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A Combined Parallel Synthesis and Screening of Macrocyclic Lanthanide Complexes for the Cleavage of Phospho Di- and Triesters and Double-Stranded DNA

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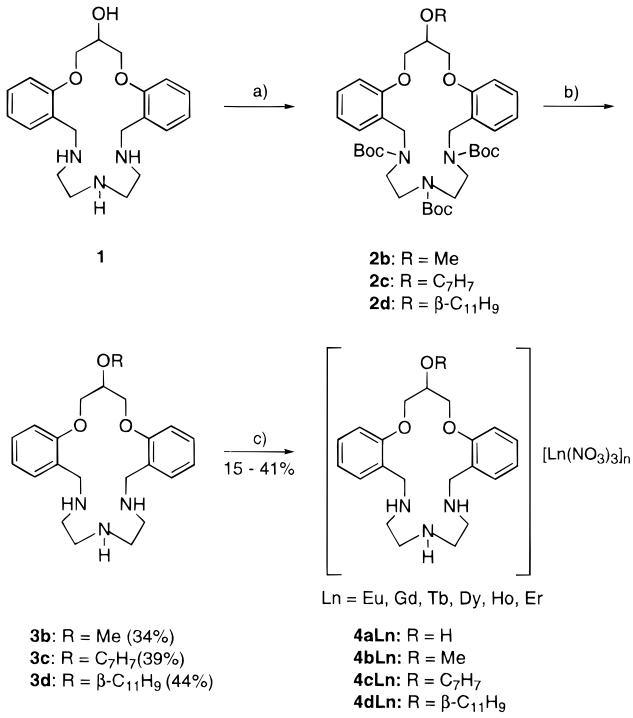
A parallel synthesis of macrocyclic lanthanide−ligand complexes **4Ln** has been developed in conjunction with a parallel screening of these ligands for catalysis of phosphate ester hydrolysis. Complexes **4Ln** were screened on a 96-well plate reader for their ability to catalyze the hydrolysis of a variety of phosphate esters efficiently. The hydrolysis of bis(4-nitrophenyl) phosphate (BNPP) **5** and *p*-nitrophenylethyl phosphate **6** was accelerated by up to 150-fold in the presence of the complex **4cGd**. The cleavage of a double-stranded DNA plasmid with this same complex obeyed saturation kinetics following a Michaelian model ($K_m = 7.4$ μM, $k_{cat} = 4.5 \times 10^{-3}$ min^{-1}). Our findings demonstrate how a combination of parallel synthesis and screening can expedite compound access, accelerate catalyst identification, and thereby dramatically increase the speed of finding good ligand−metal combinations.

Phosphate esters are crucial chemical features of both nucleic acids and a number of chemical toxins. The hydrolysis of phosphodiesters using small organic molecules is expected to have a fundamental impact on the development of artificial, possibly sequence-specific nucleases[1] for use in biotechnology as well as for the detoxification of chemical weapons and insecticides. The past few years have seen a wealth of research dedicated toward the development of catalytic systems for phosphate ester hydrolysis, and both mono-[2] and binuclear[3] metal complexes have shown good activity. In most cases, lanthanide ions have been chosen as the requisite metal center and they efficiently accelerate the hydrolysis of a range of phosphate esters;[4] however, transition metals such as Cu(II),[5] Co(III),[6] and Zn(II)[7] have also been used successfully.

Recent progress in the generation of catalysts for a number of processes linked to combinatorial methodology, a process dubbed "combinatorial catalysis",[8] has yielded a number of catalytic systems for a variety of reactions.[9] Among others, polymeric catalysts for phosphate hydrolysis have been developed.[10] However, in this report the catalysts' structures were unknown and in fact were never resolved. Previous work in our group has led to the recent report of a high-throughput synthesis and screening methodology for metal complexes that hydrolyze carboxylic acid esters.[11]

Herein we report an extension of this approach toward the generation of metal complexes that hydrolyze the more thermodynamically demanding phosphate esters. Using the azacrownether−ligand systems **3**,[11] we have developed a parallel synthesis approach to the corresponding lanthanide complexes **4Ln** (Scheme 1). The presence of the hydroxyl group in **1** is ideal for structural modification experiments to form a family of ethers. This was accomplished by protection of the amino functionalities of **1**[12] as their Boc derivatives and subsequent Williamson ether synthesis.[13] Deprotection of the Boc groups of **2a**−**c** afforded the amines **3a**−**c** in 34−44% overall yield from **1**. The parallel reaction of ligands **1**, **3a**,**b**,**c** with 1 equiv of 15 different lanthanide nitrates (La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu) gave crystalline precipitates **4Ln** in 15−41% yield.

