Reaction chemistry of tri-substituted mesitylene derivatives and the synthesis of sterically buttressed 1,3,5-triaminocyclohexyl ligands

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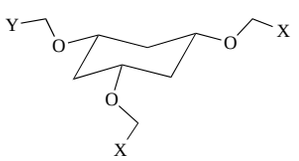
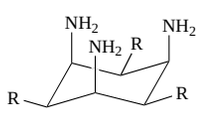
The sterically buttressed triamine *cis,cis*-2,4,6-trimethyl-1,3,5-triaminocyclohexane is weakly basic in aqueous solution (pK_a: 7.83, 6.73, 5.15; 298 K) because of steric inhibition to solvation. As a result of intramolecular hydrogen-bonding and stabilising σ_{C-H}–σ^*_{C-N} interactions, the free amine and its monoprotonated salt adopt a conformation in which the three amino groups are axially disposed. It possesses a reduced reactivity in S_N2 reactions and may be converted *via* selective alkylation or condensation to polydentate ligands incorporating carboxylate, hydroxyphenyl or phosphinate groups. An intramolecular hydride transfer mechanism accounts for the formation of a stable bicyclic amidine formed during acidic hydrolysis of a tricyclic bis-aminal derived from the parent triamine by a phosphinoxymethylation. The crystal structures of two of the mesitylene derivatives have been determined.

Ligands that are based on a *cis,cis*-1,3,5-trioxy- or -triaminocyclohexyl moiety have been studied as facially coordinating molecules for the complexation of relatively small metal ions.[1–4] Complexing agents which engender 6-ring chelate-rings on metal binding prefer to bind to metals with low coordination numbers (*e.g.* 4, 5 and 6) in complexes that possess relatively short M–X bond lengths and relatively large X–M–X bond angles.[5] Thus the hexacoordinating trioxytriamide **1a** binds

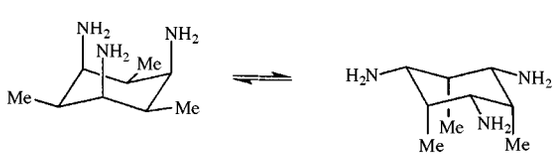


1a X = Y = $CONBu_2$
b X = $CONBu_2$, Y = *n*-Pr



2a R = Me
b R = H
c R = OH

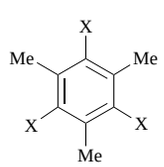
sodium preferentially with respect to the larger potassium ion (Na/K selectivity is $10^{3.1}$)[1] while the pentacoordinate analogue **1b** binds the small Li^+ ion preferentially over Na^+ (Li/Na selectivity is $10^{2.25}$). With ligands based on *cis,cis*-1,3,5-triaminocyclohexane, previous work has focused on complexes of the parent system **2b** and of tri-*N*-substituted ligands derived therefrom.[3,4a] More recently some attention has been paid to the coordination chemistry of ligands derived from 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol, **2c**.[4b,6] We were attracted by the related ligand **2a**, as a ligating sub-unit for study of its coordination properties. In this system, the three methyl groups may adopt equatorial positions in one limiting chair conformation and in the other limiting chair structure the amino-groups are placed equatorial (Scheme 1). In the triprotonated amine, this



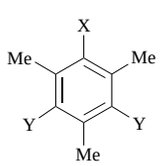
Scheme 1

conformer is preferred in order to minimise coulombic repulsion, and the X-ray structure of the trication $[H_3\mathbf{2a}]^{3+}$ confirms this preference.[7] The presence of the methyl groups in ligand **2a** exerts other effects: the steric buttressing of the alkyl groups for example may tend to inhibit ligand solvation. Although there is relatively little difference in the effective steric demand of a single methyl group compared to an amino group in polar media (*A*-values are 7.3 for Me and 7.1 for NH_2 in aqueous methoxyethanol),[8] the axial amino groups may be expected to undergo intramolecular H-bonding to alleviate lone-pair repulsion. These two effects should lead to the compound **2a** preferring the conformer with the amino groups axial. While ligands based on **2a** may not possess the same degree of conformational bias that is present in related *cis*-substituted cyclohexyl moieties, such as Kemp's tri-acid and its derivatives,[9] they may serve as useful platforms upon which to explore the coordination behaviour of sterically-buttressed ligands derived therefrom and the role of neighbouring group effects operating in such stereoelectronically well-defined systems.

A suitable precursor for the synthesis of such *cis*-substituted cyclohexyl ligands is trinitromesitylene[10] **3**. Reduction of the nitro groups affords the triamine **4** which may be reduced under



3 X = NO_2
4 X = NH_2
5a X = NCHPh
b X = $NHCH_2Ph$



6 X = NO_2, Y = NH_2
7a X = NO_2, Y = NCHPh
b X = NO_2, Y = $NHCH_2Ph$
c X = NH_2, Y = $NHCH_2Ph$

stereocontrolled hydrogenation catalysis to the desired *cis,cis*-triamine **2a**. The sterically hindered aromatic triamine **4** and congeners such as **6** are themselves potentially interesting precursors in the synthesis of dendrimer architectures: the buttressing methyl groups force the *N*-substituted amine lone-pairs out of conjugation enhancing nucleophilicity but inhibiting poly-*N*-substitution.

We report the synthesis of **2a** and of dibasic N_3O_2 and tribasic N_3O_3 ligands, including carboxy, phenoxy and phosphinoxy derivatives in addition to some simple reaction chemistry based on the aromatic nitro and amino-derivatives. Aspects of this work have appeared in a preliminary communication.[7]

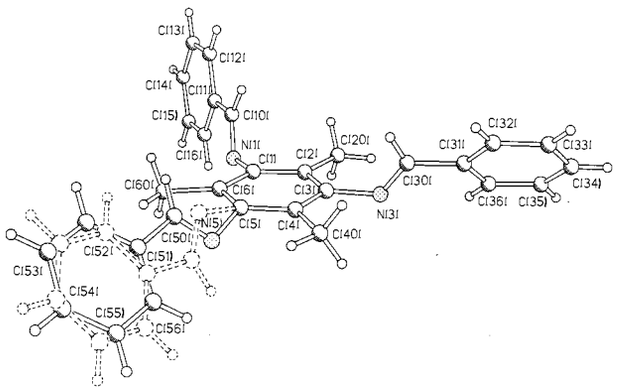


Fig. 1 Molecular structure of **5a** in the crystal, showing positions A (solid) and B (dashed) of the disordered N=CHPh group. C=N bonds are not conjugated with the central benzene ring, torsion angles around the C(1)–N(1), C(3)–N(3), C(1)–N(5A), C(1)–N(5B) bonds being 76, 74, 61 and 65°, respectively.

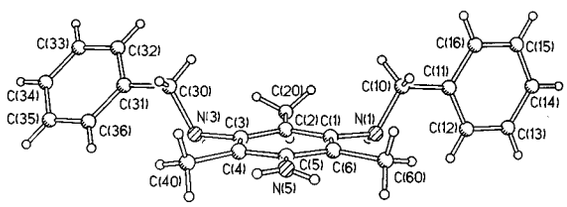


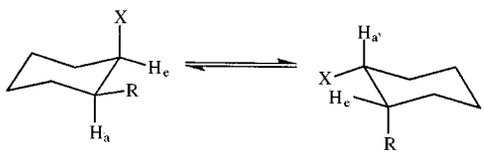
Fig. 2 Molecular structure of **7c** in the crystal. The bond geometry at N(1) and N(3) atoms is pyramidal, at N(5) nearly planar [sums of bond angles 332(3), 334(3) and 358(5)°, respectively]; the latter plane is inclined by 6(2)° to the central benzene ring. The lone pairs at N(1) and N(3) form angles of 49 and 51° with the p_π orbitals of C(1) and C(2). Bond distances C(1)–N(1) 1.439(3), C(3)–N(3) 1.437(3), C(5)–N(5) 1.406(3) Å.

