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Synthesis and characterisation of macrocycles containing both tetrazole and pyridine functionalities

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ABSTRACT

The syntheses of tetra-tetrazole macrocycles containing at least one 2,6-bis(tetrazole)pyridine unit, linked by a variety of *n*-alkyl (*n*=3, 5, 7 or 9 carbon atoms) chain lengths, are described. There has been no previous incorporation of the pyridine moiety into a tetra-tetrazolophane macrocycle. The crystal structure of one such tetra-tetrazole macrocycle has also been structurally characterised and revealed a bowl-shaped conformation.

1. Introduction

There are many articles and reviews on tetrazoles in the literature, including their use as carboxylic acid bioisosteres in drug discovery and as functional ligands in coordination chemistry.[1–5] The development of 'click' chemistry methodology, as described by Sharpless and co-workers,[6,7] has resulted in a recent increase in tetrazole structures, which suggests that molecular recognition studies of tetrazoles will become increasingly important.[8–15] We are interested in tetrazoles as precursors for the formation of new functionalised polytetrazole macrocycles, which could find application, for example, as sensors or in molecular recognition. We have previously reported the synthesis and structural characterisation of tetra-tetrazole macrocycles from 1,2-, 1,3- and 1,4-dicyanobenzene derivatives as well as the first example of a host–guest interaction between a tetra-tetrazole macrocycle and a solvent molecule.[16–18] Previous work in our group has shown that the use of odd-numbered carbon chains gave higher yields than when even-numbered chains were used.[18] This paper focuses on the synthesis and characterisation of bis-tetrazoles from 2,6-pyridinedicarbonitrile (**1**), their *n*-alkyl halide derivatives (where *n*=3, 5, 7 or 9), and their resulting tetra-tetrazole macrocycles (see Scheme 1). To our knowledge, there has been no previous incorporation of the pyridine moiety into a tetra-tetrazolophane macrocycle. The X-ray crystal structure of one such macrocyclic derivative (**7c**), which is obtained from the reaction of **3c** with 1,3-bis(tetrazol-5-yl)benzene (**6**), is also described.

2. Results and discussion

2.1. Syntheses and characterisation of bis-tetrazoles

The reaction of 2,6-pyridinedicarbonitrile (**1**) with sodium azide was carried out, following a similar procedure to that we have previously described,[19] to give 2,6-di(2*H*-tetrazol-5-yl)pyridine (**2**) in good yield. The IR spectrum of **2** showed the indicative loss of the nitrile and azide bands at ca. 2200 and ca. 2060 cm^{-1}, respectively. The ^{1}H NMR spectrum of **2** showed a multiplet at 8.32 ppm due to the pyridyl ring proton signals, and a broad singlet at 3.56 ppm due to the NH proton. The ^{13}C NMR spectrum confirmed the formation of the tetrazole system with the signal at 158.5 ppm, indicative of the tetrazole moiety.[16–19]

The alkylation of **2** was carried out using the appropriate α,ω-dibromoalkane in the presence of triethylamine as base in methanol for 3 h at reflux temperature. In each case, after cooling and reaction work-up, only two products were obtained, which were purified by column chromatography on silica gel. These products were the N2,N1′ (major) (**3a–d**) and N2,N2′ (minor) (**4a–d**) dialkylated systems. The melting points of the symmetric and

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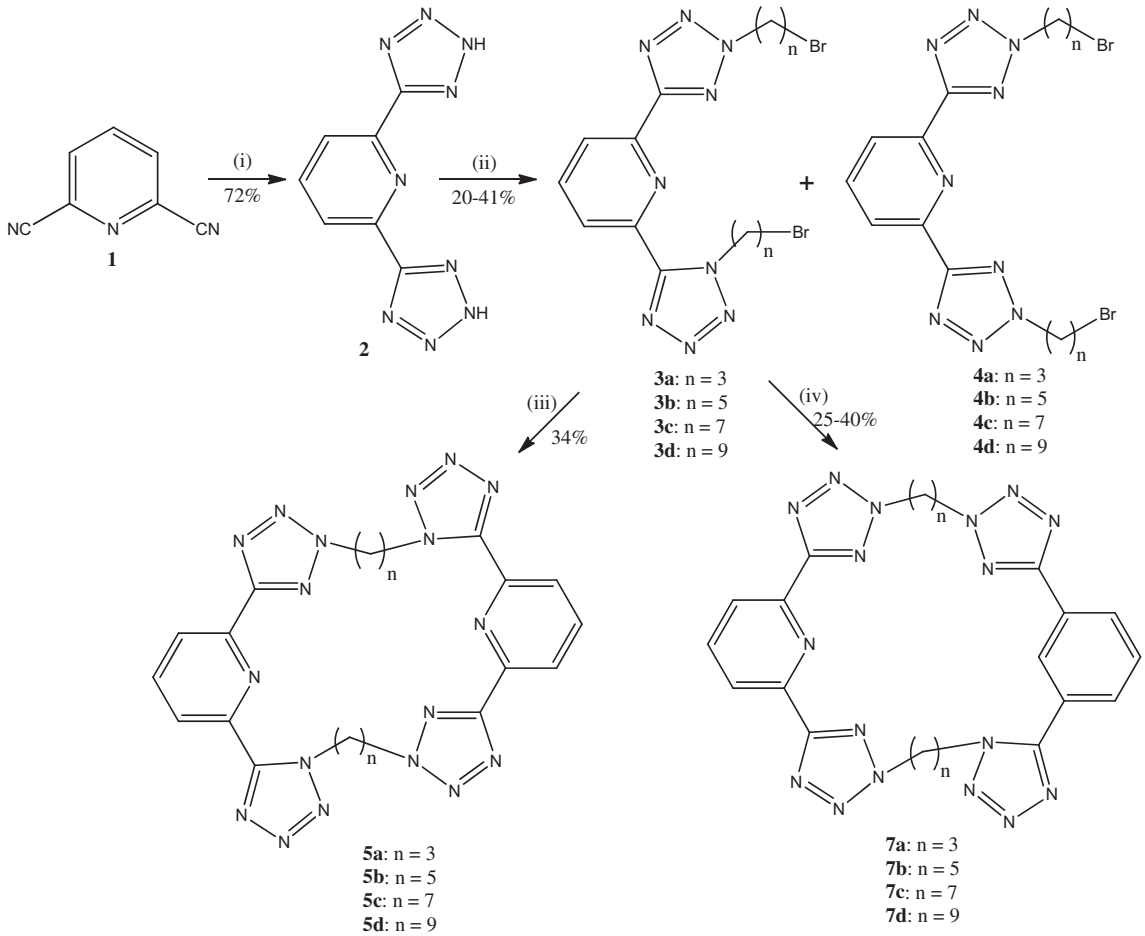

