

Ionophoric properties of a tetra-tetrazole functionalised calix[4]arene

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The synthesis and characterisation of *p*-*t*-butylcalix[4]arene functionalised at the lower rim with four tetrazole moieties is reported. The macrocycle is found to be a poorer ionophore for lanthanoid cations than the bis-tetrazole substituted analogue. Solution phase photophysical studies strongly suggested that the cations interacted only weakly with the calixarene ligand. A mixed sodium / triethylammonium salt of the calixarene ligand was crystallised in the presence of lanthanoid cations and structurally characterised. Strong intramolecular interactions are hypothesised to be the cause of the observed behaviour.

Keywords: calixarene; tetrazole; lanthanide; crystal structure

Introduction

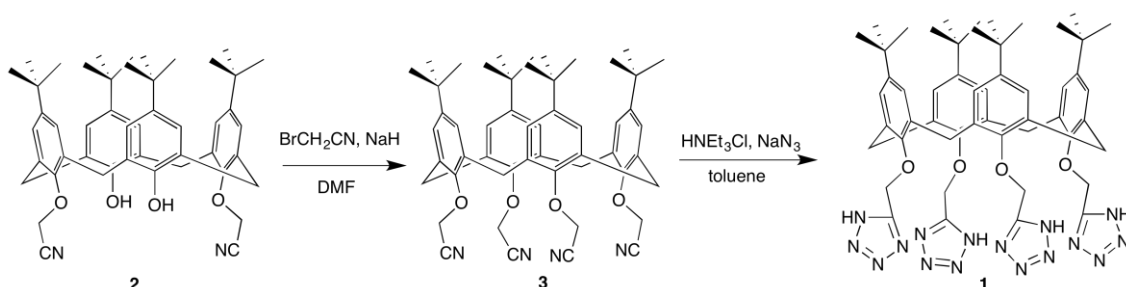
Calixarenes, and particularly calix[4]arenes, are well established as a useful macrocyclic framework upon which to assemble ligating groups to form ionophores.⁽¹⁾ The most common examples introduce neutral O donor atoms as ester or amide moieties (2-5), or negatively charged groups such as the carboxylate (6-8), but many other variations are known (9, 10). We have been investigating the coordination chemistry of tetrazolates, a functional group often used as an isostere of carboxylate in medicinal chemistry, but relatively unexplored in the context of calixarene chemistry (11). Calix[4]arenes substituted with tetrazole groups at the upper rim have been reported and used for anion binding (11), and palladium coordination (12). The tetrazole moiety has also been used as a linker to attach sugars to the upper rim of a calix[4]arene (13). A calixarene has been reported with two tetrazole groups at the lower rim, and azo functional groups at the upper rim, to form a colorimetric sensor for calcium ions where binding at the tetrazole-substituted rim was proposed (14). We have reported the synthesis of a lower rim bis-tetrazole functionalised *p*-*t*-butylcalix[4]arene (15), which was found to form typical 1:1 complexes with lanthanoids in presence of triethylamine with the lanthanide ion occupying the lower rim cavity of the ligand (15), but when triethylamine was replaced with aqueous ammonium carboxylates crystallisation of elongated Ln₁₉ or Ln₁₂ clusters occurred (16).

We have now extended this work to the synthesis of a lower rim substituted tetra-tetrazole derivative, **1**. We report here investigation of the interaction of this new ionophore with lanthanoid cations, and the structural characterisation of the ligand, and a mixed sodium / triethylammonium salt.

Results and discussion

Ligand synthesis and characterisation

5,11,17,23-Tetra-*p*-*t*-butyl-25,26,27,28-tetrakis(cyanomethoxy)calix[4]arene was synthesised *via* the bis-cyanomethoxy substituted precursor (*17*), based on the reported procedure (Scheme 1) (*18*). While the literature reports heating the reaction mixture to 75 °C, in our hands this resulted in substantial degradation. Stirring the reaction at room temperature improved the yield to ~70% of the desired product. Conversion of the nitrile groups to tetrazole moieties was achieved using an altered Koguro method (*19*), as reported previously for the bis-tetrazole calixarene (*15*). Purification of the tetra-tetrazole calixarene **1** proved to be difficult, with sodium cations often retained in the product, but an analytically pure sample and crystals appropriate for a single crystal X-ray structure determination were obtained by slow evaporation of an ethanol solution of **1**.