Synthesis and characterisation

Reduction of trinitromesitylene **3** with sodium borohydride in the presence of copper(II) acetate in aqueous ethanol afforded the triamine **4** in a yield of 80%. Condensation of **4** directly with benzaldehyde under reduced pressure gave the yellow triimine **5a** and an X-ray crystallographic analysis of this molecule revealed that the imine double bonds were almost orthogonal to the plane of the aromatic ring (Fig. 1). Hydrogenation of **5a** did not proceed at ambient temperature or pressure using Pd on C catalysts but over Pt/C in ethanol at 3 atmospheres and 20 °C, reduction proceeded cleanly allowing the isolation of the tri-*N*-benzylamine **5b**. The reduction of **3** could also be carried out with this Pt/C catalyst giving **4** in 99% yield after a reaction time of 3 days. When **3** was allowed to react under these conditions for only 1 hour, the partially reduced diamine **6** was obtained in 47% yield following crystallisation from ethanol. Condensation of **6** with neat benzaldehyde gave the imine **7a** and subsequent borohydride reduction yielded the diamine **7b**. A crystallographic analysis of the derived amine **7c** revealed that only the *N*-substituted amine lone-pairs were substantially out of conjugation with the aryl π molecular orbitals (Fig. 2).

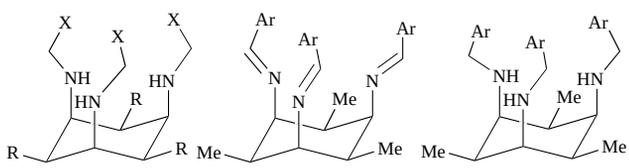
Catalytic hydrogenation of the aromatic ring in **4** required the use of a rhodium on carbon catalyst, doped with Pd (1% Pd on Rh/C). Similar catalysts have been used for the stereoselective reduction of polysubstituted aryl rings, as in the preparation of **2c**.[4b] Using moderately dilute aqueous sulfuric acid (0.3 mol dm^{-3}), hydrogenation of **4** occurred cleanly (20 °C, 3 atm H_2, 6 days) to give a 4:1 mixture of the *cis*,*cis*- and *cis*,*trans*-diastereoisomers. The desired *cis*,*cis*-isomer was separated by crystallisation of the sulfate salt from H_2O–EtOH–CH_2Cl_2. The crystallographic analysis of this salt has been reported previously[7] and revealed that the $^+NH_3$ groups occupied the equatorial sites.

Information on the preferred solution conformation of such cyclohexyl derivatives may be gleaned by analysis of the ^1H NMR spectral details. In cyclohexyl systems, the stereoelectronic preference for a C–X (X = Hal, OR, NR_2) bond to be antiperiplanar to a C–H bond arises from a favourable σ_{C-H}–σ^*_{C-X} interaction.[11] When the CHMe proton is *anti* to the electronegative group, this stereoelectronic effect manifests itself in a reduction of the vicinal coupling constant $J(H_a,H_e)$ (Scheme 2) by 1 or 2 Hz, with respect to that seen in the alternative



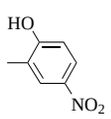
Scheme 2

conformer where the CHMe proton is *syn* to the group X. For example, when X = OCD_3 and R = H, the relevant coupling constants are 2.5 and 4.1 Hz for the favoured and disfavoured conformers respectively.[12] In $CDCl_3$ (293 K), the observed coupling constant J (H_a, H_e) was measured as 3.0 Hz (±0.2) in both **2a** and the *N*-benzyl derivative **9b**. A preliminary X-ray structural analysis of **9b** had previously shown that the



8 X = CO_2Et, R = Me
9a X = CO_2H, R = Me
b X = Ph, R = Me
c X = CO_2H, R = H

10 Ar =



11

$NHCH_2Ph$ groups were axially disposed.[7] The chemical shift of the C*H*NH resonance in **2a** was independent of solvent, appearing at 2.8 (±0.05) ppm in CD_3OD, $CDCl_3$ and CD_2Cl_2, with the same 3 Hz coupling constant. Addition of excess CF_3CO_2H to a solution containing **2a** in CD_3OD, shifted the C*H*NH_3^+ resonance to higher frequency (3.73 ppm) and the coupling constant increased to 5.1(3) Hz. In the triprotonated amine, $H_{a'}$ (Scheme 2) is now *anti* to a methyl group, and the vicinal coupling constant increases as the stabilising σ_{C-H}–σ^*_{C-X} interaction is lost. When the amino groups are in axial positions an array of three intramolecular hydrogen bonds is set up with each group accepting and donating one proton, with the methyl groups shielding this arrangement from solvent interactions. Protonation disrupts this ideal arrangement. It therefore seems likely that in both **2a** and **9b**, the preferred solution conformer at room temperature ($CDCl_3$) is the one with the amino groups placed axial in accord with stabilisation involving intramolecular H-bonding and favourable σ_{C-H}–σ^*_{C-X} interactions and with their slightly smaller size with respect to the methyl groups. Of course, in reality the observed coupling constant is a weighted average of the *J* values associated with the two major chair conformers [eqn. (1)], where n_e and n_a represent the mole

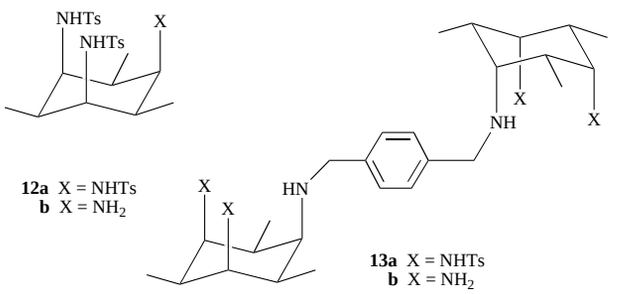
$$J_{obs} = n_e J(H_{a'}H_{e'}) + n_a J(H_aH_e) \quad (1)$$

fractions of each solution conformer and $J(H_{a'}H_{e'})$ and $J(H_aH_e)$ are the geminal coupling constants for the conformers with the NHR groups equatorial and axial respectively. Variable temperature ^1H NMR studies (−90 to +30 °C) of **2a** in CD_2Cl_2 and CD_3OD revealed no significant shifts in either the position or the coupling constant of the CHNH resonances (nor of the CHMe or Me doublets) so that one predominant (≥95%) conformer exists in these solvents with the amino groups axial.

Reaction chemistry

Reaction of **2a** with ethyl bromoacetate in dimethylformamide (DMF) in the presence of caesium carbonate afforded the triester **8** in 83% isolated yield after purification by chromatography on neutral alumina. The buttressing methyl groups inhibit alkylation of the secondary amine sites, explaining the lack of polyalkylated products. Acid hydrolysis (6 mol dm^{-3} HCl, 110 °C, 18 h) gave the corresponding amino acid **9a**, as a hydrate of the trihydrochloride salt. Reductive alkylation of **2a** using benzaldehyde in ethanol followed by borohydride reduction gave the tri-*N*-benzyl derivative **9b** and the analogous hexadentate ligand **11** was prepared similarly *via* the yellow trisimine **10**. Attempted reaction of **9b** with ethyl bromoacetate in ethanol (80 °C, 72 h) gave rise to no tertiary amine products and the starting material was recovered unchanged. Such behaviour is also consistent with the steric inhibition to S_N2 attack caused by the introduction of the proximate methyl groups. Nucleophilic attack at an sp^2 carbon centre is usually less prone to steric inhibition, but attempted reaction of **9b** with paraformaldehyde in the presence of $MeP(OEt)_2$ [75 °C, anhydrous tetrahydrofuran (THF), 4 Å sieves] gave less than 10% of the expected condensation product.

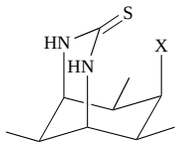
Sulfonylation of the triamine **2a** was also subject to some degree of control by the neighbouring methyl groups. In this case it allowed the isolation of the ditosylamide derivative **12b**.



