SHORT COMMUNICATION

Reaction of *ortho*-Methylbenzonitrile with Lithium *N*,*N*,*N*′-Trimethylethylenediamide: Assembly and Crystal Structure of a Primary Isoquinolinoamidolithium–Secondary Amine Complex

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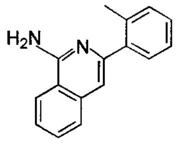
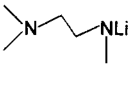
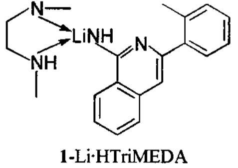
The product of reaction between *ortho*-methylbenzonitrile (*o*-MeC$_6$H$_4$CN) and lithium *N*,*N*,*N*′-trimethylethylenediamide [LiN(Me)(CH$_2$)$_2$NMe$_2$], the 1:1 complex 1-lithioamido-3-(2-methylphenyl)isoquinoline–*N*,*N*,*N*′-trimethylethylenediamine (**1**-Li·HTriMEDA), has a solid-state structure which shows a new type of (NCNLi)$_2$ core and a solution structure in which the coordination mode of the diamine by-product varies with temperature.

The reactions of organolithium reagents with benzonitrile have long been known to induce cyclotrimerisation[1] to yield, amongst other products, fully unsaturated 2,4,6-triphenyl-1,3,5-triazine[2] by 1,4-elimination of organolithium from a lithio-1,4-dihydrotriazine precursor. More recently, we reported a nitrile addition product, an imidolithium species of the type which probably acts as an initial intermediate in the cyclisation reaction[3]. Given this latter result, we sought to investigate the reactions of organolithium reagents with *ortho*-methylbenzonitrile, for which addition across the nitrile triple bond is known to be in competition with *ortho* lithiation[4]. It has also been reported[5] for this system that a nitrile self-condensation product, a substituted 1-aminoisoquinoline (**1**-H), can result in various yields (2−80%) depending on the organolithium reagent employed and on the reaction conditions.


1-H


LiTriMEDA


1-Li·HTriMEDA

The reaction of lithium *N*,*N*,*N*′-trimethylethylenediamide (LiTriMEDA) with *o*-methylbenzonitrile in toluene at −78 °C affords a red solution which becomes yellow at room temperature. Addition of hexane and storage at ambient temperature overnight yields orange crystals identified as the 1:1 complex, 1-lithioamido-3-(2-methylphenyl)isoquinoline−*N*,*N*,*N*′-trimethylethylenediamine (**1**-Li·HTriMEDA). X-ray crystallography shows that in the solid state **1**-Li·HTriMEDA is a transoid dimer (Figure 1), in which the primary amidolithium centre[6] in the self-assembled 1-lithioamidoisoquinolino moiety is chelated by the concomitantly formed secondary amine. This dimer demonstrates several unusual structural features. At first sight it appears to incorporate a straightforward four-membered Li(1)−N(2)−Li(1A)−N(2A) ring at its core, with further stabilisation of the metal being afforded by isoquinoline N centre donation to lithium. However, closer inspection reveals that, within the supposed four-membered ring, two of the N−Li distances are short [Li(1A)−N(2) 2.055(6) A] while the other two are unusually long [Li(1)−N(2) 2.394(7) A]. It seems, therefore, to be the relatively short (isoquinoline)N−Li interactions [N(1)−Li(1) 2.081(6) A] which are mainly responsible for dimerisation. Consequently, the central unit of the structure is best viewed as being an eight-membered [(isoquinoline)N−C−(amido)N−Li]$_2$ ring resulting from inter-monomer (isoquinoline)N−Li interactions, with very weak (amido)N−Li cross-ring interactions. A search of the Cambridge Crystallographic Database locates only two examples of eight-membered (NCNLi)$_2$ rings[7], neither of which shows any cross-ring interactions whatsoever. Thus the structure of **1**-Li·HTriMEDA, containing as it does partial cross-ring contacts, is unique. The coordination sphere of each metal centre is completed by chelation of the HTriMEDA ligands which, unusually, have also been formed during the reaction. While at 2.130(7) A the Li(1)−N(4) bond is of a length normal for such an interaction, the Li(1)−N(3) bond is, at 2.358(7) A, surprisingly long. Alkali metal complexes containing protic amine bases are not common, and those which are known have generally been synthesised by allowing an organolithium compound to react with an excess of amine[8], by having the amine ligand present in a 1:1 reaction between a lithiating agent and a (more acidic) organic substrate, or by adding the amine after the lithiation reaction

