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Synthesis and characterisation of tetra-tetrazole macrocycles

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Abstract—The syntheses of tetra-tetrazole macrocycles, containing two bis-tetrazole units linked by a variety of alkyl-chain lengths from four to eight carbons, are described. The crystal structures of three of these derivatives are reported, and the molecular conformation in the solid state is compared to that of the previously reported tetra-tetrazole macrocycle and to other bis- and tris(tetrazole)benzene structures. The macrocycle conformation is influenced by the length of the alkyl-chain linker, the relative orientation of the tetrazole rings on the benzene ring and by intermolecular interactions. In the macrocycles based on 1,2-bis(tetrazole)benzene, the adjacent tetrazole rings on the benzene ring are prevented from becoming co-planar on intramolecular (steric) grounds. In the 1,3- and 1,4-bis(tetrazole)benzene derivatives, there is no such impediment, and a co-planar arrangement is observed where intra- and/or intermolecular stacking interactions exist. Deviations from co-planarity are associated with optimisation of intermolecular interactions between the tetrazole rings and adjacent alkyl chains. In the macrocycle based on 1,4-bis(tetrazole)benzene with four-carbon linkers, an intramolecular stacking interaction exists, which precludes the presence of any cavity. In the macrocycle based on 1,3-bis(tetrazole)benzene with six-carbon linkers, a cavity of 10.8×9.4 Å is observed for each molecule in the solid state, although the packing of adjacent molecules is such that there are no extended channels running through the crystal.

1. Introduction

The growth of tetrazole chemistry over the last 25 years has been significant, mainly as a result of the roles played by tetrazoles in coordination chemistry as ligands, in medicinal chemistry as stable surrogates for carboxylic acids and in materials' applications, including explosives and photography.[1] The synthesis of tetrazoles by cycloaddition reactions between azides and nitriles is well documented.[2] Recently, attention has been directed towards the use of polydentate aromatic nitrogen heterocycles, specifically ligands with five-membered rings, that is, azoles. Tetrazoles exhibit a strong networking ability usually acting as mono- or bidentate ligands in most of the reported complexes.[3] One possible application of these materials is in generating supramolecular arrays, which embody additional functional groups that are capable of metal complexation. This would result in a metallotetrazole framework with possible potential as novel antimicrobial or therapeutic agents. Our interest in tetrazoles concerns their use as precursors for the formation of new functionalised poly-tetrazole macrocycles, which can find application, for example, as sensors or in molecular recognition. We have previously reported some preliminary synthetic steps concerning the addition of pendant short-chain alkyl halides, from dihaloalkanes, to some bis-tetrazoles.[4] These reactions yield bis-tetrazole derivatives with pendant alkyl halide arms and also bis-tetrazole derivatives with pendant vinyl arms. We have also described the reactions of 1,4-bis(tetrazole)benzenes with various long chain α,ω-dibromoalkanes.[5] Butler and co-workers have synthesised both 1,2- and 1,3-bis(bromoalkyltetrazolyl)benzenes from *N*-unsubstituted tetrazoles and have succeeded in using these bis-(bromoalkyltetrazolyl)benzenes to generate the tetra-tetrazole macrocycle.[6] The latter compound includes a cavity that can be tailored by both the length and flexibility of the alkyl chain and also by the substitution pattern on the benzene ring.[7] In this paper, we describe the synthesis and characterisation of tetra-tetrazole macrocycles from 1,2-, 1,3- and 1,4-benzene derivatives, using short four-carbon, medium six-carbon and long eight-carbon alkyl linkers. The X-ray crystal structures of the 1,2- and 1,4-benzene derivatives with four-carbon chain linkers are described, as well as the 1,3-benzene derivative containing the six-carbon linker. Our principal focus is on the variation of the macrocycle's cavity shape and dimensions through the series.

Keywords: Tetrazole; Macrocycles; Synthesis; X-ray crystal structure; NMR.
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2. Results and discussion

2.1. Syntheses

Butler and co-workers have described the synthesis of tetra-tetrazole macrocycles, based on either 1,2- or 1,3-bis(tetrazol-5-yl)benzene, with alkyl chains having either six or eight-carbon chain linkers.[6] We have extended this class of compounds by preparing macrocycles with four-carbon chain linkers, and also new macrocycles based on 1,4-bis(tetrazol-5-yl)benzene (Fig. 1). The syntheses were carried out in a manner similar to that described,[6] by reacting 1,*x*-[bis(2-(*y*-bromoalkyl)tetrazol-5-yl]benzene (*x*=2, 3 or 4; *y*=4, 6 or 8; alkyl=butyl, hexyl or octyl) with 1,*n*-bis(tetrazol-5-yl)-benzene (*n*=2, 3 or 4) in dimethylformamide, using K_2CO_3 as base. Compounds **2**, **3**, **5** and **6** have been reported previously.[6]

In several of our reactions, carried out in relatively dilute conditions, two macrocyclic compounds were isolated, one containing all four tetrazole rings substituted at N-2, and the other containing three rings substituted at N-2 and the other one substituted at N-1, as reported previously.[6] The macrocycles with all four tetrazole rings substituted in the same way will be designated hereafter with the suffix **a**, while those with one different substitution will be designated with the suffix **b**.

In all reactions undertaken, on average 40% of the starting bis-tetrazole compounds was recovered. Extensive column chromatography, using a hexane/ethyl acetate mixture as eluent, was required to separate the product macrocycles from the starting materials and other intractable polymeric material. The isolated yields of the macrocyclic products were in the range 20–25%, which are comparable to those reported by Butler,[6] and are reasonable for the syntheses of this type. One possible reason for the low yields in these reactions is the potential to form polymeric chains between the two bis-tetrazole units, rather than macrocycles. Evidence that some polymeric chains were synthesised came from the fact that intractable material, which could not be dissolved in any solvent we tried, was obtained from all the reactions we attempted. The isomeric 1-*N*- and 2-*N*-tetrazole derivatives should be readily distinguishable from their respective ^{1}H and ^{13}C NMR spectra,[4,5a,6,8] with the ^{13}C NMR chemical shift of the tetrazole carbon atom appearing at ca. 154.0 and 164.0 ppm in N-1 and N-2 substituted tetrazoles, respectively. Macrocycles containing four tetrazole rings all substituted at N-2 gave rise to only a single resonance at ~164.0 ppm, while both signals were apparent in the macrocycles containing tetrazole rings substituted at both N-1 and N-2. The high symmetry in the macrocycles containing four tetrazole rings substituted at N-2 also gave a corresponding decrease in the number of signals in the ^{1}H NMR spectra compared to those substituted at both N-1 and N-2.