Scheme 1. Synthesis of Lanthanide Complexes **4Ln**[a]



[a] Reagents and conditions: (a) (1) $(Boc)_2O$, NEt_3, CH_2Cl_2, 0 °C, 12 h; (2) NaH, RX, 20 °C, 1 h. (b) CF_3COOH/CH_2Cl_2, 20 °C, 1 h. (c) $[Ln(NO_3)_3]$/MeOH, 1 h, precipitate.

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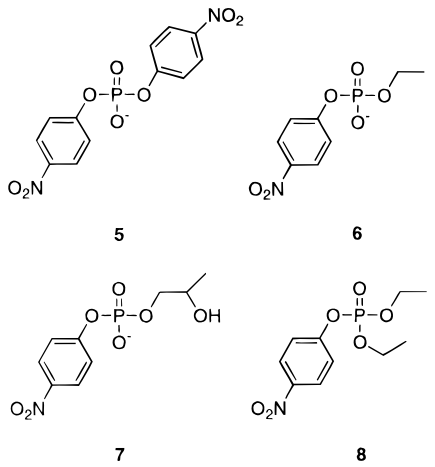

Figure 1. Phospho di- and triesters **5**−**8** used as substrates.

Compounds **4Ln** were screened in a parallel format on a 96-well kinetic plate reader for their ability to catalyze the hydrolysis of bis(*p*-nitrophenyl) phosphate (BNPP) **5**, *p*-nitrophenylethyl phosphate **6**,[14] *p*-nitrophenyl-2-hydroxypropyl phosphate **7,**[15] and the neurotoxic phosphotriester Paraoxon **8** (Figure 1).[16] Furthermore, we investigated the cleavage of double-stranded DNA in the presence of selected complexes.

From the whole family of potential lanthanide−ligand complexes we focused our investigations on the precipitates obtained with Eu, Gd, Tb, Dy, Ho, and Er as the complexes obtained with the other metals could not be redissolved in organic solvents. The catalytic activities of the precipitates proved to be much better than the activity of the whole reaction mixture. This was noted with the complexes of lanthanide chlorides which, while reported to give more active catalysts than the nitrates,[3a] did not form precipitates with our ligand systems and possessed lower catalytic activity.

On the basis of the four substrates chosen for examination (**5**−**8**), a 96-well kinetic plate reader assay was utilized to identify any potential catalysts from **4Ln**. In applying such an approach, ligand−metal, substrate, and cosolvent could all be manipulated in a highly efficient optical assay. The whole process from setting up the library of complexes in the 96-well plate to screening on the kinetic plate reader and highlighting of a catalytic complex takes only 1−2 h. Once a catalyst and assay conditions were identified, second-order rate constants were determined in a conventional serial manner on a UV spectrometer.[17] In general, the complexes with the metals Eu, Gd, and Tb usually give better rate accelerations than those with the metals Dy, Ho, and Er (Table 1). Second, the rates generally increase with increasing size of the R group. An X-ray structure obtained for the nickel complex of ligand **1** suggests that a bulky R group weakens the coordination of the oxygen adjacent to the secondary alcohol, thereby facilitating the coordination of substrate molecules to the metal.[11] The best catalyst for the hydrolysis of substrates **5** and **6** is complex **4cGd**, synthesized from the ligand **3c** (R = β-naphthyl) and $Gd(NO_3)_3$, which increases the rate of hydrolysis of BNPP **5** by 127-fold. This rate is about 75% higher than the best rate obtained with a recently reported praseodymium complex of a hexaazatetraoxo crownether.[3a] Hydrolysis of *p*-nitrophenylethyl phosphate **6** is accelerated by 150-fold. The efficiency of catalysts **4Ln** is lower for *p*-nitrophenyl-2-hydroxypropyl phosphate **7** (possessing a hydroxyl group on the carbon adjacent to the activated phosphate ester), giving rate increases of between 3- and 7-fold.[18] However, the rate acceleration (115-fold) obtained with compound **4cGd** is comparable to that recently reported with Cu(II) complexes, when normalized for concentrations of catalyst used.[5] Hydrolysis of the phosphotriester Paraoxon **8** was accelerated by compounds **4Ln** by up to 7-fold.