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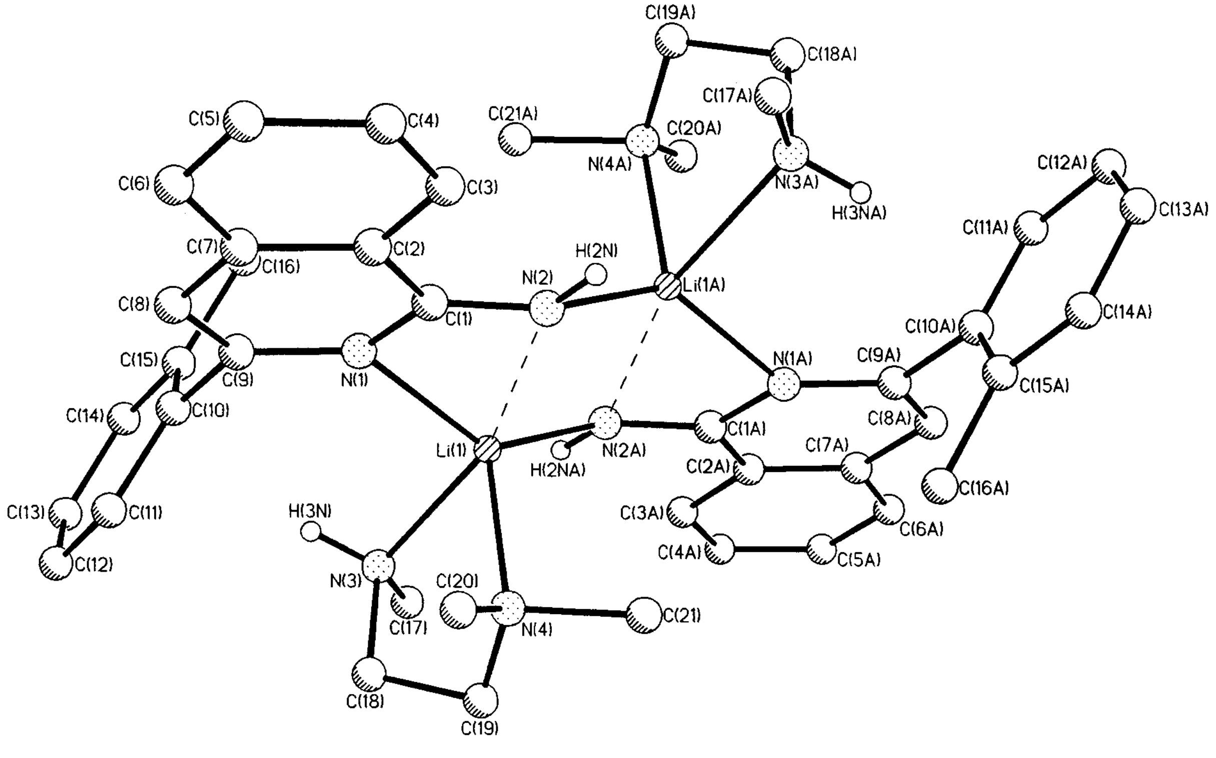
is complete. Indeed, the last method has been used to give enolatolithium and amidolithium complexes containing HTriMEDA itself[9]. In both of these cases diamine chelation of the metal centre was accompanied by a hydrogen bonding interaction involving the acidic proton of HTriMEDA. While in $[H_2C{=}C(NMe_2)OLi{\cdot}HTriMEDA]_2$ the interaction was directed towards the enamine N-centre, in $[H_2C{=}C(t\text{Bu})OLi{\cdot}HTriMEDA]_2$ it was directed towards the enolato π system [N−H···C distances 2.62 and 2.73 A]. This last structural feature pinpoints a final interesting facet of the structure of **1**-Li·HTriMEDA in that here a somewhat analogous, but rather stronger, interaction is observed. The N(3)−H(3N) bond points approximately at the *centre* of the 3-(2-methylphenyl) ring [H(3N)···ring centroid 2.440 A, N(3)−H(3N)−ring centroid 172.3°]. This interaction appears to account for the massive N(1)C(9)C(10)C(11) torsional angle of 114.3°. However, it is also noticeable that in $[H_2C{=}C(t\text{Bu})OLi{\cdot}HTriMEDA]_2$, where the hydrogen bonding interaction is somewhat weaker than in **1**-Li·HTriMEDA, bonds between the lithium centre and the chelating diamine are essentially equivalent and, at 2.11(1) and 2.09(1) A[9], of lengths typical for such interactions. It seems, therefore, that the relative strength of the hydrogen bond in **1**-Li·HTriMEDA is the most likely reason for the surprising length of the Li(1)−N(3) interaction.

