Macrocyclic Inclusion Complexes.[1a,b] Synthesis, X-ray Structural Analysis, and Formation of Mono- and Dinuclear Transition-Metal Complexes of Dipyridino Crown Ethers

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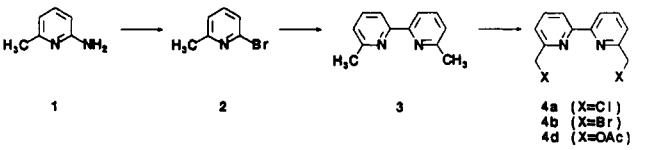
The synthesis of crown ether derivatives containing the dipyridino subunit is described. Direct nucleophilic displacement by the glycolates of di-, tri-, tetra-, penta-, and hexaethylene glycol on 6,6′-bis(chloromethyl)-2,2′-dipyridine resulted in an extensive series of macrocycles; the addition of Co(II), Cu(II), Zn(II), and Pd(II) salts to the 1:1- and 2:2-macrocycles generated the corresponding complexes. X-ray crystallography confirmed the structure of the 2:2-macrocycle derived from diethylene glycol as well as the related unsymmetrical derivative arising from glycol fragmentation. The ligands were fully characterized by ^{1}H NMR spectroscopy, and a europium shift study was conducted on a representative 1:1-macrocycle in order to establish the preferred site of complexation.

Introduction

Since our entry into the field of polyfunctionalized macrocycles,[2] one of our primary objectives has been the design of molecules possessing tailored internal cavities which can encapsulate a specific metal ion[3] and neutral organic guest.[4] In general, the "crown ether" macrocycles with two-dimensional circular cavities have been widely studied[5] with respect to their complexation of predominantly alkali and alkaline earth metals and ammonium salts; the occurrence of transition-metal inclusion is less frequent. The incorporation of a 2,6-pyridino moiety into a polyethereal macrocycle augmented the alkali and alkaline earth metal complexing ability, whereas introduction of the 2,2′-dipyridino or polypyridino subunit would increase the propensity of the macrocycle to bind transition-metal ions. Although there are now examples of macrocycles which incorporate the 2,2′-dipyridino moiety, the Schiff base[6] or bis-lactam[7] variety predominate due to the availability of the respective dialdehyde or diacid starting materials. Only recently has facile methyl functionalization[8] of substituted bipyridyl progressed to the point where they can be readily prepared and easily incorporated[9] into a macrocyclic framework by direct nucleophilic displacement.

Scheme I



In view of the interest in mono- and dinuclear complexes which can model metalloproteins,[10] the synthesis of 1:1-

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(2) Newkome, G. R.; Robinson, J. M. *J. Chem. Soc., Chem. Commun.* **1973**, 831.

(3) Newkome, G. R.; Kohli, D. K.; Fronczek, F. R.; Hales, B. J.; Case, E. E.; Chiari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7608.

(4) Newkome, G. R.; Taylor, H. C. R.; Fronczek, F. R.; Delord, T. J.; Kohli, D. K.; Vögtle, F. *J. Am. Chem. Soc.* **1981**, *103*, 7376. (b) Newkome, G. R.; Fronczek, F. R.; Kohli, D. K. *Acta Crystallogr.* **1981**, *B37*, 2114. (c) Newkome, G. R.; Pappalardo, S.; Gupta, V. K.; Fronczek, F. R. *J. Org. Chem.* **1983**, *48*, 4848. (d) Weber, E.; Newkome, G. R.; Fronczek, F. R.; Franken, S. *J. Inclusion Phenom.* **1988**, *6*, 1.

(5) (a) Izatt, R. M.; Christensen, J. J. *Synthetic Multidentate Macrocyclic Compounds*; Academic Press: New York, 1978. (b) *Progress in Macrocyclic Chemistry*; Izatt, R. M., Christensen, J. J., Eds.; Wiley-Interscience: New York, 1979; Vol. 1. (c) *Ibid.* 1987; Vol. 3. (d) Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Chem. Rev.* **1974**, *74*, 351. (e) Christensen, J. J.; Hill, J. O.; Izatt, R. M. *Science* **1971**, *174*, 459. (f) Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513. (g) Majestic, V. K.; Newkome, G. R. *Top. Curr. Chem.* **1982**, *106*, 79. (h) Newkome, G. R.; Gupta, V. K.; Sauer, J. D. in *Pyridine and Its Derivatives*; Newkome, G. R., Ed.; Wiley-Interscience: New York, 1984; Part 5, Chapter 3, pp 447–633. (i) Cram, D. J.; Cram, J. J. *Acct. Chem. Res.* **1978**, *11*, 8. (j) Cram, D. J. *Science* **1988**, *183*, 760.

(6) (a) Lewis, J.; Wainwright, K. P. *J. Chem. Soc., Chem. Commun.* **1974**, 169. (b) Hague, Z. P.; Liles, D. C.; McPartlin, M.; Tasker, P. A. *Inorg. Chim. Acta* **1977**, *23*, L21. (c) Hague, Z. P., McPartlin, M.; Tasker, P. A. *Abstracts of Papers*; American Chemical Society–Chemical Society of Japan Chemical Congress, Honolulu, HI, April 1979; INORG 297. (d) Bishop, M. M.; Lewis, J.; O'Donoghue, T. K.; Raithby, P. R. *J. Chem. Soc., Chem. Commun.* **1978**, 476. (e) Bishop, M. M.; Lewis, J.; O'Donoghue, T. D.; Raithby, P. R.; Ramsden, J. N. *J. Chem. Soc., Chem. Commun.* **1978**, 828. (f) Constable, E. C.; Lewis, J.; Liptrot, M. C.; Raithby, P. R. *J. Chem. Soc., Dalton Trans.* **1984**, 2177. (g) Constable, E. C.; Holmes, J. M. *Polyhedron* **1988**, *7*, 2531.

(7) (a) Buhleier, E.; Wehner, W.; Vögtle, F. *Chem. Ber.* **1978**, *111*, 200. (b) Belser, P.; DeCola, L.; v. Zelewsky, A. *J. Chem. Soc., Chem. Commun.* **1988**, 1057.

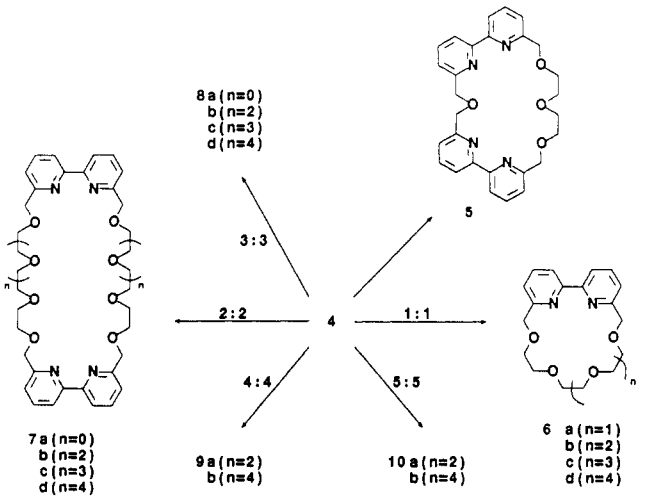
(8) (a) Kauffmann, Th.; König, J.; Woltermann, A. *Chem. Ber.* **1976**, *109*, 3864. (b) Newkome, G. R.; Puckett, W. E.; Kiefer, G. E.; Gupta, V. K.; Xia, Y.; Coreil, M.; Hackney, M. A. *J. Org. Chem.* **1982**, *47*, 4116. (c) Pijper, P. J.; Goot, H. v. d.; Timmerman, H.; Nauta, W. Th. *Eur. J. Med. Chem., Chim. Ther.* **1984**, 399. (d) Newkome, G. R.; Kiefer, G. E.; Xia, Y.-J.; Gupta, V. K. *Synthesis* **1984**, 676. (e) Rode, T.; Breitmaier, E. *Synthesis* **1987**, 574.