Table 1. Rate Enhancements[20] v_{4Ln}/v_{Ln}[a] Observed with Lanthanide Complexes **4Ln** in the Hydrolysis of Substrates **5**,[b] **6**,[c] **7**,[d] and **8**[e]

R	Eu	Gd	Tb	Dy	Ho	Er
H	36	48	25	13	15	14
	100	81	35	22	24	18
	4	*3*	*5*	*5*	*5*	*7*
	2	3	*2*	2	2	1
Me	60	46	37	21	15	19
	56	66	37	40	18	11
	4	*4*	*3*	*4*	*5*	*7*
	2	3	2	3	1	1
benzyl	55	55	46	31	17	18
	81	93	46	33	35	28
	6	*6*	*7*	*6*	*5*	*6*
	3	3	2	3	2	2
β-naphthyl	97	127	76	45	32	36
	146	150	82	44	28	21
	6	*6*	*7*	*5*	*5*	*3*
	4	7	7	5	4	2

[a] v_{4Ln} [mM s^{-1}] is the observed rate for the reaction catalyzed by complexes **4Ln**. v_{Ln} [mM s^{-1}] is the observed rate for the reaction catalyzed by the corresponding lanthanide salts. [b] Upper line: v_{4Ln}/v_{Ln} for bis(*p*-nitrophenyl) phosphate **5** (EPPS: 10 mM, pH 7.0; substrate: 34 μM; catalyst: 1 mM, 20% DMSO, 50 °C). [c] Upper middle line (underlined): rate enhancements v_{4Ln}/v_{Ln} for *p*-nitrophenyl ethyl phosphate **6** (EPPS: 10 mM, pH 7.0; substrate: 34 μM; catalyst: 1 mM, 20% DMSO, 50 °C). [d] Lower middle line (in italics): rate enhancements v_{4Ln}/v_{Ln} for 2-hydroxy propyl-*p*-nitrophenyl phosphate **7** (EPPS: pH 7.0, 10 mM; substrate: 40 μM, catalyst: 150 μM, 3% DMSO, 37 °C; k_0 (pseudo-first-order rate constant without metal) = 9.8×10^{-8} s^{-1}). [e] Lower line (double-underlined): rate enhancements v_{4Ln}/v_{Ln} for Paraoxon **8** (EPPS: 10 mM, pH 7.0; substrate: 34 μM; catalyst: 1 mM, 30% DMSO, 50 °C).

Encouraged by the good rate accelerations obtained for the hydrolysis of **5** and **6**, we investigated the lanthanide complexes **4Ln** in the cleavage of double-stranded DNA. In an initial screen, the plasmid pCGMT[19] (3379 base pairs) was incubated separately with all 24 complexes and with the free metal nitrates (as a control). The degree of DNA cleavage by each complex was compared qualitatively to that observed by the metal alone. It was shown that the activity of the lanthanide complexes in the DNA cleavage followed the same qualitative trends as for the hydrolysis of the activated substrates **5** and **6**. On the basis of this initial screen, it was determined that the complex **4cGd** showed the best rate accelerations and was thus subjected to further kinetic studies. At the concentrations employed (plasmid: 3.58×10^{-5} M base pairs; Gd-complex: 0−15 μM), linear behavior was observed based on pseudo-first-order kinetics.[4c] The