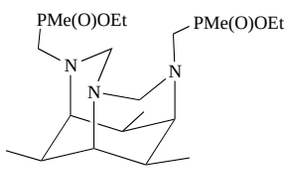
Thus reaction of **2a** with three or more equivalents of TsCl (THF, Et_3N; Ts = *p*-$MeC_6H_4SO_2$) afforded the tritosylamide **12a** in 75% isolated yield after recrystallisation, whereas use of 1.8 equivalents of TsCl under the same conditions yielded the ditosylamide **12b** in 80% yield. The tritosylamide **12a** was also remarkably unreactive in attempted alkylation reactions. Attempted alkylation with methyl iodide under a variety of different reaction conditions (*e.g.* MeI–Cs_2CO_3–DMF–100 °C; NaH, THF, MeI; MeI–Cs_2CO_3–EtOH; MeI–Et_3N–MeCN; 3 equiv. NaOEt–EtOH then DMF–MeI) led to none of the trimethylated product being isolated. The ditosylamide **12b** did react selectively with alkyl halides at the free amino group: in the presence of K_2CO_3 in acetonitrile, alkylation with *p*-bis(bromomethyl)benzene yielded the tetratosylamide **13a** and subsequent detosylation using sodium in liquid ammonia gave the hexamine **13b**. From the stereochemical analyses obtained with the *N*-benzylamine **9b** and the parent triamine **2a**, it is likely that in non-polar solvents the hexamine will adopt the conformation shown with the amino groups axial, and the *para*-substituted benzyl group disposed in an *anti*-conformation. When in the *syn*-conformation (not shown), the aryl group effectively bridges two facially coordinating N_3 donor sets which are held in close proximity.

Neighbouring group effects

The juxtaposition of the amino groups in the 'triaxial' conformer may be expected to lead to some unusual intramolecular effects. Reaction of **2a** with carbon disulfide in ethanol simply led to formation of the monoisothiocyanate of the cyclic thiourea, **14**. Basic hydrolysis of the isothiocyanate group gave the corresponding mono-amine **15**. Such transformations allow an alternative strategy to selective *N*-tosylation in distinguishing one amino site from the other two.



14 X = NCS
15 X = NH_2



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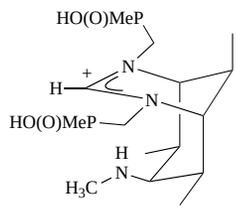

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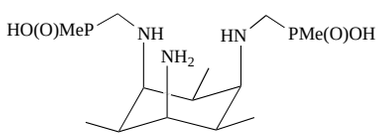
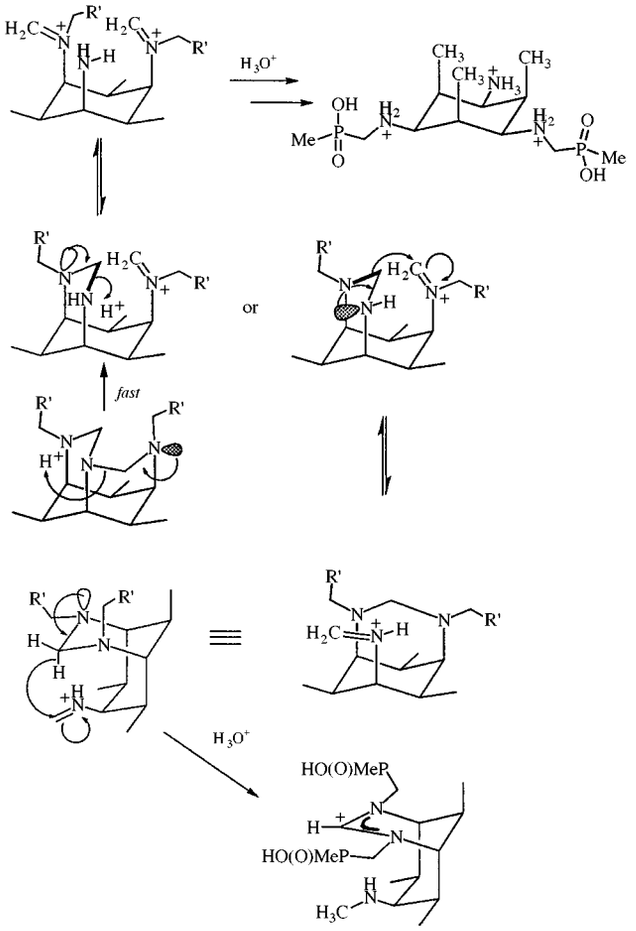


18

The condensation reaction of **2a** with freshly resublimed paraformaldehyde in the presence of $MeP(OEt)_2$ in boiling THF[13] resulted in the formation of the tricyclic bis-aminal **16**. There are two remote stereogenic centres at phosphorus in this product and the compound was isolated as an almost equimolar mixture of the two sets of diastereoisomers, *i.e.* (*RR*/*SS*) and (*RS*/*SR*). In each chiral diastereoisomer the P atoms are non-equivalent and four distinct ^{31}P resonances were obtained almost in a 1:1:1:1 ratio. Acid hydrolysis of the diester **16** gave a mixture of two products whose constitution was established by a combination of 2-D NMR methods. Analysis by ^{31}P NMR revealed two resonances (δ_P 36.8, 33.5 at pD 1.5) in an approximate ratio of 55:45. Electrospray mass spectral analysis of the reaction mixture gave peaks at *m/z* 380 and 356 in positive ion mode and correspondingly *m/z* 378 and 354 in negative ion mode. One product gave resonances typical of an amidinium group ($\overset{+}{N}CHN$: δ_C 154.0; δ_H 8.20) and in this same product ^{13}C-DEPT and ^1H NMR analysis revealed an *N*-Me group. When the acid hydrolysis reaction was carried out in 6 mol dm^{-3} DCl, ^1H and ^{13}C NMR analysis revealed that there was no incorporation of the D-label into any of the CH, CH_2 or CH_3 resonances. Taken together, this information was consistent with the formation of the bridged amidine **17**. The second product was the 'expected' hydrolysis product **18**, characterised by its mass spectral behaviour (*m/z* 356 [$M^+ + 1$]) by 2-D ^{13}C/^1H analysis, and by the fact that it formed a 1:1 complex with Cu^{2+} ions in water [λ_{max} = 700 nm, ε = 90 dm^3 mol^{-1} cm^{-1}; *m/z* (ESMS) = 416 ($M^+ + 1$), 428 ($M + Na^+$)].

Formation of this pair of products may be rationalised in terms of a mechanism involving intramolecular hydride transfer to an iminium ion (Scheme 3). Protonation of **16** is likely to be accompanied by ring-opening of the strained 1,3-diazine boat conformer, with the nitrogen lone-pair *anti* to the breaking C–N bond providing some assistance. In the resulting structure, the 'exo-anomeric' effect[11] dictates that the lone-pair *anti* to the C–N may labilise that bond with respect to acid-promoted cleavage. Thus, considering the tertiary N lone-pair and notwithstanding the acidic reaction conditions which will lead to predominant protonation of the amine groups, protonation of the antiperiplanar C–N bond yields a bis-iminium salt which rapidly hydrolyses to afford the pentadentate ligand **18**. Alternatively, using the lone-pair of the secondary nitrogen atom, the antiperiplanar C–N bond is activated and attacks the proximate iminium ion with formation of a different iminium ion



Scheme 3

possessing a mirror plane. In this species (Scheme 3) one of the nitrogen lone-pairs is likely to be *trans* and antiperiplanar to a C–H bond. Intramolecular hydride transfer may then occur generating the N–Me group, leading to formation of the thermodynamically stable amidinium ion.

