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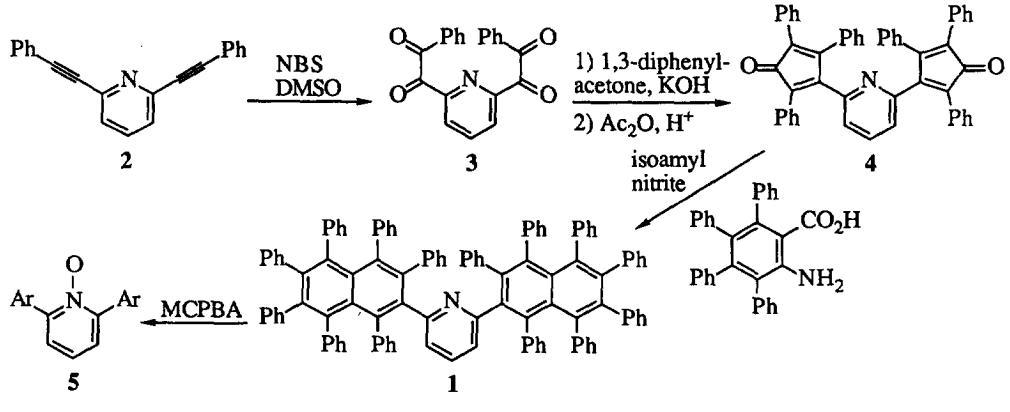
Albatrossidine: A Large, Easily Synthesized Molecular Cleft

Ling Tong, Douglas M. Ho, Nancy J. Vogelaar, Clarence E. Schutt, and Robert A. Pascal, Jr.*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544 USA

Abstract: 2,6-Bis(heptaphenyl-2-naphthyl)pyridine (**1**) was prepared in three steps from 2,6-bis(phenylethynyl)pyridine, and its X-ray structure was determined. The pyridine nitrogen lies at the base of a broad, chiral molecular cleft created by the perphenylnaphthyl "wings" of **1**.

We recently described the synthesis of octaphenylnaphthalene by the addition of tetraphenylbenzyne, generated from 3,4,5,6-tetraphenylanthranilic acid, to tetraphenylcyclopentadienone.[1] Octaphenylnaphthalene is a roughly rectangular slab with a 12 Å × 14 Å surface, and its ease of synthesis suggested that large organic structures containing clefts or cavities defined by appropriately placed perphenylnaphthyl groups should be easily accessible. We report here the preparation and characterization of the first such compound, 2,6-bis(heptaphenyl-2-naphthyl)pyridine (**1**), in which a pyridine nitrogen is buried deep between two perphenylnaphthyl "wings", to which we give the trivial name albatrossidine.



The synthesis of **1** is very short. Oxidation of 2,6-bis(phenylethynyl)pyridine[2] with NBS/DMSO[3] gives the tetraketone **3** in 49% yield.[4] Condensation of **3** with two equivalents of 1,3-diphenylacetone then yields the

corresponding biscyclopentadienone[5] (**4**) as a purple solid which, without further purification, is treated with 3,4,5,6-tetraphenylanthranilic acid[1] and isoamyl nitrite to give compound **1**[6] in 10% yield from **3**.

The ^{1}H and ^{13}C NMR spectra of **1** are broadened at room temperature (some coalescence and sharpening are observed at 100 °C, but this is not yet the fast exchange limit), suggesting the presence of one or more conformational exchange processes with moderate barriers (*ca.* 15-20 kcal/mol). The FAB mass spectrum shows the expected M+H ion, and an X-ray analysis confirms the structure. Only small, thin plates of **1** could be obtained (from $CHCl_3$-EtOH), but data collection on a diffractometer equipped with a rotating anode and image plate gave good results. The solution and refinement of this large "small molecule" structure were ultimately accomplished,[7] and the result is illustrated in Figures 1 and 2.