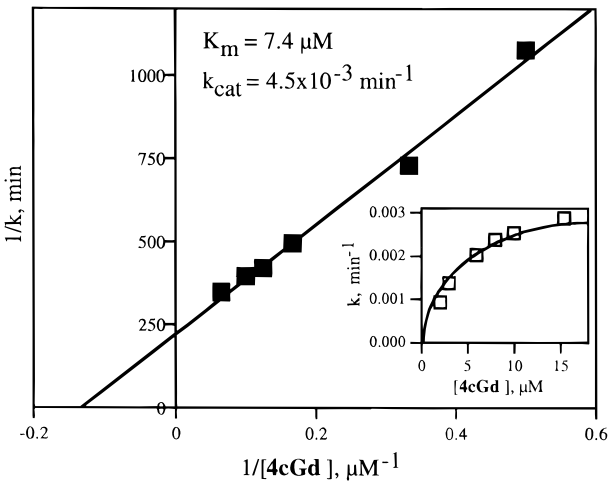

Figure 2. Saturation kinetics and Lineweaver−Burk plot of the cleavage of plasmid DNA using complex **4dGd**.

pseudo-first-order rate constants from the time course (0−150 min) experiments were plotted against the complex concentrations, as shown in the inset of Figure 2, and revealed saturation kinetics, implicating that the complex binds the plasmid in an enzyme-like manner. From the double-reciprocal plot (of 1/substrate concentration versus 1/rate), a K_m value of 7.4 μM and a k_{cat} value of 4.5 $\times$ 10^{-3} min $^{-1}$ were obtained. Although the k_{cat} value places the Gd complex derived from ligand **3c** at the lower end of the range previously reported with a hexaazatetraoxo crownether,[3a] the K_m of the substrate is indicative of fairly tight binding and hence affinity of the substrate−catalyst Michaelian complex.[3a]

The stoichiometry of the complexes could not be unambiguously determined. Characterization of the complexes by inductively coupled plasma mass spectrometry (ICP-MS)[20] suggest that complexes **4Ln** contain two metal ions complexed per ligand.[21] This is in line with findings for related lanthanide complexes.[3a] The activity of the catalysts decreases to 8% after addition of 1 equiv of EDTA. This suggests either that both metal ions are necessary for the complexes to be catalytically active or, less likely, that a single metal is involved in catalysis. We note that the complexes **4Ln** are not stable to exchange the metal with EDTA as it has been observed by other authors.[3a,4a]

In summary, we have developed both a parallel synthesis and screening of macrocyclic lanthanide complexes **4Ln** that catalyze the efficient hydrolysis of a variety of phosphate esters. The hydrolysis of *p*-nitrophenylethyl phosphate **6** was accelerated by 150-fold in the presence of complex **4cGd**. In the cleavage of double-stranded DNA with this same complex, saturation kinetics were observed with a k_{cat} value of 4.5 $\times$ 10^{-3} min^{-1} and a low K_m value of 7.4 μM. Our findings demonstrate the power of parallel synthesis and screening for catalyst discovery. It provides simple access to a number of metal−ligand complexes, with the 96-well screening of substrates and ligand−metal complexes dramatically increasing the speed of finding good catalyst combinations.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification. Analytical TLC (thin-layer chromatography) was carried out on precoated plates (Merck silica gel 60, F_{254}). Column chromatography was performed with silica gel (Merck, 70−230 mesh). ^{1}H and ^{13}C NMR were recorded at 250 and 62.5 MHz, respectively. High-resolution mass spectrometry (HRMS) was performed in the analytical department of The Scripps Research Institute. Parallel 96-well assays were performed on a SPECTRAmax 250 microplate spectrophotometer (Molecular Devices, Sunnyvale, CA). Kinetic assays were performed using a Hewlett-Packard UV/vis spectrophotometer and the Hewlett-Packard UV−visible ChemStation software.