Scheme 1. Reagents and conditions: (i) NaN_3, NH_4Cl, LiCl, DMF, 110 °C, 10 h; (ii) 1,*n*-dibromoalkane (*n*=3, 5, 7, 9), Et_3N, MeOH, Δ, 24 h; (iii) **2**, K_2CO_3, DMF, 75 °C, 24 h; (iv) **6**, K_2CO_3, DMF, 75 °C, 24 h.

asymmetric products differed. It was observed that the symmetric analogues N2,N2′ had slightly higher melting point values, which may have been due to the symmetric system experiencing greater intermolecular bonding.

The range of asymmetric product yields (**3a**–**d**) varied from 17% to 37% (see Experimental section) and were considerably higher than the symmetric products (**4a**–**d**). It was observed that as the chain length increased the yield also increased. This may be due to the possibility of the species containing shorter chains forming polymeric adducts. The IR spectra of **3a**–**d** showed the characteristic bands of the tetrazole at 1668, 1523 and 1254 cm^{-1} and the >C=N– band of the pyridine at 1458 cm^{-1}, respectively. The ^1H NMR spectra of **3a**–**d** clearly showed the asymmetry that is present in the products. The aromatic protons that are *ortho* to the tetrazole rings are both split into two separate doublets at 8.50 ppm, beside the N1 tetrazole ring, and at 8.38 ppm for the N2 tetrazole ring of **3a**. The pseudo-triplet signal for the remaining proton on the pyridine ring at 8.12 ppm is not affected by asymmetry, probably due to its distance from the point of asymmetry. The methylene groups directly attached to the tetrazole ring appear as two separate triplets in the ^1H NMR spectra of **3a**–**d** with the N1-CH_2 triplet being observed at 5.25 ppm and the N2-CH_2 signal being observed at 4.96 ppm in **3a**. The signal associated with the CH_2Br appeared at ~3.4 ppm as a multiplet in all compounds in the series apart from compound **3a**, where two triplets at 3.62 ppm and 3.51 ppm (N1 and N2) were observed. This was probably due to the short distance from the N1 and N2 alkylated tetrazoles to the CH_2Br. As a comparison, in the ^1H NMR spectra of the 1,3-bis[(bromoalkylyl) tetrazol-5-yl]benzene (2-*N*, 2-*N*′),[18] the N2-CH_2 signals appear at ~4.70 ppm while those for the CH_2Br appear at ~3.40 ppm. All other methylene signals can be observed as multiplets between 2.1 and 1.3 ppm. The ^{13}C NMR spectra of **3a**–**d** also showed the asymmetric nature of the product with two tetrazole peaks at ~164 ppm for the N2-substituted tetrazole and ~151 ppm for the N1-substituted tetrazole.

The ^1H NMR spectra for the symmetric bis-tetrazoles **4a**–**d** are much simpler that those observed for the asymmetric bis-tetrazoles **3a**–**d**, just discussed. The aromatic protons, *ortho* to the tetrazole rings, appear as a single doublet at ~8.36 ppm while the remaining proton on the pyridine ring appears as a triplet at ~8.38 ppm. Furthermore, the methylene groups directly attached to the tetrazole ring now appear as a single triplet in the ^1H NMR spectra of **4a**–**d** at 4.95 ppm for **4a** and at ~4.75 ppm for **4b**–**d**. The ^{13}C NMR spectra confirmed the symmetric nature of the compounds with a signal at 164.4 ppm, due to the tetrazoles being substituted in the N2 position. The IR spectra of **4a**–**d** were very similar to those of the asymmetric derivatives. Apart from the NMR spectra, the other major difference between the asymmetric and symmetric derivatives was in the yield of material recovered. The yield of the symmetric products **4a**–**d** was surprisingly low, falling in the range of 2–5%. One possible reason for these low yields in the symmetric cases may be the presence of a pyridinium salt, formed during the acidification work-up of the bistetrazole derivative **2**. Due to the difference in pK_a between pyridine (ca. pK_a 5.2) and tetrazole (ca. pK_a 4.5), it is believed that the pyridine nitrogen will be protonated. However, this does not explain the difference in

yield between the asymmetric and symmetric derivatives, as this pyridinium salt would also have been present in the reaction.

2.2. X-ray crystal structure of 3b

Crystals of compound **3b**, suitable for an X-ray diffraction study, were obtained as colourless plates by the diffusion method of chloroform in methanol. The diffraction data were of poor quality but the significant features of the structure are clear. The structure confirmed the presence of the pendant bromoalkyl groups substituted in the N2,N1′ positions, see Fig. 1.

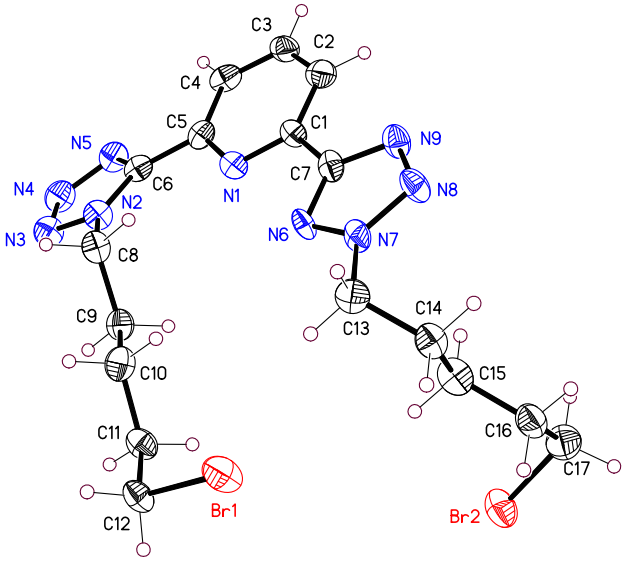

Fig. 1. Molecular structure of **3b** with displacement ellipsoids at the 50% probability level for non-H atoms.

