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Molecular scaffolds for di-metallic complexation: the synthesis, characterisation and complexation properties of tetrakis-terpyridinyl-calix[4]arene

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Abstract—The ligand tetrakis-terpyridinyl-calix[4]arene is used as a rigid scaffold and pre-organiser of supramolecular assemblies by complexation of the Ni(II), Cu(II) and Co(II) cations. The ligand synthesis was carried out using peptide synthesis conditions by coupling 4′-(2-aminoethoxy)-2,2′/6′,2″-terpyridine to the tetra-succinimidoyl activated ester of *p-tert*-butylcalix[4]arene. The studies on complexation by UV show the existence of M_2L-type complexes.

The terpyridine fragment (tpy) is a highly versatile terdentate ligand, of considerable interest in transition metal coordination chemistry.[1] A wide range of applications have appeared in the literature; for example in therapeutical applications they have been used to chelate ^{199}Au and ^{109}Pd radioisotopes.[2] In this case the terpyridine units act as bifunctional chelates and are linked in a covalent manner to transport molecules for specific targeting. Investigation in the biomimetic area has been concentrated in the complexation of metals [3–6]; the Cu(II)–tpy complexes are highly active for the transesterification of phosphodiesters.[4] In order to improve the catalytic hydrolysis of RNA, Hamilton et al. have used dinuclear complexes containing a Cu(II)-bis-terpyridine system.[5] Suh et al. used Cu(II)-tpy or Ni(II)-tpy functionality couples to the synthetic poly(ethylenimine) (PEI) to hydrolyse polyadenylic acid.[6] Research has focused on increasing the number of catalytic metal sites and also on modifying the local hydrophobic environment.

The calix[4]arenes are an attractive system on which to construct spacer recognition sites for cations at the upper rim,[7] or anions at the lower rim.[8] Reinhoudt has reported model complexes based on di- and tri-nuclear Zn(II) calix[4]arene systems. In this case, the 2,6-bis(aminomethyl)pyridyl group was attached at the upper rim of the calix[4]arene.[9]

In view of the above, it seemed of interest to us to couple multiple terpyridine functions to a rigid scaffold. This presents multiple complexation sites with a predefined but somewhat flexible geometry so as to allow complexation to proceed accompanied by energy relaxation and hence eliminate too highly sterically constrained stereochemistries. The use of *p-tert*-butylcalix[4]arene as the rigid skeleton to which four terpyridinyl units are coupled via short flexible spacer functions appeared an interesting prospect for the construction of such a molecular edifice. In this paper we report the synthesis of the *p-tert*-butylcalix[4]arene tetra-terpyridine system and the study by UV spectroscopy of the complexation of metal cations Ni(II), Cu(II), Co(II).

In view of previous work and given our own competence in the lower rim modification of calix[4]arene **1**[10] we have chosen to use the calix[4]arene tetra-acid **3** prepared via the tetraester **2** as the base unit for the construction of a novel supramolecular system: tetrakis-terpyridinyl-*p-tert*-butylcalix[4] arene **6** (Scheme 1). The presence of the carboxylate functions on the macrocycle allows the use of a covalent amide linkage with the terpyridine ligand substituted at the position 4′. The tpy derivative may be synthesised using two routes, depending on whether the spacer arm between the calix[4]arene and the tpy is coupled at the tpy by a C–C linkage or by an ether functionality. The 4′-thiomethyl-2,2′/6′,2″-terpyridine available via a literature method[11] was coupled with the Grignard of benzyloxycarbonylamino ethylbromide in a nickel-catalysed reaction. However,

