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Mg^{2+}-Induced Thermal Enediyne Cyclization at Ambient Temperature

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The use of metal ions to promote the thermal Bergman cyclization of enediynes is a rapidly developing area of research that may lead to advances in synthetic transformations, as well as the development of potential biochemical and therapeutic agents.[1−12] Strategies toward these goals have included the preparation of coordination complexes where enediyne chelation leads to a metalloenediyne framework with a diminished activation temperature due to modulation of the alkyne termini separation.[1−3,5,6,8,12] In addition, π-complexation of metals to enediyne substructures has also been shown to geometrically or electronically influence the activation barrier to thermal Bergman cyclization.[10] These approaches have yielded significant conceptual and practical advances in the ability to control thermal cyclization temperatures across a variety of enediynes with metals such as Ni, Cu, Ru, Pd, and Pt.

The emerging theme from our contribution to this area is that the metal center geometry, ligand flexibility, and steric bulk adjacent to the alkyne termini can have profound effects upon the enediyne cyclization temperatures, and the dynamic range accessible by sampling oxidation states of a given metal center.[5,6,11−13] For biological applications, however, the ability to employ in vivo metals or those which are traditionally less toxic, leads to advantages for potential biological uses of metalloenediynes. Within this theme, we have reported the synthesis and facile thermal reactivity of a novel bis(pyridine)enediyne ligand and the corresponding Mg(II) complex.

The ligand (*Z*)-*N*,*N′*-bis[1-pyridin-2-yl-meth-(*E*)-ylidene]oct-4-ene-2,6-diyne-1,8-diamine (**3**) was prepared in 75% yield by reaction of 1,8-diaminooct-4-ene-2,6-diyne (**1**)[13] with pyridine-2-carboxaldehyde (**2**) in dichloromethane (Scheme 1). Reduction of the **3** with 2.5 equiv of NaBH$_4$ leads to the formation of the reduced enediyne (*N*,*N′*-bis-pyridin-2-ylmethyl-oct-4-ene-2,6-diyne-1,8-diamine, **4**) in 84% yield. The Mg(II) complex (**5**) was prepared by incubation of **3** with MgCl$_2$•6H$_2$O in MeOH at 0 °C for 8 h followed by removal of the solvent under vacuum and washing with ether.

The thermal reactivity of **3** was evaluated by differential scanning calorimetry (DSC). As a neat material, **3** exhibits an exothermic peak ($\Delta H = -52.1$ kcal/mol) at 100 °C, indicative of thermal Bergman cyclization.[1,3,6,13] The enhanced flexibility and reduced steric crowding within the ligand deriving from introduction of three atoms between the alkyne termini and the bulky pyridine rings give compound **3**, to our knowledge, the lowest thermal cyclization temperature for an acyclic enediyne ligand to date. In solution, **3** is stable for 12 h at room temperature but degrades slowly over a 48-h period.

The thermal reactivity of **5** is also striking. In methanolic solution containing 20-fold 1,4-cyclohexadiene, warming of **5** to room temperature, or addition of Mg^{2+} to **3** leads to rapid and pronounced changes in both the ^{1}H and {^{1}H}^{13}C NMR spectra. The most diagnostic features are those associated with the $-$CH$_2-$N═ unit as well as the developing aromatic resonances of the Bergman cyclized product **6** (Scheme 1). After warming of **5** to room temperature, new resonances are observed at δ 4.99 ppm (ph$-$CH$_2-$N═) as well as an aromatic multiplet at δ 7.35 ppm in the ^{1}H NMR spectrum. The resonances match very closely with those observed for the uncomplexed benzylimine derivative 5-phenyloxazole-2-carboxaldehyde-*N*-benzylimine (4.97 ppm),[14] indicating formation of the Bergman cyclized product. Since the imine framework is very unstable under these experimental conditions, identification of the reaction product was accomplished by in situ NaBH$_4$ reduction of **6** at 2 h into the reaction, followed by EDTA treatment to generate the more stable demetalated benzylamine **7** (Scheme 1). Four new singlets are now observed in the ^{1}H NMR spectrum, two at $\delta = 4.02$ ($-$N$-$CH$_2-$py) and 3.68 ppm ($-$CH$_2-$N$-$) characteristic of the reduced enediyne ligand **4**, and two at δ 3.97 ($-$N$-$CH$_2-$py) and 3.89 ppm (ph$-$CH$_2-$N$-$) deriving from the reduced Bergman cyclized product **7** (Scheme 1). These signatures match those of the literature compound benzyl-pyridin-2-ylmethyl-amine[15] confirming formation of benzylamine linkage.

