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Anion Control of Lanthanoenediyne Cyclization

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Abstract

A suite of lanthanoenediyne complexes of the form $\text{Ln}(\text{macrocycle})\text{X}_3$ ($\text{Ln} = \text{La}^{3+}, \text{Ce}^{3+}, \text{Eu}^{3+}, \text{Gd}^{3+}, \text{Tb}^{3+}, \text{Lu}^{3+}$; $\text{X} = \text{NO}_3^-, \text{Cl}^-, \text{OTf}^-$) was prepared by utilizing an enediyne-containing [2 + 2] hexaaza-macrocycle (**2**). The solid-state Bergman cyclization temperatures, measured via DSC, decrease with the denticity of X (bidentate NO_3^- , $T = 267\text{--}292^\circ\text{C}$; monodentate Cl^- , $T = 238\text{--}262^\circ\text{C}$; noncoordinating OTf^- , $T = 170\text{--}183^\circ\text{C}$). ^{13}C NMR characterization shows that the chemical shifts of the acetylenic carbon atoms also rely on the anion identity. The alkyne carbon closest to the metal binding site, C_A , exhibits a $\delta > 3$ ppm downfield shift, while the more distal alkyne carbon, C_B , displays a concomitant $\delta \sim 2.5$ ppm upfield shift, reflecting a depolarization of the alkyne on metal inclusion. For all metals studied, the degree of perturbation follows the trend $2 < \text{NO}_3^- < \text{Cl}^- < \text{OTf}^-$. This belies a greater degree of electronic rearrangement in the coordinated macrocycle as the denticity of X and its accompanying shielding of the metal's Lewis acidity decrease. Computationally modeled structures of LnX_3 show a systematic increase in the lanthanide–2 coordination number ($\text{CN}_{\text{La-mc}} = 2$ (NO_3^-), 4 (Cl^-), 5 (H_2O , model for OTf^-)) and a decrease in the mean Ln–N bond length ($\text{La-N}_{\text{average}} = 2.91 \text{ \AA}$ (NO_3^-), $2.78 \text{ \AA}$ (Cl^-), $2.68 \text{ \AA}$ (H_2O)), further suggesting that a decrease in the anion coordination number correlates with an increase in the metal–macrocycle interaction. Taken together, these data illustrate a Bergman cyclization landscape that is influenced by the bonding of metal to an enediyne ligand but whose reaction barrier is ultimately dominated by the coordinating ability of the accompanying anion.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorg-chem.9b00856.

Details of the crystallographic characterization of **2** and **2'**, full NMR characterization of **2** and **8c**, titration of **3a** with excess lanthanum, IR spectra of **3–8c**, and coordinates for DFT-computed structures (PDF)

Accession Codes

CCDC 1903497–1903498 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. Crystallographic data (excluding structure factors) for **2** and **2'** have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting depository numbers CCDC 1903497 and 1903498 (Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk, <http://www.ccdc.cam.ac.uk>).

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INTRODUCTION

The controlled generation of reactive intermediates is a fundamental priority for metal-mediated catalysis and is achieved via a balance of geometric and electronic properties of the active metal center and its carefully engineered ligand scaffold.¹ These properties are selected to engender the desired reactivity, including the coordination equilibria of the substrate and product, reaction rates, and enantiomeric selectivity in the overall transformation. Within this parameter space, lanthanides offer an attractive alternative to more traditional transition-metal catalysts; these high-valent, hard Lewis acids can readily bind substrates even in aqueous environments,^{2,3} but penetration of the f orbitals renders the noncovalent ligation labile enough for product release after substrate transformation.⁴ Additionally, all lanthanides are stable in their trivalent form, so the systematic contraction in size across the period enables tuning of the size-to-charge ratio of the active site (i.e., relative hardness of the acid).⁵ The coordination sphere flexibility also allows the steric properties of the ancillary ligand to strongly influence the catalyst behavior. An excellent example of this is the modular Cp* ligand class, where the addition of a chiral pendant dictates product stereochemistry and tethering two Cp* moieties enhances metal access to improve the catalytic activity (Figure 1a).^{6,7} The tunability of these properties defines the catalytic utility of lanthanides, allowing for applications spanning from fundamental organic transformations^{8–10} to a variety of π -manifold activations including polymerization^{11–13} and functionalization.^{14,15}

Beyond this direct active site influence, the rare earth catalyst behavior can be modified by a change as inconspicuous as the choice of the accompanying anion. When lanthanide triflates are used to catalyze the nitration of aromatic rings, the activity is inversely related to the metal radius.^{16–18} Smaller metals have larger charge-to-size ratios and thus wield increased polarizing power to facilitate the transformation of NO_3^- to the active nitration species, NO_2^+ . Conversely, when this reaction is catalyzed by lanthanide nitrobenzenesulfonate (NBS), the size–activity relationship is reversed and the lighter, larger metals yield the highest catalytic activity.¹⁹ This is a consequence of anion coordination (NBS) versus outer-sphere counterion (triflate) interactions.^{20–22} Bulky NBS hinders the substrate approach to the active site, a situation that is exacerbated by smaller metal radii.

Bergman cyclization reactions also demonstrate an anion dependence of the *cis*-enediyne ligand.^{23–25} This intra-molecular cycloaromatization reaction proceeds via a highly reactive diradical intermediate and generally benefits from the inclusion of a controlled reaction trigger such as a photo- or redox-active metal.^{26–30} Typically, the chelation of an enediyne ligand to a metal lowers the barrier to Bergman cyclization both geometrically, by decreasing the interalkynyl distance across which the new σ -bond will form,^{31,32} and electronically, by the more subtle influence of the charged metal fragment on the enediyne orbital framework energies (Figure 1b).^{23,25,33} Though it is often difficult to isolate the two effects, the electronic contribution can be evaluated by keeping the geometric component (i.e., structure) constant and modulating the electronic determinant, which is typically the ancillary ligand or counterion. This has been demonstrated within tetrahedral zinc halide complexes of an ethylenediamine-strapped enediyne, which exhibit nearly identical interalkynyl distances but have solid-state reaction temperatures that span a range of 60 °C (Cl[−], 207 °C; Br[−], 154 °C; I[−], 144 °C) because of the differential through-space repulsion of the halogen lone pairs with the enediyne frontier orbital electrons.^{23–25}

In this work, we demonstrate metal-induced, anion-mediated Bergman cyclization as a model catalysis reaction via the first lanthanide metalloenediyne complexes reported. The nature of the anion strongly influences metal–ligand bond lengths and coordination numbers, thereby modulating observed enediyne cyclization temperatures in the solid state. ¹³C NMR data and computed model structures highlight the intimate relationship between electronic and structural considerations. Because the strength of the lanthanide–macrocycle interaction (i.e., bond lengths and numbers) relies on the anion present, so too does the electron distribution about the ligand (i.e., alkyne polarity), ultimately perturbing the temperature required for Bergman cyclization by over 100 °C. The ability to use simple anion coordination to influence metalloenediyne cyclization further accentuates the role metals can play in driving “one of the most fascinating rearrangements in chemistry.”³⁴

EXPERIMENTAL SECTION

Materials.

