37. Synthesis and Structure of a Macrocyclic Europium Complex and Its Possible Role as a Catalyst for Phosphodiester Transesterification

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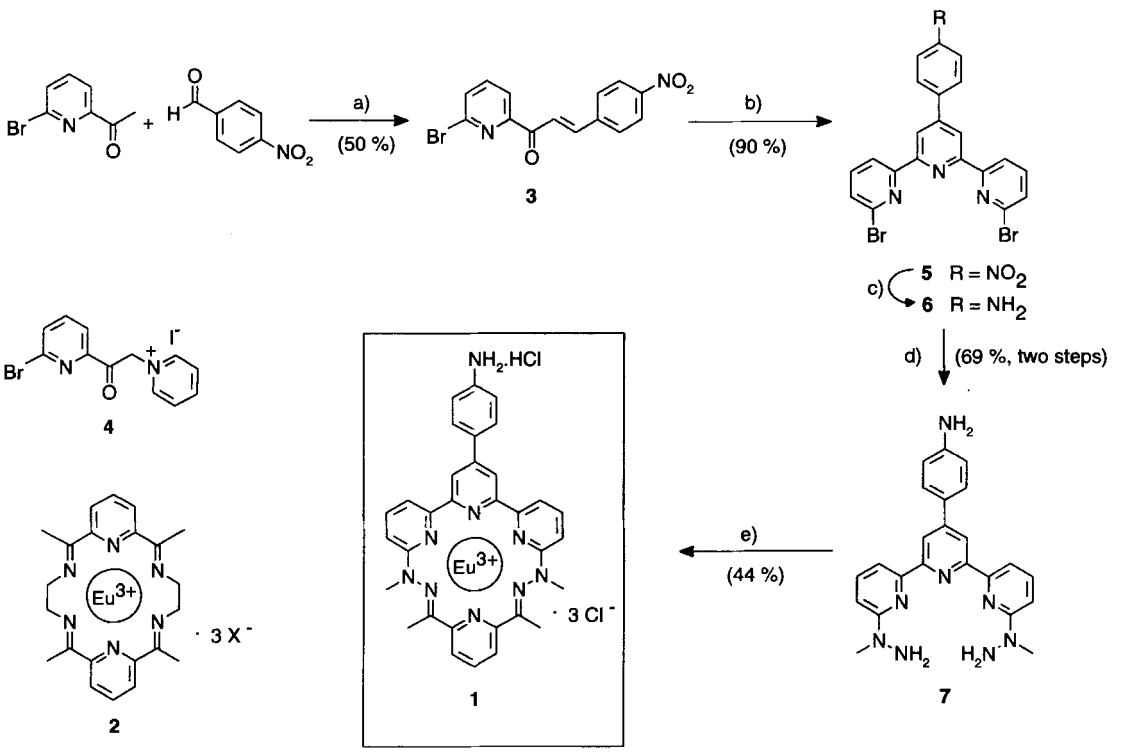
The synthesis and X-ray crystal structure of a europium macrocyclic complex **1**, an important catalyst used for the sequence-specific cleavage of RNA, is reported. The role of this metal complex in facilitating phosphate transesterification is discussed.

1. Introduction. – Lanthanide complexes have an increasingly important role to play in medicine. They find use as diagnostic as well as therapeutic agents. Gadolinium complexes [1], for example, are indispensable agents for magnetic resonance imaging and, more recently, lutetium complexes have been shown to possess great potential as radiosensitizers for the treatment of certain types of cancer [2]. In addition, the use of rare earth metals and their complexes for the hydrolysis of phosphodiesters is an active field of research [3–12]. We have reported the use of macrocyclic lanthanide complexes conjugated to oligonucleotides, such as **1**, for the sequence-specific cleavage of RNA, which is important within the context of antisense technology [13] [14]. Although, for a similar type of complex (**2**; X = Cl), it is established that the reaction occurs *via* transesterification of the phosphodiester by nucleophilic attack of the 2′-OH group to give a 2′,3′-cyclic phosphate [3], the exact mechanism by which **1** catalyzes the transesterification is not clear. Detailed structural information of the complex might contribute to a better understanding of the process. Here, we report the synthesis and the X-ray crystal structure of the macrocyclic Eu^{III} complex **1**.

