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Macrocyclic Metalloenediynes of Cu(II) and Zn(II): A Thermal Reactivity Comparison

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The syntheses of tetradentate enediyne macrocycles with 24 (tact1:1)-, 26 (tact1:2)-, and 28 (tact2:2)-membered rings are described, along with their thermal reactivities and those of the corresponding Cu(II) (Cu(tact1:1), Cu-(tact1:2)) and Zn(II) (Zn(tact1:1), Zn(tact1:2)) complexes. These enediyne macrocyclic ligands are not benzannulated and thus exhibit thermal Bergman cyclization temperatures near 200 °C by differential scanning calorimetry (DSC). Moreover, the synthetic route allows incorporation of additional carbon atoms into the macrocycles which increases their conformational flexibilities and lowers their Bergman cyclization temperatures. Specifically, as the size of the macrocycle increases, the temperatures at which these compounds undergo Bergman cyclization decrease by ∼5 °C per additional carbon atom, leading to an overall decrease across the series of 19 °C. Incorporation of Cu(II) and Zn(II) into these macrocycles further reduces their cyclization temperatures relative to those of the free ligands. More uniquely, for Cu(tact1:1) and Zn(tact1:1), the observed cyclization temperatures vary by 27 °C with the Zn(II) complex lying to higher temperature (Cu(tact1:1) = 121 °C, (Zn(tact1:1) = 148 °C). As the macrocycle size is increased, the decrease in the Bergman cyclization temperatures observed for the free ligands does not systematically hold for the Cu(II) and Zn(II) derivatives. Rather, the Cu(II) complex exhibits the expected 9 °C decrease in the cyclization temperature (Cu(tact1:2) = 112 °C), whereas the temperature for the Zn(II) analogue increases by 15 °C (Zn(tact1:2) = 163 °C). From the X-ray crystal structure of the free ligand and the geometric structural preferences of the electronic configurations of Cu(II) and Zn(II), the higher cyclization temperatures for the Zn(II) complex with the larger ring size can be explained by a distortion of the macrocycle toward a more tetrahedral metal center geometry.

Introduction

Metal ions, by virtue of their ability to dictate the conformational disposition of bound ligands through the geometric preferences of their electronic configurations, are emerging as key co-reagents for influencing the temperatures for thermal Bergman cyclization of bound enediynes.[1−11] Within this paradigm, it is intuitively apparent that the largest variations in the temperature required to generate the 1,4-phenyl diradical intermediate[12] will result from geometries that stabilize the enediyne framework by increasing the distance between the alkyne termini.[1,4,5,10,11] Indeed, this simple model is born out by experiments which show that the most dramatic differences in Bergman cyclization temperatures for compositionally analogous metalloenediynes occur between reactive planar or tetragonal ML_4 structures and their considerably more stable tetrahedral counterparts.[1,4,5,10,11] Moreover, the limits to which these reactivity differences can be extended is directly related to the degree of enediyne ligand conformational flexibility.[5,11] Experimentally, rigid tetrahedral structures are only activated for cyclization at extremely high temperatures, while their planar or tetragonal analogues can react at dramatically reduced temperatures (Δ = ∼170 °C). These fundamental structural inorganic chemistry arguments and examples have led to a predictive model for the thermal reactivities of simple metalloenediyne constructs derived from chelating enediyne ligands.

Although the coordination chemistry/thermal reactivity correlations are becoming clear for simple enediyne ligands, extension of these concepts to tetradentate, macrocyclic, metalloenediyne constructs is important because such designs may have considerable advantages for biological applications due to their enhanced metal-binding constants. However, to date, few examples of such metalloenediynes are available to document structure/function relationships of these macrocycles and their metalated counterparts.[3,6] To this end, we report the preparation of a series of macrocyclic enediynes derived from the tetradentate bis(ethylenediamine) binding motif which are linked by two enediyne subunits (Figure 1). These ligands are not benzannulated and, as a result, are somewhat more thermally labile than previously published analogues.[3,6] To probe the role of macrocycle flexibility in affecting the Bergman cyclization temperature, we have extended the size of these tetradentate ligands by introduction of additional carbon atoms between the metal-binding motif and the enediyne termini to generate 24-, 26-, and 28-membered rings. Incorporation of Cu(II) and Zn-(II) into these macrocycles leads to thermal cyclization temperatures that are governed by the electronic configuration of

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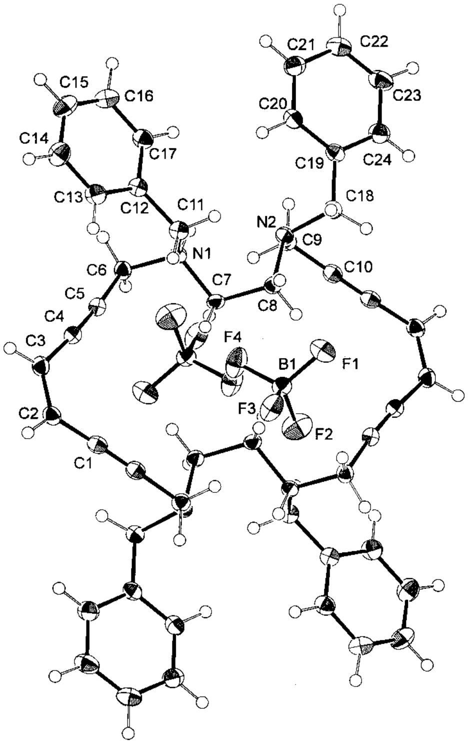

Figure 1. ORTEP of the X-ray crystal structure of **8a** (top view). Thermal ellipsoids are shown at 50% probability. The BF_4^- counterions lie above and below the plane of the page.

the metal and the ability of the macrocycle to adopt corresponding conformation.

Experimental Section

Materials and Methods. All chemicals and solvents used in synthetic procedures were of the highest purity available from Aldrich and Fluka. Reactions were carried out under nitrogen using Schlenk and drybox techniques. Benzene and diethyl ether were distilled from sodium/benzophenone prior to use. Methylene chloride and *n*-butylamine were dried and distilled from calcium hydride. The organic enediynes were purified by flash chromatography using silica gel (200−440 mesh).

Physical Measurements. Electron paramagnetic resonance spectra were recorded on an ESP 300 Bruker instrument under the following conditions: microwave frequency, ~9.5 GHz; microwave power, 10 mW; modulation amplitude, 3.16 G; modulation frequency, 100 kHz; receiver gain, 2.0×10^4. ^1H NMR and ^{13}C NMR spectra were recorded on a VXR 400 NMR spectrometer using the residual proton resonance of the solvent as an internal reference. The multiplicities of the ^{13}C NMR signals were determined by the DEPT technique. Infrared spectra were recorded on a Nicolet 510P FTIR spectrometer. Elemental analyses on all of the samples were obtained from Robertson Microlit Laboratories Inc., and ESI and FAB mass data were obtained at the University of Illinois with a micromass Quatto-I mass spectrometer. Differential scanning calorimetry (DSC) traces were recorded on a V4.1 Dupont 910 DSC differential scanning calorimeter coupled to a DuPont thermal analyst 2100 at a heating rate of 10 °C min^{-1}.