One of the tetrazole rings and the pyridine ring are almost coplanar, with the other tetrazole ring being distinctly tilted relative to the other two rings. Both bromohexyl arms lie on the same face of the pyridine ring. A π–π interaction between neighbouring molecules is observed and shown in Fig. 2.

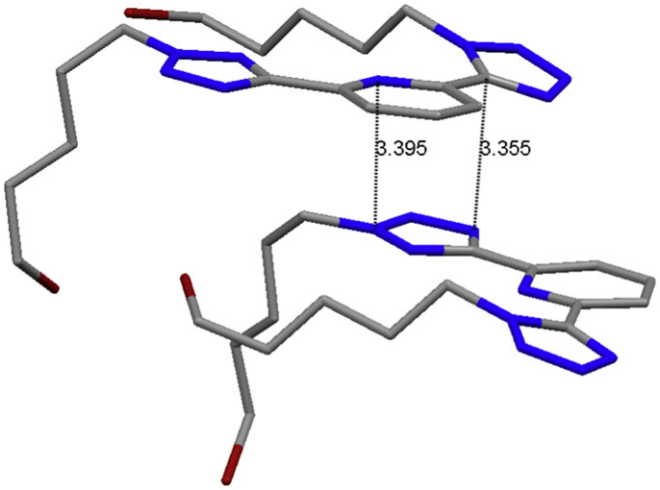

Fig. 2. Observed π–π interaction of **3b**.

2.3. Synthesis of pyridyl-tetra-tetrazole macrocycles

Since the yields of the asymmetric alkylated bis-tetrazoles (**3a**–**d**) were substantially better than those of the symmetric derivatives, it was decided to attempt the synthesis of an asymmetric pyridine tetra-tetrazole macrocycle. When an asymmetric alkylated product (**3a**–**d**) was reacted with 2,6-bis-(2*H*-tetrazol-5-yl)-pyridine (**2**) using previously reported conditions,[18] a number of products were observed by TLC analysis. However, these products could not be separated by conventional chromatography methods. This may have been due to the likelihood of pyridine macrocycles (N2,N1′,N2″,N1‴) and (N2,N1′,N1″,N2‴) having similar R_f values. The ^{1}H NMR spectra of the single spot by TLC for each of the tetra-tetrazole macrocycles (**5a**–**d**) were very complicated but clearly showed signals for two macrocycles (N2,N1′,N2″,N1‴) and (N2,N1′,N1″,N2‴).

We have previously reported the synthesis and structural characterisation of tetra-tetrazole macrocycles from 1,2-, 1,3- and 1,4-dicyanobenzene derivatives, using alkyl linkers.[16,18] The cyclisation reaction, in all cases, formed predominantly the symmetric product, where the alkyl chains are joined to the tetrazole moieties at the N2 position, with very little asymmetry being observed. It was therefore postulated that if the asymmetric alkylated products (**3a**–**d**) were clipped with 1,3-bis(tetrazol-5-yl)benzene (**6**) that one major product would be obtained, which was the alkylation of the 2N,2N′ positions of 1,3-bis(tetrazol-5-yl)benzene (see Experimental section). The major products in all of these reactions were the (N2,N2′,N2″,N1‴) macrocycles (**7a**–**d**), with high yields of ~40% in all cases, except in the case of **7d**, which is probably due to the difficulty in forming the large ring system. The HRMS results obtained for the four products (**7a**–**d**) confirmed the formation of the macrocycles.

The IR spectra of **7a**–**d** were very similar to those of the alkylated precursors (**3a**–**d**) with characteristic shifts for pyridine, tetrazole and phenyl ring systems being observed (see Experimental section). In the ^{1}H NMR spectra of all the cyclisation products, the signal for the CH_2Br at ~3.4 ppm had disappeared, and the accompanying loss of the CH_2Br signal in the ^{13}C NMR spectra confirmed that cyclisation had occurred. The ^{1}H NMR spectra of **7a**–**d** have a complex aromatic region. The signals in the ^{1}H NMR spectrum of **7a** at 8.41(s), 8.17(d) and 7.60(t) ppm are due to the protons of the phenyl ring while those at 8.31(d), 8.04(d) and 7.91(t) ppm are due to the protons on the pyridine ring. The aromatic regions in the ^{1}H NMR spectra of **7b**–**d** are similar. The asymmetric nature of the macrocycle is observed by the appearance of two sets of doublets for the pyridine protons *ortho* to the different tetrazole rings. This asymmetry also manifests itself in the signals of the methylene groups attached to the tetrazole rings. A triplet is observed at 5.30 ppm for the methylene protons attached to the tetrazole ring at N1. A multiplet for the methylene protons attached to the symmetric 1,3-bis(tetrazol-5-yl)benzene is observed at 5.03 ppm. Another multiplet is observed at 4.74 ppm for the methylene group bonded to the second tetrazole attached to the pyridine group. These two multiplets at 5.03 and 4.74 ppm are not observed as the alkyl chain increases, presumably because the environment in which the methylene groups attached to the N2-tetrazole becomes similar. In compounds **7b**–**d**, a single multiplet is observed at ca. 4.70 ppm, which accounts for the six protons associated with the N2-CH_2 substituted tetrazoles. The remaining alkyl protons appear at 1.67 ppm. With increased alkyl chain length further multiplets can be observed at ca. 2.10 ppm.

The ^{13}C NMR spectra of **7a**–**d** confirmed the macrocyclic structure with three signals observed at 164.6, 164.2 and 163.9 ppm, respectively, for the N2-substituted tetrazoles. A single signal was observed at 151.5 ppm for the N1-substituted tetrazole, confirming the substitution pattern of the macrocycles. Furthermore, four peaks are observed for the methylene carbons adjacent to the tetrazole nitrogens at 51.3, 50.4 and 49.4 ppm for the N2-substituted tetrazoles and 46.1 ppm for the N1-substituted tetrazole.