Results and Discussion. – The Eu^{III} complex **1** was synthesized in analogy to the procedure described for a similar Ni^{II} complex (*Scheme 1*) [15]. Thus, the α,β-unsaturated ketone **3** was obtained by aldol condensation of 2-acetyl-6-bromopyridine with 4-nitrobenzaldehyde in 50% yield. Compound **3** was subsequently reacted with 1-[(6-bromopyridin-2-yl)carbonyl]pyridinium iodide (**4**) to give terpyridine **5** in a *Krohnke* reaction (90%). The NO_2 group of **5** was selectively reduced in the presence of the two bromides by treatment with Ti^0, generated *in situ* from $TiCl_4$ and $LiAlH_4$, and the resulting anilino derivative **6** was treated with *N*-methylhydrazine to give a clean substitution of the two bromides. Terpyridine derivative **7** was obtained in 69% yield over the two steps. Formation of the macrocyclic compound was achieved by treating **7** with

Scheme 1



a) KOH/MeOH. b) **4**, AcOH/NH_4OAc. c) $TiCl_4/LiAlH_4$. d) *N*-Methylhydrazine. e) $Eu(OAc)_3$, HCl, 2,6-diacetylpyridine.

2,6-diacetylpyridine in the presence of 1 equiv. of europium(III) acetate and a small quantity of conc. HCl to give pure **1** in 44% yield. Crystals suitable for structure determination by X-ray diffraction were obtained by recrystallization of **1** from a mixture H_2O/MeOH/i-PrOH (3:1:1).

Crystals of complex **1** belong to the triclinic space group. An ORTEP plot of the structure is shown in *Fig. 1*. The complex crystallizes with four H_2O molecules, two of which are coordinated through their O-atoms to the Eu^{3+} ion, the other two are included in the crystal lattice. The Eu metal is threefold positively charged and has a coordination number of nine. It is bound to six N-atoms, two H_2O molecules, and one Cl^- ion. The central pyridine of the terpyridine and the solitary pyridine ring are inclined towards each other, giving a concave and a convex side to the molecule (see *Fig. 2, a*). The six metal-coordinating N-atoms form a slightly distorted boat with the two metal-bound H_2O molecules accommodated on the concave side of the molecule, and the coordinating Cl^- ion on the convex side of the complex.

The molecule would possess an almost perfect C_s-symmetry if not for the aniline ring, which forms a dihedral angle of 25° with the neighboring pyridine. The intramolecular distances between the Me groups C(43)–C(45) and C(44)–C(46) (2.94(2) Å and

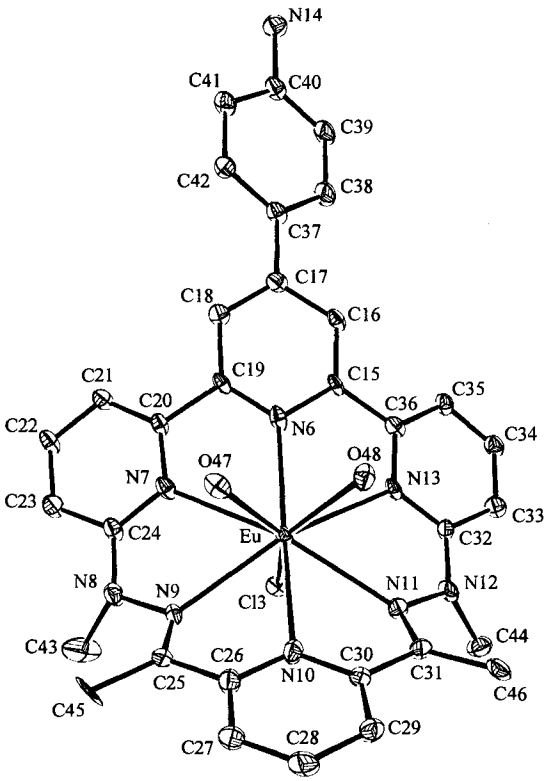


Fig. 1. *ORTEP Plot of complex* **1**

3.04(2) Å, resp.) are considerably shorter than the sum of the *van der Waals* radii of two Me groups, which is *ca.* 3.40 Å [16]. A planar arrangement of the macrocycle would lead to an even closer positioning of these Me groups. Therefore, the ruffling observed in the structure is almost certainly not only the result of a tight coordination of the cation by the N-atoms, but also of partial release of strain caused by the proximity of the said Me groups[1]).