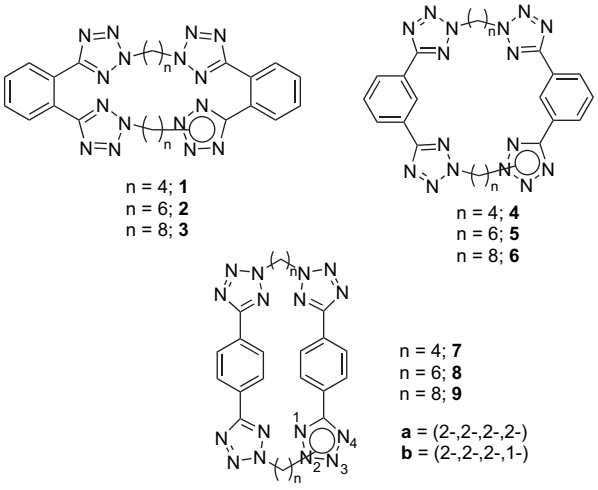

Figure 1. Tetra-tetrazole macrocycles.

2.2. X-ray crystal structures

We were able to obtain single crystals of the three symmetrical macrocycles **1a**, **5a** and **7a**. The crystal structure of **2a** has already been reported.[7] Attempts to obtain suitable crystals of any of the unsymmetrical macrocycles have so far been unsuccessful. The molecular structures of **1a**, **2a**, **5a** and **7a** are shown in Figures 2–4 and 6, respectively. In each case, the molecule is centrosymmetric and is sited on a crystallographic centre of inversion. For comparison, in particular with regard to the orientations of the tetrazole substituents relative to the benzene ring, 16 further bis- and tris(tetrazole)-benzene structures were identified in the Cambridge Structural Database (Version 5.27 plus January, May and August updates; 388720 structures in total)[9] and are listed in Table 1.

The molecular structures of **1a** (Fig. 2) and **2a** (Fig. 3) are broadly comparable. One of the two unique tetrazole rings

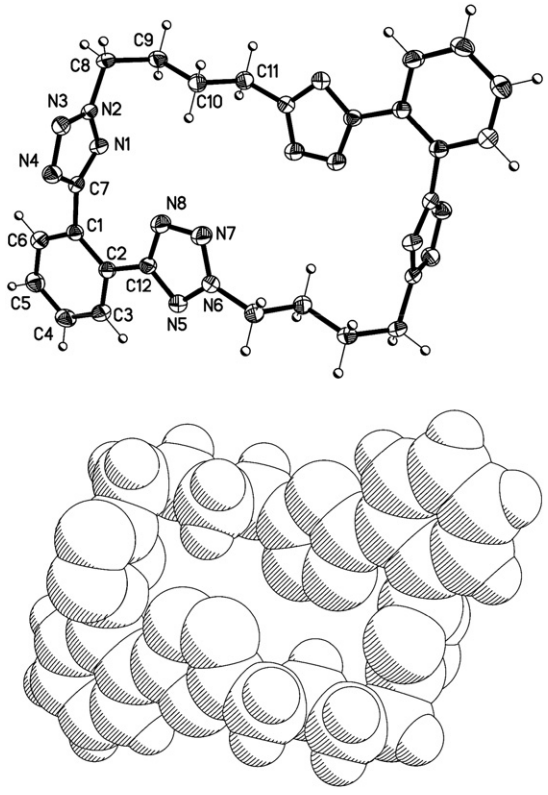

Figure 2. Molecular structure of **1a** showing displacement ellipsoids at the 50% probability level for non-H atoms (top) and a space-filling representation (bottom).

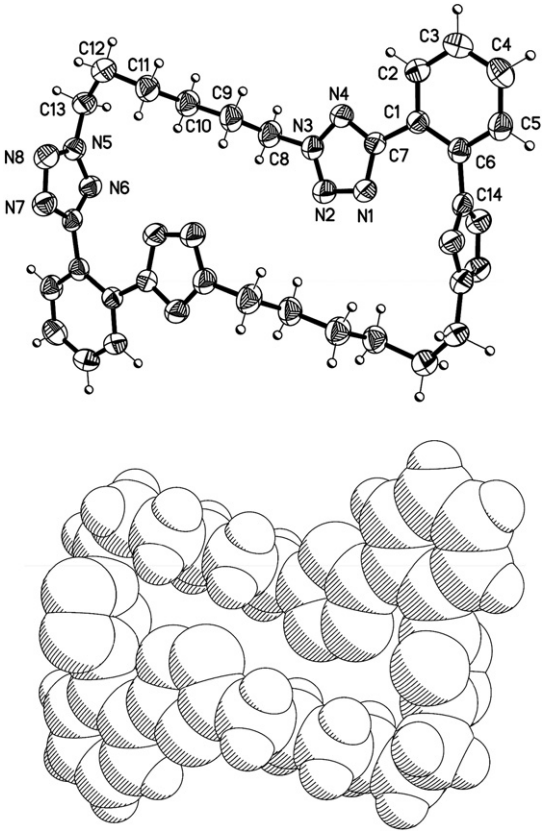

Figure 3. Molecular structure of **2a** showing displacement ellipsoids at the 50% probability level for non-H atoms (top) and a space-filling representation (bottom).[7]

