Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 7321–7324
Tetrahedron Letters

Diels–Alder reactions of pyrrolo[3,4-*b*]porphyrins

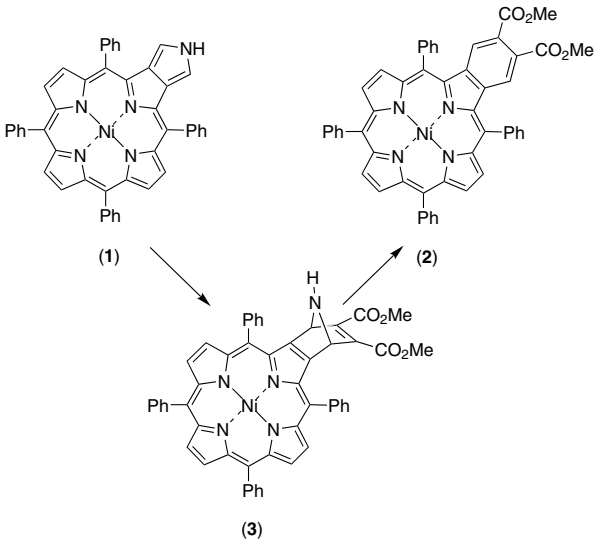
Wei Liu, Frank R. Fronczek, M. Graça H. Vicente and Kevin M. Smith*

Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA

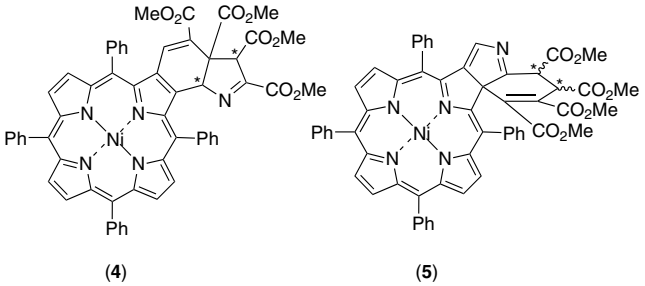
Received 22 July 2005; revised 24 August 2005; accepted 25 August 2005
Available online 13 September 2005

Abstract—In the presence of excess dimethylacetylene dicarboxylate (DMAD), nickel(II) pyrrolo[3,4-*b*]porphyrins undergo both Diels–Alder cycloaddition and Michael addition in toluene to give two bis-adducts, identified as compounds **4** and **5**; the reaction can be accelerated by the addition of Lewis or Brønsted–Lowry acids. Refluxing the reaction mixture in 1,2,4-trichlorobenzene (220 °C) leads to a nickel(II) monobenzoporphyrin **2** as the main product. The structure of compound **4** was confirmed by X-ray crystallography.

Porphyrin systems bearing fused aromatic rings have been the subject of intense research over the past several years. Since benzoporphyrins were discovered in petroleum and related deposits,[1–6] literally dozens of novel synthetic approaches to aroporphyrins have been described.[7] Novel examples also include fused picenoporphyrins,[8–11] metallocenoporphyrins[12] and pyrrolo[3,4-*b*]-porphyrins.[13–16]



In 1998, Knapp et al.[16] showed that nickel(II) *N*-*tert*-butoxycarbonyl-pyrroloporphyrins underwent cycloaddition to give a *N*-substituted bicycloadduct. Shortly thereafter, we reported[17] that copper(II) and also nickel(II) pyrrolo[3,4-*b*]porphyrins **1** undergo Diels–Alder cycloaddition reactions with dimethyl acetylene-dicarboxylate (DMAD) to give eventually benzoporphyrins **2** by way of the adduct **3**. Both **2** and **3** were isolated[17] and fully characterized, and an X-ray structure of **2** was obtained. At that time, we were puzzled by the deamination required to transform **2** into **3** and proposed a 'dienophile-induced deamination' for which there is literature precedent.[18] A bis-DMAD adduct, featuring multiple methoxyl resonances in its ^{1}H NMR spectrum, was also isolated but no structure was proposed for it at that time. We now report on the structure of no less than two bis-DMAD-Diels–Alder adducts from Diels–Alder reactions between **1** and DMAD, and clarify the mechanistic processes by which the deamination takes place.



