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The consistent hexameric paddle-wheel crystallisation motif of a family of 2,4-bis(*n*-alkylamino)nitrobenzenes: alkyl = pentyl, hexyl, heptyl and octyl

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Three examples of 2,4-bis(*n*-alkylamino)nitrobenzenes have been crystallised (alkyl = pentyl, hexyl and heptyl) and the single crystal structures were determined. The three structures are similar and adopt a cyclic hydrogen bonded hexameric motif. *n*-Octyl alkyl chains prevented a crystal structure determination owing to disorder.

Keywords: hexameric, hydrogen bond, supramolecular, crystallisation, porous, 2,4-bis(alkylamino)nitrobenzenes

DNA is known for its ability to store and transfer genetic information.[1] However, the discovery of the guanine-quadruplex structure has highlighted a new function for DNA in biology.[2] Guanine-quadruplexes are four-stranded nucleic acid secondary structures formed by DNA molecules (Fig. 1). The planar, stacked, guanine-quadruplexes are formed by Hoogsteen hydrogen bonding of guanine bases rather than by Watson–Crick base pairing.[3] They can form readily in solution under physiological conditions. Their stabilisation is dependent on the presence of the monovalent cations sodium and potassium.[4] Potassium ions are more physiologically relevant than sodium ions owing to their high intracellular concentration. The stabilisation of the quadruplex is due to the coordination of the cations by the guanine oxygen atoms in the channel formed by the stacked guanine-tetrads.[5]

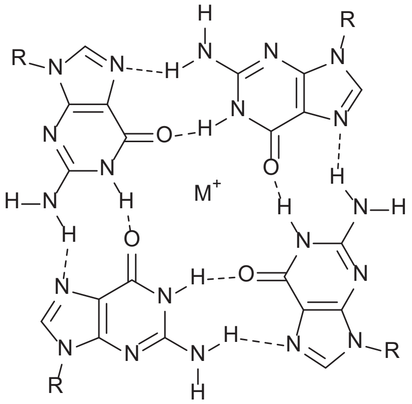
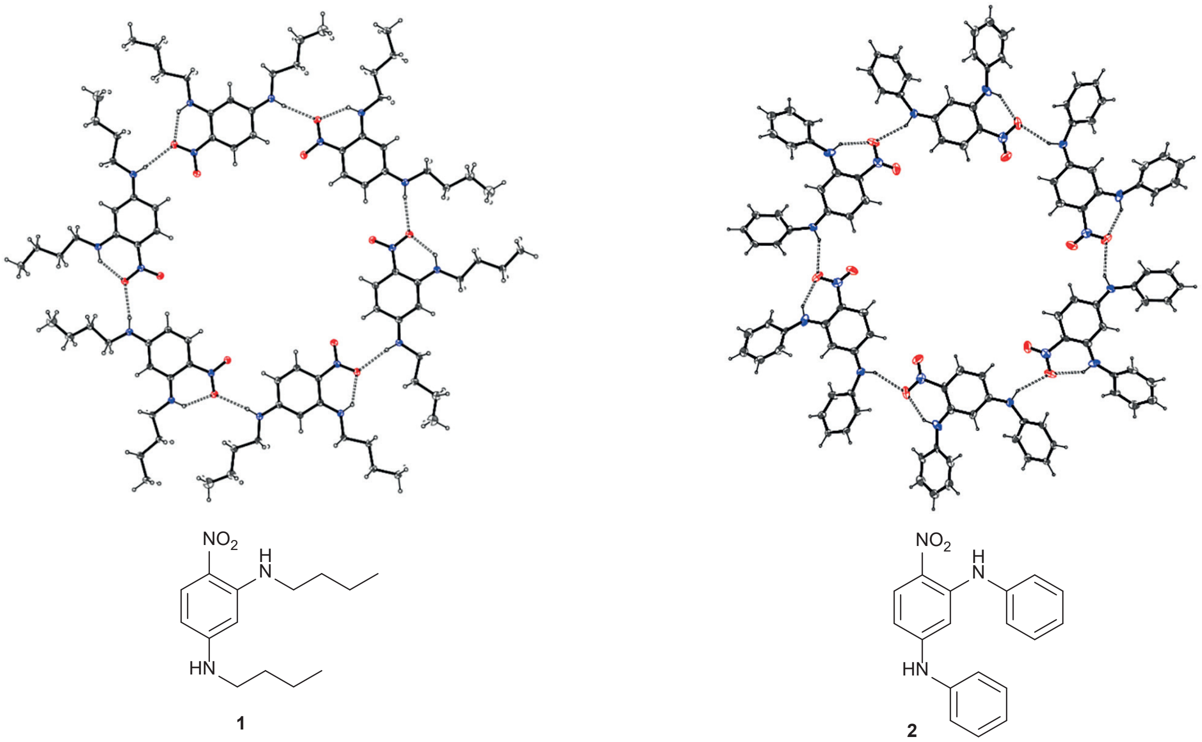