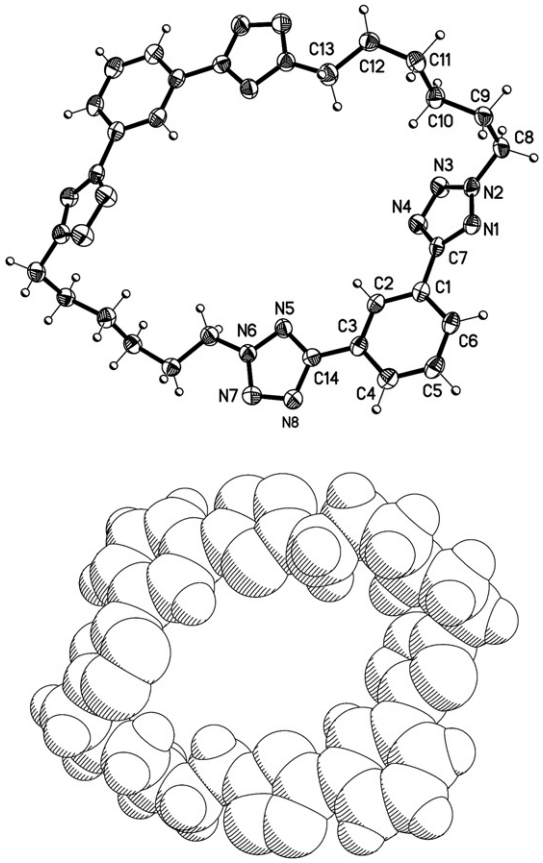

Figure 4. Molecular structure of **5a** showing displacement ellipsoids at the 50% probability level for non-H atoms (top) and a space-filling representation (bottom).

(containing N5–N8) lies close to co-planar with the benzene ring to which it is attached (dihedral angle between ring planes=2.9° in **1a** and 9.6° in **2a**), while the other ring (containing N1–N4) is approximately orthogonal to it (dihedral angle between ring planes=86.1° in **1a** and 82.5° in **2a**). This arrangement eliminates potential repulsion between adjacent tetrazole rings (e.g., N1···N8) that would arise if they were co-planar. Comparable arrangements have been observed in two other 1,2-bis(tetrazole)benzene derivatives, namely SADDAC and SARCEU (Table 1). In all other 1,2-derivatives reported to date (Table 1), both tetrazole rings are twisted from the plane of the benzene ring, with dihedral angles in the range 34.1–66.6°.

In **1a** and **2a**, the planes of the benzene and tetrazole rings on opposite sides of the rectangular macrocycle (N5–N8 and its symmetry equivalent) are parallel. The four-carbon chain linkers in **1a** adopt an approximately fully extended conformation, with all four-carbon atoms lying in the same plane. In **2a**, five of the six carbons of the linker adopt a similar fully extended conformation, while the sixth (C13) lies *gauche* with respect to the remainder of the chain (Fig. 3). Macrocycle **1a** appears close to a regular rectangle, while **2a** is sheared parallel to the long axis of the alkyl linker. The internal dimensions of the macrocycle (defined as the cross-macrocycle distances between the centroids of the tetrazole rings) are 9.7×5.3 Å in **1a**, compared to 11.1×5.6 Å in **2a**. Thus, the cross-macrocycle distance between the two co-planar tetrazole rings (5.3–5.6 Å) changes only slightly with variation of the chain linker. As noted by Butler and co-workers,[7] space-filling representations of **1a** and **2a** (Figs. 2 and 3) show that the central 'cavity' of the macrocycle is largely illusory, at least for the conformation observed in the solid state.

In the structure of **5a** (Fig. 4), both unique tetrazole rings remain close to co-planar with the benzene ring to which they are attached. The dihedral angle between the tetrazole and benzene ring is 25.2 and 5.6° for N1–N4 and N5–N8, respectively. Comparison with other 1,3-bis(tetrazole)benzene structures (Table 1) shows that approximate co-planarity (considered to encompass the range 6.2–14.7°) is common, and the structures of DEBQUW, SARCAQ and ZUMXAG show explicitly that there is no intramolecular impediment to approximate co-planarity of both rings. The moderate deviation from co-planarity for N1–N4 in **5a** seems attributable, therefore, to the optimisation of intermolecular contacts (see Fig. 4) rather than any intramolecular feature. Similar to **2a**, the six-carbon chain linker in **5a** exhibits an essentially fully extended conformation for five of its six-carbon atoms, while the sixth (C13) lies approximately *gauche* with respect to the remainder of the chain. The macrocycle geometry, in this case, is close to a regular square, with cross-macrocycle dimensions 10.8×9.4 Å. A space-filling representation of the structure (Fig. 4) shows that a genuine cavity is retained in the solid state.

Adjacent macrocycles in **5a** are arranged so that one benzene-tetrazole unit lies over the cavity of the adjacent

Table 1. 1,2-Bis, 1,3-bis, 1,4-bis and 1,3,5-tris(tetrazole)benzene structures identified in the CSD

Compound	CSD Refcode	Dihedral angles between planes of tetrazole and benzene rings (°)	Ref.
1,2-Bis(tetrazole)benzenes			
	DEBSOS	34.1, 34.8	8
	MARPOK	55.7, 55.7	10a
	SADCUV	38.3, 58.5	10b
	SADDAC	7.7, 85.6	10b
	SARCEU	13.3, 83.7	4
	ZUMWOT	47.9, 57.5	10c
	ZUMWUZ	54.0, 56.6; 52.5, 66.6	10c
1,3-Bis(tetrazole)benzenes			
	DEBQUW	13.7, 13.7	8
	FELZOM	29.4, 42.0	10d
	FELZUS	14.7, 24.3; 10.1, 38.6	10d
	SARCAQ	6.2, 8.8	4
	ZUMXAG	8.3, 12.1	10c
1,4-Bis(tetrazole)benzenes			
	ICEGAZ	6.4, 6.4	10e
	ICEGED	3.9, 3.9; 10.0, 10.0; 29.4, 29.4	10e
1,3,5-Tris(tetrazole)benzenes			
	HUKRUA	3.6, 4.7, 7.5	10f
	TAWRIS	1.2, 22.4, 24.6	10g