2.4. X-ray crystal structure of 7c

Crystals of **7c** were obtained from chloroform solution, and the crystal structure confirms the expected tetra-tetrazole macrocyclic structure, with three of the tetrazole rings substituted at the N2 position and one tetrazole ring substituted at the N1 position, as suggested by ^{13}C NMR spectroscopy (Fig. 3). The structure also shows that N8 of one tetrazole ring and N9 of the pyridine ring are potentially available for use as metal ion chelators.

Bond lengths and angles are similar to other tetrazole macrocyclic compounds we have previously reported.[16,18] One striking difference between **7c** and a macrocycle which contains two phenyl rings, such as **8**,[16] is the overall geometry of both macrocycles, which is bowl-shaped in the case of **7c** (Fig. 4) but is more step-like in **8** (Fig. 5). This geometry change is likely to be a packing effect due to the different alkyl chain lengths. Furthermore, there is now only one π–π interaction present between the ring containing N10–N13 and its symmetry equivalent (under symmetry operation 1−*x*, 1−*y*, z), with a centroid–centroid distance of 3.478 Å, which results in the packing arrangement shown in Fig. 6. This type of arrangement is different to that observed in **8** where adjacent macrocycles are arranged so that one benzene-tetrazole unit lies over the cavity of the adjacent macrocycle (Fig. 5), forming a local stacking arrangement.

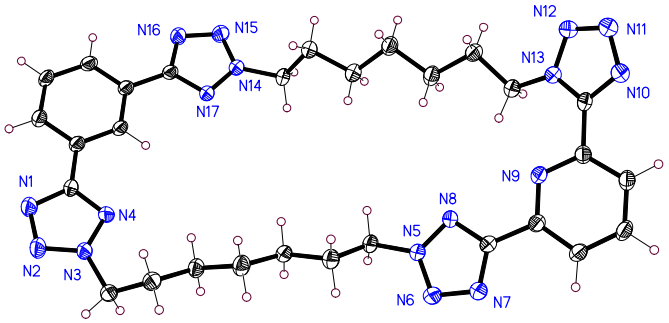

Fig. 3. Molecular structure of **7c** with displacement ellipsoids at the 50% probability level for non-H atoms.

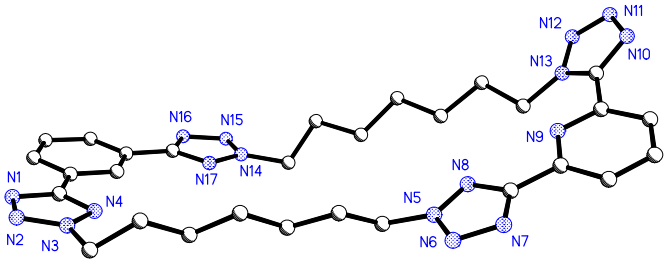

Fig. 4. Side view of **7c**.

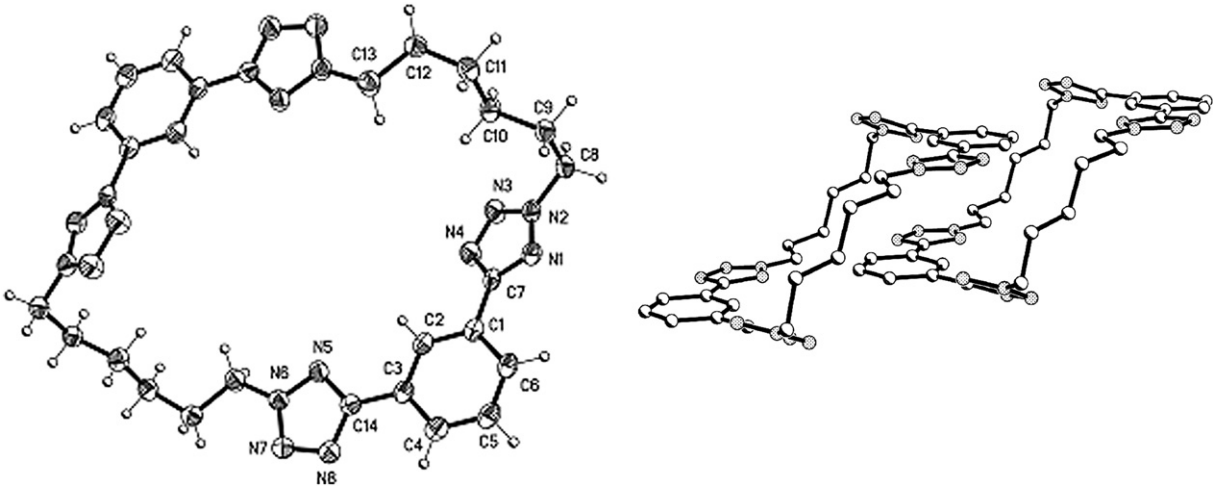

Fig. 5. Molecular structure of **8** showing displacement ellipsoids at the 50% probability level for non-H atoms (left), and a stacking interaction between adjacent macrocycles in **8** (right).[16]

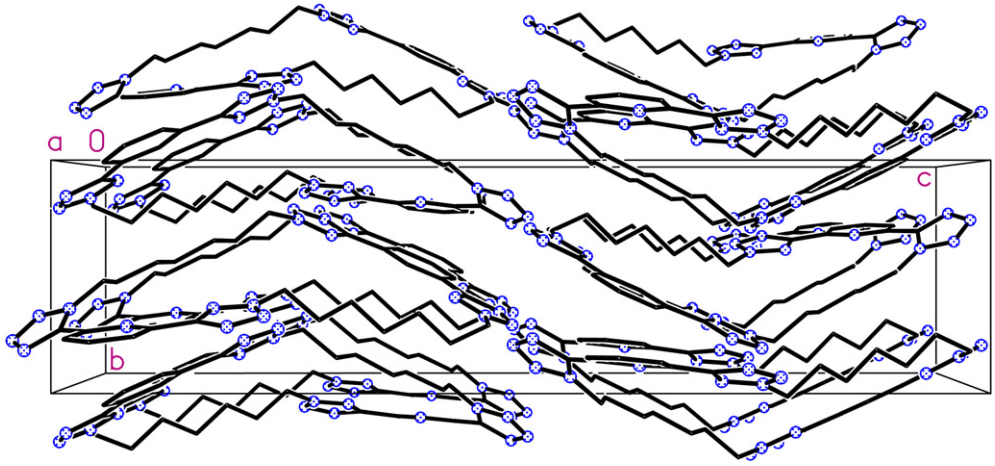

Fig. 6. Unit cell of **7c** viewed down the *a* axis, showing the packing arrangement of the macrocycle.

