Communication

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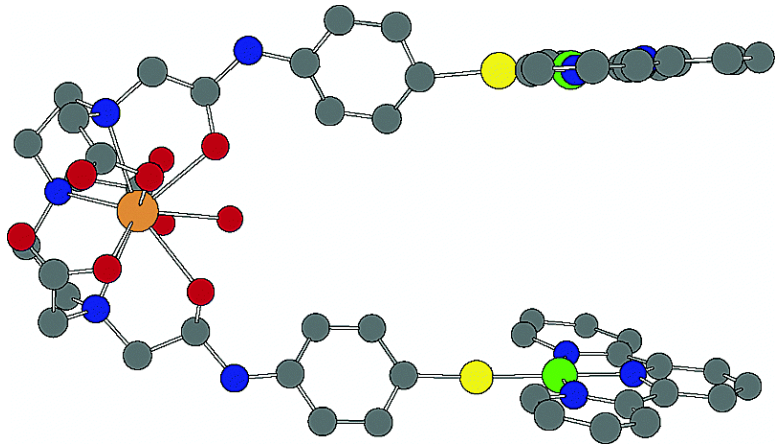
J. Am. Chem. Soc., **2003**, 125 (33), 9918-9919• DOI: 10.1021/ja029886s • Publication Date (Web): 24 July 2003



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Published on Web 07/24/2003

Hairpin-Shaped Heterometallic Luminescent Lanthanide Complexes for DNA Intercalative Recognition

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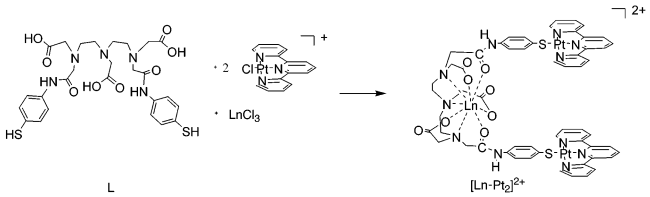
Using molecular shape for the functional control of multicomponent systems is one of the challenges in the field of supramolecular chemistry. Interaction of synthetic supramolecular systems with biologically active molecules has been of particular interest to address recognition features important to biomolecular function.[1] We have been interested in the assembly of ligands around lanthanide ions using either steric crowding or replacement of water molecules to control the coordination sphere around the ion.[2] In this paper, we wish to introduce the assembly of lanthanide and transition metal building blocks that lead to metallohairpins. Hairpin-shaped molecules have attracted particular interest for targeting specific DNA sequences.[3] Heterometallic lanthanide complexes have attracted interest in diverse applications ranging from catalytic activity,[4] magnetic devices,[5] and liquid crystalline materials,[6] to sensor design.[7,8] Most of the synthetic strategies have used either transition metal moieties with free sites for lanthanide complexation or ligands with coordination sites designed for metal "induced fit"; there is one example of a covalent bond formation between a lanthanide complex and a metal−porphyrin moiety.[9] The latter complex has been shown to interact with nucleic acids, although most of the lanthanide complexes reported for DNA recognition bear an organic group as an intercalator unit.[10]

In our approach, we use a versatile ligand design that can wrap around a lanthanide, leaving two grafted donor sites for binding of transition metal units. The lanthanide complex is formed using ligand L, a derivative of diethylenetriaminepentaacetic acid[11] with bisamide thiophenol moieties (Scheme 1).

This ligand was developed to provide a hard binding core for lanthanide complexation, via the five oxygens and three nitrogens, and two arms with soft thiol binding sites for binding other metals. Lanthanide complexation orients the ligand to a hairpin-shape with the two thiol sites available for binding. We attached platinum(II) terpyridyl moieties onto these sites using the platinum interaction with aromatic thiolates.[12,13] Platinum(II) terpyridyl moieties are well established as DNA intercalators.[14] The beauty of our approach is the accessibility of the Ln−Pt_2 complexes by self-assembly of the different components in one pot or in a sequential manner, regardless of the order of the addition of the components. Reaction of L, $LnCl_3 \cdot xH_2O$ (Ln = Nd, Eu, La) (the analogous Y(III) complexes were also prepared for NMR spectroscopic characterization), and [Pt(tpy)Cl](CF_3SO_3),[15] where tpy = 2,2′:6′,2″-terpyridine, in a 1:1:2 molar ratio, in methanol under reflux for 2 h yielded exclusively the desired purple Ln−Pt_2 complexes (Scheme 1). Fluorescence titration demonstrates the 1:1 binding of a lanthanide ion and ligand L; see the Supporting Information. The heterometallic complexes were isolated as the PF_6 salts, by precipitation with a methanolic solution of NH_4PF_6 following the addition of water in the reaction mixture and raising of the pH to 5 by NaOH. The same Ln−Pt_2 complexes were obtained independently by two routes: (a) reaction between L and $[Pt(tpy)Cl]^+$ to give L−Pt_2 which was isolated and then reacted with the lanthanide chloride, or (b) by isolation of the complex of L with $LnCl_3$ and subsequent reaction with [Pt(tpy)Cl](CF_3SO_3).