Scheme 1. Synthesis of tetra-tetrazole functionalised calixarene **1**.

The results of the structure determination showed that the calixarene has the expected structure, crystallising as a solvate with one water molecule and one ethanol molecule (Figure 1). The calixarene conformation exhibits the common “pinched” distortion from the possible 4-fold symmetry with two opposite phenyl rings arranged more ‘vertical’ than the other opposite pair. Dihedral angles between the plane

containing the four methylene carbon atoms and the four phenyl rings 1-4 are: 81.2(1), 49.8(1), 91.0(1), and 55.8(1)°. There are intramolecular hydrogen bonds between one tetrazole hydrogen atom, H212, and the phenoxy oxygen atom, O41, on the opposite group and also between the tetrazole hydrogen atom, H312, and a tetrazole nitrogen atom, N415, on an adjacent group. There are also hydrogen bonds from the remaining tetrazole hydrogen atoms to the water molecule and to the ethanol oxygen atom. The water molecule hydrogen atoms are involved in further hydrogen bonds to nitrogen atoms on molecules related by an *n*-glide plane and by a cell translation in the *a*-direction. The solvent ethanolic hydrogen atom also forms a hydrogen bond to a nitrogen atom of a molecule related by an *n*-glide thus forming a two dimensional hydrogen-bonded polymer in the *ac*-plane; this is shown in Fig. S1.

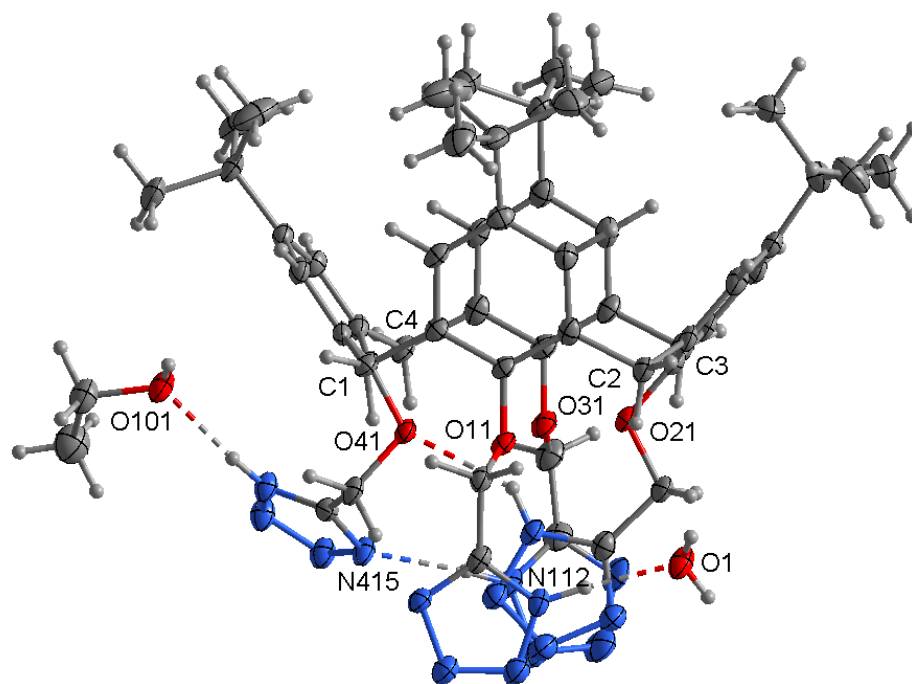


Figure 1. Molecular structure of **1**·H₂O·EtOH projected oblique to the planes of the four methylene carbon atoms. Ellipsoids have been drawn at the 50% probability level.