Protonation equilibria

The successive protonation constants for **2a** were measured under standard conditions, and are compared to reported values for the related triamines **2b** and **2c** (Table 1). Similar data were obtained for the amino acid **9a**, and a comparison has been made to pK_a measurements obtained by Zompa on the analogue **9c**.[3b] The base strength of **2a** is considerably lower than that of the parent triamine **2b** in aqueous solution. This may simply reflect the steric inhibition to solvation of the conjugate acids $[H\mathbf{2a}]^+$, $[H_2\mathbf{2a}]^{2+}$ and $[H_3\mathbf{2a}]^{3+}$ accorded by the bulky methyl groups. It is entirely reasonable, on the basis of coulombic repulsion, that the amino groups in the di- and triprotonated species of **2a** adopt equatorial sites. ^{1}H NMR analysis of the free amine of CD_3OD had revealed a triplet for the axial C*H*N resonance at 2.85 ppm (*J* 3 Hz). Addition of one equivalent of CF_3CO_2H caused this resonance to shift to 3.24 ppm and although the resonance was broadened, the coupling pattern could still be discerned with *J* = 3.3(5) Hz. When an excess of CF_3CO_2H was added, the triplet shifted up to 3.73 ppm and the coupling constant was 5.2 Hz. This behaviour is consistent with the monoprotonated amine *also* preferring a conformation which places the amino groups axial. The surprisingly low first pK_a may be accounted for by the disruption to the ideal hydrogen-bonded network present in the free triamine caused by protonation. Addition of one proton leaves two favourable hydrogen-bonding interactions but introduces a repulsive interaction between the NH_3^+ group and one NH_2 group. Relief of steric compression between the 1,3 *syn*-axial Me groups may occur only on deprotonation of the diprotonated amine $[H\mathbf{2a}]^{2+}$. However, this effect alone probably does not explain the reduction in the protonation constants seen in the second and third pK_a values for which the consequences of steric inhibition of solvation[15] probably provide a satisfactory explanation.

Table 1 Protonation equilibria for triamines (298 K, *I* = 0.1 mol dm^{-3} NMe_4NO_3)

Ligand	pK_1	pK_2	pK_3	pK_4
2a	7.83	6.73	5.15	
2b[a]	10.17	8.66	7.17	
2c[b]	8.90	7.40	5.95	
9a	9.50	7.14	5.92	3.87
9c[c]	9.60	8.06	6.45	

[a] In 0.1 mol dm^{-3} KCl.[3a,3b] [b] In 0.1 mol dm^{-3} KNO_3.[14] [c] Values given are the mean of 3 independent measurements (±0.03).

Conclusions

The sterically buttressed triamine **2a** adopts a preferred solution conformation which places the NH_2 groups axial and therefore in close proximity. In this orientation a favourable intramolecular hydrogen-bonded array is established and a favourable stabilising σ_{C-H}–σ^*_{C-N} interaction may occur which has been suggested by a reduced ^{1}H NMR coupling constant between the axial proton (*anti* to the C–N bond) and the vicinal equatorial proton. The proximate methyl groups sterically inhibit solvation of the protonated forms and lead to a diminished reactivity of the amine in nucleophilic attack at both sp^3 and sp^2 centres. The C_3-symmetric aromatic precursors and derivatives thereof possessing 'AB_2' functionality are potentially interesting starting materials for dendrimer synthesis.

Experimental

All reactions were carried out in apparatus that had been oven-dried and cooled under argon. All solvents were dried using an appropriate drying agent and water was purified from the 'Purite' system. Alumina refers to Merck Alumina activity II–III that had been soaked in ethyl acetate for at least 24 h prior to use. Silica refers to Merck silica gel F60 (230–400 mesh).

^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC 250 operating at 250.13 and 62.90 MHz respectively, Varian Gemini 200 operating at 200 and 50.1 MHz, respectively, Varian XL 200 operating at 200.1 MHz and a Varian VXR 400S operating at 400.1 MHz. All chemical shifts are given in ppm relative to the residual solvent resonance and coupling constants are in Hz.

Mass spectra were recorded on a VG 7070E, operating in FAB, EI$^+$ or DCI ionisation modes as stated. Electrospray mass spectra were recorded using a VG Platform (Fisons instruments) operating in ES$^+$ mode or were performed by the EPSRC Mass Spectroscopy service at Swansea. Accurate mass spectroscopy was performed by the EPSRC Mass Spectroscopy service.

Infra-red spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer as a thin film or KBr disc as stated. Ultraviolet spectra were recorded on a UVIKON 930 spectrometer. Combustion analysis was performed using an Exeter Analytical Inc CE440 elemental analyser. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Potentiometric titrations were performed on a Molspin 1 cm^3 auto titrator using a Corning semi-micro electrode to measure the pH.

Measurement of pK_a

The ligand solution (3 cm^3; 0.001 mol dm^{-3}) was added to the titration cell and the calibrated pH electrode placed into the

solution so that its frit was below the liquid surface. With the solution temperature maintained at 25 °C and with efficient stirring the base solution (NMe_4OH, 0.05 mol dm^{-3}) was titrated (in increments of 0.002 cm^3, time delay of 5 s). The pH curve was analysed as previously described[16] to determine the pK_a values of the ligand.

1,3,5-Triamino-2,4,6-trimethylbenzene 4

To a mixture of trinitromesitylene (11.6 g, 45.5 mmol) in ethanol (300 cm^3) in a Parr hydrogenator vessel (1 dm^3), was added 5% Pt on carbon catalyst (750 mg) and the mixture was allowed to react with H_2 (40 psi, 20 °C) for 3 days. After removal of the catalyst by filtration through a 0.5 cm plug of silica gel, the solvent was removed under reduced pressure and the solid dried under high vacuum (0.1 mmHg) to yield a pale yellow solid, 7.54 g (99%), mp 103–104 °C (Found: C, 65.2; H, 9.27; N, 2.44. $C_9H_{15}N_3$ requires C, 65.4; H, 9.14; N, 2.54%); $\delta_H(CDCl_3)$ 1.99 (9H, s, Me), 3.52 (6H, s, NH_2); $\delta_C(CDCl_3)$ 10.69 (Me), 98.64 (*C*–Me), 140.86 (C–NH_2); *m/z* (DCI) 165.1 (M^+).

1,3-Diamino-5-nitro-2,4,6-trimethylbenzene 6

A suspension of trinitromesitylene (7.8 g, 30.6 mmol) and 5% Pt on carbon (600 mg) in ethanol (300 ml) was allowed to react under H_2 gas (40 psi) for 1 hour at room temperature. The catalyst was removed by filtration through a 0.5 cm plug of silica gel and the solvent evaporated to approximately one third of its original volume. On standing for 4 h, orange crystals had deposited which were collected by filtration, washed with cold ethanol (2 × 10 cm^3), and dried in vacuum to constant weight to give an orange microcrystalline product (2.81 g, 47%), mp 169–170 °C; Found (EIMS) 195.1007; $C_9H_{13}N_3O_2$ requires 195.1008; $\delta_H(CDCl_3)$ 2.09 (6H, s, CH_3), 2.11 (3H, s, CH_3), 3.76 (4H, br s, NH_2); λ_{max}/nm (EtOH) 290 (ε 3550 dm^3 mol^{-1} cm^{-1}), 368 (825).

1,3,5-Tris(benzylideneamino)-2,4,6-trimethylbenzene 5a

A suspension of **4** (2.27 g, 13.7 mmol) and freshly distilled benzaldehyde (7.3 g, 69 mmol) was heated at 50 °C under reduced pressure (*ca.* 25 mmHg) for 45 min. The resultant brown tar was dissolved in hot ethanol (100 cm^3) and water was slowly added to the solution until it became cloudy. The mixture was cooled to 0 °C, and after standing for 4 h, a crystalline precipitate was collected by filtration, washed with water (3 × 10 cm^3) and dried to constant weight (0.01 mmHg, 40 °C) to afford a yellow crystalline product (4.37 g, 72%), mp 155–156 °C; Found (EIMS) 429.2255; $C_{30}H_{27}N_3$ requires 429.2255; $\delta_H(CDCl_3)$ 8.35 (3H, s, CH=N), 8.04 (6H, *ortho* H), 7.61 (9H, m, ArH), 2.05 (9H, s, CH_3); $\delta_C(CDCl_3)$ 163.42 (d), 150.21 (s), 136.38 (s), 131.68 (d), 129.04 (d), 128.80 (d), 112.60 (s), 13.86 (q).