Scheme 1. Preparation of Ln−Pt_2 Metallohairpins



The complexes have been fully characterized and analyzed by spectroscopic methods [selected spectroscopic data **[L−Pt_2]-(PF_6)$_2$** ^{1}H NMR (500 MHz, d_7-DMF, 25 °C) δ 10.3 (br s, NH), 9.06 (m, 6-tpy), 8.79 (m, 3′-tpy), 8.72 (m, 3-tpy), 8.65 (t, 4′-tpy), 8.49 (m, 4-tpy), 7.88 (dd, 5-tpy), 7.56 (m, ArH), 3.4, 3.5, 3.6 (water peak obscures CH_2COO), 3.13 (t, CH_2), 3.00 (t, CH_2); MS (ES^+) *m*/*z* 1460 $\{M - 2(PF_6) - H\}^+$, 731 $\{M\}^{2+}$. Calculated for $C_{56}H_{53}N_{11}O_8S_2Pt_2P_2F_{12}$: C, 38.4; H, 3.1; N, 8.8. Found: C, 38.5; H, 3.2; N 8.6. **[Nd−Pt_2](PF_6)$_2$** MS (MALDI-TOF^+): *m*/*z* 1601 $\{M - 2PF_6\}^+$, (ES^+) *m*/*z* 1748 $\{M - (PF_6)\}^+$, 1601 $\{M - 2(PF_6) - H\}^+$, 801 $\{M - 2(PF_6)\}^{2+}$. Calculated for $C_{56}H_{66}N_{11}O_{16}S_2Pt_2NdP_2F_{12}Na_2Cl_2$: C, 31.2; H, 3.1; N, 7.2. Found: C, 31.3; H, 2.8; N, 7.3. UV−vis (MeOH:H_2O, 4:1): λ_{max} in nm (log ϵ) 515 (3.4), 375 (3.7), 345 (4.4), 330 (4.4), 280 (4.8), 250 (4.8)]. Full assignment of the ^{1}H NMR was achieved by ^{1}H−^{1}H COSY spectroscopy. Electrospray mass spectra for L−Pt_2 and Ln−Pt_2 reveal peaks corresponding to the single charged species $\{M - 2(PF_6) - H\}^+$ and the doubly charged $\{M - 2(PF_6)\}^{2+}$ with the characteristic isotope patterns.

The UV−visible absorption spectra of the Nd−Pt_2 complexes exhibit peaks corresponding to the sum of the bands of the individual components, Pt(tpy)[16] and NdL, with a slight shift of the aromatic thiolate peak and a new broad band centered at 515 nm. This latter band is attributed to a LLCT transition, $p\pi(RS^-) \rightarrow \pi^*$(tpy) previously observed in $[Pt(tpy)SR]^+$ complexes.[13,17] The appearance of this band is a signature of the formation of the heterometallic complex. The complexes provide two chromophoric components for lanthanide sensitization based on the thiophenol link and the LLCT transition. The emission properties of the Ln−Pt_2 complexes were examined. The Eu−Pt_2 complex does not show any visible emission as expected due to the absorption of the charge-transfer band in this spectral region. However, the Nd−Pt_2 complex shows NIR emission characteristic of the Nd(III) ion at 1060 and

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10.1021/ja029886s CCC: $25.00

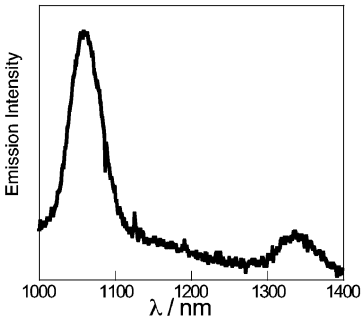

Figure 1. Emission spectrum of $[Nd-Pt_2](PF_6)_2$ in d_6-DMSO, $\lambda_{exc} = 337$ nm.

