3 H), 2.06 (s, 3 H), 4.3–4.4 (br m, 1 H), AB quartet (4.35, 4.93; 2 H, J = 12.5 Hz), 5.08–5.24 (br m, 1 H), 5.96–6.06 (br s, 1 H) ppm; IR ($CHCl_3$) 1740 (br) cm^{-1}; ^{13}C NMR ($CDCl_3$) 170.54, 169.82, 169.53, 134.41, 133.10, 81.74, 76.98, 74.37, 61.42, 58.00, 53.66, 38.18, 35.93, 33.48, 21.05, 15.37, 14.82 ppm; High-resolution MS, molecular ion at *m/e* 337, 337.1506 (calcd for $C_{17}H_{23}O_6N$, 337.1525).

Determination of Absolute Configuration of 26 and 27. The acetate **26** (12 mg) in 10% HCl (3 mL) was refluxed for 4 h, followed by continuous extraction with diethyl ether to afford *trans*-**3** (5.3 mg). The ORD spectrum of this sample showed a positive Cotton effect at 237 nm, identical with that of (−)-*trans*-**3** (obtained by resolution of (±)-**3** by using cinchonine). It was assigned a 4*R*,5*S* configuration based on the work of Cervinka and co-workers.[46] Similarly, acetate **27** (13 mg) afforded *trans*-**3** (5.5 mg), which was assigned the 4*S*,5*R* configuration based on its negative Cotton effect at 235 nm,[46] identical with that of (+)-*trans*-**3**.

Attempted Deacetylation of 26 by 10% HCl. A solution of acetate **26** (15.2 mg) in 10% HCl (0.5 mL) was refluxed for 25 min and then basified to pH 9 by the addition of sodium carbonate. Acetonitrile (15 mL) was added, and the mixture was concentrated in vacuo. The solid residue was filtered through celite with acetonitrile and methylene chloride. Removal of solvents in vacuo provided 14.8 mg of residue which contained retronecine and lactonic ester **18** in a ratio 3:1, based on NMR analysis.

Attempted Deacetylation of 27 by 10% HCl. A solution of acetate **27** (99 mg) in 10% HCl (0.9 mL) was refluxed for 20 min and then basified to pH 9 by the addition of sodium carbonate. Acetonitrile (15 mL) was added, and the mixture was concentrated in vacuo. The solid residue was filtered through celite with acetonitrile and methylene chloride. Removal of solvents in vacuo provided 54 mg of residue which was chromatographed on alumina (activity I) with methylene chloride–methanol (50:1) as the eluting solvent. Deaceylated **7** (18 mg, 21%) was the first component to elute, followed immediately by lactonic ester **18**, and then retronecine in later fractions. The hydrolysis product, **7**, gave the following spectral data: ^1H NMR ($CDCl_3$) characteristic peaks only, 1.11 (d, 3 H, J = 6.5 Hz), 1.33 (s, 3 H), 4.30–4.45 (br m, 1 H), 4.58 and 4.75 (AB quartet, 2H, J = 12 Hz), 5.15–5.35 (br m, 1 H), 5.99 (br s, 1 H) ppm; ^1H NMR (D_2O) 1.08 (d, 3 H, J = 6.5 Hz), 1.33 (s, 3 H), 4.92 (s, 1 H), 5.15 (br m, 2 H), 6.22 (br s, 1 H) ppm [lit.:[13] characteristic peaks, 1.07 (d, 3 H, J = 6.5 Hz), 1.32 (s, 3 H), 4.81 and 5.28 (AB quartet, J = 16 Hz), 6.27 (m) ppm; a spectrum obtained directly from the authors,[47] however, showed the 4.8–5.5 ppm region much obscured]; IR (KBr) 3400, 1735 cm^{-1} [lit.:[13,47] 3300, 1735 cm^{-1}]; EIMS, *m/e* (relative intensity) 295 (M^+, 18), 251 ($M^+ - CO_2$, 5), 208 ($M^+ - CO_2 - C_2H_3O$, 3) 138 (40), 136 (38), 121 (13), 120 (37), 119 (37), 95 (31), 93 (98), 80 (40); [lit.:[13] 295 (83), 251 (29), 208 (14), 138, 136, 121, 120, 119, 95, 93, 80]; CIMS, *m/e* (relative intensity) 296 ($M^+ + 1$, 100), 251 ($M^+ - CO_2$, 5), 138 (26), 120 (94); High-resolution MS, molecular ion at *m/e* 295.1439 (calcd for $C_{15}H_{21}O_5N$, 295.14196).