Metal complexation studies

The interaction of ligand **1** was investigated in the solution phase by probing the photophysical behaviour of solutions of **1** in the presence of lanthanoid cations and added base, typically triethylamine. In our previous studies, it was shown how the addition of triethylamine of a 1:1 solution of bis-tetrazolyl calix[4]arene and Tb³⁺ ions produced a significant increase in luminescence intensity and a change in the excited state lifetime.⁽¹⁵⁾ Following the same experimental conditions, we have probed the photophysical behaviour of a 1:1 solution of **1** and [Tb(NO₃)(DMSO)_n] in dichloromethane upon sequential addition of triethylamine (see Figures S2-S4). In this case, it is evident that the emission intensity of the Tb³⁺ ions remains relatively unaffected by the addition of base, with an overall photoluminescence quantum yield remaining at ca. 1%. The lack of change suggests that the deprotonation of the tetrazole rings in **1** does not drive the complexation of the Tb³⁺ within the lower rim cavity. Furthermore, the excited state lifetime of the Tb³⁺ emission remains unchanged, with a monoexponential decay of ca. 1.1 ms. Only after the addition of 6 equivalents of triethylamine, is the decay best fitted as bi-exponential with a major component of 1.1 ms (94%) and a minor component of 0.4 ms. However, the minor component could be due to the formation of hydroxo species caused by the addition of triethylamine and the presence of adventitious water. While the data suggest that no inclusion of the Tb³⁺ ions within the cavity of **1** is occurring, it can not be excluded that the Tb³⁺ ions are still interacting with the tetrazole moieties: in fact, the excitation spectra of the solutions, obtained by monitoring the 548 nm emission of the Tb³⁺, is analogous to the absorption spectrum of **1**, indicating sensitisation via the antenna effect⁽²⁰⁾.

Consistent with the solution phase studies, attempts to crystallise lanthanoid complexes of **1** were not successful, typically resulting in isolation of the ligand alone.

In one case, presumably caused by the presence of sodium as an impurity in **1**, a mixed triethylammonium / sodium salt formed crystals appropriate for a single crystal structure determination. The results are consistent with the formulation $(\text{HNEt}_3)_2[\text{Na}(\mathbf{1}-\text{H})(\mathbf{1}-2\text{H})]\cdot 2\text{H}_2\text{O}$. The sodium ion is on a crystallographic inversion centre with the coordination consisting of two N atoms from two tetrazole groups and four water molecules. There are intramolecular hydrogen bonds between the hydrogen atoms of the coordinated water molecules and nitrogen atoms of the tetrazole rings, between the tetrazole hydrogen atoms N215 and N312, and also between the tetrazole hydrogen H412 and the calixarene oxygen atoms O21. The calixarene ligand thus interacts with both the primary and secondary coordination spheres of the sodium cation (16, 21), as shown in Figure 2. There is also an intermolecular hydrogen bond between H115 on N115 and the centrosymmetrically related N115. The calixarene phenyl rings again deviate considerably from possible 4-fold symmetry, with the dihedral angles between opposite phenyl ring planes being $7.91(8)^\circ$ (between rings 1n and 3n) and $103.45(8)^\circ$ (between rings 2n and 4n).