o-methylbenzonitrile in THF/HMPA [HMPA = $O{=}P(NMe_2)_3$] at −78 °C afforded predominantly *o*-lithiomethylbenzonitrile, **1**-H was best synthesised by the 1:1 reaction of Me_2NLi with the nitrile in THF/HMPA at −78 °C, subsequent addition of a second equivalent of nitrile and heating at 60 °C for 1 hour resulting, after work-up, in the high yield formation (80%) of **1**-H. In this current work, a 2:2 reaction of LiTriMEDA with *o*-methylbenzonitrile affords **1**-Li·HTriMEDA, the immediate precursor to **1**-H, essentially quantitatively (first batch yield of crystals 90%, with respect to nitrile) in non-donor media (toluene) at ambient or sub-ambient temperature. The yield of the complex, with respect to nitrile, is unaffected if the correct stoichiometry (2:1 nitrile/LiTriMEDA) is used. It is logical, therefore, that the initial 1:1 reaction, which yields either an imidolithium (**2a**, which rapidly isomerises to *o*-lithiated imine **2b**) or, more probably, a complexed *o*-lithiated nitrile (**2c**) (Scheme 1) is *slow* relative to subsequent insertion of the second equivalent of *o*-methylbenzonitrile (yielding **3b/c**). Presumably ring closure by **3b/c** yields **4b/c** which, in turn, gives the title complex via a simple rearrangement (accompanied by elimination of HTriMEDA in the case of **4b**). It is presently impossible to say whether the first stage of the reaction is addition/isomerisation or *o*-lithiation, although it has been observed that in the presence of benzonitrile, LiTriMEDA readily gives an extremely stable addition product[3].

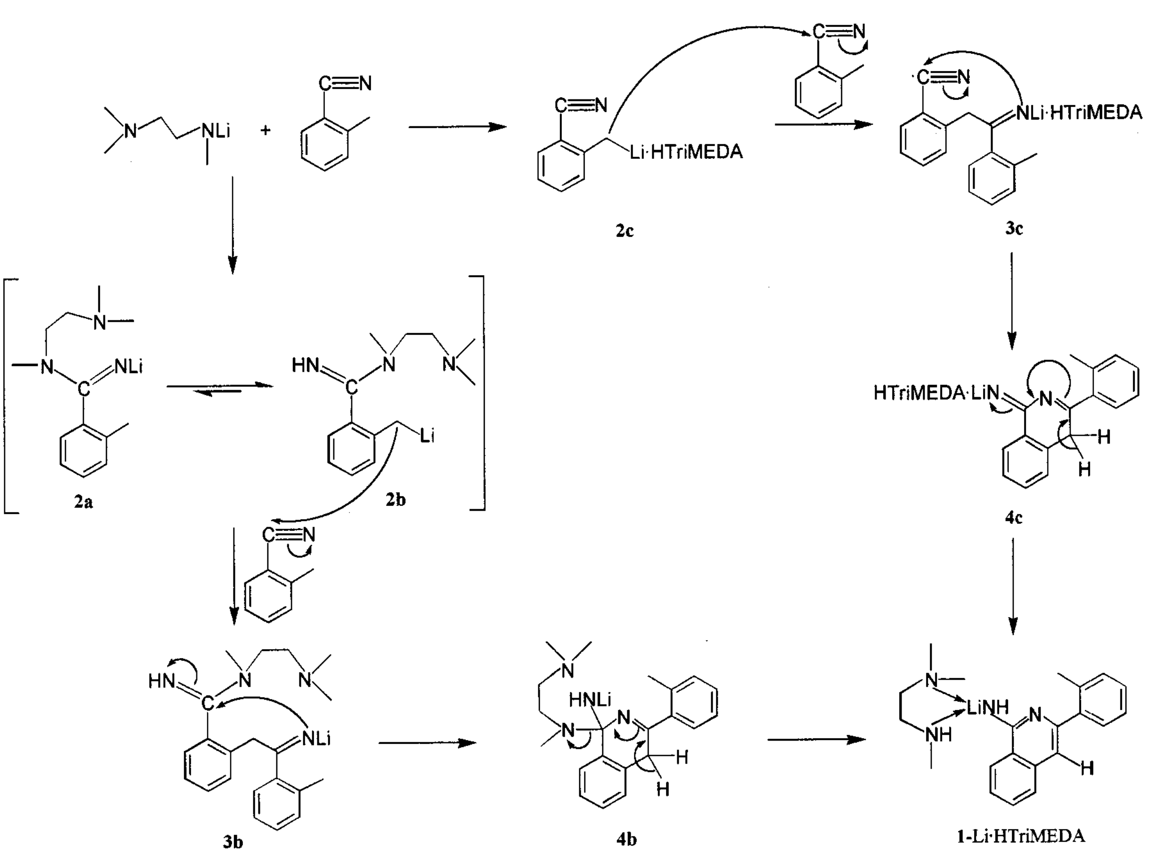
Figure 1. Structure of dimeric **1**-Li·HTriMEDA; hydrogen atoms (except the primary amidolithium and secondary amine hydrogen atoms) have been omitted for clarity; the symmetry operation which relates original atoms to their "A" equivalents is −*x* + 1, −*y* + 1, −*z* +1



