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Synthesis and Characterization of Pyrrolidin-2-one Fused N-Confused Calix[4]phyrins

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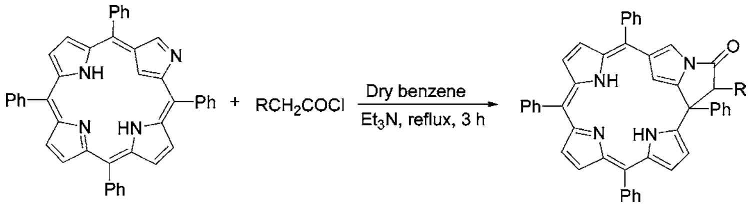
ABSTRACT



A facile method for the synthesis of pyrrolidin-2-one fused N-confused calix[4]phyrins is provided by reactions of 5,10,15,20-tetraaryl-2-aza-21-carbaporphyrin with acyl chlorides in the presence of triethylamine. The ^{1}H NMR and UV–vis spectra of products indicate their loss of macrocyclic aromaticity.

N-Confused porphyrin (NCP), a porphyrin isomer with an “inverted” pyrrole ring, was first synthesized by the groups of Furuta[1] and Latos-Grażyñski[2] independently in 1994. The chemistry of N-confused porphyrins has progressed rapidly in recent years[3] owing to the nonconventional coordination modes of the NCP complexes,[4] incorporating classic organometallic chemistry into porphyrin research,[5] and to the unusual reactivity of the internal carbon on the inverted pyrrole ring.[6] The synthetic efforts toward new NCP derivatives have been focused mainly on the reaction of the internal carbon[5b,7] or external nitrogen[8] of the inverted pyrrole ring,

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(1) Furuta, H.; Asano, T.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 767.

(2) Chmielewski, P. J.; Latos-Grażyñski, L.; Rachlewicz, K.; Głowiak, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 779.

(3) (a) Furuta, H.; Maeda, H.; Ogawa, T. *Chem. Commun.* **2002**, 1795. (b) Ghosh, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1918. (c) Srinivasan, A.; Furuta, H. *Acc. Chem. Res.* **2005**, *38*, 10.

(4) (a) Harvey, J. D.; Ziegler, C. J. *Coord. Chem.Rev.* **2003**, *247*, 1 and references therein. (b) Chmielewski, P. J.; Latos-Gra×c0yñski, L. *Coord. Chem.Rev.* **2005**, *249*, 2510 and references therein.

(5) (a) Furuta, H.; Ishizuka, T.; Osuka, A.; Uwatoko, Y.; Ishikawa, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2323. (b) Chmielewski, P. J.; Latos-Grazynski, L.; Glowiak, T. *J. Am. Chem. Soc.* **1996**, *118*, 5690. (c) Furuta, H.; Kubo, N.; Maeda, H.; Ishizuka, T.; Osuka, A.; Nanami, H.; Ogawa, T. *Inorg. Chem.* **2000**, *39*, 5424. (d) Furuta, H.; Ishizuka, T.; Osuka, A. *J. Am. Chem. Soc.* **2002**, *124*, 5622. (e) Chmielewski, P. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6417.

(6) (a) Ghosh, A.; Wondimagegn, T.; Nilsen, H. J. *J. Phys. Chem. B* **1998**, *102*, 10459. (b) Ghosh, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *34*, 1028.

(7) (a) Schmidt, I.; Chmielewski, P. J. *Chem. Commun.* **2002**, 92. (b) Schmidt, I.; Chmielewski, P. J.; Ciunik, Z. *J. Org. Chem.* **2002**, *67*, 8917. (c) Schmidt, I.; Chmielewski, P. J. *Inorg. Chem.* **2003**, *42*, 5579. (d) Xiao, Z.; Patrick, B. O.; Dolphin, D. *Chem. Commun.* **2003**, 1062. (e) Xiao, Z.; Patrick, B. O.; Dolphin, D. *Inorg. Chem.* **2003**, *42*, 8125.

(8) (a) Chmielewski, P. J.*Org. Lett.* **2005**, *7*, 1789. (b) Chmielewski, P.; Latos-Grażyñski, L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 503. (c) Furuta, H.; Ishizuka, T.; Osuka, A.; Dejima, H.; Nakagawa, H.; Ishikawa, Y. *J. Am. Chem.* Soc. **2001**, *123*, 6207. (d) Furuta, H.; Ishizuka, T.; Osuka, A.; Ogawa, T. *J. Am. Chem. Soc.* **2000**, *122*, 5748.. (e) Schmidt, I.; Chmielewski, P. *Tetrahedron Lett.* **2001**, *42*, 6389. (f) Ishikawa, Y.; Yoshida, I., Akaiwa, K.; Koguchi, E.; Sasaki, T.; Furuta, H. *Chem. Lett.* **1997**, 453. (g) Chmielewski, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5655.