macrocycle (Fig. 5a), forming a local stacking arrangement similar to that seen within **7a** (Fig. 6). On account of this packing arrangement, there are no extended channels running through the crystal. The interplanar separation between stacked benzene rings in this region is 3.68 Å and the benzene centroid-to-centroid distance is 5.16 Å. A shorter contact of 4.05 Å exists between the centroid of the benzene ring and the centroid of one adjacent tetrazole ring (N5–N8). Involvement of the N5–N8 ring in this stacking interaction is consistent with its co-planarity with the benzene ring. In projection (Fig. 5b), the stacked macrocycles closely resemble **7a** (Fig. 6). They are arranged in a herringbone manner, which brings the tetrazole ring N1–N4 into the vicinity of an adjacent alkyl chain. The 25.2° twist of the tetrazole ring with respect to the benzene ring brings its mean plane parallel to that of the fully extended section of the alkyl chain (C8–C12). Thus, the moderate twist of ring N1–N4 can be attributed clearly to the optimisation of this intermolecular interaction.

In **7a** (Fig. 6), the four-carbon chain linkers permit an intramolecular stacking interaction, similar to that observed in macrocyclic systems such as bis(1,4-phenylene)crown ethers

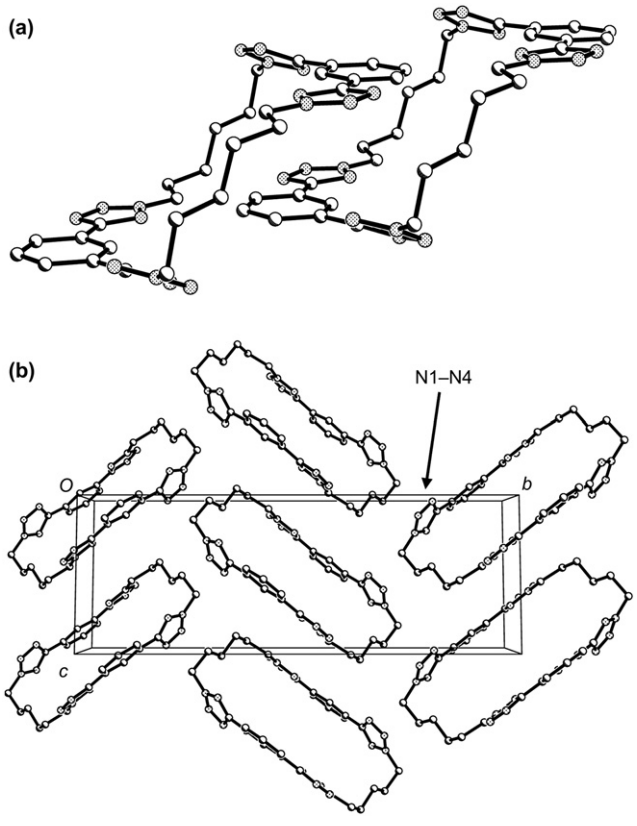

Figure 5. (a) Stacking interaction between adjacent macrocycles in **5a**. (b) Projection of **5a** approximately along the *a* axis, showing the herringbone arrangement, which brings tetrazole ring N1–N4 into close contact with an alkyl chain of the adjacent macrocycle.

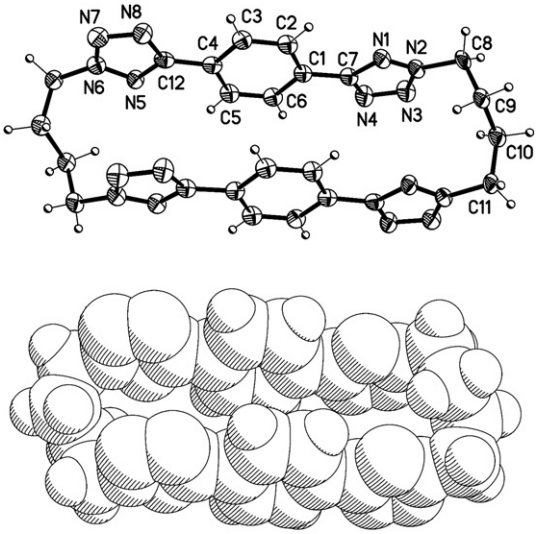

Figure 6. Molecular structure of **7a** showing displacement ellipsoids at the 50% probability level for non-H atoms (top) and a space-filling representation (bottom).

with ether chain linkers of appropriate length.[11] The interplanar separation is 3.44 Å and the benzene centroid-to-centroid distance is 3.91 Å. Clearly, this precludes the existence of any cavity within the macrocycle, and this interaction is likely to persist in solution. The tetrazole rings lie approximately co-planar with the benzene rings to which they are attached, forming dihedral angles 10.8 and 4.8° for the N1–N4 and N5–N8 rings, respectively, consistent with their participation in the stacking interaction. The approximately co-planar arrangement is most common in all previously examined 1,4-bis(tetrazole)benzene structures (Table 1). Face-to-face stacking of 1,4-bis(tetrazole)benzene units is also observed between macrocycles of **7a** in the solid state. The shortest additional contacts to the tetrazole ring are in-plane C–H···N interactions.