Unless otherwise noted, all chemicals were purchased from commercial sources and used as received. Reagents pyridine-2,6-dicarboxyaldehyde and (Z)-octa-4-en-2,6-diyne-1,8-diamine were synthesized according to previously published procedures.^{35,36} All lanthanide salts were obtained from Strem Chemical. Where necessary, waters of hydration were determined via complexometric titration.³⁷

Physical Measurements.

NMR spectra were collected on a Varian Inova 400 or 500 MHz spectrometer using residual proton solvent signals as an internal reference. Mass spectrometry data were collected by one of two methods. 3a, 3b, 8a, and 8b were analyzed by direct infusion into a Synap HDMS quadrupole TOF-MS (Waters, Beverly, MA) with a resolving power of 9000. The remainder of the positive ion mass spectra were recorded by direct infusion into an Orbitrap XL MS (Thermo-Fisher Scientific, Waltham, MA) at a resolving power of 30 000. Differential scanning calorimetry traces were recorded on a TGA Q10 DSC system with a TA

Instruments thermal analyzer at a heating rate of 10 °C min⁻¹. Elemental analyses were collected by Robertson Microлит Laboratories, Inc. IR spectra were recorded via the dropcast method from methanolic solution onto a KBr plate with a Thermo Nicolet 6700 FT-IR. For each spectrum, the resolution was 4 cm⁻¹ and 256 scans were collected. X-ray crystallographic data were collected by the Indiana University Molecular Structure Center on a Bruker APEX II Kappa Duo diffractometer using Mo K α radiation (graphite monochromator) at 150 K. Details of the X-ray analysis can be found in the Supporting Information.

Computations.

Gas-phase geometries were optimized and vibrational frequencies were calculated with DFT using the PBE0 hybrid functional with *Gaussian 16*.^{38,39} Light atoms were modeled using the 6-31G** basis set; the Stuttgart relativistic, small-core segmented ECP was used to model lanthanum and lutetium.⁴⁰ Starting geometries placed the metal within the binding pocket of the ligand with anions (or water) randomly oriented above and below the macrocycle. Ground-state structures were confirmed by the absence of imaginary vibrational frequencies.

Cyclo[bis(pyridine-2,6-diylldimethanimine-(Z)-octa-12-en-10,14-diyne)] (1).—A solution of (*Z*)-octa-4-en-2,6-diyne-1,8-diamine (650 mg, 4.8 mmol) in dichloromethane (2.0 L) was stirred at 0 °C over sodium sulfate. Solid pyridine-2,6-dicarboxaldehyde (650 mg, 4.8 mmol) was added to this solution, and the reaction mixture was allowed to stir while gradually warming to room temperature overnight. The sodium sulfate was removed via gravimetric filtration before the volume of the remaining dichloromethane solution was reduced in vacuo. The addition of methanol to this solution resulted in the precipitation of **1** as a fibrous white solid. Yield: 62%. ¹H NMR (400 MHz, 298 K, CDCl₃) δ_{H} (ppm): 8.89 (s, 4H), 8.01 (d, *J* = 7.7 Hz, 4H), 7.81 ppm (t, *J* = 7.8 Hz, 2H), 5.96 (s, 4H), 4.97 (s, 8H). ¹³C{¹H} NMR (101 MHz, 298 K, CD₂Cl₂) δ_{C} (ppm): 163.3, 154.9, 137.8, 123.1, 119.9, 93.0, 85.4, 48.9. HRMS-ESI: *m/z* calcd for [C₃₀H₂₃N₆]⁺, 467.1984; found, 467.1978 (M + H)⁺. DSC: 122 °C (onset), 157 °C (max). Elemental analysis calcd for C₃₀H₂₂N₆·H₂O: C, 74.36; H, 4.99; N, 17.34. Found: C, 74.31; H, 4.71; N 17.12.

Cyclo[bis(pyridine-2,6-diylldimethanamine-(Z)-octa-12-en-10,14-diyne)] (2).—Methanol (75 mL) and sodium borohydride (110 mg, 2.9 mmol) were added to a vigorously stirred solution of **1** (98 mg, 210 μ mol) in dichloromethane (75 mL). Nitrogen was bubbled through the reaction mixture as it was stirred at 0 °C for 1 h. Aqueous sodium bicarbonate was added, the mixture was extracted with 3 $\times$ 50 mL of dichloromethane, and the combined organic layers were dried over sodium sulfate. The volume of the solution was reduced in vacuo before hexanes were added to produce **2** as a fluffy pale-yellow solid. Yield: 97%. Crystals suitable for X-ray analysis were grown from the slow diffusion of ether into a dichloromethane solution of **2** at -20 °C. ¹H NMR (400 MHz, 298 K, CDCl₃) δ_{H} (ppm): 7.53 (t, *J* = 7.7 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 4H), 5.83 (s, 4H), 3.98 (s, 8H), 3.70 (s, 8H). ¹H NMR (400 MHz, 298 K, CD₃OD) δ_{H} (ppm): 7.64 (t, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 4H), 5.90 (s, 4H), 3.93 (s, 8H), 3.59 (s, 8H). ¹³C{¹H} NMR (101 MHz, 298 K, CDCl₃) δ_{C} (ppm): 159.1, 136.9, 120.7, 119.7, 95.5, 81.7, 53.8, 39.0. ¹³C{¹H} NMR (126 MHz, 298 K,

CD₃OD) δ_C (ppm): 159.5, 138.6, 122.2, 120.6, 95.2, 83.0, 53.8, 39.0. HSQC and HMBC correlational NMR spectra and full assignments can be found in the Supporting Information. HRMS-ESI: m/z calcd for [C₃₀H₃₁N₆]⁺, 475.2610; found, 475.2625 (M + H)⁺. DSC: 118.9 °C (melt), 158.9 °C (max).

Tetrahydrogen(cyclo[bis(pyridine-2,6-diyl)dimethanamine-(Z)-octa-12-en-10,14-diyne]) chloride (2').—Excess concentrated HCl was added to a solution of **2** (11 mg, 23 μ mol) in methanol (5 mL). On standing, the product precipitated as a light-orange solid. Crystals suitable for X-ray analysis were grown by slow evaporation from methanol at room temperature. Yield: 35%. ¹H NMR (400 MHz, 298 K, CD₃OD) δ_H (ppm): 7.96 (t, J = 8.1 Hz, 2H), 7.53 (d, J = 7.6 Hz, 4H), 6.12 (s, 4H), 4.54 (s, 8H), 4.28 (s, 8H). ¹³C{¹H} NMR (101 MHz, 298 K, CD₃OD) δ_C (ppm): 152.3, 140.5, 124.0, 121.8, 87.7, 86.5, 50.9, 38.5. DSC: 209 °C (onset), 217 °C (max).

