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Thermal reactivities of isostructural d^{10} metalloenediynes: metal-dependent Bergman cyclization[†]

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Isostructural d^{10} metalloenediynes of Cu(I), Pd(0) and Ag(I) exhibit metal-dependent variations in their thermal Bergman cyclization temperatures which correlate with differences in their alkyne termini separations.

The intriguing chemical reactivities and antitumor properties of the enediyne antibiotics[1] have generated considerable interest in controlling thermal Bergman cyclization reactions with simple synthetic motifs. Within this theme, structure/activity relationships for organic enediynes have documented the importance of the alkyne termini separation (*d*) as well as molecular strain in the ground and transition states.[2–5]

Recent work documenting that metal ions can greatly influence the conformation of the enediyne linkage thereby modulating the thermal reactivity of the resulting complex[6–8] broke ground for metal geometry control of Bergman cyclization reactions. It has now been shown that Bergman cyclization temperatures of metalloenediyne complexes of a given metal and enediyne ligand can be reduced by > 80 °C by variations in metal center geometry from tetrahedral to planar or tetragonal.[6,9–11] However, the influence of different metal ions on the Bergman cyclization temperature for a specific enediyne ligand within a well defined metal complex geometry has not been systematically evaluated. To this end, we report the X-ray structures and thermal reactivities of two homoleptic d^{10} metalloenediyne complexes [Cu(I) and Ag(I)] of 1,2-bis(diphenylphosphinoethynyl)benzene (dppeb, **1**). In conjunction with the Pd(dppeb)$_2$ analog **2**,[9] these complexes comprise a unique isoelectronic and isostructural set which exhibit significant differences in alkyne termini separation and consequently Bergman cyclization temperatures.

The Cu(I)[‡] and Ag(I)[§] metalloenediyne complexes were prepared by reacting 2 equivalents of **1** with the appropriate monovalent metal salt under N$_2$ to generate the [M(dppeb)$_2$]$^+$ d^{10} metalloenediyne cation.

Complexes **3** and **4** were isolated and purified by recrystallization from CH$_2$Cl$_2$–diethyl ether and MeCN–H$_2$O, respectively, as well as characterized in solution by NMR (^{1}H, ^{13}C) and mass spectrometry.

The X-ray crystal structures[¶] of the cations of **3** (Fig. 1) and **4** (Fig. 2) reveal the isostructural identities of these complexes with respect to **2**.[9] Both d^{10} metal centers have local tetrahedral geometries with nearly idealized P–M–P angles (**3**: 107°, **4**: 108°). The tetrahedral geometries of these species promote a decrease in the alkyne termini separation *d*, relative to the free ligand but force an increase in *d* relative to square planar or tetragonal geometries.[10,11] For **2–4**, the average alkyne termini separation increases by 0.19 Å along the series Cu(I) (3.44 Å) < Pd(0) (3.47 Å) < Ag(I) (3.62 Å). For **2** and **3**, the differences in *d* are statistically insignificant. The average M–P bond lengths also increase from Cu(I) (2.33 Å) ≈ Pd(0) (2.33 Å) < Ag(I) (2.52 Å), reflecting contributions from both variations in atomic radii as well as metal–ligand covalency. Both structures exhibit bent alkyne units due to distortion of the enediyne unit induced by metal chelation. For **3**, the P–C≡C and C≡C–C angles are 166 and 170°, respectively, while for **4**, the same angles are 165 and 173°. The dppeb ligands in both complexes are also planar which minimizes out-of-plane structural contributions to the thermal reactivities of the complexes.

Off-resonance (λ = 785 nm) Raman spectra of **1–4** as a neat oil (for **1**) or solid states have been obtained in order to assess electronic contributions to the geometric structures which may influence thermal Bergman cyclization reactivities. The spectra (**1**, **3** in Fig. 3) are comprised primarily of alkyne (2150–2170 cm^{-1}), as well as phenyl ring and 1,2-disubstituted benzene group frequencies (500–1600 cm^{-1}).[12] The spectra of the metal complexes **2–4** are remarkably similar, indicating that with exception of the alkyne stretch, all of the ligand normal modes are relatively isolated from the effects of metal ion coordination. To this end, $\nu_{C\equiv C}$ for **1** (2160 cm^{-1}) is nearly degenerate with the average alkyne stretch for **3** (2168, 2155 cm^{-1}) and **4** (2165,

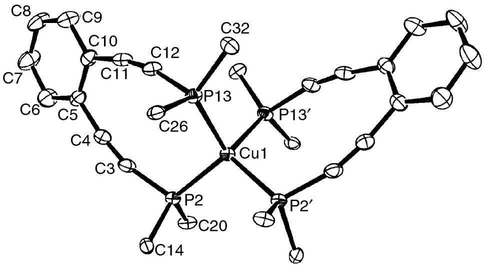

Fig. 1 ORTEP of the X-ray structure of the cation of **3** shown at 50% probability. Only the *ipso* carbon atoms of the phenyl rings are shown for clarity. Selected bond lengths (Å) and angles (°): Cu(1)–P(2) 2.3176(14), Cu(1)–P(13) 2.3406(14); P(2)–Cu(1)–P(2′) 110.14(7), P(2)–Cu(1)–P(13) 111.17(5), P(2)–Cu(1)–P(13′) 110.25(5), P(13)–Cu(1)–P(13′) 103.72(7), P(2)–C(3)–C(4) 166.3(5), P(13)–C(12)–C(11) 167.0(4), C(3)–C(4)–C(5) 171.1(5), C(10)–C(11)–C(12) 169.0(5).