Acknowledgment. We are grateful to the National Institutes of Health (Grant No. AI-12020) for the partial support of this research. The technical assistance of Mr. Michael Sofia is acknowledged with pleasure, and discussions with Drs. Satoru Masamune and David Wiemer were especially helpful.

Preparation of Tribenzo[21]aneN$_6$: A Metal Template Synthesis

G. J. Grant and D. J. Royer*

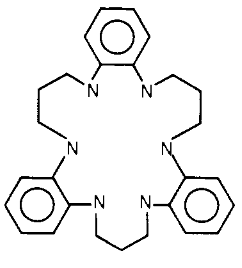
Contribution from the School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332.

Received April 25, 1980

Abstract: The nitrogen-containing macrocycle tribenzo[*b,i,p*]-1,4,8,11,15,18-hexaazacycloheneicosane (**1**) was synthesized by a series of reactions involving the alkylation of doubly deprotonated aromatic amine complexes of cobalt(III). The synthesis was successful starting with either (1,2-diaminobenzene)[1,3-bis[(*o*-aminophenyl)amino]propane]cobalt(III) (**2**) or tris(1,2-diaminobenzene)cobalt(III) (**4**) but the yield was considerably better with **2** (67%) than with **4** (25%). The electronic spectrum of the cobalt(III) complex of **1** shows a charge-transfer band in the visible region and a transition localized on the aromatic rings of the ligand in the UV region. The UV and CD spectra give some information about the configuration of the complex. The free macrocycle **1** was recovered from its cobalt(III) complex and characterized.

The synthesis of polyheteroatom-containing macrocycles and their interactions with cations have been subjects of considerable interest.[1] Many of the more successful synthetic procedures for the preparation of these materials involve so-called template reactions in which the macrocycle is assembled around a metal ion. We report the preparation of the nitrogen-containing macrocycle tribenzo[*b,i,p*]-1,4,8,11,15,18-hexaazacycloheneicosane (**1**) (tribenzo[21]aneN$_6$) in reasonable yield by means of a series of reactions involving the alkylation of deprotonated aromatic amine moieties coordinated to cobalt(III).

It would seem as though the general synthetic procedure outlined here might be useful for the introduction of short chains into a variety of coordinated ligands.



1

Results and Discussion

[1,3-Bis[(*o*-aminophenyl)amino]propane](1,2-diaminobenzene)cobalt(III) (**2**) was prepared by a modified Bauer and Drinkard procedure.[2] Sodium tris(carbonato)cobaltate(III) was reacted with 1 equiv of the hydrochloride salt of 1,3-bis[(*o*-aminophenyl)amino]propane,[3] followed by 1 equiv of 1,2-diaminobenzene (eq 1).

2 is quite acidic (p$K_1 \simeq 2.0$, p$K_2 \simeq 4.7$, p$K_3 \simeq 5.7$), and the reasonably stable doubly deprotonated species proved to be suf-

---

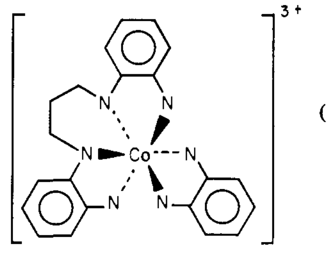
(1) Some recent reviews: (a) Christensen, J. J.; Eatough, D. J.; Izatt, R. *Chem. Rev.* **1974**, *74*, 351–384. (b) Lindoy, L. F. *Chem. Soc. Rev.* **1975**, *4*, 421–443. (c) Gokel, G. W.; Durst, H. D. *Synthesis* **1976**, 168–184. (d) Busch, D. H. *Acc. Chem. Res.* **1978**, *11*, 392–400. (e) "Progress in Macrocyclic Chemistry"; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1979; Vol. 1.

