triflate 8 in 2 mL of THF was added, and purging was continued for an additional 10 min. The reaction mixture was stirred at 25 °C under an atmosphere of carbon monoxide until thin-layer chromatography indicated the complete dissappearance of starting material (ca. 8 h). The reaction mixture was diluted with water and extracted with ether, and the ether layers were dried ($MgSO_4$). Solvent evaporation gave the crude product, which was purified by flash column chromatography on silica gel, eluting with 10% ethyl acetate in hexane. The yield of **9** (mp 142 °C, recrystallized from ether-hexane) was 26 mg (72% yield): $[\alpha]^{23}_D$ -219° (*c* 1.5, ethanol) [lit.[10] $[\alpha]_D$ -302° (ethanol)]; ^{1}H NMR (300 MHz, $CDCl_3$) 7.02 (br s, 1 H), 6.25 (s, 1 H), 6.14 (s, 1 H), 5.49 (s, 1 H, exchangeable with D_2O), 3.85 (dd, J = 8.7, 3.3 Hz, 1 H), 3.76 (s, 3 H), 2.67 (dt, J = 16.2, 4.5 Hz, 1 H), 2.43 (t, J = 7.8 Hz, 2 H), 2.06-1.92 (br m, 3 H), 1.82 (dt, J = 11.7, 4.2 Hz, 1 H), 1.39 (s, 3 H), 1.32-1.26 (br m, 4 H), 1.12 (s, 3 H), 0.88 (t, J = 6.9 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 168.15, 155.28, 154.58, 142.97, 138.05, 130.95, 109.63, 109.43, 107.72, 76.03, 51.79, 44.16, 35.47, 31.53, 31.22, 30.55, 30.08, 28.53, 27.51, 22.52, 18.28, 13.99 ppm; IR ($CHCl_3$) 3405, 2960, 2940, 2860, 1715, 1695, 1630, 1580, 1440, 1270, 1190, 1075 cm^{-1}; mass spectrum, m/e 358 (M^+, 100), 302 (49), 283 (23), 231 (66), 193 (29), 69 (18); mass calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2165. As a further check of the optical purity of **9**, the Mosher ester was prepared from (*R*)-(+)-MTPA: ^{19}F NMR (CD_3COCD_3, 283 MHz, $CFCl_3$ used as reference) -71.236 (s, CF_3) ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.61-7.58 (m, 2 H), 7.34-7.29 (m, 3 H), 6.86 (br s, 1 H), 6.59 (s, 1 H), 6.49 (s, 1 H), 3.82 (s, 3 H), 3.64 (s, 3 H), 2.69 (br d, J = 8.4 Hz, 1 H), 2.52 (t, J = 7.5 Hz, 2 H), 2.35-2.25 (m, 1 H), 2.12 (dt, J = 9.6, 4.2 Hz, 1 H), 1.37 (s, 3 H), 1.33-1.24 (m, 6 H), 1.09 (s, 3 H), 0.88 (t, J = 5.4 Hz, 3 H) ppm.

Oxalate 10: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.04 (br t, J = 2.7 Hz, 1 H), 6.27 (s, 1 H), 6.12 (s, 1 H), 4.94 (s, 1 H, exchangeable with D_2O), 3.89 (s, 3 H), 2.67 (dt, J = 11.1, 4.2 Hz, 1 H), 2.45 (t, J = 6.3 Hz, 2 H), 2.19-2.05 (m, 2 H), 1.98-1.82 (m, 2 H), 1.40 (s, 3 H), 1.35-1.21 (m, 6 H), 1.13 (s, 3 H), 0.88 (t, J = 6.6 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 187.44, 164.79, 154.79, 154.59, 147.01, 143.29, 136.77, 110.03, 109.02, 107.82, 75.86, 52.50, 44.11, 35.44, 31.52, 30.76, 30.57, 29.37, 28.21, 27.47, 22.52, 18.27, 14.00 ppm; IR ($CHCl_3$) 3480, 2960, 2940, 2860, 1745, 1675, 1635, 1590, 1440, 1265, 1190, 1170, 1020 cm^{-1}; mass spectrum, m/e 386 (M^+, 7), 330 (8), 231 (6), 205 (10), 85 (33), 71 (53), 57 (100); mass calcd for $C_{23}H_{30}O_5$ 386.2093, found 386.2092.

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Registry No. **4**, 35408-03-8; **5**, 128660-91-3; **6**, 128660-92-4; **7**, 128660-93-5; **8**, 128660-94-6; **9**, 51263-84-4; **10**, 128660-95-7; CH_2=CHOEt, 109-92-2; olivetol, 500-66-3; olivetol bis(ethoxyethyl) ether, 125265-27-2.

Supplementary Material Available: Spectra for **5** and **7-9** (11 pages). Ordering information is given on any current masthead page.

1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione Ketals: Synthesis, Structural Analysis, and Complexation[1a]

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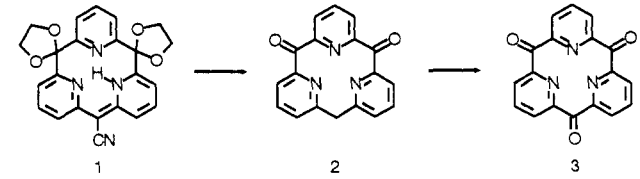
The synthesis, molecular distortions, and chemical behavior of 1,3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione ketals are described. The electron-deficient nature of the carbonyl bridges was confirmed by the facile addition of protic solvent to generate a stable hemiketal. The bridging methylene moiety of the carbonyl precursor exhibited novel chemical behavior, which results in a facile dimerization of a radical intermediate. X-ray structural analyses of the ketals and dimers afforded insight into the molecular deviations caused by changing the bond angles of the bridging carbon atoms.