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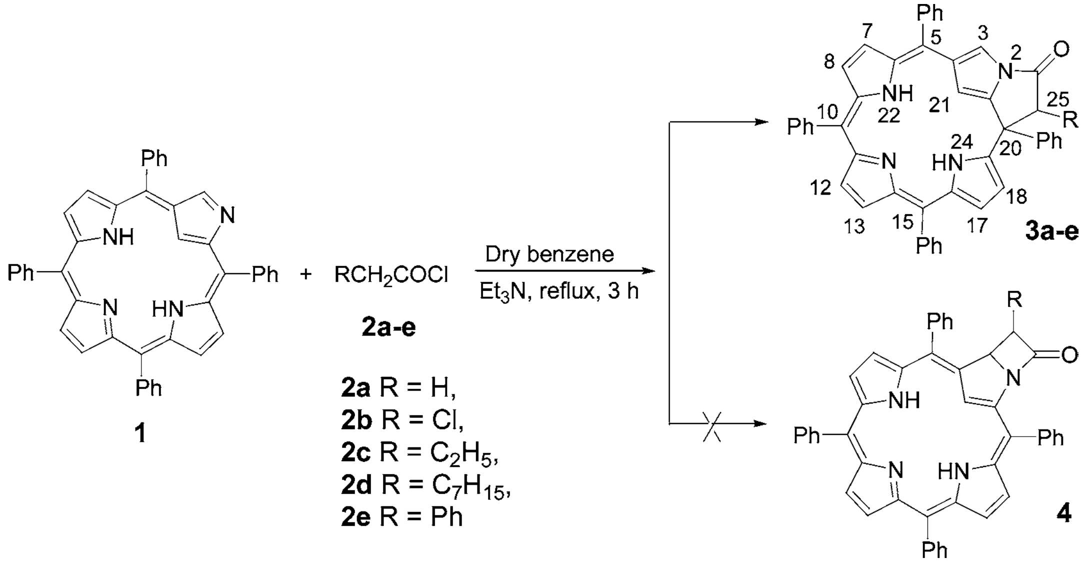
Scheme 1



while reactions involving the peripheral carbon−nitrogen double bond[9] or meso carbon[10] are rarely observed in N-confused porphyrin chemistry.

Due to a partial isolation of the peripheral carbon−nitrogen double bond of NCP from the macrocyclic conjugation pathway, the system shows parallels with the chemistry of a simple N−C double bond, such as the pericyclic reactions.[9] The reaction of imines with ketenes, generated from acyl chlorides and tertiary amines, is recognized as one of the most convenient approaches to β-lactams.[11] Although the cycloaddition reactions of porphyrinoid including 1,3 dipolar cycloaddition and Diels−Alder reaction have been sufficiently studied,[12] there are no reports concerning the 2 + 2 reaction of porphyrinoids.

In the present work, we report the results of our attempt to apply the Staudinger protocol[11] in the reaction involving N-confused porphyrin **1** and several acyl chlorides **2**. Such an approach, however, resulted in a synthesis of various pyrrolidin-2-one-fused N-confused calix[4]phyrins **3** instead of the expected β-lactam-fused N-confused porphyrins **4** (Scheme 1).

N-Confused porphyrins were prepared using the procedure described by Lindsey.[13] A solution of N-confused tetraphenylporphyrin **1** (NCTPP) and excess acetyl chloride **2a** was stirred in dry benzene under a nitrogen atmosphere. When an excess of triethylamine was added in one portion, the black-red color of the solution was changed to blue-green immediately, revealing that the reaction took place, which was confirmed concurrently by a TLC analysis. Further reflux for 3 h was for total consumption of the starting material and maximized the reaction yield. The solvent was then removed by vacuum, and the residue was chromatographed on a silica gel column with CH$_2$Cl$_2$. A product with a R_f value ($R_f = 0.57$, silica gel plate, CH$_2$Cl$_2$) higher than that of **1** ($R_f = 0$, silica gel plate, CH$_2$Cl$_2$) was obtained in 71% yield (Scheme 1) and identified as the pyrrolidin-2-one fused N-confused calix[4]phyrin **3a** on the basis of its mass, UV−vis, and NMR (^{1}H, ^{13}C, COSY, HMQC, HMBC, NOESY) spectra.