Keywords: Diels–Alder cycloadditions; Pyrrolo[3,4-*b*]porphyrins; Benzoporphyrins; Mechanism; Michael addition.
* Corresponding author. Tel.: +1 225 578 7442; fax: +1 225 578 3458; e-mail: kmsmith@lsu.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.135

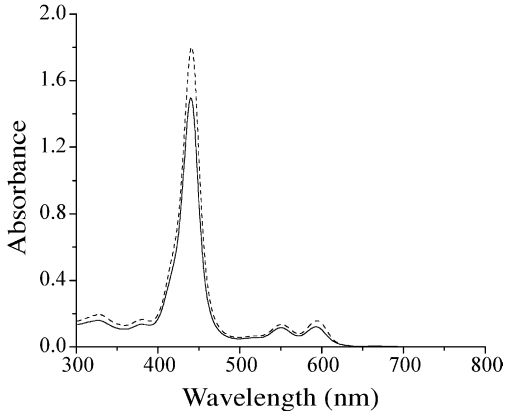


Figure 1. Optical spectra (in $CHCl_3$) of 4 (—) and 5 (---) at equal concentrations.

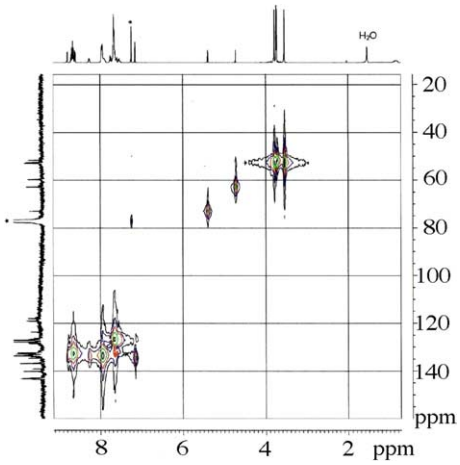


Figure 2. 2D NMR spectrum of **5** in $CDCl_3$. * = $CHCl_3$.

When the nickel(II) pyrrolo[3,4-*b*]porphyrin **1** and DMAD were heated in 1,2,4-trichlorobenzene (TCB), a 49% yield of the nickel(II) benzoporphyrin **2** was obtained.[19] Treatment of **1** with DMAD in boiling toluene containing acetic acid instead gave two new compounds that were identified as **4** and **5**, in 45% and 51% yield, respectively.[20] In agreement with previous reports on pyrroles,[21–24] Lewis or Brønsted–Lowry acid catalysis accelerated the reaction greatly, providing enhanced yields of **4** and **5**.[20]

Bis-adducts **4** and **5** have the same molecular weight and similar UV–vis absorption spectra. In $CHCl_3$, they show (Fig. 1) a Soret band at 439 and 441 nm, and two Q-bands at 549, 592 nm and 551, 595 nm, respectively. The absorption spectrum of **1** in $CHCl_3$ features a blue-shifted Soret band at 433 nm and two Q-bands at 546 and 579 nm.

Despite the similarity of the mass and UV–vis spectra for **4** and **5**, these isomers can be distinguished readily by ^{1}H NMR spectroscopy in $CDCl_3$. A long-range coupling between the asterisked protons of compound **4** with $J = 1.75$ Hz can be observed, which was also found in the simple pyrrole analog previously reported.[25,26] In compound **5**, the asterisked protons appear as two doublet peaks at $\delta = 5.40$ and 4.72 ppm with a $J = 1.50$ Hz. Further evidence in support of structure **5** was obtained from carbon–proton coupling 2D NMR spectroscopy (Fig. 2). The two asterisked protons show couplings with carbons in the 60–80 ppm region of the spectra; these shifts are in the chemical shift range expected for carbons adjacent to double bonds.

The proposed structure of compound **4** was confirmed by X-ray crystallography (Fig. 3).[†] The exterior pyrroline ring is, as expected, cis-fused to the six-membered

