An efficient metal-templated route to C-functionalised derivatives of [12]aneN_4

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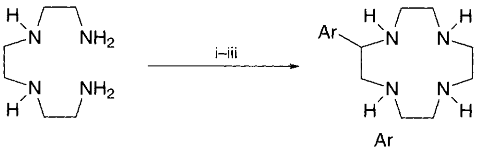
The cyclo cocondensation of triethylenetetramine with arylpyruvaldehydes is templated by iron(III) chloride, to give a [12]aneN_4 type diimine complex intermediate which may be reduced and demetallated *in situ* with sodium borohydride giving the saturated [12]aneN_4 metal-free macrocycle in up to 60% overall yields; photophysical studies are used to demonstrate the similarity between the aryl functionalised [12]aneN_4 derivatives formed by this route and analogues derived from [12]aneN_4 itself.

Octadentate ligands based on the saturated 1,4,7,10-tetraazacyclododecane ring skeleton form kinetically robust complexes with rare-earth and lanthanide ions which are finding applications in radiolabelled bioconjugates,[1,2] in contrast agents for magnetic resonance imaging[3,4] and as luminescent probes for biochemical analysis.[5,6] The synthesis of such twelve-membered tetraaza rings has tended to rely upon medium or high-dilution syntheses,[7] for example using tosylamide cycloalkylation methodology, as used in the preparation of a variety of C-alkylated [12]aneN_4 derivatives.[8–10] Larger-ring polyaza macrocyclic ligands may sometimes be conveniently prepared by metal-templated syntheses, as in the preparation of the [14]aneN_4 ligand 1,4,8,11-tetraazacyclotetradecane (cyclam) where a nickel(II) or copper(II) ion sits in the plane of the four nitrogens. With a small [12]aneN_4 macrocycle, no six- or four-coordinate metal is sufficiently small to form square-planar N_4 complexes and this has inhibited viable metal-templated [12]aneN_4 syntheses to date. However, triethylenetetramine (L^1) forms well defined *cis*-[$MLCl_2$] complexes with a variety of first-row transition-metal chlorides, and cyclo cocondensation reactions with 1,2-dicarbonyl compounds are feasible.[11] In pursuing short and versatile synthetic routes to aryl C-substituted [12]aneN_4 derivatives, such a strategy is attractive, particularly in light of the ease of preparation of arylglyoxals (SeO_2 oxidation of aryl methyl ketones) and the conjugative stabilisation imparted by the aryl group in the putative imine intermediate.

Reaction of phenylglyoxal in dry methanol with the *cis*-iron(III) dichloride complex [FeL^1Cl_2]Cl, (generated *in situ*) led to formation of a reddish brown diimine intermediate. Subsequent addition of excess sodium borohydride (10 equiv.) led to rapid formation of a pale yellow solution from which the cyclic tetraamine (L^2) was isolated in 60% yield following filtration of the crude product through a plug of basic alumina (Scheme 1). This 'one-pot' procedure has also been applied successfully in the synthesis of substituted phenyl (L^3, L^4), 3-phenanthryl (L^5) and 2-fluorenyl (L^6) derivatives, the precursor arylglyoxals for which were obtained by SeO_2 oxidation of the corresponding aryl methyl ketones. The efficiency of this procedure may be contrasted with the much more lengthy methods used in the reported syntheses of analogous C-linked ligands where at least six steps are involved and overall yields vary between 5 and 18%.[8–10] The advantage of using an iron(III) ion template is that borohydride reduction of the diimine intermediate also promotes reduction of the iron centre, and leads to efficient demetallation. Parallel reactions with the dichloro-nickel and -chromium complexes of L^1, led to the corresponding moisture-sensitive cyclic diimine intermediates, but after borohydride reduction the metal-free ligand proved much more difficult to isolate successfully.

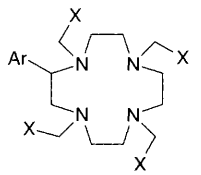


	Ar
L^2	Ph
L^3	*m*-C_6H_4CN
L^4	*m*-$C_6H_4NO_2$
L^5	3-phenanthryl
L_6	2-fluorenyl

Scheme 1 *Reagents and conditions*: i, $FeCl_3$, MeOH, 20 °C; ii, ArCOCHO; iii, $NaBH_4$, MeOH

The C-linked [12]aneN_4 ligands (L^2–L^6) could be transformed into the corresponding tetraacetate (H_4dota derivatives†) or tetramethylphosphinate derivatives following reaction with $ClCH_2CO_2^-$ (pH 9.5, H_2O, 80 °C, 18 h), *e.g.* H_4L^7, or with $(CH_2O)_n$–$MeP(OEt)_2$–thf (4 Å sieves, 12 h), followed by acid hydrolysis (6 mol dm^{-3} HCl, 24 h) *e.g.* H_4L^8–H_4L^{10}.