X-ray Structure of the $H_2(BF_4)_2$ Salt of 8. X-ray quality crystals were grown from a CH_3CN/Et_2O solvent mixture. A colorless crystal (approximate dimensions $0.48 \times 0.35 \times 0.08$ mm^3) was placed on the tip of a glass capillary and mounted on a Bruker SMART system. The data were collected at 115(2) K using MoKα radiation (graphite monochromator) with a frame time of 5 s and a detector distance of 4.98 cm. A randomly oriented region of a sphere in reciprocal space was surveyed to a resolution of 0.71 Å. Four major sections of frames were collected with 0.30° steps in ω at four different ϕ settings and a detector position of −43° in 2θ. An additional set of 50 frames was collected in order to model decay, and the intensity data were corrected for absorption and decay (SADABS).[13] Final cell constants were calculated from the *xyz* centroids of 842 strong reflections from the actual data collection after integration (SAINT).[14]

The structure was solved using SIR-92[15] and refined using SHELXL-97.[16] The space group, $P\bar{1}$, was determined on the basis of systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least-squares/difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located from the difference map and refined with individual isotropic displacement parameters. The final full-matrix least-squares refinement converged to R1 = 0.0469 and wR2 = 0.1229 (F^2, all data).

Syntheses. 3-Butyn-1-yl methanesulfonate (2). Compound **2** was prepared by a modified literature method.[17] A reaction flask containing methylene chloride (50 mL) and triethylamine (7.9 g, 78 mmol) was charged with 3-butyn-1-ol (5.0 g, 71 mmol) under a nitrogen atmosphere at 20 °C. The reaction mixture was cooled to 0−5 °C, and a solution of methanesulfonyl chloride (8.18 g, 71 mmol) in methylene chloride (50 mL) was added over 30 min. The reaction was warmed to 20 °C and allowed to stir for 1 h. After completion, the reaction was quenched by pouring the mixture into chilled water (200 mL). The aqueous and organic layers were separated, and the latter was washed with water (2 × 50 mL). The organic material was dried over anhydrous sodium sulfate, and the solvent was subsequently removed under reduced pressure to give a colorless oil. Yield: 10 g, 95%. ^1H NMR ($CDCl_3$): 2.07 (t, $J = 2.5$ Hz, 1H, CH), 2.63−2.67 (m, 2H, CH_2), 3.05 (s, 3H, SO_2Me), 4.30 (t, $J = 8$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 20.04 (CH_2), 37.97 (CH_3), 52.88 (CH_2), 67.40 (CH_2), 71.23 (CH), 78.95 (Cquart).

***N*,*N*′-Dibenzyl-*N*,*N*′-di-prop-2-ynyl-ethane-1,2-diamine (4).**[3] A flask was charged with *N*,*N*′-dibenzylethylenediamine (**3**) (10.0 g, 42 mmol) followed by dry dimethylformamide (50 mL), and the mixture was allowed to stir at 15 °C for 10 min. Anhydrous potassium carbonate (17.25 g, 125 mmol) was then added, and the mixture was cooled to 10 °C. A solution of propargyl bromide (11.04 g, 93 mmol) in dry dimethylformamide (50 mL) was then added dropwise over 1 h. The reaction mixture was stirred for 8 h. After completion of the reaction, the solid was filtered and washed with dimethylformamide (2 × 25 mL). The combined organic layers were poured into water (1.5 L) and then extracted with methylene chloride (300 mL). The methylene chloride layer was washed with water (3 × 500 mL) and dried over anhydrous sodium sulfate. Finally, the solvent was removed under reduced pressure. The crude product was purified on a silica gel column with ethyl acetate/hexane (2:8) which gives the desired product in good yield. Yield: 12.0 g, 91%. ^1H NMR ($CDCl_3$): 2.24 (t, $J = 4$ Hz, 2H, 2CH), 2.75 (s, 4H, $2CH_2$), 3.39 (s, 4H, $2CH_2$), 3.66 (s, 4H, $2CH_2$), 7.26−7.37 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$): 42.06 (CH_2), 51.50 (CH_2), 58.43 (CH_2), 73.48 (CH), 79.04 (Cquart), 127.39 (CH), 128.55 (CH), 129.37 (CH), 139.02 (Cquart). Mass: *m*/*z* 317 ($M^+ + 1$), 315, 277, 225, 158. IR (KBr, cm^{-1}): 3281, 3060, 2955, 2833, 2090, 1956, 1891, 1771, 1600, 1493, 1367, 1286, 1177, 1088, 1027, 977, 942, 863, 783, 700.

***N*,*N*′-Dibenzyl-*N*,*N*′-di-but-3-ynyl-ethane-1,2-diamine (5).** A Schlenk flask was charged with **3** (5.0 g, 21 mmol) in dimethylformamide (50 mL) and anhydrous potassium carbonate (10.0 g, 72 mmol). The mixture was stirred at 50−55 °C for 10 min. A solution of **2** (10.0 g, 68 mmol) in dimethylformamide (50 mL) was then added dropwise over 30 min. The mixture was further stirred at 50−55 °C for 12 h, and the progress of the reaction was monitored by TLC and NMR over this period. The mixture was cooled to 25 °C, filtered, washed with dimethylformamide (2 × 25 mL), and poured into 1.5 L of water. The product was extracted with methylene chloride (2 × 200 mL) and

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washed with water (3 × 500 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The viscous oil obtained was purified on silica gel with ethyl acetate/hexane (2:8) to give **5**. Yield: 3.0 g, 42%. ^{1}H NMR ($CDCl_3$): 1.91 (t, 2H, 2CH), 2.53 (bs, 4H, $2CH_2$), 3.31−3.40 (m, 4H, $2CH_2$), 4.22 (t, $J = 4$ Hz, 4H, $2CH_2$), 4.58 (t, $J = 8$ Hz, 4H, $2CH_2$), 7.21−7.33 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$): 19.63 (CH_2), 44.14 (CH_2), 44.49 (CH_2), 44.75 (CH_2), 45.36 (CH_2), 50.84 (CH_2), 51.28 (CH_2), 63.49 (CH_2), 70.15 (CH), 80.56 (Cquart), 80.76 (Cquart), 127.70 (CH), 127.90 (CH), 128.12 (CH), 128.34 (CH), 128.81 (CH), 137.36 (Cquart), 156.36 (Cquart). Mass: *m/z* 344 (M^+), 253, 216, 91. IR (KBr, cm^{-1}): 3231, 3061, 2947, 2120, 1690, 1432, 1289, 1236, 1105, 1027, 879, 769.