Although the self-condensation reaction of two equivalents of *o*-methylbenzonitrile in the presence of one equivalent of certain lithium reagents has been reported earlier[5], no lithiated intermediates have been isolated previously. Given the finding[4] that the reaction of Me_2NLi with

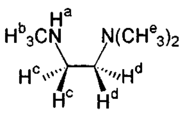
A solution of **1**-Li·HTriMEDA (12.0 mg ml^{-1} in [D$_6$]benzene) yields a ^{1}H-NMR spectrum in which, unusually, extensive coupling is observed through the secondary amine

Scheme 1



N centre. Consequently, therefore, the $H_3C(H)NCH_2$ triplet at δ = 2.46 ($^3J_{H\text{-}(C)H}$ = 5.46 Hz) is split into two ($^3J_{H\text{-}(N)H}$ = 6.64 Hz) and the $H_3C(H)N$ resonance at δ = 2.26 is a doublet ($^3J_{H\text{-}(N)H}$ = 6.43 Hz); irradiation of the $H_3C(H)N$ multiplet at δ = 0.93 causes these signals to appear as a triplet and singlet respectively. At the same concentration, ^{1}H-NMR spectroscopy in [D$_8$]toluene indicates that as a function of temperature there is a significant change in the behaviour of the HTriMEDA with respect to the metal centre. It appears either to change from (i) free base to mono- or bidentate coordinated ligand or (ii) monodentate ligand to bidentate chelate of the lithium centre. This is suggested by the observation that while at 60°C the HTriMEDA methylene protons bonded to either N centre (Table 1, H^c and H^d) demonstrate chemical shifts downfield of the (same species) *N*-methyl protons (H^b and H^e) bonded to *the same N-centre* [i. e. $\delta(H^c) > \delta(H^b)$ and $\delta(H^d) > \delta(H^e)$], as the temperature is lowered so the former protons drift to positions *upfield* relative to their methyl counterparts [i. e. $\delta(H^b) > \delta(H^c)$ and $\delta(H^e) > \delta(H^d)$]. This observation is consistent with the known behaviour of free and complexed TMEDA $[(H_3C)_2N(CH_2)_2N(CH_3)_2]$[10], and indeed a comparison of the spectra of **1**-Li·HTriMEDA with those of pure HTriMEDA in toluene suggests that it is only in the range 25−60°C that the base is essentially free. Moreover, extensive coordination of the metal centres by HTriMEDA at low temperature is suggested by variable-temperature ^{7}Li-NMR spectroscopy. In toluene the dominant lithium

Table 1. ^{1}H-NMR data for the secondary amine ligand in **1**-Li·HTriMEDA in [D$_8$]toluene over the range 60°C to −80°C; (−) indicates that the signal was not observable at that temperature; the H^a signal was obscured by that of H^e at low temperature while those of H^b and H^c were obscured by the [D$_8$]toluene resonance



Temp. [°C]	δ [ppm] H^a	H^b	H^c	H^d	H^e
60	0.84	2.26	2.46	2.20	2.03
40	0.91	2.25	2.42	2.18	2.01
25	1.10	2.17	2.29	2.03	1.93
0	1.41	−	−	1.87	1.84
−25	−	−	2.05	1.72	1.76
−50	−	−	1.95	1.61	1.71
−80	−	−	1.90	1.48	1.65

