ORGANIC LETTERS

2011
Vol. 13, No. 17
4632–4635

Unexpected Alkyl Group Migration in Palladium(II) Benzocarbaporphyrins†

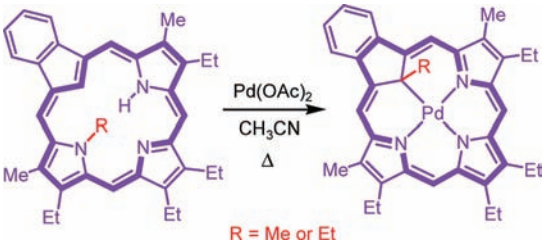
Timothy D. Lash*

Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, United States

tdlash@ilstu.edu

Received July 9, 2011

ABSTRACT



Reaction of a benzocarbaporphyrin with methyl or ethyl iodide and potassium carbonate in refluxing acetone primarily afforded the 22-alkylation products. Subsequent metalation with palladium(II) acetate in refluxing acetonitrile gave the palladium(II) organometallic derivatives where the alkyl group had migrated to the 21-position.

Carbaporphyrinoid systems have been widely studied,[1,2] in part due to their ability to form organometallic derivatives under mild conditions. In this regard, N-confused porphyrins (NCPs, **1**) have been intensively investigated[3] but other carbaporphyrinoids like azuliporphyrins **2**,[4] oxybenziporphyrins **3**,[5,6] oxynaphthiporphyrins,[6] tropiporphyrins,[7] and pyrazoloporphyrins **4**[8] also give similar organometallic derivatives. Benzocarbaporphyrins **5**[9] have been shown to act as trianionic ligands forming silver(III) and gold(III) complexes **6**,[10] although the related oxacarbaporphyrins **7** are dianionic ligands and form nickel(II) and/or palladium(II) complexes **8** and **9** (Scheme 1).[11,12] It occurred to us that *N*-alkylation of benzocarbaporphyrins **5** might allow this system to act as a dianionic ligand as well.

The alkylation of NCPs is well documented,[13] and we recently reported the synthesis of *N*-alkyl derivatives of an oxidized benziporphyrinoid system.[14] Benzocarbaporphyrin

† Part 59 in the series `Conjugated Macrocycles Related to the Porphyrins'. For part 58, see ref 14.

(1) (a) Lash, T. D. *Synlett* **2000**, 279–295. (b) Lash, T. D. *Eur. J. Org. Chem.* **2007**, 5461–5481.

(2) Lash, T. D. In *The Porphyrin Handbook*, Vol. 2; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; pp 125−199.

(3) (a) Srinivasan, A.; Furuta, H. *Acc. Chem. Res.* **2005**, *38*, 10–20. (b) Harvey, J. D.; Ziegler, C. J. *Coord. Chem. Rev.* **2003**, *247*, 1–19. (c) Chmielewski, P. J.; Latos-Grazynski, L. *Coord. Chem. Rev.* **2005**, *249*, 2510–2533.

(4) (a) Lash, T. D.; Chaney, S. T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 839–840. (b) Graham, S. R.; Ferrence, G. M.; Lash, T. D. *Chem. Commun.* **2002**, 894–895. (c) Colby, D. A.; Lash, T. D. *Chem.—Eur. J.* **2002**, *8*, 5397–5402. (d) Lash, T. D.; Colby, D. A.; Ferrence, G. M. *Eur. J. Org. Chem.* **2003**, 4533–4548. (e) Lash, T. D.; Colby, D. A.; Graham, S. R.; Ferrence, G. M.; Szczepura, L. F. *Inorg. Chem.* **2003**, *42*, 7326–7338. (f) Lash, T. D.; Colby, D. A.; Graham, S. R.; Chaney, S. T. *J. Org. Chem.* **2004**, *69*, 8851–8864. (g) Lash, T. D.; El-Beck, J. A.; Ferrence, G. M. *J. Org. Chem.* **2007**, *72*, 8402–8415. (h) El-Beck, J. A.; Lash, T. D. *Eur. J. Org. Chem.* **2007**, 3981–3190.