3. Conclusions

In this paper, we have reported the syntheses and characterisation of bromoalkyl derivatives of 2,6-bis(tetrazole)pyridine, where the alkyl chain contains either 3, 5, 7 or 9 carbons atoms. Interestingly, the predominant compound formed in these reactions is the asymmetric 1-*N*,2-*N*′-bistetrazole isomer, whereas the same reactions carried out with 1,3-bis(tetrazole)benzene have previously yielded symmetric 2-*N*,2-*N*′-bistetrazole derivatives. Four new tetra-tetrazole macrocycles, containing one pyridine ring, were synthesised and the X-ray crystal structure of one such macrocycle (**7c**) showed a bowl-shaped conformation. Complexation studies of these new tetra-tetrazole macrocycles with various metal ions are currently being undertaken.

4. Experimental

4.1. General

All reagents and solvents were commercially obtained and used without further purification. The petroleum ether used for chromatography was 40:60 reagent grade. ^{1}H and ^{13}C NMR (δ ppm; *J* Hz) spectra were recorded on a JEOL JNM-LA300 FT-NMR spectrometer using saturated $CDCl_3$ solutions with Me_4Si reference, unless indicated otherwise. Infrared spectra (cm^{-1}) were recorded as KBr discs or liquid films between KBr plates using a Nicolet Impact 410 FT-IR spectrophotometer. Melting point analysis was carried out using either a Stewart Scientific SMP1 or a Mettler FP62 melting point apparatus and are uncorrected. Microanalysis was carried out at the Microanalytical Laboratory of University College, Dublin. Mass spectrometry was carried out at the Centre for Synthesis and Chemical Biology (CSCB), University College, Dublin using Quattro *micro*™ LC-MS/MS and LCT mass spectrometers. Standard Schlenk techniques were used throughout. The synthesis of compounds **6**[19] has been described previously.

CAUTION: owing to their potentially explosive nature, all preparations of and subsequent reactions with azides and tetrazoles were conducted under an inert atmosphere behind a rigid safety screen.

4.2. Synthesis of 2,6-di(2*H*-tetrazol-5-yl)pyridine (2)

A suspension of 2,6-pyridinedicarbonitrile (2.57 g, 20 mmol), sodium azide (2.86 g, 43 mmol), ammonium chloride (2.35 g, 43 mmol) and lithium chloride (0.6 g, 14 mmol) in anhydrous dimethylformamide (60 mL) was stirred for 10 h at 110 °C. After this time, the solution was cooled and the insoluble salts were removed by filtration. The solvent was then evaporated under reduced pressure and the residue was dissolved in deionised water (200 mL) and acidified with concentrated HCl (3 mL), to initiate precipitation. The product was filtered, washed with water (3×40 mL) and dried to give 2,6-di(2*H*-tetrazol-5-yl)pyridine (**2**) as a white crystalline powder. Purification by recrystallisation from methanol to give white needles of **2** (3.08 g, 14.3 mmol, 72%); mp >300 °C; IR (KBr cm^{-1}) 3415 (N–H), 2851, 1654, 1596, 1458, 1278; ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ_H 8.49 (1H, t, *J*=7.8 Hz, Ar*H*), 8.23 (2H, d, *J*=7.6 Hz, Ar*H*), 3.56 (2H, s (br), N*H*); ^{13}C NMR (75.4 MHz, $(CD_3)_2SO$): δ_C 158.5, 145.5, 142.9, 119.3, 125.4. Anal. Calcd for $C_7H_5N_9$: C, 39.07; H, 2.34; N, 58.59%. Found C, 38.98; H, 2.36; N, 58.45%.

4.3. General syntheses of alkylated bis-tetrazoles (3 and 4)

Compound **2** (1.51 g, 7.0 mmol) was dissolved in methanol (60 mL) and to the stirred solution was added triethylamine (4.23 mL, 42 mmol). The resulting solution was stirred at reflux temperature for 30 min, then to the hot solution was added the corresponding dibromoalkane (21.0 mmol). The reaction mixture was then stirred at reflux for a further 24 h. On cooling, the solid was removed by filtration and the solvent was removed from the filtrate under vacuum. The resulting products were purified by column chromatography on silica gel (initially at a ratio of petroleum ether/ethyl acetate 70:30, followed by the ratio 60:40).

*4.3.1. 2-[2-(3-Bromopropyl)-2H-tetrazol-5-yl]-6-[1-(3-bromopropyl)-1H-tetrazol-5-yl]pyridine (**3a**).* White solid (0.55 g, 1.2 mmol, 17.2%); mp 88–90 °C; R_f=0.32 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2968, 1668 (>C=N–), 1523 (–N=N–), 1458 (C=N, pyridine), 1434, 1254; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.67 (4H, m, CH_2), 3.51 (2H, t, *J*=6.1 Hz, CH_2Br (N2)), 3.62 (2H, t, *J*=6.6 Hz, CH_2Br (N1)), 4.96 (2H, t, *J*=6.6 Hz, CH_2N2), 5.25 (2H, t, *J*=6.7 Hz, CH_2N1), 8.12 (1H, t, *J*=7.8 Hz, py*H*), 8.38 (1H, d, *J*=7.8 Hz, py*H*), 8.50 (1H, d, *J*=7.8 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 28.7, 29.3, 31.9, 32.9, 48.9, 51.6, 124.0, 125.3, 138.5, 145.0, 146.7, 151.4, 164.1. Anal. Calcd for $C_{13}H_{15}N_9Br_2$: C, 34.16; H, 3.31; N, 27.58%. Found: C, 34.48; H, 3.44; N, 27.21%.