The X-ray crystal structure of complex **1** is similar to that of compound **2** (X = NCS) [18], which was obtained from a search of the *Cambridge Crystallographic Data File*. The Eu^{3+} cation in **2** is nine-fold coordinated, the pyridine rings are inclined towards each other as in complex **1**, and the six Eu–N coordination bond lengths in the two complexes are equivalent, within the limits of measurement. Complex **2** differs from **1**, however, in that it is of C_2-symmetry (due to twisting of the pyridines against each other). Furthermore, two of the NCS ligands are coordinating to the metal on the *convex* side of the molecule and one on the *concave* side (see *Fig. 2, b*), in direct contrast to the ligand arrangement in **1**.

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[1]) The short intramolecular distances of the two Me groups are in close agreement with the Me · · · Me distances observed in macrocyclic Co^{II} complex; see [17].

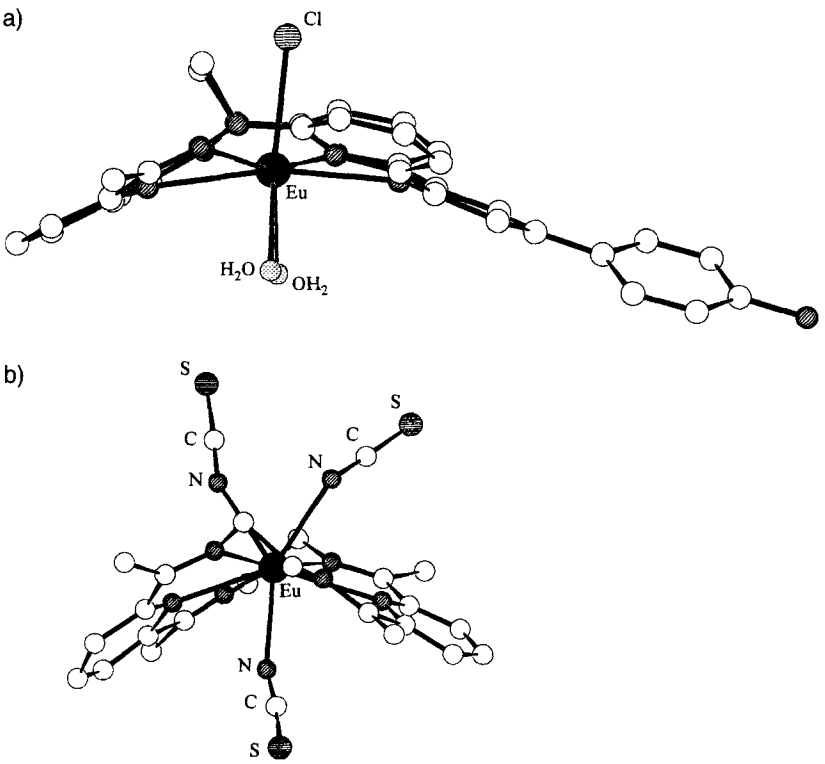
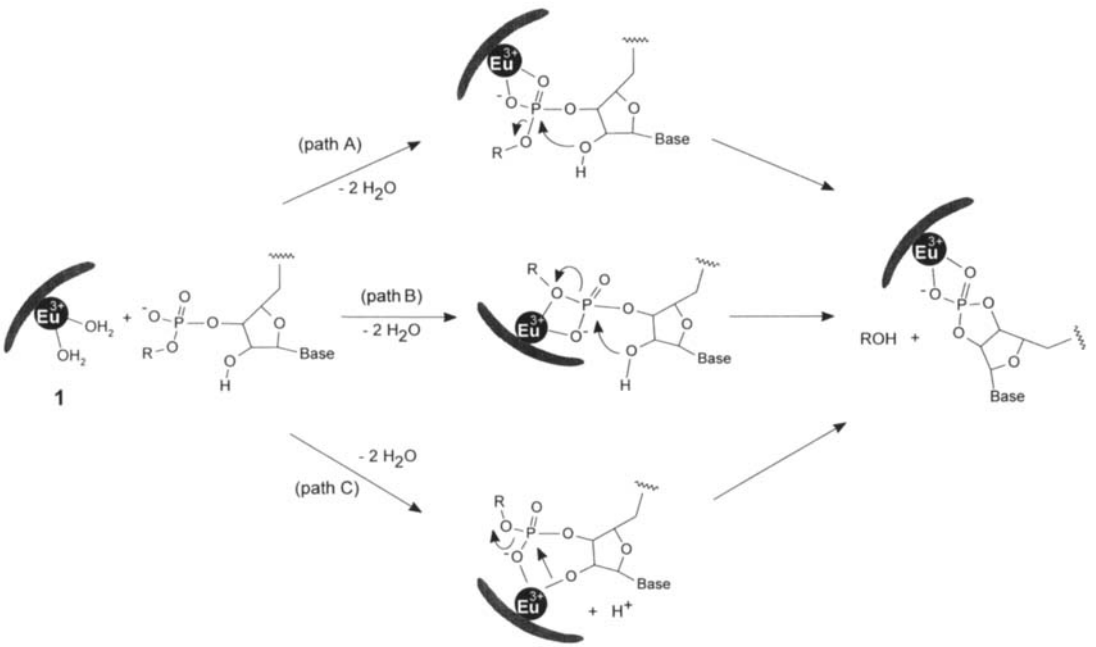