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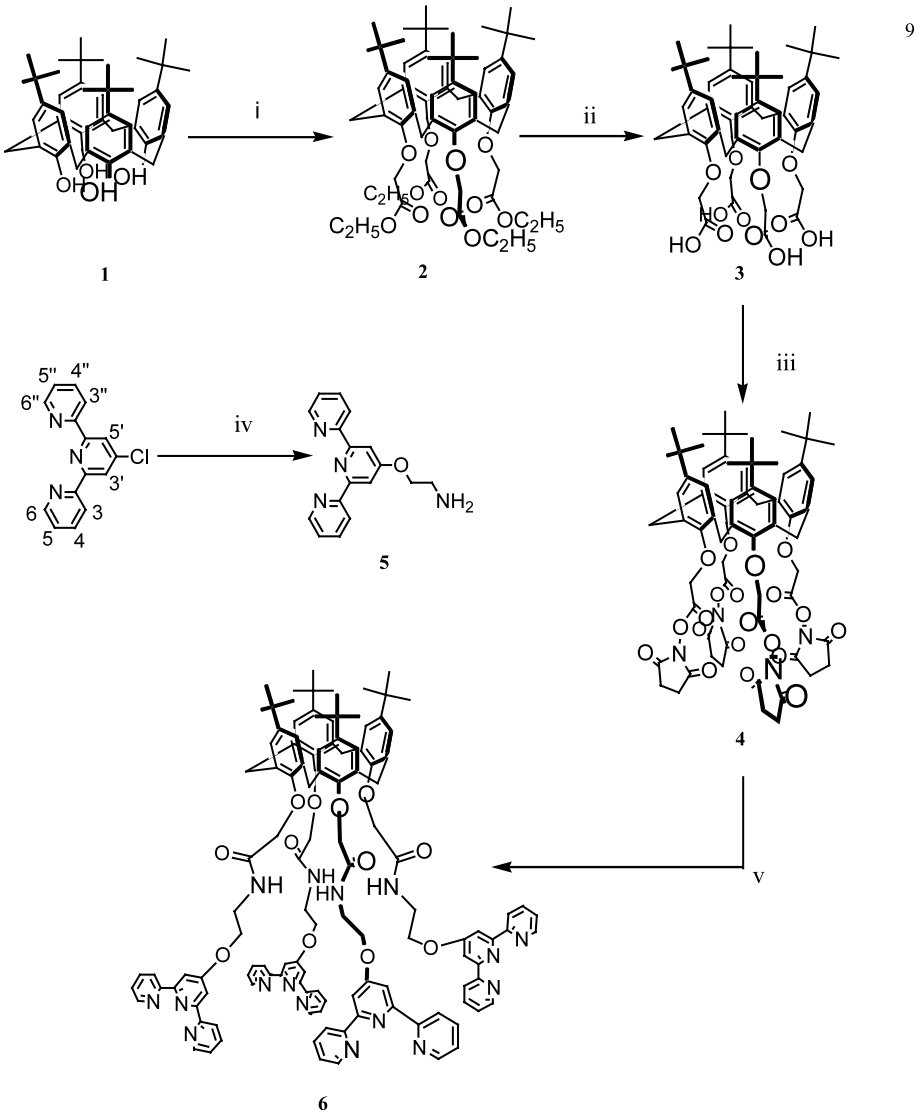

Scheme 1. Synthesis of tetrakis-terpyridinyl *p-tert*-butylcalix[4]arene **6**; (i) NaH, $BrCH_2CO_2Et$, THF, 60°C, 1 h; (ii) NaOH, EtOH, H_2O, 40°C, 48 h; (iii) *N*-hydroxy-succinimide (NHS), DCC, CH_3CO_2Et, 25°C, 48 h; (iv) 2-aminoethanol, KOH, DMSO, 1 h at 25°C and 40 h at 50°C; (v) compound **5**, DIEA, CH_2Cl_2, 5 days at 25°C.

this versatile starting material and Grignard reagent did not couple efficiently. The terpyridine moiety **5**[12] was obtained in 71% yield at 50°C for 40 h by substitution of 4′-chloro-2,2′/6′,2″-terpyridine (1 g, 3.74 mmol) with 1.2 equiv. of a solution of the alkoxide (2-aminoethanol/KOH) (0.25 mL, 4.12 mmol/0.26 g, 4.53 mmol) in dry DMSO (30 mL) to give an ether linkage. Purification of **5** was carried out by step gradient column chromatography (Al_2O_3; eluent $CHCl_3$ then 90% $CHCl_3$/10% MeOH). The grafting of four tpy O-alkylated in the position 4′ (0.61 g, 2.09 mmol) to the tetra-succinimidoyl activated tetraester **4**[10] of the tetra-acid of calix[4]arene **3** (0.60 g, 0.47 mmol) is realised in basic conditions in the presence of DIEA (diisopropyl-ethylamine) (0.4 mL, 2.09 mmol) in CH_2Cl_2 (20 mL). The new ligand tetrakis-terpyridinyl-*p-tert*-butyl-calix[4]arene **6** was obtained by precipitation from a CH_2Cl_2/*n*-hexane mixture and isolated in the 55% yield. The novel calix[4]arene ligand **6** has been characterised by ^1H, ^{13}C NMR, electrospray mass spectrometry and elemental analyses.[13] The cone conformation[14] is confirmed by the presence of an AB ($J=13.2$ Hz) system characteristic of methylene bridges ($ArCH_2Ar$) and by the position of the carbon atoms of the methylene bridges in the ^{13}C NMR: 31.90 ppm.