General Syntheses of Compounds 2, 3, and 4. To a suspension of ligand **1** in CH_2Cl_2 (0.125 mM) at 0 °C were added 1.05 equiv of *t*-butoxycarbonyl anhydride and 3.15 equiv of triethylamine (NEt_3), and the mixture was allowed to warm to room temperature overnight. After purification on silica gel, the protected macrocycle was dissolved in dry THF (0.25 mM). At room temperature, NaH (3 equiv) and nucleophile (CH_3I, $C_6H_5CH_2Br$, or $C_{10}H_7CH_2Br$) (1.05 equiv) were added, and the mixture was stirred overnight. Aqueous workup and purification on silica afforded the Boc-protected compounds **2**, which were deprotected by dissolving in CH_2Cl_2 (0.25 mM) and adding 95% triflouroacetic acid (0.25 mM). After 1 h, the reaction mixture was neutralized with Na_2CO_3 solution and ligands **3** were purified by chromatography on silica (MeOH/NEt_3 9/1). Under reflux, solutions of **3** in MeOH (0.1 mM) were treated with 1 equiv of solutions of lanthanide nitrates in MeOH (0.1 mM), and reflux was continued overnight. The precipitate of complexes **4Ln** was filtered and washed with MeOH.

2a: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 7.2 (m, 4 H, C_6H_4), 6.9 (m, 4 H, C_6H_4), 4.4 (m, 3 H), 4.1 (m, 6 H) ($PhCH_2N$, CHO, $CH_2CH(O)CH_2$), 3.5 (s, 3 H, OCH_3), 3.1 (m, 8 H, NCH_2CH_2N), 1.40 (s, 27 H, *t*-Bu); HRMS ($C_{37}H_{55}N_3O_9Cs$) calcd, 818.2993; found, 818.3029.

2b: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 7.2 (m, 9 H, C_6H_5, C_6H_4), 6.9 (m, 4 H, C_6H_4), 4.7 (s, 2 H, $CH_2C_6H_5$), 4.4 (m, 3 H), 4.2 (m, 6 H) ($PhCH_2N$, CHO, $CH_2CH(O)CH_2$), 3.2 (m, 8 H, NCH_2CH_2N), 1.45 (s, 18 H, *t*-Bu), 1.40 (s, 9 H, *t*-Bu); HRMS ($C_{43}H_{59}N_3O_9Cs$) calcd, 894.3305; found, 894.3272.

2c: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 7.8 (m, 4 H, H-arom), 7.5 (m, 3 H, H-arom), 7.2 (m, 4 H, H-arom), 6.9 (m, 4 H, H-arom), 4.9 (s, 2 H, $CH_2C_{10}H_7$), 4.4 (m, 3 H), 4.2 (m, 6 H) ($PhCH_2N$, CHO, $CH_2CH(O)CH_2$), 3.2 (m, 8 H, NCH_2CH_2N), 1.44 (s, 18 H, *t*-Bu), 1.38 (s, 9 H, *t*-Bu); HRMS ($C_{47}H_{61}N_3O_9Cs$) calcd, 944.3462; found, 944.3428.

3a: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 7.28 (m, 4 H, C_6H_4), 6.98 (m, 4 H, C_6H_4), 4.33 (m, 4 H, $PhCH_2N$), 4.09 (m, 1 H, CHOMe), 3.85 (m, 4 H, $CH_2CH(OH)CH_2$), 3.62 (s, 3H, OCH_3), 2.71 (m, 8 H, NCH_2CH_2N); HRMS ($C_{22}H_{31}N_3O_3$) calcd, 386.2444; found, 386.2456.

3b: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 7.35 (m, 9 H, C_6H_5, C_6H_4), 7.02 (m, 4 H, C_6H_4), 4.86 (s, 2 H, $CH_2C_6H_5$), 4.36 (m, 5 H, $PhCH_2N$, CHO), 3.87 (m, 4 H, $CH_2CH(OH)CH_2$), 2.64 (m, 8 H, NCH_2CH_2N), 2.42 (s (br), 3 H, NH); HRMS ($C_{28}H_{35}N_3O_3$) calcd, 462.2757; found, 462.2757.

3c: ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 7.75 (m, 4 H), 7.44 (m, 3 H), 7.20 (m, 4 H), 6.90 (m, 4 H), 4.87 (s, 2 H,

$CH_2C_{10}H_7$), 4.36 (m, 5 H, $PhCH_2N$, CHO), 3.80 (s, 4 H, $CH_2CH(OH)CH_2$), 3.45 (s (br), 3 H, NH), 2.48 (m, 8 H, NCH_2CH_2N); HRMS ($C_{32}H_{37}N_3O_3$) calcd, 512.2913; found, 512.2895.

