Novel synthesis and new chemistry of naphthochlorins

Bénédicte Krattinger, Daniel J. Nurco and Kevin M. Smith*†

Department of Chemistry, University of California, Davis, CA 95616, USA

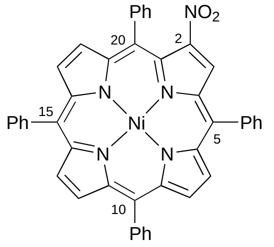
Reactions of 2-nitro-5,10,15,20-tetraphenylporphyrin with alkyl α-isocyanoacetates afford naphthochlorins (in addition to the expected pyrroloporphyrins) which undergo free radical dimerization; the X-ray structure of one such naphthochlorin dimer is reported.

Tetrapyrrole macrocycles bearing fused aromatic rings have attracted considerable attention, with examples including benzoporphyrins,[1] benzochlorins,[2] pyrroloporphyrins,[3a,b] naphthoporphyrins,[4] naphthochlorins[5] and others.[6] Many of these possess long wavelength absorptions and are therefore potential candidates as second generation photodynamic therapy photosensitizers.[7] The approaches to naphthochlorins described to date have involved acid-catalyzed intramolecular cyclizations. Thus, naphthochlorins were prepared from Ni^{II} and Cu^{II} 2-formyl-TPPs[5b–d] and from Ni^{II} 2-vinyl-TPPs.[5a] Herein we report a novel base-promoted reaction which affords naphthochlorins; we also show that naphthochlorins possess novel free-radical chemistry wherein, in the presence of oxygen, a unique covalently linked naphthochlorin dimer is obtained. This naphthochlorin dimer represents the first example of a β–β′ linked bis(chlorin).

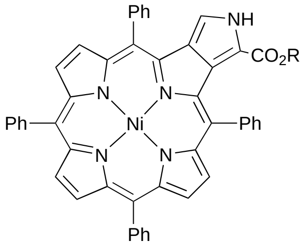
Nitroalkenes have been shown to react with α-isocyanoacetates to give pyrroles.[3c] Treatment of nitroporphyrin **1** with methyl or ethyl α-isocyanoacetate has been shown to afford pyrroloporphyrins **2** and **3**.[3a,b] Under similar reaction conditions we have now discovered that reaction of **1** with *tert*-butyl α-isocyanoacetate affords the expected pyrroloporphyrin **4**‡ in 32% yield and an additional porphyrinic product, the naphthochlorin **5**,‡ in 19% yield. Since our reaction conditions involved basic rather than acidic conditions it is necessary to postulate a new mechanistic route for naphthochlorin formation (Scheme 1). We propose that addition of the *tert*-butyl α-isocyanoacetate anion to nitroporphyrin **1** gives nitrochlorin **6** which eliminates HNO_2 to afford porphyrin **7**. Further reaction of DBU with porphyrin **7** yields chlorin **8** which subsequently undergoes two electrocyclic rearrangements (Scheme 1) to afford naphthochlorin **5**. Test reactions confirmed that naphthochlorin **5** did not arise from pyrroloporphyrin **4**. Further reaction of nitroporphyrin **1** [refluxing 10 : 1 THF–EtOH, DBU (4 equiv.)] with ethyl α-isocyanoacetate (2 equiv.) yielded a mixture of naphthochlorin **10** and pyrroloporphyrin **3**; when EtOH was replaced with BnOH a mixture of naphthochlorin **11** and pyrroloporphyrin **12** was obtained. A test reaction to prepare naphthochlorin free of pyrroloporphyrin was undertaken; isopropyl cyanoacetate (2 equiv.) was used instead of an alkyl α-isocyanoacetate [refluxing 10 : 1 THF–Pr^iOH, nitroporphyrin **1**, DBU (4 equiv.)] and formation of naphthochlorin **13** was observed. Although we were able to isolate naphthochlorins **10**, **11** and **13**, yields for each were < 1% [λ_{max}/nm (rel. int.) (CH_2Cl_2); **10**: 440 (1), 604 (0.08), 662 (0.15); **11**: 444 (1), 606 (0.08), 662 (0.18); **13**: 440 (1), 604 (0.08), 668 (0.16); these optical data agree well with those of naphthochlorin **5** (the structure of which has been confirmed by the crystal structure of naphthochlorin dimer **14**) and with those of previously reported naphthochlorins[5]]. Full characterization of naphthochlorins **10**, **11** and **13** was not possible owing to the scarcity and instability of these compounds.