Fig. 1 A guanine-quadruplex formed from Hoogsteen hydrogen bonds and a templating monovalent cation.

Recently we reported the crystal structures of non-biological cyclic hexameric motifs formed from six 2,4-bis(butylamino) nitrobenzene molecules or six 2,4-bis(phenylamino) nitrobenzene molecules in which adjacent molecules are linked by N–H···O hydrogen bonds (Fig. 2).[6] The hexamers formed from 2,4-bis(butylamino)nitrobenzene have a staggered stacking arrangement so that channels do not occur in the crystal but the hexamers formed from 2,4-bis(phenylamino) nitrobenzene are stacked on top of each other so that large channels arise. This work might be related to solution studies by Whitesides and Reinhoudt on melamine–cyanuric/barbituric acid hexamers, although the building blocks here are different and there are fewer hydrogen bonds to support



1

2

Fig. 2 Hexameric hydrogen-bonded motifs: 2,4-bis(butylamino)nitrobenzene (**1**) and 2,4-bis(phenylamino)nitrobenzene (**2**).

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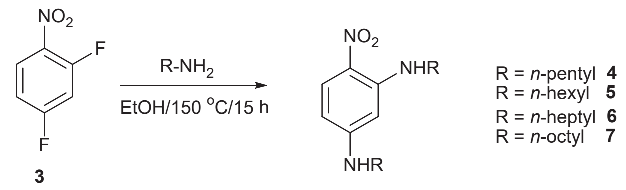

Scheme 1 Synthesis of the alkyl-substituted building units.

the self-assembly of the hexamer.[7–10] Derivatives of melamine and dibutylbarbituric acid can aggregate into different motifs, but the use of a more crowded melamine derivative favours the formation of single hexamers known as rosettes.[11–13] In the light of these interesting studies we sought further examples to explore the structural requirements of the building block **1** that lead it to crystallise in the hexamer motif. However, it should be noted that not all derivatives crystallise as hexamers.[6]

Discussion

Compounds **4–7** were prepared in yields ranging from 44–70% by reacting 2,4-difluoronitrobenzene (**3**) with the appropriate long-chain amine (Scheme 1). Both of the fluorine atoms in **3** are activated by the nitro group and can be displaced by nucleophilic substitution (S_NAr). Our previous studies showed that the fluorine atoms can be distinguished with good selectivity and that the *ortho* fluorine atom is completely displaced first.[6] The *para* fluorine atom is slower to displace but this does occur with an excess of amine present.