***N*,*N*′-Dibenzyl-*N*,*N*′-bis-((*Z*)-5-chloropent-4-ene-2-ynyl)-ethane-1,2-diamine (6).** To a stirred mixture of $Pd(PPh_3)_4$ (0.219 g, 0.18 mmol), CuI (0.120 g, 0.63 mmol), *n*-butylamine (1.15 g, 16 mmol), and *cis*-dichloroethylene (0.67 g, 6.9 mmol) was added **4** (1.0 g, 3.1 mmol) in benzene (50 mL) dropwise under nitrogen at 40 °C over 30 min. The reaction mixture was stirred for an additional 2 h, over which time the reaction was monitored by TLC and ^{1}H NMR. The resulting solid was filtered and washed with ether (3 × 50 mL), and the combined benzene/ether layers were concentrated under reduced pressure. The viscous material was chromatographed (silica gel) with ethyl acetate/hexane (2:10) to give the desired product **6** in 72% yield. Viscous colorless oil, R_f: 0.3. ^{1}H NMR ($CDCl_3$): 2.81 (s, 4H, $2CH_2$), 3.57 (d, 4H, $2CH_2$), 3.71 (s, 4H, $2CH_2Ph$), 5.90−5.93 (m, 2H, 2CH), 6.37 (d, $J = 7$ Hz, 2H, 2CH), 7.25−7.39 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$): 42.66 (CH_2), 51.41 (CH_2), 58.32 (CH_2), 79.74 (Cquart), 93.67 (Cquart), 112.21 (CH), 127.26 (CH), 128.40 (CH), 129.27 (CH), 138.81 (Cquart). Mass: *m/z* 436 (M^+), 438 ($M^+ + 2$), (^{35,37}Cl), 347, 345, 220, 218, 91. IR (neat, cm^{-1}): 3060, 2920, 2828, 2199, 1675, 1601, 1584, 1494, 1392, 1264, 1099, 890, 769.

***N*,*N*′-Dibenzyl-*N*,*N*′-bis-((*Z*)-6-chloro-hex-5-ene-3-ynyl)-ethane-1,2-diamine (7).** Compound **7** was prepared in 82% yield by a procedure analogous to that given for **6**. Viscous colorless oil, R_f: 0.2. ^{1}H NMR ($CDCl_3$): 2.74 (bs, 4H, $2CH_2$), 3.33 (t, $J = 16$ Hz, 4H, $2CH_2$), 4.26 (t, $J = 4$ Hz, 4H, $2CH_2$), 4.45 (d, $J = 14$ Hz, 4H, $2CH_2$), 5.79 (d, $J = 9$ Hz, 2H, 2CH), 6.31 (d, $J = 10$ Hz, 2H, 2CH), 7.22−7.34 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$): 20.92 (CH_2), 44.20 (CH_2), 44.77 (CH_2), 45.43 (CH_2), 51.35 (CH_2), 51.48 (CH_2), 63.51 (CH_2), 72.26 (Cquart), 94.99 (Cquart), 95.11 (Cquart), 112.33 (CH), 127.84 (CH), 128.02 (CH), 128.25 (CH), 128.39 (CH), 128.90 (CH), 137.87 (Cquart), 156.46 (Cquart). Mass: *m/z* 464 (M^+), 466 ($M^+ + 2$), (^{35,37}Cl), 397, 395, 278, 276, 256, 254, 210, 167, 113, 91. IR (neat, cm^{-1}): 3058, 3028, 2960, 2272, 2218, 1700, 1590, 1495, 1424, 1320, 1133, 1106, 1047, 961, 821, 700.

1,4,13,16-Tetrabenzyl-1,4,13,16-tetraaza-cyclotetracosa-8,20-diene-6,10,18,22-tetrayne (tact1:1) (8). A mixture of **6** (1.0 g, 2.2 mmol) in benzene (20 mL), $Pd(PPh_3)_4$ (0.160 g, 0.138 mmol), CuI (0.086 g, 0.45 mmol), and *n*-butylamine (0.83 g, 11.4 mmol) was stirred under nitrogen at 40 °C. A solution of **4** (0.8 g, 2.5 mmol) in benzene (50 mL) was added dropwise under nitrogen over 2 h at 40 °C. The reaction mixture was stirred for 10 h with completion of the reaction determined by ^{1}H NMR. The reaction mixture was cooled to room temperature, and the salt was filtered and washed with ether (2 × 50 mL). The solvent was removed under reduced pressure, and the residue was extracted with methylene chloride (200 mL). The organic layer was washed with a saturated sodium chloride solution (2 × 100 mL) and finally with water (2 × 50 mL). Upon concentration under reduced pressure, the organic layer yields a viscous oil. Purification was performed on a silica gel column eluted initially with methylene chloride and finally with ethyl acetate/hexane (2:8) to yield the desired 1,4,-13,16-tetrabenzyl-1,4,13,16-tetraaza-cyclotetracosa-8,20-diene-6,10,18,-22-tetrayne macrocycle (0.2 g, 13%). Viscous oil. ^{1}H NMR ($CDCl_3$): 2.78 (s, 8H, $4CH_2$), 3.58 (s, 8H, $4CH_2$), 3.66 (s, 8H, $4CH_2Ph$), 5.86 (s, 4H, 4CH), 7.23−7.34 (m, 20H, Ar). ^{13}C NMR ($CDCl_3$): 42.82 (CH_2), 51.35 (CH_2), 58.54 (CH_2), 83.68 (Cquart), 92.66 (Cquart), 119.55 (CH), 127.40 (CH), 128.56 (CH), 129.45 (CH), 139.03 (Cquart). Mass: FAB *m/z* 681 ($M^+ + 1$), 589, 497, 340, 220, 191, 91. IR (neat, cm^{-1}): 3060, 3027, 2920, 2828, 2199, 1675, 1601, 1471,1320, 1264, 1073, 1028, 738, 698.

1,4,15,18-Tetrabenzyl-1,4,15,18-tetraaza-cyclooctacosa-9,23-diene-7,11,21,25-tetrayne (tact2:2) (9). To a stirring benzene solution (10 mL) consisting of a mixture of $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol), CuI (0.1 g, 0.52 mmol), and *n*-butylamine (0.36 g, 5 mmol) was added a solution of **7** (1.0 g, 2.1 mmol) in benzene (30 mL)which was stirred for 20 min under nitrogen. A solution of **5** (0.8 g, 2.3 mmol) in benzene (50 mL) was then added to the above solution dropwise over 1 h at 50−55 °C. The mixture was stirred for 2 h, during which the progress of the reaction was monitored by ^{1}H NMR. The crude mixture was then cooled to room temperature and quenched by pouring into cold water (200 mL). The product was extracted with benzene (200 mL) and washed with a saturated sodium chloride solution (2 × 100 mL). The solvent was removed under reduced pressure, and the residue obtained was purified by column chromatography (silica gel). Initial elution of the column with methylene chloride and subsequent elution with methanol/methylene chloride (1:9) give the desired bis(diazaenediyne) macrocycle. Yield: 0.5 g, 32%. ^{1}H NMR ($CDCl_3$): 2.71 (bs, 8H, $4CH_2$), 3.27−3.39 (m, 8H, $4CH_2$), 4.24 (bs, 8H, $4CH_2$), 4.41−4.46 (m, 8H, $4CH_2$), 5.69 (bs, 4H, 4CH), 7.26−7.31 (m, 20H, Ar). ^{13}C NMR ($CDCl_3$): 20.96 (CH_2), 44.20 (CH_2), 44.73 (CH_2), 45.46 (CH_2), 51.02 (CH_2), 51.40 (CH_2), 63.64 (CH_2), 79.68 (Cquart), 93.93 (Cquart), 119.36 (CH), 127.84 (CH), 128.01 (CH), 128.29 (CH), 128.37 (CH), 128.88 (CH), 137.85 (Cquart), 156.38 (Cquart). Mass: FAB *m/z* 737 ($M^+ + 1$), 645, 587, 369, 279. IR (neat, cm^{-1}): 3055, 2940, 2800, 2150, 1698, 1471, 1228, 1105, 736, 699.