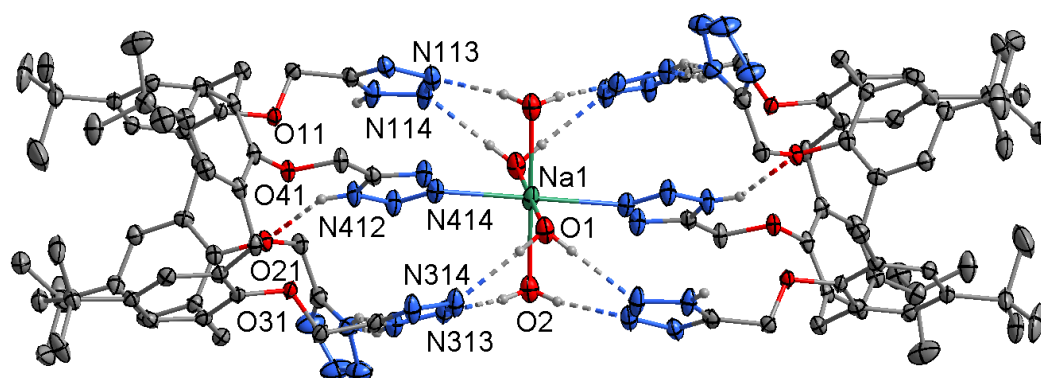


Figure 2. The structure of the anion of $\mathbf{1}\text{-Na}^+/\text{HNEt}_3^+$ showing the intramolecular hydrogen bonding, with one component of the disordered atoms omitted for clarity. Ellipsoids have been drawn at the 50% probability level.

Conclusions

A calix[4]arene substituted at the lower rim with four tetrazole moieties has been synthesised and characterised. In contrast to the known bis-tetrazole analogue, the new receptor is found to interact only weakly with lanthanoid cations under the conditions examined. Structural studies of the ligand in neutral form, and as a mixed sodium / triethylammonium salt suggest that these weak interactions might be due to extensive intramolecular hydrogen bonding.

Experimental

1²,5²-bis(cyanomethoxy)-3²,7²-dihydroxy-1⁵,3⁵,5⁵,7⁵-*t*-butylcalix[4]arene, **2**, was synthesised followed the literature method (17). Proton NMR spectra for **1**, **2**, and **3** are shown in Figures S5-7.

*Synthesis of 1²,3²,5²,7²-tetra(cyanomethoxy)-1⁵,3⁵,5⁵,7⁵-*t*-butylcalix[4]arene, 3*

The literature method (18) was adapted as follows. Sodium hydride (1.06 g, 44.0 mmol) and calixarene **2** (2.13 g, 2.93 mmol) were added to dry DMF (100 mL) and allowed to stir for 20 minutes. To this, bromoacetonitrile (0.96 mL, 13.7 mmol) was added and stirred overnight at room temperature under a nitrogen atmosphere. This resulted in a black, completely opaque, solution. Water (150 mL) was slowly added causing a pale brown precipitate to occur, which was filtered off and washed several times with water. The solid was dissolved in a minimum amount of dichloromethane and purified by column chromatography (silica gel, dichloromethane), to afford a white solid, **3** (1.62 g, 69%). ¹H NMR (DMSO, δ, ppm) 6.91 (s, 8H, Ar-**H**), 2.00 (s, 8H, Ar-O-**CH**₂), 4.28 (d, 4H, *axial* Ar-**CH**₂-Ar, J=13.2 Hz), 3.32 (d, 4H, *equatorial* Ar-**CH**₂-Ar, J=13.3 Hz), 1.05 (s, 36H, Ar-C**CH**₃). ¹³C NMR (DMSO, δ, ppm) 151.5, 146.7, 133.8, 125.8, 118.0, 59.5, 34.2, 31.7, 31.4. IR (ATR): ν/cm⁻¹ 2959 (s), 2868 (m), 1604 (w), 1473 (s), 1362 (m),

1190 (s), 1024 (s), 878 (w).