(2) Bauer, H. F.; Drinkard, W. C. *J. Am. Chem. Soc.* **1960**, *82*, 5031–5032.

(3) Tasker, P. A.; Fleischer, E. B. *J. Am. Chem. Soc.* **1970**, *92*, 7072–7077.

0002-7863/81/1503-867$01.00/0

$$Na_3[Co(CO_3)_3]\cdot 3H_2O + C_{15}H_{20}N_4\cdot 4HCl \rightarrow [Co(C_{15}H_{20}N_4)CO_3]^+ + C_6H_8N_2\cdot 2HCl \rightarrow$$

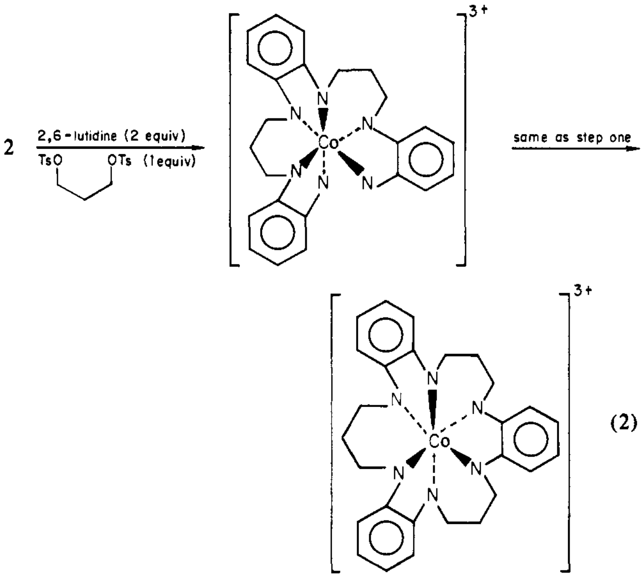


2

(1)

ficiently nucleophilic to undergo alkylation under rather mild conditions.

The macrocycle **1** was completed by the insertion of two bridging groups into **2** by two successive dialkylations of the appropiate species[4] with 1,3-propyl ditosylate:



(2)

3

The two reactions were carried out in situ without isolation of the intermediate product. The intensely colored red-brown **3** was isolated as the chloride salt.

3 was also prepared in lower yield by three successive alkylations of tris(1,2-diaminobenzene)cobalt(III) (**4**), but recovery of the desired product from the reaction mixture was more difficult due to extensive decomposition.

The three cobalt(III) complexes containing three coordinated *o*-phenylenediamine groups (**2**–**4**) have very similar UV–visible spectra. There are two principal regions of absorption; a complex pH-dependent band in the 20 000–24 000-cm^{-1} region ($\epsilon_{max} \sim$ 250–5000) (Figure 1) and two closely spaced peaks at 36 000 cm^{-1} ($\epsilon_{max} \sim$3000) and 38 900 cm^{-1} ($\epsilon_{max} \sim$5000) in the UV region. The visible band appears to be a ligand-to-metal charge-transfer transition. A transition of this type would be expected to show the observed sensitivity to deprotonation.

The UV bands appear to be an exciton-split transition[6] largely localized on the aromatic rings of the ligand (1,2-diaminobenzene in acid solution shows a band at 39 000 cm^{-1}). The circular dichroism spectrum of resolved **3** (no observable rotation in the visible band and a positive–negative couplet associated with the 36 000- and 38 900-cm^{-1} bands) and the Kuhn dissymmetry factor ($(\epsilon_l - \epsilon_r)/\epsilon \sim 7 \times 10^{-6}$) are consistent with this interpretation. The charge-transfer band would be expected to be optically inactive because it would have the same symmetry as the Bosnich[6] "short-axis" transitions (T_1 octahedral parentage) while the UV transitions should be of the "long-axis" type (T_2 octahedral parentage). The Kuhn dissymmetry factor is quite low, indicating that the complex might not be totally resolved, but repeated recrystallizations did not increase the rotation.