Introduction

We have previously reported[2,3] the synthesis of tri- and tetraketo[2,6]pyridinophanes, which have N-electron-rich, highly rigid cavities comprised of only sp^2 ring atoms. Even though trione **3** should be essentially flat, deformations from planarity were observed, predominantly due to N,N,N-electron pair repulsions. The higher homologue, pyridinocalix[4]arene,[3,4] which is severly distorted from planarity, possesses a saddle shape with N-lone pairs pointing alternately above and below the best plane of the macrocycle. The contiguous electron-poor substituents instill a novel chemical behavior analogous to that experienced by the central carbonyl group in ninhydrin. We herein describe the preparation and reactivity these trione derivatives.

Scheme I



Results and Discussion

Trione 3. The initial C-bridged 2,6-pyridino macrocycle **1** was prepared (50%) in two steps from 2,6-bis(6-bromo-

(1) (a) Chemistry of Heterocyclic Compounds. Part 136. For previous part, see: Newkome, G. R.; Joo, Y. J.; Evans, D. W.; Pappalardo, S.; Fronczek, F. R. *J. Org. Chem.* **1988**, *53*, 786. (b) Address correspondence to: Center for Molecular Design and Recognition, Department of Chemistry, University of South Florida, Tampa, FL 33620. (c) Louisiana State University.

(2) Newkome, G. R.; Joo, Y. J.; Theriot, K. J.; Fronczek, F. R. *J. Am. Chem. Soc.* **1986**, *108*, 6074.

(3) Newkome, G. R.; Joo, Y. J.; Fronczek, F. R. *J. Chem. Soc., Chem. Commun.* **1987**, 854.

(4) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989; pp 62-69.

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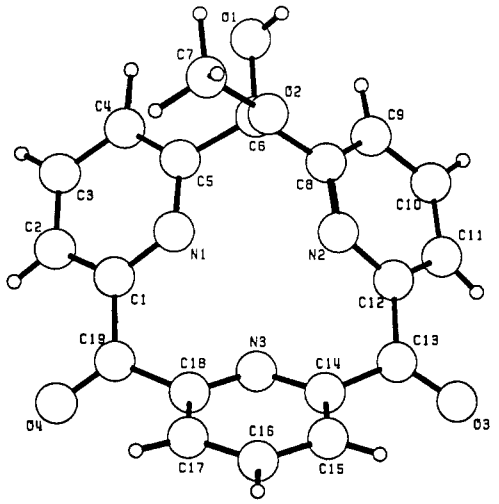
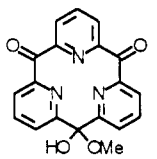


Figure 1. Hemiketal 4, illustrating the molecular conformation and numbering scheme. Important bond distances (Å) and angles (deg): C_{Ar}-C_{Ar} 1.378 (6); C-O 1.217 (5); C=O 1.498 (4); C-N-C 118.4 (3); N-C-C 122.4 (3); C-C-O 121.0 (3).

pyridinoyl)pyridine[5] via ketalization[6] and cyclization with $LiCH_2CN$, which was generated[7] from anhydrous CH_3CN with LiH in 5% TMEDA–toluene. Diketal 1 was hydrolyzed to give intermediate 2, which under the aerobic conditions was readily oxidized to give (60%) the desired trione 3, as colorless crystals (Scheme I). The ^1H and ^{13}C NMR data confirmed[2] the inherent symmetry for the trione, whereas the crystal structure exhibited approximate C_s symmetry in which two pyridines tip out-of-the-plane on one side of the macrocyclic plane, while the third tips in the opposite direction. In view of substituent distances ascertained from the crystal data, the structural deformation from planarity was attributed to repulsive N,N,N-electron interactions.

Hemiketal 4. The novel electronic and structural characteristics of trione 3 are illustrated by the easy formation of hemiketal 4. Recrystallization of 3 from MeOH during preliminary attempts to obtain a suitable single crystal gave 4 as the major product. Addition of protic solvents to a carbonyl possessing electron-attracting groups is a facile process[8] in that the ring strain and repulsive electronic interactions can in part be reduced. For example, Ortego et al. reported[9] that coordinated bis(2-pyridyl) ketone readily underwent 1,2-addition of water, alcohols, and certain amines to the C=O group. Furthermore, carbonyl addition in aqueous solution is pH dependent, with hydration occurring at pH values above ca. 6.5.[10]



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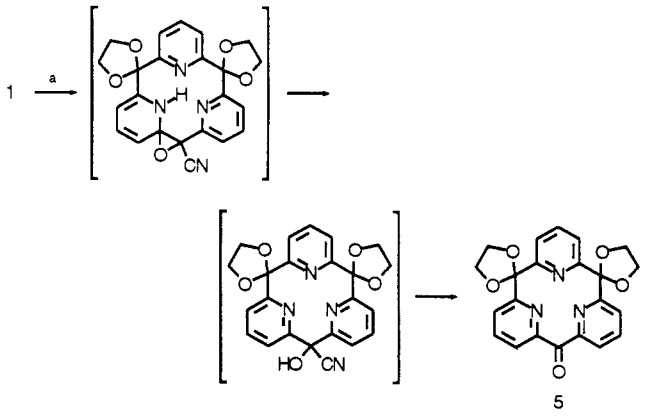
Scheme II[a]



[a] (a) m-$ClC_6H_4CO_3H$, $CHCl_3$, 0 °C, 5 h.

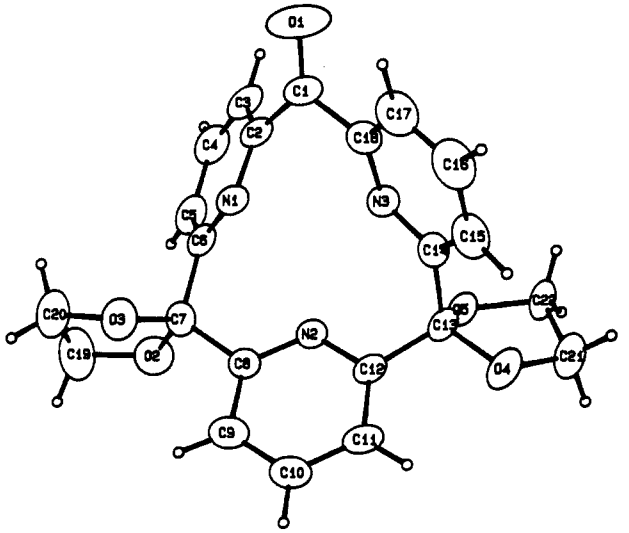


Figure 2. Diketal 5, illustrating the molecular conformation and numbering scheme for one of the two independent molecules in the crystal.