Lanthanide Complexes of 2 (3a–8c).—Unless otherwise noted, lanthanide complexes of **2** were prepared by the addition of the appropriate lanthanide salt to a solution of ~1.1 mol equiv of **2** in 1:1 by volume dichloromethane and methanol. To avoid oxidative degradation in a concentrated aerobic solution, **2** was utilized directly from dilute solution once purified without collection as a neat solid. These solution concentrations were quantitated in triplicate by NMR with an internal standard of DMSO. Reaction mixtures of **2** and the appropriate lanthanide were allowed to stir for 18–24 h for nitrate (**3–8a**) and chloride (**3–8b**) salts and 2–4 h for triflate (**3–8c**) salts before solvent was reduced to a minimal volume. The addition of diethyl ether and subsequent washing with hexanes yielded each compound as a solid. Compounds with triflate counterions (**3–8c**) were additionally washed with cold water. Physical descriptions, amounts, and characterization data are given for each complex below.

[La(2)(NO₃)₃] (3a).—La(NO₃)₃·6H₂O (25.0 mg, 57.7 μ mol) was added to **2** (61.1 μ mol in 100 mL of 1:1 DCM/MeOH) to afford **3a** as an off-white solid (17 mg, 40% yield). ¹H NMR (500 MHz, 298 K, CD₃OD) δ_H (ppm): 7.77 (t, J = 7.7 Hz, 2H), 7.34 (d, J = 7.7 Hz, 4H), 6.00 (s, 4H), 4.15 (s, 8H), 3.84 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 157.6, 139.3, 123.1, 121.3, 93.2, 84.2, 53.1, 38.6. HRMS-ESI: m/z calcd for [LaC₃₀H₃₀N₈O₆]⁺, 737.1352; found, 737.1339 (M-NO₃)⁺. DSC: 246 °C (onset), 285 °C (max).

[La(2)Cl₃] (3b).—LaCl₃·7H₂O (35.0 mg, 94.2 μ mol) was added to **2** (102 μ mol in 84 mL of 1:1 DCM/MeOH) to afford **3b** as a tan solid (47 mg, 69% yield). ¹H NMR (400 MHz, 298 K, CD₃OD) δ_H (ppm): 7.80 (t, J = 7.7 Hz, 2H), 7.37 (d, J = 7.7 Hz, 4H), 6.03 (s, 4H), 4.22 (s, 8H), 3.91 (s, 8H). ¹³C{¹H} NMR (101 MHz, 298 K, CD₃OD) δ_C (ppm): 156.7, 139.5, 123.3, 121.3, 92.3, 84.6, 52.7, 38.6. HRMS-ESI: m/z calcd. for [LaC₃₀H₃₀N₆Cl₂]⁺, 683.0973; found, 683.0983 (M – Cl)⁺. DSC: 216 °C (onset), 238 °C (max).

[La(2)](CF₃SO₃)₃ (3c).—La(CF₃SO₃)₃ (184 mg, 314 μ mol) was added to **2** (173 μ mol in 50 mL of 1:1 DCM/MeOH). These were stirred together at a temperature of 50 °C for 2 h before the solution was concentrated in vacuo. The solution was then washed with ether,

hexanes, and cold water to afford **3c** as a light-tan solid (57 mg, 31% yield). ^1H NMR (400 MHz, 298 K, CD_3OD) δ_{H} (ppm): 7.79 (t, $J = 7.5$ Hz, 2H), 7.36 (d, $J = 7.7$ Hz, 4H), 6.02 (s, 4H), 4.19 (s, 8H), 3.87 (s, 8H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, 298 K, CD_3OD) δ_{C} (ppm): 155.4, 139.5, 123.3, 121.3, 92.5, 84.5, 52.9, 38.6. HRMS-ESI: m/z calcd for $[\text{LaC}_{32}\text{H}_{30}\text{N}_6\text{F}_6\text{S}_2\text{O}_6]^+$, 911.0636; found, 911.0632 ($\text{M} - \text{CF}_3\text{SO}_3$) $^+$. DSC: 177 °C (onset), 183 °C (max).

[Ce(2)(NO₃)₃] (4a).— $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (41.9 mg, 97.2 μmol) was stirred together with **2** (50.0 mg, 105 μmol) in 10 mL of methanol to afford **4a** as a tan solid (45 mg, 51% yield). ^1H NMR (400 MHz, 298 K, CD_3OD) δ_{H} (ppm): 7.78 (t, $J = 7.7$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 4H), 6.01 (s, 4H), 4.17 (s, 8H), 3.86 (s, 8H). ^{13}C NMR (101 MHz, 298 K, CD_3OD) δ_{C} (ppm): 157.3, 139.4, 123.2, 121.3, 92.9, 84.3, 53.0, 38.6. HRMS-ESI: m/z calcd for $[\text{CeC}_{30}\text{H}_{30}\text{N}_8\text{O}_6]^+$, 738.1343; found, 738.1320 ($\text{M} - \text{NO}_3$) $^+$. DSC: 264 °C (onset), 282 °C (max).

[Ce(2)Cl₃] (4b).— $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (36.9 mg, 99.0 μmol) was added to **2** (102 μmol in 84 mL of 1:1 DCM/MeOH) to afford **4b** as a tan solid (42 mg, 58% yield). ^1H NMR (400 MHz, 298 K, CD_3OD) δ_{H} (ppm): 7.82 (t, $J = 7.8$ Hz, 2H), 7.39 (d, $J = 7.7$ Hz, 4H), 6.05 (s, 4H), 4.25 (s, 8H), 3.95 (s, 8H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, 298 K, CD_3OD) δ_{C} (ppm): 155.9, 139.7, 123.5, 121.4, 91.5, 84.9, 52.4, 38.6. HRMS-ESI: m/z calcd for $[\text{CeC}_{30}\text{H}_{30}\text{N}_6\text{Cl}_2]^+$, 684.0963; found, 684.0964 (MCl) $^+$. DSC: 231 °C (onset), 259 °C (max).

[Ce(2)(CF₃SO₃)₃] (4c).— $\text{Ce}(\text{CF}_3\text{SO}_3)_3$ (30.6 mg, 52.1 μmol) was added to **2** (61.1 μmol in 60 mL of 1:1 DCM/MeOH) to afford **4c** as an off-white solid (15 mg, 27% yield). ^1H NMR (500 MHz, 298 K, CD_3OD) δ_{H} (ppm): 7.93 (t, $J = 7.8$ Hz, 2H), 7.49 (d, $J = 7.8$ Hz, 4H), 6.11 (s, 4H), 4.44 (s, 8H), 4.18 (s, 8H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, 298 K, CD_3OD) δ_{C} (ppm): 155.7, 140.3, 124.4, 121.5, 89.1, 85.8, 51.6, 38.5. HRMS-ESI: m/z calcd for $[\text{CeC}_{32}\text{H}_{30}\text{N}_6\text{F}_6\text{S}_2\text{O}_6]^+$, 912.0627; found, 912.0628 ($\text{M} - \text{CF}_3\text{SO}_3$) $^+$. DSC: 139 °C (onset), 175 °C (max).

