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# Isolation of electronic from geometric contributions to Bergman cyclization of metalloenediynes†

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**Conformationally constrained ethylene-diamine metalloenediyne compounds exhibit alkyne termini separations that are constant and independent of metal center geometry. Ancillary chloride ligand electron donation into the Bergman cyclization reaction coordinate, however, dramatically influences the observed temperatures.**

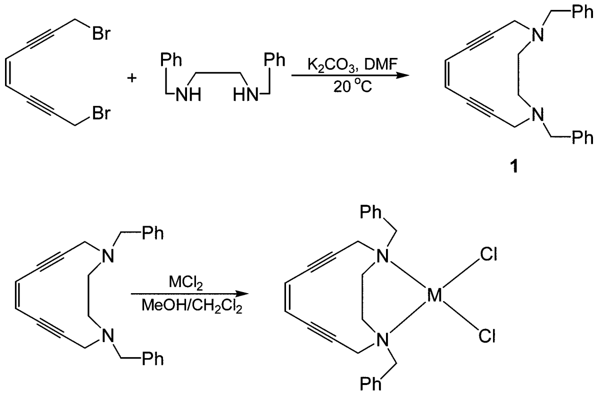
Bergman cyclization[1] of enediynes is often geometrically regulated by conformational changes associated with the immediate structural environment of the cyclic enediyne framework.[2] Geometric[3] and steric[4] contributions to Bergman cyclization thermodynamics have also been observed in synthetic enediyne structures. Only recently have the electron withdrawing effects at the alkyne termini (*i.e.* lowering of the cyclization transition state energy)[5] and vinyl (*i.e.* raising of the cyclization transition state energy)[6,7] positions been elucidated. In contrast, although the geometric influence of metal ions to lowering of the cyclization barrier for bound enediyne ligand is now established,[8–13] only skeletal information regarding the electronic effects of the metal center or ancillary ligands is available.[14,15] To a first approximation, the proximity of the metal-ancillary ligand fragment may appear too distant for electronic communication with the enediyne unit. However, the metal center geometry can influence the disposition of the ancillary ligands, thus stimulating their contribution to the Bergman cyclization reaction coordinate and the observed activation barrier.‡

To this end, the ethylenediamine-enediyne ligand 1,4-dibenzyl-1,4-diaza-cyclododec-8-ene-6,10-diyne (**1**) was prepared by reacting 1,8-dibromooct-4-ene-2,6-diyne[10] with N,N′-dibenzylethylenediamine in DMF at 20 °C (Scheme 1). The corresponding Cu(II) (**2**) and Zn(II) (**3**) compounds were obtained by reaction of a 1 : 1 mixture of **1** and the appropriate $MCl_2$ salt in a 1 : 1 dichloromethane : methanol solution.

The X-ray structure of **1** (Fig. 1) shows that the methylene carbons of the enediyne unit (C1, C8) connect the planar *cis*-enediyne framework to the nitrogen atoms (N1, N2) across the ethylenediamine unit. Therefore, the enediyne backbone lies perpendicular to the *trans*–N1–C9–C10–N2 plane and thus the alkyne termini (C2···C7) are forced to a separation distance of 3.90 Å. The alkyne bond angles show only very modest distortion from linearity averaging ~ 172°.

The $d^9$ electronic configuration of the Cu(II) compound **2** enforces a distorted square planar geometry common to 4-coordinate *cis*–$CuN_2Cl_2$ structures.[10,11] The tightly chelated nitrogens (~ 2.07 Å) cause buckling of the ethylenediamine unit leading to a compression of the alkyne termini separation (C2···C7) from 3.90 Å to 3.76 Å relative to that of the free ligand. Topologically, the conformation of the ligand places the plane of the 6-carbon enediyne unit nearly perpendicular to that of the $CuCl_2$ plane. In contrast, for the Zn(II) analogue **3**, the spherically symmetric $d^{10}$ electronic configuration leads to a tetrahedral disposition of the ligands about the *cis*-$ZnN_2Cl_2$ core. Despite the change in metal center geometry, the ethylenediamine chelate maintains a nearly identical alkyne termini separation (3.75 Å) to that of **2**. However, the tetrahedral geometry of Zn(II) center has farther reaching effects; the geometry places one of the ancillary chloride ligands (Cl1) to within 3.25 Å of the plane of the enediyne unit. This allows chloride lone pair donation to electronically influence Bergman cyclization as the ligand is spatially proximal to the developing bond between the C2 and C7 carbons.