[Cu(tact1:1)]$(BF_4)_2$ (10). A Schlenk flask was charged with a solution of $Cu(BF_4)_2 \cdot xH_2O$ (0.034 g, 0.14 mmol) in acetonitrile (10 mL) under nitrogen. The solution was heated to 40 °C, at which temperature a solution of the bis(diazaenediyne) macrocycle **8** (0.10 g, 0.14 mmol) in methylene chloride (10 mL) and acetonitrile (10 mL) was added dropwise over 30 min. The reaction mixture was stirred at 40 °C for 8 h, and the solvent was removed under reduced pressure. The crude product obtained was dissolved in acetonitrile (5 mL) and stirred for 3 h prior to precipitation with dry ether (20 mL). The solid was filtered, washed with ether (2 × 5 mL), and dried under vacuum. The solid was further stirred in ether (25 mL) for 2 h, filtered, and finally dried under vacuum at 40 °C. Yield: 120 mg, 90%. Mass: ESI *m/z* 743, 745, ^{63,65}Cu (M^+ calcd for $C_{48}H_{48}N_4Cu$, 743, 745), 681, 682, 339, 251, 91. IR (KBr, cm^{-1}): 3030, 2934, 2200, 1633, 1455, 1083. Anal. Calcd for $C_{48}H_{48}N_4Cu \cdot 2BF_4 \cdot 3H_2O$: C, 59.30; H, 5.61; N, 5.76. Found: C, 59.20; H, 5.60; N, 5.71.

[Zn(tact1:1)]$(CH_3COO)_2$ (11). A Schlenk flask was charged with $Zn(CH_3COO)_2 \cdot 2H_2O$ (0.032 g, 0.145 mmol) and methanol (10 mL) under a nitrogen atmosphere. The mixture was stirred for 10 min at 40 °C. A solution of **8** (0.10 g, 0.145 mmol) in methylene chloride (5 mL) and methanol (10 mL) was added over 30 min. The resulting solution was allowed to stir for 12 h at 40 °C. The solvent was removed, and the residue was stirred in ether (50 mL) for 2 h to remove uncomplexed ligand. After filtration of the crude metal complex and washing with ether (2 × 10 mL), the solid was dried under vacuum to yield **11** in 80%. ^{1}H NMR (CD_3CN): 2.0 (s, 6H, $2CH_3$), 3.05 (s, 8H, $4CH_2$), 3.66 (s, 8H, $4CH_2$), 3.93 (s, 8H, $4CH_2$), 6.06 (s, 4H, 4CH), 7.34 (bs, 20H, Ar). ^{13}C NMR (CD_3CN): 23.26 (CH_3), 43.10 (CH_2), 51.48 (CH_2), 59.04 (CH_2), 84.35 (Cquart), 93.21 (Cquart), 120.34 (CH), 128.27 (CH), 129.32 (CH), 130.22 (CH), 139.55 (Cquart), 180.65 (Cquart). Mass: ESI *m/z* 743, 745, ^{63,65}Zn (M^+ calcd for $C_{48}H_{48}N_4Zn$, 743, 745), 682, 681, 368, 365, 339, 325, 323, 251, 242, 239, 146, 132, 130. IR (KBr, cm^{-1}): 3050, 2820, 2220, 1628, 1456, 1100, 928, 740, 700, 623. Anal. Calcd for $C_{48}H_{48}N_4Zn \cdot 2CH_3COO$: C, 72.24; H, 6.30; N, 6.48. Found: C, 72.25; H, 6.51; N, 6.52.

1,4,14,17-Tetrabenzyl-1,4,14,17-tetraaza-cyclohexacosa-8,22-diene-6,10,20,24-tetrayne (tact2:1) (12). A solution of $Pd(Ph_3P)_4$ (0.10 g, 0.086 mmol), CuI (0.08 g, 0.42 mmol), **6** (0.6 g, 1.37 mmol), *n*-butylamine (0.35 g, 4.7 mmol), and benzene (25 mL) was stirred for 10 min at 50 °C under nitrogen. A solution of *N*,*N*′-dibenzyl-*N*,*N*′-dibut-3-ynyl-ethane-1,2-diamine **5** (0.48 g, 1.39 mmol) in benzene (50 mL) was added dropwise over 1.5 h. The mixture was stirred for an additional 4 h, during which time the progress of the reaction was monitored by ^{1}H NMR and TLC. After cooling, the reaction was quenched by pouring the mixture into chilled water (200 mL). The crude product was subsequently extracted with benzene (200 mL). The organic material was washed initially with a saturated sodium chloride solution (2 × 200 mL) and finally with water (2 × 100 mL). The crude product was then dried over anhydrous sodium sulfate and concentrated under vacuum. The viscous material obtained was dissolved in ethyl acetate (50 mL) and then mixed with hexane (100 mL) and allowed to stand at ambient temperature for 4 h. The solvent was then decanted, and the viscous oil was passed through a silica gel column eluted initially with methylene chloride and finally with methanol/methylene chloride (1:9). Reduction of the solvent volume under vacuum yields the macrocycle **12** (0.3 g, 30%). Viscous oil. ^{1}H NMR ($CDCl_3$): 2.69 (bs, 4H, $2CH_2$), 2.75 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 3.22−3.35 (m, 4H, $2CH_2$), 3.52 (s, 4H, $2CH_2$), 3.67 (bs, 4H, $2CH_2$), 4.19 (t, $J = 6$ Hz, 4H, $2CH_2$,), 4.39 (t, 4H, $2CH_2$), 5.67−5.80 (m, 4H, 4CH), 7.20−7.34 (m, 20H, Ar). ^{13}C NMR ($CDCl_3$): 21.00 (CH_2), 42.82 (CH_2), 42.95 (CH_2), 44.19 (CH_2), 44.68 (CH_2), 51.02 (CH_2), 51.41 (CH_2), 51.69 (CH_2), 58.34 (CH_2), 58.46 (CH_2), 63.60 (CH_2), 80.04 (Cquart), 83.38 (Cquart), 92.58 (Cquart), 94.04 (Cquart), 119.55 (CH), 127.38 (CH), 127.83 (CH), 128.02 (CH), 128.25 (CH), 128.39 (CH), 128.53 (CH), 128.87 (CH), 129.44 (CH), 137.84 (Cquart), 139.00 (Cquart), 156.32 (Cquart). Mass: FAB *m*/*z* 709 ($M^+ + 1$), 703, 617, 496, 493, 457, 327, 266, 251, 117, 91. IR (neat, cm^{-1}): 3028, 2924, 2180, 1699, 1603, 1494, 1453, 1364, 1230, 1106, 1075, 1028, 738, 699.