[Eu(2)(NO₃)₃] (5a).— $\text{Eu}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (29.9 mg, 67.0 μmol) was added to **2** (73.7 μmol in 78 mL of 1:1 DCM/MeOH) to afford **5a** as an off-white solid (33 mg, 60% yield). ^1H NMR (500 MHz, 298 K, CD_3OD) δ_{H} (ppm): 7.78 (t, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 7.3$ Hz, 4H), 6.01 (s, 4H), 4.16 (s, 8H), 3.85 (s, 8H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, 298 K, CD_3OD) δ_{C} (ppm): 157.7, 139.2, 123.1, 121.2, 93.3, 84.1, 53.1, 38.6. HRMS-ESI: m/z calcd for $[\text{EuC}_{30}\text{H}_{30}\text{N}_8\text{O}_6]^+$, 751.1501; found, 751.1477 ($\text{M} - \text{NO}_3$) $^+$. DSC: 224 °C (onset), 267 °C (max).

[Eu(2)Cl₃] (5b).— $\text{EuCl}_3 \cdot 6\text{H}_2\text{O}$ (38.8 mg, 106 μmol) was added to **2** (96.7 μmol in 84 mL of 1:1 DCM/MeOH) to afford **5b** as a tan solid (45 mg, 63% yield). ^1H NMR (500 MHz, 298 K, CD_3OD) δ_{H} (ppm): 7.81 (t, $J = 7.3$ Hz, 2H), 7.38 (d, $J = 7.3$ Hz, 4H), 6.03 (s, 4H), 4.24 (s, 8H), 3.94 (s, 8H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, 298 K, CD_3OD) δ_{C} (ppm): 156.6, 139.5, 123.3, 121.3, 92.2, 84.7, 52.7, 38.6. HRMS-ESI: m/z calcd for $[\text{EuC}_{30}\text{H}_{30}\text{N}_6\text{Cl}_2]^+$, 697.1102; found, 697.1081 (MCl) $^+$. DSC: 192 °C (onset), 240 °C (max).

[Eu(2)](CF₃SO₃)₃ (5c).—Eu(CF₃SO₃)₃ (45.0 mg, 75.1 μmol) was added to **2** (82.2 μmol in 88 mL of 1:1 DCM/MeOH) to afford **5c** as a beige solid (49 mg, 61% yield). ¹H NMR (500 MHz, 298 K, CD₃OD) δ_H (ppm): 7.89 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 4H), 6.09 (s, 4H), 4.37 (s, 8H), 4.10 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 154.5, 140.1, 124.1, 121.4, 89.9, 85.5, 51.8, 38.5. HRMS-ESI: *m/z* calcd for [EuC₃₂H₃₀N₆F₆S₂O₆]⁺, 925.0785; found, 925.0788 (M – CF₃SO₃)⁺. DSC: 162 °C (onset), 170 °C (max).

[Gd(2)(NO₃)₃] (6a).—Gd(NO₃)₃·6H₂O (19.7 mg, 43.6 μmol) was added to **2** (47.5 μmol in 54 mL of 1:1 DCM/MeOH) to afford **6a** as a yellow solid (24 mg, 66% yield). ¹H NMR (500 MHz, 298 K, CD₃OD) δ_H (ppm): 7.78 (t, *J* = 5.8 Hz, 2H), 7.35 (d, *J* = 6.2 Hz, 4H), 6.00 (s, 4H), 4.16 (s, 8H), 3.84 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 157.6, 139.3, 123.1, 121.3, 93.3, 84.2, 53.1, 38.6. HRMS-ESI: *m/z* calcd for [GdC₃₀H₃₀N₈O₆]⁺, 756.1530; found, 756.1500 (M – NO₃)⁺. DSC: 255 °C (onset), 287 °C (max).

[Gd(2)Cl₃] (6b).—GdCl₃·6H₂O (37.0 mg, 99.5 μmol) was added to a solution of **2** (105 μmol in 50 mL of 1:1 DCM/MeOH) to afford **6b** as a light-tan solid (61 mg, 72% yield). ¹H NMR (400 MHz, 298 K, CD₃OD) δ_H (ppm): 7.81 (t, *J* = 6.7 Hz, 2H), 7.38 (d, *J* = 6.6 Hz, 4H), 6.04 (s, 4H), 4.23 (s, 8H), 3.92 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 156.0, 139.6, 123.5, 121.4, 91.8, 84.9, 52.5, 38.6. HRMS-ESI: *m/z* calcd for [GdC₃₀H₃₀N₆Cl₂]⁺, 702.1150; found 702.1118 (M – Cl)⁺. DSC: 226 °C (onset), 262 °C (max).

[Gd(2)](CF₃SO₃)₃ (6c).—Gd(CF₃SO₃)₃ (33.9 mg, 56.1 μmol) was added to **2** (61.1 μmol in 100 mL of 1:1 DCM/MeOH) to afford **6c** as a light-orange solid (43 mg, 72% yield). ¹H NMR (400 MHz, 298 K, CD₃OD) δ_H (ppm): 7.89 (t, *J* = 7.7 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 4H), 6.10 (s, 4H), 4.38 (s, 8H), 4.10 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 154.4, 140.1, 124.1, 121.4, 89.8, 85.6, 51.8, 38.5. HRMS-ESI: *m/z* calcd for [GdC₃₂H₃₀N₆F₆S₂O₆]⁺, 930.0814; found, 930.0828 (M – CF₃SO₃)⁺. DSC: 178 °C (onset), 183 °C (max).

[Tb(2)(NO₃)₃] (7a).—Tb(NO₃)₃·6H₂O (18.9 mg, 41.7 μmol) was added to **2** (47.5 μmol in 54 mL of 1:1 DCM/MeOH) to afford **7a** as an off-white solid (18 mg, 54% yield). ¹H NMR (500 MHz, 298 K, CD₃OD) δ_H (ppm): 7.73 (br, 2H), 7.30 (br, 4H), 5.97 (br, 4H), 4.07 (br, 8H), 3.75 (br, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 158.4, 139.1, 122.8, 121.10, 94.1, 83.8, 53.5, 38.8. HRMS-ESI: *m/z* calcd for [TbC₃₀H₃₀N₈O₆]⁺, 757.1542; found 757.1537 (M – NO₃)⁺. DSC: 253 °C (onset), 279 °C (max).

[Tb(2)Cl₃] (7b).—TbCl₃·6H₂O (36.6 mg, 98.0 μmol) was added to **2** (105 μmol in 100 mL of 1:1 DCM/MeOH) to afford **7b** as an off-white solid (68 mg, 82% yield). ¹H NMR (500 MHz, 298 K, CD₃OD) δ_H (ppm): 7.84 (br, 2H), 7.41 (br, 4H), 6.05 (s, 4H), 4.28 (s, 8H), 3.98 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 155.7, 139.6, 123.4, 121.4, 91.3, 85.0, 52.3, 38.5. HRMS-ESI: *m/z* calcd for [TbC₃₀H₃₀N₆Cl₂]⁺, 703.1163; found, 703.1139 (MCl)⁺. DSC: 207 °C (onset), 246 °C (max).