The complexation of cations in solution was investigated by UV spectroscopy between $\lambda=300$–400 nm. The stoichiometry of the complexes **7** and **8** prepared, respectively, from $Ni(NO_3)_2$, $6H_2O$ and $Cu(NO_3)_2$, $2.5H_2O$ and the ligand tetra-tpy-calix[4]arene **6** in a CH_2Cl_2/EtOH (1/1) solution were calculated using a continuous variation method.[15] Three transitions (MLCT) are permitted for the six coordinated nickel complex and the three bands at 900, 540 and 330 nm are displayed.[16] The formation of complex **7** is followed by the appearance of bands at $\lambda_{max}=327$ nm ($\varepsilon=34\,000$ dm^3 mol^{-1} cm^{-1}) and $\lambda_{max}=314$ nm ($\varepsilon=44\,800$ dm^3 mol^{-1} cm^{-1}) (Fig. 1a). Fig. 1b presents the evolution of

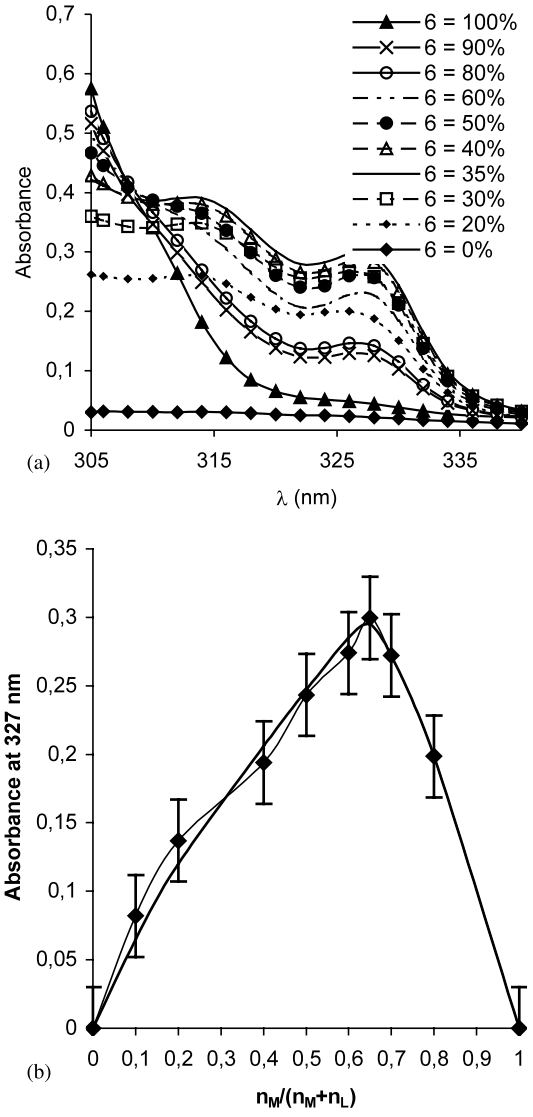

Figure 1. (a) UV spectra of the complexation of Ni(II) and the ligand **6** (2.5×10^{-5} M) in CH_2Cl_2/EtOH (1/1). (b) Measurement of the variation of the absorption maximum at 327 nm as a function of the molar ratio $n_M/(n_M+n_L)$ according to the continuous variation method. The stoichiometry is M_2L (the maximum obtained is at 0.65).