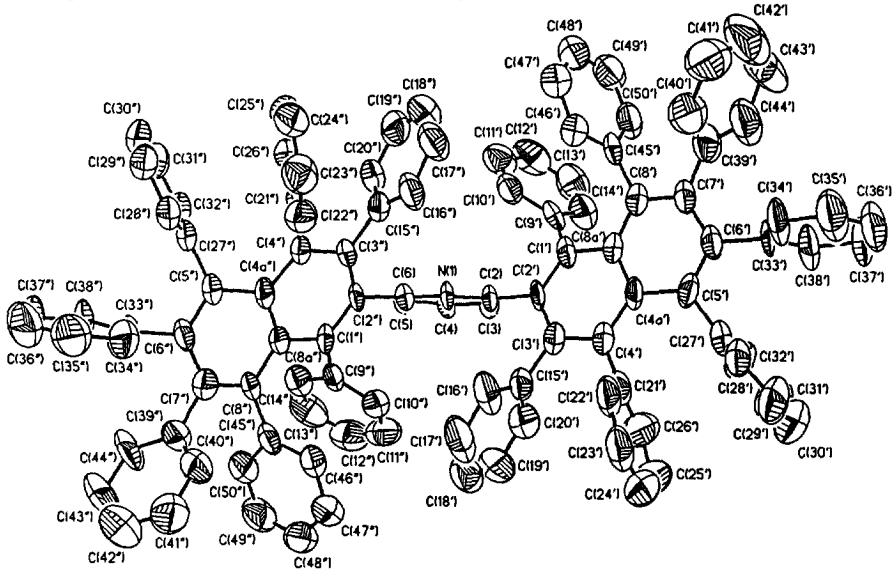


Figure 1. X-ray structure of albatrossidine (**1**). Thermal ellipsoids are drawn at the 50% probability level, and hydrogens have been omitted for clarity.

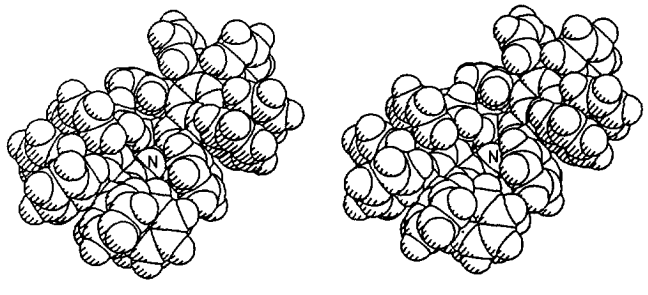


Figure 2. Space-filling stereoscopic view of compound **1** which illustrates the molecular cleft.

Compound **1** adopts a conformation of approximate C_2 symmetry, with the two perphenylnaphthyl groups providing the walls of a V-shaped cleft 6 Å deep and 16 Å wide. The mean planes of the two

perphenylnaphthyl "wings" are roughly perpendicular to the central pyridine, and the naphthalenes are oriented *trans* to one another. Although **1** appears to have many rotational degrees of freedom, its conformation is highly constrained by severe steric interactions. First, the C-1 phenyl of each naphthalene strongly interacts with the C-3 phenyl of the opposite naphthalene, with an *ortho*-hydrogen of each C-1 phenyl pressing into the face of the opposing C-3 phenyl. Thus the edges of the C(1')- and C(1")-phenyls (see Figure 1), press into the faces of the C(3")- and C(3')-phenyls, so that the C(10')- and C(10")-hydrogens are only 2.72 Å and 2.92 Å, respectively, from the centers of the opposing phenyl groups. It is probably these two protons which give rise to the most upfield resonances in the ^{1}H NMR spectrum of **1**. Second, the naphthyl groups themselves cannot be planar because of the steric bulk of the eight aryl substituents on each. Octaphenylnaphthalene exhibits an undulating, approximately C_i-symmetric conformation,[1] but each of the naphthyl groups in **1** is twisted; both have an end-to-end twist[13] of 20°. In fact, AM1 calculations indicate that such twisted conformations should be slightly favored in octaarylnaphthalenes,[1] and the collision of the C-1 and C-3 phenyls may provide a further bias in favor of the twisted conformation. Finally, the interaction of the four C-1 and C-3 phenyl groups also tends to lock the wings of **1** in place. Molecular mechanics calculations (SYBYL) show only two low energy conformations, the *trans* geometry found in the X-ray structure and a similar *cis* conformation less than one kcal/mol higher in energy. However, if both conformations are present to a significant extent in solution, then they must be able to interconvert by rotation about the pyridine-naphthalene bonds (since only one isomer of **1** is observed), and this exchange process may be responsible for the broadening observed in the NMR spectra of **1**.

This last hypothesis was confirmed in an unexpected way. The pyridine nitrogen of **1**, deep within the cleft (see Figure 2), appears to be sterically encumbered, but it is in fact accessible to common reagents. Most significantly, compound **1** was smoothly oxygenated with MCPBA to give *two separable isomers* of the corresponding N-oxide **5**, which presumably arise from the *cis* and *trans* conformations of the parent **1**. The ^{1}H NMR spectra of the oxides are distinct and sharp,[14,15] unlike that of **1**. Thus the introduction of the oxygen substituent is sufficient to halt the rotation about the pyridine-naphthalene bonds on both the NMR and laboratory time scales. The assignment of the two oxides is uncertain at this time, but the *trans*-oxide should have C_2 symmetry and a large chiral cleft, and, because of the high barrier to rotation, it should be resolvable.

The syntheses of a variety of albatross molecules are now underway, as are studies of their use as molecular hosts.

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References and Notes

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4. For **3**: mp 127-130 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.16 (m, 4H), 7.38 (m, 6H), 8.05 and 8.20 (A_2B system, 3H); ^{13}C NMR ($CDCl_3$) δ 126.6, 128.6, 128.8, 132.6, 134.4, 139.4, 151.0, 193.9, 195.5 (9 of 9 expected resonances); MS, *m/z* 343 (M^+, 15), 105 (100), 72 (40).