(5) (a) Lash, T. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2533–2535. (b) Lash, T .D.; Chaney, S. T.; Richter, D. T. *J. Org. Chem.* **1998**, *63*, 9076–9088. (c) Stepien, M.; Latos-Grazynski, L.; Lash, T. D.; Szterenberg, L. *Inorg. Chem.* **2001**, *40*, 6892–6900. (d) El-Beck, J. A.; Lash, T. D. *Org. Lett.* **2006**, *8*, 5263–5266.

(6) (a) Lash, T. D.; Rasmussen, J. M.; Bergman, K. M.; Colby, D. A. *Org. Lett.* **2004**, *6*, 549–552. (b) Lash, T. D.; Young, A. M.; Rasmussen, J. M. *J. Org. Chem.* **2011**, *76*, 5636–5651.

(7) (a) Lash, T. D.; Chaney, S. T. *Tetrahedron Lett.* **1996**, *37*, 8825–8828. (b) Bergman, K. M.; Ferrence, G. M.; Lash, T. D. *J. Org. Chem.* **2004**, *69*, 7888–7897.

(8) (a) Lash, T. D.; Young, A. M.; Von Ruden, A. L.; Ferrence, G. M. *Chem. Commun.* **2008**, 6309–6311. (b) Young, A. M.; Von Ruden, A. L.; Lash, T. D. *Org. Biomol. Chem.* **2011**, DOI:10.1039/C1OB05603D.

(9) (a) Lash, T. D.; Hayes, M. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 840–842. (b) Lash, T. D.; Hayes, M. J.; Spence, J. D.; Muckey, M. A.; Ferrence, G. M.; Szczepura, L. F. *J. Org. Chem.* **2002**, *67*, 4860–4874. (c) Liu, D.; Lash, T. D. *J. Org. Chem.* **2003**, *68*, 1755–1761.

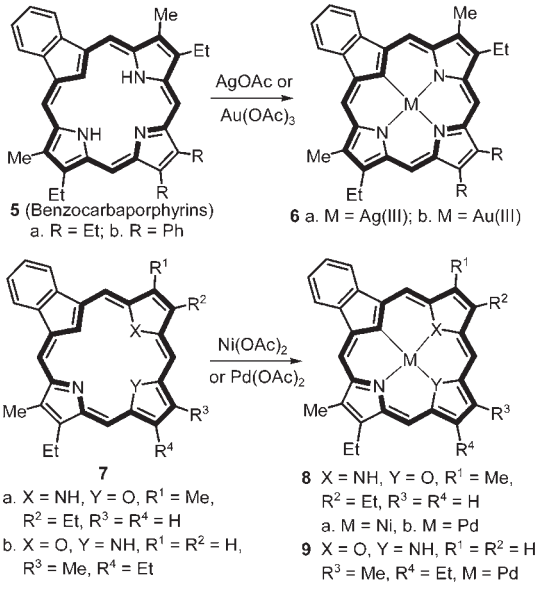
(10) (a) Muckey, M. A.; Szczepura, L. F.; Ferrence, G. M.; Lash, T. D. *Inorg. Chem.* **2002**, *41*, 4840–4842. (b) Lash, T. D.; Colby, D. A.; Szczepura, L. F. *Inorg. Chem.* **2004**, *43*, 5258–5267.

(11) (a) Liu, D.; Lash, T. D. *Chem. Commun.* **2002**, 2426–2427. (b) Liu, D.; Ferrence, G. M.; Lash, T. D. *J. Org. Chem.* **2004**, *69*, 6079–6093.

(12) Jain, P.; Ferrence, G. M.; Lash, T. D. *J. Org. Chem.* **2010**, *75*, 6563–6573.