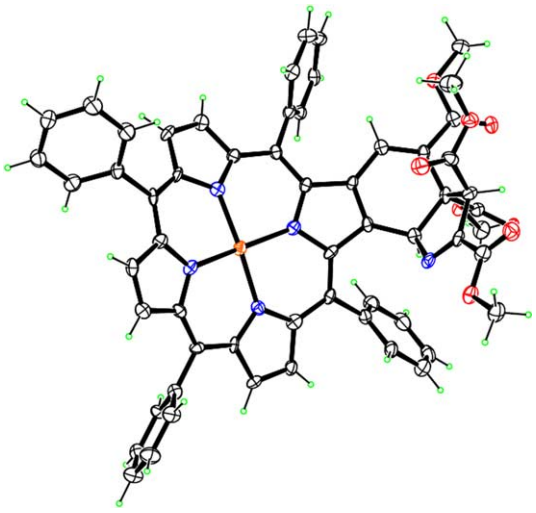


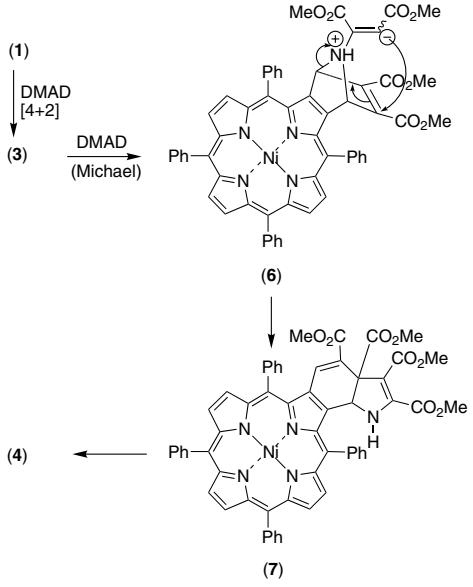
Figure 3. X-ray structure of nickel(II) bis-DMAD adduct (**4**).

ring, and the two methoxycarbonyl groups bonded to sp^3 carbon atoms are trans to each other.

Simple *N*-unsubstituted pyrroles tend to resist cycloaddition reactions, and even *N*-protected pyrroles give a variety of products depending upon the substituents on the N and/or on the pyrrole ring, and the reaction conditions. According to Noland and co-workers,[25,26] the reaction of pyrroles with common dienophiles appears to follow two different pathways. These are (i) [4+2] cycloaddition or (ii) Michael-type addition at the 2-(5-) position or at the ring N. It therefore appears that the presence of the fused porphyrin chromophore does not divert the reaction from the pathway shown in simple pyrroles. In the formation of both **4** and **5**, the two pathways (i) and (ii) are taking place consecutively, but in the reverse order, to give the observed products. Mechanistically, we propose that compound **4** arises from the mono-Diels–Alder adduct **3** by way of a Michael addition of excess DMAD, to give the adduct **6** [i.e., reaction (i) followed by reaction (ii)]. Zwitterion **6** then undergoes the electron-shifts shown,

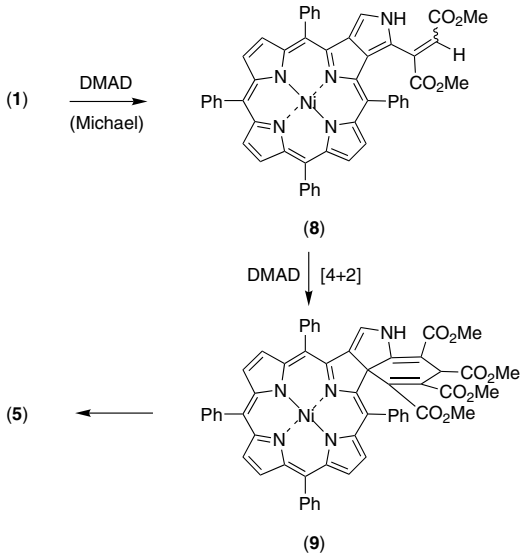
[†] Bis-DMAD adduct (**4**), $C_{58}H_{41}N_5O_8Ni$, monoclinic space group $P2_1/n$, $a = 21.925(2)$, $b = 10.1477(15)$, $c = 22.598(3)$ Å, $\beta = 113.011(4)°$, $V = 4627.7(10)$ Å^3, $T = 100$ K, $Z = 4$, $R = 0.048$ ($F^2 > 2\sigma$), $Rw = 0.119$ (all F^2) for 3259 unique data and 653 refined parameters. CCDC 264347.

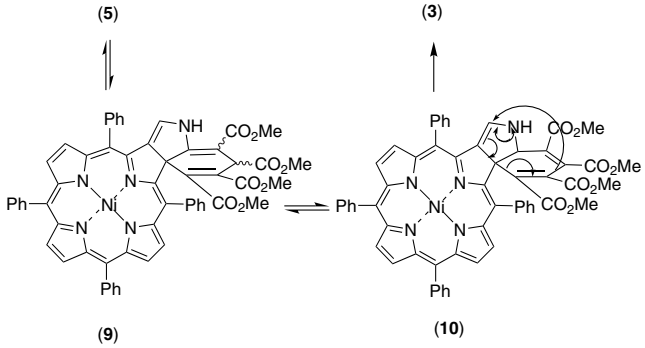
to give **7**, which suffers enamine–imine tautomerization to give **4**, the thermodynamically most stable product with both methoxycarbonyl groups trans to each other.