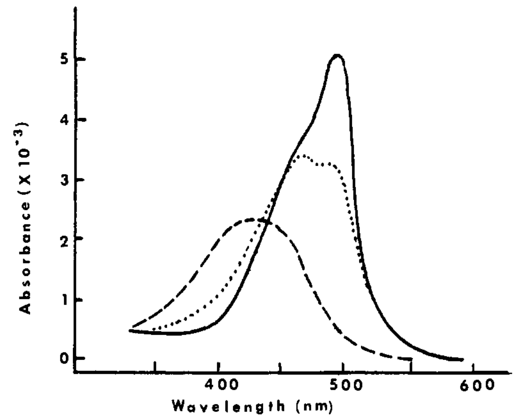


Figure 1. Changes in the visible spectrum of tris(1,2-diaminobenzene)cobalt(III) with pH: (—) pH 1.9; (···) pH 3.5; (---) pH 5.6.

The sign of the exciton couplet would indicate that the absolute configuration with respect to the arrangement of the aromatic rings about the cobalt is Λ. The examination of a model indicates that the most probable overall configuration of **3** then gives the six-membered (propyl) rings the Δ configuration. This overall absolute cofiguration is illustrated by the structural formula in eq 2. This configuration can be denoted as an all-*fac* isomer of D_3 symmetry.

A second possible geometrical isomer can be generated by rotating any one of the *o*-phenylenediamine units 180° in a clockwise direction and inverting the configuration of the chiral nitrogens involved. This new isomer has two meridional linkages, the overall symmetry is C_2, and the six-membered rings are now Λ. However, the models also indicate that this C_2 isomer would probably contain considerably more steric strain than the D_3 isomer. In addition, the apparent fact that only one macrocycle was produced (vide infra) would seem to make the presence of this isomer unlikely.

The NMR spectra of the free macrocycle, recovered for **3**, clearly indicate that oxidation of the aromatic amine moieties has not occurred. This serves to confirm that the cobalt(III) complexes prepared by the methods described here (which avoid the presence of cobalt(II)) contain the unchanged *o*-phenylenediamine units and not the benzoquinone diimide structures produced when mixtures of cobalt(II) and 1,2-diaminobenzene are subjected to oxidizing conditions.[7]

The macrocycle seems to be essentially pure tribenzo[21]aneN$_6$ with no detectable quantities of dibenzo[14]aneN$_4$, benzo[7]aneN$_2$, or more complex species present. The elemental analysis and osmometry results do not completely rule out small amounts of byproducts. However, both the proton and carbon-13 NMR spectra were quite sharp and clean, and we conservatively estimate that any byproducts present should have been detectable at a level of 5%. This specificity can be rationalized on steric grounds with the assumption that only facial linkages are formed on the cobalt octahedron. This restriction is sufficient to uniquely determine the stereochemical course of the entire reaction sequence to that sequence illustrated in eq 1 and 2.

It would seem as though procedures of this type could be applied to a variety of amines coordinated to a variety of metal ions, as the most apparent limitation is that the metal complex must be sufficiently robust that it can be doubly deprotonated and that this species must survive long enough under the appropriate

---

(4) The use of the sterically hindered base 2,6-lutidine to carry out the deprotonation in this case was simply a matter of convience. More drastic conditions would be required for the deprotonation of a less acidic complex.

(5) Malitizkii, W. *J. Chim. Ukraine* **1925**, *1*, 374–377. This seems to be the only previous report of the preparation of cobalt(III)-*o*-phenylenediamine complexes.

(6) Bosnich, B. *Acc. Chem. Res.* **1969**, *2*, 266–273 and references therein.

(7) Zehnder, M.; Löliger, H. *Helv. Chim. Acta* **1980**, *63*, 754–760.

conditions to react with an appropriate electrophile.

Experimental Section

Materials and Methods. 1,2-Diaminobenzene was purified by recrystallization from ethanol, using charcoal as an adsorbent. All other chemicals were of the best commercially available grade and were used without further purification.