*4.3.2. 2,6-Bis[2-(3-bromopropyl)-2H-tetrazol-5-yl]-pyridine (**4a**).* White solid (0.10 g, 0.22 mmol, 3.1%); mp 94–96 °C; R_f=0.21 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2922, 2855, 1648 (>C=N–), 1587 (–N=N–), 1459 (C=N, pyridine), 1436, 1263; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.68 (4H, q, *J*=6.1 Hz, CH_2), 3.48 (4H, t, *J*=6.8 Hz, CH_2Br), 4.95 (4H, t, *J*=6.8 Hz, CH_2N), 8.02 (1H, t, *J*=7.8 Hz, py*H*), 8.37 (2H, d, *J*=7.8 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 29.7, 31.8, 51.7, 123.8, 138.5, 148.3, 164.4. Anal. Calcd for $C_{13}H_{15}N_9Br_2$: C, 34.16; H, 3.31; N, 27.58%. Found: C, 34.38; H, 3.24; N, 27.24%.

*4.3.3. 2-[2-(5-Bromopentyl)-2H-tetrazol-5-yl]-6-[1-(5-bromopentyl)-1H-tetrazol-5-yl]-pyridine (**3b**).* White solid (1.21 g, 2.36 mmol, 33.6%); mp 78–80 °C; R_f=0.41 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2925, 2857, 1651 (>C=N–), 1582 (–N=N–), 1460 (C=N, pyridine), 1434, 1261; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.71 (4H, m, CH_2), 1.93 (4H, m, CH_2), 2.17 (4H, m, CH_2), 3.42 (4H, m, CH_2Br), 4.76 (2H, t, *J*=7.1 Hz, CH_2N2), 5.16 (2H, t, *J*=7.8 Hz, CH_2N1), 8.12 (1H, t, *J*=7.8 Hz, py*H*), 8.36 (1H, d, *J*=6.9 Hz, py*H*), 8.49 (1H, d, *J*=6.9 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 25.0, 26.4, 27.2, 27.9, 28.6, 28.9, 29.7, 32.9, 49.8, 53.3, 123.9, 125.2, 138.8, 145.2, 146.9, 151.2, 164.0. Anal. Calcd for $C_{17}H_{23}N_9Br_2$: C, 39.78; H, 4.52; N, 24.56%. Found: C, 39.83; H, 4.46; N, 24.53%.

*4.3.4. 2,6-Bis-[2-(5-bromopentyl)-2H-tetrazol-5-yl]-pyridine (**4b**).* White solid (0.10 g, 0.2 mmol, 2.8%); mp 82–84 °C; R_f=0.32 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2926, 2856, 1649 (>C=N–), 1581 (–N=N–), 1462 (C=N, pyridine), 1435, 1258; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.68 (4H, m, CH_2), 1.91 (4H, m, CH_2), 2.19 (4H, m, CH_2), 3.41 (4H, t, *J*=6.6 Hz, CH_2Br), 4.77 (4H, t, *J*=7.1 Hz, CH_2N), 8.06 (1H, t, *J*=7.8 Hz, py*H*), 8.45 (2H, d, *J*=7.8 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 28.0, 28.2, 28.5, 31.8, 53.2, 123.6, 138.4, 147.5, 164.3. Anal. Calcd for $C_{17}H_{23}N_9Br_2$: C, 39.78; H, 4.52; N, 24.56%. Found: C, 39.79; H, 4.54; N, 24.51%.

*4.3.5. 2-[2-(7-Bromoheptyl)-2H-tetrazol-5-yl]-6-[1-(7-bromoheptyl)-1H-tetrazol-5-yl]-pyridine (**3c**).* White solid (1.32 g, 2.32 mmol, 33%); mp 64–66 °C; R_f=0.53 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2923, 2857, 1653 (>C=N–), 1581 (–N=N–), 1464 (C=N, pyridine), 1434, 1261; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.41 (12H, m, CH_2), 1.83 (4H, m, CH_2), 2.09 (4H, m, CH_2), 3.40 (4H, m, CH_2Br), 4.73 (2H, t, *J*=7.1 Hz, CH_2N2), 5.14 (2H, t, *J*=7.4 Hz, CH_2N1), 8.10 (1H, t, *J*=7.8 Hz, py*H*), 8.36 (1H, d, *J*=6.8 Hz, py*H*), 8.48 (1H, d, *J*=6.8 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 26.1, 26.2, 27.8, 27.9, 28.1, 28.2, 29.3, 30.0, 32.5, 32.6, 33.8, 33.9, 50.1, 53.5, 123.8, 125.1,

138.8, 145.2, 146.9, 151.2, 164.0. Anal. Calcd for $C_{21}H_{31}N_9Br_2$: C, 44.30; H, 5.49; N, 22.14%. Found: C, 44.36; H, 5.54; N, 22.17%.

*4.3.6. 2,6-Bis-[2-(7-bromoheptyl)-2H-tetrazol-5-yl]-pyridine (**4c**).* White solid (0.20 g, 0.35 mmol, 5%); mp 70–72 °C; R_f=0.43 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2928, 2856, 1653 (>C=N–), 1581 (–N=N–), 1463 (C=N, pyridine), 1430, 1260; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.37 (12H, m, CH_2), 1.89 (4H, m, CH_2), 2.11 (4H, m, CH_2), 3.44 (4H, t, J=7.3 Hz, CH_2Br), 4.76 (4H, t, J=7.3 Hz, CH_2N), 8.12 (1H, t, J=7.7 Hz, py*H*), 8.36 (2H, d, J=7.8 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 27.2, 28.6, 28.7, 29.8, 32.7, 34.1, 53.6, 123.5, 138.3, 147.6, 164.2. Anal. Calcd for $C_{21}H_{31}N_9Br_2$: C, 44.30; H, 5.49; N, 22.14%. Found: C, 44.26; H, 5.44; N, 22.09%.