In the case of compound **5**, we propose that the first step is Michael addition of the DMAD to the 2-carbon of the fused pyrrole ring, to give **8**, followed by Diels–Alder cycloaddition of a second molecule of DMAD [i.e. reaction (ii) followed by reaction (i)]. The second addition would give initially **9**, which would then tautomerize to **5**.

Heating of compound **4** or **5** in TCB at 220 °C caused each of them to give the nickel(II) benzoporphyrin **2**. In the case of compound **4**, we anticipate a simple reverse [3+2] dipolar cycloaddition. The degradation of **5** to give **2** is not as easy to formulate; a reverse [4+2] cycloaddition involving **5** via the tautomers **9** and **10** would yield the initial mono-DMAD adduct **3** and DMAD. Since the transformation to **2** from **3** probably involves a Michael addition as described above, one must postulate that the released DMAD then reacts with **3** to give the zwitterion **6**. These observations do, however, appear to link the degradation pathways of both **4** and **5** to give nickel(II) benzoporphyrin **2**.





Acknowledgements

This work was supported by grants from the National Science Foundation (CHE-0296012 and CHE-304833) and the National Institutes of Health (R01 EB002064).

References and notes

1. Baker, E. W. *J. Am. Chem. Soc.* **1966**, *88*, 2311.
2. Baker, E. W.; Yen, T. F.; Dikie, J. P.; Rhodes, R. E.; Clarke, L. F. *J. Am. Chem. Soc.* **1967**, *89*, 3631.
3. Kaur, S.; Chicarelli, M. I.; Maxwell, J. R. *J. Am. Chem. Soc.* **1986**, *108*, 1347.
4. Kaur, S.; Gill, J. P.; Evershed, R. P.; Eglinton, G.; Maxwell, J. R. *J. Chromatogr.* **1989**, *473*, 135.
5. Quirke, J. M. E.; Dale, T.; Britton, E. D.; Yost, R. A.; Trichet, J.; Belayouni, H. *Org. Geochem.* **1990**, *15*, 169.
6. Review: Callot, H. J.; Ocampo, R. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, pp 349–398.
7. Review: Lash, T. D. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 2, pp 125–199.
8. Aihara, H.; Jaquinod, L.; Nurco, D. J.; Smith, K. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3439.
9. Nath, M.; Huffman, J. C.; Zaleski, M. J. *Chem. Commun.* **2003**, 858.
10. Nath, M.; Huffman, J. C.; Zaleski, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11484.
11. Chandra, T.; Kraft, B. J.; Huffman, J. C.; Zaleski, M. J. *Inorg. Chem.* **2003**, *42*, 5158.
12. Wang, H. J. H.; Jaquinod, L.; Nurco, D. J.; Vicente, M. G. H.; Smith, K. M. *Chem. Commun.* **2001**, 2646.
13. Jaquinod, L.; Gros, C. P.; Olmstead, M. M.; Antolovich, M.; Smith, K. M. *Chem. Commun.* **1996**, 1475.
14. Gros, C. P.; Jaquinod, L.; Khoury, R. G.; Olmstead, M. M.; Smith, K. M. *J. Porphyrins Phthalocyanines* **1997**, *1*, 201.
15. Silva, A. M. G.; Faustino, M. A. F.; Tome, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2752.
16. Knapp, S.; Vasudevan, J.; Enge, T. J.; Arison, B. H.; Potenza, J. A.; Schugar, H. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2368.