Molecular modeling[11] of 3 gave a minimized structure in close agreement with the crystal geometry, where the three N-lone pairs repel each other due to their directed juxtaposition. Such unfavorable N,N-interactions were further relieved during the facile formation of hemiketal 4, whose crystal structure[12] is illustrated in Figure 1. The molecular structure of 4 is severely distorted from a planar conformation similar to that described for 3. The two pyridine rings containing N1 and N2 tip out-of-the-plane on one side of the molecule, and the other pyridine (N3) tips in the opposite direction resulting in an approximate C_s symmetry in which a mirror plane contains N3 and the hemiketal carbon (C6). The N3 pyridine forms dihedral angles of 46.3° and 46.6° with the N1 and N2 rings, respectively; these angles are larger than those (35.4–46.5°) of the parent trione 3. However, the N1 pyridine ring is rotated away from the position anti to O1 and, thus, forms a dihedral angle of 73.4° with the N2 ring, similar to those of strained spiromacrocycles[6] containing 2,6-pyridino and polyethereal subunits. In the solid state, an intermolecular H-bond exists between the hemiketal hydrogen and O3 of

(5) Newkome, G. R.; Nayak, A.; Sauer, J. D.; Mattschei, P. K.; Watkins, S. F; Fronczek, F. R.; Benton, W. H. *J. Org. Chem.* **1979**, *44*, 3816.
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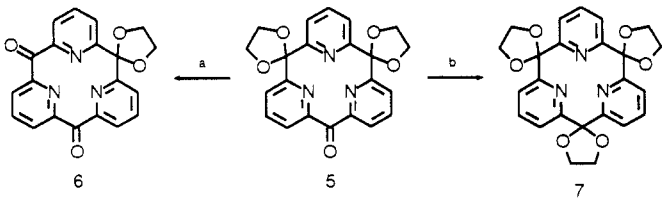
(7) (a) Friedrich, H. J.; Guckel, W.; Scheibe, G. *Chem. Ber.* **1962**, *95*, 1378. (b) Aksel'rod, Z. I.; Berezovski, V. M. *Russ. Chem. Rev.* **1970**, *39*, 627.
(8) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 783.
(9) Ortego, J. D.; Upalawanna, S.; Amanoilahi, S. *J. Inorg. Nucl. Chem.* **1979**, *41*, 595.
(10) Fischer, B. E.; Siegel, H. *J. Inorg. Nucl. Chem.* **1975**, *37*, 2127.
(11) QUANTA/CHARMm: Polygen Corporation, 200 Fifth Avenue, Waltham, MA.
(12) Crystal data for 4: $C_{19}H_{13}N_3O_4$, MW = 347.31, monoclinic space group $P2_1/n$, a = 13.125 (2) Å, b = 8.190 (3) Å, c = 15.872 (2) Å, β = 110.92 (1)°, Z = 4, D_c = 1.446 g cm^{-3}, R = 0.044 for 1549 observed reflections (1° < θ < 22.5°, Mo Kα).

Scheme III[a]



6 5 7

[a] (a) EtOH, HCl, Δ, 2 h; (b) $HOCH_2CH_2OH$, $C_6H_5CH_3$, H_2SO_4, Δ, 7 days.

the adjacent molecule at a distance of 2.08 Å.

1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione Mono-, Di-, and Triketal. Under rigorous hydrolysis, 1 was transformed to the desired trione via initial conversion of the nitrile to the acid, decarboxylation, followed by ketal hydrolysis and aerobic oxidation. Diketal **5** was prepared (68%) by oxidation of 1 with *m*-CPBA (Scheme II). The first step of the reaction probably involved an epoxidation[13] with *m*-CPBA to afford an intermediate, which can undergo epoxide cleavage to give a cyanohydrin, which eliminated HCN to afford (68%) diketal **5**. The ^1H NMR spectrum of **5** exhibited a singlet (8 H) at δ 4.24, indictive of two ketal methylenes, and a complex heteroaromatic region. The VT NMR spectral data for **5** supported the relative flexibility of the pyridine rings. The ^{13}C NMR spectrum showed 11 signals and the MS showed a molecular ion [*m*/*z* 404 (M^+ + 1) and 403 (M^+, 83)].

Figure 2 illustrates the molecular structure[14] of one of the two independent molecules of **5**. In both cases, the three pyridine rings deviate more from coplanarity than those of the parent trione **3**. The N1 (and N1′) pyridine forms dihedral angles of 125.6° (and 92.5°) with the N2 (and N2′) rings and 50.2° (and 45.8°) with the N3 (and N3′) rings, respectively, which in turn form a dihedral angle of 104.8° (and 126.6°) with each other. The major features of its solid-state conformation are described by several key torsion angles [C18–C11–C2–N1, 43.7(4)°; N1–C6–C7–C8, −51.6(4)°; and C12–C13–C14–N3, −65.4(3)°], which indicate that all three lone pairs of the pyridyl nitrogens are not directed into the cavity, where two nitrogens (N2, N3) tip up and the other tips below the plane of the molecule.