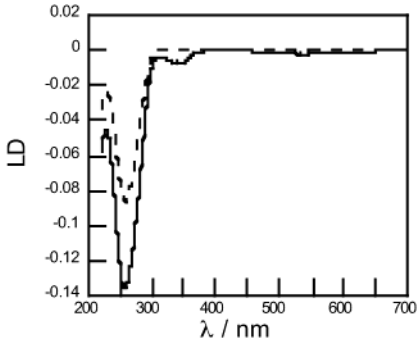

Figure 2. LD spectra of CT-DNA (dashed line), 40:1 CT-DNA:$[Nd-Pt_2]$ complex (solid line); [CT-DNA] = 1000 μM in 10 mM HEPES buffer.

1340 nm corresponding to $^4F_{3/2} \rightarrow {}^4I_{11/2}$, $^4I_{13/2}$ transitions (Figure 1) with a lifetime of 670 ns. The relative quantum yield of the $Nd-Pt_2$ complex upon excitation at 515 nm remains constant in the formation of the complex with calf-thymus DNA. The lanthanide unit acts as a luminescent "reporter" group, the ion being encapsulated by the aminocarboxylate ligating site, which does not interact with DNA. For molecular models, see the Supporting Information.

We have used flow linear dichroism (LD)[18] to detect the binding of the $Nd-Pt_2$ complex to calf-thymus DNA (CT-DNA). The metal complexes will show an LD signal only if bound to DNA. Transitions more parallel than perpendicular to the DNA helix axis will have positive LD signals, while transition moments at an angle of greater than 54° from the helix axis (as is the case for the $\pi-\pi^*$ transitions of planar aromatic intercalators) will result in a negative signal. The LD spectra (Figure 2) show negative signals at 260, 340, and 550 nm.

The 450−610 nm region is composed of a range of transitions that are polarized in the plane of the terpyridines. The LD signal of this region is negative with a very large flat negative LD^r (LD^r = LD/absorbance) signal, indicating that the different terpyridine transitions all lie at the same angle with respect to the DNA helix axis. This indicates the molecule is lying perpendicular to the helix axis. Furthermore, the LD signal of DNA with $Nd-Pt_2$ increases more than the absorbance signal upon $Nd-Pt_2$ binding, showing that the DNA stiffens upon binding. The magnitude of the LD^r signal is significantly greater than that for other bis-intercalators.[19] Control LD experiments with an Ln complex bearing butyl amide arms instead of the −ArSPt(tpy) units show no negative signal for the metal complex, confirming that the neutral lanthanide unit does not bind to DNA. From these results and the shape of the $Nd-Pt_2$ complex, we conclude that the $Nd-Pt_2$ binds to DNA via an intercalative mode that results in significant stiffening of the DNA. This is not only consistent with intercalation but indicative of bis-intercalation of the two −Pt(terpy) units because all of the terpyridyl transition moments are parallel to one another and the terpyridyl region has a LD^r signal more than twice the magnitude of the average DNA base pair even when the DNA is stiffened by the complex binding. The binding constant of $Nd-Pt_2$ with DNA is estimated to be at least an order of magnitude larger than that of ethidium bromide, $K = 9.5 \times 10^6\ M^{-1}$ (see Supporting Information).

We have demonstrated an assembly approach to luminescent heterotrimetallic lanthanide complexes as metallohairpins. The $Ln-Pt_2$ metallohairpins bear intercalating groups that direct the complex to DNA recognition, leading to considerable DNA stiffening with high LD^r values. The lanthanide luminescent unit is "remote" from the negatively charged DNA backbone. Further studies are currently underway to introduce specific recognition sites to target certain DNA sequences.

Acknowledgment. We thank the Royal Society and EPSRC for funding.