Attempted crystallization of naphthochlorin **5** from $CDCl_3$–MeOH afforded crystals of naphthochlorin dimer **14**.‡ We were able to reproduce the dimerization *via* the following methods. A solution of naphthochlorin **5** in 1 : 1 CH_2Cl_2–MeOH (MeOH optional) was stirred while exposed to the air. After 5 days the presence of **5** was no longer detectable and naphthochlorin dimer **14** was isolated in 37% yield. Alternatively, refluxing **5** in dry benzene under argon with benzoyl peroxide (0.5 equiv.) afforded **14** in 53% yield. The reaction presumably proceeds by way of a π-stabilized radical on the non-aromatic β-carbon, followed by a radical dimerization. There is ample precedent for this type of reaction in the porphyrin literature; π-stabilized radicals have been obtained from oxophlorins[8] and some of them dimerize[9] by a mechanism similar to those involved in phenolic chemistry.[10]

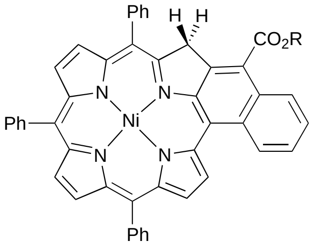
The identity of naphthochlorin dimer **14**‡ was confirmed by a crystal structure, as shown in Fig. 1. This structure is unique among porphyrinoid crystal structures in that the dimeric linkage features a direct C_{β}–$C_{\beta'}$ bond. The macrocycles are both