Subsequent partial deketalization of diketal **5** with alcoholic HCl gave (54%) the crystalline monoketal **6** (Scheme III). The ^1H NMR spectrum of **6** showed a singlet at δ 4.30 for two methylenes and a multiplet at δ 7.84–7.93. However, a triplet at δ 8.04 and a doublet at δ 8.28 are almost the same pattern as that observed for the triketone. Figure 3 illustrates the crystal structure[15] of monoketal **6**. The N3 pyridine forms dihedral angles of 40.0° and 42.2° with the N1 and N2 rings, respectively, which form a dihedral angle of 78.2° with each other. The carbonyl oxygen atoms are not exactly anti to pyridine nitrogen, with O–C–C–N torsion angle magnitude averaging 153.8°. The pyridine rings (N2 and N3) are turned with respect to the dioxolane ring such that the nitrogen atoms are essentially anti to oxygen (O3), with average O–C–C–N torsion angle magnitude 173.3°.

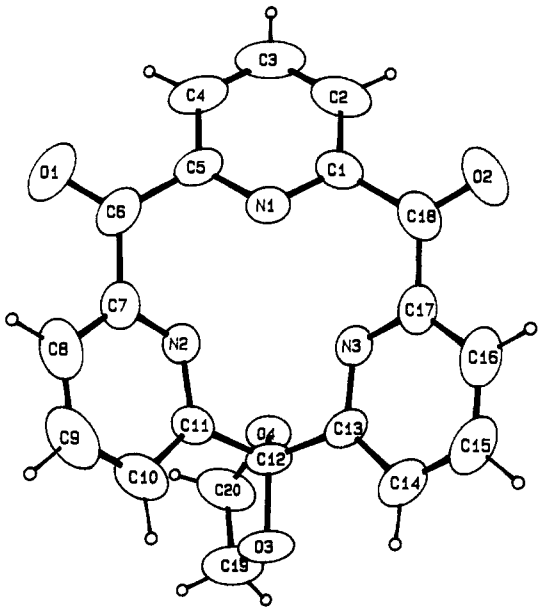


Figure 3. Monoketal **6**, illustrating the molecular conformation and numbering scheme.

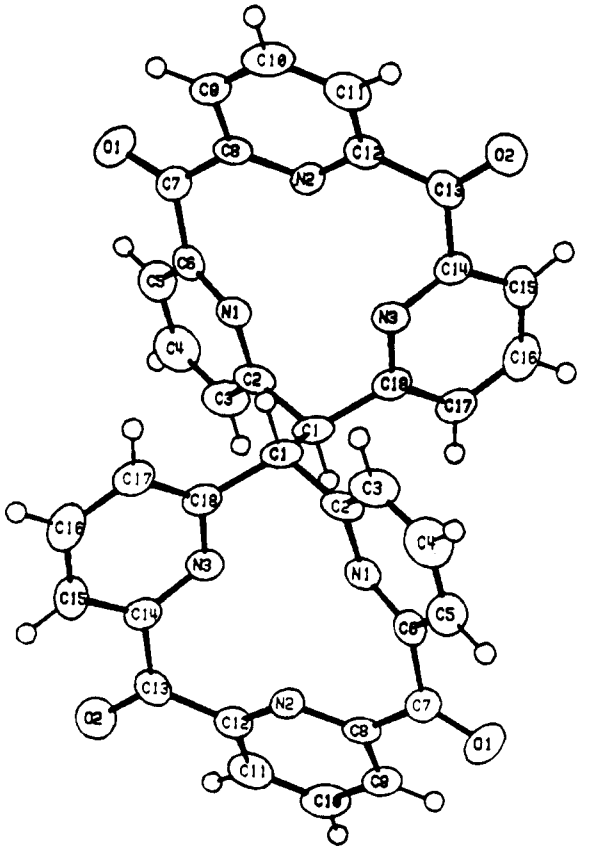


Figure 4. Molecular structure of dimer **8** showing one of the two independent molecules. Important bond distances (Å) and bond angles (deg): C1–C1, 1.531 (8); C1–C2, 1.516 (6); C1–C18, 1.524 (6); C5–C6–C7, 118.5 (4); C12–C13–C14, 119.0 (4); C2–C1–C18, 108.0 (4).

Triketal **7** was synthesized from **5** through traditional, albeit prolonged, ketalization techniques with freshly distilled ethylene glycol and a catalytic amount of concentrated H_2SO_4 in toluene using of a Dean–Stark trap. Triketal **7** is extremely insoluble in most common solvents. Although triketal **7** is only marginally soluble in $CDCl_3$, its ^1H NMR spectrum showed a singlet (12 H) at δ 4.27 for the methylenes and complicated peaks (9 H) between

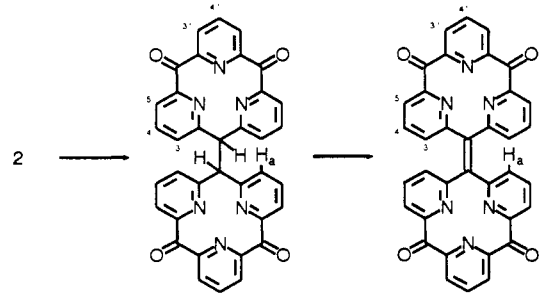
(13) (a) Linn, W. *J. Org. Chem.* **1969**, *49*, 103. (b) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; pp 292–321.

(14) Crystal data for **5**: $C_{22}H_{17}N_3O_5$, MW = 403.4, triclinic space group $P\bar{1}$, a = 10.3233 (12) Å, b = 11.209 (3) Å, c = 16.233 (2) Å, α = 81.939 (16)°, β = 89.056 (10)°, γ = 88.536 (15)°, Z = 4, D_c = 1.441 g cm^{-3}, R = 0.066 for 5690 observed reflections (2° < θ < 75°, Cu Kα).

(15) Crystal data for **6**: $C_{20}H_{13}N_3O_4$, MW = 359.3, orthorhombic space group $Pna2_1$, a = 6.8766 (15) Å, b = 15.5581 (9) Å, c = 15.5471 (16) Å, Z = 4, D_c = 1.435 g cm^{-3}, R = 0.042 for 1413 observed reflections (2° < θ < 75°, Cu Kα).