(9) (a) Buhleier, E.; Vögtle, F. *Ann. Chem.* **1977**, 1080. (b) Newkome, G. R.; Nayak, A.; Fronczek, F. R.; Kawato, T.; Taylor, H. C. R.; Meade, L., Mattice, W. *J. Am. Chem. Soc.* **1979**, *101*, 4472. (c) Newkome, G. R.; Kohli, D. K.; Fronczek, F. R. *J. Chem. Soc., Chem. Commun.* **1980**, 9. (d) Pappalardo, S.; Bottino, F.; Finocchiaro, P.; Mamo, A. *J. Polym. Sci., Part A, Polym. Chem.* **1987**, *25*, 1793. (e) Grammenudi, S.; Vögtle, F. *Angew. Chem.* **1986**, *98*, 1119. (f) Rebek, J., Jr.; Luis, S. V.; Marshall, L. R. *J. Am. Chem. Soc.* **1986**, *108*, 5011. (g) Rebek, J., Jr. *Acct. Chem. Res.* **1984**, *17*, 258. (h) Kim, W. K.; Chung, S. R. *J. Korean Chem. Soc.* **1985**, *29*, 205. (i) Weber, E.; Josel, H.-P.; Puff, H.; Franken, S. *J. Org. Chem.* **1985**, *50*, 3125. (j) Katz, H. D. *Tetrahedron Lett.* **1984**, *25*, 4905. (k) Rodriguez-Ubis, J.-C.; Alpha, B.; Plancherei, D.; Lehn, J.-M. *Helv. Chim. Acta* **1984**, *67*, 2264. (l) Bottino, F.; DiGrazia, M.; Finocchiaro, P.; Fronczek, F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521. (m) Pappalardo, S.; Bottino, F.; DiGrazia, M.; Finocchiaro, P.; Mamo, A. *Heterocycles* **1985**, *23*, 1881. (n) Chambron, J.-C.; Sauvage, J.-P. *Tetrahedron* **1987**, *43*, 895; *Tetrahedron Lett.* **1986**, *27*, 865. (o) Alpha, B.; Lehn, J.-M.; Mathis, G. *Angew. Chem.* **1987**, *99*, 1254. (p) Abraham, R. J.; Leighton, P.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1985**, *107*, 3472. (q) Rebek, J., Jr.; Costello, T.; Wattley, R. *J. Am. Chem. Soc.* **1985**, *107*, 7487. (r) Alpha, B.; Anklam, E.; Deschenaux, R.; Lehn, J.-M.; Pietraskiewicz, M. *Helv. Chim. Acta* **1988**, *71*, 1042. (s) Lehn, J.-M.; Schmidt, F.; Vigneron, J.-P. *Tetrahedron Lett.* **1988**, *29*, 5255. (t) Dürr, H.; Zengerle, K.; Trierweiler, H.-P. *Z. Naturforsch.* **1988**, *43b*, 361. (u) DeCola, L.; Barigelletti, F.; Balzani, V.; Belser, P.; von Zelewsky, A.; Vögtle, F.; Ebmeyer, F.; Grammenudi, S. *J. Am. Chem. Soc.* **1988**, *100*, 7210. (v) Grammenudi, S.; Vögtle, F.; Franke, M.; Steckhan, E. *J. Inclusion Phenom.* **1987**, *5*, 695. (w) Vögtle, F. *Supramolekulare Chemie*; B. G. Teubner: Stuttgart, 1989; Chapter 2. (x) Campa, C.; Camps, J.; Font, J.; DeMarch, P. *An. Quim.* **1988**, *88C*, 128. (y) Gu, K.; Martes, K. B.; Mertes, M. P. *Tetrahedron Lett.* **1989**, *30*, 1323.

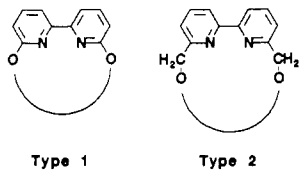
(10) (a) Ostfield, D.; Tsutsui, M. *Acct. Chem. Res.* **1974**, *7*, 52. (b) Tsutsui, M. *Pure Appl. Chem.* **1978**, *50*, 735.

0022-3263/89/1954-5105$01.50/0

Scheme II



and 2:2-bis(2,2′-dipyridino) macrocycles was undertaken. Our initial dipyridino crowns (type 1) were shown to be poor metal chelating agents; however, positive observations were realized from the preliminary studies including: (1) insight into the temperature dependent conformational mobility of crown ethers,[9b,11] and (2) structural constraints in cyclophanes.[12] In order to circumvent the structural problems associated with type 1 ligands, type 2 ligands were constructed and evaluated with respect to their ability to form two-dimensional dinuclear "tête-à-tête complexes". We herein report the synthesis, complexation, and structural analyses of representative 1:1- and 2:2-ligands and their corresponding complexes.



Results and Discussion

A. Ligand Formation. The pivotal starting material for ligand synthesis was the difunctional 6,6′-bis(chloromethyl)-2,2′-dipyridine (**4a**), which was prepared via a simple three-step procedure from a readily available, inexpensive amine **1** (Scheme I), as previously described.[8a] The herein reported chlorination of **3** with NCS gave **4a** in typically 75% yield, whereas the related bromo derivative **4b** has been prepared (23%,[9t] 59%[9k]) via NBS bromination.[9t] Alternatively, the 6,6′-bis(hydroxymethyl)-2,2′-dipyridine[8b] (**4c**) can be transformed (75%) to **4a** upon treatment with pure $SOCl_2$ or to **4b** by refluxing with excess HBr or to **4d** by treatment with acetic anhydride.

Subsequent macrocyclization was conducted by treatment of **4** with the appropriate glycolate generated in situ using 2 equiv of sodium hydride in anhydrous THF. Glycol size was sequentially varied, resulting in an extensive series of the expected macrocycles with the exception of the unsymmetrically bridged derivative **5**, which resulted from a mixture of glycols generated in situ via a known fragmentation process (Scheme II).[13] A single-crystal X-ray structure confirmed the disparate nature of the ethereal bridges in **5** (Figure 1).