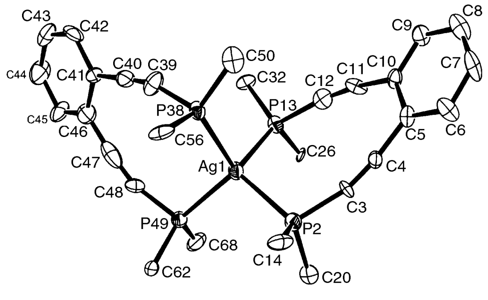

Fig. 2 ORTEP (50% probability) of the X-ray structure of the cation of **4** with phenyl rings removed for clarity. Selected bond lengths (Å) and angles (°): Ag(1)–P(2) 2.477(4), Ag(1)–P(13) 2.524(4), Ag(1)–P(38) 2.527(4), Ag(1)–P(40) 2.508(4); P(2)–Ag(1)–P(13) 110.52(14), P(2)–Ag(1)–P(38) 110.49(12), P(2)–Ag(1)–P(49) 109.97(9), P(13)–Ag(1)–P(38) 105.08(8), P(13)–Ag(1)–P(49) 108.40(12), P(38)–Ag(1)–P(49) 112.26(13), P(2)–C(3)–C(4) 165.1(13), P(13)–C(12)–C(11) 170.0(13), P(38)–C(39)–C(40) 159.9(16), P(49)–C(48)–C(47) 164.6(15), C(3)–C(4)–C(5) 172.6(14), C(10)–C(11)–C(12) 170.7(14), C(39)–C(40)–C(41) 175.9(15), C(46)–C(47)–C(48) 173.4(16).

[†] Electronic supplementary information (ESI) available: differential scanning calorimetry data for complexes **2–4**. See http://www.rsc.org/suppdata/cc/b0/b008337m/

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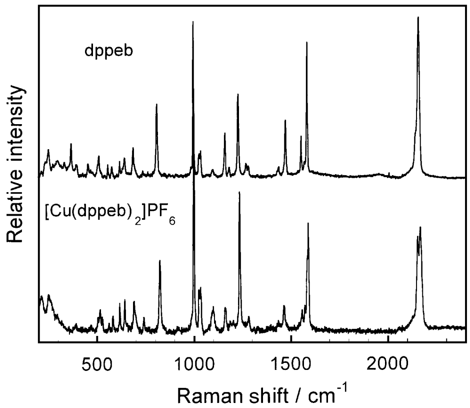

Fig. 3 Off-resonance Raman spectra of neat samples of dppeb **1** and [Cu(dppeb)$_2$]PF$_6$ **3** obtained with 1 mW at λ = 785 nm.

2153 cm^{-1}) which are comprised of two anisotropic vibrational components within the solid state. For **2** however, these values are shifted to lower energy by an average of 9 cm^{-1} (2155, 2149 cm^{-1}) indicative of only very modest back-donation from Pd(0) to the alkyne π-system through the empty p- and d-orbitals of the phosphine. This electronic contribution is not significant and likely does not strongly influence enediyne reactivity.

The Bergman cyclization temperatures for **2–4** have been determined by DSC in the solid state (Table 1) and show the following dependence on metal ion: Cu(I) (227 °C) ≈ Pd(0) (222 °C) < Ag(I) (266 °C). The DSC temperatures correspond to formation of the Bergman cyclized 1,4-phenyl diradical intermediate and rapid reaction to generate intractable black product complexes in the solid state. Unlike thermal cyclization reactions in the presence of H-atom donor in solution, the absence of a large excess of H-atom donor in the solid-state reaction inhibits quenching of the intermediate to specifically trap the disubstituted benzene product. In the absence of H-atom donor, we and others[13] have observed formation of black, insoluble polymeric products for various enediyne thermal cyclization reactions.

Table 1 Bergman cyclization temperatures of d^{10} metalloenediynes

Compound	Cyclization temperature/°C	Alkyne termini separation/Å
2	222[a]	3.47
3	227	3.44
4	266	3.62

[a] This value was originally reported as an onset temperature (209 °C).[9]

The Bergman cyclization temperatures directly correlate with the increased alkyne termini separation between **2** and **3**, and **4**. The 44 °C variation in the cyclization temperatures reflects the intimate relationship between the geometric structure of the metalloenediyne and the Bergman cyclization temperature of the resulting complex. Unlike previous examples of diverse structural variations in either metalloenediyne composition and/or geometry which strongly influence Bergman cyclization temperatures, in this case subtle variations in M–P bonding can introduce significant increases in *d* and consequently the thermal stabilities of the complexes. These results systematically reveal the prominent role that metal ions can play in affecting Bergman cyclization of the enediyne ligands and the intimate contribution that the specific metal ion has in modulating the reactivities of these metalloenediynes.