δ 7.71 and 7.93 for the heteroaromatic protons. The MS data exhibited peaks at m/z 488 ($M^+ + 1$, 10) and 447 (M^+, 39) for the molecular ion.

Dimer Formation. Ketal 1 was expected to generate the dione 2 under standard hydrolysis conditions. However, when the hydrolysis was conducted under an inert atmosphere, dimer 8 was isolated (80%) along with trione 3. The structural assignment of 8 was supported, in part,



8 9

by ^1H and ^{13}C NMR data, which suggested a high degree of symmetry and the presence of a unique alkyl carbon (δ 41.1) possessing a single proton (δ 5.66). The crystal structure[16] of 8 shown in Figure 4 afforded direct evidence for the dimeric structure and insight into the molecular deformations. The crystal possesses two independent molecules of 8, each lying on a center of symmetry, with only minor structural differences. Each tripyridine subunit has a conformation analogous to trione 3, yielding local C_s symmetry. In this case, the approximate mirror of this subunit is also a pseudosymmetry element of the entire molecule, which has overall local symmetry C_{2h}. The pyridine rings containing N1, N2, and N3 form the following dihedral angles with each other: N1/N2, 37.7°; N1/N3, 75.3°; N2/N3, 41.7°. In the second molecule, these dihedral angles are 37.1°, 63.7°, and 36.5°, respectively. The rings themselves exhibit small deviations from planarity, with the N-atom generally having the largest deviation (0.029 Å average).

Dehydrogenation of 8 was effected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene to afford (87%) the ethylene bridged 9, as colorless crystals. The ^1H NMR spectral data for 9 supported the symmetrical structure similar to 8, except for the downfield ($\Delta\delta$ = 0.33) shift of H_a due to their juxtaposition to the neighboring π-system.[17] The X-ray structure of 9[18] indicates that the molecule lies on a center of symmetry and has approximate C_{2h} symmetry. The disposition of the pyridyl rings is analogous to 8 in which the dihedral angles between planes of pyridine rings are N1/N2, 32.6°; N1/N3, 61.9°; and N2/N3, 32.5°; N-deviations from these best planes average 0.022 ± 0.004 Å. The central olefinic bond has length 1.360 (7) Å.

Alternatively, a $CHCl_3$ solution of dimer 8 was aerated at 25 °C for 7 days to give 9 in quantitiative yeild. Both

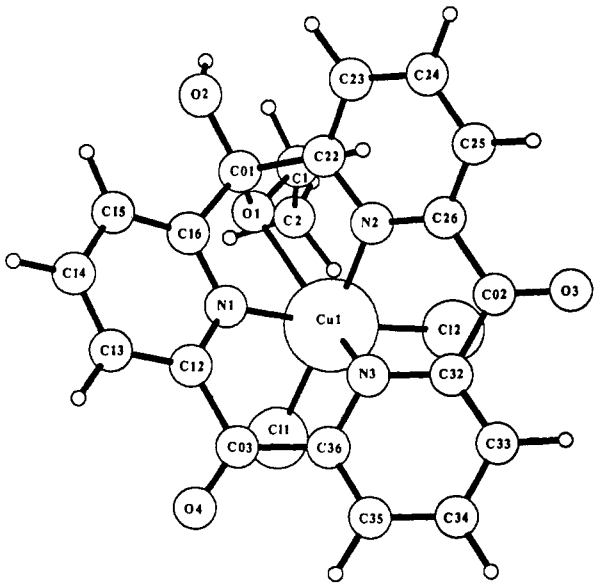


Figure 5. Complex 4·$CuCl_2$·EtOH, illustrating the molecule configuration and numbering scheme.

8 and 9 were readily oxidized with SeO_2 in glacial acetic acid to afford (>80%) trione 3. Hydrolysis of 1 under strictly anaerobic conditions afforded the crude diketone 2, which was unstable, and was directly oxidized with SeO_2 to afford trione 3 in 65% overall yield from 1. Attempted recrystallization of crude 2 gave a mixture comprised of dione 2 (δ 4.40; CH_2), trione 3, and 8 in variable yields depending on solvent and dissolution times. In view of the lability of the α-alkyl hydrogen in both 2 and 8, a radical intermediate, which in the former can couple to give the dimer, or in the latter can be trapped with oxygen to generate a hydroperoxide intermediate that leads to the ketone or olefin, respectively, is most reasonable.[19]

Transition-Metal Complexation of Trione 3. Inspection of a CPK molecular model of trione 3, as well as NMR and crystal data, indicated that it probably could form "sandwich"-type transition-metal complexes, similar to tribenzo[*b,f,j*][1,5,9]triazacycloduodecine.[20] The slight conformational mobility and potential directed N-electron density in the cavity should facilitate complexation.

Treatment of 3 with $CuCl_2$ in anhydrous EtOH/$CHCl_3$ gave initially a pale green solution, which was refluxed under an inert atmosphere for 8 h. Crystals grown from this solution quickly clouded, probably due to solvent loss. To circumvent this problem, slow evaporation of EtOH/$CHCl_3$ from the complex afforded large, dark green crystals suitable for an X-ray structure determination.

The crystals[21] were shown (Figure 5) to be the Cu(II) complex of a neutral hemiketal. The Cu(II) coordination sphere exhibits a distorted octahederal array of the three nitrogen atoms, two chloride ions, and one hemiketal oxygen atom. The hemiketal ligand, which arose from the conversion of strained trione 3 during reaction in EtOH/$CHCl_3$, is severely distorted from a planar conformation. The planar pyridine rings make dihedral angles of 64.2° (N1–N2), 33.0° (N1–N2), and 35.5° (N2–N3). The

(16) Crystal data for 8: $C_{36}H_{20}N_6O_4$, MW = 600.6, triclinic $P\bar{1}$, a = 8.2009 (8) Å, b = 10.0829 (12) Å, c = 17.6076 (14) Å, α = 91.493 (8)°, β = 100.188 (8)°, γ = 95.061 (10)°, V = 1426.1 (5) Å^3, D_c = 1.399 g cm^{-3}, μ(Mo Kα) = 0.88 cm^{-1}, R = 0.073 for 2306 data having $I > \sigma(I)$, 1° < θ < 23°, μ(Mo Kα), λ = 0.71073 Å, 416 variables. Two independent molecules lying on centers of symmetry.