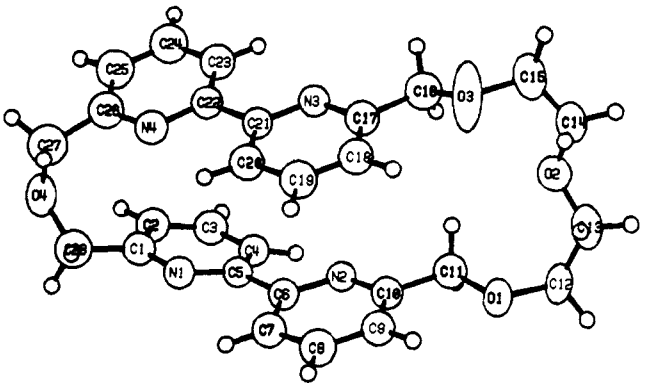


Figure 1. ORTEP drawing of **5**.

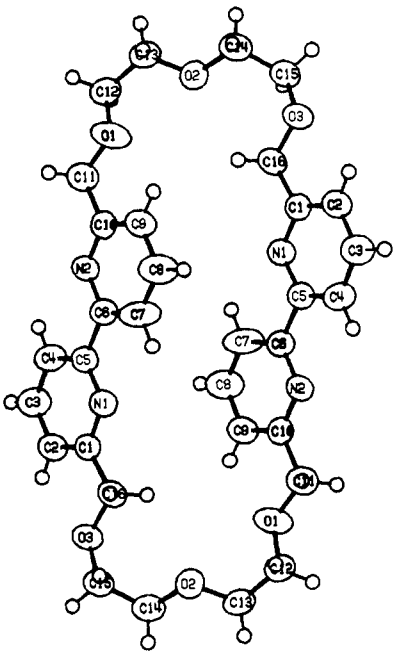


Figure 2. ORTEP drawing of **7a**.

Two independent molecules exist in the asymmetric unit of **5**. The conformations of the two are nearly identical; the pyridine rings of each dipyridine are anti and the two dipyridine moieties are stacked in a syn fashion. The N–C–C–N torsion angles of the dipyridines range from 174.3 to 160.8°, and average 171.1° in absolute value. The stacking of the dipyridine moieties is such that the nitrogen atoms approximate a square of ca. 3.6 Å on a side. Due to the unequal lengths of the chains bridging the two dipyridine subunits, the intramolecular N2···N3 distance (average 4.11 Å) is longer than the N1···N4 distance (average 3.30 Å).

The corresponding 2:2-macrocycle (**7a**) was formed without fragmentation. The X-ray structure of **7a** is illustrated in Figure 2. The molecule lies on an inversion center in the crystal and has a similar, albeit more symmetric, conformation to **5**. Each dipyridine moiety is in the anti conformation, with an N1–C5–C6–N2 torsion angle of −179.9°. The dipyridines are stacked in a syn fashion with transannular N1···N2 separation of 4.91 Å. This molecule may be considered to be 18-crown-6 with dipyridine inserted into opposite C–C bonds (C11···C16). Indeed, the conformation of the 11-atom chain C10 through C1′ is $aag^-aag^+g^-a$, which is identical with that found in the crystal structure of uncomplexed 18-crown-6.[14]

(11) Mattice, W. L.; Newkome, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 4477.
(12) Newkome, G. R.; Kawato, T. *J. Am. Chem. Soc.* **1979**, *101*, 7088.
(13) (a) Newkome, G. R.; Nayak, A.; McClure, G. L.; Danesh-Khoshboo, F.; Broussard-Simpson, J. *J. Org. Chem.* **1977**, *42*, 1500. (b) Newkome, G. R.; McClure, G. L.; Broussard-Simpson, J.; Danesh-Khoshboo, F. *J. Am. Chem. Soc.* **1975**, *97*, 3232.

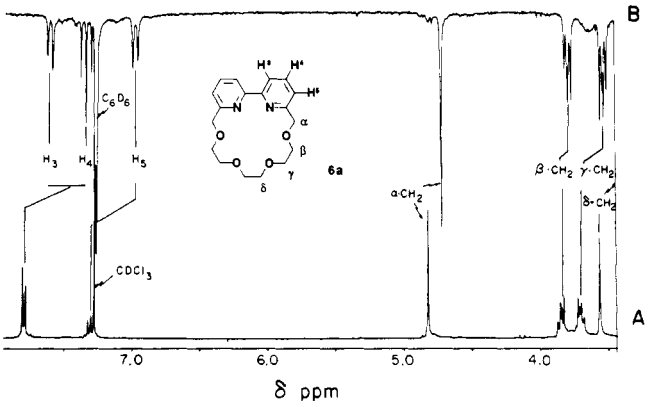


Figure 3. ^1H NMR spectra for **6a** depicting the solvent shift effects.

Table I. Solvent Dependent Shift ^1H NMR Data

compound	chemical shift change Δδ ($CDCl_3$ – C_6D_6) H-3	H-4	H-5	CH_2
6a (n = 1)	+0.20	+0.17	+0.54	+0.17
6b (n = 2)	−0.15	+0.39	+0.19	+0.00
6c (n = 3)	−0.14	+0.39	+0.21	+0.03
6d (n = 4)	−0.22	+0.29	+0.12	+0.02
4d $(OAc)_2$	−0.15	+0.40	+0.22	+0.04

A similar conformation is also found in the analogous portion of asymmetric **5**. The C10 through C17 chain has the same conformation with individual torsion angles even more closely matching those of 18-crown-6. Macrocycle **5** may be viewed as 12-crown-4 with asymmetrically inserted dipyridine fragments.

The 1:1 18-crown-6 analogue **6a** was prepared in 6% yield and exists in the syn conformation as suggested by the singlet at δ 3.56 for the γ-methylene protons and the multiplet arising at δ 7.87 for the 3,4-pyridyl protons. In order to confirm the structural assignment, the ^1H NMR spectrum of **6a** was acquired in both $CDCl_3$ and C_6D_6 (Figure 3). The C_6D_6 spectrum clearly shows separation of the complex region which appears at δ 7.87 in the $CDCl_3$ spectrum. Table I lists the differences in chemical shifts Δδ($CDCl_3$ – C_6D_6) for **6a–d** and the diacetoxy compound **4d**; the similar solvent dependent shifts for **6b–d** and **4d** are indicative of an anti conformation. Further, the downfield shift in H-3 (Δδ 0.3) is characteristic of the change from syn to the anti conformation in the dipyridine moiety.[7a]

The ^1H NMR spectrum of the pentaethylene glycol derivative **6c** displayed a singlet at δ 3.29 for the ζ-bridge protons which suggests (1) a macrocycle with reflection symmetry and (2) a ring current juxtaposed to the central methylenes as shown by their upfield shift (Δδ = 0.27 as compared to the γ-CH_2 of **6a**). The doublet of doublets at δ 8.40 for the 3-pyridyl hydrogens further confirms the anti conformation of the dipyridyl subunit;[4a] such a chemical shift is similar to that observed for the noncyclic starting material **4** (δ 8.49). In the larger 2:2- and 3:3-macrocycles (**7c** and **8c**), the diagonally oriented polyethereal bridge spanning the 6- and 6′-positions has been removed; however, due to the conformational flexibility in these larger macrocycles, the dipyridyl subunits still possess the anti conformation.