Crystal structures

Compound **4** is essentially isostructural with the same space group and packing[6] as compound **1** (compare to Fig. 2), with one molecule in the asymmetric unit in the trigonal space group. The pentyl chains adopt extended conformations, with the terminal methyl group of the *para*-chain statistically disordered over two adjacent sites and an intramolecular N–H···O hydrogen bond from the *ortho*-NH group to one of the nitro group oxygen atoms, which closes an S(6) ring (Fig. 3). The nitro group is almost coplanar with its attached ring [dihedral angle = 2.34(2)°]. In the crystal, the molecules are linked by N–H···O [H···O = 1.96(2) Å; N–H···O = 132(2)°] hydrogen bonds (from the *para*-NH group) to generate hexamers (Fig. 4), which have point symmetry about their centroids. Each intermolecular N–H···O [H···O = 2.23(3) Å; N–H···O = 165(2)°] hydrogen bond is reinforced by an adjacent short C–H···O [H···O = 2.35 Å; C–H···O = 168°] interaction from the 5-position of the benzene ring, as seen previously.[6] No other short directional intermolecular interactions could be identified. The rhombohedral crystal symmetry for **4** means that the stacking pattern for the hexamers in the *c* direction is staggered and therefore no channels are apparent as they are in compound **2**.[6] However, a PLATON[14] analysis indicated a significant void of volume ~240 Å^3, centred at the origin, the centroid of the hexamer and symmetry equivalent locations presumably corresponding to regions of highly disordered solvent molecules.

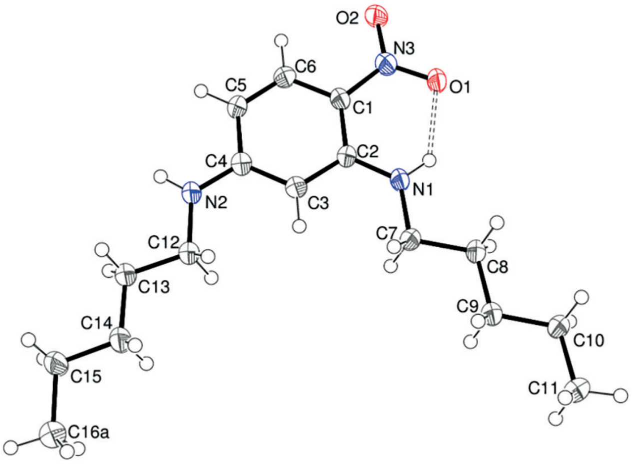

Fig. 3 The molecular structure of compound **4**, showing 50% displacement ellipsoids. The intramolecular N–H···O hydrogen bond is indicated by a double-dashed line. The alkyl chain disorder is not shown.

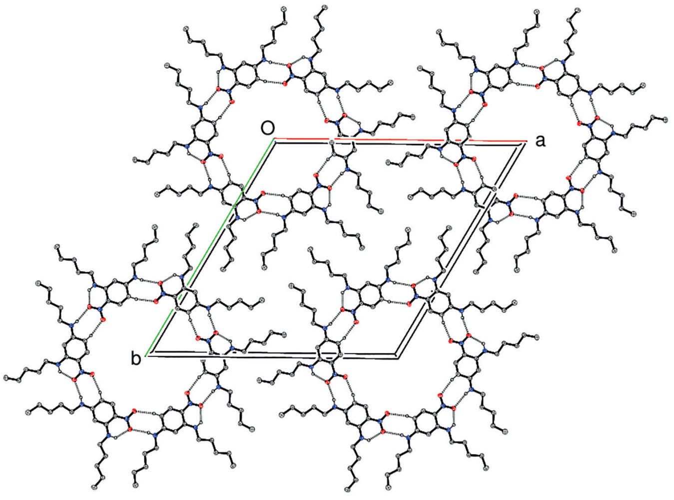

Fig. 4 Partial packing diagram for compound **4** showing the N–H···O plus C–H···O hydrogen-bonded hexameric motifs and the 'nestled' alkyl chains. The C-bound H atoms not involved in hydrogen bonds are omitted for clarity. The alkyl chain disorder is not shown.