(17) Bailey, N. A.; Hull, E. *J. Chem. Soc., Chem. Commun.* **1971**, 960. Rabinovitz, M.; Agranat, I.; Bergmann, E. D. *Tetrahedron Lett.* **1965**, 1265.

(18) Crystal data for 9: $C_{36}H_{18}N_6O_4$·4$CHCl_3$, MW = 1076, monoclinic $P2_1/c$, a = 7.2001 (5) Å, b = 10.6962 (15) Å, c = 29.371 (5) Å, β = 94.439 (8)°, V = 2255 (2) Å^3, D_c = 1.585 g cm^{-3}, μ(Cu Kα) = 73.34 cm^{-1}, R = 0.066 for 2283 data having $I > 3\sigma(I)$, 2° < θ < 70°, Cu Kα, λ = 1.54184 Å, 317 variables.

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(21) Crystal data for Cu(II) complex: $C_{22}H_{21}N_3O_5Cl_2Cu$: MW = 541.5, monoclinic space group $P2_1/c$, a = 9.294 (5) Å, b = 28.014 (6) Å, c = 9.799 (3) Å, β = 114.48°, Z = 4, D_c = 1.549 g cm^{-3}, R = 0.085 for 2257 observed reflections (1° < θ < 25°, Mo Kα).

three nitrogens of the pyridine rings are coordinated; the bond lengths of Cu–N1 and Cu–N2 are 2.033 (9) Å and 2.022 (8) Å, respectively; however, the Cu–N3 bond length is 2.362 (10) Å. The two "nondistorted" pyridine rings are tilted 55.0 and 53.5° out of the plane of the CuN_2Cl_2 plane. Distortion of the octahedral geometry by axial elongation results in a Cu–hemiketal O1 distance 2.468 (8) Å indicative of the relatively weak interaction. Axial elongation also permits chelation to occur with "bite" angles of 83.6 (4)° for N1–Cu–N2, 76.3 (4)° for N1–Cu–N3, and 77.2 (4)° for N2–Cu–N3; Cu–N bonds are tilted slightly away from the pyridine rings. The Cl1–Cu–Cl2 angle is 95.5 (2)° and Cu–Cl lengths are 2.228 (3)/2.253 (3) Å.

The solvent molecule in the complex was highly disordered, preventing a well-refined model from being obtained. Thus, the hemiketal OH appeared to be pointing toward an adjacent solvent molecule (O5), but the uncertainties of these positions make any statement as to the existence of a H-bond unrealistic.

The X-ray data have afforded direct evidence to the "noncone" conformation[4] in the free pyridacalix[3]arene ligands. The "cone" conformation was demonstrated for the metal complex of **4**, thus conformational mobility in solution is possible. A more detailed study of the dimers, their polymerization, and their electron-transfer reactions and complexation are presently in progress.

Experimental Section

General. All melting points were taken in capillary tubes and are uncorrected. The ^1H NMR spectra were measured at 80, 200, or 400 MHz using $CDCl_3$ as solvent, except where noted. ^{13}C NMR spectra were determined at 20 or 50 MHz; the middle peak of the $CDCl_3$ triplet (δ 77.0) was used as reference. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The X-ray intensity data were collected by ω–2θ scans on Enraf-Nonius CAD4 diffractometers equipped with Mo Kα (λ = 0.710 73 Å) or Cu Kα (λ = 1.541 84 Å) radiation and graphite monochromators. Structures were solved using MULTAN, SHELX, and the Enraf-Nonius Structure Determination Package and refined by full-matrix least-squares methods based on F with weights $w = \sigma^{-2}(F_o)$. Non-hydrogen atoms were refined anisotropically; hydrogen atoms were included as fixed contributions, except for the pyridinyl H-atoms of **6**, which were refined isotropically.

19,20,21-Triazatetracyclo[13.3.1.1^{3,7}.1^{9,13}]heneicosa-1-(19),3,5,7(20),9,11,13(21),15,17-nonaene-2,8,14-trione or 1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione (3). Method A. A stirred mixture of diketal **1** (110 mg, 0.3 mmol; mp 268–269 °C)[2] in concentrated HCl (20 mL) was refluxed under aerobic conditions for 36 h. Additional concentrated HCl (10 mL) was added four times in ca. 8-h intervals. The solution was neutralized carefully with solid NaOH, extracted with $CHCl_3$, dried over anhydrous $MgSO_4$, concentrated in vacuo, and column chromatographed (SiO_2), eluting with $CHCl_3$/EtOH to give the crude product, which was recrystallized ($CHCl_3$/EtOH) to afford (60%) trione **3**, as colorless crystals: 52 mg; mp 236–236.5 °C; ^1H NMR δ 8.12 (dd, 4-pyH, $J_{3,4} = J_{4,5}$ = 7.9 Hz, 3 H), 8.34 (d, 3,5-pyH, J = 7.9 Hz, 6 H); ^{13}C NMR δ 126.7 (C3), 138.0 (C4), 152.9 (C2), 188.1 (C=O); IR (KBr) 1667 cm^{-1}; MS m/z 316 (M^+ + 1, 21) 315 (M^+, 100); UV (MeCN) λ 227 nm (log ϵ = 4.43), 250 (sh, 4.32); (MeOH) 201 (4.43), 215 (sh, 4.36), 245 (sh, 4.11), 270 (sh, 4.04). Anal. Calcd for $C_{18}H_9N_3O_3$: C, 68.57; H, 2.88; N, 13.33. Found: C, 68.17; H, 2.87; N, 13.11.