[Tb(2)](CF₃SO₃)₃ (7c).—Tb(CF₃SO₃)₃ (45.0 mg, 74.2 μmol) was added to **2** (82.2 μmol in 88 mL of 1:1 DCM/MeOH) to afford **7c** as a tan solid (30 mg, 38% yield). ¹H NMR (400 MHz, 298 K, CD₃OD) δ_H (ppm): 7.92 (t, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 4H), 6.11 (s, 4H), 4.42 (s, 8H), 4.16 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 153.9, 140.3, 124.3, 121.4, 89.3, 85.8, 51.6, 38.5. HRMS-ESI: *m/z* calcd for [TbC₃₂H₃₀N₆F₆S₂O₆]⁺, 931.0826; found, 931.0831 (M – CF₃SO₃)⁺. DSC: 161 °C (onset), 182 °C (max).

[Lu(2)(NO₃)₃] (8a).—Lu(NO₃)₃·5H₂O (32.1 mg, 71.2 μmol) was added to **2** (77.5 μmol in 90 mL of 1:1 DCM/MeOH) to afford **8a** as a pale-yellow solid (25 mg, 42% yield). ¹H NMR (500 MHz, 298 K, CD₃OD) δ_H (ppm): 7.80 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 4H), 6.03 (s, 4H), 4.23 (s, 8H), 3.93 (s, 8H). ¹³C{¹H} NMR (126 MHz, 298 K, CD₃OD) δ_C (ppm): 156.4, 139.5, 123.4, 121.3, 92.0, 84.6, 52.6, 38.6. HRMS-ESI: *m/z* calcd for [LuC₃₀H₃₀N₈O₆]⁺, 773.1697; found, 773.1691 (M – NO₃)⁺. DSC: 269 °C (onset), 292 °C (max).

[Lu(2)Cl₃] (8b).—LuCl₃·6H₂O (34.9 mg, 89.6 μmol) was added to **2** (102 μmol in 84 mL of 1:1 DCM:MeOH) to afford **8b** as a tan solid (45 mg, 66% yield). ¹H NMR (400 MHz, 298 K, CD₃OD) δ_H (ppm): 7.85 (t, *J* = 7.7 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 4H), 6.07 (s, 4H), 4.33 (s, 8H), 4.04 (s, 8H). ¹³C{¹H} NMR (101 MHz, 298 K, CD₃OD) δ_C (ppm): 155.2, 139.8, 123.6, 121.5, 90.8, 85.2, 52.1, 38.5. HRMS-ESI: *m/z* calcd for [LuC₃₀H₃₀N₆Cl₂]⁺, 719.1317; found, 719.1310 (M – Cl)⁺. DSC: 225 °C (onset), 252 °C (max).

[Lu(2)](CF₃SO₃)₃ (8c).—Lu(CF₃SO₃)₃ (44.6 mg, 71.7 μmol) was added to **2** (82.2 μmol in 88 mL of 1:1 DCM/MeOH) to afford **8c** as a tan solid (41 mg, 53% yield). ¹H NMR (500 MHz, 298 K, CD₃OD) δ_H (ppm): 7.88 (t, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 4H), 6.09 (s, 4H), 4.36 (s, 8H), 4.08 (s, 8H). ¹³C{¹H} NMR (101 MHz, 298 K, CD₃OD) δ_C (ppm): 154.6, 140.0, 124.0, 121.3, 90.0, 85.4, 51.9, 38.5. HRMS-ESI: *m/z* calcd for [LuC₃₂H₃₀N₆F₆S₂O₆]⁺, 947.0980; found, 947.0982 (M – CF₃SO₃)⁺. DSC: 168 °C (onset), 181 °C (max).

RESULTS AND DISCUSSION

Synthesis.

[2 + 2] macrocycle **1** is synthesized by the condensation of (*Z*)-octa-4-en-2,6-diyne-1,8-diamine with pyridine-2,6-dicarboxaldehyde; it forms in relatively good yield (ca. 60%) without the need for a templating agent or acid catalyst. Subsequent reduction of **1** with sodium borohydride yields macrocycle **2** (Scheme 1).

Ligand **2** can be treated with hydrochloric acid to yield the acid salt, **2'** (Scheme 2), or with metal salts to form metalloenediynes. Use of either nitric or triflic acid results in NMR spectra identical to those obtained for **2'**. Differential scanning calorimetry (DSC) shows that **2** melts at a temperature of 119 °C (endotherm minimum), after which Bergman cyclization in the liquid phase is immediate. Acid salt **2'** does not melt and exhibits a solid-state Bergman cyclization temperature of 217 °C (exotherm maximum).

The X-ray crystal structure of **2** (Scheme 2, Table S1) is planar with four of the six nitrogen atoms oriented inward, toward the metal binding pocket. The alkyne carbons of **2** are separated by 4.20 Å, a distance that is generally consistent with Bergman cyclization onset well above ambient temperature.⁴¹ Upon crystallographic characterization of **2'** (Scheme 2, Table S1), hydrogen atoms were found in the difference map and refined for all parameters, confirming protonation at the amine nitrogen sites. The interalkynyl distance (4.21 Å) is slightly widened from that of **2**. Bending about the amine nitrogen atoms forms a structure wherein two planes, each consisting of one pyridine–enediyne pair, are offset from one another.

Metalloenediynes **3a–8c** are formed by the addition of the appropriate trivalent lanthanide salt to a solution of **2** in 1:1 methanol/dichloromethane. Because of the Lewis acidic nature of lanthanide triflates,^{42,43} reactions to form **3–8c** compete with the protonation of **2**. In the presence of wet methanol, the metal coordinates water and/or alcohol^{44,45} and subsequently decreases the pH of the solution, eventually leading to the formation of the triflic acid salt of **2**. However, the rate of metalation was found to markedly exceed the rate of ligand protonation, so syntheses of **3–8c** were limited to shorter stir times than their chloride and nitrate counterparts. Subsequently, the products were washed with cold water in order to remove any residual acid salt. Once isolated, these complexes were stable and exhibited no change in their ¹H NMR spectrum when stored in methanolic solution for several days.