The thermal Bergman cyclization reactivities of ligand **1** and the corresponding metalloenediynes **2, 3** have been evaluated by a combination of differential scanning calorimetry (DSC)



**2**, M = Cu
**3**, M = Zn

**Scheme 1** Syntheses of enediyne ligand **1** and metalloenediyne compounds **2, 3**.

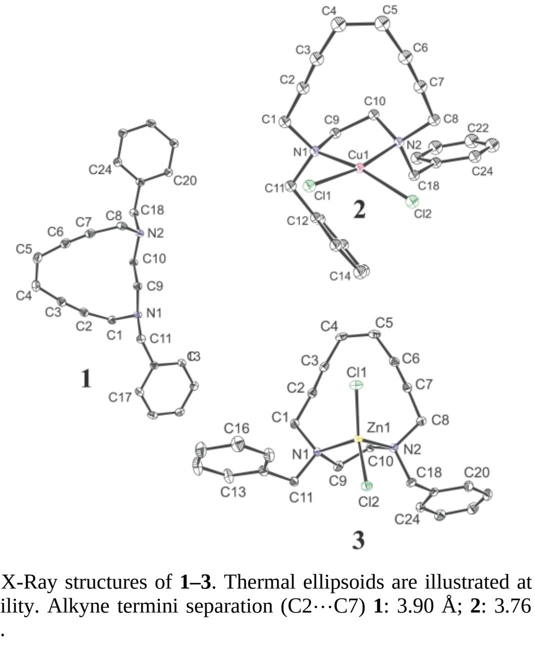


**Fig. 1** X-Ray structures of **1–3**. Thermal ellipsoids are illustrated at 40% probability. Alkyne termini separation (C2···C7) **1**: 3.90 Å; **2**: 3.76 Å **3**: 3.75 Å.

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† Electronic supplementary information (ESI) available: syntheses, characterizations and DSC traces of **1–3**, crystallographic data of **1–4**. See http://www.rsc.org/suppdata/cc/b3/b301690k/

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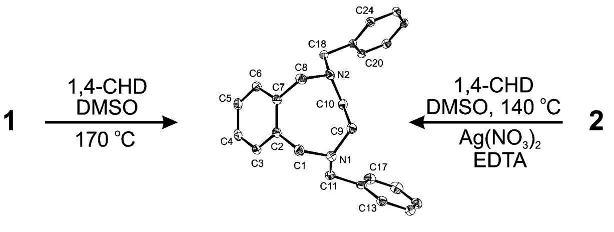
and product isolation studies. The thermal reactivity of **1** shows a melting endotherm at 70 °C that is followed by a large, irreversible exothermic peak at 170 °C in the melt. Heating of **1** in DMSO solution with 100-fold excess 1,4-cyclohexadiene (CHD) for 12 h at 170 °C yields the Bergman cyclized product **4** in 70% yield (Scheme 2). In contrast, heating of the ligand at 140 °C for 12 h under the same conditions leads to no reaction and recovery of only unreacted ligand starting material.

For metalloenediynes **2** and **3**, heating of solid samples results in only large exothermic peaks at 141 and 207 °C, respectively, indicating cyclization of the enediyne unit in the solid state. Control experiments with the corresponding $MLCl_2$ (L = N,N′-dibenzylethylenediamine) model compounds show no such features in the DSC traces, effectively ruling out reactivity associated with the local $MN_2Cl_2$ framework as the origin of the exotherms.

Heating of **2** in DMSO–CHD solution for 6 h at 140 °C followed by demetallation with $Ag(NO_3)_2$ and excess EDTA, results in generation of Bergman cyclized product **4** in 25% isolated yield (Scheme 2). The remaining mass balance consists of insoluble polymeric[16] and decomposition products, without persistence of unreacted starting material. Compound **4**† was characterised by NMR, Mass, and X-ray crystallography§ (Scheme 2). The structure verifies formation of the C2–C7 bond in the Bergman cyclization reaction. The reduced reaction temperature for cyclization of metalloenediyne **2** relative to free ligand **1** not only verifies the observed trend in DSC temperatures, but confirms complexation-induced reduction of the activation barrier to Bergman cyclization. In comparison of **1** and **2**, the origin of this effect is that of a metal-mediated conformational change of the enediyne ligand and consequential reduction of the alkyne termini separation. Attempts to cyclize **3** in DMSO solution resulted in ligand exchange with solvent at 100 °C, and thus only cyclization data by DSC in the absence of solvent could be obtained.