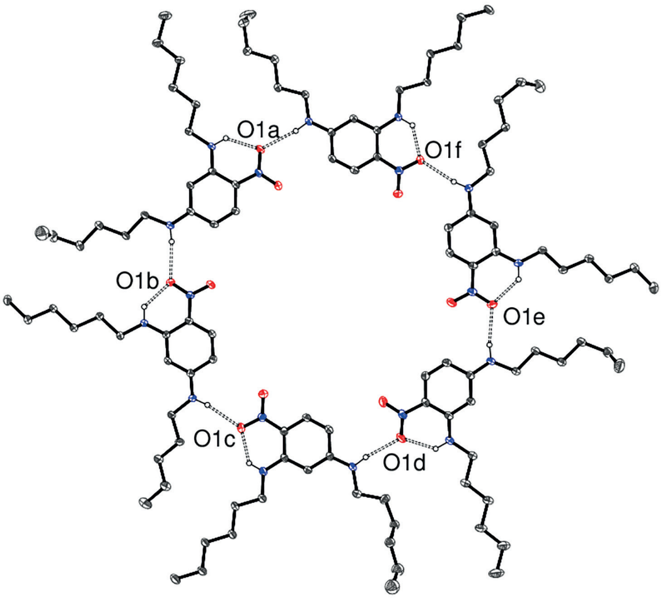

Fig. 5 The molecular structure of compound **5**, showing 50% displacement ellipsoids. The hydrogen bonds are indicated by double-dashed lines. Note that some of the terminal methyl groups are orientated out of the plane of the hexamer. The alkyl chain disorder is not shown.

Compound **5** crystallises in the triclinic space group with six molecules in the asymmetric unit (Fig. 5). Four of the six molecules feature disorder of the terminal atoms of the *para*-alkyl chains and an intramolecular N–H···O hydrogen bond occurs within each molecule. Despite the lower crystal symmetry, the packing for compound **5** is essentially the same as for compound **4** and a hexamer arises, with N–H···O hydrogen bonds and reinforcing C–H···O links between molecules. One reason for the symmetry lowering may be that some of the *para*-hexyl chains adopt non-extended conformations (*i.e. gauche*

C–C–C–CH_3 torsion angles), with the terminal methyl groups displaced either above or below the plane of the hexamer. In terms of stacking, the hexamers are staggered and no channels are apparent in the extended structure.

Compound **6** crystallises in the triclinic space group with nine molecules in the asymmetric unit (see ESI, Figs 6 and 7), but again hexamers arise in the crystal. One of these is comprised of six independent molecules and the other is centrosymmetric (*i.e.* has point symmetry about its centroid) and comprises three unique molecules and their inversion-generated clones. In both cases, cooperative N–H ··· O and C–H ··· O bonds link adjacent molecules within their hexamers, as seen for compounds **4** and **5**. No channels are evident in the extended structure.

In terms of compound **7**, the refinement is extremely poor and the terminal portions of some of the octyl chains are badly disordered or indistinct (see ESI, Figs 8 and 9). However, it may be discerned that compound **7** (triclinic, space group) crystallises with no fewer than 12 molecules in the asymmetric unit. Here, there are two independent hexamers, each comprised of six unique molecules, with the same complementary N–H ··· O and C–H ··· O links between the molecules as seen in compounds **4–6**.

Conclusion

The syntheses and crystal structures of the family of 2,4-bis(alkylamino)nitrobenzenes (alkyl = nC_5–C_8) have been described. Although the crystal symmetries are different, which possibly correlates with different orientations of the terminal parts of the alkyl chains, a robust supramolecular hexameric N–H ··· O hydrogen-bonded motif is present in each structure.

Experimental

The IR spectra were recorded on an ATI Mattson FTIR spectrometer using KBr discs. The UV spectra were recorded using a PerkinElmer Lambda 25 UV-Vis spectrometer with CH_2Cl_2 as the solvent. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100.5 MHz respectively using a Varian 400 spectrometer. Chemical shifts (δ) are given in ppm and measured by comparison with the residual solvent. Coupling constants (J) are given in Hz. Low resolution and high resolution mass spectra were obtained at the University of Wales, Swansea using electron impact ionisation and chemical ionisation. Melting points were determined on a Kofler hot-stage microscope.

Single crystal growth

For all samples, the starting material was dissolved in dichloromethane/petroleum ether (40–60 °C) and the solution was left to evaporate slowly at room temperature.