10.1021/ol2018483
Published on Web 08/03/2011

Scheme 1



5 (Benzocarbaporphyrins)
a. R = Et; b. R = Ph

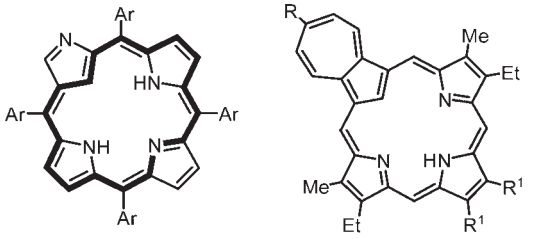
6 a. M = Ag(III); b. M = Au(III)

7
a. X = NH, Y = O, R^1 = Me, R^2 = Et, R^3 = R^4 = H
b. X = O, Y = NH, R^1 = R^2 = H, R^3 = Me, R^4 = Et

8 X = NH, Y = O, R^1 = Me, R^2 = Et, R^3 = R^4 = H
a. M = Ni, b. M = Pd

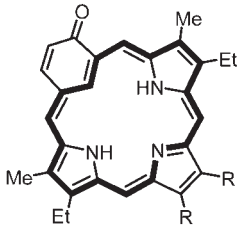
9 X = O, Y = NH, R^1 = R^2 = H, R^3 = Me, R^4 = Et, M = Pd

5a was reacted with methyl iodide in the presence of a stirred suspension of potassium carbonate in refluxing acetone for 16 h (Scheme 2). Following extraction into dichloromethane and washing with water, the products were run through a silica column, eluting with chloroform. The initial fraction corresponded to a minor alkylation

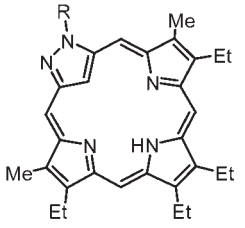


1 (N-Confused porphyrins)

2 (Azuliporphyrins)



3 (Oxybenziporphyrins)



4 (Pyrazoloporphyrins)

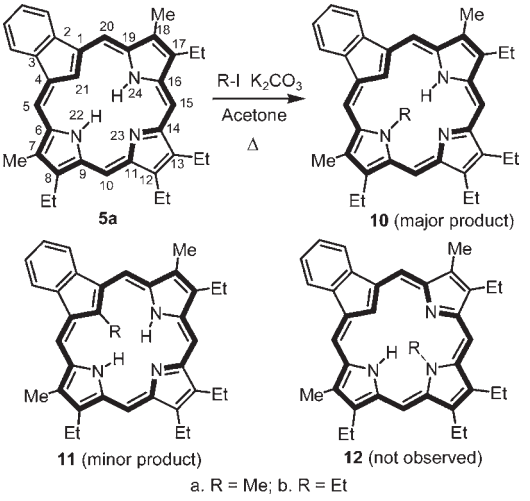
product, and a major product fraction eluted subsequently. Following recrystallization from chloroform–methanol, the two alkylation products were isolated in 10% and 62% yields, respectively. The 500 MHz proton NMR spectrum for the major product showed that the macrocycle no longer had a plane of symmetry (Figure 1). Four 1H singlets for the *meso*-protons were observed at 9.52, 9.67, 9.92, and 9.94 ppm, and two different 3H singlets were seen for the external methyl substituents at 3.18 and 3.55 ppm. In the upfield region, a 1H singlet was present at −6.20 ppm, a 3H singlet was observed at −4.10 ppm, and a broad resonance was noted at −2.45 ppm. The EI MS for this product showed a molecular ion at *m*/*z* 513, demonstrating the addition of a single methyl group, and the carbon-13 NMR spectrum confirmed that there was no longer a plane of symmetry in this structure. These data unambiguously show that the 22-methyl derivative **10a** had been formed. It is worth noting that **10a** is a chiral system due to the porphyrinoid core being too small to allow the *N*-alkyl substituent to pass through its center and therefore consists of two enantiomeric forms. As a consequence of this asymmetry, the proton NMR spectrum shows that the ethyl CH_2's are diastereotopic. The EI MS for the minor product also gave a molecular ion at *m*/*z* 513, but in this case the proton and carbon-13 NMR spectra showed that this product still retained a plane of symmetry. In the proton NMR spectrum, the *meso*-protons gave rise to two 2H singlets at 9.62 and 9.78 ppm, and the two peripheral methyl groups gave a 6H singlet at 3.57 ppm. In addition, the upfield CH resonance was replaced by a 3H singlet at −5.16 ppm. These results show that the minor product is in fact a *C*-alkylation product **11a**, rather than the alternative *N*-methyl derivative **12a**. This result is not particularly surprising as *C*-protonation of **5a** has been observed previously.[9] In essence, this system is acting like a vinylogous enamine and the pyrrolic nitrogens facilitate this electrophilic substitution (Scheme 3). In the carbon-13 NMR spectrum, the internal methyl group gave a resonance at 10.9 ppm, confirming that this moiety must be attached to a carbon rather than a nitrogen atom. Similar results were obtained using ethyl iodide, although these reactions were run for 2–3 days to ensure that the reactions went to completion. The 22-ethyl carbaporphyrin **10b** was again the major product but could not be recrystallized due to its high solubility in organic solvents, including methanol, hexanes, and petroleum ether. In order to obtain pure material, it was necessary to chromatograph this product three times on silica, but it was still isolated in 69% yield. As expected, the *C*-ethyl derivative **11b** was generated as a minor product and, following recrystallization, was isolated in 10% yield. The internal ethyl unit gave rise to a 2H quartet at −5.50 ppm and a 3H triplet at −2.38 ppm in the proton NMR spectrum. The UV–vis spectra for **10a** and **10b** resembled the spectra previously reported for **5a**, showing a strong Soret band at 434 nm and a series of Q-bands between 500 and 700 nm. The UV–vis spectra for *C*-alkylcarbaporphyrins were similar, but the intensities of the Soret bands were somewhat diminished.