Synthesis of 1²,3²,5²,7²-tetra(tetrazolyl)-1⁵,3⁵,5⁵,7⁵-t-butylcalix[4]arene, 1

Toluene (30 mL) was placed into a round bottom flask immersed in an ice bath. To the cold solvent, triethylamine (0.69 mL, 4.97 mmol) and hydrochloric acid (0.48 mL, 4.97 mmol) was added and the flask stoppered immediately. A white gas was evolved but upon stirring the solution for five minutes this dissolved into solution resulting in a white residue on the walls of the flask. Calixarene **3** (0.40 g, 0.50 mmol) was then added to the solution along with sodium azide (0.21 g, 3.2 mmol) and heated under reflux for 12 hours. The solution was cooled to room temperature and the solvent was removed under reduced pressure yielding a white solid. The residue was dissolved in ethyl acetate resulting in a cloudy pale cream solution which was filtered and washed with hydrochloric acid (1 M, 3×50 mL). The organic fraction was dried over magnesium sulfate, filtered and solvent removed by reduced pressure evaporation. The residue was washed with small amounts of cold dichloromethane to remove the coloured impurity, furnishing the tetrazole calixarene **1** as a white solid (0.396 g, 81%). Crystals suitable for single crystal X-ray structure determination were obtained by slow evaporation of an ethanol solution of **1**. ¹H NMR (DMSO, δ, ppm) 6.81 (s, 8H, Ar-**H**), 5.21 (s, 8H, Ar-O-CH₂), 3.84 (d, 4H, *axial* Ar-CH₂-Ar, J=12.7 Hz), 2.95 (d, 4H, *equatorial* Ar-CH₂-Ar, J=12.8 Hz), 1.02 (s, 36H, Ar-CCH₃). ¹³C NMR (DMSO, δ, ppm) 151.4, 145.1, 133.2, 125.1, 63.0, 33.6, 31.0, 30.7, 30.4 N.B. Tetrazole carbon not observed. (m+1)/z = 977.514 (m+Na)/z = 999.517. IR (ATR): ν/cm⁻¹ 3279 (w), 2961 (s), 2904 (m), 2869 (m), 1780 (w) 1574 (w), 1479 (s), 1363 (m), 1302 (w), 1192 (s), 1124 (m), 1006 (m), 871 (m). Anal. Calculated for C₅₂H₆₄O₄N₁₆·H₂O: C, 62.75; H, 6.685 %; N, 22.52, Found C, 62.57; H, 6.45; N, 22.42 %.

Crystallisation of a mixed sodium / triethylammonium salt of 1

The triethylammonium and sodium salt of the tetra-tetrazole ligand **1** was crystallised by the slow evaporation of ethanol/ethyl acetate (50/50, 10 mL) from a solution of free ligand (30 mg, 0.04 mmol) and Tb(NO₃)₃(DMSO)₄ (21.4 mg, 0.04 mmol) along with ten equivalents of triethylamine (51 μL). Clear needle-like crystals evolved which were characterised by single crystal X-ray structure determination.

Crystallography

Crystallographic data for **1**·H₂O·EtOH and **1**-Na⁺/HNEt₃⁺: were collected at 100(2) K on an Oxford Diffraction Gemini diffractometer fitted with Mo K α radiation.

Following multi-scan absorption corrections and solution by direct methods, the structures were refined against F^2 with full-matrix least-squares using the program SHELXL-97 (22). Crystallographic data for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre with supplementary publication numbers CCDC 1404328 (**1**·H₂O·EtOH), 1404329 (**1**-Na⁺/HNEt₃⁺). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Rd, Cambridge CB21EZ, UK (fax +441223336033; email deposit@ccdc.cam.ac.uk).

Refinement details

1·H₂O·EtOH : The water molecule hydrogen atoms were refined with restrained geometries. All remaining hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on those

of the parent atoms. Anisotropic displacement parameters were employed throughout for the non-hydrogen atoms.

1-Na⁺/HNEt₃⁺: One tertiary butyl group and the triethylammonium cation were modelled as being disordered over two sets of sites with occupancies constrained to 0.5 after trial refinement. Geometries of the disordered atoms were restrained to ideal values. Water molecule hydrogen atoms were located in difference maps and refined with geometries restrained to ideal values. Hydrogen atoms on the tetrazole groups were located in difference maps. The proximity of the nitrogen atoms N312 and N215 indicates that the hydrogen is involved in an intramolecular hydrogen bond. This was modelled as being disordered between the two N atoms on the basis of the electron density. The hydrogen atom on N115 was assigned a site occupation of 0.5 due to hydrogen bonding to a centrosymmetrically related N115. All remaining hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on those of the parent atoms. Anisotropic displacement parameters were employed throughout for the non-hydrogen atoms.