In order to establish the preferred site of complexation in the 1:1-macrocycles, **6c** was treated with $Eu(fod)_3$ in $CDCl_3$ (Table II); the minor shifts in the ^1H NMR signals for H-3 and the α-methylenes are indicative of minimal N-complexation with the shift reagent.[15] Since the crown ether portion does undergo a noticeable shift, it is evident that the europium shift reagent prefers O- vs N-coordination. The lack of N,N-coordination is again noted by the chemical shift of the 3-pyridyl hydrogen. Variable-temperature NMR studies were also conducted on **6a–d** in hopes that a conformational preference might be realized. However, unlike the type 1 macrocycle **11**,[4a] which has been shown to be temperature sensitive, **6a–d** showed little or no tendency to undergo an anti to syn conformational change at diminished temperatures (<−70 °C). The rigid imidate moieties[16] ($pyOCH_2$) of **11** must be partially responsible for the conformational differences observed between the type 1 and 2 macrocycles.

Table II. Europium Shift Study of 6c

shift reagent, %	chemical shift,[a] δ H-3	H-4	H-5	CH_2
0	8.40	7.89	7.50	4.82
1	8.33	7.83	7.43	4.78
4	8.33	7.83	7.43	4.78
10	8.33	7.83	7.43	4.80
20	8.39	7.87	7.45	4.85
40	8.51	7.92	7.51	4.96

[a] All spectra taken in $CDCl_3$ with TMS (δ = 0.0) as the internal standard.

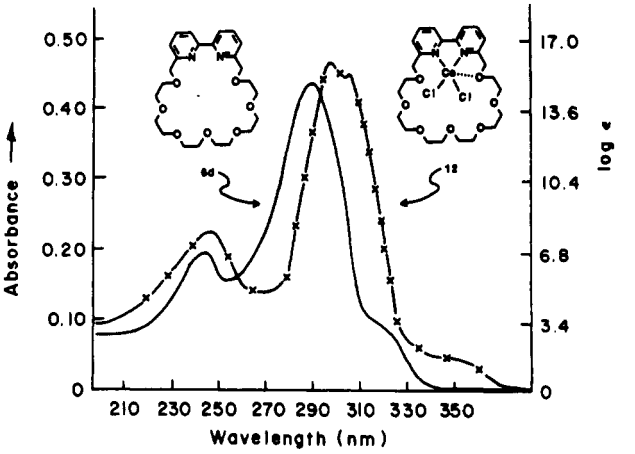
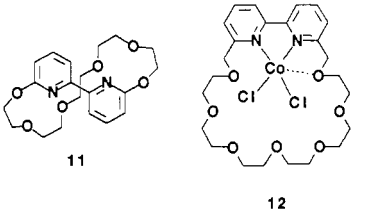


Figure 4. UV spectra in 95% EtOH for **6d** and its Co(II) complex **13**.



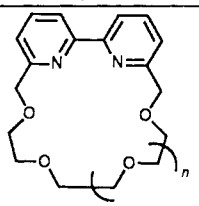
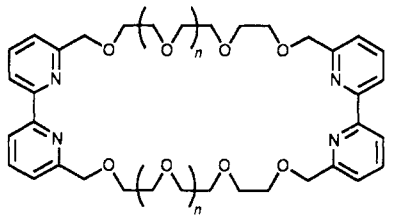
B. Complex Formation. When **6d** was refluxed in absolute methanol with an equimolar quantity of $CoCl_2 \cdot 6H_2O$ followed by trituration with ethyl acetate, a blue crystalline complex **12** was isolated.[9c] Recrystallization of **12** from ethyl acetate, C_6H_6, or $CHCl_3$ afforded crystals suitable for X-ray analysis. The crystal structure of **12**

(14) Dunitz, J. D.; Seiler, P. *Acta Crystallogr.* **1974**, *B30*, 2739.

(15) Newkome, G. R.; Kawato, T. *Tetrahedron Lett.* **1978**, *47*, 4643.

(16) (a) Newkome, G. R.; Nayak, A.; Sauer, J. D.; Mattachei, P. K.; Watkins, S. F.; Fronczek, F. R.; Benton, W. H. *J. Org. Chem.* **1979**, *44*, 3816. (b) Newkome, G. R.; Kawato, T. *J. Org. Chem.* **1979**, *44*, 2693.

Table III. Physical Data for Co(II), Cu(II), Zn(II), and Pd(II) Complexes of 6 and 7

ligand	metal salt	product stoichiometry (ligand/metal salt)	yield (%)	mp (°C)	anal. [calcd (found)] C	H	N	IR,[a] cm^{-1}
								
6a (n = 1)	$Co(SCN)_2$	1:1 (H_2O)	50	300	45.87 (46.02)	4.62 (4.44)	10.74 (10.70)	2075 (SCN), 1082 (COC)
6b (n = 2)	$CoCl_2 \cdot 6H_2O$	1:1 (H_2O)	45	130	46.00 (46.09)	5.36 (5.25)	5.40 (5.23)	2970, 1600, 1448, 1088 (COC), 793
6c (n = 3)	$CoCl_2 \cdot 6H_2O$	1:1	70	220	48.17 (48.27)	5.51 (5.65)	5.10 (4.89)	2870, 1595, 1100 (COC)
6c (n = 3)	$PdCl_2 \cdot (C_6H_5CN)_2$	1:1[b]	75	155	– –	– –	– –	2938, 1598, 1568, 1470, 1350, 1095 (COC), 803
6c (n = 3)	$ZnCl_2$	1:1[c]	30	225	47.63 (47.42)	5.45 (5.65)	5.40 (5.23)	2970, 1595, 1470, 1145, 1110 (COC), 795
6d (n = 4)	$CoCl_2 \cdot 6H_2O$	1:1	80	141	48.66 (48.78)	5.78 (5.75)	4.72 (4.74)	2860, 1597, 1100 (COC)
								
7b (n = 2)	$CuCl_2$	1:2	73	212	47.19 (46.90)	5.15 (5.20)	5.52 (5.34)	2892, 1600, 1575, 1470, 1450, 1380, 1108, 1075 (COC), 799
7b (n = 2)	$CoCl_2 \cdot 6H_2O$	1:2	61	281	47.62 (47.51)	5.20 (5.21)	5.57 (5.47)	2895, 1600, 1572, 1452, 1112, 1085 (COC), 793
7c (n = 3)	$CuCl_2$	1:3 (H_2O)	75	89	41.47 (41.28)	4.84 (4.67)	4.85 (4.69)	3160, 1595, 1100 (COC)
7c (n = 3)	$ZnCl_2$	1:2[d]	35	175	47.63 (47.62)	5.45 (5.35)	5.05 (4.99)	2940, 1597, 1575, 1470, 1435, 1100 (COC), 795
7d (n = 4)	$CoCl_2 \cdot 6H_2O$	1:2	50	163	48.66 (48.29)	5.78 (5.53)	4.72 (4.82)	2870, 1600, 1100 (COC)