From the X-ray structure it is evident that chelation of ligand **1** to Cu(II) results in a decrease in alkyne termini separation by 0.14 Å relative to the free ligand, and thus a corresponding decrease in cyclization temperature in solution by ~30 °C. However, comparison of X-ray structures of metalloenediynes **2** and **3** reveals that despite variation in metal center geometry, the ethylenediamine linker constrains the conformation of the enediyne unit resulting in statistically identical C2···C7 distances. Thus, the geometric contribution to the activation barrier to Bergman cyclization is essentially constant for **2** and **3**, but their thermal cyclization temperatures vary by > 60 °C.

To understand the disparity in the Bermgan cyclization temperatures of **2** and **3**, single point density functional theory (DFT) calculations of **1–3** were performed at their crystal structure geometries using the UB3LYP combination of functionals (6–31G* basis on C, N, H) and the LANL2 pseudopotential with the LANL2DZ basis on Cu, Zn, Cl within Gaussian 98. The results show that the highest energy occupied enediyne-centered orbital is the HOMO-2 for **1**, and the HOMO for metalloenediynes **2** and **3** (Fig. 2). For **1**, the HOMO-2 is delocalized across the enediyne and ethylenediamine fragments of the ligand. This electronic configuration is preserved in the HOMO of **2**, but additional, localized contributions from the chloride lone pairs are observed parallel to the plane of the enediyne. This case differs substantially from that of **3** where the tetrahedral geometry of the Zn(II) center juxtaposes one of the chloride lone pairs directly above enediyne plane, allowing significant through-space contribution from the lone pairs to the enediyne π-centered HOMO of **3** due to close spatial proximity. The additional electron density provided by this interaction in the vicinity of the developing C2–C7 bond effectively increases the activation barrier for generation of Bergman cyclized product. An analogous lone pair-radical interaction argument has been shown to account for the increase in the transition state energy upon chloro-substititution at the vinyl position of the enediyne unit.[6,7] In the case of metalloenediynes **2** and **3**, such an effect is the first confirmation of an electronic contribution to Bergman cyclization from an ancillary ligand. This study, in a systematic way, has isolated geometric and electronic contributions to metalloenediyne cyclization, and further develops the array of factors that can influence the Bergman cyclization thermodynamics of simple metalloenediyne constructs. Additional work to further elucidate these electronic effects is progress.



**Scheme 2** Bergman cyclization of **1** and **2** in solution. X-Ray structure of cyclized product **4** obtained by heating of **1** at 170 °C for 12 h. Thermal ellipsoids are illustrated at 40% probability.

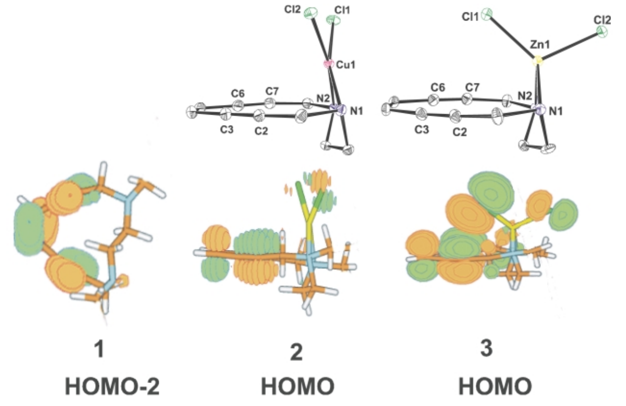


**Fig. 2** Highest occupied enediyne centered orbitals of **1–3**. Phenyl groups have been omitted for clarity. Color differences denote orbital phases.

## Notes and references

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§ CCDC 204062–204065. See http://www.rsc.org/suppdata/cc/b3/b301690k/ for crystallographic data in .cif or other electronic format.

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