*4.3.7. 2-[2-(9-Bromononyl)-2H-tetrazol-5-yl]-6-[1-(9-bromononyl)-1H-tetrazol-5-yl]-pyridine (**3d**).* White solid (1.61 g, 2.6 mmol, 36.7%); mp 51–53 °C; R_f=0.67 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2923, 2857, 1653 (>C=N–), 1581 (–N=N–), 1464 (C=N, pyridine), 1434, 1261; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.34 (12H, m, CH_2), 1.61 (8H, m, CH_2), 1.83 (4H, m, CH_2), 2.08 (4H, m, CH_2), 3.40 (4H, m, CH_2Br), 4.72 (2H, t, J=7.1 Hz, CH_2N2), 5.16 (2H, t, J=7.3 Hz, CH_2N1), 8.09 (1H, t, J=8.1 Hz, py*H*), 8.36 (1H, d, J=7.8 Hz, py*H*), 8.48 (1H, d, J=7.8 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 24.7, 24.8, 24.9, 25.0, 25.1, 25.1, 25.2, 25.3, 25.3, 25.4, 25.5, 26.4, 27.2, 28.9, 28.1, 29.7, 32.9, 49.7, 53.3, 123.9, 125.2, 138.7, 145.4, 146.8, 151.3, 164.4. Anal. Calcd for $C_{25}H_{39}N_9Br_2$: C, 48.01; H, 6.29; N, 20.16%. Found: C, 48.06; H, 6.28; N, 20.19%.

*4.3.8. 2,6-Bis-[2-(9-bromononyl)-2H-tetrazol-5-yl]-pyridine (**4d**).* White solid (0.20 g, 0.3 mmol, 4.6%); mp 58–60 °C; R_f=0.54 (60:40 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2925, 2855, 1651 (>C=N–), 1582 (–N=N–), 1460 (C=N, pyridine), 1434, 1261; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.37 (16H, m, CH_2), 1.61 (4H, m, CH_2), 1.89 (4H, m, CH_2), 2.11 (4H, m, CH_2), 3.40 (4H, t, J=7.1 Hz, CH_2Br), 4.72 (4H, t, J=7.1 Hz, CH_2N), 8.12 (1H, t, J=7.7 Hz, py*H*), 8.36 (2H, d, J=7.8 Hz, py*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 26.3, 26.8, 27.2, 28.6, 28.7, 29.8, 32.7, 34.0, 53.5, 123.5, 138.3, 147.6, 164.2. Anal. Calcd for $C_{25}H_{39}N_9Br_2$: C, 48.01; H, 6.29; N, 20.16%. Found: C, 48.10; H, 6.32; N, 20.21%.

4.4. General syntheses of di-pyridyl-tetra-tetrazole macrocycles (5a–d)

A mixture of **2** (0.86 g, 4.0 mmol) and potassium carbonate (2.78 g, 20.0 mmol) in anhydrous dimethylformamide (50 mL) was stirred at 75 °C under a nitrogen atmosphere, then treated with **3a**–**d** (4.0 mmol) and stirred at 75 °C for 24 h. The insoluble salts, which were removed from the cooled mixture by filtration, were washed with ethyl acetate. The combined washings and mother-liquor were evaporated under reduced pressure. The residue was dissolved in chloroform and chromatographed on a silica gel column using ethyl acetate/petroleum ether (70:30 v/v) as eluent to give a white solid. Only ^{1}H NMR data was obtained for all mixtures.

*4.4.1. Macrocycle **5a**.* ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.97 (4H, br m, CH_2), 4.75 (4H, br t, CH_2N2), 5.27 (4H, br t, CH_2N1), 8.15 (2H, br t, py*H*), 8.35 (2H, br d, py*H*), 8.48 (2H, br d, py*H*).

*4.4.2. Macrocycle **5b**.* ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.42 (8H, br m, CH_2), 1.83 (4H, br m, CH_2), 4.79 (4H, br t, CH_2N2), 5.23 (4H,br t, CH_2N1), 8.14 (2H, br t, py*H*), 8.33 (2H, br d, py*H*), 8.50 (2H, br d, py*H*).

*4.4.3. Macrocycle **5c**.* ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.45 (12H, br m, CH_2), 1.79 (8H, br m, CH_2), 4.72 (4H, br t, CH_2N2), 5.30 (4H, br t, CH_2N1), 8.18 (2H, br t, py*H*), 8.39 (2H, br d, py*H*), 8.46 (2H, br d, py*H*).

*4.4.4. Macrocycle **5d**.* ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.35 (12H, br m, CH_2), 1.65 (8H, br m, CH_2), 1.81 (8H, br m, CH_2), 4.73 (4H, br t, CH_2N2), 5.12 (4H, br t, CH_2N1), 8.09 (2H, br t, py*H*), 8.04 (1H, d, J=6.8 Hz, py*H*), 8.17 (2H, m, Ar*H*), 8.31 (1H, d, J=6.7 Hz, py*H*), 8.41 (1H, s, Ar*H*).

4.5. General syntheses of pyridyl-tetra-tetrazole macrocycles (7a–d)

A mixture of **6** (0.86 g, 4.0 mmol) and potassium carbonate (2.78 g, 20.0 mmol) in anhydrous dimethylformamide (50 mL) was stirred at 75 °C under a nitrogen atmosphere, then treated with **3a**–**d** (4.0 mmol) and stirred at 75 °C for 24 h. The insoluble salts, which were removed from the cooled mixture by filtration, were washed with ethyl acetate. The residue was dissolved in chloroform and chromatographed on a silica gel column using ethyl acetate/petroleum ether (70:30 v/v) as eluent to give the pyridine tetra-tetrazolophane macrocycles (**7a**–**d**).

*4.5.1. Macrocycle **7a**.* White crystalline solid (0.43 g, 0.84 mmol, 21%); mp 210–212 °C; R_f=0.03 (50:50 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2926, 2851, 1654 (>C=N–), 1596 (–N=N–), 1458 (C=N, pyridine), 1433, 1261; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.67 (4H, m, CH_2), 4.74 (2H, m, CH_2N2), 5.03 (4H, m, CH_2N2), 5.30 (2H, t, J=7.1 Hz, CH_2N1), 7.60 (1H, t, J=7.6 Hz, Ar*H*), 7.91 (1H, t, J=7.9 Hz, py*H*), 8.04 (1H, d, J=6.8 Hz, py*H*), 8.17 (2H, m, Ar*H*), 8.31 (1H, d, J=6.7 Hz, py*H*), 8.41 (1H, s, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 29.4, 29.7, 46.1, 49.4, 50.4, 51.3, 123.9, 125.7, 125.8, 127.8, 128.1, 128.2, 128.8, 129.8, 138.7, 144.5, 146.8, 151.5, 163.9, 164.2, 164.6; HRMS $(M+H)^+$ calcd for $C_{21}H_{20}N_{17}$=510.2009, found=510.2085. Anal. Calcd for $C_{21}H_{19}N_{17}$: C, 49.51; H, 3.76; N, 46.74%. Found: C, 49.62; H, 3.88; N, 46.91%.

