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Synthesis of a New Macrocyclic Ligand with Six Amide Receptor Sites

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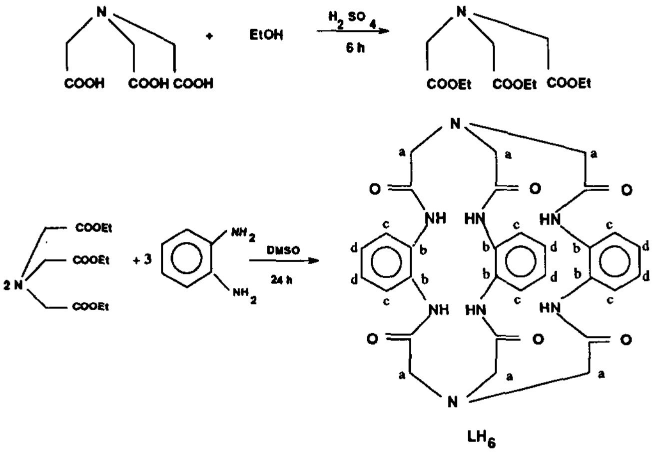
Abstract: The macrobicyclic hexaamide ligand LH_6 has been synthesized from double condensation of triethyl ester of nitrilotriacetic acid and 1,2 - diaminobenzene in 60% yield.

Macropolycyclic molecules display unique and exciting chemistries in that they can function as receptors for substrates of widely differing physical and chemical properties and upon complexation can drastically alter these properties. Selective substrate recognition, stable complex formation, transport capabilities and catalysis are examples of wide ranging properties of these molecules. Molecular complex formation is crucial to various biochemical processes like drug action, enzyme-substrate interactions etc[1]. Macrocycles can recognise cations[2], anions[3] and neutral molecules[4]. Interactions between a macrocyclic ligand and substrates are governed by electronic and structural effects. Herein we report the synthesis of a hitherto unknown hexaamide macrobicyclic ligand.

It may be pointed out that groups with high dipole moments, such as amide, are predicted to behave as good receptor sites, due to stronger dipole *versus* induced dipole interactions[4,5] and amide moieties are found in naturally occuring macrocyclic ionophores[4].



Scheme1

The synthesis of the ligand was achieved by steps shown in scheme 1 [6,7] in 60% yield. The product thus obtained was analytically pure. The compound was characterized by elemental analyses, IR, UV-visible, ^{1}H and ^{13}C NMR spectroscopy[7].

The ligand shows excellent ligation properties towards transition metal ions. Thus, when the ligand is treated with $FeCl_3$ in EtOH it forms a 1:1 red complex wherein the amide remains protonated and it forms a $[Fe(LH_6)]Cl_3$ type of complex. Similarly it forms a brown 1:1 complex with $CuCl_2.2H_2O$ in EtOH and in both the complexes the metal ion is in an octahedral environment as evidenced by EPR and UV-visible spectral studies. The details of the work on metal complexes are now in progress.

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6. Nitrilotriacetic acid (19.1 g ; 100 mmol) was mixed with 100 cm^3 of ethanol and 4cm^3 of conc H_2SO_4. The reaction mixture was refluxed for 6h, cooled to RT and the reaction solution was concentrated to about 15 cm^3 on a rotory evaporator. The residue was then extracted with chloroform (50 cm^3) and the chloroform extract was washed with saturated solution of sodium bicarbonate (3 times), dried (Na_2SO_4) and chloroform was removed to give oily triester. ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm:1.3 (9H, *t*, CH_3), 3.7 (6H,*s*, NCH_2), 4.2 (6H,*q*, OCH_2).

7. The triester (5.22g, 20 mmol) and 1,2-diaminobenzene (3.24g, 30 mmol) were dissolved in 60 cm^3 of DMSO and the reaction solution refluxed for 24h. The reaction solution was then cooled to RT and added dropwise to 200 cm^3 of water containing crushed ice with constant stirring, whereupon light brown solid product precipitated out which was filtered, washed (4-5 times) with water and finally dried *in vacuo* over fused $CaCl_2$. The compound melts at 230-233 °C (decomposes). ν_{max}(KBr)cm^{-1} 1650, 1450,840,670.λ_{max}(DMSO)nm 279 ($\epsilon = 23,690$) and 257 ($\epsilon = 19,400$) and a weak shoulder at 315 . ^{1}H NMR (200 MHz, d_6 DMSO) δppm: 4.1 (12H,*s*, a) , 7.2 (6H,*q*,J ortho=9.2Hz, J meta=3.2Hz, d), 7.6 (6H, *q*, J ortho=9.2Hz, J meta=3.2Hz, c); ^{13}C NMR (50 MHz, d_6 DMSO) δppm : 51.43 (a), 114.82 (b), 121.66 (d), 152.16 (c). *Anal:* Calcd for $C_{30}H_{30}N_8O_6$(598): C,60.20; H,5.02; N,18.73.Found: C,60.64; H,5.43; N,19.09.

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