SCIENCE

Molecular Borromean Rings

Kelly S. Chichak,[1] Stuart J. Cantrill,[1] Anthony R. Pease,[1] Sheng-Hsien Chiu,[1] Gareth W. V. Cave,[2] Jerry L. Atwood,[2] J. Fraser Stoddart[1]*

SUPPORTING INFORMATION

Revised Version

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[1]Department of Chemistry and Biochemistry and the California NanoSystems Institute, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90095, USA. [2]Department of Chemistry, University of Missouri-Columbia, MO 65211, USA.

*To whom correspondence should be addressed. E-Mail: stoddart@chem.ucla.edu

Synthesis and Characterization

The diamine **DAB** containing the bipyridyl ligand was obtained (Scheme S1) as its $4CF_3CO_2^-$ salt **DAB**-H_4·4TFA in five steps starting from 4-methoxybenzylamine. Nucleophilic cleavage of the methyl ether in refluxing 48% HBr afforded (92%) the hydrobromide **1**-H·Br of 4-hydroxybenzylamine. When this salt was treated with 1.1 equivalents of (*t*-Boc)$_2$O in a methanolic suspension of $NaHCO_3$, the *t*-butyloxy-carbonyl-protected amine **2** was isolated in 93% yield. In the meantime, the bipyridyl-*N,N*′-dioxide **3** was prepared by the treatment of 4,4′-dinitro-2,2′-bipyridyl-*N,N*′-dioxide (*S1*) with the sodium salt of **2** in anhydrous DMF at 50 °C. Compound **4** was produced (93%) by the catalytic transfer hydrogenation of **3** using 10% Pd/C with NaH_2PO_2 as the source of H_2 in a mixture of EtOH/AcOH under mild conditions. In the final step, **DAB**-H_4·4TFA was isolated in almost quantitative yield following *t*-Boc deprotection using CF_3CO_2H in CH_2Cl_2. Depending on whether MeOH or 95% EtOH are employed as solvent in reactions between equimolar amounts of **DFP**, **DAB**-H_4·4TFA, and $Zn(OAc)_2$, two outcomes prevail—(i) one in MeOH, where a single product (**BR**) containing six Zn(II) ions is isolated and (ii) in 95% EtOH where two inseparable products, one (**BR**) containing six Zn(II) ions as before, and the other (**Zn@BR**) containing seven Zn(II) ions—as indicated by ^{1}H NMR spectroscopy and ESI mass spectrometry (see Fig. 2 and Fig. 4 in the article itself).

Materials and Methods

All solvents (EM Science) were dried prior to use according to literature procedures. 95% Ethanol (Pharmco) and deuterated solvents (Cambridge Isotope Laboratories) for NMR spectroscopic analyses were used as received. All reagents and starting materials, including 2,6-diformylpyridine (**DFP**), were purchased from Aldrich and used without further purification. 4,4′-Dinitro-2,2′-bipyridyl-*N,N*′-dioxide was synthesized according to a known literature procedure (*S1*). Thin-layer chromatography (TLC) was performed either on aluminum sheets coated with silica-gel 60F (Merck 5554) or on aluminum sheets coated with aluminum oxide 60F (Merck 5550/7, neutral). The plates were inspected by UV light. Column chromatography was carried out, either by using silica-gel 60 (Merck 9358, 230–400 mesh) or by using aluminum oxide (Aldrich, 150 mesh, neutral, activity II). Melting points were determined on an Electrothermal 9100 melting-point apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance600 (600 MHz and 150 MHz, respectively), Bruker

Avance500 (500 MHz and 125 MHz, respectively), or Bruker ARX500 (500 MHz and 125 MHz, respectively). All chemical shifts are quoted in ppm, relative to tetramethylsilane, using the residual solvent peak as a reference standard. Mass spectra were measured on an IonSpec 7.0T Ultima FTMS with MALDI and ESI ion sources. MALDI Mass spectra were obtained using dihydroxybenzoic acid as the supporting matrix. Electrospray mass spectra were obtained with either MeOH or MeCN as the liquid carrier.