[a] KBr pellet. [b] ^{1}H NMR ($CDCl_3$) δ 3.62–3.77 (m, OCH_2CH_2, 20 H), 5.17 (s, $pyCH_2O$, 4 H), 7.47 (d, 5-py$H$, J = 7.5 Hz, 2 H), 8.0 (t, 4-py$H$, J = 7.5 Hz, 2 H), 8.22 (d, 3-py$H$, J = 7.5 Hz, 2 H). [c] ^{1}H NMR ($CDCl_3$) δ 3.84 (m, OCH_2CH_2, 12 H), 4.02 (s, OCH_2CH_2O, 8 H), 5.19 (s, $pyCH_2O$, 4 H), 7.66 (d, 5-py$H$, J = 7.0 Hz, 2 H), 8.04 (t, 4-py$H$, J = 7.0 Hz, 2 H), 8.08 (d, 3-py$H$, J = 7.0 Hz, 2 H). [d] ^{1}H NMR ($CDCl_3$) δ 3.72 (m, OCH_2CH_2O, 12 H), 3.84 (m, OCH_2, 4 H), 4.02 (m, OCH_2, 4 H), 5.17 (s, $pyCH_2O$, 4 H), 7.52 (d, 5-py$H$, J = 7.5 Hz, 2 H), 7.85 (t, 4-py$H$, J = 7.5 Hz, 2 H), 8.07 (d, 3-py$H$, J = 7.5 Hz, 2H).

revealed the Co(II) core to be pentacoordinate with one coordination site occupied by an ethereal oxygen atom.[9c] A comprehensive list of Co(II), Cu(II), Zn(II), and Pd(II) complexes derived from the 1:1- and 2:2-macrocycles is summarized in Table III. It should be noted that as the ligand size decreases, the melting point of the corresponding complexes increases, which is indicative of an overall increase in ionic character (Table III). Characteristic UV spectral data are depicted for **6d** (Figure 4) with a typical bathochromic shift of the 290-nm absorption maxima to 300 nm upon formation of the $CoCl_2$ complex. We are continuing our studies in the design of new heteromacrocycles; however, attention is now being focused on the encapsulation of neutral host molecules as opposed to metal ion inclusion.

Experimental Section

General Comments. All melting points were taken in capillary tubes and are uncorrected. The ^{1}H NMR spectra were determined at 80 or 200 MHz using $CDCl_3$ as solvent, except where noted. Mass spectral (MS) data were determined by D. A. Patterson (LSU) on a Hewlett-Packard HP 5985 GC/mass spectrometer and reported herein as: assignment (relative intensity). Preparative thick-layer chromatography (ThLC) was performed on 20 × 40 cm glass plates coated with a 2 mm layer of Brinkmann EM Aluminum Oxide PF-254-366 (Type T). IR spectra were recorded using KBr or neat techniques for the crystals and oils, respectively.

Care must be exercised in handling all of the halomethyl derivatives since they are extremely irritating to the skin and mucous membranes.

6,6′-Bis(chloromethyl)-2,2′-dipyridine (4a) (method A) was prepared (75%) by the reaction of 6,6′-dimethyl-2,2′-dipyridine (**3**)[8a] with N-chlorosuccinimide:[8b] mp 157–158 °C (lit.[8b] mp 157–158 °C); ^{1}H NMR δ 4.79 (s, CH_2Cl, 4 H), 7.55 (dd, 5-py$H$, J = 7.8, 1.2 Hz, 2 H), 7.91 (t, 4-py$H$, J = 7.8 Hz, 2 H), 8.49 (dd, 3-py$H$, J = 7.8, 1.2 Hz, 2 H).

Method B. The crystalline **4a** was also prepared (73%) from 6,6′-bis(hydroxymethyl)-2,2′-dipyridine [**4c**; mp 146–147 °C (recryst H_2O)][8b] by treatment with excess purified[17] $SOCl_2$ by standard procedures: mp 157–158 °C [$CHCl_3$–C_6H_{12} (1:1)].

6,6′-Bis(bromomethyl)-2,2′-dipyridine (4b) was prepared from the above diol **4c** by refluxing with excess aqueous HBr (48%) for 8 h. After neutralization with 6 N NaOH, the precipitate was dried in vacuo and chromatographed (ThLC, SiO_2), eluting with $CHCl_3$/EtOAc (1:1) to afford (65%) **4b** as colorless needles: mp 192–195 °C (lit.[9k,9r] mp 180–181 °C); ^{1}H NMR δ 4.65 (s, CH_2Br, 4 H), 7.50 (dd, 5-py$H$, J = 7.5, 1.5 Hz, 2 H), 7.87 (t,

(17) Vogel, A. I. *Practical Organic Chemistry*; Longman: London, 1973; p 189. Rigby, W. *Chem. Ind.* **1969**, 1508.

4-py*H*, J = 7.5 Hz, 2 H), 8.47 (dd, 3-py*H*, J = 7.5, 1.5 Hz, 2 H).

A second fraction, after recrystallization from $CHCl_3/C_6H_{12}$ (1:1), gave (8%) **6-(hydroxymethyl)-6′-(bromomethyl)-2,2′-dipyridine**: mp 130–131 °C; ^{1}H NMR δ 4.65 (s, CH_2Br, 2 H), 4.85 (s, CH'_2OH, 2 H), 7.28 (dd, 5′-py*H*, J = 7.5, 1.5 Hz, 1 H), 7.50 (dd, 5-py*H*, J = 7.5, 1.5 Hz, 1 H), 7.86 (dd, 4,4′-py*H*, J = 7.5 Hz, 2 H), 8.38 (dd, 3′-py*H*, J = 7.5, 1.5 Hz, 1 H), 8.45 (dd, 3-py*H*, J = 7.5, 1.5 Hz, 1 H). Anal. Calcd for $C_{12}H_{11}N_2OBr$: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.48; H, 4.06; N, 10.01.

6,6′-Bis(acetoxymethyl)-2,2′-dipyridine (4d). Diol **4c** (100 mg, 460 μmol) was dissolved in a stirred mixture of anhydrous pyridine (1.5 mL) and Ac_2O (2 mL) at 80 °C. After 3 h, the mixture was concentrated to dryness, and the residue was recrystallized from $CHCl_3/C_6H_{12}$ (1:20) to give (95%) diacetate **11** as white needles: mp 102–103 °C; ^{1}H NMR δ 2.2 (s, CH_3CO, 6 H), 5.34 (s, α-CH_2, 4 H), 7.40 (dd, 5-py*H*, J = 8.0, 2.0 Hz, 2 H), 7.86 (dd, 4-py*H*, J = 8.0, 8.0 Hz, 2 H), 8.45 (dd, 3-py*H*, J = 8.0, 2.0 Hz, 2 H). Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.17; H, 5.36; N, 9.25.

Macrocycle Synthesis: General Procedure. To a stirred suspension of NaH (2.4 mmol) in anhydrous THF (30 mL) was added dropwise the designated glycol (1.2 mmol) in THF (20 mL) under N_2. After 1 h, **4a** (1.2 mmol) in anhydrous THF (75 mL) was added dropwise, and then the mixture stirred for 60 h at 25 °C. After quenching with H_2O, the mixture was concentrated in vacuo, and the residue was triturated with $CHCl_3$, followed by drying over anhydrous $MgSO_4$. After filtration and concentration in vacuo, the resulting thick yellow oil was eluted through a short neutral alumina column with $CHCl_3$/EtOH (9:1) and then chromatographed (ThLC), as noted below, to give the specific macrocycles.