The matrix-assisted laser desorption ionization−time-of-flight mass spectrometry (MALDI-TOFMS) of **3a** gave the molecular ion peak at m/z 656 which indicates the addition of ethenone to the N-confused tetraphenylporphyrin.

The optical properties of the system are significantly altered by the reaction. The UV−vis spectrum of **3a** is presented in Figure 1 along with that of the starting material **1**.

The spectrum of **3a**, characterized by two major bands at ∼398 and 685 nm, resembles those observed for N-strapped phlorin **5**[14a] or *N*-phenylphlorin **6**[14b] (Figure 2). The disappearance of Soret band characteristic of porphyrin as well

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[9] Xiao, Z.; Patrick, B. O.; Dolphin, D. *Chem. Commun.* **2002**, 1816.

[10] (a) Harvey, J. D.; Ziegler, C. J. *Chem. Commun.* **2003**, 2890. (b) Furuta, H.; Maeda, H.; Osuka, A. *Org. Lett.* **2002**, *4*, 181. (c) Hung, C.-H.; Wang, S.-L.; Ko, J.-L.; Peng, C.-H.; Hu, C.-H.; Lee, M.-T. *Org. Lett.* **2004**, *6*, 1393.

[11] (a) Banik, I.; Becker, F. F.; Banik, B. K. *J. Med. Chem.* **2003**, *46*, 12. (b) Banik, B. K.; Becker, F. F. *Tetrahedron Lett.* **2000**, *41*, 6551. (c) Alcaide, B.; Rodriguez-Vicente, A. *Tetrahedron Lett.* **1999**, *40*, 2005. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.

[12] (a) Li, X. F.; Zhuang, J. P.; Li, Y. L.; Liu, H. B.; Wang, S.; Zhu, D. B. *Tetrahedron Lett.* **2005**, *46*, 1555. (b) Silva, A. M. G.; Tome, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Org. Chem.* **2005**, *70*, 2306. (c) Desjardins, A.; Flemming, J.; Sternberg, E. D.; Dolphin, D. *Chem. Commun.* **2002**, 2622. (d) Tomé, A. C.; Lacerda, Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *Chem. Commun.* **1999**, 1767. (f) Silva, A. M. G.; Tome, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Org. Chem.* **2002**, *67*, 726. Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2000**, *41*, 3065.

[13] Geier, G. R., III; Haynes, D. M.; Lindsey, J. S. *Org. Lett.* **1999**, *1*, 1455.

[14] (a) Ishimaru, Y.; Sumida, S.; Iida, T. *Tetrahedron Lett.* **2001**, *42*, 419. (b) Ruppert, R.; Jeandon, C.; Sgambati, A.; Callot, H. J. *Chem. Commun.* **1999**, 2123.

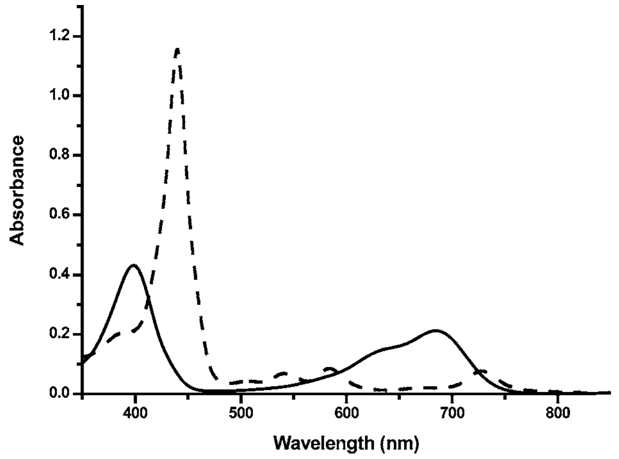
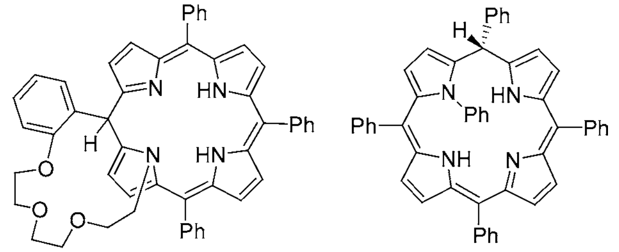


Figure 1. UV−vis spectra of **3a** (solid line) and **1** (dotted line) in $CHCl_3$ (8.5×10^{-6}M).

as the characteristic increase of the bands intensity at higher wavelengths reflect loss of the macrocyclic aromaticity in **3a**.