1-H·Br: The following procedure is a modified one based on that reported (*S2*) in the patent literature. When 4-methoxybenzylamine (11.6 g, 84.6 mmol) was added with stirring to 48% HBr (30 mL), a precipitate was formed. *Since an extremely exothermic reaction ensues, the addition was done very slowly.* The mixture was then stirred under reflux for 6 h, before being cooled down to room temperature and concentrated to dryness, giving a light pink solid. MeCN (20 mL) was added to this residue and the product **1**-H·Br was collected by filtration and dried under vacuum. Yield: 16.2 g, 92%. The product was identified by ^{1}H NMR spectroscopy and then employed in the next step without further purification. ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 3.95 (s, 2H), 6.79 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H).

2: Di-*tert*-butyl dicarbonate (18.5 g, 84.8 mmol) was added with stirring under an atmosphere of argon to a solution of **1**-H·Br (16.0 g, 78.4 mmol) and $NaHCO_3$ (26.3 g, 313 mmol) in MeOH (200 mL) at room temperature. After stirring the reaction mixture for 24 h, it was filtered to remove excess of $NaHCO_3$. The solvents were removed under reduced pressure and the oily residue was purified by column chromatography [SiO_2: EtOAc/hexanes (1:4)] to afford **2** as a yellow oil. Yield: 16.2 g, 93%. ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): δ = 1.46 (s, 9H), 4.19 (d, J = 5.5 Hz, 2H), 5.09 (bs, 1H), 6.77 (d, J = 8.5 Hz, 2H), 6.96 (bs, 1H), 7.09 (d, J = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C): δ = 28.5, 44.4, 115.8, 129.1, 130.8, 156.0; HRMS (MALDI): *m/z* 246.1100 $[M+Na]^+$.

3: Solid NaH (550 mg, 22.8 mmol) was added in small portions (each addition was made after the evolution of gases subsided) to a stirred solution of **2** (4.69 g, 21.0 mmol) in DMF (10 ml) under an argon atmosphere. 4,4′-Dinitro-2,2′-bipyridyl-*N*,*N*′-dioxide (2.54 g, 9.13 mmol) was added to this solution and the resulting brown reaction mixture was heated at 50 °C for 4 h. Thereafter, the solution was cooled down to room temperature and poured into H_2O (250 mL) before being extracted with EtOAc (3 × 125 mL) and once with CH_2Cl_2 (100 mL). The combined organic extracts were then washed

with water (3 × 125 mL), brine (125 mL), and dried over Na_2SO_4. The solvents were removed under reduced pressure to give an orange-colored product which was recrystallized from EtOAc, affording **3** as light orange plates. Yield: 3.71 g, 64%. M.p. 217–218 °C; ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): δ = 1.44 (s, 18H), 4.08 (d, J = 5.8 Hz, 4H), 5.12 (bs, 2H), 6.92 (dd, J = 3.5, 7.3 Hz, 2H), 7.08 (d, J = 8.5 Hz, 4H), 7.15 (d, J = 3.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 4H), 8.12 (d, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C): δ = 28.5, 44.1, 115.8, 116.6, 120.8, 129.6, 137.5, 141.1, 143.0, 153.7, 155.2; HRMS (MALDI): *m/z* 631.2762 $[M+H]^+$.

4: The following procedure is a modified one based on that reported (*S3*) for the deoxygenation of 2,2′-bipyridyl-*N*,*N*′-dioxide. An excess of NaH_2PO_2 (4.28 g, 47.6 mmol) was added in one portion to a three-necked flask equipped with a condenser containing a stirred suspension of **3** (3.00 g, 4.76 mmol) and 10% Pd/C (1.00 g) in 75/15 EtOH/AcOH (90 mL). The reaction flask was sealed with a balloon to prevent the loss of the H_2 gas which evolves from the decomposition of NaH_2PO_2 and the mixture was heated at 70 °C for 15 h. The reaction mixture was then cooled down to room temperature and filtered through Celite. The filter cake was washed with CH_2Cl_2 (3 × 100 mL). The filtrates were combined and the volume was concentrated to 50 mL under reduced pressure, giving a light yellow solution. The AcOH was neutralized by adding solid $NaHCO_3$ (6 g) in H_2O (50 mL). The solution was concentrated to dryness, producing a beige product which was suspended in H_2O, collected by filtration, washed with H_2O, and dried. Yield: 2.62 g, 93%. The crude product was recrystallized from EtOAc/hexanes, affording **4** as fine white needles. Yield: 2.21 g, 78%. M.p. 158–160 °C; ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): δ = 1.45 (s, 18H), 4.33 (d, J = 7.1 Hz, 4H), 5.04 (bs, 2H), 6.86 (dd, J = 3.5, 7.3 Hz, 2H), 7.11 (d, J = 8.5 Hz, 4H), 7.37 (d, J = 8.5 Hz, 4H), 7.92 (d, J = 3.5 Hz, 2H), 8.44 (d, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C): δ = 28.5, 44.2, 109.3, 112.9, 121.2, 129.5, 137.0, 151.0, 153.7, 158.1, 166.1; HRMS (MALDI): *m/z* 621.2684 $[M+Na]^+$.