17. Vicente, M. G. H.; Jaquinod, L.; Khoury, R. G.; Madrona, A. Y.; Smith, K. M. *Tetrahedron Lett.* **1999**, *40*, 8763.
18. Kricka, L. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 766.
19. A mixture of nickel(II) pyrroloporphyrin **1** (50 mg, 0.07 mmol) and DMAD (100 mg, 0.70 mmol) in 1,2,4-trichlorobenzene (TCB) (10 mL) was deaerated with argon for 10 min and then refluxed under argon for 2 h. The mixture was cooled down and purified by column chromatography on silica gel using CH_2Cl_2/hexane (3:2) as eluent, giving the title porphyrin **2** in 49% yield (34 mg). UV–vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) 433 (5.08), 546 (3.94), 579 (3.74) nm; ^{1}H NMR ($CDCl_3$): δ 8.70 (m, 6H), 7.97–7.90 (m, 8H), 7.78–7.68 (m, 12H), 7.39 (s, 2H), 3.88 (s, 6H); MS (HRMS) $C_{52}H_{34}N_4NiO_4(M^+)$: Calcd 836.1934; Found 836.1916.
20. Nickel(II) pyrroloporphyrin **1** (50 mg, 0.07 mmol), DMAD (100 mg, 0.70 mmol) and three drops of acetic acid in dry toluene (20 mL) were deaerated with argon for 10 min and then refluxed under argon for 2 h. The mixture was evaporated in vacuo and purified by column chromatography on silica gel using CH_2Cl_2 as the eluent until all unreacted DMAD was removed, then CH_2Cl_2/ethyl acetate 10:1, to afford 45% of compound **4** (32 mg) and 51% of compound **5** (36 mg). For porphyrin **4**: UV–vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) 326 (4.18), 439 (5.17), 549 (4.09), 592(4.08) nm; ^{1}H NMR ($CDCl_3$): δ 8.67 (m, 4H), 8.60 (m, 2H), 8.19–8.08 (broad, 2H), 7.97 (m, 4H), 7.68 (m, 14H), 7.05 (s, 1H), 5.19 (q, 2H, $J = 1.75$ Hz), 3.70 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 3.54 (s, 3H) ppm; HRMS: $C_{58}H_{41}N_5NiO_8(M^+)$: Calcd 993.2308; Found 993.2298; Anal. Calcd for $C_{58}H_{41}N_5NiO_8{\cdot}2H_2O$: C, 67.59; H, 4.40; N, 6.79. Found: C, 67.81; H, 4.18; N, 6.68. For porphyrin **5**: UV–vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) 330 (4.26), 441 (5.25), 551 (4.14), 595 (4.19) nm; ^{1}H NMR ($CDCl_3$): δ 8.79 (d, 1H, $J = 5.0$ Hz), 8.69–8.60 (m, 5H), 8.28 (broad, 1H), 7.97 (m, 6H), 7.68 (m, 13H), 7.15 (s, 1H), 5.39 (d, 1H, $J = 1.50$ Hz), 4.72 (d, 1H, $J = 1.50$ Hz), 3.81 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.56 (s, 3H) ppm; MS (HRMS) $C_{58}H_{41}N_5NiO_8$ (M^+): Calcd 993.2308; Found 993.2355; Anal. Calcd for $C_{58}H_{41}N_5NiO_8{\cdot}4H_2O$: C, 67.30; H, 4.63; N, 6.57. Found: C, 67.63; H, 4.10; N, 6.40. In an alternative route to **4** and **5**, a mixture of nickel(II) pyrroloporphyrin **1** (50 mg, 0.07 mmol), DMAD (100 mg, 0.70 mmol) and dry toluene (20 mL) was deaerated with argon for 10 min and then refluxed under argon for 3 h, until complete disappearance of the starting porphyrin. After cooling the reaction mixture, 10 mg anhydrous $AlCl_3$ was added and the mixture was stirred at 40 °C for 4 h before being concentrated in vacuo and purified as described above to give compounds **4** and **5** in 35% and 42% yields, respectively. Finally, a mixture of **1** (50 mg, 0.07 mmol) and DMAD (100 mg, 0.70 mmol) in dry toluene (20 mL) was deaerated with argon for 10 min and then refluxed under argon for 4 d. The mixture was evaporated in vacuo and purified by column chromatography on silica gel as described above to give porphyrin **4** in 29% yield (20 mg) and porphyrin **5** in 36% yield (25 mg).
21. Acheson, R. M.; Vernon, J. M. *J. Chem. Soc.* **1963**, 1008.
22. Acheson, R. M.; Vernon, J. M. *J. Chem. Soc.* **1962**, 1148.
23. Blazejewski, J. C.; Cantacuzène, D.; Wakselman, C. *Tetrahedron Lett.* **1975**, 363.
24. Noland, W. E.; Lee, C. K. *J. Org. Chem.* **1980**, *45*, 4573.
25. Lee, C. K.; Hahn, C. S.; Noland, W. E. *J. Org. Chem.* **1978**, *43*, 3727.
26. Noland, W. E.; Kin, K. J.; Lee, C. K.; Bae, S. K.; Hahn, C. S. *J. Org. Chem.* **1980**, *45*, 4582.