Reaction of 4a with Diethylene Glycol. Via the general procedure using diethylene glycol (127 mg, 4.8 mmol; 4× scale), three major fractions were isolated by chromatography (ThLC, Al_2O_3), eluting with C_6H_{12}/EtOAc (3:2):

Fraction A gave **8,21,24,27-tetraoxa-33,34,35,36-tetraazapentacyclo[28.3.1.$1^{2,6}$.$1^{10,14}$.$1^{15,19}$]hexatriaconta-1(33),2,4,6(34),10,12,14(35),15,17,19(36),29,31-dodecaene (5)** as colorless crystals: 12 mg (3.5%); mp 148–150 °C (EtOH); R_f = 0.61; ^{1}H NMR δ 3.75 (s, β,γ-CH_2, 8 H), 4.65 and 4.96 (2 s, α-CH_2, 8 H), 7.11 (d, 5′-py*H*, J = 7.8 Hz, 2 H), 7.30 (m, 4,5-py*H*, 4 H), 7.43 (t, 4′-py*H*, J = 7.8 Hz, 2 H), 7.85 (d, 3′-py*H*, J = 7.8 Hz, 2 H), 7.92 (dd, 3-py*H*, J = 6.8, 2.4 Hz, 2 H); IR (neat) 1585, 1575, 1445, 1127, 1072 (COC), 798 cm^{-1}; MS (m/e) 484 (M$^+$, 3), 287 (33), 199 (100), 198 (30), 187 (91), 183 (32). Anal. Calcd for $C_{28}H_{28}N_4O_4$: C, 69.42; H, 5.79; N, 11.57. Found: C, 69.30; H, 5.62; N, 11.60.

Fraction B afforded **8,11,14,27,30,33-hexaoxa-39,40,41,42-tetraazapentacyclo[33.3.1.$1^{2,6}$.$1^{16,20}$.$1^{21,25}$]dotetraconta-1(39),2,4,6(40),16,18,20(41),21,23,25(42),35,37-dodecaene (7a)** as colorless needles: 29 mg (8.4%); mp 145–146 °C (EtOAc); R_f = 0.39; ^{1}H NMR δ 3.78 and 3.80 (2 s, β,γ-CH_2, 16 H), 4.78 (s, α-CH_2, 8 H), 7.41 (d, 5-py*H*, J = 7.9 Hz, 4 H), 7.59 (t, 4-py*H*, J = 7.9 Hz, 4 H), 8.12 (d, 3-py*H*, J = 7.9 Hz, 4 H); IR (KBr) 1572, 1562, 1435, 1325, 1120 (COC), 780 cm^{-1}; MS (m/e) 572 (M$^+$, 7), 301 (23), 287 (46), 199 (100), 198 (50), 184 (81), 183 (53). Anal. Calcd for $(C_{16}H_{18}N_2O_3)_2$: C, 67.13; H, 6.29; N, 9.79. Found: C, 66.77; H, 6.41; N, 9.88.

Fraction C afforded **8,11,14,27,30,33,46,49,52-nonaoxa-58,59,60,61,62,63-hexaazaheptacyclo[52.3.1.1^{2,6}.1^{16,20}.1^{21,25}.1^{35,39}.1^{40,44}]trihexaconta-1(58),2,4,6(59),16,18,20(60),21,23,25(61),35,37,39(62),40,42,44(63),54,56-octadecaene (8a)** as a viscous yellow oil: 22 mg (6.3%); R_f = 0.09; ^{1}H NMR δ 3.78 (s, β,γ-CH_2, 24 H), 4.78 (s, α-CH_2, 12 H), 7.48 (d, 5-py*H*, J = 7.9 Hz, 6 H), 7.73 (t, 4-py*H*, J = 7.9 Hz, 6 H), 8.25 (d, 3-py*H*, J = 7.9 Hz, 6 H); IR (neat) 1705, 1560, 1090 (COC), 770 cm^{-1}. Anal. Calcd for $(C_{16}H_{18}N_2O_3)_3$: C, 67.13; H, 6.29; N, 9.79. Found: C, 66.98; H, 6.12; N, 9.72.

Reaction of 4a with Triethylene Glycol. Via the general procedure using triethylene glycol (180 mg, 1.2 mmol), **8,11,14,17-tetraoxa-23,24-diazatricyclo[17.3.1.1^{2,6}]tetracosa-1(23),2,4,6(24),19,21-hexaene (6a)** was isolated by chromatography (ThLC, Al_2O_3), eluting with EtOH/$CHCl_3$ (0.5:99.5), as a light yellow oil: 25 mg (6%); R_f = 0.05; ^{1}H NMR see Figure 3; IR (neat) 1575, 1560, 1420, 1080 (COC), 776 cm^{-1}; MS (m/e) 330 (M$^+$). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.32; H, 6.81; N, 8.46.

Reaction of 4a with Tetraethylene Glycol. Via the general procedure using tetraethylene glycol (230 mg, 1.2 mmol), five fractions were isolated by chromatography (ThLC, Al_2O_3), eluting three times with C_6H_{12}/EtOAc (2:3).

Fraction A afforded **8,11,14,17,20-pentaoxa-26,27-diazatricyclo[20.3.1.1^{2,6}]heptacosa-1(26),2,4,6(27),22,24-hexaene (6b)** as a colorless oil: 13 mg (3%); R_f = 0.45; ^{1}H NMR δ 3.24 (m, ϵ-CH_2, 4 H), 3.34 (m, δ-CH_2, 4 H), 3.56 (m, γ-CH_2, 4 H), 3.81 (m, β-CH_2, 4 H), 4.76 (s, α-CH_2, 4 H), 7.38 (d, 5-py*H*, J = 7.9 Hz, 2 H), 7.81 (t, 4-py*H*, J = 7.9 Hz, 2 H), 8.18 (d, 3-py*H*, J = 7.9 Hz, 2 H); IR (neat) 1560, 1420, 1090 (COC), 775 cm^{-1}; MS (m/e) 374 (M$^+$, 1), 199 (100), 198 (61), 197 (46), 184 (88). Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.13; H, 7.00; N, 7.48. Found: C, 63.96; H, 7.20; N, 7.33.

Fraction B afforded **8,11,14,17,20,33,36,39,42,45-decaoxa-51,52,53,54-tetraazapentacyclo[45.3.1.1^{2,6}.1^{22,26}.1^{27,31}]tetrapentaconta-1(51),2,4,6(52),22,24,26(53),27,29,31(54),47,49-dodecaene (7b)** as colorless needles: 57 mg (13%); mp 101–103 °C; R_f = 0.29; ^{1}H NMR δ 3.69 and 3.73 (2 s, ϵ-β-CH_2, 32 H), 4.72 (s, α-CH_2, 8 H), 7.45 (d, 5-py*H*, J = 7.9 Hz, 4 H), 7.74 (t, 4-py*H*, J = 7.9 Hz, 4 H), 8.21 (d, 3-py*H*, J = 7.9 Hz, 4 H); IR (KBr) 1560, 1425, 1103 (COC), 778 cm^{-1}; MS (m/e) 748 (M$^+$, 2), 241 (24), 199 (100), 198 (61), 197 (51), 184 (92), 183 (87). Anal. Calcd for $(C_{20}H_{26}N_2O_5)_2$: C, 64.13; H, 7.00; N, 7.48. Found: C, 64.22; H, 7.03; N, 7.59.