*4.5.2. Macrocycle **7b**.* White crystalline solid (0.45 g, 0.79 mmol, 20%); mp 195–197 °C; R_f=0.16 (50:50 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2925, 2855, 1654 (>C=N–), 1596 (–N=N–), 1458 (C=N, pyridine), 1433, 1261; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.64 (4H, m, CH_2), 2.19 (8H, m, CH_2), 4.74 (6H, m, CH_2N2), 5.10 (2H, t, J=7.2 Hz, CH_2N1), 7.68 (1H, t, J=7.8 Hz, Ar*H*), 7.94 (1H, t, J=7.9 Hz, py*H*), 8.13 (1H, d, J=6.8 Hz, py*H*), 8.31 (2H, m, Ar*H*), 8.40 (1H, d, J=6.8 Hz, py*H*), 8.69 (1H, s, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 23.4, 23.5, 28.1, 28.3, 28.8, 29.4, 49.7, 52.3, 53.0, 53.1, 123.8, 125.2, 125.5, 128.0, 128.2, 128.3, 128.4, 129.7, 138.6, 145.0, 146.7, 151.4, 164.0, 164.2, 164.6; HRMS $(M+H)^+$ calcd for $C_{25}H_{28}N_{17}$=566.2635, found=566.2695. Anal. Calcd for $C_{25}H_{27}N_{17}$: C, 53.09; H, 4.81; N, 42.10%. Found: C, 52.89; H, 4.71; N, 42.54%.

*4.5.3. Macrocycle **7c**.* White crystalline solid (0.43 g, 0.69 mmol, 17.3%); mp 185–187 °C; R_f=0.35 (50:50 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2924, 2855, 1658 (>C=N–), 1597 (–N=N–), 1459 (C=N, pyridine), 1432, 1261; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.43 (10H, m, CH_2), 2.08 (10H, m, CH_2), 4.70 (6H, m, CH_2N2), 5.10 (2H, t, J=7.2 Hz, CH_2N1), 7.64 (1H, t, J=7.7 Hz, Ar*H*), 8.04 (1H, t, J=7.9 Hz, py*H*), 8.25 (1H, d, J=7.0 Hz, py*H*), 8.32 (2H, m, Ar*H*), 8.44 (1H, d, J=6.9 Hz, py*H*), 8.83 (1H, s, Ar*H*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 25.6, 25.8, 26.1, 26.2, 27.6, 28.4, 28.8, 29.2, 29.7, 29.9, 49.9, 52.8, 53.2, 53.4, 123.8, 125.2, 125.3, 128.2, 128.3, 128.4, 128.5, 129.7, 138.7, 145.2, 146.9, 151.3, 163.9, 164.4, 164.6; HRMS $(M+H)^+$ calcd for $C_{29}H_{36}N_{17}$=622.3261, found=622.3317. Anal. Calcd for $C_{29}H_{35}N_{17}$: C, 56.03; H, 5.67; N, 38.30%. Found: C, 56.34; H, 5.83; N, 38.19%.

*4.5.4. Macrocycle **7d**.* White crystalline solid (0.41 g, 0.61 mmol, 15%); mp 167–168 °C; R_f=0.58 (50:50 petroleum ether/ethyl acetate); IR (KBr, cm^{-1}): 2920, 2852, 1656 (>C=N–), 1596 (–N=N–), 1459 (C=N, pyridine), 1434, 1260; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.33 (22H, m, CH_2), 2.07 (10H, m, CH_2), 4.69 (6H, m,

CH_2N2), 5.12 (2H, t, J=7.3 Hz, CH_2N1), 7.64 (1H, t, J=7.2 Hz, ArH), 8.07 (1H, t, J=7.8 Hz, py$H$), 8.29 (3H, m, py$H$ and ArH), 8.46 (1H, d, J=6.9 Hz, py$H$), 8.89 (1H, s, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 25.8, 26.1, 28.3, 28.4, 28.7, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.7, 30.3, 50.1, 53.1, 53.3, 53.5, 123.7, 125.1, 125.2, 128.3, 128.4, 129.6, 138.7, 145.2, 146.9, 151.3, 163.9, 164.4, 164.5; HRMS $(M+H)^+$ calcd for $C_{33}H_{44}N_{17}$=678.3887, found=678.3944. Anal. Calcd for $C_{33}H_{43}N_{17}$: C, 58.48; H, 6.39; N, 35.13%. Found: C, 58.34; H, 6.43; N, 35.19%.

4.6. Crystallography

Data for **3b** and **7c** were collected at 150(2) K on a Bruker Apex II CCD diffractometer using Mo Kα radiation (λ=0.71073 Å). The structures were solved by direct methods and refined on F^2 using all the reflections.[20] All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. Crystallographic data for **3b** and **7c** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 799907 and 799908. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Compound **3b**. *Crystal data*: $C_{17}H_{23}Br_2N_9$, M=513.26, orthorhombic, a=9.99029(19), b=10.2310(19), c=40.898(8) Å, U=4143.6(13) Å^3, space group *Pbca*, Z=8, μ=3.936 mm^{-1}, ρ_{calcd}=1.646 Mg cm^{-3}, 28973 data (3639 unique, R_{int}=0.1246) were measured in the range $1.99<\theta<25.00°$. $R_1(I>2\sigma(I))$=0.0883 and wR_2(all data)=0.2113. Goodness of fit on F^2=1.178. CCDC No. 799907.

Compound **7c**. *Crystal data*: $C_{29}H_{35}N_{17}$, M=621.74, monoclinic, a=11.5821(13), b=8.1191(9), c=32.691(4) Å, β=90.034(2)°, U=3074.1(6) Å^3, space group $P2_1/c$, Z=4, μ=0.090 mm^{-1}, ρ_{calcd}=1.343 Mg cm^{-3}, 26150 data (6321 unique, R_{int}=0.0478) were measured in the range $1.76<\theta<26.42°$. $R_1(I>2\sigma(I))$=0.0432 and wR_2(all data)=0.1087. Goodness of fit on F^2=1.021. CCDC No. 799908.

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