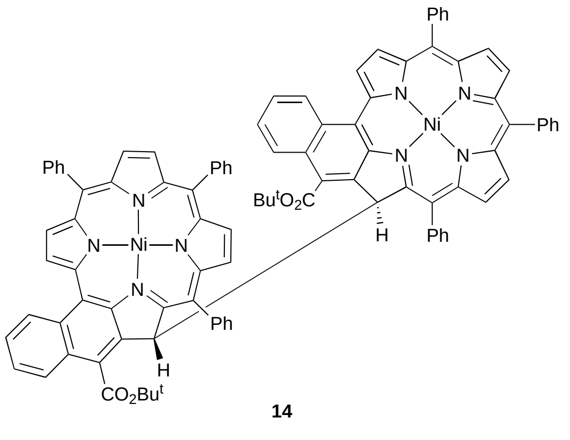
1



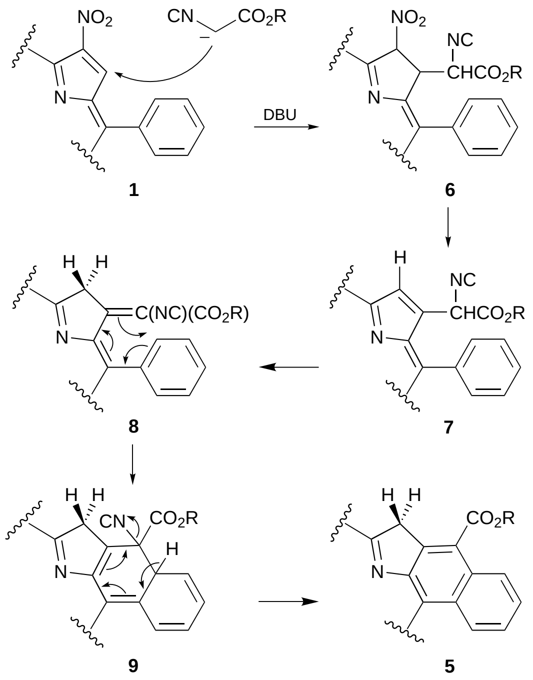
2 R = Me
3 R = Et
4 R = Bu^t
12 R = Bn



5 R = Bu^t
10 R = Et
11 R = Bn
13 R = Pr^i



14



Scheme 1

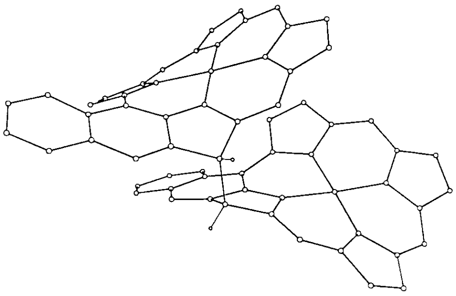


Fig. 1 Molecular structure of naphthochlorin dimer **14**;‡ esters, non-fused phenyl rings and hydrogen atoms (with the exception of those associated with the direct dimer link) have been omitted for clarity

significantly ruffled[11] with 0.33 and 0.36 Å mean deviations of the macrocyclic atoms from their least-squares planes (calculated based upon the 24 core carbon and nitrogen atoms); the average Ni–N bond length was 1.914(6) Å. The two macrocycles were nearly coplanar and exhibited an interplanar angle of 30.1°, a mean plane separation of 3.70(14) Å, and a metal to metal distance of 5.68 Å. Macrocyclic overlap was limited to one pyrrolic subunit of each naphthochlorin monomer. A lateral shift of 4.54 Å and a slip angle of 53(13)° were observed; in this regard this structure bears a marked similarity to the bacterial PRC 'special pair' which exhibits an overall geometry which is generally similar and a lateral shift of *ca.* 6.6 Å.[12]

This work was supported by grants from the National Science Foundation (CHE-96-23117) and the National Institutes of Health (HL-22252). We thank Dr Timothy P. Forsyth for carrying out the cyclic voltammetry experiments.

Notes and References

† E-mail: kmsmith@ucdavis.edu

‡ *Selected data* for **4**: $\lambda_{\max}(CH_2Cl_2)$/nm 444 (ε 182 000), 538 (9400), 558 (9800), 606 (14 200); *m/z* (LSIMS) 809.3 (M^+ 100%). C,H,N combustion analysis satisfactory.

For **5**: $\lambda_{\max}(CH_2Cl_2)$/nm 444 (ε 153 000), 614 (11 000), 662 (29 000); $\delta_H(CDCl_3)$ 5.19 (s, 2 H, reduced pyrrole ring H); *m/z* (LSIMS) 782.3 (M^+ 100). C,H,N combustion analysis satisfactory. Cyclic voltammetric measurements were carried out with a Cypress Systems CS-1087 computer controlled potentiostat. Naphthochlorin **5** undergoes two one electron oxidations at $E_{1/2} = -1.14$ and 0.74 V; a single compartment cell was used with a platinum disk working electrode, Ag/AgCl reference electrode, and silver wire auxiliary electrode. Measurements (scan rate 110 mV s^{-1}) were made in CH_2Cl_2, with Bu_4NPF_6 as supporting electrolyte. Ferrocene was added as an internal reference.

For **14**: $\lambda_{\max}(CH_2Cl_2)$/nm 440 (ε 109 000), 668 (16 500), 712 (6800). Crystals of *meso*-**14** ($C_{100}H_{70}N_8O_4Ni_2\cdot3.4CHCl_3\cdot0.5MeOH$) were grown by the slow diffusion of MeOH into a $CHCl_3$ solution of **5**. The selected crystal (0.20 × 0.25 × 0.50 mm) had a triclinic unit cell, space group $P\bar{1}$ and cell dimensions $a = 14.925(3)$, $b = 17.025(3)$, $c = 18.395(3)$ Å, $\alpha = 90.896(12)$, $\beta = 99.902(13)$, $\gamma = 105.083(13)°$, $V = 4436.9(12)$ Å^3 and $Z = 2$ (FW = 1987.0). Data were collected on a Siemens P4 diffractometer with a rotating anode [λ(Cu-Kα) = 1.54178 Å] at 130(2) K in $\theta/2\theta$ scan mode to $2\theta_{\max} = 112°$. Of 12 130 reflections measured ($+h,\pm k,\pm l$) 11 578 were independent ($R_{int} = 0.090$) and 8509 had $I > 2\sigma$ ($T_{min} = 0.50$, $T_{max} = 0.56$, $\rho_{calc} = 1.487$ g cm^{-3}, $\mu = 3.85$ mm^{-1}). The structure was solved by direct methods and refined (based on F^2 using all independent data except for two suppressed reflections) by full-matrix least-squares methods with 1038 parameters (Siemens SHELXTL V. 5.03). Hydrogen atom positions were generated by their idealized geometry and refined using a riding model. An empirical absorption correction was applied (ref. 13). All of the solvate molecules were disordered; further description of the solvate disorder and how it was treated is given in the supplementary material. Final R factors were $R1 = 0.092$ (observed data) and $wR2 = 0.25$ (all data). CCDC 182/768.