the absorbance of metal:ligand mixtures versus the ratio $n_M/(n_M+n_L)$. Analysis of the absorptions at 327 and 314 nm yields a stoichiometry 0.65 in accordance with octahedral geometry around Ni(II) i.e. [$(Ni(NO_3)_2)_2$ (ttpy-calix)]. Similar experiments were carried out with hydrated copper nitrate ($Cu(NO_3)_2$, 2.5 H_2O).[15] The UV spectra are given in Fig. 2a. The bands situated at $\lambda_{max}=314$ nm ($\varepsilon=40\,000$ dm^3 mol^{-1} cm^{-1}) and $\lambda_{max}=325$ nm ($\varepsilon=40\,000$ dm^3 mol^{-1} cm^{-1}) correspond to the $\sigma_L\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions centred on the ligand. The formation of complex **8** is followed by the decreasing of the intensity of these bands as soon as the stoichiometry (0.65) of the mixture is exceeded. The studies of Ni(II) and Cu(II) complexation by UV show the existence of M_2L-type complexes and allow the determination of stability constants of, respectively: Log $K_{21}=13.4$ and 12.8. In the case of the formation of complex **9**, the concentration of cobalt ($CoCl_2$) and ligand **6** is 5×10^{-4} M.[15] The formation of the two entities is characterised by the appearance of two isobestic points at 550 and 668 nm. Three species are present in solution, in equilibrium, as free $CoCl_2$, a tetrahedral complex and an octahedral complex. Analysis of the absorption at 450 nm indicates an M_2L stoichiometry in accordance with the molar ratio of 0.5 whereas the same follow-up at 693 nm gives an M_4L stoichiometry with the molar ratio of 0.25. With $CoCl_2$, in solution we have revealed the existence of an equilibrium between the M_2L and M_4L type complexes where chlorine intervenes in the coordination.

The use of terpyridine and of calixarene group is a good way of obtaining structures by the complexation of metal cations. We have shown that the pre-organisation of the calixarene ligand around metal illustrates its

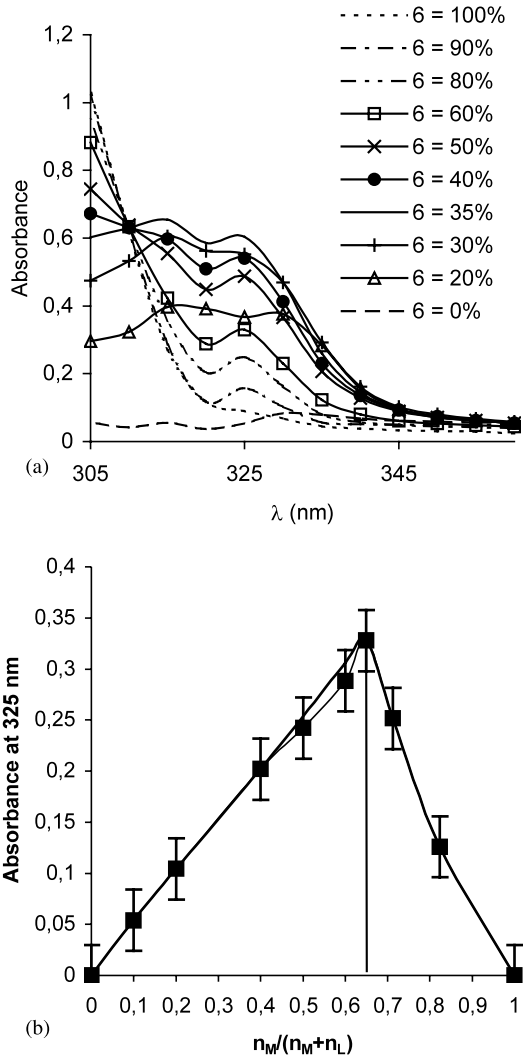

Figure 2. (a) UV spectra of the complexation of $Cu(NO_3)_2$, $2.5H_2O$ and the ligand **6** (5.1×10^{-5} M) in CH_2Cl_2/EtOH (1/1). (b) Measurement of the variation of the absorption maximum at 325 nm as a function of the molar ratio $n_M/(n_M+n_L)$ according to the continuous variation method. The stoichiometry of the complex is M_2L [(ttpy-calix)$(Cu(NO_3)_2)_2$].

aptitude to gather and to form new supramolecular edifices by intermolecular interaction.