DAB-H_4·4TFA: The Boc protecting groups in **4** were removed by the addition of CF_3CO_2H (4 mL) to a solution of **4** (1.00 g, 1.67 mmol) in CH_2Cl_2 (50 mL) with stirring at room temperature for 48 h. The reaction mixture was concentrated to dryness, leaving a sticky residue. The excess of CF_3CO_2H was removed by three repeated additions and removals of MeOH (20 mL) by rotary evaporation under reduced pressure at 50 °C, leaving a pink sticky residue. This residue was treated with CH_2Cl_2 and the solvent was removed by rotary evaporation under reduced pressure at 40 °C until a light pink

amorphous solid remained that is moisture sensitive. It was employed as one of the starting materials in the next step without further purification. Yield of crude **DAB**-H_4·4TFA: 1.32 g, 95%; ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ = 4.20 (s, 4H), 7.18 (dd, J = 3.5, 7.3 Hz, 2H), 7.33 (d, J = 8.5 Hz, 4H), 7.64 (d, J = 8.5 Hz, 4H), 8.06 (d, J = 3.5 Hz, 2H), 8.66 (d, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD, 25 °C): δ = 43.6, 112.8, 114.8, 117.9 (q, J = 291 Hz, TFA), 122.6, 132.8, 133.0, 149.8, 152.2, 155.2, 162.3 (q, J = 35.5 Hz, TFA) 170.0; HRMS (ESI): *m/z* (%) 399.1836 (100) $[M–4CF_3CO_2H+H]^+$, 819.3428 (62) $[2M–8CF_3CO_2H+Na]^+$.

BR·12TFA and **Zn@BR**·14TFA: The reaction to make the Borromean links was carried out in both reagent grade MeOH and 95% EtOH. Hence, the solvent in the procedure will be referred to as an alcohol. $Zn(OAc)_2$ (32.9 mg, 0.179 mmol) was added to a stirred alcoholic solution (15 mL) containing **DAB**-H_4·4TFA (153 mg, 0.179 mmol) and DFP (24.2 mg, 0.179 mmol) and the reaction mixture was heated under reflux for 36 h producing a pale yellow colored solution. The solvents were removed by rotary evaporation under reduced pressure at 50 °C, leaving pale yellow-colored products. The crude products were purified by recrystallization from a MeOH (2 mL) solution into which Et_2O was allowed to diffuse slowly. Yield of **BR**·12TFA from the reaction in MeOH solution: 110 mg, 78%; ^{1}H NMR (600 MHz, CD_3OD, 25 °C): δ = 4.84 (s, 24H), 6.50 (bs, 12H), 6.68 (d, J = 8.4 Hz, 24H), 6.74 (d, J = 8.4 Hz, 12H), 7.97 (d, J = 2.4 Hz, 12H), 8.31 (d, J = 7.8 Hz, 24H), 8.62 (d, J = 7.8 Hz, 12H), 8.89 (s, 12H); ^{13}C NMR (150 MHz, CD_3OD, 25 °C) 15 of 16 signals: δ = 63.1, 112.6, 113.9, 117.9 (q, J = 296 Hz, TFA), 122.3, 130.8, 131.2, 135.1, 145.5, 148.2, 151.7, 153.3, 162.0, 162.5 (q, J = 34.6 Hz, TFA) 169.8; HRMS (ESI): *m/z* (%) 1465.1902 (10) $[M–3CF_3CO_2]^{3+}$, 1070.1398 (100) $[M+Zn–4CF_3CO_2]^{4+}$, 833.7088 (50) $[M–5CF_3CO_2]^{5+}$. Yield of **BR**·12TFA and **Zn@BR**·14TFA in admixture from the reaction in 95% EtOH: 92 mg, 65%. For the ^{1}H NMR spectra and ESI mass spectra of **BR**·12TFA plus **Zn@BR**·14TFA, see Fig. 2 and Fig. 4 in the article.