For all lanthanide complexes synthesized, ¹H NMR serves as a key indicator of the metalation of **2**; the resonances of the methylene protons, those closest to the metal binding pocket, exhibit a downfield shift of up to 0.59 ppm. To determine the correct assignment of both proton and carbon resonances (Table S2), HSQC (¹J_{H–13C} coupling, Figure S1) and

HMBC (²J_{H–13C}, ³J_{H–13C} and ⁴J_{H–13C} coupling, Figures S2 and S3) spectra of **2** were obtained. These illustrate distinct coupling between distal and proximal alkyne carbons to vinyl and methylene protons, respectively (Table S3), consistent with ²J_{H–13C} and ³J_{H–13C} coupling patterns previously reported for enediynes.⁴⁶ Additionally, the HMBC spectrum of **8c** (Figures S4 and S5, Table S4) confirms that the relative ordering of peaks is conserved. The titration of **3a** with excess lanthanum nitrate (Figures S6 and S7) reveals no change in the ¹H NMR spectrum, demonstrating that **2** forms a stable Ln(**2**)X₃ complex. Metalation is further confirmed both by high-resolution mass spectrometry and by changes in thermal reactivity reflected in DSC.

Anion Control of Thermal Reactivity.

Considerable precedent exists for utilizing the bonding properties of transition metals to modulate enediyne reactivity.^{31,32,47,48} In general, control of the bite angle of an enediyne-bearing ligand alters the interalkynyl distance, consequently tuning the barrier to Bergman cyclization. In the lanthanide arena, the nuclear penetration of the f electrons renders ligand field theory moot,^{49,50} and the extent of metal–ligand interaction is strongly tempered by the affinity of the accompanying anion.⁵¹ Therefore, in this study, the coordination strength of

the anion was varied to tune the degree of the lanthanide–macrocycle interaction in order to evaluate the effects on the Bergman cyclization temperature of the complex. Because of the high oxophilicity exhibited by the 4f metals, nitrate is most often a strongly coordinating bidentate ligand for lanthanides,^{52–54} while chloride is more weakly monodentate and triflate is frequently noncoordinating.⁵⁵ The noncoordinating behavior of triflate in **3–8c** was confirmed via IR (Figure S8).⁵⁶

DSC is well established as a method both to induce Bergman cyclization via the observation of exothermic events and to determine a relative measure of its activation barrier via the reaction temperature.^{57–59} The product identity has been independently confirmed by our laboratory and others.^{26–30} Consistent with these themes, DSC traces of complexes where the anion is substituted on identical Lewis acid centers show a significant variation (~100 °C) in the solid-state Bergman cyclization temperature (Figure 2a, Table 1). The highest cyclization temperatures are detected when nitrate is the counterion (**3–8a**), temperatures are intermediate for chlorides (**3–8b**), and triflate compounds (**3–8c**) exhibit the lowest reaction temperatures. When the anion identity is held constant and the metal is varied (Figure 2b), differences in the solid-state cyclization temperature are slight. The disparity in exotherm maxima between the smallest (Lu^{3+} , $r = 103.2 \text{ pm}$)⁶⁰ and largest (La^{3+} , $r = 121.6 \text{ pm}$) lanthanides ranges from 14 °C (**3b** and **8b**) to only 2 °C (**3c** and **8c**). Because of the small range of temperature across the cation series, there is no evident trend based on the metal radius. This Bergman cyclization temperature dependence on the anion thus implicates both geometric (i.e., bond length and number) and electronic (i.e., cation charge screening) contributions to the reaction profile based upon the established coordination chemistry of $[\text{Ln}(\text{macrocycle})\text{X}_3]$ complexes.^{61–64}

NMR Reveals the Enediyne Charge Distribution.

Because NMR reports on the magnetic environment of atoms, it can be used to infer the degree of electron density about the coordinated enediyne macrocycle.^{65–67} In the ^1H NMR, the complexation of **2** results in a significant ($\delta > 0.5 \text{ ppm}$) downfield shift of the methylene resonances, with the magnitude of δ as a function of the anion (Figure 3a). Commensurate with their distance from the metal, a smaller degree of deshielding is exhibited by the pyridine ($\delta \sim 0.2 \text{ ppm}$) and more distant vinyl protons ($\delta \sim 0.1 \text{ ppm}$). The deshielding of the methylene signals, which are proximal to the metal binding pocket, reflects a decrease in electron density about these ligand protons relative to **2**. Acid salt **2'** displays the largest values of δ for all peaks, a consequence of inclusion of four protons rather than one trivalent metal. This demonstrates a systematic difference in ligand electron distribution across the series and calibrates the introduction of a Lewis acid into the macrocycle.

^{13}C NMR is a particularly sensitive reporter for alkyne carbons.^{68,69} As is the case for the methylene protons, the distal alkyne carbon atoms (C_B) exhibit deshielding (^{13}C : $\delta \sim 2.5 \text{ ppm}$) indicative of a decrease in electron density at this site (Figure 3b). There is a concomitant increase in the shielding of C_A , the alkyne carbons proximal to the site of metalation (^{13}C : $\delta > 3 \text{ ppm}$), consistent with increased electron density adjacent to the metal center. The introduction of the trivalent atom thus draws electron density toward this

Lewis acid, depolarizing the alkyne carbons and driving their ^{13}C NMR resonances toward equivalence. These shifts indicate that electron-poor C_A in **2** becomes more electron rich in **3a–8c** as a result of the contribution from both C_B and the methylene substituents.

Closer analysis of the shifts (δ) in the ^1H methylene and ^{13}C alkyne resonances reveals a marked anion-dependent trend for the lanthanoenediynes, which fall between neutral free ligand **2** and acid salt **2'** (Figure 4). With the exception of lanthanum, for each metal the magnitude of δ increases across the series **2** < $[\text{Ln}(\text{2})(\text{NO}_3)_3]$ < $[\text{Ln}(\text{2})\text{Cl}_3]$ < $[\text{Ln}(\text{2})](\text{OTf})_3$ < **2'**. Lanthanum shows attenuated perturbation of the ligand's electronic structure, particularly in **3c**. With the largest radius of any metal studied, this may be due to lanthanum's ability to host larger coordination numbers where increased solvent coordination may temper the metal–macrocyclic interaction.^{50,51} This outlier aside, the δ of both ^1H and ^{13}C resonances shows only a very modest dependence on the identity of the metal ion, mirroring the trends in cyclization temperature and suggesting structural similarity across the f block for complexes of the same anion. Combined, these observations show that the degree of electron density at the alkyne carbons is controlled by the relative Lewis acidity of the cation, which is in turn modulated by the basicity of the anion. More strongly coordinating anions mask the metal charge to a larger degree. With the inclusion of four cations, **2'** is most depolarized. However, because of its large interalkynyl distance, the barrier to cyclization is intermediate relative to the metalloenediynes despite the fact that it contains the least polar alkynes observed. The sharp difference in NMR resonances between **2** and **2'**, which have very similar geometries, implicates the need for both electronic and geometric considerations.

Implications of the Alkyne Charge Distribution in Cyclization.