Crystallography

The intensity data for compounds **4–7** were collected on a Rigaku Mercury CCD diffractometer (Mo Kα radiation, λ = 0.71073 Å, T = 100 K). The structures of compounds **4** and **5** were routinely solved by direct methods with SHELXS-97,[15] but uninterpretable E-maps emerged for compounds **6** and **7** with SHELXS-97. However, the 'dual-space' algorithm in SHELXT[16] gave recognisable structures in space group $P1$ for compounds **6** and **7**, which were both transformed to the centrosymmetric space group prior to refinement. All of the structural models were completed and refined against $|F|^2$ with SHELXL-2014. Some of the terminal groups of the alkyl chains are disordered over two orientations. The N-bound H atoms were located in difference maps and refined freely for compound **4** or placed in idealised locations (N–H = 0.88 Å) for compounds **5**, **6** and **7** and refined as riding atoms. The C-bound H atoms were placed in idealised locations (C–H = 0.97–0.99 Å) in all cases and refined as riding atoms. The constraint $U_{iso}(H) = 1.2U_{eq}$(carrier) or $1.5U_{eq}$(methyl C) was applied in all cases. For compound **7**, the benzene rings were modelled as rigid hexagons (C–C = 1.39 Å). For compound **4**, a PLATON[17] analysis indicated a significant void of volume ~240 Å^3 centred at the origin, the centroid of the hexamer and symmetry equivalent locations, presumably corresponding to regions of highly disordered solvent molecules. The application of PLATON/SQUEEZE[17] indicated a very low electron density of about 14 *e* per cavity, although a small reduction in R-factors was achieved. The final R-factors for compound **6** and especially compound **7** are extremely high (see below), but chemically plausible structures have resulted and their gross features can at least be discerned.

4: $C_{16}H_{27}N_3O_2$, M_r = 293.40, yellow block, 0.06 × 0.05 × 0.03 mm, trigonal, space group (No. 148), Z = 18, a = 29.6593(7) Å, c = 10.4920(6) Å, V = 7993.0(6) Å^3 at 100 K. Number of measured and unique reflections = 35044 and 4071 respectively ($-38 \le h \le 32$, $-38 \le k \le 38$, $-13 \le l \le 13$; $2\theta_{max}$ = 54.9°; R_{int} = 0.069). Final $R(F)$ = 0.067, $wR(F^2)$ = 0.163 for 199 parameters and 2641 reflections with $I > 2\sigma(I)$ (corresponding R-values based on all 4071 reflections = 0.108 and 0.185 respectively), CCDC reference number 1518390. The presumed disordered solvent is not included in the calculations of M_r *etc.*

5: $C_{18}H_{31}N_3O_2$, M_r = 321.46, orange rod, 0.31 × 0.06 × 0.06 mm, triclinic, space group (No. 2), Z = 12, a = 18.3214(3) Å, b = 18.6127(4) Å, c = 20.0953(4) Å, α = 104.147(2)°, β = 105.226(2)°, γ = 111.987(2)°, V = 5663.6(2) Å^3 at 100 K. Number of measured and unique reflections = 89863 and 25863 respectively ($-23 \le h \le 23$, $-24 \le k \le 24$, $-26 \le l \le 26$; $2\theta_{max}$ = 55.0°; R_{int} = 0.048). Final $R(F)$ = 0.063, $wR(F^2)$ = 0.143 for 1240 parameters and 16177 reflections with $I > 2\sigma(I)$ (corresponding R-values based on all 25863 reflections = 0.111 and 0.165 respectively), CCDC reference number 1518391.

6: $C_{20}H_{35}N_3O_2$, M_r = 349.51, orange block, 0.30 × 0.10 × 0.07 mm, triclinic, space group (No. 2), Z = 18, a = 11.2731(3) Å, b = 30.5744(7) Å, c = 31.0881(8) Å, α = 62.603(2)°, β = 85.518(2)°, γ = 87.659(2)°, V = 9484.0(4) Å^3 at 100 K. Number of measured and unique reflections = 109635 and 35305 respectively ($-13 \le h \le 13$, $-37 \le k \le 37$, $-37 \le l \le 37$; $2\theta_{max}$ = 51.0°; R_{int} = 0.055). Final $R(F)$ = 0.094, $wR(F^2)$ = 0.234 for 2015 parameters and 20746 reflections with $I > 2\sigma(I)$ (corresponding R-values based on all 35305 reflections = 0.156 and 0.267 respectively), CCDC reference number 1518392.