1,3-Bis(benzylideneamino)-5-nitro-2,4,6-trimethylbenzene 7a

The procedure used to prepare **5a** was followed giving **7a** as a pale yellow crystalline solid in a 93% overall yield, mp 142–143 °C; Found (EIMS) 371.1629; $C_{23}H_{21}N_3O_2$ requires 371.1634; $\delta_H(CDCl_3)$ 8.22 (2H, s, CH=N), 7.93 (4H, m, *ortho* ArH), 7.52 (6H, m, ArH), 2.07 (6H, s, CH_3), 1.96 (3H, s, CH_3); $\delta_C(CDCl_3)$ 164.60 (d), 151.59 (s), 150.48 (s), 135.68 (s), 132.28 (d), 129.13 (d), 128.95 (d), 119.47 (s), 114.09 (s), 14.12 (q), 13.24 (q).

1,3,5-Tris(benzylamino)-2,4,6-trimethylbenzene 5b

Compound **5a** was hydrogenated using the conditions used for the preparation of **4** (40 psi H_2, 20 °C, 62 h). The product was recrystallised from ethanol to yield a colourless crystalline solid, mp 45 °C (Found: C, 82.4; H, 7.89; N, 9.40. $C_{30}H_{33}N_3$ requires C, 82.7; H, 7.64; N, 9.65%); $\delta_H(CDCl_3)$ 7.48–7.33 (15H, m), 4.12 (6H, s, CH_2N), 2.80 (3H, br s, NH), 2.32 (9H, s); $\delta_C(CDCl_3)$ 145.16 (s), 140.64 (s), 128.75 (d), 128.24 (d), 127.44 (d), 118.28 (s), 53.81 (t), 13.34 (q). *m/z* (DCI) 435 (M^+).

1,3-Bis(benzylamino)-5-nitro-2,4,6-trimethylbenzene 7b

To a solution of the imine **7a** (0.7 g, 1.92 mmol) in boiling ethanol (25 cm^3) was added excess sodium borohydride (2.0 g) in ten equal portions over a period of 10 days. After removal of solvent under reduced pressure, the residue was treated with water (15 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with water (2 × 10 cm^3), dried (K_2CO_3) and solvent removed under reduced pressure to yield a yellow solid, 606 mg (85%), mp 92–93 °C; Found (EIMS) 375.1946; $C_{23}H_{25}N_3O_2$ requires 375.1947; $\delta_H(CDCl_3)$ 7.45 (10H, m), 4.16 (4H, s, CH_2N), 3.38 (2H, br s, NH), 2.36 (3H, s), 2.23 (6H, s); $\delta_C(CDCl_3)$ 152.13 (s), 145.46 (s), 139.65 (s), 128.72 (d), 127.90 (d), 127.57 (d), 125.56 (s), 115.32 (s), 53.33 (t), 13.87 (q), 12.82 (q); λ_{max}/nm (EtOH) 340 (ε 1360 dm^3 mol^{-1} cm^{-1}).

1-Amino-3,5-bis(benzylamino)-2,4,6-trimethylbenzene 7c

To a suspension of **7b** (1.2 g, 3.28 mmol) in absolute ethanol (80 cm^3) was added 5% Pt on carbon (200 mg), and the mixture was shaken under 2.5 atmospheres of H_2 gas for 6 days. The catalyst was removed by filtration through a thin (0.5 cm) layer of silica gel and the solvent was reduced to one fifth of its original volume. After standing for 2 days, a colourless crystalline solid was collected by filtration, washed with cold ethanol (3 × 5 cm^3), and dried under vacuum (0.1 mmHg) to constant weight, to yield the crystalline solid, 0.84 g (74%), mp 91–92 °C; $\delta_H(CDCl_3)$ 7.56–7.40 (10H, m, ArH), 4.13 (4H, s, CH_2N), 3.50 (2H, br s), 3.25 (2H, br s, NH), 2.30 (3H, s), 2.29 (6H, s, Me); $\delta_C(CDCl_3)$ 144.53 (s, C–N), 142.08 (s, C–N), 128.76 (d), 128.25 (d), 127.44 (d), 114.46 (s, *C*–Me), 110.98 (s, *C*–Me), 54.23 (t, CH_2N), 12.79 (q), 12.40 (q); Found (EIMS) 375.2206; $C_{23}H_{27}N_3$ requires 345.2205.

***cis,cis*-1,3,5-Triamino-2,4,6-trimethylcyclohexane 2a**

A suspension of the 10% Rh–0.1% Pd on carbon hydrogenation catalyst (200 mg) in sulfuric acid solution contained in a pressurised hydrogenation vessel (3 mol dm^{-3}, 80 cm^3) was treated with H_2 gas (3 atm) at room temperature for 1 h. A solution of the amine **4** (2 g, 12.1 mmol) in sulfuric acid (25 cm^3) solution was added by cannula under argon and the mixture was continuously shaken in a Parr hydrogenator (3 atm H_2, 20 °C, 10 days). Reaction progress was monitored towards the end of this period by analysing a sample by ^{13}C NMR spectroscopy, inspecting the disappearance of the aromatic carbon signals. The catalyst was removed by filtration and the solvent removed under reduced pressure to leave a volume of *ca.* 30 cm^3. To this solution was added ethanol (30 cm^3) and then sufficient dichloromethane (*ca.* 15–20 cm^3) to give a cloudy solution. On standing, a salt precipitated which was collected by filtration and dried under reduced pressure (0.1 mmHg, 40 °C), giving the sulfate salt as a colourless solid, 4.6 g (82%); *m/z* (DCI) 174 (M^+) for the *cis*,*cis*-major isomer; $\delta_H(D_2O$, pD 1) 0.90 (9H, d, ^3J 7.5, C*H*CH_3), 2.30 (3H, br m, CHC*H*$_3$), 3.38 (3H, br m, NH_2C*H*); $\delta_C(D_2O$, pD 1) 12.03 (s, CH_3), 34.59 (d, CH), 54.12 (d, CHN). The major *cis*,*cis*-isomer was separated as the sulfate salt by crystallisation from warm water and 1.9 g was isolated. The constitution and nature of this isomer has been established by X-ray crystallographic analysis, as reported previously. The sulfate salt of **7** (1.5 g, 3.2 mmol) was added to dilute aqueous potassium hydroxide solution (pH 12, 25 cm^3) and the solution was extracted with dichloromethane (4 × 20 cm^3). The combined extracts were dried (K_2CO_3), filtered and solvent removed under reduced pressure to leave a colourless solid, mp 68–70 °C (0.4 g, 74% recovery); *m/z* (DCI) 171 (M^+); $\delta_H(CDCl_3)$ 1.18 (9H, d, ^3J 7.3, CH_3), 1.65 (3H, tq, C*H*CH_3), 1.60 (6H, br s, NH_2), 2.81 (3H, t, *J* 3.0, C*H*NH_2). In CD_3OD solution, addition of excess CF_3CO_2H gave a triplet for the C*H*NH_3^+ resonance: δ_H 3.73 (t, *J* 5.1 Hz). $\delta_C(CDCl_3)$ 16.00 (q, CH_3), 40.88 (d, *C*HCH_3), 56.52 (d, CHN) (Found: C, 63.2; H, 12.0; N, 24.2. $C_9H_{21}N_3$ requires: C, 63.2; H, 12.3; N, 24.5%).

***cis,cis*-1,3,5-Tris(ethoxycarbonylmethylamino)-2,4,6-trimethylcyclohexane 8**

To a solution of the triamine **2a** (0.12 g, 0.7 mmol) in dry DMF (2 cm^3) under argon was added caesium carbonate (0.9 g, 2.8 mmol) and ethyl bromoacetate (0.25 cm^3, 2.2 mmol) and the suspension was heated overnight at 60 °C. After removal of solvent under reduced pressure the residue was taken up in the minimum volume of dichloromethane, filtered and purified by chromatography on neutral alumina to yield a colourless oil (R_f = 0.25, Al_2O_3, CH_2Cl_2), 0.25 g (83%) *m/z* (ES^+) 430 ($M^+ + 1$); δ_H($CDCl_3$) 1.07 (3H, d, CH_3), 1.16 (6H, dd, CH_3), 1.19 (9H, t, OCH_2CH_3), 1.55 (2H, m, C*H*CH_3), 1.70 (1H, m, C*H*CH_3), 2.35 (2H, t, *J* 3, C*H*NH), 2.40 (1H, t, *J* 3, C*H*NH), 3.30 (4H, s, CH_2CO), 3.33 (2H, s, CH_2CO), 4.10 (6H, q + q, CH_2O); δ_C($CDCl_3$) 14.0 (2C, s, CH_3), 17.5 (1C, s, CH_3), 40.1 (1C, s, *C*HCH_3), 41.5 (2C, s, *C*HCH_3), 54.0 (1C, s, N*C*H_2CO), 54.5 (2C, s, N*C*H_2CO), 60.0 (2C, s, CHN), 60.5 (1C, s, CHNH), 64.0 (1C, s, OCH_2), 64.5 (2C, s, OCH_2); ν_{max}/cm^{-1} (thin film), 3580 (br w, NH), 3319 (br m), 2977–2875 (CH), 1739 (s, CO), 1505 (m), 1465 (m), 1373 (m), 1333 (w), 1268 (m), 1201 (s, COC), 1142 (s), 1077 (m), 1030 (m), 920 (w), 857 (w), 733 (w).