Crystal data

1·H₂O·EtOH : Empirical formula C₅₄H₇₂N₁₆O₆; formula weight 1041.28, monoclinic, space group *Cc*, *a* 11.5045(7), *b* 41.964(2), *c* 12.3762(6) Å, β 108.656(6)°, *V* 5661.0(5) Å³, *Z* 4, *D_c* 1.222 Mg/m³, μ 0.083 mm⁻¹, crystal size 0.47 x 0.23 x 0.10 mm³, θ_{min,max} 3.61, 30.75°, reflections collected 37551, independent reflections 8252 (*R*_{int} 0.0837), data/restraints/parameters 8252/4/708, goodness-of-fit on *F*² 0.904, final *R* indices [*I* > 2σ(*I*)] *R*₁ 0.0636, *wR*₂ 0.1323, *R* indices (all data) *R*₁ 0.1192, *wR*₂ 0.1483.

1-Na⁺/HNEt₃⁺: Empirical formula C₁₁₆H₁₆₉N₃₄O₁₄Na; formula weight 2286.84,

monoclinic, space group $P2_1/c$, a 11.5310(4), b 46.1981(12), c 12.1227(3) Å, β 106.787(3)°, V 6182.7(3) Å³, Z 2, D_c 1.228 Mg/m³, μ 0.087 mm⁻¹, crystal size 0.43 x 0.12 x 0.10 mm³, $\theta_{\min, \max}$ 3.46, 26.75°, reflections collected 32504, independent reflections 12953 (R_{int} 0.0443), data/restraints/parameters 12953/157/867, goodness-of-fit on F^2 1.026, final R indices [$I > 2\sigma(I)$] R_1 0.0649, wR_2 0.1434, R indices (all data) R_1 0.0998, wR_2 0.1581.

Photophysical Measurements

Absorption spectra were recorded at room temperature using a Perkin Elmer Lambda 35 UV/Vis spectrometer. Uncorrected steady state emission and excitation spectra were recorded using an Edinburgh FLSP980-stm spectrometer equipped with a 450 W xenon arc lamp, double excitation and emission monochromators, a Peltier cooled Hamamatsu R928P photomultiplier tube (185–850 nm). Emission and excitation spectra were corrected for source intensity (lamp and grating) and emission spectral response (detector and grating) by a calibration curve supplied with the instrument.

Excited state decays (τ) were recorded on the same Edinburgh FLSP980-stm spectrometer using a microsecond flashlamp the above-mentioned R928P PMT photomultiplier as the detector. The goodness of fit was assessed by minimizing the reduced χ^2 function and by visual inspection of the weighted residuals.

According to the approach described by Demas and Crosby (23), the luminescence quantum yield was measured in optically dilute solutions (O.D. < 0.1 at excitation wavelength) obtained from absorption spectra on a wavelength scale [nm] and compared to the reference emitter by the following equation:

$$F_x = F_r \frac{\epsilon_{A_r}(\lambda_r) \epsilon_{I_r}(\lambda_r) \epsilon_{n_x^2} \epsilon_{D_x}}{\epsilon_{A_x}(\lambda_x) \epsilon_{I_x}(\lambda_x) \epsilon_{n_r^2} \epsilon_{D_r}}$$

where A is the absorbance at the excitation wavelength (λ), I is the intensity of the excitation light at the excitation wavelength (λ), n is the refractive index of the solvent, D is the integrated intensity of the luminescence and Φ is the quantum yield. The subscripts r and x refer to the reference and the sample, respectively. The quantum yield determinations were performed at identical excitation wavelength for the sample and the reference, therefore cancelling the $I(\lambda_r)/I(\lambda_x)$ term in the equation. The reference used for the determination was an air-equilibrated H₂O solution of [Ru(bipy)₃]Cl₂ used as reference ($\Phi_r = 0.028$) (24).