3. Conclusions

In the solid state, the conformation of the macrocycle is influenced by the orientation of the tetrazole rings on the benzene ring, by the length of the alkyl-chain linkers and by intermolecular interactions. In the macrocycles based on 1,2-bis(tetrazole)benzene, the adjacent tetrazole substituents on the benzene ring are prevented from becoming co-planar on steric grounds. In both **1a** and **2a**, the resulting conformation is such that no genuine cavity is retained. In the macrocycles based on 1,3- and 1,4-bis(tetrazole)benzene, there is no intramolecular impediment to co-planarity of the tetrazole rings with the benzene ring, and co-planarity is observed where stacking interactions are present. In **5a**, these stacking interactions are intermolecular, while in **7a** they are intramolecular. In the former case, one tetrazole ring is twisted slightly out of the plane of the benzene ring to which it is bound, apparently to optimise intermolecular interactions with an adjacent alkyl chain. In **7a**, the intramolecular stacking interaction precludes the existence of any cavity, and this interaction is likely to persist in solution. In **5a**, however, a genuine cavity of dimensions 10.8×9.4 Å is retained in the solid state, and appears feasible in solution. Currently, metal complexation reactions with this macrocycle are being investigated. We are interested in looking at first row transition metal ions as well as some smaller alkali and alkaline earth metals, as metal ions from these groups using tetrazoles as ligands in coordination chemistry are described in the literature.[12]

4. Experimental

4.1. General

^{1}H and ^{13}C NMR (δ ppm, J Hz) spectra were recorded on a JEOL JNM-LA300 FTNMR spectrometer using saturated $CDCl_3$ solution with Me_4Si reference, unless indicated otherwise, with resolutions of 0.18 Hz and 0.01 ppm, respectively. Infrared spectra (cm^{-1}) were recorded as KBr discs or liquid films between KBr plates using a Nicolet Impact 410 FTIR. Melting point analysis was carried out using a Stewart Scientific SMP 1 melting point apparatus and are uncorrected. Mass spectra were carried out in the Mass Spectroscopy unit in the Centre for Synthesis and Chemical Biology, University College, Dublin. Microanalysis was carried out at the Microanalytical Laboratory of University College, Dublin. Standard Schlenk techniques were used throughout. Starting materials were commercially obtained and used without further purification. The synthesis of compounds **2a**,[6b] **3a**,[6b] **5a**[6c] and **6a**[6c] has been described in the literature previously.

4.2. General syntheses of tetra-tetrazolophanes

A mixture of 1,*n*-bis(tetrazol-5-yl)benzene (1.1 mmol) and potassium carbonate (1.5 g, 11 mmol) in dimethylformamide (60 ml) was stirred for 1 h at 75 °C under nitrogen atmosphere, and treated with 1,*n*-[bis(2-(*n*-bromoalkyl)-tetrazol-5-yl)]benzene (1.1 mmol) and stirred at 75 °C for 24 h. Insoluble salts, filtered from the cooled mixture, were washed with ethyl acetate and the combined washings and mother-liquor were evaporated under reduced pressure. The oily residue was chromatographed on silica gel using ethyl acetate/hexane (50:50) as eluent to give the cyclophane. All compounds were then recrystallised from chloroform.

4.2.1. Di-*ortho*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(4)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (1a). White solid. Analysis: found: C, 54.02; H, 4.81; N, 41.42. Calcd for $C_{24}H_{24}N_{16}$: C, 53.72; H, 4.51; N, 41.77. Yield: 33 mg, 12.3%, 0.06 mmol; R_f 0.52 (50:50 hexane/ethyl acetate); mp 224–228 °C; ν_{max} (KBr) 3150, 3090, 2955, 2828, 1724, 1500, 1499, 1467, 1440, 1391, 1359, 1285, 1178, 1038, 787, 775, 730, 668 cm^{-1}; δ_H: 1.89 (m, 8H, CH_2), 4.64 (t, 8H, J=13.6 Hz, NCH_2), 7.81 (m, 4H, Ar–H), 7.95 (m, 4H, Ar–H); δ_C: 29.1, 52.0 (tetrazole N2–CH_2), 127.6, 130.3, 131.1, 164.5 (2,5-tetrazole); HRMS (EI) Calcd: 537.2448, found: 537.2422.

4.2.2. Di-*ortho*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(4)]-cyclophane (1-N, 2-N′, 2-N″, 2-N‴) (1b). White waxy solid. Analysis: found: C, 53.57; H, 4.84; N, 41.99. Calcd for $C_{24}H_{24}N_{16}$: C, 53.72; H, 4.51; N, 41.77. Yield: 22 mg, 8.2%, 0.04 mmol; R_f 0.42 (50:50 hexane/ethyl acetate); ν_{max} (KBr) 3440, 2942, 2870, 1625, 1520, 1435, 1389, 1360, 1199, 1087, 1050, 910, 812, 787, 745, 692 cm^{-1}; δ_H: 1.91 (m, 6H, CH_2), 2.13 (m, 2H, CH_2), 4.64 (t, 2H, J=14.6 Hz, N^1CH_2), 4.77 (t, 6H, J=13.6 Hz, N^2CH_2), 7.48 (d, 1H, J=6.6 Hz, Ar–H), 7.66 (t, 1H, J=13.0 Hz, Ar–H), 7.76 (d, 3H, J=6.6 Hz, Ar–H), 8.37 (t, 3H, J=13.0 Hz, Ar–H); δ_C: 29.0, 29.1, 46.6 (tetrazole N1–CH_2), 52.6 (tetrazole N2–CH_2), 52.8 (tetrazole N2–CH_2), 52.9 (tetrazole N2–CH_2), 122.9, 127.2, 127.3, 127.5, 129.4, 130.3, 130.6, 130.8, 131.1, 131.5, 154.1 (1,5-tetrazole), 162.7 (2,5-tetrazole), 163.1 (2,5-tetrazole), 164.1 (2,5-tetrazole); HRMS (EI) Calcd: 537.2448, found: 537.2437.

4.2.3. Di-*ortho*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(6)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (2a).[6b] White solid. Analysis: mp 178–180 °C; R_f 0.50 (50:50 hexane/ethyl acetate); δ_H: 1.37 (m, 8H, CH_2), 2.00 (m, 8H, CH_2), 4.59 (t, 8H, J=13.5 Hz, NCH_2), 7.59 (m, 4H, Ar–H), 7.91 (m, 4H, Ar–H).