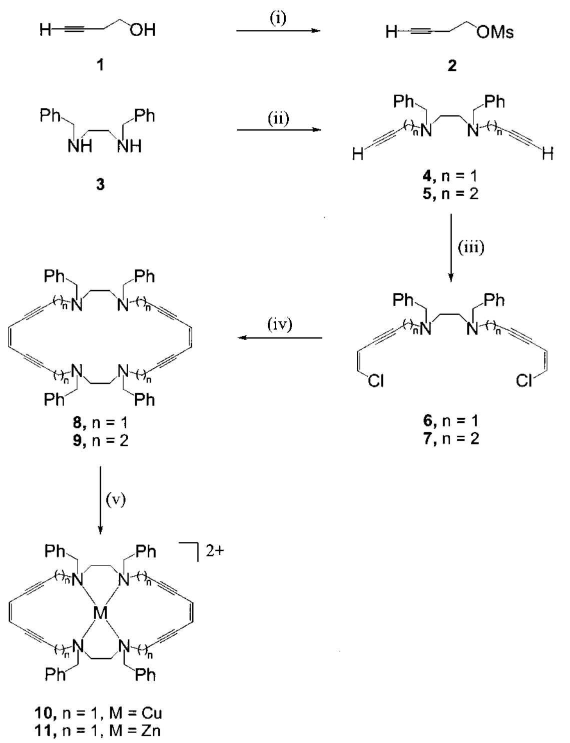
[Cu(tact1:2)](BF_4)$_2$ (13). Compound **13** was prepared in 62% yield by a procedure analogous to that given for **10**. Brown solid. Mass: ESI *m*/*z* 945, 943 (M^+), ^{63,65}Cu (M^+ calcd for $C_{50}H_{52}N_4Cu{\cdot}2BF_4$, 945, 943), 797, 708, 384, 382, 341, 339, 225. IR (KBr, cm^{-1}): 2960, 2225, 1697, 1495, 1454, 1425, 1365, 1233, 1063, 895, 760. Anal. Calcd for $C_{50}H_{52}N_4Cu{\cdot}2BF_4{\cdot}3.5\ H_2O$: C, 59.50; H, 5.89; N, 5.55. Found: C, 59.17; H, 5.67; N, 6.05.

[Zn(tact1:2)](CH_3COO)$_2$ (14). A solution of **12** (0.120 g, 0.16 mmol) in methylene chloride (5 mL) and acetonitrile (10 mL) was added (30 min) to a solution of $Zn(CH_3COO)_2{\cdot}2H_2O$ (0.037 g, 0.16 mmol) in acetonitrile (10 mL) at 50 °C under nitrogen. The reaction mixture was stirred for 8 h at 50 °C. The solvent was removed, and the solid material was dried under vacuum. The residue was stirred in ether (50 mL) for 2 h, filtered, washed with hexane (2 × 10 mL), and finally dried under vacuum at 50 °C. Yield: 0.10 g, 66%. ^{1}H NMR ($CDCl_3$): 2.13 (s, 6H, $2CH_3$), 2.68 (s, 4H, $2CH_2$), 2.75 (s, 4H, $2CH_2$), 3.21−3.33 (m, 4H, $2CH_2$), 3.52 (s, 4H, $2CH_2$), 3.67 (s, 4H, $2CH_2$), 4.19 (s, 4H, $2CH_2$), 4.34−4.40 (m, 4H, CH_2Ph), 5.70−5.78 (m, 4H, 4CH), 7.37 (bs, 20H, Ar). ^{13}C NMR ($CDCl_3$): 20.99 (CH_2), 22.81 (CH_3), 42.87 (CH_2), 44.18 (CH_2), 44.71 (CH_2), 45.43 (CH_2), 51.40 (CH_2), 58.30 (CH_2), 63.57 (CH_2), 80.02 (Cquart), 83.56 (Cquart), 92.27 (Cquart), 94.06 (Cquart), 119.31 (CH), 127.54 (CH), 127.83 (CH), 128.23 (CH), 128.36 (CH), 128.57 (CH), 128.87 (CH), 129.59 (CH), 137.78 (Cquart), 156.07 (Cquart), 156.33 (Cquart), 180.10 (Cquart). Mass: ESI 773, 771 (^{63,65}Zn), 678, 631, 617, 605, 603, 589, 587, 341, 339, 293. IR (KBr, cm^{-1}): 3060, 2290, 2180, 1966, 1699, 1597, 1495, 1421, 1228, 1103, 1027. Anal. Calcd for $C_{50}H_{52}N_4Zn{\cdot}2CH_3COO$: C, 72.66; H, 6.56; N, 6.27. Found: C, 72.75; H, 6.72; N, 6.50.

Results and Discussion

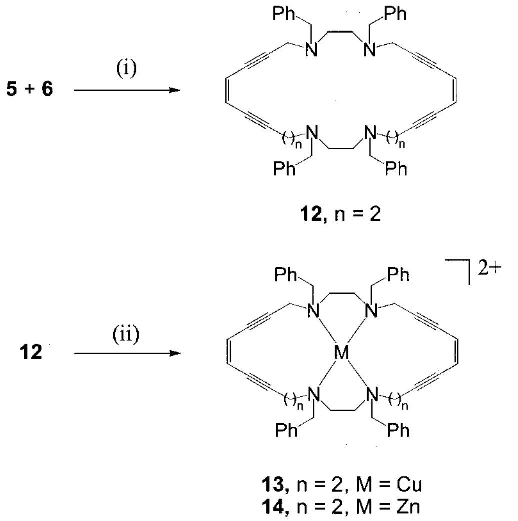
Syntheses of Enediyne Macrocycles 8−14. The 24-, 26-, and 28-membered macrocycles **8**, **9**, and **12** were prepared by alkylation of *N*,*N*′-dibenzylethylenediamine and subsequent Pd(0)-catalyzed Sonogashira coupling (Schemes 1 and 2).[18] Construction of a 24-membered macrocycle derives from double alkylation of *N*,*N*′-dibenzylethylenediamine, **3**, with 2.2 equiv of propargyl bromide in the presence of anhydrous potassium carbonate and dimethylformamide (10 °C). The resulting terminal alkynes were subsequently coupled with *cis*-1,2-dichloethylene (excess) to give the chloro-ene-yne product in good yield (72%). The cross coupling reaction of alkyne **4** with chloro-ene-yne **6** in the presence of Pd(0), CuI, and *n*-butylamine in benzene at 40 °C gives the macrocycle **8** in low yield (13%, Scheme 1). Following purification on silica gel, the identity of the product was confirmed by using ^{1}H NMR, ^{13}C NMR (DEPT), and mass spectrometry. The ^{1}H NMR spectrum of **8** exhibits a singlet at 2.78 ppm for the $-NCH_2-$ unit of enediyne (8H) and another singlet at δ 3.58 corresponding to the ethylene protons of the diamine substructure (8H). In the ^{13}C NMR spectrum, the chemical shifts of the alkyne carbons are readily detected at δ 83.68 and 92.66 ppm confirming the identity of the product and synthetic strategy.