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References

- (1) Gutsche, C. D., *Calixarenes: An Introduction*. 2nd ed.; RSC Publishing: Cambridge, 2008.
- (2) Lincheneau, C.; Quinlan, E.; Kitchen, J. A.; McCabe, T.; Matthews, S. E.; Gunnlaugsson, T., *Supramol. Chem.* **2013**, *25*, 869-880.
- (3) Horvat, G.; Stilinovic, V.; Kaitner, B.; Frkanec, L.; Tomisic, V., *Inorg. Chem.* **2013**, *52*, 12702-12712.
- (4) Horvat, G.; Stilinovic, V.; Hrenar, T.; Kaitner, B.; Frkanec, L.; Tomisic, V., *Inorg. Chem.* **2012**, *51*, 6264-6278.
- (5) Ennis, B. W.; Muzzioli, S.; Reid, B. L.; D'Alessio, D. M.; Stagni, S.; Brown, D. H.; Ogden, M. I.; Massi, M., *Dalton Trans.* **2013**, *42*, 6894-6901.
- (6) Hwang, D.; Lee, E.; Jung, J. H.; Lee, S. S.; Park, K. M., *Crystal Growth & Design* **2013**, *13*, 4177-4180.
- (7) Redshaw, C.; Rowe, O.; Hughes, D. L.; Fuller, A. M.; Ibarra, I. A.; Humphrey, S. M., *Dalton Trans.* **2013**, *42*, 1983-1986.
- (8) Brancatelli, G.; De Zorzi, R.; Hickey, N.; Siega, P.; Zingone, G.; Geremia, S., *Crystal Growth & Design* **2012**, *12*, 5111-5117.
- (9) Gramage-Doria, R.; Armspach, D.; Matt, D., *Coord. Chem. Rev.* **2013**, *257*, 776-816.
- (10) Semeril, D.; Matt, D., *Coord. Chem. Rev.* **2014**, *279*, 58-95.
- (11) Pinter, T.; Jana, S.; Courtemanche, R. J. M.; Hof, F., *J. Org. Chem.* **2011**, *76*, 3733-3741.
- (12) Boyko, V.; Rodik, R.; Danylyuk, O.; Tsymbal, L.; Lampeka, Y.; Suwinska, K.; Lipkowski, J.; Kalchenko, V., *Tetrahedron* **2005**, *61*, 12282-12287.
- (13) Dondoni, A.; Marra, A., *Tetrahedron* **2007**, *63*, 6339-6345.

- (14) Chen, Y. J.; Chung, W. S., *Eur. J. Org. Chem.* **2009**, 4770-4776.
- (15) D'Alessio, D.; Muzzioli, S.; Skelton, B. W.; Stagni, S.; Massi, M.; Ogden, M. I., *Dalton Trans.* **2012**, *41*, 4736-4739.
- (16) D'Alessio, D.; Sobolev, A. N.; Skelton, B. W.; Fuller, R. O.; Woodward, R. C.; Lengkeek, N. A.; Fraser, B. H.; Massi, M.; Ogden, M. I., *J. Am. Chem. Soc.* **2014**, *136*, 15122-15125.
- (17) Collins, E. M.; Mckerverey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J., *Journal of the Chemical Society-Perkin Transactions I* **1991**, 3137-3142.
- (18) Halouani, H.; Dumazet-Bonnamour, I.; Perrin, M.; Lamartine, R., *J. Org. Chem.* **2004**, *69*, 6521-6527.
- (19) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R., *Synthesis-Stuttgart* **1998**, 910-914.
- (20) Eliseeva, S. V.; Bunzli, J. C. G., *Chem. Soc. Rev.* **2010**, *39*, 189-227.
- (21) Beer, P. D.; Drew, M. G. B.; Ogden, M. I., *J. Chem. Soc., Dalton Trans.* **1997**, 1489-1491.
- (22) Sheldrick, G. M., *Acta Crystallographica Section A* **2008**, *64*, 112-122.
- (23) Crosby, G. A.; Demas, J. N., *J. Phys. Chem.* **1971**, *75*, 991-1024.
- (24) Nakamaru, K., *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2697-2705.