Fig. 2. *Side views of complexes* **1** (a) *and* **2** (b)

One of the most notable features of the crystal structure of **1** is that only one of the Cl^- anions directly coordinates to the metal center, whereas the other two, which are required for charge neutralization, are distributed (though well located) in the crystal lattice. The two remaining coordination sites are, instead, occupied by two H_2O molecules. It can, therefore, be assumed that this complex has a strong tendency to bind to other O-ligands, such as phosphate groups. Since binding of a strong *Lewis* acid, such as Eu^{III}, to a phosphodiester will lead to activation of the phosphate group to nucleophilic attack, the process of metal-complex-mediated RNA transesterification could, therefore, proceed as illustrated in *Scheme 2*. As the two coordinating H_2O molecules are located on the same side of the complex, it is conceivable that they are both replaced by coordinating O-atoms from the ribonucleotide during the course of the reaction (*Scheme 2*). There are three possibilities here which all lead to the 2′,3′-cyclic phosphate and the 5′-OH moiety: bidentate binding of the phosphodiester to the cation (*Path A*), chelation of the phosphodiester and the 5′-OH leaving group of the ribose (*Path B*), or chelation of the phosphodiester and the 2′-OH nucleophile of the ribose (*Path C*). Whereas *Path A* simply leads to activation of the phosphodiester, the complex as shown in *Path B* not only activates the phosphate group, but, at the same time, also binds to the 5′-O-atom. Such coordination would greatly facilitate the formation and expulsion of the 5′-alkoxide due to neutralization of the negative charge formed upon breakdown

Scheme 2



of the preceeding intermediate[2]). Finally, as illustrated in *Path C*, the complex might coordinate simultaneously to both the phosphate and the 2′-OH group. Metal binding to the 2′-OH would increase the acidity of this group, thus facilitating proton abstraction followed by intramolecular attack of the 2′-O-atom leading to the transesterification products as described above. This latter process is in agreement with the proposal by *Bamann et al.* to explain the enormous acceleration of RNA hydrolysis by lanthanide hydroxides [20].

A greater insight into the modes of complex binding and, eventually, the mechanism of RNA cleavage mediated by lanthanide complexes, such as **1**, might be obtained from a crystal structure of co-crystals of the metal complex with ribonucleotide derivatives.

Experimental Part

General. 2-Acetyl-6-bromopyridine [21] and *iodide* (**4**) [22] were prepared as described in the literature. THF, Me, AcOH, toluene, and AcOH were obtained from *Fluka* and used without further purification. IR Spectra: *Perkin-Elmer 1710*; in cm^{-1}. MS (FD): *8430 Finnigan*. ^{1}H-NMR Spectra: on a *Bruker DPX400* MHz machine. Chemical shifts are given in ppm and coupling constants J in Hz using solvent peaks as internal references. Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectra: on a *Linear Scientific LDI 1700* machine in the positive mode; samples were dissolved in a soln. of 2,4,6-trihydroxyacetophenone soln. (0.1M in EtOH).

[2]) On the role of metal coordination to the oxy anion of the leaving alcohol in lanthanum-catalyzed phosphonate-ester cleavage, see [19].