Method B. A stirred mixture of **2** (680 mg, 2.3 mmol) and sublimed SeO_2 (800 mg) in glacial AcOH (50 mL) was refluxed for 8 h. After filtration through Celite, the solvent was removed in vacuo to give the colorless trione **3**, which was column chromatographed on SiO_2, eluting with $CHCl_3$/EtOH, affording a solid. Recrystallization from $CHCl_3$/EtOH gave (65% from **1**) pure trione **3**, identical in all respects to that made from method A.

1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione Ethylene Glycol Diketal (5). A stirred mixture of *m*-chloroperbenzoic acid (200 mg, 1.0 mmol, 85%) and **1** (380 mg, 0.9 mmol) in $CHCl_3$ (50 mL) was maintained at 0 °C for 5 h. The colorless solution was washed with saturated aqueous $NaHCO_3$ and then saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give a solid, which was recrystallized from $CHCl_3$/EtOH to afford (68%) **5**, as colorless crystals: 250 mg; mp 280 °C dec; ^1H NMR δ 4.24 (s, ketal CH_2, 8 H), 7.47–7.95 (m, ArH); ^{13}C NMR δ 65.9 (CH2), 107.7 (OCO), 119.4 (C3′), 122.2 (C5), 122.7 (C3), 136.2 (C4′), 136.6 (C4), 153.6 (C2′), 157.8 (C6), 158.1 (C2), 192.1 (C=O); MS m/z 404 (M^+ + 1, 20), 403 (M^+, 83), 360 ($M^+ - C_2H_3O$, 23), 332 ($M^+ - C_3H_3O_2$, 63), 316 ($M^+ - C_4H_7O_2$, 14), 288 ($M^+ - C_6H_7O_2$, 100). Anal. Calcd for $C_{22}H_{17}N_3O_5 \cdot {}^1/_2H_2O$: C, 64.07; H, 4.40; N, 10.19. Found: C, 63.97; H, 4.34; N, 9.91.

1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione Ethylene Glycol Monoketal (6). A stirred mixture of diketal **5** (250 mg, 0.6 mmol) in concentrated HCl (5 mL) and EtOH (50 mL) was refluxed for 2 h. The resulting solution was carefully neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo, affording a colorless solid, which was recrystallized ($CHCl_3$/EtOH) to give (54%) monoketal **6**, as colorless needles: 120 mg; mp 235 °C dec; ^1H NMR δ 4.30 (CH_2, 4 H), 7.84–7.98 (m, 3′,4′,5′-pyH, 6 H), 8.07 (t, 4-pyH, J = 7.5 Hz, 1 H), 8.28 (d, 3-pyH, J = 7.5 Hz, 2 H); MS m/z 360 (M^+ + 1, 9), 359 (M^+, 34), 288 ($M^+ - C_3H_3O_2$, 100). Anal. Calcd for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.65; N, 11.69. Found: C, 66.72; H, 3.55; N, 11.78.

1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione Ethylene Glycol Triketal (7). A stirred toluene (50 mL) solution of diketal **5** (10 mg, 0.3 mmol), freshly distilled ethylene glycol (2 mL), and concentrated H_2SO_4 (3 drops) was refluxed for 7 days. The cooled solution was concentrated in vacuo, and the residue was dissolved in $CHCl_3$ (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and then saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a slightly yellow triketal **7**. Further purification was unsuccessful due to extremely low solubility in common organic solvents: mp 280 °C dec; ^1H NMR δ 4.27 (s, CH_2, 12 H), 7.71–7.93 (m, pyH, 9 H); MS m/z 448 (M^+ + 1, 10), 447 (M^+, 39), 404 ($M^+ - C_2H_3O_2$, 27), 360 ($M^+ - C_4H_7O_4$, 13), 332 ($M^+ - C_5H_7O_5$, 51).

19,20,21-Triazatetracyclo[13.3.1.1^{3,7}.1^{9,13}]heneicosa-1-(19),3,5,7(20),9,11,13(21),15,17-nonaene-2,8-dione (2). A mixture of **1** (720 mg, 1.7 mmol) in concentrated HCl (25 mL) in EtOH (25 mL) was refluxed under anerobic conditions for 5 h. The colorless solution was cooled to 0 °C and neutralized with solid NaOH and extracted with $CHCl_3$. The combined extract was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$. After concentration, the resulting solid was recrystallized from CH_2Cl_2/EtOH to afford diketone **2**, which was unstable (easily oxidized to **3**): ^1H NMR δ 4.40 (s, CH_2, 2 H), 6.99–8.41 (m, pyH, 2 H); MS m/z 302 (M^+ + 1, 21), 301 (M^+, 100), 272 (M^+ – CHO).

2,2′-Bis[19,20,21-triazatetracyclo[13.3.1.1^{3,7}.1^{9,13}]heneicosa-1-(19),3,5,7(20),9,11,13(21),15,17-nonaene-8,14-dione] (8). A mixture of **1** (470 mg, 1.1 mmol) in concentrated HCl (10 mL) and EtOH (10 mL) was refluxed for 7 h. The resulting colorless solution was cooled to 0 °C and neutralized with solid NaOH and extracted with $CHCl_3$. The extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a solid, which was column chromatographed (SiO_2 eluting with $CHCl_3$/EtOH, then 10% AcOH/EtOH) and recrystallized to afford (80%) pure dimer **8**, as colorless crystals: 380 mg; mp 250 °C dec; ^1H NMR δ 5.66 (s, CHCH, 2 H), 7.02 (dd, 3-pyH, J = 7.5, 1.1 Hz, 4 H), 7.46 (t, 4-pyH, J = 7.5 Hz, 4 H), 7.71 (dd, 5-pyH, J = 7.5, 1.1 Hz, 4 H), 8.13–8.40 (m, 3′,4′-pyH, 6 H); ^{13}C NMR δ 41.1 (CH), 121.5 (C3), 125.9, 126.6 (C3′,5), 136.5 (C4), 137.9 (C4′), 147.1 (C2), 153.0, 153.1 (C2′,6), 187.9 (C=O); MS m/z 601 (M^+ + 1, 30), 600 (M^+, 77), 301 ($M^+/2$ + H, 100). Anal. Calcd for $C_{36}H_{20}N_6O_4 \cdot {}^1/_2H_2O$: C, 70.93; H, 3.47; N, 13.93. Found: C, 70.47; H, 3.51; N, 13.68.