7: $C_{22}H_{39}N_3O_2$, M_r = 377.56, orange rod, 0.32 × 0.09 × 0.08 mm, triclinic, space group (No. 2), Z = 24, a = 21.8346(12) Å, b = 24.4599(11) Å, c = 25.5751(12) Å, α = 97.386(4)°, β = 92.123(4)°, γ = 90.780(4)°, V = 13534.0(12) Å^3 at 100 K. Number of measured and unique reflections = 112684 and 52845 respectively ($-26 \le h \le 26$, $-30 \le k \le 29$, $-30 \le l \le 31$; $2\theta_{max}$ = 52.0°; R_{int} = 0.099). Final $R(F)$ = 0.204, $wR(F^2)$ = 0.404 for 2463 parameters and 18381 reflections with $I > 2\sigma(I)$ (corresponding R-values based on all 52845 reflections = 0.359 and 0.461 respectively), CCDC reference number 1518393.

*Synthesis of 2,4-bis(*n*-pentylamino)nitrobenzene* (**4**) *and general procedure*

2,4-Difluoronitrobenzene (1.0 g, 6.28 mmol) and n-pentylamine (3.0 mL, 25.1 mmol) in EtOH (8 mL) were sealed in a teflon-lined Parr bomb and heated at 150 °C for 15 h. On cooling, the mixture was mixed with CH_2Cl_2 (50 mL), extracted with aqueous HBr (8% 60 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and then purified by chromatography on silica gel. Elution with ether/petroleum ether (40–60 °C) (25:75) gave compound **4:** Yield 0.63 g (70%); yellow solid; m.p. 123–124 °C [from CH_2Cl_2/petroleum ether (40–60 °C)]; λ_{max} (EtOH)/nm 415 (log ε 4.8), 405 (4.83), 402 (4.83) and 398 (4.82); ν_{max}(KBr)/cm^{-1} 3317s, 2955m, 2929m, 2857m, 1614vs, 1579vs, 1543vs, 1459m, 1400s, 1328m, 1310vs, 1260vs, 1248vs, 1189vs, 1165vs, 1131vs, 1030vs, 817vs, 793w, 767w, 751s, 734s, 671s, 652m, 605m, 591vs and 555vs; δ_H (400 MHz; $CDCl_3$) 0.91–0.96 (6H, m), 3.42–4.0 (8H, m), 3.72–3.76 (4H, m) and 3.20–3.28 (4H, m), 5.80 (1H, s), 5.91 (1H, dd, J = 9, 2) and 8.0 (1H, d, J = 9) (2 × NH peaks missing); δ_C (100.1 MHz; $CDCl_3$) 13.4, 13.4, 22.4, 22.4, 28.5, 28.5, 29.1, 29.3, 43.0, 44.0, 90.0, 105.3, 123.5, 129.1, 148.6 and 154.2; *m/z* (orbitrap ASAP): 294.2175 $[M+H]^+$ 100%, $C_{16}H_{28}N_3O_2$; requires: 294.2176

*Synthesis of 2,4-bis(*n*-hexylamino)nitrobenzene* (**5**)

Following the procedure for **4**, but using n-hexylamine (3.0 mL) in place of n-pentylamine gave compound **5:** Yield 603 mg (59%);

yellow solid; m.p. 85–86 °C [from ether/petroleum ether (40–60 °C)]; λ_{max} (EtOH)/nm 403 (log ε 4.8) and 252 (log ε 4.82); ν_{max} (KBr)/cm^{-1} 3320m, 3071w, 2929m, 2856m, 2952m, 1614vs, 1579s, 1543s, 1462m, 1401s, 1313s, 1259vs, 1191vs, 1167s, 1129s, 819vs, 752m, 593s and 564s; δ_H (400 MHz; $CDCl_3$) 0.89–0.95 (6H, m), 1.30–1.49 (12H, m), 1.65–1.79 (4H, m), 3.18–3.28 (4H, m), 5.86 (1H, s), 6.03 (1H, dd, J = 9, 2 Hz) and 8.05 (1H, d, J = 9) (2 × NH peaks missing); δ_C (100.1 MHz; $CDCl_3$) 13.9, 14.1, 22.6, 26.7, 28.7, 31.5, 42.9, 44.0, 91.2, 105.1, 124.1, 129.2, 148.4, 153.5 (4 peaks are overlapping); *m/z* (orbitrap ASAP): 322.2497 $[M+H]^+$ 100%, $C_{18}H_{32}N_3O_2$; requires: 322.2497