N-Methyl carbaporphyrin **10a** was reacted with palladium(II) acetate in refluxing acetonitrile for 30 min (Scheme 4). Following extraction with dichloromethane and washing with water, the product was purified by column chromatography on silica. Proton NMR spectroscopy showed that the product fraction was a mixture of two compounds and only the minor component

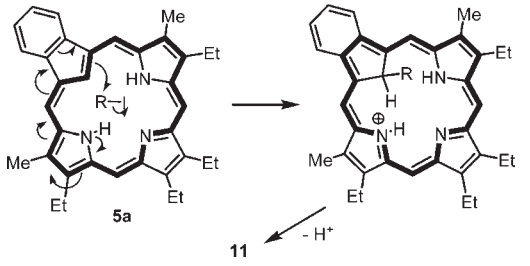
(13) (a) Chmielewski, P. J.; Latos-Grazynski, L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 503–509. (b) Xiao, Z.; Dolphin, D. *Tetrahedron* **2002**, *58*, 9111–9116.

(14) Lash, T. D.; Miyake, K.; Xu, L.; Ferrence, G. M. *J. Org. Chem.* **2011**, *76*, 6295–6308.

Scheme 2



Scheme 3



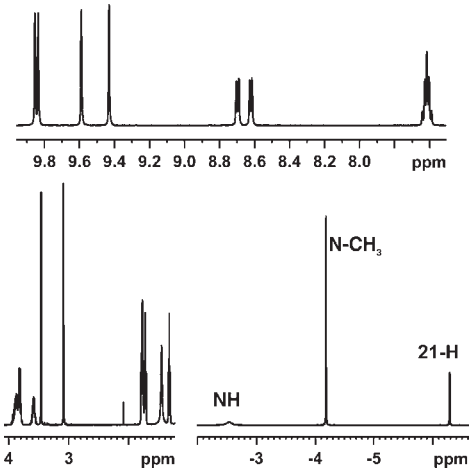
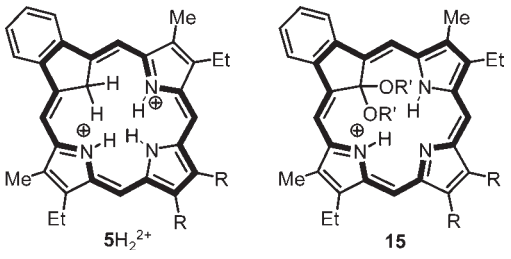