Both the luminescence lifetime (Eu, Tb) and the NMR relaxivities (Gd) of [12]aneN_4 derived complexes are dependent on the number of bound inner-sphere water molecules.[2,3] These properties of the lanthanide complexes of H_4L^7 and H_4L^8 have been investigated to ensure that such C-aryl substituted [12]aneN_4 derivatives exhibit similar properties to analogous compounds such as H_4dota and the methylphosphinate derivative, H_4L^{11}. The number of bound water molecules, *q*, can be established by comparison of the luminescence lifetimes of the complexes in H_2O and D_2O.[12] The results of these experiments are summarised in Table 1 along with comparative data for related complexes. The values of *q* for the Eu and Tb complexes of H_4L^7 are very similar to those of analogous complexes of H_4dota.[13] For both complexes, the overall quantum yields for



	Ar	X
H_4L^7	Ph	CO_2H
H_4L^8	3-phenanthryl	$PMeO_2H$
H_4L^9	*m*-$C_6H_4NO_2$	$PMeO_2H$
H_4L^{10}	2-fluorenyl	$PMeO_2H$
H_4L^{11}	H	$PMeO_2H$

Table 1 Excited-state lifetimes[a] and hydration states, *q*, of europium and terbium complexes (293 K, H_2O, pH 5.5)

	τ_{H_2O}/ms	τ_{D_2O}/ms	*q*
[Eu(dota)]$^-$ [13]	0.64	2.44	1.2
[Tb(dota)]$^-$ [13]	1.4	2.03	0.9
[EuL^{11}]$^-$ [13]	1.25	1.85	0.27
[EuL^7]$^-$	0.57	1.60	1.16
[TbL^7]$^-$	0.53	0.62	1.2
[EuL^8]$^-$	0.12, 0.57	0.11, 0.85	0.38

[a] The photophysical properties were investigated using a Perkin Elmer LS50B spectrofluorimeter. Uncertainties in lifetimes are ≤10%. Excitation was carried out at 250 nm, except for [EuL^8]$^-$ (λ_{ex} = 280 nm).

metal-based emission are low ($< 10^{-3}$, following excitation at 250 nm). For the europium complex this is due to competitive photoinduced electron transfer to the Eu centre, but for terbium the quantum yield is lower than expected.

By contrast, the excited state of the europium complex of H_4L^8 undergoes a decay which can be fitted only as a double exponential, while the excitation spectrum obtained by observing the terbium emission shows a broad band not observed in the absorption spectrum of the complex. A similar effect has been observed with an anthrylmonoamide triphosphinate complex.[13] The short-lived component of the luminescence is independent of solvent, while analysis of the solvent dependence of the longer lived component demonstrates that the q value is analogous to that of the [12]aneN$_4$ derived phosphinate H_4L^{11}, which has a similar binding site. The short-lived component has previously been attributed to a formally disallowed population of the anthryl T_1 state from the S_0 state prior to energy transfer to the metal. The terbium complex of H_4L^8 is different again, having a very short-lived emission whose intensity increases markedly on deoxygenation of the solution, consistent with back-energy transfer from the metal to the ligand triplet. Further studies on these systems using laser excitation spectroscopy are in progress.

The ease of synthesis of this family of aryl functionalised ligands,‡ notwithstanding their racemic nature,§ augurs well for the study of conjugates involving them.

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Footnotes

† H_4dota = 1,4,7,10-tetraazacyclododecane tetraacetic acid.

‡ *Selected data.* **2**: m/z (ES$^+$) 249 (M$^+$ + 1); δ_H (CDCl$_3$) 1.9 (4 H, br s, NH), 1.97 (1 H, t, J 10.6, H-3′) 2.09 (1 H, dt, J 11.2, 3.3 Hz, H-12), 2.44 (2 H, t, J 5.6 Hz, CHH′N), 2.60 (2 H, t, J 5.6 Hz, CHH′N), 2.65 (2 H, t, J 6.0 Hz, CHH″N), 2.73 (2 H, t, J 6.0 Hz, CHH″N), 2.80 (1 H, t, J 11.0 Hz), 2.81 (1 H, t, J 10.6 Hz, H-3), 2.94 (1 H, dt, J 11.2, 2.8 Hz, H-12′), 2.99 (1 H, br t, J 11.0, 2.8 Hz), 3.77 (1 H, dd, J 10.6, 2.0 Hz, H-2), 7.17 (1 H, t, J 7.2), 7.24 (2 H, t, J 7.4), 7.30 (2 H, d, J 7.4); δ_C (CDCl$_3$) 41.44, 45.99, 46.02, 52.93, 53.17, 57.99(CH$_2$N), 60.15 (CHN), 61.37 (C-2), 126.81 (m-aryl), 127.28 (p-aryl), 128.19, 142.32(s). **8**: m/z (ES$^-$) 831 (M − 1), 854 (M + Na); δ_P (CDCl$_3$) 52.6 (m).

§ Resolution of the chiral tetraamine using tartaric acid and its derivatives is in progress.

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