*Synthesis of 2,4-bis(*n*-heptylamino)nitrobenzene* (**6**)

Following the procedure for **4**, but using *n*-heptylamine (3.0 mL) in place of *n*-pentylamine gave compound **6**: Yield 777 mg (70%); yellow solid; m.p. 79–80 °C [from ether/petroleum ether (40–60 °C)]; λ_{max} (EtOH)/nm 406 (log ε 4.8) and 251 (log ε 4.83); ν_{max} (KBr disc)/cm^{-1} 3319m, 2626m, 2853m, 1614vs, 1578s, 1542s, 1514m, 1466m, 1403s, 1382m, 1313s, 1258vs, 1226s, 1188vs, 1167vs, 1130s, 1087s, 819vs, 752m, 593s and 564s; δ_H (400 MHz; $CDCl_3$) 0.88–0.93 (6H, m), 1.31–1.46 (16H, m), 1.64–1.79 (4H, m), 3.18–3.27 (4H, m), 5.79 (1H, s), 6.00 (1H, dd, J = 9, 2 Hz) and 8.04 (1H, d, J = 9) (2 × NH peaks missing); δ_C (100.1 MHz; $CDCl_3$) 14.0, 22.5, 26.9, 27.1, 28.8, 28.9, 28.9, 30.8, 31.7, 42.9, 43.7, 90.83, 105.0, 123.9, 129.2, 148.4, 153.8 (3 peaks are overlapping); *m/z* (orbitrap ASAP): 350.2810 $[M + H]^+$ 100%, $C_{20}H_{36}N_3O_2$; requires: 350.2810.

*Synthesis of 2,4-bis(*n*-octylamino)nitrobenzene* (**7**)

Following the procedure for **4**, but using *n*-octylamine (3.0 mL) in place of *n*-pentylamine gave compound **7**: Yield 523 mg (44%); Yellow solid; m.p. 70–71 °C [from ether/petroleum ether (40–60 °C)]; λ_{max} (EtOH)/nm 404 (log ε 4.8) and 254 (log ε 4.81); ν_{max} (KBr disc)/cm^{-1} 3323m, 2926m, 2853m, 1614vs, 1577s, 1540s, 1514m, 1465m, 1401s, 1379m, 1329m, 1312s, 1259vs, 1219s, 1188vs, 1166s, 1129s, 1090s, 1055m, 820vs, 752m, 594s and 570s; δ_H (400 MHz; $CDCl_3$) 0.88–0.92 (6H, m), 1.30–1.41 (20H, m), 1.64–1.79 (4H, m), 3.18–3.30 (4H, m), 5.80 (1H, s), 6.00 (1H, dd, J = 9, 2 Hz) and 8.04 (1H, d, J = 9) (2 × NH peaks missing); δ_C (100.1 MHz; $CDCl_3$) 14.0, 22.6, 27.0, 27.1, 29.2, 30.8, 31.7, 42.9, 43.8, 91.1, 105.0, 124.0, 129.18, 148.4, 153.6 (7 peaks are overlapping); *m/z* (orbitrap ASAP): 378.3123 $[M + H]^+$ 100%, $C_{22}H_{40}N_3O_2$; requires: 378.3126.

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Electronic Supplementary Information

The ESI [molecular structures of compound **6** (Figs 6 and 7) and compound **7** (Figs 8 and 9)] is available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data CCDC1518390. CCDC1518391, CCDC1518392 and CCDC1518393 contain the crystallographic supplementary data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* https://summary.ccdc.cam.ac.uk/structure-summary-form

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