Table 2. Cryoscopic data for **1**-Li·HTriMEDA in benzene over the concentration range 2.0−15.4 mg ml^{-1}

Conc. [mg ml^{-1}]	Av. mol. mass (±5)	*n* (±0.1)
2.0	274	0.8
3.9	305	0.9
7.0	349	1.0
10.3	386	1.1
15.4	413	1.2

environment moves from δ = 1.79 (at 60°C) to δ = 1.43 (at 25°C) to δ = 0.90 (at 0°C) and finally to δ = 0.53 (at −80°C). Clarification comes from cryoscopy in benzene. Results suggest (Table 2) that whereas at low concentration (2.0 mg ml^{-1}) HTriMEDA is ostensibly free in solution, at higher concentrations (ca. 10−15 mg ml^{-1}) the secondary amine and metal centre interact. This clearly suggests, given the evidence from NMR spectroscopy, that at these higher concentrations **1**-Li·HTriMEDA dissolves in non-donor solvents to give a species in which, at or about cryoscopy temperature (5°C), the secondary amine acts as a *monodentate* ligand, probably [judging from the relative Li(1)−N(3) and Li(1)−N(4) distances observed in the solid-state structure] through its $(H_3C)_2N$ centre, and as a *bidentate* one only at much lower temperatures.

The reaction of LiTriMEDA with *o*-methylbenzonitrile clearly demonstrates the significant effect of ring substituents on the chemistry of benzonitriles. The observed condensation reaction is enabled by the contrasting behaviour of LiTriMEDA as either a nucleophile (with benzonitrile)[3] or a base (with *o*-methylbenzontrile)[4], the isolated complex, **1**-Li·HTriMEDA, demonstrating a variety of interesting features in both the solid state and in non-polar solution.

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Experimental Section

General: All operations were carried out using standard inert-atmosphere Schlenk techniques with a dual nitrogen/vacuum line. Schlenk tubes were pre-dried at 180°C prior to evacuation to less than 0.1 Torr three times, being filled with dry nitrogen from the house supply between each evacuation. *N,N,N′*-Trimethylethylenediamine and *o*-methylbenzonitrile were used as received from Aldrich Chemical Company and stored over 4 A molecular seive. Toluene (freshly distilled and maintained at reflux over sodium), hexane (freshly distilled and maintained at reflux over sodium-potassium amalgam) and *n*-butyllithium were added directly to the nitrogen-filled Schlenk tube using standard syringe techniques. − NMR spectroscopy: Bruker AM 400 and DRX 400 (400.137 MHz and 155.508 MHz, for ^1H and ^7Li, respectively). For ^1H-NMR spectroscopy, [D_6]benzene and [D_8]toluene as solvents, TMS at 25°C as external standard; for ^7Li-NMR spectroscopy, [D_6]benzene and [D_8]toluene as solvents, PhLi in [D_6]benzene and [D_8]toluene respectively at 25°C as external standards.

N,N,N′-Trimethylethylenediamine (HTriMEDA): ^1H NMR (60°C, 3.6 mg ml^{-1} in [D_8]toluene): δ = 2.52 [t, 2 H, $H_3C(H)NCH_2$, $^3J_{H\text{-}(C)H}$ = 6.01 Hz], 2.32 [s, 3 H, $H_3C(H)N$], 2.27 [t, 2 H, $CH_2N(CH_3)_2$, $^3J_{H\text{-}(C)H}$ = 6.01 Hz], 2.07 [s, 6 H, $N(CH_3)_2$], 0.88 [s, br., 1 H, $H_3C(H)N$]. Spectra at 60, 40, 25, 0, −25, −50, and −80°C showed no significant variation.