5. For **4**: mp 115-117 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.83-7.38 (m); MS, *m/z* 691 (M^+, 100), 662 (M–HCO, 54).
6. For **1**: mp 350-352 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.04 (br s, 1H), 5.68 (br s, 1H), 5.81 (br s, 2H), 5.93 (br s, 1H), 6.12 (br s, 1H), 6.25 (br s, 1H), 6.34 (br s, 1H), 6.40-6.94 (br m, 65H); ^{13}C NMR ($CDCl_3$) δ 123.4, 124.8, 125.2, 125.4, 126.4*, 126.7*, 127.6, 127.8, 128.4, 128.6, 129.1, 129.4, 130.2, 130.9, 131.4*, 131.8*, 132.6*, 132.9, 133.5*, 134.2*, 138.8, 139.0, 140.4*, 141.3, 141.4, 142.3*, 142.7, 142.9 (28 of 41 expected resonances, but starred resonances are broad and/or multiple); FAB MS, *m/z* 1396 (M+H, 100), 1319 (M – C_6H_5, 14).
7. A crystal of **1** measuring 0.02 mm x 0.31 mm x 0.58 mm, and mounted in a sealed glass capillary containing a small amount of the mother liquor to inhibit loss of solvent, was used for X-ray measurements. Crystal data: $C_{109}H_{73}N{\cdot}CHCl_3$; monoclinic, space group $P2_1/c$; a = 21.88 (7) Å, b = 34.57 (7) Å, c = 13.72 (2) Å, β = 98.04 (11)°, V = 10274 (41) Å^3, Z = 4, D_{calcd} = 0.980 g/cm^3. Intensity data were collected out to 2θ = 90° by using Cu Kα radiation (λ = 1.54178 Å) at 298 K on a Rigaku R-AXIS IIC image plate system equipped with a rotating anode and double-focusing mirrors. 293 frames of data were collected with 2° of oscillation per frame. The 29537 observed reflections were indexed, integrated, and corrected for Lorentz and polarization effects (using the program DENZO[8]), and then the reflections were scaled and merged (SCALEPACK[8]). The final data set contained 7502 unique reflections (R_{int} = 0.096). The structure was solved by molecular replacement (PATSEE[9]), and refined by full-matrix least-squares on F^2 (SHELXL-93[10]) to $R(F)$ = 0.174 with all heavy atoms anisotropic and inclusion of hydrogen atoms with a riding model [U(H) = 1.2U(C)]. A difference-Fourier synthesis at this stage revealed no peak larger than 1.7 eÅ^{-3} in the two symmetry related channels running parallel to the c-axis, but the clustering of peaks was suggestive of two badly disordered $CHCl_3$ sites. However, all attempts to fit the electron density within the channels with discrete solvent molecules were without success, so the SQUEEZE/BYPASS[11] procedure implemented in PLATON-94[12] was used to account for the solvent electron density. A total electron count of 205.9 e in a total volume of 3181.7 Å^3 was found for the two channels, consistent with approximately four $CHCl_3$ (58 e) per cell. (Attempts to determine independently the identity and amount of solvent present by NMR analysis were without success due to rapid solvent loss by the crystals during handling in the absence of the mother liquor.) The SQUEEZE-processed data was used for all subsequent cycles of refinement, which converged to $R(F)$ = 0.098, w$R(F^2)$ = 0.274, and S = 1.15 for 6183 reflections with $F > 4\sigma(F)$, and $R(F)$ = 0.107, w$R(F^2)$ = 0.286, and S = 1.08 for 7502 unique reflections and 992 variables.
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14. For **5** isomer A (major): R_f 0.31 (9:1 hexanes-EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (t, J = 8 Hz, 1H), 5.90 (br s, 2H), 6.05 (br s, 2H), 6.09 (d, J = 8 Hz, 2H), 6.42 (m, 8H), 6.50-6.75 (m, 54H), 6.78 (t, J = 7 Hz, 2H), 6.85 (t, J = 7 Hz, 2H); FAB MS, *m/z* 1412 (M+H, 100), 1307 (56).
15. For **5** isomer B (minor): R_f 0.15 (9:1 hexanes-EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.72 (t, J = 8 Hz, 1H), 5.93 (d, J = 8 Hz, 2H), 6.05 (m, 6H), 6.23 (t, J = 8 Hz, 2H), 6.30 (d, J = 8 Hz, 2H), 6.33 (t, J = 7 Hz, 2H), 6.40 (m, 4H), 6.52-6.82 (m, 46H), 6.94 (m, 6H), 7.12 (d, J = 7 Hz, 2H); FAB MS, *m/z* 1412 (M+H, 100), 1307 (46).

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