4.2.4. Di-*ortho*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(6)]-cyclophane (1-N, 2-N′, 2-N″, 2-N‴) (2b). White solid. Analysis: found: C, 56.96; H, 5.18; N, 37.86. Calcd for $C_{28}H_{32}N_{16}$: C, 56.74; H, 5.44; N, 37.81. Yield: 49 mg, 18.2%, 0.08 mmol; R_f 0.40 (50:50 hexane/ethyl acetate);

mp 128–130 °C; ν_{max} (KBr) 3435, 2925, 2858, 1629, 1555, 1450, 1359, 1275, 1198, 1049, 1099, 855, 746, 729, 671 cm^{-1}; δ_H: 1.30 (m, 14H, CH_2), 1.75 (m, 2H, CH_2), 4.03 (t, 2H, J=14.2 Hz, N^1CH_2), 4.63 (t, 6H, J=13.5 Hz, N^1CH_2), 7.48 (d, 1H, J=6.6 Hz, Ar–H), 7.66 (t, 1H, J=13.0 Hz, Ar–H), 7.73 (d, 3H, J=6.6 Hz, Ar–H), 8.30 (t, 3H, J=13.0 Hz, Ar–H); δ_C: 25.1, 25.3, 25.4, 25.5, 28.2, 28.6, 28.7, 28.8, 47.1 (tetrazole N1–CH_2), 52.5 (tetrazole N2–CH_2), 52.7 (tetrazole N2–CH_2), 53.4 (tetrazole N2–CH_2), 122.8, 127.2, 127.5, 129.5, 130.0, 130.2, 130.3, 130.8, 131.5, 153.8 (1,5-tetrazole), 162.8 (2,5-tetrazole), 164.1 (2,5-tetrazole), 164.1 (2,5-tetrazole); HRMS (EI) Calcd: 593.3074, found: 593.3100.

4.2.5. Di-*ortho*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(8)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (3a).[6b] White solid. Analysis: mp 148–150 °C (lit. 147–148 °C); R_f 0.53 (50:50 hexane/ethyl acetate); δ_H: 1.35 (m, 12H, CH_2), 1.96 (m, 12H, CH_2), 4.57 (t, 8H, J=13.9 Hz, NCH_2), 7.60 (m, 4H, Ar–H), 7.91 (m, 4H, Ar–H).

4.2.6. Di-*ortho*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(8)]-cyclophane (1-N, 2-N′, 2-N″, 2-N‴) (3b). White solid. Analysis: found: C, 59.60; H, 6.41; N, 34.40. Calcd for $C_{32}H_{40}N_{16}$: C, 59.24; H, 6.21; N, 34.54. Yield: 55 mg, 20.4%, 0.08 mmol; R_f 0.40 (50:50 hexane/ethyl acetate); mp 146–148 °C; ν_{max} (KBr) 3435, 2940, 2868, 1625, 1522, 1430, 1390, 1360, 1199, 1087, 1048, 910, 810, 787, 745, 690 cm^{-1}; δ_H: 1.34 (m, 22H, CH_2), 1.72 (m, 2H, CH_2), 4.05 (t, 2H, J=14.6 Hz, N^1CH_2), 4.55 (t, 6H, J=13.6 Hz, N^2CH_2), 7.48 (d, 1H, J=6.6 Hz, Ar–H), 7.66 (t, 1H, J=13.0 Hz, Ar–H), 7.74 (d, 3H, J=6.6 Hz, Ar–H), 8.35 (t, 3H, J=13.0 Hz, Ar–H); δ_C: 25.8, 25.9, 26.1, 26.1, 28.4, 28.4, 28.5, 28.6, 28.6, 28.8, 29.1, 29.2, 47.3 (tetrazole N1–CH_2), 52.8 (tetrazole N2–CH_2), 52.8 (tetrazole N2–CH_2), 53.1 (tetrazole N2–CH_2), 123.1, 127.4, 127.7, 129.5, 130.1, 130.4, 130.4, 130.5, 130.8, 131.6, 153.9 (1,5-tetrazole), 162.9 (2,5-tetrazole), 164.1 (2,5-tetrazole), 164.3 (2,5-tetrazole); HRMS (EI) Calcd: 649.3700, found: 649.3679.

4.2.7. Di-*meta*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(4)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (4a). White solid. Analysis: found: C, 53.39; H, 4.43; N, 41.85. Calcd for $C_{24}H_{24}N_{16}$: C, 53.72; H, 4.51; N, 41.77. Yield: 24 mg, 9.0%, 0.04 mmol; R_f 0.50 (50:50 hexane/ethyl acetate); mp 284–286 °C; ν_{max} (KBr) 3430, 2952, 2830, 1724, 1520, 1468, 1442, 1390, 1359, 1285, 1179, 1038, 787, 774, 730, 667 cm^{-1}; δ_H: 1.89 (m, 8H, CH_2), 4.65 (t, 8H, J=13.5 Hz, NCH_2), 7.63 (t, 2H, J=15.5 Hz, Ar–H), 8.27 (d, 4H, J=6.6 Hz, Ar–H), 8.82 (s, 2H, Ar–H); δ_C: 29.1, 52.0 (tetrazole N2–CH_2), 125.2, 128.2, 128.5, 129.6, 164.6 (2,5-tetrazole); HRMS (EI) Calcd: 537.2448, found: 537.2452.

4.2.8. Di-*meta*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(6)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (5a).[6c] White solid. Analysis: mp 150–152 °C (lit. 150–152 °C); R_f 0.52 (50:50 hexane/ethyl acetate); δ_H: 1.37 (m, 8H, CH_2), 2.04 (m, 8H, CH_2), 4.67 (t, 8H, J=13.5 Hz, NCH_2), 7.63 (t, 2H, J=6.5 Hz, Ar–H), 8.27 (d, 4H, J=6.5 Hz, Ar–H), 8.82 (s, 2H, Ar–H).