Electron density at the alkyne carbons is of particular importance to the Bergman cyclization reaction coordinate because the energy of the ground-state enediyne configuration is dominated by the in-plane π -bonding orbital, which is destabilized by increasing repulsion of the two out-of-phase π -bonding fragments.^{31,70} Here, ^{13}C NMR shifts confirm the relative electron density of alkynes in the ground state, with the dipole oriented such that C_B is more electron-rich than C_A . The magnitude of this dipole decreases along the series **3–8a** > **3–8b** > **3–8c**. As Bergman cyclization begins, electron density is moved away from C_A , where rehybridization from sp to sp^2 progresses with new bond formation, and toward C_B , where the radicals will be housed in the intermediate.^{33,71} As such, an enediyne with relatively little electron density at C_A , as in **3–8a**, is expected to exhibit increased δ^+ character at that atom in the transition state. Likewise, electron-rich C_B in the same molecule increases in δ^- character along the reaction trajectory, resulting in a highly polar transition state. Conversely, if the alkyne has little polarization in the ground state, as in **3–8c**, then this electronic reorganization results in a transition state which contains a dipole with the same orientation but of a smaller magnitude. Because more polar Bergman cyclization transition states are higher in energy,³³ the relative energies of the transition states are therefore proposed to follow **3–8a** > **3–8b** > **3–8c**. This ordering of transition-state energies is consistent with the known ordering of barrier heights, as observed by solid state cyclization temperature, **3–8a** > **3–8b** > **3–8c**.

Anion Influence on Lanthanum-Ligand Bonding.

The trend in alkyne polarity characterized by NMR suggests that lanthanide–macrocycle coordination across the series is strongly influenced by the available anion. Thus, to address the structural impact on the bound macrocycle, gas-phase-optimized DFT structures of **3a**, **3b**, and $[\text{La}(\mathbf{2})(\text{H}_2\text{O}_3)]^{3+}$ (**3c'**, model for **3c**) were computed (Figure 5, Tables S6–8), as well as those for **8a** and **8b** (Figure S9, Tables S5, S9, and S10), in order to describe the structural behavior of both the largest and the smallest cations studied, respectively. In the calculation protocol, three nitrates or chlorides were included on the basis of crystallographically characterized macrocyclic lanthanide compound analogues.^{72–75} Similarly, the behavior of lanthanide triflates in aqueous media illustrate out-competition by water to give the outer-sphere salts, $[\text{Ln}(\text{H}_2\text{O})_n](\text{OTf})_3$, indicating the preferential coordination of water over the triflate anion.²¹ The noncoordinating nature of the triflate in **3–8c** was further confirmed by IR (Figure S8).

All computed structures show the favorable placement of lanthanide in the binding pocket of **2** with the macrocycle twisting out of plane to orient the nitrogen donors toward the metal. The eight sp^3 methylene linkers within **2** engender significant flexibility for the ligand to adopt a range of conformations. This leads to a relatively flat potential energy surface with multiple thermally accessible minima associated with methylene inversion. As a result, alkyne termini separation within these energetically comparable structures has significant variability, and thus the reaction coordinate is not dominated by the interalkynyl distances in these complexes, as it is in many metallocene-diyne structural motifs. As in the above analogues, all three nitrate anions bind in a bidentate fashion ($\text{La}-\text{O} = 2.57\text{--}2.69\text{ \AA}$ for **3a**, $\text{La}-\text{O} = 2.28\text{--}2.64\text{ \AA}$ for the model;⁷² $\text{Lu}-\text{O} = 2.30\text{--}2.39\text{ \AA}$ for **8a**, $\text{Lu}-\text{O} = 2.33\text{--}2.40\text{ \AA}$ for the model⁷⁵), and likewise, all three chlorides are found to coordinate the metal center ($\text{La}-\text{Cl} = 2.72\text{--}2.82\text{ \AA}$ for **3b**, $\text{La}-\text{Cl} = 2.78\text{--}2.87\text{ \AA}$ for the model;⁷³ $\text{Lu}-\text{Cl} = 2.58\text{--}2.68\text{ \AA}$ for **8b**, $\text{Lu}-\text{Cl} = 2.55\text{--}2.58\text{ \AA}$ for the model⁷⁴).

Commensurate with ligand flexibility, the computed structures show variability in the coordination number with respect to macrocycle **2** ($\text{CN}_{\text{mc}} = 2\text{--}5$) even though the overall coordination number is relatively consistent ($\text{CN}_{\text{Tot}} = 6\text{--}8$) (Table 2, Table S5). The denticity of **2** is inversely related to the bonding strength of the ancillary base (anion or water). This is reflected in the $\text{La}-\mathbf{2}$ bond lengths, where mean $\text{La}-\text{N}$ distances are longest for **3a** ($2.91\text{ \AA}$), intermediate for **3b** ($2.78\text{ \AA}$), and shortest for **3c'** ($2.68\text{ \AA}$). The sum of covalent radii of lanthanum and nitrogen is $2.78\text{ \AA}$,⁷⁶ therefore these distances represent a range of metal–nitrogen interactions, from weak ($2.91\text{ \AA}$ with nitrate)^{77–79} to moderately strong ($2.68\text{ \AA}$ with water),^{80,81} as a function of the coordination strength of the ancillary base. This trend also holds for the smallest metal studied, where mean $\text{Lu}-\text{N}$ distances decrease modestly from **8a** ($2.59\text{ \AA}$) to **8b** ($2.54\text{ \AA}$), showing weak to moderate metal–ligand interactions, respectively (Table S5).^{82,83} Taken together, these structures are in agreement with the hypothesis that the strength of the Lewis base–metal interaction serves to mask the charge of the lanthanide to varying degrees.

Furthermore, this trend in anion-dependent lanthanide–ligand bond contraction is consistent with crystallographically characterized $[\text{La}(\text{18-crown-6})(\text{NO}_3)_3]$ ⁸⁴ and $[\text{La}(\text{18-crown-6})\text{Cl}_3]$,

⁸⁵ where the mean lanthanum to macrocycle lengths (La–O) are 2.72 and 2.66 Å, respectively. Similarly, computed structures of [La(terpy)(NO₃)₃H₂O], [La(terpy)Cl₃], and [La(terpy)(H₂O)₆]³⁺, which are in good agreement with X-ray crystal data where available, show that the mean La–N bond distances decrease from nitrate (2.74 Å) to chloride (2.66 Å) to water (2.62 Å).^{86–88} Thus, at the limits, our lanthanoenediyne constructs resemble classic macrocyclic metal–ligand complexes with weakly bound anions or, at the other extreme, host–guest adducts such as those formed by ion–dipole interactions between crown ethers and traditionally noncovalent metals.⁸⁹ The effective Lewis acidity of the lanthanide–anion fragment follows [Ln(NO₃)₃] < [LnCl₃] < [Ln(H₂O)₃]³⁺, and when the metal’s Lewis acidity is not masked by a strongly coordinating anion, the metal makes both more and shorter bonds to **2**.

