ABSTRACT

Critical Molecular Design Parameters For Novel Polynuclear Lanthanide (III) Complexes As Novel Biomedical Diagnostic Agents

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Very few polynuclear lanthanide (III) complexes have been synthesis due to difficulty in preparation. It is on this basis that the possibility of preparing precursors for macrocyclic Schiff base chelates bearing CH_2CH_2OH and CH_2COOH moieties and designed to facilitate solubility and solution stability of dinuclear lanthanide complexes was explored. In order to selectively attach groups to secondary N-H sites of amine precursors such as triethylenetetramine and diethylenetriamine, protection of adjacent NH_2 groups was essential. This was attempted using a mixture of acetic acid, phthalic anhydride, and the relevant polyamine (A-P-P protocol). Surprisingly, this reaction took unusual routes: the major product was diphthalimidodiethylammonium-hydrogen phthalate (**DPDAH-HP**) for diethylenetriamine, which was isolated as an unhydrated (**DPDAH-HP**) and hydrated (**DPDAH-HP.1.75H_2O**) complex. Refluxing **DPDAH-HP** under basic conditions yielded the desired

diphthalimidodiethylamine (**DPDA**). For the longer chain triethylenetetramine, ethylene migration products N,N-Bis(2-phthalimidoethyl)-piperazine (**19**) and N,N$^{/}$,N$^{//}$-(nitrilotriethylene)-trisphthalimide (**20**) were obtained from room temperature and refluxing reaction mixtures respectively.

The crystal structures of **19**, **20**, **DPDAH-HP** and **DPDAH-HP.1.75H$_2$O** revealed a series of stabilizing complimentary non-covalent interactions such as offset π-π stacking and possibly C-H...N hydrogen bonds (**19**), and electrostatic interactions between the amine and pyrrolic functionalities (**20**), offset π-π stacking, carbonyl-carbonyl and N-H...O hydrogen bonding for **DPDAH-HP** and **DPDAH-HP.1.75H$_2$O**. To our knowledge, this is the first time that an n-pyrrolic stabilizing interaction (found in **19**) has been definitely proven by x-ray crystallography. The **DPDAH-HP** units stacked along a screw axis parallel to the *b*-direction to yield a striking [phthalimide-phthalimide-hydrogen phthalate]$_n$ supramolecular motif, and are linked in the *a* and *c* directions by N-H...O bonds. On the other hand, the horseshoe conformation of the **DPDAH** units of **DPDAH-HP.1.75H$_2$O** into which the hydrogen phthalate anion is trapped, form extended chains linked via hydrogen bonds to the water molecules, to give a supramolecular sheet that extends in 011 plane.

Solution ^{1}H NMR studies of **20** revealed unusual temperature (178 - 420 K) evolution of sharp aromatic proton resonances in various solvents. Typically, the spectra exhibited a spectacular temperature evolution from a sharp doublet of quartets at high temperature to complex second order behavior and then a singlet. As the temperature was further lowered, a complex second order spectrum reappeared followed by a doublet of quartets. The unusual NMR behavior was attributed to the phthalimide-amine, of which an interaction energy of *ca.* 20 kJ/mol was determined from temperature dependent NMR studies. Solid state ^{13}C aromatic resonances were broadened by π-π interactions in **19** and **DPDAH-HP** while two sets of ^{13}C resonances were found for **20** as expected from the solid state structures. The hydrogen phthalate anion in **DPDAH-HP** exchanged rapidly with free phthalic acid (300 K equilibrium constant, $K \simeq 4 \times 10^{2}$ l/mol); this phthalate exchange exhibited almost temperature independent behavior indicating a predominantly entropy driven process.

Functionalization of the N-H site of **DPDA**, followed by hydrolysis of the phthalimide moiety, to yield dendritic precursors to systems such as **16** which are capable of trapping numerous lanthanide ions, proved not to be straightforward. A competing formylation reaction dominated instead of the desired alkylation reaction, giving a new compound 2,2′-(formamidedi-2,1-ethanediyl)bis-1H-indole-1,3(2H)-dione (**22**). NMR showed almost non-existent rotation about the formamide moiety resulting in effective shielding of one of the two ethylenephthalimide arms, and x-ray proved relatively strong methylene and aromatic C-H...O intermolecular interactions responsible for stabilizing this adopted conformation. These interactions were also responsible for the dimerization observed in the Fast Atom Bombardment Mass Spectrum (FAB MS).

Luminescence spectroscopy of **19**, **20** and **DPDAH-HP** indicated these compounds to be potentially good antennas for lanthanide ion emissions. Metal binding derivatives of the simpler phthalimide, **DPDA**, were synthesized producing novel compounds; ammonium-N-(ethylenephthalimide)-N-(ethylenebenzamide-2-oate) (**23**) and ammonium-N-bis(ethylenebenzamide-2-oate) (**24**). X-ray crystallographic studies showed **H23**.H_2O to be stabilized by carbonyl-carbonyl, and O-H...O and N-H...O hydrogen bonding interactions. FAB MS showed for **H23**.H_2O, dimerization and for **24**, dimerization and trimerization, indicating the presence of strong stabilizing non-covalent intermolecular interactions.

The structural results revealed the inadequacy of the popularly used phthalimide electronic structure **26** and a more appropriate model **27** was proposed.

Chromoionophores **23** and **24** were found to be excellent sensitizers (antennas) for unprecedented intense red and almost temperature independent ($77 < T < 300$ K) Eu^{3+} ($^5D_0$) emission. Time resolved 77 K luminescence spectroscopy of **23** showed both a long- and short-lived component, while for **24**, only the short-lived component was observed. The "antenna effect" was proposed to be due to the interaction between Ln^{3+} ions and the phthalate-amide functionality in which ligand-to-metal excitation transfer is efficient but back metal-to-ligand transfer is slow.

Functionalization of secondary N-H site was then sought for, using another strategy. Novel precursor triethylenetetramine-N,N'''-diacetic acid (**$H_2$28**) and triethylenetetramine-N,N'''-diethanol (**29**) were prepared. Subsequent condensation attempts of 2,6-dimethylchloro-p-cresol with **$H_2$28** and **29** to synthesize desired novel water soluble and stable macrocyclic complexes were unsuccessful, but attempted condensation with **29** serendipitously gave a new and remarkably simple way of activating, reducing and coupling CO_2 to oxalate anions. A novel inclusion supramolecular $[Pr_2(C_2O_4)_3(H_2O)_6].3H_2O.0.5HNO_3$ complex encapsulating a nitrate anion was formed.

The energy transport dynamics of simple lanthanide acetates as models for the more complex supramolecular systems, were studied. Anhydrous lanthanide acetate complexes using a new and simple

method, were prepared and x-ray crystallography revealed a 3-dimensional polymeric structure for La^{3+} acetate (coordination number of ten) with Ln^{3+} ions bridged by oxygen atoms of the acetates. Preliminary studies on Eu^{3+} and Tb^{3+} doped lanthanide acetates as well as mixed Eu^{3+}/Tb^{3+} acetates indicated energy transfer between these ions.