepared as described for **1**. The corresponding bromomethyl derivative was prepared by the action of $LiAlH_4$ followed by BBr_3 and purified by silica gel column chromatography (2% $MeOH/CH_2Cl_2$, $R_f = 0.75$). ^1H NMR ($CDCl_3$): δ −2.74 (bs, 2H, NH), 2.73 (s, 9H, CH_3), 4.87 (s, 2H, CH_2), 7.59–8.55 (m, 16H, H_{arom}), 8.89 (d, 8H, β-pyrrole). UV–vis (CH_2Cl_2) λ_{max} (ε, M^{-1} cm^{-1}) 420 (596×10^3), 515, 548, 593, 649 nm.
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9. **Dimer 2**: A mixture of cyanoporphyrin **1** (0.64 g, 1 mmol), hydrazine dihydrochloride or sulfate (1 mmol) and hydrazine hydrate (3 mmol) was heated at 125°C with stirring under nitrogen for 24 h. After cooling, the solvent was removed under vacuum and the dimer produced was purified by plate chromatography (2% acetone/dichloromethane, $R_f = 0.48$) giving 0.12 g of **2** (9%). ^{13}C NMR ($CDCl_3$): δ 36.35 (CH_2), 111.96, 112.26, 117.61, 119.5, 121.08, 121.95, 124.29, 127.24, 128.35, 130.98, 131.55, 132.67, 135.02, 135.47, 142.38, 142.4, 143.16, 147.68, 149.67, 150.82; MS (DCI): *m*/*z* 1310 (M, 25%). **Dimer 3**: A mixture of monobromoporphyrin (0.38 g, 0.5 mmol), 3,5-(*p*-hydroxyphenyl)-4-amino-1,2,4-triazole[2] (0.07 g, 0.25 mmol) and 1.5 g of anhydrous potassium carbonate was stirred magnetically in 30 ml of DMF for 48 h. The solvent was then removed under vacuum at room temperature and the product was purified on silica gel TLC (CH_2Cl_2, $R_f = 0.63$) to yield 0.35 g of **3** (43%). ^1H NMR ($CDCl_3$): δ −2.76 (s, 4H, NH), 2.73 (s, 18H, CH_3), 4.87 (s, 4H, CH_2), 6.58 (bs, 2H, NH_2), 7.02–8.55 (m, 40H, $H_{arom.}$), 8.88 (m, 16H, β-pyrrole). MS (ESI): *m*/*z* 1589 (M, 30%). **Dimer 4**: A solution of monobromoporphyrin (0.38 g, 0.5 mmol) and 0.04 g (0.25 mmol) of 4,4′-dipyridine was refluxed in 30 ml of anhydrous DMF. The reaction was monitored by silica gel TLC (5% methanol/dichloromethane). After six hours, the product with R_f of 0.42 began to appear on the TLC, along with unreacted monomer. The reaction was quenched when the TLC no longer exhibited significant change (48 h). The solvent was evaporated under vacuum and the product was purified by TLC (0.39 g, 43%). ^1H NMR (DMSO-d_6): δ −2.78 (bs, 4H, NH), 2.64 (s, 6H, CH_3), 2.7 (s, 12H, CH_3), 6.28 (s, 4H, CH_2), 6.76–8.08 (m, 36H, H_{arom}), 8.68–8.86 (m, 16H, β-pyrrole), 9.35 (s, 1H, H_{arom}); MS (ESI): *m*/*z* 1494 (M, 15%), 825. **Dimer 5**: was prepared and purified as described for **4** ($R_f = 0.30$, 0.42 g, 53%). ^1H NMR (DMSO-d_6): δ −2.97 (bs, 4H, NH), 2.75 (s, 12H, CH_3), 2.78 (s, 6H, CH_3), 6.65 (s, 4H, CH_2), 6.84 (s, 2H, CH), 7.59–8.05 (m, 36H, H_{arom}), 8.57–8.8 (m, 20H, β-pyrrole+pyridine), 9.35 (s, 1H, pyridine); ^{13}C NMR (THF-d_8): δ 21.43 (CH_3), 28.35 (CH_2), 45.81 (CH), 120.66, 120.83, 121.67, 127.81, 128.14, 131.18, 135.16, 138.13, 140.25, 141.72, 144.25, 151.15; MS (ESI): *m*/*z* 1520 (M, 5%).