4.2.9. Di-*meta*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(6)]-cyclophane (1-N, 2-N′, 2-N″, 2-N‴) (5b). White solid. Analysis: found: C, 57.05; H, 5.20; N, 37.53. Calcd for $C_{28}H_{32}N_{16}$: C, 56.74; H, 5.44; N, 37.81. Yield: 26 mg, 9.8%, 0.04 mmol; R_f 0.40 (50:50 hexane/ethyl acetate); mp 148–150 °C; ν_{max} (KBr) 3440, 2925, 2850, 1630, 1560, 1451, 1360, 1274, 1196, 1046, 1005, 854, 746, 730, 669 cm^{-1}; δ_H: 1.26 (m, 8H, CH_2), 1.75 (m, 2H, CH_2), 4.48 (t, 2H, J=14.4 Hz, N^1CH_2), 4.67 (t, 6H, J=13.5 Hz, N^2CH_2), 7.63 (t, 2H, J=6.6 Hz, Ar–H), 7.81 (d, 2H, J=6.6 Hz, Ar–H), 8.27 (d, 2H, J=6.6 Hz, Ar–H), 8.83 (s, 2H, Ar–H); δ_C: 26.1, 26.2, 26.3, 26.4, 29.5, 29.5, 29.6, 29.7, 49.0 (tetrazole N1–CH_2), 53.8 (tetrazole N2–CH_2), 53.9 (tetrazole N2–CH_2), 54.0 (tetrazole N2–CH_2), 124.7, 125.3, 127.0, 128.6, 128.9, 129.2, 129.8, 129.9, 130.1, 130.5, 130.9, 154.1 (1,5-tetrazole), 162.8 (2,5-tetrazole), 164.3 (2,5-tetrazole), 165.0 (2,5-tetrazole); HRMS (EI) Calcd: 593.3074, found: 593.3065.

4.2.10. Di-*meta*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(8)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (6a).[6c] White solid. Analysis: mp 144–148 °C (lit. 144–146 °C); R_f 0.53 (50:50 hexane/ethyl acetate); δ_H: 1.35 (m, 12H, CH_2), 1.96 (m, 12H, CH_2), 4.59 (t, 8H, J=13.6 Hz, NCH_2), 7.63 (t, 2H, J=6.6 Hz, Ar–H), 8.27 (d, 4H, J=6.6 Hz, Ar–H), 8.82 (s, 2H, Ar–H).

4.2.11. Di-*meta*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(8)]-cyclophane (1-N, 2-N′, 2-N″, 2-N‴) (6b). White solid. Analysis: found: C, 59.45; H, 6.20; N, 34.35. Calcd for $C_{32}H_{40}N_{16}$: C, 59.24; H, 6.21; N, 34.54. Yield: 24 mg, 9.0%, 0.04 mmol; R_f 0.41 (50:50 hexane/ethyl acetate); mp 136–142 °C; ν_{max} (KBr) 3436, 2938, 2860, 1623, 1520, 1433, 1390, 1358, 1199, 1087, 1045, 911, 810, 787, 744, 691 cm^{-1}; δ_H: 1.23 (m, 22H, CH_2), 1.72 (m, 2H, CH_2), 4.48 (t, 2H, J=14.6 Hz, N^1CH_2), 4.64 (t, 6H, J=13.5 Hz, N^1CH_2), 7.63 (t, 2H, J=6.6 Hz, Ar–H), 7.81 (d, 2H, J=6.6 Hz, Ar–H), 8.27 (d, 2H, J=6.6 Hz, Ar–H), 8.83 (s, 2H, Ar–H); δ_C: 25.9, 26.0, 26.1, 26.1, 28.4, 28.4, 28.5, 28.5, 28.6, 28.8, 29.1, 29.2, 47.3 (tetrazole N1–CH_2), 52.8 (tetrazole N2–CH_2), 52.8 (tetrazole N2–CH_2), 53.1 (tetrazole N2–CH_2), 123.1, 124.8, 125.3, 127.4, 127.7, 129.5, 129.8, 129.9, 130.1, 130.5, 130.9, 153.9 (1,5-tetrazole), 162.9 (2,5-tetrazole), 164.1 (2,5-tetrazole), 164.3 (2,5-tetrazole); HRMS (EI) Calcd: 649.3700, found: 649.3688.

4.2.12. Di-*para*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(4)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (7a). White solid. Analysis: found: C, 53.45; H, 4.41; N, 41.83. Calcd for $C_{24}H_{24}N_{16}$: C, 53.72; H, 4.51; N, 41.77. Yield: 82 mg, 30.6%, 0.15 mmol; R_f 0.52 (50:50 hexane/ethyl acetate); mp>300 °C; ν_{max} (KBr) 3150, 3090, 2950, 2830, 1725, 1500, 1478, 1465, 1440, 1390, 1359, 1285, 1178, 1037, 787, 770, 733, 665 cm^{-1}; δ_H: 2.09 (m, 8H, CH_2), 4.69 (t, 8H, J=13.5 Hz, NCH_2), 7.97 (s, 8H, Ar–H); δ_C: 29.7, 52.0 (tetrazole N2–CH_2), 127.1, 129.6, 164.6 (2,5-tetrazole); HRMS (EI) Calcd: 537.2448, found: 537.2463.

4.2.13. Di-*para*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(6)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (8a). White solid. Analysis: found: C, 56.45; H, 5.20; N, 37.95. Calcd for $C_{28}H_{32}N_{16}$: C, 56.74; H, 5.44; N, 37.81. Yield: 84 mg, 31.3%, 0.14 mmol; R_f 0.50 (50:50 hexane/ethyl acetate); mp 240–244 °C; ν_{max} (KBr) 3150, 3090, 2924, 2860, 1623, 1450, 1379, 1281, 1205, 1125, 1075, 1048, 860,

746 cm^{-1}; δ_H: 1.33 (m, 8H, CH_2), 2.04 (m, 8H, CH_2), 4.66 (t, 8H, J=13.8 Hz, NCH_2), 8.17 (s, 8H, Ar–H); δ_C: 25.3, 29.7, 52.8 (tetrazole N2–CH_2), 127.3, 129.0, 164.6 (2,5-tetrazole); HRMS (EI) Calcd: 593.3074, found: 593.3088.