Fraction C afforded **8,11,14,17,20,33,36,39,42,45,58,61,64,67,70-pentadecaoxa-76,77,78,79,80,81-hexaazaheptacyclo[70.3.1.1^{2,6}.1^{22,26}.1^{27,31}.1^{47,51}.1^{52,56}]henoctaconta-1(76),2,4,6(77),22,24,26(73),27,29,31(79),47,49,51(80),52,54,56(81),72,74-octadecaene (8b)** as a yellow oil: 22 mg (5%); R_f = 0.13; ^{1}H NMR δ 3.68, 3.73 (2 s, ϵ-β-CH_2, 48 H), 4.74 (s, α-CH_2, 12 H), 7.46 (d, 5-py*H*, J = 7.9 Hz, 6 H), 7.77 (t, 4-py*H*, J = 7.9 Hz, 6 H), 8.26 (d, 3-py*H*, J = 7.9 Hz, 6 H); IR (neat) 1555, 1422, 1096 (COC), 755 cm^{-1}. Anal. Calcd for $(C_{20}H_{26}N_2O_5)_3$: C, 64.13; H, 7.00; N, 7.48. Found: C, 64.20; H, 7.00; N, 7.36.

Fraction D afforded the 4:4-macrocycle **9b** as a yellow oil: 69 mg (15%); R_f = 0.04; ^{1}H NMR and IR are identical with those of the 3:3-macrocycle. Anal. Calcd for $(C_{20}H_{26}N_2O_5)_4$: C, 64.13; H, 7.00; N, 7.48. Found: C, 64.17; H, 7.09; N, 7.54.

Fraction E afforded the 5:5-macrocycle **10b** as a yellow oil: 50 mg (11%); R_f = 0.02; ^{1}H NMR δ 3.70 and 3.75 (2 s, ϵ-β-CH_2, 80 H), 4.76 (s, α-CH_2, 20 H), 7.48 (d, 5-py*H*, J = 7.9 Hz, 10 H), 7.79 (t, 4-py*H*, J = 7.9 Hz, 10 H), 8.27 (d, 3-py*H*, J = 7.9 Hz, 10 H). Anal. Calcd for $(C_{20}H_{26}N_2O_5)_5$: C, 64.13; H, 7.00; N, 7.48. Found: C, 64.12; H, 6.97; N, 7.48.

Reaction of 4a with Pentaethylene Glycol. Via the general procedure using pentaethylene glycol (286 mg, 1.2 mmol), three major fractions were isolated by chromatography (ThLC, Al_2O_3), eluting with C_6H_{12}/EtOAc (1:1).

Fraction A afforded **8,11,14,17,20,23-hexaoxa-29,30-diazatricyclo[23.3.1.1^{2,6}]triaconta-1(29),2,4,6(30),25,27-hexaene (6c)** as a colorless oil: 105 mg (21%); R_f = 0.25; ^{1}H NMR δ 3.29 (s, ζ-CH_2, 4 H), 3.43 (m, δ,ϵ-CH_2, 8 H), 3.75 (m, γ,β-CH_2, 8 H), 4.82 (s, α-CH_2, 4 H), 7.50 (dd, 5-py*H*, J = 7.8, 1.2 Hz, 2 H), 7.89 (t, 4-py*H*, J = 7.8 Hz, 2 H), 8.40 (dd, 3-py*H*, J = 7.8, 1.2 Hz, 2 H); IR (neat) 1568, 1430, 1150 (COC), 780 cm^{-1}. Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.12; H, 7.23; N, 6.70. Found: C, 62.97; H, 7.09; N, 6.61.

Fraction B afforded **8,11,14,17,20,23,36,39,42,45,48,51-dodecaoxa-57,58,59,60-tetraazapentacyclo[51.3.1.1^{2,6}.1^{25,29}.1^{30,35}]hexaconta-1(57),2,4,6(58),25,27,29(59),30,32,34(60),53,55-dodecaene (7c)** as a light yellow oil: 40 mg (10%); R_f = 0.10; ^{1}H NMR δ 3.70 (s, ζ-δ-CH_2, 24 H), 3.77 (s, γ,β-CH_2, 16 H), 4.78 (s, α-CH_2, 8 H), 7.52 (dd, 5-py*H*, J = 7.8, 1.2 Hz, 4 H), 7.84 (t, 4-py*H*, J = 7.8 Hz, 4 H), 8.37 (dd, 3-py*H*, J = 7.8, 1.2 Hz, 4 H); IR (neat) 1560, 1425, 1335, 1100 (COC), 775 cm^{-1}. Anal. Calcd for $(C_{22}H_{30}N_2O_6)_2$: C, 63.12; H, 7.23; N, 6.70. Found: C, 62.95; H, 7.21; N, 6.65.

Fraction C afforded **8,11,14,17,20,23,36,39,42,45,48,51,64,67,70,73,76,79-octadecaoxa-85,86,87,88,89,90-hexaazaheptacyclo[79.3.1.1^{2,6}.1^{25,27}.1^{30,34}.1^{53,57}.1^{58,62}]nonaconta-1(85),2,4,6(86),25,27,29(87),30,32,34(88),53,55,57(89),58,60,62(90),81,83-octadecaene (8c)** as a yellow oil: 30 mg (3%); R_f = 0.02; ^{1}H NMR δ 3.69 (s, ζ-δ-CH_2, 36 H), 3.77 (s, γ,β-CH_2, 24 H), 4.80 (s, α-CH_2, 12 H), 7.53 (dd, 5-py*H*, J = 7.8, 1.2 Hz, 6 H), 7.86 (t, 4-py*H*, J = 7.8 Hz, 6 H), 8.36 (dd, 3-py*H*, J = 7.8, 1.2 Hz, 6 H); IR (neat) 1562, 1430, 1105 (COC), 780 cm^{-1}; Anal. Calcd for $(C_{22}H_{30}N_2O_6)_3$: C, 63.12; H, 7.23; N, 6.70. Found: C, 63.05; H, 7.20; N, 6.64.

Reaction of 4 with Hexaethylene Glycol. Via the general procedure using hexaethylene glycol (334 mg, 1.2 mmol), five fractions were isolated by chromatography (ThLC, Al_2O_3), eluting with C_6H_{12}/EtOAc (1:1).

Fraction A afforded **8,11,14,17,20,23,26-heptaoxa-32,33-diazatricyclo[26.3.1.1^{2,6}]tritriaconta-1(32),2,4,6(33),28,30-hexaene (6d)** as a colorless oil: 107 mg (19%); R_f = 0.49; ^{1}H NMR δ 3.41 (m, η-δ-CH_2, 16 H), 3.65 (m, γ-CH_2, 4 H), 3.71 (m, β-CH_2, 4 H), 4.74 (s, α-CH_2, 4 H), 7.44 (d, 5-py*H*, J = 7.9 Hz, 2 H), 7.81 (t, 4-py*H*, J = 7.9 Hz, 2 H), 8.31 (d, 3-py*H*, J = 7.9 Hz, 2 H); IR (neat) 1560, 1425, 1095 (COC), 780 cm^{-1}; MS (*m/e*) 462 (M$^+$, 33), 287 (30), 227 (24), 213 (43), 199 (100), 184 (91); UV (95% EtOH) see Figure 2. Anal. Calcd for $C_{24}H_{34}N_2O_7$: C, 62.30; H, 7.41; N, 6.06. Found: C, 62.38; H, 7.52; N, 5.91.