Visible and UV spectra were obtained with a Cary 14 spectrophotometer. Circular dichroism spectra were obtained with a JASCO ORD/CD-5 spectrometer. ^{1}H NMR spectra were recorded with either a Varian T-60 spectrometer or a Varian EM-360 spectrometer. ^{13}C NMR spectra were recorded on a JEOL Fourier transform NMR spectrometer. Microanalyses were performed by Atlantic Microlab Inc.

Preparation of 1,3-Bis[(*o*-aminophenyl)amino]propane. 1,3-Bis[(*o*-aminophenyl)amino]propane was prepared by a published procedure:[3] mp 78 °C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.0 (β-methylene quintet), 3.0 (NH), 3.3 (α-methylene, triplet), 6.8 (aromatic).

Preparation of [1,3-Bis[(*o*-aminophenyl)amino]propane](1,2-diaminobenzene)cobalt(III) Chloride (2). The hydrochloride salt of 1,3-bis[(*o*-aminophenyl)amino]propane (4.02 g, 10 mmol) was added to a slurry of $Na_3[Co(CO_3)_3]\cdot 3H_2O$[2] (3.62 g, 10 mmol) in 10 mL of water, and the mixture was heated to 50 °C for 1 h. At this time CO_2 evolution had stopped, and the originally green solution had become dark purple. The hydrochloride salt of 1,2-diaminobenzene (1.81 g, 10 mmol) was added, and the mixture was heated for an additional hour at 50 °C. When the reaction was complete, a small amount of a black insoluble material (probably Co_3O_4) had precipitated. The insoluble material was filtered off, and the filtrate was evaporated to dryness. The very dark reddish brown residue was dissolved in a minimum amount of hot methanol, and the complex was precipitated by adding ether to the cooled solution: yield 2.0 g, 38%.

Preparation of Tris(1,2-diaminobenzene)cobalt(III) Chloride (4). The hydrochloride salt of 1,2-diaminobenzene (30 g, 20 mmol) was added to a slurry of $Na_3[Co(CO_3)_3]\cdot 3H_2O$ (1.8 g, 5 mmol) in 10 mL of water, and the mixture was heated for 1 h. The solution was filtered, and the filtrate was evaporated to dryness. The dark residue was dissolved in a minimum amount of hot ethanol, and the desired complex was precipitated by adding ether to the cooled solution.

The complex could also be prepared in low yield by the method of Malitizkii.[5] However, the yield was considerably better with the carbonato procedure.

Preparation of (Tribenzo[21]aneN$_6$)cobalt(III) Chloride (3). **2** (1.6 g, 3.0 mmol) was dissolved in 300 mL of methanol. 2,6-Lutidine (0.65 g, 6.0 mmol) was added followed by 1,3-propyl ditosylate (1.15 g, 3.0 mmol), and the solution was stirred for 48 h at 45 °C. At the end of this time, an additional 6.0 mmol of 2,6-lutidine and 3.0 mmol of 1,3-propyl ditosylate were added, and the heating and stirring were continued for another 48 h. The solution was then cooled, filtered, acidified with dilute hydrochloric acid, and evaporated to dryness. The residue was dissolved in a minimum amount of hot ethanol and the product precipitated by adding ether to the cooled solution: yield 1.2 g, 67%.

The preparation from **4** was essentially the same except that three successive cycles of adding base, ditosylate, and heating were carried out. At the end of the reaction period, a considerable amount of Co_3O_4 had precipitated, and three reprecipitations were required to obtain a reasonably pure product: yield 24%.

No reaction was observed when 1,3-dibromopropane was substituted for the 1,3-ditsoylate in the reaction with **2**.