Scheme 1. Synthesis of Symmetric Enediyne Macrocycles **8−11**[a]



[a] (i) TEA, MsCl, methylene chloride, 20 °C; (ii) **2** or propargyl bromide, K_2CO_3, DMF; (iii) *cis*-1,2-dichloroethylene, Pd(0), CuI, *n*-BuNH$_2$, benzene, 40−50 °C; (iv) **4** or **5**, Pd(0), CuI, *n*-BuNH$_2$, benzene, 40−50 °C; (v) $Cu(BF_4)_2{\cdot}XH_2O$, CH_3CN, 40 °C/$Zn(CH_3COO)_2{\cdot}2H_2O$, CH_3CN, 40 °C.

Scheme 2. Preparation of Asymmetric Enediyne Macrocycles **12−14**[a]



[a] (i) Pd(0), CuI, *n*-BuNH$_2$, benzene, 40−50 °C; (ii) $Cu(BF_4)_2{\cdot}XH_2O$, CH_3CN, 40 °C/$Zn(CH_3COO)_2{\cdot}2H_2O$, CH_3CN, 40 °C.

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In a similar approach, the enediyne macrocycle **9** was constructed by double alkylation of *N*,*N′*-dibenzylethylenediamine with 3-butyn-1-yl methanesulfonate (**2**) in anhydrous potassium carbonate and dimethylformamide at 50−55 °C. The resulting di-alkyne was reacted with an excess of *cis*-1,2-dichloroethylene at 40 °C to give the desired bis(chloro-ene-yne) (**7**) in 82% yield. Finally, reaction of the *N*,*N′*-dibenzyl-*N*,*N′*-di-but-3-ynyl-ethane-1,2-diamine with **7** gives the desired 28-membered macrocycle **9** (Scheme 1). In the proton NMR spectrum, a broad singlet is observed at δ 2.71 for the eight protons of the four CH_2 units, while a multiplet of eight protons is detected between δ 3.27−3.39 ppm corresponding to the ethylene protons. A broad singlet was also observed at 4.24 ppm indicative of the four NCH_2 protons, and a multiplet was observed between δ 4.41−4.46 ppm arising from the benzylic protons. Finally, a singlet at δ 5.69 ppm (CH) and aromatic protons at δ 7.26−7.31 ppm complete the expected resonances for the target compound.

The Cu(II) (**10**) and Zn(II) complexes (**11**) of macrocycle **8** ($M(tact1{:}1)^{2+}$) were prepared by reacting a 1:1 molar ratio of the ligand and $Cu(BF_4)_2 \cdot xH_2O$ and $Zn(CH_3COO)_2 \cdot 2H_2O$, respectively, in acetonitrile at 40 °C. The same procedure was used to prepare the Cu(II) (**13**) and Zn(II) (**14**) complexes of macrocycle **12** ($M(tact1{:}2)^{2+}$). The identities of the macrocyclic complexes of these metals were confirmed by mass spectrometry results and elemental analyses (Cu(II), Zn(II)) as well as ^{1}H and ^{13}C NMR analyses where appropriate (Zn(II)). Due to the large ring size, systematic preparations of the Cu(II) and Zn(II) complexes of macrocycle **9**, $M(tact2{:}2)^{2+}$, did not yield products with acceptable mass spectrometry and elemental analyses corresponding to a tetradentate, 1:1 metal/ligand stoichiometry. This results from the conformational flexibility of the ethylenediamine unit which permits the nitrogen centers in the structure to invert, providing good external binding pockets for two metal ions at the periphery (vide infra). Thus, the exocyclic binding mode inhibits formation of a tetracoordinate metal center with N_4 ligation within the macrocycle.

X-ray Structure of the $H_2(BF_4)_2$ Salt of 8. Crystals (CH_3CN/Et_2O) of the $H_2(BF_4)_2$ salt of **8** (**8a**, Figure 1) were obtained as a result of slow hydrolysis (10−15 d) of the Cu(II) macrocyclic enediyne complex **10** by water introduced via the $Cu(BF_4)_2 \cdot xH_2O$ starting material during the complexation reaction. Di-protonation of the macrocycle leads to retention of the BF_4^- counterions in the structure, which, in addition to the traditional N−H···F hydrogen bond, exhibit weak, unconventional interactions[19] with hydrogens on the ligand (e.g., C7−H7···F2, 2.439 Å, 136.8°; C6−H6···F4, 2.247 Å, 151.6°). Beyond these chemical and structural distinctions, the X-ray analysis of the macrocycle itself is particularly informative for documenting the conformational flexibility of the ethylenediamine unit and its structural relationship to the disposition of the enediyne moiety.

The X-ray structure of **8a** exhibits inversion symmetry, and the asymmetric unit contains one-half of the molecule (Table 1). The independent enediyne units are planar with C≡C−C (C(4)−C(5)−C(6) = 175.49(17)°) and C−C≡C (C(3)−C(4)−C(5) = 175.92(18)°) angles near 180° (Table 2). The alkyne termini separation (C(5)- - - -C(10)#) is 4.41 Å which is expected for such a large, flexible construct. However, since there is no conjugation in the metal-binding region, the overall macrocyclic structure is not forced to be rigorously planar due the sp^3-hybridized ethylenediamine units (Figure 2). This allows metals with different geometric preferences to be readily accommodated by the tertiary nitrogen centers within the macrocycle. Moreover, as illustrated by the structure, these units can actually form a pair of bidentate, exocyclic binding pockets for metal ions, thereby accounting for the need for external heating to properly complex metals within the macrocycle. Additionally, the phenyl rings are parallel to the enediyne units but lie above and below the center of the macrocycle. Each is also directed outward from the periphery by rotation about the benzylic carbon to minimize steric repulsion.

Table 1. Crystallographic Data for the $H_2(BF_4)_2$ Salt of **8** (**8a**)

formula	$C_{48}H_{50}B_2F_8N_4$
formula weight	856.54
color of crystal	colorless
crystal system	triclinic
space group	$P\bar{1}$
a, Å	9.0324(7)
b, Å	10.5874(8)
c, Å	12.5495(10)
α, deg	93.640(2)
β, deg	106.299(2)
γ, deg	110.788(2)
V, Å^3	1058.95(14)
Z	1
ρ_{calcd}, g/cm^3	1.343
T, K	115
λ, Å	0.71073
GOF[a] on F^2	0.972
final *R* indices[b] [$I > 2\sigma(I)$]	R1 = 0.0469, wR2 = 0.1044
R indices[c] (all data)	R1 = 0.0915, wR2 = 0.1229
largest diff. peak and hole	0.345 and −0.256 e/Å^3

[a] GOF = $[\sum[w(F_o^2 - F_c^2)^2]/N_{observns} - N_{params})]^{1/2}$, all data. [b] R1 = $\sum(|F_o| - |F_c|)/\sum |F_o|$. [c] wR2 = $[\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

Table 2. Selected Bond Distances (Å) and Angles (deg) for **8**[a]

C(1)−C(10)#	1.199(2)	C(10)#-C(1)−C(2)	177.26(17)
C(1)−C(2)	1.423(2)	C(1)−C(2)−C(3)	124.67(15)
C(3)−C(4)	1.424(2)	C(2)−C(3)−C(4)	124.27(16)
C(4)−C(5)	1.197(2)	C(3)−C(4)−C(5)	175.92(18)
C(5)−C(6)	1.458(2)	C(4)−C(5)−C(6)	175.49(17)
C(6)−N(1)	1.510(2)	C(5)−C(6)−N(1)	112.22(33)
N(1)−C(7)	1.512(2)	N(1)−C(7)−C(8)	111.43(13)
C(7)−C(8)	1.521(2)	C(7)−C(8)−N(2)	110.59(13)
N(2)−C(8)	1.464	N(2)−C(9)−C(10)	114.02(13)
N(2)−C(9)	1.476(2)		
C(9)−C(10)	1.474(2)		

[a] #: $-x - 1, -y - 1, -z + 1$.