***cis,cis*-1,3,5-Tris(carboxymethylamino)-2,4,6-trimethylcyclohexane 9a**

A solution of the triester **8** (0.23 g, 0.53 mmol) in hydrochloric acid (6 mol dm^{-3}, 3 cm^3) was boiled under reflux (110 °C, 18 h). After removal of the solvent under reduced pressure and prolonged drying (0.1 mmHg, 40 °C), a colourless salt was obtained (0.24 g, 89%); *m/z* (ES^-) 344 ($M^+ - 1$); (ES^+) 346 ($M^+ + 1$); δ_C(D_2O, pD 1.5), 9.50 (CH_3), 29.80 (*C*HCH_3), 31.00 (*C*HCH_3), 45.21 (NCH_2), 58.14 (CHN), 168.03 (CO) (Found: C, 34.89; H, 7.01; N, 8.04. $C_{15}H_{27}N_3O_6$·3HCl·3H_2O requires C, 35.39; H, 7.08; N, 8.25%); ν_{max}/cm^{-1} (Nujol) 3354 (br s, OH, NH), 1731 (s, CO), 1566 (m), 1207 (s), 939 (m), 821 (s); δ_H(D_2O, pD 2), 1.16 (9H, d + d, CH_3), 2.59 (1H, br m, C*H*CH_3), 2.72 (2H, br m, C*H*CH_3), 3.54 (3H, t + t, CHN), 3.90 (4H, s, CH_2CO), 4.00 (1H, br d, NCHCO), 4.09 (1H, br d, NCHCO).

***cis,cis*-1,3,5-Tris(benzylamino)-2,4,6-trimethylcyclohexane 9b**

To a solution of the triamine **2a** (0.2 g, 1.1 mmol) in warm dry ethanol (15 cm^3) was added benzaldehyde (0.37 g, 3.3 mmol) and the solution was boiled under reflux for 2 h. After removal of solvent under reduced pressure, the residue was taken up in dry ethanol (20 cm^3) and solid excess sodium borohydride (250 mg) was added. The mixture was boiled under reflux for 2 h, solvent evaporated under reduced pressure and the residue was taken up in dry dichloromethane (2 × 5 cm^3), filtered, dried (K_2CO_2), filtered and solvent evaporated to yield a colourless solid, 0.42 g (74%), mp 92–93 °C (Found: C, 81.5; H, 8.95; N, 9.51. $C_{30}H_{39}N_3$ requires C, 81.6; H, 8.89; N, 9.57%); *m/z* (DCI) 442 (M^+); δ_H($CDCl_3$) 1.23 (9H, d, ^3J 7, CH*Me*), 1.77 (3H, tq, C*H*CH_3), 2.61 (3H, t, *J* 3.1, C*H*NH), 3.40 (3H, br s, NH), 3.77 (6H, s, CH_2N), 7.27 (15H, m, ArH); δ_C($CDCl_3$) 16.27 (q, Me), 41.35 (d, CH), 57.35 (d, CHN), 54.2 (CH_2N), 126.27 (d, *para*), 127.71 (d, *meta*), 128.05 (d, *ortho*), 142.3 (s). This product did not react with ethyl bromoacetate (EtOH, 80 °C, 72 h).

***cis,cis*-1,3,5-Tris(2-hydroxy-5-nitrobenzylamino)-2,4,6-trimethylcyclohexane 11**

To a solution of 5-nitrosalicylaldehyde (168 mg, 1.05 mmol) in ethanol (2 cm^3) was added a suspension of the triamine **2a** (60 mg, 0.35 mmol) in ethanol (1.5 cm^3). The mixture was boiled under reflux to yield a clear yellow solution after 5 min and after a further 15 min a yellow solid began to precipitate from the solution. After a total of 2 h, the mixture was cooled to room temperature and the yellow solid collected by filtration, washed with cold ethanol (3 × 3 cm^3) and dried under vacuum (0.1 mmHg, 20 °C) to give the intermediate tris-imine **10** as a microcrystalline yellow solid; δ_H($CDCl_3$) 1.00 (9H, d, CH_3), 2.52 (3H, m, C*H*Me), 3.53 (3H, t, CHN), 6.80 (3H, d, 3′-H), 8.13 (3H, dd, 4′-H), 8.23 (3H, br s, 6′-H), 8.31 (3H, s, C*H*=N), 12.98 (3H, br s, OH).

To a suspension of the imine **10** (80 mg, 0.13 mmol) in dry ethanol (10 cm^3) was added sodium borohydride (200 mg, 2.7 mmol) and the mixture was boiled under reflux for 16 h. After removal of solvent under reduced pressure, the residue was treated with water (10 cm^3), the pH adjusted to >13 (KOH pellet) and a yellow solid precipitated, which was collected by filtration and dried under high vacuum (0.02 mmHg, 30 °C) to give a yellow solid (0.07 g, 85%), mp >250 °C (Found: C, 57.4; H, 5.95; N, 13.2. $C_{30}H_{36}N_6O_9$ requires C, 57.7; H, 5.77; N, 13.5%); δ_H(D_2O, pD 10), 1.42 (9H, d, CH_3), 2.96 (3H, m, CH), 3.46 (3H, br m, CHN), 4.38 (6H, s, CH_2N), 6.90 (3H, d, 3′-H), 7.92 (3H, br d, 4′-H), 8.14 (3H, s, 6′-H); *m/z* (ESMS) 625 ($M^+ + 1$).

***cis,cis*-1,3,5-Tris(*p*-tolylsulfonylamino)-2,4,6-trimethylcyclohexane 12a**

To a solution of the triamine **2a** (0.25 g, 1.4 mmol) in warm tetrahydrofuran (15 cm^3) was added triethylamine (0.45 g, 4.4 mmol) and freshly recrystallised toluene-*p*-sulfonyl chloride (1 g, 5.2 mmol) and the mixture was boiled under reflux for 4 h. After cooling to room temperature, the precipitate was removed by filtration and solvent was removed under reduced pressure. The solid residue was taken up in dichloromethane (20 cm^3) and washed successively with dilute aqueous hydrochloric acid (2 × 10 cm^3), dilute aqueous sodium hydroxide solution (2 × 10 cm^3) and water (2 × 10 cm^3). After drying (K_2CO_3) and filtering, solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel, eluting with hexane–dichloromethane (1:2, v/v; R_f 0.5). The resulting solid was recrystallised from dichloromethane–hexane (*ca.* 1:3) to give a colourless solid, 0.7 g (75%) (Found: C, 56.8; H, 6.33; N, 6.54. $C_{30}H_{39}N_3S_3O_3$ requires C, 56.8; H, 6.20; N, 6.63%); δ_H($CDCl_3$) 0.54 (9H, d, ^3J 7, CH*Me*), 1.71 (3H, m, C*H*Me), 2.46 (9H, s, CMe), 3.30 (3H, br m, C*H*NH), 5.46 (3H, d, ^3J 5.5, NHSO), 7.32 (6H, d, *m*-ArH), 7.68 (6H, d, *o*-ArH); δ_C($CDCl_3$) 15.83 (q, Me), 21.60 (q, ArMe), 38.82 (d, *C*HMe), 58.81 (d, CHN), 127.38 (d, *meta*), 129.77 (d, *ortho*) 137.5 (s, *C*Me), 143.9 (s, C–SO).

