Nitrogen extrusion from pyrazoline-substituted porphyrins and chlorins using long wavelength visible light

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Protoporphyrin reacts with diazomethane to give pyrazolines which at long wavelength (~ 630 nm) extrude nitrogen to give the corresponding cyclopropyl derivatives.

The search for novel photosensitizers for use as drugs in photodynamic therapy (PDT), and basic research interests, have led to the synthesis of derivatives of both naturally occurring and synthetic porphyrins and chlorins. A characteristic of PDT drugs is their ability to accumulate preferentially in target tissues. Photosensitizers that accumulate exclusively in diseased tissues would have great advantages as PDT agents.

We report here on the synthesis of the novel pyrazoline derivatives (1–3) of protoporphyrin dimethylester (PP-DME), methylpyropheophorbide (MePPP), and tetrakis(pentafluorophenyl)porphyrin (pFTPP) using a 1,3-dipole cycloaddition reaction of diazomethane. These compounds were then subjected to thermal and photochemical extrusion of N₂, which produced the cyclopropane derivatives 4, 5 and 6. It is thought that the pyrazoline functionality might be used as a photocrosslinking group. The photosensitizer could then be bound to specific regions of human tissue.

To synthesize 1a–c, PP-DME was dissolved in CH₂Cl₂, and an excess (50:1 w/w) of diazomethane as a solution in ether, was condensed directly into the reaction flask. The solution, under positive N₂ pressure, was then allowed to react overnight. 78% conversion to the three products 1a–c was achieved (Scheme 1). It was anticipated that the compounds would undergo thermal cyclo-elimination through the extrusion of nitrogen (Scheme 1). The three compounds (1a–c) were refluxed in toluene until complete conversion to the corresponding cyclopropanes 4a, 4b and 4c was observed. Both 1a and 1b required 24 h to completely convert, while 1c required 47 h.

Irradiation of degassed, dilute solutions [3 × 10⁻⁶ M] of the pyrazolines with 350 nm light was then attempted. It is known that pyrazolines photo-extrude nitrogen at this wavelength (Scheme 1). This photoreaction produced 4a, 4b and 4c in 82% (23 h), 52% (52 h) and 50% (50 h) yields respectively.

These results led to the investigation of chlorins as pyrazoline adducts. The pyrazoline derivative of MePPP was synthesized in the same way as 1, giving the pyrazoline cycloadduct 2 in 78% yield (Scheme 2). Irradiation of 2 in a dilute solution [3 × 10⁻⁴ M] of oxygen purged benzene with 350 nm light produced the photoproduc 5.

The pyrazoline derivative of pFTPP was synthesized as above. The product 3 was obtained in 60% yield. Thermolysis of the pyrazoline 3 to the cyclopropane cycloadduct 6 required refluxing in mesitylene for 1 h (Scheme 3). The yield was 96%.
Cavaleiro’s group have recently reported on the reaction of diazomethane with β-nitro-meso-tetraphenylporphyrin to give a pyrazoline-fused chlorin which gave the corresponding cyclopropane adduct by refluxing in toluene.

One of the requirements of a photosensitizer for PDT is that it absorbs light at wavelengths where human tissue does not. Light penetration through human tissue increases significantly between 630 and 750 nm, which allows efficient excitation of a photosensitizer drug.9 Long wavelength irradiation of the pyrazolines was then attempted. This produced the first example of such long wavelength activation of a photoreactive functionality at the porphin periphery. The pyrazolines 1a, 1b, 1c were irradiated with filtered light with wavelengths between 550 and 650 nm (Scheme 1).10 The products 4a, 4b and 4c were observed in 35% (14 h), 52% (7 h) and 78% (38 h) yield respectively.

The chlorin 2 absorbs light more efficiently at longer wavelengths than does 1. Compound 2 has a strong Q-band absorption at 665 nm (ε = 52,700 in benzene) which is only half as intense as its Soret-band (411 nm, ε = 107,100). Compound 2 was then irradiated at 672 nm.11 An irradiated dilute solution [3 × 10−4 M] of 2 in oxygen purged benzene yielded almost quantitatively after 14 h a single photoproduct, which was shown to be the cyclopropane cycloadduct 5.

Compound 3 is also a chlorin, and absorbs light strongly at 648 nm. Thus it was irradiated with filtered light at wavelengths between 550 and 650 nm.10 After 1 h the product 6 was obtained in quantitative yield.

Pyrazolines absorb light between 300–400 nm via a n–π* transition, thus it would be expected that the photoextrusion would occur during irradiation at wavelengths in this region, as was observed in the initial experiments.12 The interesting result here is the extrusion of nitrogen at longer wavelengths. It was initially thought that a photochemical reaction of this type would be unlikely. Light of 672 nm, in the case of the MePPP pyrazoline derivative (2), would lead to an excitation to the first excited singlet state at 42.4 kcal mol−1. Nitrogen extrusion is thought to occur through S1 or T1; of the pyrazoline, excitation energies being 70–90 and 50–60 kcal mol−1 respectively.12 This would seem to suggest that there is not enough energy absorbed by the porphyrin to transfer to the pyrazoline to cause the extrusion. The results can however be explained if one assumes that the pyrazoline is not a distinct entity from the porphyrin, but is in fact an extended part of the chromophore.13 Add to this the fact that the activation energy barrier to nitrogen extrusion has been calculated at 35.2 kcal mol−1,15 then it seems reasonable that the nitrogen extrusion can occur at the long wavelengths.

To conclude, we have demonstrated the first examples of long wavelength activation of an unconjugated photoreactive functionality at the porphyrin periphery. This is an interesting development as long wavelength activation of a compound is a requirement for use in PDT, and the pyrazoline functionality might be used as a cross-linker for the chlorin chromophore to enable site-specific accumulation of a drug in diseased tissue.

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Notes and references
3 Detailed experimental and characterization data are available in the supporting information.
5 The identification of these products was completed using mass spectrometry and by comparing Rf values on silica tlc plates with the more completely characterized products of the photochemical experiments.
6 The 350 nm photochemical experiments were carried out in a Rayonet photochemical reaction chamber.
10 The 650 nm photochemical experiments were carried out using a 250 W Osram Hlx-6455 arc lamp in an Oriel lamp housing with a Corion 600 filter.
11 The 672 nm photochemical experiments were carried out using a light emitting diode panel that emits at a single wavelength (672 nm).