2-Bromo-6-[3'-(4''-nitrophenyl)-1-oxoprop-2-enyl]pyridine (**3**). To a soln. of 2-acetyl-6-bromopyridine (14.6 g, 72 mmol) in MeOH (145 ml) at 0° was added a soln. of KOH (3.15 g, 63 mmol) in H_2O (30 ml). Within 5 min, 4-nitrobenzaldehyde (44 g, 290 mmol) was added in portions, keeping the temp. below −10°. The resulting beige suspension was allowed to warm to r.t. and stirred for 30 min. The product was isolated by filtration, washed with H_2O until neutral and washed twice with AcOEt. Recrystallization from toluene (300 ml) gave **3** (12.2 g, 50%). Pale-yellow crystals. M.p. 210–212°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.71–7.79 (*m*, 2H); 7.86–7.95 (*m*, 3H); 8.16 (*d*, *J* = 7.4, 1H); 8.28–8.33 (*m*, 3H). MS (FD): 332/334 (70, M^+), 303/305 (55), 102 (100). Anal. calc. for $C_{14}H_9BrN_2O_3$: C 50.48, H 2.72, N 8.41; found: C 50.63, H 2.80, N 8.73.

6,6''-Dibromo-4'-(4'''-nitrophenyl)-2,2':6',2''-terpyridine (**5**). A mixture of **3** (10.0 g, 30 mmol), 1-[(6-bromopyridin-2-yl)carbonyl]pyridinium iodide (**4**; 12.1 g, 30 mmol), and ammonium acetate (15.4 g, 200 mmol) in AcOH (120 ml) was stirred under reflux for 3.5 h. After cooling to r.t., the precipitate was isolated by filtration, washed with AcOH (2 × 25 ml), and dried. Recrystallization from DMSO (1300 ml) gave **5** (13.9 g, 90%). Light-brown crystals. M.p. > 250° (dec.). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.57 (*d*, *J* = 7.8, 2H); 7.87 (*t*, *J* = 7.8, 2H); 8.03 (*d*, *J* = 8.9, 2H); 8.41 (*d*, *J* = 8.9, 2H); 8.60 (*dd*, *J* = 7.7, 0.9, 2H); 8.72 (*s*, 2H). MS (FD): 510/512/514 (6, M^+). Anal. calc. for $C_{21}H_{12}Br_2N_4O_2$: C 49.25, H 2.36, N 10.94; found: C 49.07, H 2.43, N 10.95.

6,6''-Dibromo-4'-(4'''-aminophenyl)-2,2':6',2''-terpyridine (**6**). $TiCl_4$ (16.7 g, 88 mmol) was added within 10 min to dry THF (150 ml) at 0° under Ar. To the resulting yellow suspension was added $LiAlH_4$ (2.44 g, 65 mmol) in portions within 20 min while keeping the temp. between 5 and 15°. The resulting black suspension was stirred for 20 min at r.t. After cooling to 0°, **5** (10.0 g, 19.5 mmol) was carefully added in portions within 10 min. The black mixture was allowed to stir for 1 h at r.t. After cooling to 0°, the reaction was stopped by the careful addition of H_2O (100 ml), followed by aq. NH_3 (25%, 100 ml). Insoluble material was removed by filtration and washed with CH_2Cl_2 (3 × 100 ml). The filtrate was washed with H_2O once, and the aq. phase was extracted twice with CH_2Cl_2. The org. phases were combined, washed with H_2O, dried (Na_2SO_4), filtered, and evaporated to give **6** (9.6 g). Brown solid. The material was used in the next step without further purification. ^{1}H-NMR (400 MHz, (D_6)DMSO): 5.7 (br. *s*, 2H); 6.78 (*d*, *J* = 8.6, 2H); 7.63 (*d*, *J* = 8.7, 2H); 7.75 (*d*, *J* = 7.8, 2H); 7.94 (*t*, *J* = 7.8, 2H); 8.42 (*s*, 2H); 8.60 (*dd*, *J* = 7.7, 0.8, 2H). MS (MALDI): Mol. wt. 482.5; calc.: 482.2.