CONCLUSIONS

A suite of lanthanide compounds of a [2 + 2] hexaaza-enediyne macrocycle, **2**, has been synthesized with anions of varying coordination strength: bidentate nitrate, monodentate chloride, and noncoordinating triflate. The strength of counterion coordination is inversely related to the solid-state Bergman cyclization temperature and thus the reaction barrier. NMR spectroscopy reveals the depolarization of the alkyne carbon atoms on lanthanide coordination, with the degree of electronic perturbation following NO₃[−] < Cl[−] < OTf[−]. When the Lewis acidity of the metal is strongly attenuated, as when nitrate is present, the metal interacts only weakly with **2**, resulting in modest effects on the enediyne’s charge distribution. Because the electronic reorganization required for Bergman cyclization only increases the magnitude of this dipole, a highly polarized and therefore unstable transition state results. This is consistent with the observed highest barrier to Bergman cyclization of the set. Conversely, strong lanthanide–macrocycle interactions, as when triflate is present, result in more significant depolarization of the alkyne carbons. The same electronic reorganization at cyclization onset therefore produces a moderately polar transition state, resulting in the lowest cyclization barrier. Structural characterization via DFT shows that as the binding affinity of the anion decreases, the metal makes both more and shorter bonds to the macrocycle. Thus, the anion controls the degree of effective Lewis acidity of the lanthanides, and the trend follows [Ln(NO₃)₃] < [LnCl₃] < [Ln(H₂O)₃]³⁺.

The behavior of this suite of lanthanoenediyne complexes illustrates how simple metal–anion charge screening effects can result in a transition from ion–dipole to more dative-like bonding and thereby determine both the geometric and electronic landscape for metal-mediated Bergman cyclization reactions. In every metalloenediyne system, the effects of the solvent, coordination sphere, and anion contribute to the geometry and distribution of electron density about the enediyne unit, which influences the barrier to alkyne activation. This is often overlooked and challenging to evaluate in solution, but here we show a simple ¹³C NMR method that reveals patterns in alkyne polarization to lend insight into the activation barriers to cyclization. This is a factor that, moving forward, should be considered in all metalloenediyne designs, particularly for biorelevant systems where counterions are in excess and medicinal viability relies very heavily on precise control of the activation barrier.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Reactivity control is composed of both electronic and geometric determinants. (a)

Lanthanide catalysts can be tuned by the selection of a metal radius and thus Lewis acidity (electronic control) and by the steric demands of the accompanying first coordination sphere (geometric control). (b) Metal–enediyne activation is often described in terms of interalkynyl distance, d , alteration (geometric control), but the metal also modifies the reaction landscape by perturbing the charge distribution about the enediyne alkynes (electronic control).

Figure 2.

Differential scanning calorimetry (DSC) traces of (a) $[\text{La}(\mathbf{2})\text{X}_3]$; $\text{X} = \text{NO}_3^-$ (**3a**), Cl^- (**3b**), and OTf^- (**3c**) and (b) $[\text{Ln}(\mathbf{2})\text{Cl}_3]$; $\text{Ln} = \text{La}$ (**3b**), Ce (**4b**), Eu (**5b**), Gd (**6b**), Tb (**7b**), and Lu (**8b**). Lanthanide-enediyne compounds show a strong dependence of the thermal reactivity on the anion identity, but cyclization temperatures vary only slightly with the modification of the metal.

Figure 3.

(a) ^1H NMR spectra (CD_3OD) of **2**, $[\text{Lu}(\mathbf{2})(\text{NO}_3)_3]$ (**8a**), $[\text{Lu}(\mathbf{2})\text{Cl}_3]$ (**8b**), $[\text{Lu}(\mathbf{2})](\text{OTf})_3$ (**8c**), and $\text{H}_4\mathbf{2}\text{Cl}_4$ (**2'**) show increasing perturbation of the methylene proton resonances ($-\text{CH}_2-$) across the series. *Denotes solvent. (b) Alkyne region of ^{13}C NMR spectra (CD_3OD) of **2**, $[\text{Lu}(\mathbf{2})(\text{NO}_3)_3]$ (**8a**), $[\text{Lu}(\mathbf{2})\text{Cl}_3]$ (**8b**), $[\text{Lu}(\mathbf{2})](\text{OTf})_3$ (**8c**), and $\text{H}_4\mathbf{2}\text{Cl}_4$ (**2'**) exhibiting increased shielding of the C_A resonances and deshielding of the C_B resonances.

Figure 4.

(a) ^1H NMR resonances of methylene protons show systematic deshielding for metalloenediynes as the associated anion grows weaker, followed by $2'$, the acid salt. (b) ^{13}C NMR alkyne carbon resonances show deshielding for the outer alkyne (C_B) and shielding for the inner alkyne (C_A) along the same series.

Figure 5. DFT-computed structures of [La(2)(NO₃)₃] (**3a**), [La(2)Cl₃] (**3b**), and [La(2)(H₂O)₃]³⁺ (**3c'**) predict that the number of La–N bonds increases as the strength of the ancillary Lewis base decreases. Hydrogen atoms except N–H are omitted for clarity.

Scheme 1. Synthesis of $[\text{Ln}(2)\text{X}_3]$ Complexes Where $\text{Ln} = \text{La}$ (3), Ce (4), Eu (5), Gd (6), Tb (7), Lu (8) and $\text{X} = \text{NO}_3^-$ (3–8a), Cl^- (3–8b), OTf^- (3–8c)^a

^a(i) DCM, Na_2SO_4 , 0 °C. (ii) 1:1 MeOH/DCM, excess NaBH_4 , 0 °C. (iii) $\text{LnX}_3 \cdot n\text{H}_2\text{O}$, 1:1 DCM/MeOH, 25 °C.

Scheme 2. X-ray Crystal Structures of 2 and 2' (H₄2Cl₄) Show That the Enediyne Is Planar in the Solid State, Though the Ligand Adopts a Bend at the Methylene Linkers on Protonation

Table 1.

DSC Trace Exotherm Maxima and Onset Temperatures (°C) Observed for Lanthanide Complexes of 2 with Various Trivalent Lanthanides and Counterions

cyclization temperature by cation-anion pair, max (onset) /°C			
	NO ₃ [−]	Cl [−]	OTf [−]
La ³⁺	285 (246)	238 (216)	183 (177)
Ce ³⁺	282 (264)	259 (231)	175 (139)
Eu ³⁺	267 (224)	240 (192)	170 (162)
Gd ³⁺	287 (255)	262 (226)	183 (178)
Tb ³⁺	279 (253)	246 (207)	182 (161)
Lu ³⁺	292 (269)	252 (225)	181 (168)

Table 2.

Coordination Numbers, Selected Bond Lengths, and Interalkynyl Distances for Computed Structures of [La(2)(NO₃)₃] (3a), [La(2)Cl₃] (3b), and [La(2)(H₂O)₃]³⁺ (3c')

bonding properties of 3a-3c'			
	NO ₃ ⁻	Cl ⁻	H ₂ O
CN _{tot}	8	7	8
CN _{mc}	2	4	5
La-N, Å (pyridine)	2.90	2.72	2.71 2.72
La-N, Å (amine)	2.93	2.76 2.80 2.85	2.57 2.63 2.76
La-N, Å (average)	2.91	2.78	2.68
interalkynyl distances, Å	3.83 3.85	3.75 4.17	3.78 3.82