Fraction B afforded **8,11,14,17,20,23,26,39,42,45,48,51,54,57-tetradecaoxa-62,63,64,65-tetraazapentacyclo[57.3.1.1^{2,6}.1^{28,32}.1^{33,37}]hexahexaconta-1(62),2,4,6(63),28,30,32(64),33,35,37(65),59,60-dodecaene (7d)** as a pale yellow oil: 17 mg (3%); R_f = 0.16; ^{1}H NMR δ 3.69 (m, η-β-CH_2, 48 H), 4.75 (s, α-CH_2, 8 H), 7.47 (d, 5-py*H*, J = 7.9 Hz, 4 H), 7.78 (t, 4-py*H*, J = 7.9 Hz, 4 H), 8.26 (d, 3-py*H*, J = 7.9 Hz, 4 H); IR (neat) 1545, 1415, 1086 (COC), 765 cm^{-1}. Anal. Calcd for $(C_{24}H_{34}N_2O_7)_2$: C, 62.30; H, 7.41; N, 6.06. Found: C, 62.40; H, 7.42; N, 5.86.

Fractions C, D, and E afforded 3:3-(**8d**) [yellow oil; 9.7%; R_f = 0.14], 4:4-(**9d**) [yellow oil; 3%, R_f = 0.08], and 5:5-(**10d**) [yellow oil; 13.4%; R_f = 0.03] macrocycles, respectively. Elemental analyses were within acceptable limits (±0.03), and all spectral data were identical with that of **7d**.

Complex Preparation. To a MeOH solution (10 mL) of the ligand (0.5 mmol) was added an equimolar amount (1 equiv/dipyridine) of the metal salt in MeOH (2 mL) with stirring. The solution was refluxed for 1 h, EtOAc was added dropwise, and the solution was allowed to stand for 4–20 h at 20 °C. The resulting crystals were collected; physical and spectral data are given in Table III.

X-ray Experimental. Intensity data for **5** and **7a** were collected on an Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator and either Mo Kα or Cu Kα radiation. Variable scan rates were employed in the $\omega - 2\theta$ scans designed to achieve approximately equal relative precision for all significant data, subject to a maximum of 120 s for any one scan. One quadrant of data within the angular limits given in Table III was collected for each crystal. Data reduction included corrections for background, Lorentz, and polarization effects. Equivalent data were averaged, and data considered observed by the criteria furnished in the supplementary material were used in the refinements. Structures were solved using MULTAN[18] and refined by full-matrix least-squares methods based on F with weights $w = \sigma^{-2}(F_o)$. Both crystals scattered rather weakly, and in the case of **5**, insufficient data were available to allow full anisotropic refinement. Only oxygen atoms and carbon atoms C12 through C15 were treated anisotropically; all other heavy atoms were refined isotropically. For **7a**, all non-hydrogen atoms were refined anisotropically. In both structures, hydrogen atoms were discernible from difference maps, but were placed in calculated positions as fixed contributions. Final R factors and residual electron densities are given in the supplementary material.

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Supplementary Material Available: Crystal data, tables of (average) bond distances, (average) bond angles, coordinates for all atoms, and anisotropic thermal parameters for $C_{28}H_{28}N_4O_4$ (**5**) and $C_{32}H_{36}N_4O_6$ (**7a**) (10 pages). Ordering information is given on any current masthead page.

(18) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN. A System of Computer Programs for the Automatic Solution of Crystal Structure from X-Ray Diffraction Data. Univs. of York, England, and Louvain, Belgium, 1978.

1(4*H*)-Naphthalenones in Anthracyclinone Synthesis: A New Route for the Total Synthesis of (±)-Aklavinone

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A brief route for total synthesis of (±)-aklavinone (**1a**), the aglycon of the anticancer antibiotic aclacinomycin (**1b**), is described. Key features of the synthesis are the development of a brief, efficient route to the 1(4*H*)-naphthalenone **11**, which was used as a synthon for the A and B rings, and homologation of keto aldehyde **17** to the keto anthraquinone acetic ester **16** via the intermediacy of the ketene thioacetal **19**.

The discovery that aclacinomycin-A1 (**1b**), shown in Figure 1, had significant anticancer activity[1-4] prompted strong interest in the synthesis of the aromatic fragment in this antibiotic. To date, some ten[5-13] syntheses of the aglycon **1a** and two[11,14] of the structurally similar auramycin aglycon **1c** have been published.

We have previously shown that regiospecific, convergent syntheses of tetracyclic intermediates to anthracycliones can be accomplished through condensation of 1(4*H*)-naphthalenones with phenylsulfonyl isobenzofuranones[15]

(1) Oki, T.; Matsuzawa, Y.; Yoshimoto, A.; Numata, Y.; Kitamura, I.; Hori, S.; Takamatsu, *J. Antibiot.* **1975**, *28*, 830.
(2) Hori, S.; Shiraim, M.; Hirano, S.; Oki, T.; Inui, T.; Tsukagoshi, S.; Ishizuka, M.; Takeuchi, T.; Umezawa, H. *Gann.* **1977**, *68*, 685.
(3) (a) Majima, H. *Recent Results in Cancer Research*; Carter, S. K., Skaurari, Y., Eds.; Springer-Verlag: Berlin, 1980; p 70. (b) Dantchev, D.; Slioussartchouk, V.; Paintrand, M.; Hayat, M.; Bourut, C.; Mathe, G. *Cancer Treat. Rep.* **1979**, *32*, 801.
(4) Oki, T.; Yoshimoto, A.; Matsuzawa, Y.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 1331.
(5) Kende, A. S.; Rizzi, P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. Kende, A. S.; Rizzi, P. *Tetrahedron* **1984**, *40*, 4693.
(6) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4249.
(7) Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251.
(8) Li, T.-T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7007. Li, T.-T.; Wu, Y. L.; Walsgrove, T. C. *Tetrahedron* **1984**, *40*, 4701.
(9) Boeckman, R. K. Jr.; Sum, F. W. *J. Am. Chem. Soc.* **1982**, *104*, 4604.
(10) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371. McNamara, J. M.; Kishi, Y. *Tetrahedron* **1984**, *40*, 4693.
(11) Maruyama, K.; Uno, H.; Naruta, Y. *Chem. Lett.* **1983**, 1767. Uno, H.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1984**, *40*, 4741.
(12) Krohn, K. *Justus Leibiegs Ann. Chem.* **1983**, 2151.
(13) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098.
(14) Gesson, J.-P.; Jacquesy, J.-C.; Renoux, B. *Tetrahedron* **1984**, *40*, 4743.
(15) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178.

0022-3263/89/1954-5110$01.50/0