6,6''-Bis(1-methylhydrazino)-4'-(4'''-aminophenyl)-2,2':6',2''-terpyridine (**7**). A soln. of **6** (5.0 g) in methylhydrazine (50 ml) was heated under reflux for 7 h. After cooling to r.t., the mixture was concentrated and dried overnight (55°/0.01 Torr). The residue was suspended in MeOH (30 ml), stirred at r.t. for 15 min, filtered, and dried to give **7** (3.7 g, 69% over the two steps). M.p. > 250° (dec.). IR (KBr): 3600–2000 (br.), 3206, 1578, 1520, 1395, 1288, 1230, 1185, 796. ^{1}H-NMR (400 MHz, (D_6)DMSO): 6.65 (*d*, *J* = 8.6, 2H); 7.18 (*d*, *J* = 8.4, 2H); 7.65 (*d*, *J* = 8.6, 2H); 7.75 (*t*, *J* = 7.9, 2H); 7.90 (*d*, *J* = 7.4, 2H); 8.54 (*s*, 2H). MS (MALDI, positive mode, matrix: isoquinolin-1-ol): Mol. wt.: 411.9; calc.: 412.5.

[4-(4'-Aminophenyl)-12,22-dimethyl-12,13,21,27,28,29,30-octaazapentacyclo[21.3.1.1^{2,6}.1^{7,11}.1^{15,19}]triaconta-1(27),2,4,6(30),7,9,11(29),13,15,17,19(28),20,23,25-tetradecaene]europium Trischloride Hydrochloride (**1**). To a suspension of **7** (2.0 g, 4.85 mmol) in MeOH (90 ml) was added $Eu(OAc)_3$ (1.59 g, 4.85 mmol). The mixture was heated to reflux and stirred for 10 min. To the resulting brown soln. was added 2,6-diacetylpyridine (0.79 g, 4.85 mmol) and conc. aq. HCl (2 ml). The mixture was stirred for 5 d at reflux. The resulting orange suspension was cooled to r.t., the product was collected by filtration, and dried to give **1** (1.68 g, 44%). Orange solid. A second crop of less pure product could be obtained by concentration of the mother liquor (1.8 g). Recrystallization from H_2O/MeOH/i-PrOH 3:1:1 gave **1** as orange crystals which were used for structure determination by X-ray diffraction. M.p. > 250° (dec.). IR (KBr): 3395, 3074, 2854, 2584, 1603, 1570, 1489, 1184, 1011, 810. MS (FD): 761 (100, $[M - Cl]^+$). Anal. calc. for $C_{32}H_{29}EuN_9Cl_3 \cdot 4H_2O \cdot HCl$: C 42.40, H 4.11, N 13.91; found: C 42.61, H 4.06, N 13.68.

Crystal Structure Analysis of **1**. The intensities were collected on an *Enraf-Nonius-CAD4* diffractometer, and corrected for *Lorentz* and polarization effects. Absorption corrections were applied based on azimuthal scans of 6 reflections with the diffractometer angle κ near 90°. The structure was solved by *Patterson*'s method using the program system DIRDIF [23]. Crystal data are given in *Table 1*. All non-H-atoms were refined anisotropically converging with $R = 0.051$. Selected bond lengths, angles and torsion angles are given in *Table 2*. Lists of fractional atomic coordinates, isotropic thermal parameters, and bond lengths and angles have been deposited at the *Cambridge Crystallographic Data Centre*[3]).

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[3]) Copies of the data can be obtained, free of charge, on application to the director, *CCDC*, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44 (0) 12 23 33 60 33 or e-mail: teched@chemcrys.cam.ac.uk).

Table 1. *Summary of Crystal Data, Data Collection, and Refinement Details*

Formula	$(C_{32}H_{34}N_9O_2ClEu)^{3+} \cdot 3Cl^- \cdot 2H_2O$
Mol. wt.	906.48
Crystal system	triclinic
Space group	$P\bar{1}$
a [Å]	8.371(3)
b [Å]	15.268(5)
c [Å]	16.212(5)
α [°]	100.87(5)
β [°]	98.86(5)
γ [°]	98.22(3)
V [Å^3]	1978(2)
Z	2
$F(000)$	912
$D_{calc.}$ [g cm^{-3}]	1.521
μ [mm^{-1}]	14.21
Temp. [°C]	−85
Crystal size [mm]	0.6 × 0.4 × 0.3
Diffractometer	*Enraf-Nonius CAD4*
Radiation (graphite monochromated)	CuK_α
Wavelength [Å]	1.5418
Scan mode	$\omega/2\theta$
Scan range [2θ]	6–130
No. of measured reflections	7220
No. of observed reflections ($I > 4s(I)$)	5361
No. of standard reflections	3 every 120 min
Intensity variation	±4%
Absorption correction	ψ-scan
Transmission factors	0.52/1.00
Refinement method	full matrix on F
No. of parameters	451
R	0.051
R_w	0.059
No. of reflections used	5361
Weighting scheme	$1/\sigma^2(F)$
Treatment of the H-atoms	not located
Max/min density in final difference map [e Å^{-3}]	0.891/−0.748