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12. **4′-(2-Aminoethoxy)-2,2′/6,2″-terpyridine 5**. mp 136°C, ^{1}H NMR ($CDCl_{3,\ 300\ MHz}$) δ (ppm) 3.16 (t, 2H, CH_2), 4.26 (t, 2H, CH_2), 7.33 (m, 2H, H_5+$H_{5''}$tpy), 7.85 (dt, 2H, H_4+$H_{4''}$tpy), 8.03 (s, 2H, $H_{3'}$+$H_{5'}$tpy), 8.62 (d, 2H, H_3+$H_{3''}$tpy), 8.68 (d, 2H, H_6+$H_{6''}$tpy); ES MS (+) m/z: $[M]^+$ 293, $[M+Na]^+$ 315; Anal. calcd for $C_{15}H_{16}ON_4$: C, 69.85; H, 5.52; N, 19.16. Found: C, 70.07; H, 5.27, N, 18.67.
13. **5,11,17,23-Tetra-(*tert*-butyl)-25,26,27,28-tetrakis[*N*-(4′-ethoxy-2,2′/6′,2″terpyridinyl)amido-methoxy] calix[4]arene 6.** Yield 55%. mp 176°C; IR (KBr disc) ν_{max} (cm^{-1}) 1406–1600 (C=C, C=N stretches); 1669 (amide C=O stretch)); 3317 (NH); UV λ_{max} (CH_2Cl_2/C_2H_5OH) 278.5 nm (ε=46 300); ^{1}H NMR ($CDCl_{3,\ 500MHz}$) δ (ppm) 0.98 (s, 36H, *tert*-butyl-CH_3), 3.20 (d, ^2J=13.2 Hz, 4H, Ar-CH_2-Ar_{eq}), 3.83 (m, 8H, N-CH_2), 4.28 (t, 8H, ^3J=5.15, O-CH_2-CH_2), 4.51 (d, ^2J=13.2 Hz, 4H, Ar-CH_2-Ar_{ax}), 4.67 (s, 8H, O-CH_2), 6.69 (s, 8H, H-Ar), 7.21 (m, 8H, H_5+$H_{5''tpy}$), 7.72 (dt, 8H, H_4+$H_{4''tpy}$), 7.88 (s, 8H, $H_{3'}$+$H_{5'tpy}$), 8.20 (t, J=5.88, 4H, -CO-NH, 8.46 (d, J=7.72, 8H, H_3+$H_{3''tpy}$), 8.56 (d, J=4.46, 8H, H_6+$H_{6''tpy}$); ^{13}C NMR ($CDCl_3$) δ: 31.65 (*tert*-butyl-CH$_3$), 31.90 (ArCH$_2$Ar), 34.18 (*tert*-butyl-C-CH$_3$s), 39.275 (CH$_2$-NH), 67.23 (O-CH$_{2tpy}$), 74.84 (O-CH$_2$), 107.74 ($C_{3'}$+$C_{5'tpy}$), 121.61 (C_5+$C_{5''tpy}$), 124.09 (C_3/C_5-Ar), 126.13 (C_4+$C_{4''tpy}$), 133.12 (C_2/C_6-Ar), 136.98 (C_3+$C_{3''tpy}$), 145.94 (C_4-Ar), 149.33 (C_6+$C_{6''tpy}$), 149.86 (C_1-Ar), 156.22 (C_2+$C_{2''tpy}$), 157.34 ($C_{2'}$+$C_{6'tpy}$), 167.07 ($C_{4'tpy}$), 170.65 (-CONH-); ES MS (+) m/z: $[M+K]^+$ 2017, $[M+Na]^+$ 2001, $[M+H]^+$ 1979, $[M+2Na]^{2+/2}$ 1012, $[M+H+K]^{2+/2}$ 1009, $[M+H+Na]^{2+/2}$ 1001, $[M+2H]^{2+/2}$ 990; Anal. calcd for $C_{120}H_{120}N_{16}O_{12}$+$H_2O$: C, 71.87; H, 6.03; N, 11.17. Found: C, 71.85; H; 6.03; N, 11.13.
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15. **Preparation of the solution of complexes 7, 8 and 9 for UV investigation:** *Y* ml (10-0 ml) of the Ni $(NO_3)_2$, $6H_2O$ in a CH_2Cl_2/EtOH (1/1) solution (2.5×10^{-5} M) or $Cu(NO_3)_2$, 2.5 H_2O solution (5.1×10^{-5} M) were added to the *X* ml (0–10 ml) of the solution of the ttpy-calix[4]arene **6** (2.5×10^{-5} M or 5.1×10^{-5} M). The formation of the complexes **7** and **8** is followed by UV. For the solution studies of the complex **9**, the cation concentration was constant. To this effect, small quantities (5 μl at a time) of parent solution of ligand **6** of 10^{-2} M concentration are added to the solution of $CoCl_2$ 5×10^{-4} M in CH_2Cl_2/EtOH (1/1).
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