***cis,cis*-1,3-Bis(*p*-tolylsulfonylamino)-5-amino-2,4,6-trimethylcyclohexane 12b**

Reaction of the triamine **2a** with toluene-*p*-sulfonyl chloride (1.8 equiv.) under the same conditions used to prepare **12a** gave rise to a colourless solid which was recrystallised from dichloromethane–hexane (1:2 v/v), mp 136–138 °C (80%) (Found: C, 57.3; H, 7.03; N, 8.42. $C_{23}H_{33}N_3O_4S_2$ requires C, 57.6; H, 6.89; N, 8.79%); δ_H($CDCl_3$) 0.40 (3H, d, CH_3), 1.10 (6H, d, CH_3), 1.60 (2H, m, C*H*Me), 1.72 (1H, m, C*H*Me), 2.52 (6H, s, MeAr), 3.11 (1H, t, CHN), 3.50 (2H, t, CHN), 7.35 (4H, d, CHAr), 7.72 (4H, d, CHAr); *m/z* (DCI) 479 (M^+), 480 ($M^+ + 1$).

Synthesis of the tetratosylamide 13a

The substituted triamine **12b** (0.24 g, 0.50 mmol) and potassium carbonate (0.55 g, 4.0 mmol) were added to anhydrous acetonitrile (15 cm^3). α,α′-Dibromo-*p*-xylene (0.064 g, 0.25 mmol) was added and the mixture was stirred vigorously and boiled under reflux for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between water (20 cm^3) and dichloromethane (20 cm^3). The organic layer was separated and dried with potassium carbonate. The solvent was removed under reduced pressure and the resultant solid was recrystallised from hexane–dichloromethane to give a colourless crystalline solid (0.2 g, 90%), mp 100–102 °C; δ_H($CDCl_3$) 0.25 (6H, d, ^3J 7.5, CH_3), 0.92 (12H, d, ^3J 7, CH_3), 1.69 (6H, m, C*H*Me), 2.40 (12H, s, *Me*–Ar), 2.65 (2H, br, N–CH), 3.31 (4H, br, N–CH), 3.66 (4H, br, CH_2Ar), 7.23 (12H, m, C*H*Ar), 7.59 (8H, d, C*H*Ar); δ_C($CDCl_3$) 15.76 (s, 2C, CH_3), 16.4 (s, 4C,

CH_3), 21.5 (s, 4C, ArCH_3), 39.2 (s, 2C, $CH{-}CH_3$), 39.7 (s, 4C, $CH{-}CH_3$), 55.9 (s, 2C, CHN), 59.1 (s, 4C, CHN), 62.65 (s, 2C, CH_2), 126.9 (s, 8C, *meta*), 128.65 (s, 4C, Ar), 129.5 (s, 8C, *ortho*), 138.32 (2C, $CH_2{-}Ar{-}C$), 143.05 (4C, C–S) (Found: C, 61.23; H, 6.85; N, 7.92. $C_{54}H_{72}N_6S_4O_8$ requires C, 61.16; H, 6.83; N, 7.91%); *m/z* (ES^+) 1061.16 ($M^+ + 1$), 1062.15 ($M^+ + 2$), 1063.10 ($M^+ + 3$), 1082.9 ($M^+ + 23$), 1084.09 ($M^+ + 24$), 1085.13 ($M^+ + 39$), 1101.05, 1115.9; *m/z* (ES^-) 1056.75, 1058.63, 1059.65, 1060.85, 1061.85, 1062.91, 1063.88.

Synthesis of the hexamine 13b

To a solution of the tetratosylamide **13a** (0.20 g, 0.18 mmol) in tetrahydrofuran (20 cm^3) and ethanol (2 cm^3) held under argon at −78 °C was added liquid ammonia (75 cm^3). To this mixture was added sodium metal (0.20 g), and the blue solution was stirred for 2 h. The dark blue solution was then allowed to warm up to room temperature while boiling off the ammonia. Ethanol (2 cm^3) followed by water (60 cm^3) were added to the residue and the organic solvents were removed under reduced pressure. The pH of the solution was lowered to 1 using conc. hydrochloric acid, and the aqueous solution was washed with diethyl ether (3 × 30 cm^3). The pH was raised to 12 (addition of 6 mol dm^{-3} KOH solution) and the solution was extracted with dichloromethane (3 × 30 cm^3). The solvent was removed under reduced pressure to give a colourless solid (60 mg, 72%) (Found: C, 70.24; H, 10.9; N, 18.77. $C_{26}H_{48}N_6$ requires C, 70.27; H, 10.81; N, 18.91%); $\delta_H(CDCl_3)$ 1.78 (18H, m, CH_3), 1.63–1.69 (16H, m, C*H*Me, NH_2, NH), 2.56 (2H, br, C*H*–NH), 2.75 (4H, br, C*H*–NH_2), 3.70 (4H, s, CH_2), 7.24 (4H, s, Ar); $\delta_C(CDCl_3)$ 16.11 (2C, s, CH_3), 16.45 (4C, s, CH_3), 41.02 (2C, s, $CH{-}CH_3$), 41.55 (4C, s, $CH{-}CH_3$), 56.73 (4C, s, $CH{-}NH_2$), 57.17 (2C, s, CH–NH), 63.55 (2C, C, CH_2), 127.79 (4C, s, Ar–C), 140.01 (2C), 63.55 (s, Ar–C); *m/z* (DCI) 444 (M^+), 445 ($M^+ + 1$).

The cyclic thiourea-isocyanate 14

To a solution of the triamine **2a** (80 mg, 0.47 mmol) in dry ethanol (4 cm^3) was added carbon disulfide (0.25 cm^3, 4.2 mmol). A white precipitate appeared after 10 min. After boiling the solution under reflux for 5 h, during which time H_2S evolution occurred, the solution was cooled, solvent removed under reduced pressure and after drying in vacuum (0.02 mmHg, 35 °C) a colourless powder was obtained, 90 mg (75%), mp 236–237 °C (Found: C, 51.8; H, 7.17; N, 16.2%. $C_{11}H_{17}N_3S_2$ requires C, 51.8; H, 6.70; N, 16.5%); $\delta_H(CDCl_3)$ 1.04 (3H, d, *J* 5.0, CH_3), 1.25 (6H, d, *J* 5.0, CH_3), 1.74 (1H, m, C*H*Me), 1.88 (2H, m, C*H*Me), 3.09 (2H, br s, CHN), 4.05 (1H, t, CHN), 6.95 (2H, br s, NH); $\delta_C(CDCl_3)$ 15.8 (2C, s, CH_3), 16.13 (1C, s, CH_3), 32.4 (1C, s, $CH{-}CH_3$), 41.12 (2C, s, $CH{-}CH_3$), 55.58 (2C, s, CHN), 59.14 (1C, s, CHN), 151 (1C, s, NC=S), 177.4 (C, s, N=C=S); ν_{max}/cm^{-1} (KBr) 3191 (s), 2123 (m, NCS), 2962 (s), 1550 (s), 1523 (s), 1455 (m), 1336 (m), 1197 (s); *m/z* (CI, MeOH) 256 ($M^+ + 1$).

The cyclic thiourea-monoamine 15

A suspension of the isothiocyanate **14** (120 mg, 0.47 mmol) in aqueous sodium hydroxide (5 mol dm^{-3}, 5 cm^3) was boiled under reflux for 18 h. The cooled solution was extracted with dichloromethane (4 × 20 cm^3), the combined extracts dried (K_2CO_3), filtered and solvent removed under reduced pressure to yield a colourless solid (80 mg, 80%), mp 174–175 °C; *m/z* (ES^-) 212 ($M^+ - 1$); *m/z* (ES^+) 235 ($M^+ - 1 + Na^+$); $\delta_H(CDCl_3)$ 1.09 (3H, d, CH_3), 1.26 (6H, d, CH_3), 1.87 (3H, m, C*H*Me), 2.50 (2H, br, NH_2), 2.99 (1H, t, *J* 3, CHN), 3.14 (2H, br m, CHN), 7.46 (2H, br s, NH); ν_{max}/cm^{-1} 3182 (s), 2959 (s), 1550 (s), 1510 (s), 1454 (s), 1260 (w), 1190 (s), 1025 (w), 907 (w).