As a control, an authentic sample of the reduced cyclized product **7** was independently synthesized by reaction of pyridine-2-carboxaldehyde with *o*-xylene diamine to yield **9**, followed by reduction with NaBH$_4$ to give the authentic product **7** (Scheme 2). The most prominent differences between the spectra of **4** and **7** derive from disappearance of the alkyne (δ 81.5, 95 ppm) and olefin (δ 119 ppm) carbons, and the appearance of three substituted benzene signals at δ 127.4, 130.2, and 138.7 ppm. In addition to these diagnostic features, detection of both ph$-$CH$_2-$N$-$ and $-$N$-$CH$_2-$py resonances at 51.4 and 54.0 ppm,[15] respectively, identify the in situ generated Bergman product. Based on the half-life for the reaction ($t_{1/2} = 2.2$ h), which was determined from the disappearance of the olefin proton of **5** at δ 6.06 ppm[16] and the developing ph$-$CH$_2-$N ═ signal for **6** at 4.99 ppm, the yield of in situ cyclized product is approximately 40% prior to radical-mediated decomposition.

To estimate the composite ^{13}C NMR spectrum of the reduced starting material and product, a 2:1 mixture of **4**:**7** was compared to the in situ thermal Bergman cyclization reaction. Although modest (<0.5 ppm) chemical shift changes are observed due to the presence of radical-mediated decomposition product,[17] the intensities and chemical shifts of the $-$N$-$CH$_2-$py and ph$-$CH$_2-$N$-$ resonances (δ 50−55 ppm), and the substituted benzene signals (δ 127−131 ppm), correlate well with the 2:1 control mixture of **4**:**7**. Combined, the ^{1}H and ^{13}C NMR data indicate the Mg^{2+}-induced formation of Bergman cyclized product **5** at ambient temperature.

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(1) Warner, B. P.; Millar, S. P.; Broene, R. D.; Buchwald, S. L. *Science* **1995**, *269*, 814−816.

(2) König, B.; Hollnagel, H.; Ahrens, B.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2538−2540.

(3) König, B.; Pitsch, W.; Thondorf, I. *J. Org. Chem.* **1996**, *61*, 4258−4261.

(4) Basak, A.; Shain, J. C. *Tetrahedron Lett.* **1998**, *39*, 1623−1624.

(5) Coalter, N.; Concolino, T. E.; Streib, W. E.; Hughes, C. G.; Rheingold, A. L.; Zaleski, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 3112−3117.

(6) Benites, P. B.; Rawat, D. S.; Zaleski, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7208−7217.

(7) Basak, A.; Shain, J. C.; Khamari, U. K.; Rudra, K. R.; Basak, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1955−1964.

(8) Basak, A.; Rudra, K. R. *Tetrahedron Lett.* **2000**, *41*, 7231−7234.

(9) König, B. *Eur. J. Org. Chem.* **2000**, 381−385.

(10) O'Connor, J. M.; Lee, L. I.; Gantzel, P.; Rheingold, A. L.; Lam, K.-C. *J. Am. Chem. Soc.* **2000**, *122*, 12057−12058.

(11) Schmitt, E. W.; Huffman, J. C.; Zaleski, J. M. *Chem. Commun.* **2001**, 167−168.

(12) Rawat, D. S.; Benites, P. J.; Incarvito, C. D.; Rheingold, A. L.; Zaleski, J. M. *Inorg. Chem.* **2001**, *40*, 1846−1857.

(13) Rawat, D. S.; Zaleski, J. M. *Chem. Commun.* **2000**, 2493−2494. HR-MS for **1**: 134.0836 [M$^+$ calcd for C$_8$H$_{10}$N$_2$: 134.084].

(14) Vedejs, E.; Piotrowski, D. W.; Tucci, F. C. *J. Org. Chem.* **2000**, *65*, 5498−5505.

(15) Boduszek, B. *Tetrahedron* **1996**, *52*, 12483−12494.

(16) Integration of the resonance at δ 6.06 ppm was performed relative to the residual proton signal (δ 3.30 ppm) of the solvent (CD$_3$OD).

(17) The presence of decomposition products is identified by broadening of the baseline in the aromatic region of the ^{1}H NMR. No specific resonances characteristic of discreet products are observed, consistent with multiple decomposition pathways.