5

6

Figure 2. N-Strapped phlorin **5** and *N*-phenylphlorin **6**.

The ^1H NMR spectrum of **3a** (223 K, $CDCl_3$) is shown in Figure 3 along with the signal assignments. There are six β-pyrrole doublets in the 6.49−7.02 ppm region and two doublets of diastereotopic methylene protons at 3.80 and 4.26 ppm ($J = 18$ Hz). The inner CH signal (H21) of the inverted pyrrole appearing at −5.1 ppm[1] in **1** is remarkably shifted downfield to 5.89 ppm in the spectrum of **3a**, while the inner NH proton signals of **1** observed around −2.5 ppm[1] appear at 8.47 and 8.79 ppm in **3a**. The assignment of the NH signals was confirmed by the deuterium exchange experiments with D_2O. The alteration of the resonance positions with respect to those observed for the starting porphyrinoid **1**, i.e., upfield shift of the β-pyrrole signals and downfield shift of the H21 and NH peaks, indicates the absence of the aromatic ring current in **3a**. Although **3a** is no longer aromatic, the integrity of its macrocyclic ring can be demonstrated by the following NMR experiments.

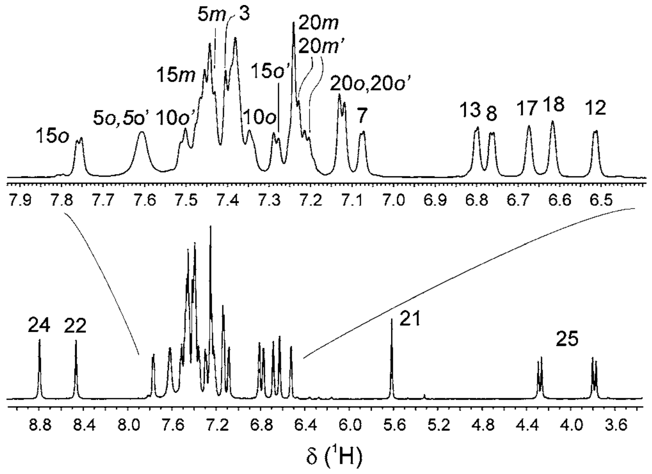


Figure 3. ^1H NMR spectrum (600 MHz, 223K, $CDCl_3$) of **3a**. Resonance assignments (obtained from COSY and NOESY maps) follow the numbering scheme given in Scheme 1.

The low-temperature COSY (223 K, $CDCl_3$) allows assignment of the NH protons to the regular pyrroles with one NH at 8.79 ppm correlating with β-pyrrole protons at 6.58 and 6.60 ppm and the other NH at 8.47 ppm scalar coupled with those resonating at 7.02 and 6.78 ppm. The $^1H-^1H$ COSY experiment shows also correlations between H3 and H21, as well as between protons belonging to phenyl substituents at different meso positions (see Scheme 1 for proton assignments).

A combination of $^1H-^{13}C$ heteronuclear 2D techniques was applied in order to assign the resonances of the carbon atoms crucial for the elucidation of the structure of **3a**. The inner carbon of inverted pyrrole at 101.6 ppm correlated to the proton at 5.89 ppm in the HMQC experiment. The position of this ^{13}C resonance is similar to those of C21 in other N-confused porphyrinoids (99.2 ppm for NCTPP[1] and 106.0 ppm for 2-NCH_3CTPP[8b]).

The chemical shifts of the outer carbon of the inverted pyrrole C3 (116.2 ppm) and that of C18 (110.8 ppm) are about 20 ppm higher than those of the appropriate carbon resonances of 2-NCH_3CTPP.[8b] This phenomenon also reflects the loss of the macrocyclic aromaticity of **3a**.

In the $^1H-^{13}C$ HMBC map of **3a** ($CDCl_3$, 298 K), the diastereotopic methylene protons at position 25 correlate with a carbonyl carbon (168 ppm), a quaternary sp^3 *meso* carbon (47 ppm), and with a quaternary sp^2 resonating at 141.3 ppm, which can be assigned to C1 since it is also coupled with H3 and H21. Thus, the HMBC spectrum provided support for the regioselectivity of the reaction at the *meso* carbon at the 20-position.