Table 2. *Selected Bond Lengths* [Å], *Bond Angles* [°], *and Torsion Angles* [°]

Eu(1)–Cl(3)	2.711(4)	N(9)–Eu(1)–N(6)	123.6(3)
Eu(1)–N(6)	2.56(1)	N(9)–Eu(1)–N(7)	61.6(3)
Eu(1)–N(7)	2.61(1)	N(10)–Eu(1)–Cl(3)	103.1(3)
Eu(1)–N(9)	2.61(1)	N(10)–Eu(1)–N(6)	167.5(4)
Eu(1)–N(10)	2.60(1)	N(10)–Eu(1)–N(7)	119.5(3)
Eu(1)–N(11)	2.59(1)	N(10)–Eu(1)–N(9)	59.3(3)
Eu(1)–N(13)	2.61(1)	N(11)–Eu(1)–Cl(3)	83.4(3)
Eu(1)–O(47)	2.42(1)	N(11)–Eu(1)–N(6)	123.3(3)
Eu(1)–O(48)	2.44(1)	N(11)–Eu(1)–N(7)	164.0(4)
N(6)–Eu(1)–Cl(3)	89.5(3)	N(11)–Eu(1)–N(9)	111.2(3)
N(7)–Eu(1)–Cl(3)	81.6(3)	N(11)–Eu(1)–N(10)	59.1(3)
N(7)–Eu(1)–N(6)	62.0(3)	N(13)–Eu(1)–Cl(3)	79.5(3)
N(9)–Eu(1)–Cl(3)	83.2(3)	N(13)–Eu(1)–N(6)	63.2(4)

Table 2 (cont.)

N(13)–Eu(1)–N(7)	121.7(3)	C(15)–N(6)–C(19)–C(20)	168
N(13)–Eu(1)–N(9)	161.4(4)	N(6)–C(19)–C(20)–N(7)	16
N(13)–Eu(1)–N(10)	118.3(3)	C(19)–C(20)–N(7)–C(24)	−174
N(13)–Eu(1)–N(11)	60.2(3)	C(20)–N(7)–C(24)–N(8)	−173
O(47)–Eu(1)–Cl(3)	146.9(3)	N(7)–C(24)–N(8)–N(9)	4
O(47)–Eu(1)–N(6)	87.6(4)	C(24)–N(8)–N(9)–C(25)	142
O(47)–Eu(1)–N(7)	67.9(4)	N(8)–N(9)–C(25)–C(26)	179
O(47)–Eu(1)–N(9)	71.3(4)	N(9)–C(25)–C(26)–N(10)	−2
O(47)–Eu(1)–N(10)	82.1(4)	C(25)–C(26)–N(10)–C(30)	−173
O(47)–Eu(1)–N(11)	125.0(3)	C(26)–N(10)–C(30)–C(31)	172
O(48)–Eu(1)–Cl(3)	146.1(3)	N(10)–C(30)–C(31)–N(11)	−1
O(48)–Eu(1)–N(6)	84.4(4)	C(30)–C(31)–N(11)–N(12)	−174
O(48)–Eu(1)–N(7)	123.3(4)	C(31)–N(11)–N(12)–C(32)	−141
O(48)–Eu(1)–N(9)	127.5(4)	N(11)–N(12)–C(32)–N(13)	−4
O(48)–Eu(1)–N(10)	85.0(4)	N(12)–C(32)–N(13)–C(36)	173
O(48)–Eu(1)–N(11)	72.6(4)	C(32)–N(13)–C(36)–C(15)	177
O(47)–Eu(1)–N(13)	127.3(4)	N(13)–C(36)–C(15)–N(6)	−16
O(48)–Eu(1)–N(13)	67.9(3)	C(36)–C(15)–N(6)–C(19)	−170
O(48)–Eu(1)–O(47)	66.3(3)		

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