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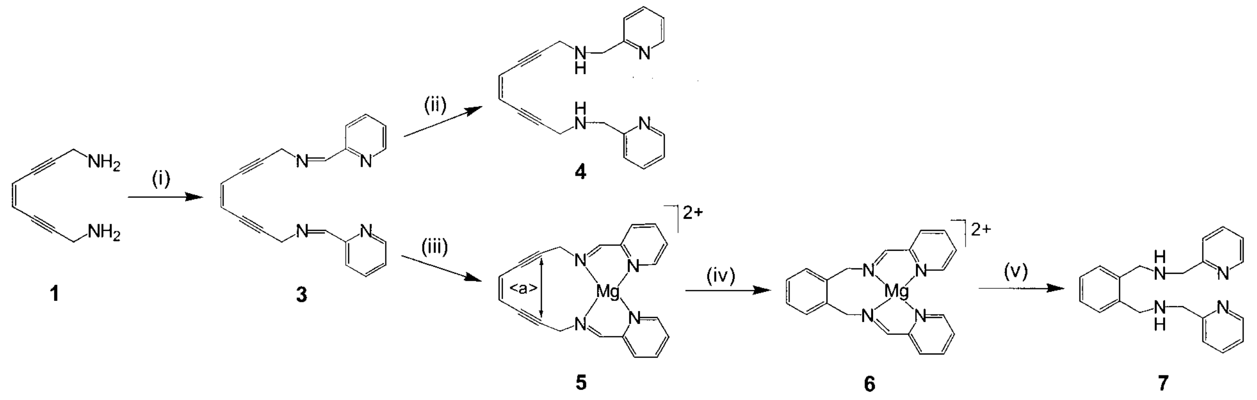
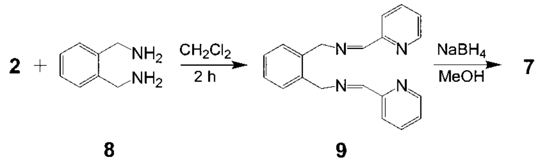
Scheme 1. Syntheses of Enediynes **3**−**5** and the in Situ Generation of Bergman Cyclized Products **6**,**7**[a]



[a] Reagents and conditions: (i) CH_2Cl_2, rt, 2.5 h, 75%; (ii) MeOH, $NaBH_4$, rt, 1 h, 84%; (iii) MeOH, $MgCl_2$, 0 °C, 8 h, 70%; (iv) MeOH, 1,4-CHD, rt; (v) $NaBH_4$, 5−10 °C, DMF, EDTA, CH_2Cl_2.

Scheme 2. Synthesis of Cyclized Product **9** and **7**



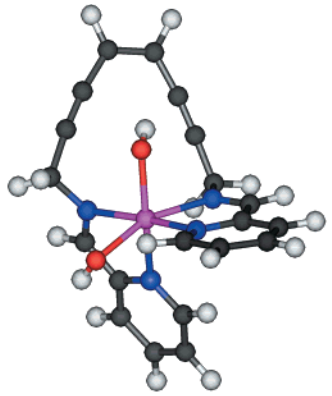


Figure 1. Geometric structure of metalloenediyne **5** ($\langle a \rangle$ = 3.79 Å), determined by molecular mechanics calculations at the MMX force field level. Atom color designations: magnesium (pink), nitrogen (blue), oxygen (red), carbon (black), hydrogen (white).