1-Lithioamido-3-(2-methylphenyl)isoquinoline−N,N,N′-trimethylethylenediamine (**1**-Li·HTriMEDA): *n*-Butyllithium (1.88 ml, 1.6 M in hexanes, 3.0 mmol) was added to *N,N,N′*-trimethylethylenediamine (0.38 ml, 3.0 mmol) in toluene (2 ml) at −78°C under nitrogen. After stirring for 15 min, *o*-methylbenzonitrile (0.36 ml, 3.0 mmol) was added and the resultant red solution was stirred for a further 15 min at −78°C. Warming to room temp. gave a yellow solution, to which hexane (1 ml) was added. Storage overnight at room temp. afforded orange crystals of **1**-Li·HTriMEDA, yield 90% (with respect to nitrile), m.p. > 300°C. − $C_{21}H_{27}LiN_4$ (342.41): calcd. C 73.68, H 7.89, Li 2.05, N 16.37; found C 73.06, H 7.97, Li 2.00, N 16.07. − ^1H NMR (60°C, 12.0 mg ml^{-1} in [D_6]benzene): δ = 7.50 (d, 1 H, Ar, $^3J_{HH}$ = 8.16 Hz), 7.38 (d, 1 H, Ar, $^3J_{HH}$ = 7.69 Hz), 7.32 (dd, 1 H, Ar, $^3J_{HH}$ = 6.92, 5.94 Hz), 7.14 (dd, 1 H, Ar), 7.07 (br., 1 H, Ar), 6.93 (br., dd, 1 H, Ar), 6.85 (d, 1 H, Ar, $^3J_{HH}$ = 6.66 Hz), 6.69 (br., 1 H, Ar), 6.43 (s, 1 H, Ar), 4.71 (s, br., 1 H, NHLi), 2.46 (dt, 2 H, $H_3C(H)NCH_2$, $^3J_{H\text{-}(C)H}$ = 5.46 Hz, $^3J_{H\text{-}(N)H}$ = 6.64 Hz), 2.26 [d, 3 H, $H_3C(H)N$, $^3J_{H\text{-}(N)H}$ = 6.43 Hz], 2.21 [t, 2 H, $CH_2N(CH_3)_2$, $^3J_{H\text{-}(C)H}$ = 5.97 Hz], 2.03 [s, 6 H, $N(CH_3)_2$], 1.99 (s, br., 3 H, $ArCH_3$), 0.93 [m, br., 1 H, $H_3C(H)N$]. − ^7Li NMR (25°C, 12 mg ml^{-1} in [D_6]benzene): δ = 1.69 (s, 1 Li), 1.38 (s, ca. 13 Li). − ^7Li NMR (25°C, 12 mg ml^{-1} in [D_8]toluene): δ = 1.86 (s, 1 Li), 1.43 (s, ca. 14 Li); (0°C): δ = 1.81 (s, 1 Li), 0.90 (s, ca. 18 Li); (−25°C): δ = 0.78 (s); (−50°C): δ = 0.55 (s); (−80°C): δ = 0.69 (s, 1 Li), 0.53 (s, ca. 11 Li).

X-ray Crystallographic Study of **1**-Li·HTriMEDA: $C_{21}H_{27}LiN_4$, triclinic, space group $P1$, a = 10.093(2), b = 11.523(4), c = 8.700(2) A, α = 93.28(2), β = 100.050(10), γ = 96.97(2)°, V = 985.7(5) A^3, M_r = 342.41, Z = 2, D_c = 1.154 Mg m^{-3}, μ(Mo-K_α) = 0.069 mm^{-1}, $F(000)$ = 368. Data were collected by the ω/2θ scan method on a Rigaku AKC5R four-circle diffractometer at 150(2) K using graphite-monochromated Mo-K_α radiation (λ = 0.71069 A) in the range 5.10 < 2θ < 50.00°, $+h$, $\pm k$, $\pm l$; 3691 reflections of which 3474 were independent (R_{int} = 0.0391) and used in all calculations. The structure was solved using direct methods[11] and subsequent Fourier difference syntheses and refined[12] by full-matrix least-squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. H(2N), H(2NA), H(3N) and H(3NA) were located from the Fourier difference map and their coordinates and isotropic temperature factors were allowed to refine. All other hydrogen atoms were placed in geometrically idealised positions and refined using a riding model or as rigid methyl groups. Methylene groups in the HTriMEDA chelates were disordered over two positions. In the final cycles of refinement a weighting scheme of the form $w^{-1} = [\sigma^2(F_o^2) + (0.0840P)^2 + 0.63P]$, where $P = (F_o^2 + 2F_c^2)/3$, was employed which produced a flat analysis of variance. Final $R(F)$ = 0.0623 for 3462 reflections with $[I > 2\sigma(I)]$, $wR(F^2)$ = 0.1865 for all data; 277 parameters; goodness of fit = 1.165. Maximum peak and hole in final Fourier difference map 0.297 and −0.210 eA^{-3} respectively. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101025. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (int. code) + 44-1223/336-033, E-mail: deposit@ccdc.cam.ac.uk, www: http://www.ccdc.cam.ac.uk].

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