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Notes and references

‡ *Synthesis* of **3**: dppeb (0.26 g, 0.53 mmol) was stirred with [Cu(MeCN)$_4$](PF$_6$) (0.098 g, 0.26 mmol) in dry, degassed MeCN (20 ml) under nitrogen overnight at room temperature. The solvent was then removed *in vacuo* and the residue was dissolved in CH$_2$Cl$_2$. The solution was filtered and an off white solid precipitated from solution upon addition of diethyl ether. A white crystalline compound was obtained after recrystallization from CH$_2$Cl$_2$–diethyl ether and dried *in vacuo*. Crystals suitable for characterization by X-ray crystallography were grown from a saturated CH$_2$Cl$_2$–diethyl ether solution. Yield 150.1 mg (42%). δ_H(400 MHz, CD$_2$Cl$_2$), 7.62–7.72 (m, 8H), 7.21–7.24 (m, 24H), 6.96 (t, 16H). δ_C(CD$_2$Cl$_2$), 132.12, 131.05, 130.89, 130.83, 130.67, 129.26, 127.10, 112.03, 88.29. ^{31}P NMR (CD$_2$Cl$_2$, −80 °C, rel. to 85% H$_3$PO$_4$) −18.20 (br s), −144.33 (sept., PF$_6$). MS, *m/z* (ESI) 1051.4 (M$^+$ − PF$_6$).

§ *Synthesis* of **4**: dppeb (0.11 g, 0.22 mmol) was stirred under nitrogen with AgNO$_3$ (0.019 g, 0.11 mmol) in degassed acetone (20 ml) at room temperature for 3 h after which the solvent volume was reduced by half *in vacuo*. A saturated, aqueous solution of NH$_4$PF$_6$ was then added producing a white solid that was removed by filtration, recrystallized from acetone–H$_2$O, and dried *in vacuo*. Crystals suitable for characterization by X-ray crystallography were grown from a saturated MeCN–H$_2$O solution. Yield 64.9 mg (46%). δ_H(400 MHz, CD$_3$CN), 7.60–7.70 (m, 8H), 7.30–7.34 (m, 24H), 7.06 (t, 16H). δ_C(CD$_3$CN), 132.82, 131.99, 131.79, 131.73, 131.33, 130.17, 126.94, 112.01, 87.60. δ_P(CD$_3$CN, rel. to 85% H$_3$PO$_4$), −17.77 (apparent doublet, unresolved $\Delta J_{Ag(x)-P}$ (x = 107, 109); apparent J_{Ag-P} 223.62 Hz), −143.28 (sept., PF$_6$). Anal. Calc. for C$_{68}$H$_{48}$AgP$_5$F$_6$·H$_2$O: C, 64.83; H, 4.00. Found: C, 64.76; H, 3.80%.

¶ *Crystallographic data*: for **3**: C$_{70}$H$_{52}$Cl$_4$CuF$_6$P$_5$, M = 1367.40, orthorhombic, space group *Pbcm*, Z = 4, a = 11.5309(4), b = 20.2376(7), c = 28.5051(11) Å, V = 6651.9(4) Å^3, μ(Mo-Kα) = 0.667 mm^{-1}, T = 135 K, 6846 unique reflections (R_{int} = 0.063) were used in all calculations. A Bruker platform goniometer equipped with a SMART 6000 CCD detector was used for data collection using the ω scan technique. Direct methods (Bruker software: SHELXS) were used in the solution of the structure. Anisotropic thermal parameters were used on the non-hydrogen atoms while isotropic thermal parameters were used on the hydrogen atoms which were included as fixed atom contributors for the final least-squares refinement. Within the unit cell, the cation, anion and solvent molecules lie in special positions. The final agreement factors were R = 0.0495 (observed data), R_w = 0.0610 (all data).

For **4**: C$_{68}$H$_{54}$AgF$_6$O$_3$P$_5$, M = 1295.9, orthorhombic space group *Pb*2$_1$*m*, Z = 4, a = 11.4950(4), b = 20.2486(7), c = 28.7007(9) Å, V = 6680.3(4) Å^3, T = 113 K, μ(Mo-Kα) = 0.4802 mm^{-1}, 8056 unique reflections (R_{int} = 0.063) were used in all calculations. Anisotropic thermal parameters were used on the non-hydrogen atoms and hydrogen atoms were included as fixed atom contributors with isotropic thermal parameters for the final least-squares refinement. The electron density map contained several other partial occupancy peaks that were attributed to water. The structure contains two PF$_6$ anions, one of which is disordered but well resolved. Both PF$_6$ anions lie on a crystallographic mirror plane. The final agreement factors were R = 0.0574 (observed data), R_w = 0.0737 (all data). CCDC 182/1867. See http://www.rsc.org/suppdata/cc/b0/b008337m/ for crystallographic files in .cif format.

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