References and Notes

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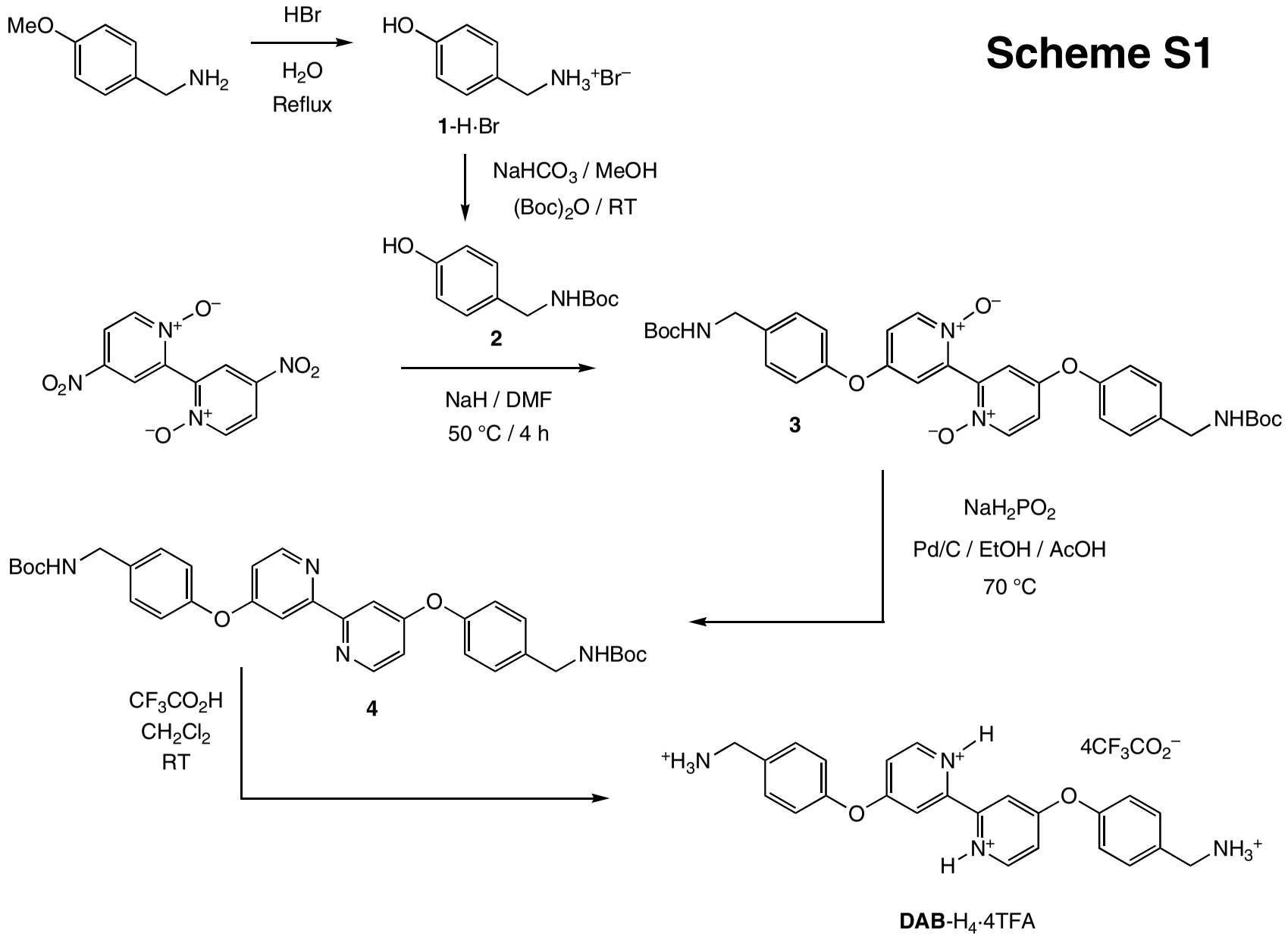
Scheme S1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NH2
HBr
H2O
Reflux
HO
NH3+Br−
1-H·Br
NaHCO3 / MeOH
(Boc)2O / RT
HO
NHBoc
2
O2N
NO2
NaH / DMF
50 °C / 4 h
BocHN
3
NHBoc
NaH2PO2
Pd/C / EtOH / AcOH
70 °C
BocHN
4
NHBoc
CF3CO2H
CH2Cl2
RT
+H3N
4CF3CO2−
NH3+
DAB-H4·4TFA