To evaluate the structural consequences giving rise to such facile thermal reactivity, molecular mechanics calculations at the MMX force field level[18] have been performed for enediyne ligand **3**, as well as a series of four- to six-coordinate Mg^{2+} structures. Since Mg^{2+} is electrophilic and frequently forms five-coordinate[19−23] or six-coordinate[21,24−31] structures in the presence of anionic ligands and coordinating solvents, the geometric starting point for the latter calculations was the five- or six-coordinate MgN_4O_x ($x = 1, 2$) construct where OH^- was used to approximate solvent (MeOH) or counterion (Cl^-) coordination in solution. Within these coordination environments, approximately 60 structures were iteratively minimized until a subset of five of the lowest-energy structures for each class were identified. The standard deviations in the energies and alkyne termini separation (<4%) were obtained from an average of these structures. The results show a systematic decrease in the alkyne termini separation $\langle a \rangle$ beginning with the uncomplexed enediyne ligand **3** with minimized $(Z)-(E)$ stereochemistry (4.03 Å), and continuing with increasing Mg^{2+} coordination number (MgN_4 (3.93 Å) > MgN_4O (3.90 Å) > MgN_4O_2 (3.79 Å). The calculated $\langle a \rangle$ values are consistent with previously reported theoretical and X-ray structural characterizations of simple enediynes and their corresponding thermal reactivities.[5,11,12,32,33] The trend in $\langle a \rangle$ and the correspondingly low activation temperature for **5** relative to uncomplexed ligand **3**, suggest that in solution **5** is best described as a six-coordinate Mg^{2+} complex (Figure 1).[34] The structure/activity correlation indicates that the facile thermal reactivity of **5** results from the ability of Mg^{2+} to coordinate both pyridine, and more importantly the imine nitrogens, to draw the alkyne termini into close proximity for cyclization. On the basis of the sluggish thermal reactivity of the reduced ligand **4** in the presence of Mg^{2+} (DSC = 181 °C, $\Delta H = -49.6$ kcal/mol), it appears that facile reactivity of this framework is very specific to the presence of the imine unit. One plausible explanation for the disparity in the reactivities of ligands **3** and **4** could derive from the poor basicity of the imine nitrogen versus the corresponding amine, and consequently the need for Mg^{2+} to adopt additional ligands (solvent or counterion) to satisfy the Lewis acidity of the metal center. As shown by the computational analysis, the increase in coordination number can reduce the alkyne termini separation and lower the barrier to thermal Bergman cyclization. Overall, the study documents the ability to use biologically prevalent and innocuous metals such as Mg^{2+} for initiating facile enediyne reactivity at ambient temperature by metal coordination.

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Supporting Information Available: Synthetic details and spectroscopic analyses of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] *PCMODEL*, v.7.5; Serena Software: Bloomington, IN 47405.

[19] Freitag, S.; Kolodziejski, W.; Pauer, F.; Stalke, D. *J. Chem. Soc., Dalton Trans.* **1993**, 3479.

[20] Corazza, F.; Floriani, C.; Chiesi-Villa, A.; Gustani, C.; Ciurli, S. *J. Chem. Soc., Dalton Trans.* **1998**, 2341.

[21] Srinivas, B.; Chang, C. C.; Chen, C. H.; Chaing, M. Y.; Chen, I. T.; Wang, Y.; Lee, G. H. *J. Chem. Soc., Dalton Trans.* **1997**, 957−963.

[22] Serlin, R.; Chow, H.-C.; Strouse, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 7237−7242.

[23] Byrn, M. P.; Curtis, C. J.; Hsiou, Y.; Khan, S. I.; Sawin, P. A.; Tendick, S. K.; Terzis, A.; Strouse, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 9480−9497.

[24] Waters, A. F.; White, A. H. *Aust. J. Chem.* **1996**, *49*, 147−154.

[25] Waters, A. F.; White, A. H. *Aust. J. Chem.* **1996**, *49*, 35−46.

[26] Walther, D.; Gebhardt, P.; Fischer, R.; Kreher, U.; Gorls, H. *Inorg. Chim. Acta* **1998**, *281*, 181−189.

[27] Schwalbe, C. H.; Goody, R.; Saenger, W. *Acta Crystallogr.* **1973**, *B29*, 2264−2272.

[28] Polyakov, V. R.; Sharma, V.; Crankshaw, C. L.; Pinwica-Worms, D. *Inorg. Chem.* **1998**, *37*, 4740−4742.

[29] McKee, V.; Rodley, G. A. *Inorg. Chim. Acta* **1988**, *151*, 233−236.

[30] Kepert, D. L.; Skelton, B. W.; Waters, A. F.; White, A. H. *Aust. J. Chem.* **1996**, *49*, 47−59.

[31] Constable, E. C.; Healy, J. *Polyhedron* **1991**, *10*, 1883−1887.

[32] Chandra, T.; Pink, M.; Zaleski, J. M. *Inorg. Chem.* **2001**. In press.

[33] Blanchette, H. S.; Brand, S. C.; Naruse, H.; Weakley, T. J. R.; Haley, M. M. *Tetrahedron* **2000**, *56*, 9581−9588.

[34] An alternative structure in which the pyridine rings are in a *trans* configuration yields an identical alkyne termini separation and is within 2 kcal/mol of the structure in Figure 1.