Supporting Information Available: Further spectroscopic data of $[Ln-Pt_2]$, UV−vis and LD^r spectra of CT-DNA and CT-DNA + $[Nd-Pt_2]$, emission titration plots of Ln binding to L and competitive binding of $L-Pt_2$ and $Nd-Pt_2$ to DNA, and models of $Nd-Pt_2$ bound to DNA (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Park, H. S.; Lin, Q.; Hamilton, A. D. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5105. Hannon, M. J.; Moreno, V.; Prieto, M. J.; Moldrheim, E.; Sletten, E.; Meistermann, I.; Isaac, C. J.; Sanders, K. J.; Rodger, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 880.
(2) Magennis, S. W.; Parsons, S.; Pikramenou, Z. *Chem.-Eur. J.* **2002**, *8*, 5761. Magennis, S. W.; Parsons, S.; Corval, A.; Woollins, J. D.; Pikramenou, Z. *Chem. Soc., Chem. Commun.* **1999**, 61. Magennis, S. W.; Craig, J.; Gardner, A.; Fucassi, F.; Cragg, P. J.; Robertson, N.; Parsons, S.; Pikramenou, Z. *Polyhedron* **2003**, *22*, 745.
(3) Dervan, P. B. *Biorg. Med. Chem.* **2001**, *9*, 2215.
(4) Fischbach, A.; Perdih, F.; Sirsch, P.; Scherer, W.; Anwander, R. *Organometallics* **2002**, *21*, 4569. Hill, M. S.; Hitchcock, P. B. *Angew. Chem.* **2001**, *40*, 4089. Aspinall, H. C.; Greeves, N. *J. Organomet. Chem.* **2002**, *647*, 151. Groeger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089.
(5) Bencini, A.; Benelli, C.; Caneschi, A.; Carlin, R. L.; Dei, A.; Gatteschi, D. *J. Am. Chem. Soc.* **1985**, *107*, 8128. Winpenny, R. E. P. *Chem. Soc. Rev.* **1998**, *27*, 447.
(6) Binnemans, K.; Gorller-Walrand, C. *Chem. Rev.* **2002**, *102*, 2303. Nozary, H.; Piguet, C.; Rivera, J. P.; Tissot, P.; Morgantini, P. Y.; Weber, J.; Bernardinelli, G.; Bunzli, J. C. G.; Deschenaux, R.; Donnio, B.; Guillon, D. *Chem. Mater.* **2002**, *14*, 1075.
(7) Edder, C.; Piguet, C.; Bunzli, J. C. G.; Hopfgartner, G. *Chem.-Eur. J.* **2001**, *7*, 3014.
(8) Klink, S. I.; Keizer, H.; van Veggel, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 4319.
(9) Beeby, A.; Dickins, R. S.; FitzGerald, S.; Govenlock, L. J.; Maupin, C. L.; Parker, D.; Riehl, J. P.; Siligardi, G.; Williams, J. A. G. *Chem. Commun.* **2000**, 1183.
(10) Bobba, G.; Frias, J. C.; Parker, D. *Chem. Commun.* **2002**, 890. Bobba, G.; Kean, S. D.; Parker, D.; Beeby, A.; Baker, G. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1738. Sammes, P. G.; Shek, L.; Watmore, D. *Chem. Commun.* **2000**, 1625. Fu, P. K. L.; Turro, C. *J. Am. Chem. Soc.* **1999**, *121*, 1.
(11) Choppin, G. R.; Schaab, K. M. *Inorg. Chim. Acta* **1996**, *252*, 299.
(12) Jennette, K. W.; Gill, J. T.; Sadownick, J. A.; Lippard, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 6159. Todd, J. A.; Rendina, L. M. *Inorg. Chem.* **2002**, *41*, 3331.
(13) Tzeng, B. C.; Fu, W. F.; Che, C. M.; Chao, H. Y.; Cheung, K. K.; Peng, S. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1017.
(14) Lippard, S. J. *Acc. Chem. Res.* **1978**, *11*, 211. Arena, G.; Monsu Scolaro, L.; Pasternack, R. F.; Romeo, R. *Inorg. Chem.* **1995**, *34*, 2994. Peyratout, C. S.; Aldridge, T. K.; Crites, D. K.; McMillin, D. R. *Inorg. Chem.* **1995**, *34*, 4484. Becker, K.; Herold-Mende, C.; Park, J. J.; Lowe, G.; Schirmer, R. H. *J. Med. Chem.* **2001**, *44*, 2784. McCoubrey, A.; Latham, H. C.; Cook, P. R.; Rodger, A.; Lowe, G. *FEBS Lett.* **1996**, *380*, 73.
(15) Buchner, R.; Cunningham, C. T.; Field, J. S.; Haines, R. J.; McMillin, D. R.; Summerton, G. C. *J. Chem. Soc., Dalton Trans.* **1999**, 711.
(16) Aldridge, T. K.; Stacy, E. M.; McMillin, D. R. *Inorg. Chem.* **1994**, *33*, 722.
(17) Yam, V. W. W.; Tang, R. P. L.; Wong, K. M. C.; Ko, C. C.; Cheung, K. K. *Inorg. Chem.* **2001**, *40*, 571. Howe-Grant, M.; Lippard, S. J. *Inorg. Synth.* **1980**, *20*, 101.
(18) Nordén, B.; Kubista., M.; Kuruscev, T. Q. *Rev. Biophys.* **1992**, *25*, 51. Nordén, B. *Appl. Spectrosc. Rev.* **1978**, *14*, 157.
(19) Kim, H. K.; Kim, J. M.; Kim, S. K.; Rodger, A.; Norden, B. *Biochemistry* **1996**, *35*, 1187.

JA029886S