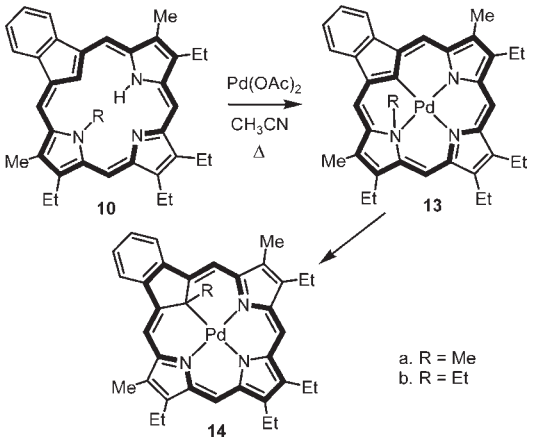
Figure 1. 500 MHz proton NMR spectrum of 22-methyl carbaporphyrin **10a** in $CDCl_3$.

corresponded to the expected palladium(II) complex **13a** (Scheme 4). The product was run through a column with 30% dichloromethane–hexanes, and this easily separated out the major component in pure form. The minor component was not obtained as a pure compound, and we noted that nearly all of the material was now in the form of the major component. The major product was isolated in 81% yield following recrystallization from chloroform–methanol. The proton NMR spectrum of this compound shows that the complex has a plane of symmetry where the *meso*-protons afford two 2H singlets at 9.56 and 10.27 ppm and the methyl substituents give a 6H singlet at 3.33 ppm (Figure 2). The internal methyl group shows up as a 3H singlet at −3.21 ppm. The results demonstrate that the palladium derivative is in fact the 21-methyl derivative **14a**. In the carbon-13 NMR spectrum, the internal methyl group gives a resonance at 11.7 ppm, while the attached sp^3 carbon appears at 45.3 ppm. The *meso*-carbons for this species showed up as two resonances near 106.6 ppm. The formation of this species implies that the methyl group must have migrated from the nitrogen atom to the indene carbon. This may have occurred during the metalation reaction itself or subsequent to the formation of palladium(II) complex **13a**. In order to assess these possibilities, the metalation reaction was carried out for 5 min in refluxing acetonitrile. In this case, the product appeared to primarily consist of **13a**, but following chromatography on a short silica, eluting with dichloromethane, the product already showed contamination with **14a**. This material was dissolved in acetonitrile and heated under reflux for 30 min. Analysis of the product following extraction and evaporation of the solvents by proton NMR spectroscopy showed that the product now consisted of >90% **14a** and only contained trace amounts of **13a**. These results show that the alkyl group migration primarily, if not entirely, occurs subsequent to the formation of the palladium complex. It is not clear whether this process takes place via a concerted [1,5]sigmatropic rearrangement, as depicted in Scheme 5, or a stepwise mechanism involving a transient Pd-alkyl species. Reaction of *N*-ethyl carbaporphyrin **10b** with palladium(II) acetate for 30 min exclusively gave the related *C*-ethyl complex **14b**. In this case, the proton NMR spectrum showed a 2H quartet at −3.10 ppm and a 3H triplet at −1.45 ppm for the internal ethyl group. In the carbon-13 NMR spectrum for **14b**, the sp^3 indene carbon atom gave a resonance at 52.4 ppm and the *meso*-carbons appeared at 106.4 and 107.0 ppm.

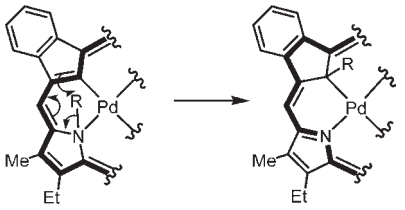
The proton NMR spectra for the palladium complexes show that they retain highly diatropic characteristics, but the 18π electron delocalization pathway is now relocated so that it runs through the fused benzo unit. In essence, these palladium derivatives represent bridged benzo[18]annulenes. This is also the case for diprotonated benzocarbaporphyrins