1 P. S. Clezy and C. W. F. Leung, *Aust. J. Chem.*, 1993, **46**, 1705; E. W. Baker, T. F. Yen, J. P. Dickie, R. E. Rhodes and L. F. Clark, *J. Am. Chem. Soc.*, 1967, **89**, 3631.

2 R. T. Holmes, J. J. Lin, R. G. Khoury, C. P. Jones and K. M. Smith, *Chem. Commun.*, 1997, 919; D. Arnold, R. Gaete- Holmes, A. W. Johnson and A. R. P. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1660.

3 (*a*) L. Jaquinod, C. Gros, M. M. Olmstead, M. Antolovich and K. M. Smith, *Chem. Commun.*, 1996, 1475; (*b*) C. P. Gros, L. Jaquinod, R. G. Khoury, M. M. Olmstead and K. M. Smith, *J. Porphyrins Phthalocyanines*, 1997, **1**, 201; (*c*) D. H. R. Barton, J. Kervagoret and S. Z. Zard, *Tetrahedron*, 1990, **46**, 7587;

4 T. D. Lash and C. P. Denny, *Tetrahedron*, 1995, **51**, 59.

5 (*a*) M. A. Faustino, M. G. P. M. S. Neves, M. G. H. Vicente, A. M. S. Silva and J. A. S. Cavaleiro, *Tetrahedron Lett.*, 1995, **36**, 5977; (*b*) Y. V. Ishkov and Z. I. Zhilina, *Zh. Org. Khim.*, 1995, **31**, 136; (*c*) L. Barloy, D. Dolphin, D. Dupre and T. P. Wijesekera, *J. Org. Chem.*, 1994, **59**, 7976; (*d*) H. J. Callot, E. Schaeffer, R. Cromer and F. Metz, *Tetrahedron*, 1990, **46**, 5253.

6 T. D. Lash and B. H. Novak, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 683; K. Henrick, P. G. Owston, R. Peters and P. A. Tasker, *Inorg. Chim. Acta*, 1980, **45**, L161.

7 S.-J. H. Lee, N. Jagerovic and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2369; D. Dolphin, *Can. J. Chem.*, 1994, **72**, 1005.

8 R. G. Khoury, L. Jaquinod, A. M. Shachter, N. Y. Nelson and K. M. Smith, *Chem. Commun.*, 1997, 215; J.-H. Fuhrhop, S. Besecke and J. Subramanian, *J. Chem. Soc., Chem. Commun.*, 1973, 1; J.-H. Fuhrhop, S. Besecke, J. Subramanian, C. Mengersen and D. Riesner, *J. Am. Chem. Soc.*, 1975, **97**, 7141.

9 R. G. Khoury, L. Jaquinod, D. J. Nurco, R. K. Pandey and K. M. Smith, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2496.

10 M. L. Mihailovic and C. Cekovic, in *The Chemistry of the Hydroxyl Group*, Part 1, ed. S. Patai, Wiley, New York, 1971, pp. 505–592.

11 D. J. Nurco, C. J. Medforth, T. P. Forsyth, M. M. Olmstead and K. M. Smith, *J. Am. Chem. Soc.*, 1996, **118**, 10 918.

12 T. E. Clement, D. J. Nurco and K. M. Smith, *Inorg. Chem.*, in the press.

13 S. R. Parkin, B. Moezzi and H. Hope, *J. Appl.Crystallogr.*, 1995, 28, 53.

Received in Corvallis, OR, USA, 4th December 1997; 7/08765I