The tricyclic bis-aminal 16

To 1,3,5-trimethyl-2,4,6-triaminocyclohexane (36 mg, 0.208 mmol) in sodium-dried THF (15 cm^3) at 110 °C under argon was added a solution of diethoxy(methyl)phosphine (114 mg, 0.831 mmol) in diethyl ether (1.3 cm^3), followed immediately by paraformaldehyde (41 mg, 1.38 mmol). The solution was boiled under reflux overnight with azeotropic removal of water using 4 Å molecular sieves. Removal of the solvent under reduced pressure yielded a colourless viscous oil. Purification of the product (R_f 0.8 on alumina using 10% methanol in dichloromethane) was effected using neutral alumina eluted with a solvent gradient (0 to 3% methanol in dichloromethane) over a period of 9 h to yield the product (51 mg, 60%) as a colourless oil; $\delta_P(CDCl_3)$ 54.72, 54.10, 52.47, 51.62; $\delta_H(CD_2Cl_2)$ 1.18 (1.5H, t, OCH_2CH_3), 1.22 (9H, CH_3 ring), 1.28 (4.5H, 3 × t, OCH_2CH_3), 1.45 (1H, br, C*H*CH_3), 1.52 (3H, d, *J* 14, PMe), 1.53 (1.5H, d, *J* 14, PMe), 1.55 (1.5H, d, *J* 14, PMe), 1.81 (2H, q, C*H*CH_3), 2.45 (1H, s, CHN), 2.54 (1H, s, CHN), 2.78–2.96 (2H, m, NCH_2P), 3.00–3.13 (2H, m, NCH_2P), 3.18 (1H, s, CHN), 3.77, 3.80, 3.92, 3.95 (4H, NCH_2N), 3.9–4.1 (4H, m, OCH_2); $\delta_C(CD_2Cl_2)$ 12.91 (0.5C, d, *J* 90, PMe), 12.95 (0.5C, d, *J* 90, PMe), 13.25 (1C, d, *J* 89, PMe), 16.84, 16.89, 16.98 (3C, OCH_2CH_3), 21.09 (3C, $CHCH_3$), 44.5 (3C, $CHCH_3$), 56.36 [1C, $CHN(CH_2)_2$], 58.13 (0.5C, d, *J* 114, NCH_2P), 58.28 (0.5C, d, *J* 113, NCH_2P), 58.96 (0.5C, d, *J* 116, NCH_2P), 59.08 (0.5C, d, *J* 116, NCH_2P), 68.24 (0.5C, d, *J* 13, H*C*NCH_2P), 68.43 (0.5C, d, *J* 13, H*C*NCH_2P), 68.84 (0.5C, d, *J* 13, H*C*NCH_2P), 68.94 (0.5C, d, *J* 14, H*C*NCH_2P), 70.27, 70.28 (d + d, *J* 12, NCH_2N), 70.44 (1C, NCH_2N); *m/z* (DCI) 436.2417 ($M^+ + 1$), $C_{19}H_{40}N_3O_4P_2$ requires 436.2417.

Acid hydrolysis of 16

The phosphinate ester **16** (50 mg, 0.11 mmol) was dissolved in 6 mol dm^{-3} HCl (10 cm^3), and the solution boiled under reflux for 18 h (110 °C). Water was removed under reduced pressure and a colourless solid was obtained. Spectral analysis revealed an approximately 1:1 mixture of the amidine salt **17**, and the amino acid **18**; *m/z* (ESMS): compound **17** (+ve): 380, (−ve) 378; $C_{15}H_{32}N_3O_4P_2$ requires 380; compound **18** (+ve): 356; (−ve) 354; $C_{13}H_{31}N_3O_4P_2$ requires 355; δ_P(pD 1.5) 36.8, 33.5; δ_H(pD 1.5): compound **17**: 8.20 (1H, s, NCHN), 3.93 (dd, 2H, NCH_2P), 3.80 (dd, 2H, NCH_2P), 3.61 (br t, 2H, CHN), 3.53 (t, 1H, CHN), 2.82 (dq, 1H, CHMe), 2.66 (dq, 2H, CHMe), 2.57 (s, 3H, NMe), 1.28 (d, 6H, PMe), 1.15 (t, 9H, Me); compound **18**: 3.61 (br m, 2H, CHN), 3.27 (t, 1H, CHN), 3.20 (d, 4H, NCH_2P), 2.40 (m, 2H, CHMe), 2.18 (q, 1H, CHMe), 1.28 (d + d, 9H, Me), 0.80 (d, 6H, PMe); δ_C(pD 1.5): compound **17**: 154.03 ($NCHN^+$), 61.91 (2C, CHN), 55.20 (d, *J* 88, NCH_2P), 51.40 (1C, CHN), 40.25 (*C*HMe), 38.40 (NMe), 30.81 (2C, *C*HMe), 29.34 (1C, *C*HMe), 15.93 (1C, Me), 14.72 (d, *J* 94, PCH_3), 13.42 (2C, Me); compound **18**: 63.54 (1C, CHN), 59.59 (2C, CHN), 43.46 (d, *J* 86, NCH_2P), 40.25 (2C, *C*HMe), 31.48 (1C, *C*HMe), 14.44 (d, *J* 100 Hz, PMe), 9.33 (Me). ^{13}C NMR and ^1H assignments were confirmed by DEPT and HETCOR spectra.

X-Ray crystallography

The diffraction experiments were carried out at room temperature, on a Rigaku AFC6S 4-circle diffractometer (**5a**) and a Siemens SMART 3-circle diffractometer with a CCD area detector (**7c**). An empirical absorption correction was applied for **5a** using TEXSAN software[17] (on 36 ψ-scans of 1 reflection, min./max. transmission 0.86/1.00). The structures were solved by direct methods (SHELXS-86 programs[18]) and refined by full-matrix least squares against F^2 of all data (SHELXL-93 software[19]). In **5a**, the N(5), C(50) atoms and the adjacent phenyl group are disordered over two positions, A and B, with the occupancies refined to 55(1) and 45(1)%, respectively. These atoms were refined with isotropic displacement parameters (Ph ring as rigid body), other non-H atoms in **5a** and **7c** with anisotropic ones. In **5a**, all H atoms were treated as 'riding'. In **7c**, amino-H were refined isotropically, Me groups refined as rigid bodies, other H atoms treated as 'riding' (with refined U_{iso}).

Table 2 Crystal data for **5a** and **7c**

Compound	**5a**	**7c**
Formula	$C_{30}H_{27}N_3$	$C_{23}H_{27}N_3$
Molecular weight	429.55	345.48
Crystal size/mm	0.5 × 0.5 × 0.05	0.34 × 0.28 × 0.22
Colour	Yellow	Light green
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
a/Å	11.425(3)	11.575(1)
b/Å	20.314(3)	17.152(2)
c/Å	10.901(4)	10.250(1)
β/°	98.20(2)	106.09(1)
V/Å^3	2504(1)	1955.0(5)
Setting reflections, θ/°	25, 23–40	442, 10–23
D_x/g cm^{-3}	1.14	1.18
Radiation	Cu-Kα	Mo-Kα
$\bar{\lambda}$/Å	1.541 84	0.710 73
μ/cm^{-1}	5.2	0.7
Scan mode	$2\theta/\omega$	ω (0.3° frames)
Max. 2θ/°	150	51
Data total, unique, R(int)	3975, 3516, 0.023	8650, 3215, 0.038
Data observed, $I > 2\sigma(I)$	1925	1938
Number of least squares variables	259	268
R (F, obs. data)	0.067	0.050
wR (F^2, all data)	0.208	0.146
Goodness-of-fit	1.02	1.10
Max, min $\Delta\rho$/e Å^{-3}	0.21, −0.25	0.14, −0.14

Crystal data and experimental details are listed in Table 2. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans.* 2, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/76.

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