$\Delta^{2,2'}$-Bis[19,20,21-triazatetracyclo[13.3.1.1^{3,7}.1^{9,13}]heneicosa-1(19),3,5,7(20),9,11,13(21),15,17-nonaene-8,14-dione]. Method A. A stirred solution of **8** (49 mg, 80 μmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (54 mg, 240 μmol) in dry toluene (30 mL) was refluxed for 23 h under an inert atmosphere. The mixture was cooled, and the solid was filtered and then washed with toluene. The combined toluene extract was washed with

aqueous saturated Na_2CO_3 and then aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a residue which was recrystallized from $CHCl_3$ to give (87%) pure olefin **9**, as colorless crystals: 43 mg; mp 410 °C dec; ^1H NMR δ 7.35 (dd, 3-pyH, J = 7.6, 1.2 Hz, 4 H), 7.62 (t, 4-pyH, J = 7.6 Hz, 4 H), 7.96 (dd, 5-pyH, J = 7.6, 1.1 Hz, 4 H), 8.15 (dd, 4'-pyH, $J_{3',4'} = J_{4',5'}$ = 7.8 Hz, 2 H), 8.42 (dd, 3'-pyH, J = 7.8, 1.1 Hz, 4 H); MS m/z 598 (M^+, 3), 597 ($M^+ - H$, 4), 301 ($M^+/2 + 2H$, 100). Anal. Calcd for $C_{36}H_{18}N_6O_4 \cdot {}^1/_2CHCl_3$: C, 66.60; H, 2.83; N, 12.77. Found: C, 67.04; H, 2.55; N, 12.92.

Method B. A stirred solution of dimer **8** (105 mg, 170 μmol) in $CHCl_3$ was aerated for 7 days. The solvent was removed in vacuo to give (99%) pure **9** (103 mg): mp 408 °C dec.

Cu(II) Complexation of Trione 3. To a stirred solution of **3** (15.8 mg, 0.05 mmol) in boiling EtOH (10 mL) was added a solution of anhydrous $CuCl_2$ (0.05 mmol) in EtOH (10 mL). The mixture was refluxed under a N_2 atmosphere for 12 h and then stirred at 25 °C for an additional 12 h, during which time a green precipitate formed. The solid was filtered, washed with EtOH, and recrystallized from EtOH/$CHCl_3$ to afford large dark green crystals. Anal. Calcd for $C_{20}H_{15}N_3O_4 \cdot CuCl_2 \cdot {}^1/_2CHCl_3$: C, 44.32; H, 2.81; N, 7.56. Found: C, 44.09; H, 2.84; N, 7.73.

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Supplementary Material Available: Tables of atomic coordinates, coordinates of hydrogen atoms, bond lengths, and bond angles for **4**, **5**, **6**, **4**·$CuCl_2$·EtOH complex, dimer **8**, and olefin **9** (25 pages). Ordering information is given on any current masthead page.

Synthesis of Pyrrolizidines and Indolizidines by the Intramolecular Cycloaddition of Azides with Electron-Rich 1,3-Dienes. A Synthetic Equivalent of a Nitrene–Diene Cycloaddition

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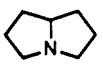
Alkyl azides were found to undergo intramolecular cycloadditions with certain 1,3-dienes to provide 2,3,5,7a-tetrahydro-1*H*-pyrrolizines and 3,5,6,7,8,8a-hexahydroindolizines in one operation (e.g., **12** → **13** and **17** → **18**). The presence of an electron-donating group on the diene (sulfur, selenium, or oxygen) was required to avoid alternative rearrangement processes. The cyclization of chiral azidodienes proceeded with high diastereoselectivity to produce materials that are closely related to several alkaloidal natural products. New methods for the synthesis of the requisite heterosubstituted 1,3-dienes were developed.

Many classes of alkaloids have either a pyrrolizidine (**1**) or indolizidine (**2**) skeleton as a key structural element.[1-3] A general, flexible, and efficient route to such a subunit would obviously be useful.



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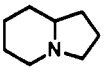
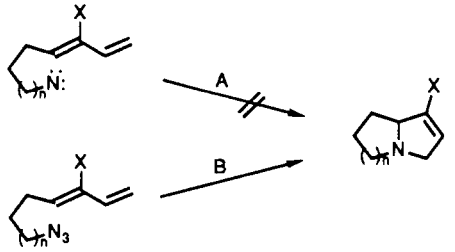


2

Perhaps the most efficient ring constructions are those that form more than one bond in a single operation. We have chosen to study a [4 + 1] approach[4] to the pyrroline ring of **1** and **2**. A conceptually simple approach would be an intramolecular nitrene–diene cycloaddition[5] (eq 1, pathway A). Realizing that the use of alkylnitrenes is unsatisfactory,[6] and that more stabilized nitrenes form aziridines with dienes rather than produce the desired 3-pyrrolines,[7-9] we have focused on developing a formal equivalent of this transformation. Herein we report the details of our basic studies on a synthetic equivalent of a nitrene–diene cycloaddition (eq 1, pathway B). The intramolecular cycloaddition of aliphatic azides with certain electron-rich 1,3-dienes directly provides 2,3,5,7a-tetra-



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‡ Department of Medicinal Chemistry.

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