The detailed analysis of the low-temperature $^1H-^1H$ NOESY experiment (223 K, $CDCl_3$, see the Supporting Information) allows construction of a reliable molecular model of **3a** (Figure 4) that was energy-optimized by the semiempirical PM3 method[15] taking into account restraints coming from the observed interprotonic through-space interactions. Crucial for the structural elucidation of **3a** is observation of a dipolar interaction involving methylene

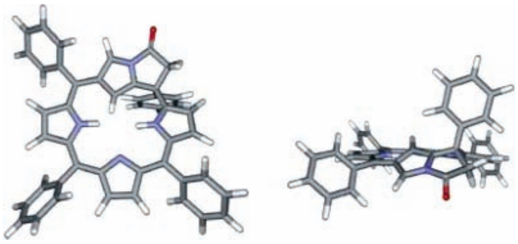


Figure 4. Energy-minimized molecular model of **3a** (left, aerial view; right, side view).

protons at position 25, H21, and ortho protons of phenyl at the *meso* position 20.

To study the generality of this kind of reaction, other acyl chlorides (**2b**−**e**), including those with a long-chain alkyl residue or aryl group, were examined. The acyl chlorides containing no hydrogen atom at the α-carbon, such as trichloroacetyl chloride, did not react with **1**. The other acid chlorides under study showed similar reactivity with the 60−70% yield of the products **3b**−**e**. These results indicate that the steric factors introduced by the substituent do not influence the effectiveness of the exocyclic ring fusion. It seems, however, that the spatial overcrowding at the reaction sites may determine stereochemistry of the process. Although the presence of two stereogenic centers in **3b**−**e** (C20 and C25) implies formation of NMR-distinguishable diastereomers, in each case only one set of signals was observed in the ^{1}H NMR spectra of the reaction mixture, indicating diastereoselectivity of the reaction. The preference for a arrangement on the same side of the mean plane of the macrocycle of the phenyl at position 20 and the non-H substituent at C25 can be accounted for such stereoselectivity. The semiempirical calculations for **3b** and **3c** suggest higher stability of the stereoisomers in which these substituents adopt a cis orientation (Figure 5, $\Delta E = 20.7$ kcal/mol for **3b** and $\Delta E = 24.3$ kcal/mol for **3c**; see the Supporting Information for details). The arrangement on the same side of the mean plane of the macrocycle of the 20-Ph and the substituents at C25 can be inferred from the NOESY experiments for **3c** (see the Supporting Information for details). The dipolar interactions between ortho-protons of 20-Ph, the unique proton at C25, and the diastereotopic methylene protons of the ethyl group as well as lack of correlation between the latter group and the neighboring *β*-pyrrole proton (H18) are in line with the formation of the cis-isomer.

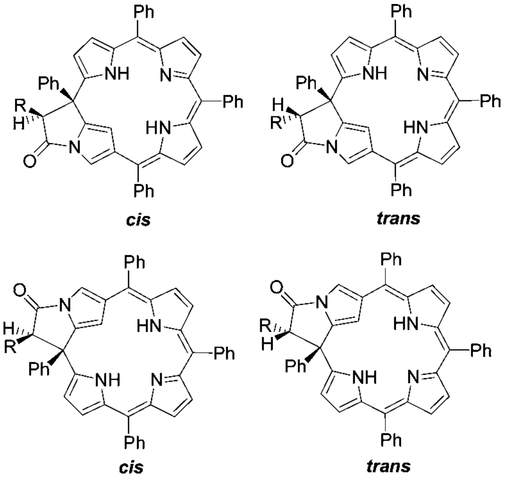


Figure 5. Possible stereoisomers of **3b**−**e**.

Mechanistic studies on this reaction, which is of interest for the understanding of reactivity of the inverted pyrrole, as well as on the other reactions involving the *meso*-carbon of NCTPP, are currently underway in our laboratory.

In summary, a novel type of N-confused calix[4]phyrin derivatives was obtained in a moderate yield. The reaction occurs regio- and diastereoselectively on the external nitrogen and the neighboring *meso* carbon. The ^{1}H NMR and UV−vis spectra of products indicate their loss of macrocyclic aromaticity.

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Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The PM3 semiempirical method in the RHF formalism was selected to carry out the calculations with the HyperChem program (HyperChem 6 Molecular Modeling System, Hypercube Inc., 2000). The distances between protons giving NOE correlations were initially fixed at 2.7−3 Å. In the final run of the calculation geometries were optimized without constraint.