4bHo: ^{1}H NMR (250 MHz, DMSO, 25 °C) δ 6.5−7.5 (m, br), 2.5−4.5 (s, br); ^{13}C NMR (62.5 MHz, DMSO, 25 °C) δ 130.39, 128.31, 120.54, 112.40, 78.39, 67.45, 49.65, 49.02, 48.68.

4cHo: ^{1}H NMR (250 MHz, DMSO, 25 °C) δ 6.5−8.0 (m, br), 3.0−5.0 (s, br); ^{13}C NMR (62.5 MHz, DMSO, 25 °C) δ 157.05, 130.42, 129.09, 128.28, 127.78, 127.51, 120.54, 112.40, 76.52, 71.40, 67.71, 49.68, 48.97, 48.70.

4dTb: ^{1}H NMR (250 MHz, DMSO, 25 °C) δ 6−8 (m, br), 2.5−5 (s, br); ^{13}C NMR (62.5 MHz, DMSO, 25 °C) δ 130.47, 128.34, 128.25, 127.78, 127.54, 120.57, 112.42, 77.73, 74.38, 71.44, 67.71, 49.59, 48.82, 48.56.

Parallel 96-Well Assay of Substrates 5, 6, 7, and 8. A typical kinetic experiment for the hydrolysis of substrates **5**, **6**, and **8** was carried out as follows: Complexes **4Ln** were freshly dissolved in DMSO to give a 5 mM solution. The activity of the solutions decreased upon standing at room temperature and upon repeated freezing and thawing. To a mixture of 100 μL of EPPS (20 mM, pH 7.0) and 60 μL of water at 30 °C were added 10 μL of substrate solution (2 mM, **5** and **6**: in water; **8**: in DMSO) and 30 μL of catalyst (5 mM in DMSO), and the absorption at 405 nm was followed in the ELISA plate reader. A typical kinetic experiment for the hydrolysis of substrate **7** was carried out as follows: To a mixture of 100 μL of EPPS (20 mM, pH 7.0) and 80 μL of water at 30 °C were added 10 μL of substrate solution (2 mM in water) and 10 μL of catalyst (5 mM in DMSO), and the absorption at 405 nm was followed in the ELISA plate reader.

Kinetic Assay of Substrates 5, 6, 7, and 8. Complexes **4Ln** were freshly dissolved in DMSO to give a 5 mM solution. The activity of the solutions decreased upon standing at room temperature and upon repeated freezing and thawing. To a mixture of 500 μL of EPPS (20 mM, pH 7.0) and 283 μL of water at 50 °C were added 17 μL of substrate solution (2 mM, **5** and **6**: in water; **8**: in DMSO) and 200 μL of catalyst (5 mM in DMSO), and the absorption at 405 nm was followed. A typical kinetic experiment for the hydrolysis of substrate **7** was carried out as follows: To a mixture of 500 μL of EPPS (20 mM, pH 7.0) and 450 μL of water at 37 °C were added 20 μL of substrate solution (2 mM in water) and 30 μL of catalyst (5 mM in DMSO), and the absorption at 405 nm was followed.

Assay for DNA Cleavage. Solutions of plasmid pCGMT (3379 base pairs)[19] in EPPS (20 mM, pH 7.0) were mixed with the appropriate volumes of stock solutions of the lanthanide complexes or free metals (both as nitrates) in DMSO and incubated at 37 °C for the indicated times. The assays were quenched by addition of excess EDTA and immediate freezing at −80 °C. For DNA electrophoresis, the quenched assays were mixed with loading dye, loaded onto 0.8% agarose gel, and separated at 110 V. The bands of RF I (supercoiled) and RF II (relaxed) were quantitated by the Kodak Digital Science 2.0 software after scanning the gels with Kodak DC-120 digital camera (Eastman Kodak). In control experiments, overnight incubation of plasmid with DMSO yielded no measurable increase in the percentage of RF II.

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(21) As the presence of a 1:1 complex could not completely be excluded, we based our calculations on the molecular weight of the 1:1 complexes in order to prevent too high rate enhancements due to a too high molecular weight of the metal complexes **4Ln**.

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