Characterization of the Cobalt(III) Complexes. One problem with the preparation of cobalt(III) complexes by the carbonato procedure (which was necessary in these cases because of the well-known catalysis of the oxidation of phenylenediamine by cobalt(II)) is that sodium chloride is generated as a byproduct, and the complete removal of the sodium chloride from the desired product is frequently very difficult. For this reason satisfactory elemental analyses for the cobalt complexes were not obtained. The analyses all indicated coprecipitation of sodium chloride. The C, H, and N analyses were typically several percent low and variable from sample to sample, while the Cl analyses were high. However, the ratios of C to H and N were satisfactory for the expected ligands on the assumption that the ligands were the only source of these elements. The NMR spectra were qualitatively correct but badly broadened, presumably due to a low-lying triplet state. The conductivities were determined and found to be appropriate for a 3:1 electrolyte (molar conductance 35 020 Ω^{-1} M^{-1} cm^2). In addition, pH titrations and absorption spectra indicated typical purities of 90% to 95%.

pK_a's of the Cobalt Complexes. The pK_a's of complex **4** were determined spectrophotometrically. Equal amounts of complex **4** were dissolved in a series of 13 buffer solutions (total ionic strength 1.0) having pHs ranging from 0.0 to 7.9. The pK_a's were calculated by means of a least-squares fit of the 350–600-nm region of the absorption spectra. It was necessary to include three ionization steps in order to obtain a satisfactory fit to the experimental spectra. pK_1 = 2.0 ± 0.1; pK_2 = 4.7 ± 0.2; pK_3 = 5.7 ± 0.3.[8] At higher pHs, additional spectral changes and precipitation occurred.

A pH titration was carried out in order to confirm these values, and the same value of pK_1 was obtained, but pK_2 and pK_3 were too close together to be separated on the basis of the titration data alone. However, a calculated pH titration curve based on the pK values given above was in agreement with the experimental curve within experimental error up to a pH of 8.0.

More limited studies with complexes **2** and **3** indicated very similar spectral behavior and pK_a values. **3** may be slightly less acidic, but the difference in the pK_a's was not statistically significant.

Optical Resolution of Complex 3. Ammonium α-bromocamphorsulfonate (4.0 g) was added slowly to a solution of 0.4 g of **3** in 30 mL of water. The precipitate was filtered off and recrystallized from water. The circular dichroism and absorption spectra were taken, and the recrystallization was repeated twice with the CD and absorption spectra taken after each recrystallization. The Kuhn dissymmetry factor, $(\epsilon_l - \epsilon_r)/\epsilon$, was unchanged after the first recrystallization, and so it was assumed that the resolution was complete.[9] The complex was then converted back to the chloride salt by passing it through a Dowex 1 ion-exchange column in the chloride form.

Recovery of Tribenzo[21]aneN$_6$ (1). Complex **3** (0.85 g, 1.14 mmol) was dissolved in 30 mL of water. The solution was made strongly basic with sodium hydroxide and stirred for several hours. The aqueous solution was extracted with three 25-mL portions of ether. The ether extracts were combined and the ether was removed. The residue was dissolved in 0.5 M hydrochloric acid and extracted three times with ether, and the ether extracts were discarded. The aqueous layer was then made basic with sodium hydroxide and reextracted with three more 25-mL portions of ether. The combined ether extracts were dried over magnesium sulfate and evaporated to dryness. The light brown solid was then recrystallized twice from 50% ethanol–water containing charcoal. The product was obtained as colorless hygroscopic needles: recovery of purified **1**, 0.150 g (0.34 mmol), 30%; mp 189 °C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.1 (NH), 1.6 (6 H, β-methylene, quintet), 2.8 (12 H, α-methylene, triplet) ($J_{\alpha\beta}$ = 6.6Hz), 6.7 (12 H, aromatic); ^{13}C NMR ($CDCl_3$, Me_4Si, $\{^1H\}$) δ 37.07 and 39.62 (methylene), 115.94, 119.40, and 134.02 (aromatic); osmometry molecular weight 435 ± 20 (in H_2O); theoretical 444.

Mass spectra were not definitive, a complex fragmentation pattern with no molecular ion was observed. The heaviest strong peak in the mass spectrum corresponded to molecular ion − 14.

Elemental analysis $C_{27}H_{36}N_6\cdot 3H_2SO_4$: C, H, N.

---

(8) The quoted uncertainties are the range over which the pK_a's could be varied while maintaining the fit between the calculated and experimental spectra within the expected experimental uncertainties.

(9) The other complexes, **2** and **4**, could not be resolved by the same procedure, presumably because of the more rapid racemization that would be expected for these structures.