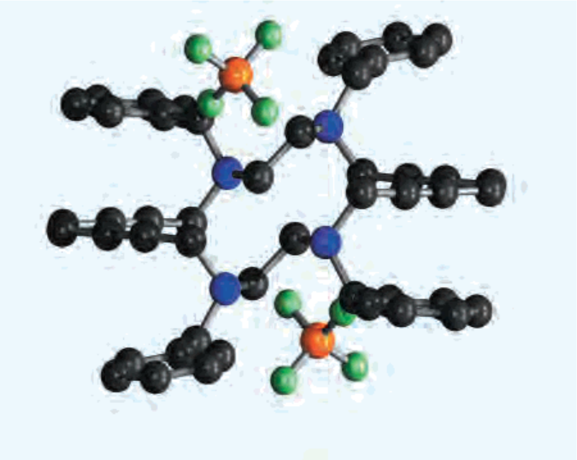

Figure 2. Side view of the structure of **8a** illustrating the nonplanar conformation of the macrocycle with respect to the two independently planar enediyne functionalities (hydrogen atoms removed for clarity). Atom color designations: carbon (black), nitrogen (blue), boron (orange), and fluorine (green).

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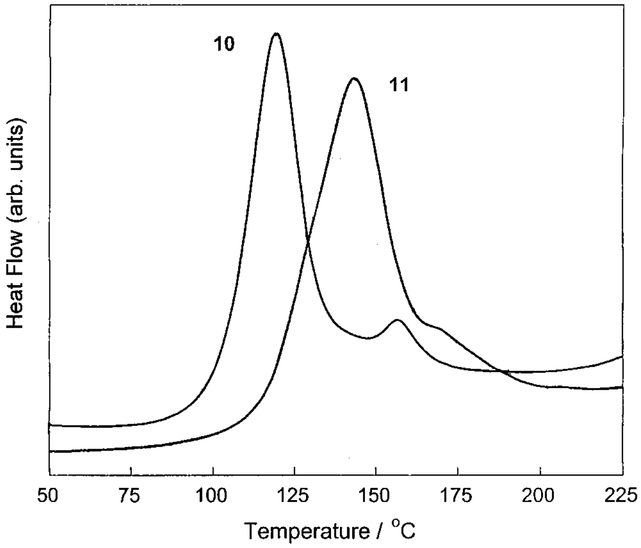

Figure 3. Differential scanning calorimetry traces for the thermal cyclization of enediynes **10** and **11**.

Table 3. Bergman Cyclization Temperatures of **8**−**14** Determined by Differential Scanning Calorimetry (DSC)

compound	temp (°C)
tact1:1 (**8**)	203
tact1:2 (**12**)	189
tact2:2 (**9**)	184
[Cu(tact1:1)]$^{2+}$ (**10**)	121
[Zn(tact1:1)]$^{2+}$ (**11**)	148
[Cu(tact1:2)]$^{2+}$ (**13**)	112
[Zn(tact1:2)]$^{2+}$ (**14**)	163

Thermal Reactivities of 8−14. The thermal Bergman cyclization temperatures for these enediyne macrocycles have been measured by differential scanning calorimetry (DSC) and are given in Table 3. As we and others have shown, DSC is a convenient technique for correlating the thermal reactivities of enediynes and is especially useful for paramagnetic complexes that are more challenging to screen by NMR or for complexes that can react with solvent upon modest heating.[4] Large, irreversible, exothermic peaks are observed between 100 and 210 °C upon heating of all enediyne macrocycles (**8**−**14**). Overall, the cyclization temperatures of these macrocyclic ligands (**8**, **9**, **12**) are >50 °C lower than that of the benzannulated tetraazaenediyne ligand prepared from an alternative synthetic approach by Basak.[3,6] For the free macrocyclic ligands (**8**, **9**, **12**), a 19 °C decrease in the cyclization temperatures is observed along the sequence tact1:1 (203 °C), tact1:2 (189 °C), and tact2:2 (184 °C) corresponding to an increase in the number of carbon atoms between the ethylenediamine linkage and the terminal alkyne carbon, which increases the flexibility and size of the macrocycle. Although the temperature decrease is modest, it is consistent with trends observed in other metal-binding enediyne ligands as a function of ligand rigidity.[5,11,20]

The Cu(II) complex of tact1:1, **10**, exhibits a Bergman cyclization temperature of 121 °C (Figure 3). The cyclization temperature is nearly identical to those reported for other [Cu(N)$_4$]$^{2+}$ metalloenediyne constructs whose tetragonal X⋯Cu(N$_4$)⋯X structures have been characterized by EPR, ligand field region electronic absorption spectroscopy, and molecular mechanics calculations.[5,11] The presence of distortion of the Cu(N$_4$) plane toward a tetrahedral geometry would result in a significant increase in the Bergman cyclization temperature of the Cu(II) complex to values between 200 and 360 °C depending upon the ligand structure as observed for tetrahedral [Cu(N)$_4$]$^+$ metalloenediyne analogues.[5,11] As Figure 2 illustrates, the binding pocket of ligand **8** is not restricted to a planar geometry. Thus, the planar-to-tetragonal geometric preference of Cu(II) governs the disposition of the ethylenediamine-binding motif which reduces the distance between the alkyne termini lowering the cyclization temperature. Indeed, the X-band EPR spectrum of **10** obtained in 1:1 CH$_3$CN/toluene (Figure 4) reveals spin-Hamiltonian parameters that indicate a slightly rhombic center with preferential nitrogen coordination ($g_z = 2.25$; $g_x = 2.04$; $g_y = 2.08$; $A_z = 162 \times 10^{-4}$ cm^{-1}; $A_x = 16 \times 10^{-4}$ cm^{-1}; $A_y = 19 \times 10^{-4}$ cm^{-1}).[21−23] The spectral signature and parameters correlate very well with other Cu(II) macrocyclic complexes previously reported[21,22] and document the connection between near planar or tetragonal metal-center geometries and reduced Bergman cyclization temperatures.[1,5,11]

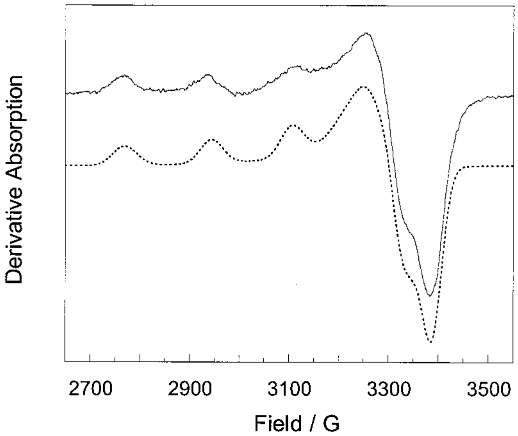

Figure 4. X-band EPR spectrum of **10** in 1:1 CH$_3$CN/toluene at 77 K. The simulated EPR parameters including isotopic distribution are $g_z = 2.25$, $g_x = 2.04$, $g_y = 2.08$; $A_z = 162 \times 10^{-4}$ cm^{-1}, $A_x = 16 \times 10^{-4}$ cm^{-1}, $A_y = 19 \times 10^{-4}$ cm^{-1}.