Scheme 4



Scheme 5



$\mathbf{5}H_2^{2+}$ and the benzoporphyrin ketals **15**.[9,15,16] The proton NMR spectra provide supporting evidence for the relocation of the favored aromatic delocalization pathway. In the proton NMR spectrum for **5a**, the benzo-protons give rise to an AA′XX′ system with resonances at 7.73 and 8.79 ppm. However, the equivalent protons in **14a** show up at 8.22 and 9.41 ppm while the values noted for **14b** correspond to 8.16 and 9.31 ppm. The substantial downfield shifts to the benzo-protons closest to the porphyrinoid macrocycle are presumably due to the increased proximity of these protons to the relocated macrocyclic ring current. The diamagnetic ring current appears to be slightly smaller for the *C*-ethyl derivative **14b**, possibly due to increased steric congestion leading to decreased macrocyclic planarity. The UV−vis spectra for **14a** and **14b** are also significantly altered compared to **10**, showing relatively weak Soret bands near 420 nm and a fairly strong absorption close to 700 nm. The absorptions for **14b** are bathochromically shifted by 4−5 nm compared to **14a**, a result that is consistent with the presence of a more distorted chromophore in this case.

(15) (a) Hayes, M. J.; Spence, J. D.; Lash, T. D. *Chem. Commun.* **1998**, 2409–2410. (b) Lash, T. D.; Muckey, M. A.; Hayes, M. J.; Liu, D.; Spence, J. D.; Ferrence, G. M. *J. Org. Chem.* **2003**, *68*, 8558–8570.

(16) Carbaporphyrin ketals show promise as agents for the treatment of leishmaniasis: Morgenthaler, J. B.; Peters, S. J.; Cedeño, D. L.; Constantino, M. H.; Edwards, K. A.; Kamowski, E. M.; Passini, J. C.; Butkus, B. E.; Young, A. M.; Lash, T. D.; Jones, M. A. *Bioorg. Med. Chem.* **2008**, *16*, 7033–7038.

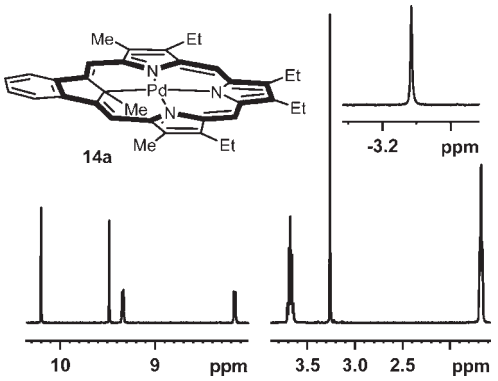
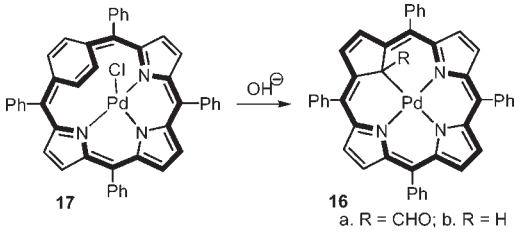


Figure 2. 500 MHz proton NMR spectrum of palladium(II) complex **14a** in $CDCl_3$.

Scheme 6



These results demonstrate that palladium(II) derivatives are easily obtained from 22-alkyl benzocarbaporphyrins and that alkyl group migration readily occurs within the macrocyclic cavity. In addition, the palladium(II) cation forms a bond to an sp^3 carbon atom and therefore differs significantly from the silver(III) and gold(III) complexes reported previously.[10] In independent work, it was very recently reported that related palladium(II) complexes **16** were obtained by the base promoted rearrangement of a palladium(II) *p*-benziporphyrin **17** (Scheme 6).[17] In this case, an intriguing ring contraction of the arene subunit has occurred.[17] Clearly there is still much to be learned about the organometallic chemistry of carbaporphyrinoid systems.

Acknowledgment. This work was supported by the National Science Foundation under Grant No. CHE-0911699. Funding for a 500 MHz NMR spectrometer was also provided by the National Science Foundation under Grant No. CHE-0722385.

Supporting Information Available. Experimental procedures and selected ^1H NMR, $^1H-^1H$ COSY, HMQC, ^{13}C NMR, MS, and UV−vis spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Szyszko, B.; Latos-Grazynski, L.; Szterenberg, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 6587–6591.