In contrast, the cyclization temperature for the Zn(II) analogue **11** is slightly higher (148 °C) than that observed for the Cu (II) complex **10**. Given that the atomic radii of Cu^{2+} and Zn^{2+} are very similar (71−88 pm depending upon coordination number),[24] the difference in the cyclization temperatures between **10** and **11** must derive from small structural differences of the macrocyclic metalloenediyne complexes. Unlike Cu(II), Zn(II) is d^{10} and, therefore, has different geometric structural preferences depending upon the nature of the binding ligands. In chemical structures, Zn(II) is frequently 4−6 coordinate and can adopt geometries ranging from planar[25−30] or tetrahedral[31−37] for coordination number 4 to square pyramidal[38−42] or trigonal bipyramidal[43−46] for 5-coordinate complexes or psuedo-octahedral[47−51] for hexacoordinate centers. Most commonly, the d^{10} electronic configuration will result in a 4-coordinate, tetrahedral structure unless otherwise constrained by the con-

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formational rigidity of the ligand. For ligands with constrained binding pockets such as porphyrins, 4-coordinate, square-planar structures can be readily obtained. In the presence of strongly coordinating anions or other good ligands, square-pyramidal or octahedral geometries are attainable via axial coordination. For tetradentate macrocycles with structural flexibility, 5-coordinate pyramidal or 6-coordinate pseudo-octahedral geometries are common.[38,44−47,52−60] Thus, the d^{10} configuration for Zn(II) mandates that the structure of the resulting complex be governed by a valence bond description, where the ability of the ligand set to adopt the requisite geometry determines whether the final complex obeys or deviates from this predictive model. The Bergman cyclization temperature for **11** is between that expected for a planar or tetrahedral $[Zn(N)_4]^{2+}$ structure. This can be rationalized by considering that the tetrahedral valence bond structural preference of Zn(II) for 4-coordination will compete with the steric constraints of the macrocyclic conformation. From Figure 2, it is clear that tact1:1 possesses the conformational flexibility required to adopt a distorted geometry. Therefore, a distorted 4-coordinate or 5-coordinate square-pyramidal geometry with an axial CH_3COO^- or H_2O ligand would explain the elevated Bergman cyclization temperature for **11**.

When the macrocycle size is increased from 24 to 26 atoms by addition of two aliphatic carbons (Scheme 1), the ligand becomes more flexible, and the Bergman cyclization temperature decreases. For the $[Cu(tact1{:}2)]^{2+}$ complex, **13**, there is a modest decrease in the cyclization temperature of 9 °C relative to **10** paralleling the trend in the free ligand cyclization temperatures. The data indicate that both Cu(II) complexes **10** and **13** are structurally very similar and must possess planar-to-tetragonal geometries about the metal center.

In contrast to the decrease in the Bergman cyclization temperature upon an increase in the macrocycle size for the free ligands and corresponding Cu(II) complexes, $[Zn(tact1{:}2)]^{2+}$ exhibits a 15 °C *increase* in the temperature for the Bergman cyclization reaction (163 °C) relative to **11**. In light of the structural preference of Zn(II) for a distortion from planarity for 4-coordination, the increase in the cyclization temperature can be ascribed to further distortion in the resting structure toward a more tetrahedral geometry due to the increased flexibility of the macrocycle. The relatively low temperature of **14**, however, suggests that the distortion is modest relative to the tetrahedral geometries and correlated cyclization temperatures (200−360 °C) of characterized Cu(I) metalloenediyne structures.[5,11] Therefore, the geometric preferences of the metal center and conformational flexibility of the ligand mandate the thermal cyclization temperatures of these metalloenediyne macrocycles.

Finally, the similarities in the structures of **8** and **10** to Basak's benzannulated tetraazaenediyne macrocycle and the corresponding $[Cu(tetraazaenediyne)]^{2+}$ complex warrant direct comparison of their thermal reactivities.[3,6] It is clear from the DSC data that uncomplexed ligand **9** is considerably more reactive ($\Delta =$ 52 °C) than is its benzannulated counterpart. The additional stability gained by delocalization of the π-electrons of the ene unit is certainly the dominating factor in the increased activation energy. The disparity in reactivity is diminished, however, between **10** and Basak's benzannulated $[Cu(tetraazaenediyne)]^{2+}$ complex. Using the onset temperature for **10** from Figure 3 (∼80 °C) and the reported onset temperature by Basak (90 °C), there is a ∼10 °C difference in the cyclization temperatures, indicating that the geometric influence of the Cu(II) center supersedes and nearly neutralizes the electronic influence of benzannulation in this case. This structure/reactivity pattern may be especially important to future metalloenediyne designs that require considerable hydrophobic character for lipophilic targeting applications.

Conclusions

We have discussed the syntheses of macrocyclic enediynes possessing two diyne-ene functionalities by a route that does not require benzannulation. As expected, these enediyne macrocycle variants have reduced cyclization temperatures relative to those of their benzannulated derivatives.[3,6] The synthetic route allows incorporation of additional carbon atoms into the macrocycles which increases their conformational flexibilities and lowers their Bergman cyclization temperatures. Moreover,

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incorporation of Cu(II) and Zn(II) into these macrocycles further reduces their cyclization temperatures relative to those of the free ligands. For the tact1:1 macrocycle, the Cu(II) and Zn(II) complexes exhibit comparable reactivities, but the cyclization temperature for the Zn(II) analogue is slightly higher (27 °C) suggesting a dihedral distortion from the tetragonal geometry of the Cu(II) complex. Addition of a second carbon to both arms of one side of the macrocycle further increases the flexibility of the ligand and decreases the cyclization temperature. Concomitant with this behavior, the cyclization temperature of the Cu(II) analogue decreases by 9 °C indicating a geometry nearly identical to that of the 24-membered macrocyclic Cu(II) complex. In contrast, incorporation of Zn(II) into this enlarged macrocycle leads to an increase in the Bergman cyclization temperature due to the valence bond preference of the d^{10} electronic configuration of the Zn(II) center to adopt a distorted geometry toward tetrahedral local symmetry for 4-coordination. Overall, these studies show that small changes in ligand conformational flexibility can lead to incremental variations in Bergman cyclization temperatures. These effects are amplified by a judicious choice of the metal center due to the geometric preferences of the electronic configuration of the metal. The results document the intimate relationship between enediyne ligands and their corresponding metal centers for finely tuning the Bergman cyclization temperatures of the resulting complexes.

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Supporting Information Available: Crystallographic data (CIF format) including complete tables of bond distances and angles, final fractional coordinates, and thermal parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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