4.2.14. Di-*para*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(6)]-cyclophane (1-N, 2-N′, 2-N″, 2-N‴) (8b). Off-white solid. Analysis: found: C, 56.40; H, 5.68; N, 37.45. Calcd for $C_{28}H_{32}N_{16}$: C, 56.74; H, 5.44; N, 37.81. Yield: 27 mg, 10.2%, 0.05 mmol; R_f 0.39 (50:50 hexane/ethyl acetate); mp 160–164 °C; ν_{max} (KBr) 3150, 3090, 2926, 2856, 1629, 1556, 1451, 1359, 1275, 1196, 1046, 1003, 854, 746, 729, 670 cm^{-1}; δ_H: 1.30 (m, 8H, CH_2), 1.75 (m, 2H, CH_2), 1.86 (m, 4H, CH_2), 1.99 (m, 2H, CH_2), 4.03 (t, 2H, J=14.5 Hz, N^1CH_2), 4.61 (t, 6H, J=13.6 Hz, N^2CH_2), 7.61 (m, 4H, Ar–H), 7.85 (d, 2H, J=6.6 Hz, Ar–H), 8.17 (s, 8H, Ar–H), 8.38 (d, 2H, J=6.6 Hz, Ar–H); δ_C: 25.1, 25.3, 25.4, 25.5, 28.2, 28.6, 28.7, 28.8, 47.1 (tetrazole N1–CH_2), 52.5 (tetrazole N2–CH_2), 52.7 (tetrazole N2–CH_2), 53.4 (tetrazole N2–CH_2), 129.1, 125.5, 122.8, 127.2, 127.5, 127.7, 129.5, 153.8 (1,5-tetrazole), 162.8 (2,5-tetrazole), 164.1 (2,5-tetrazole), 164.1 (2,5-tetrazole); HRMS (EI) Calcd: 593.3074, found: 593.3057.

4.2.15. Di-*para*-benzenotetra(5′,2′-tetrazolo)[5′-(2)-2′-(8)]-cyclophane (2-N, 2-N′, 2-N″, 2-N‴) (9a). White solid. Analysis: found: C, 59.06; H, 6.18; N, 34.54. Calcd for $C_{32}H_{40}N_{16}$: C, 59.24; H, 6.21; N, 34.54. Yield: 50 mg, 18.5%, 0.08 mmol; R_f 0.53 (50:50 hexane/ethyl acetate); mp 284–286 °C; ν_{max} (KBr) 3150, 3090, 2925, 2855, 1624, 1520, 1455, 1431, 1390, 1366, 1210, 1085, 1045, 909, 786, 745, 690, 670 cm^{-1}; δ_H: 1.32 (m, 8H, CH_2), 1.36 (m, 8H, CH_2), 2.04 (m, 8H, CH_2), 4.62 (t, 8H, J=13.3 Hz, NCH_2), 8.25 (s, 8H, Ar–H); δ_C: 25.9, 28.5, 29.2, 53.2 (tetrazole N2–CH_2), 127.3, 129.1, 164.6 (2,5-tetrazole); HRMS (EI) Calcd: 649.3700, found: 649.3720.

4.3. X-ray crystallography

Crystals of **1a**, **5a** and **7a** suitable for X-ray analysis were obtained by recrystallisation from chloroform solution. Data were collected at 180(2) K on a Bruker Nonius X8 APEX II diffractometer,[13] and a multi-scan correction was applied.[14] The structures were refined against F^2 using all data.[15] Hydrogen atoms were placed at calculated positions and refined using a riding model.

4.3.1. Compound 1a. *Crystal data*: $C_{24}H_{24}N_{16}$, M=536.59, triclinic, a=8.5805(3), b=8.7679(4), c=9.4091(4) Å, α=81.976(2), β=70.235(2), γ=66.642(2)°, U=611.56(5) $Å^3$, space group P-1, Z=1, μ(Mo Kα)=0.099 mm^{-1}, ρ_{calcd}=1.457 g cm^{-3}; 22,917 data (2300 unique, R_{int}=0.0243) were measured in the range 4.07<θ<25.74°. $R_1(I>2\sigma(I))$=0.0292 and wR_2(all data)=0.0740. Goodness of fit on F^2=1.05. CCDC No. 633941.

4.3.2. Compound 5a. *Crystal data*: $C_{28}H_{32}N_{16}$, M=592.70, monoclinic, a=6.8210(6), b=24.146(3), c=8.7297(10) Å, β=96.924(4)°, U=1427.3(3) $Å^3$, space group $P2_1/n$, Z=2, μ(Mo Kα)=0.092 mm^{-1}, ρ_{calcd}=1.379 g cm^{-3}; 17,057 data (2620 unique, R_{int}=0.0600) were measured in the range 3.59<θ<25.43°. $R_1(I>2\sigma(I))$=0.0441 and wR_2(all data)=0.1194. Goodness of fit on F^2=1.01. CCDC No. 633942.

4.3.3. Compound 7a. *Crystal data*: $C_{24}H_{24}N_{16}$, M=536.59, triclinic, a=6.7596(12), b=7.1970(12), c=12.9550(19) Å, α=91.008(7), β=100.326(6), γ=100.409(6)°, U=609.02(17) $Å^3$, space group P-1, Z=1, μ(Mo Kα)=0.099 mm^{-1}, ρ_{calcd}=1.463 g cm^{-3}; 10,192 data (2101 unique, R_{int}=0.0602) were measured in the range 3.76<θ<25.14°. $R_1(I>2\sigma(I))$=0.0716 and wR_2(all data)=0.2158. Goodness of fit on F^2=1.11. CCDC No. 633943.

5. Supplementary material

Crystallographic data for **1a**, **5a** and **7a** have been deposited at the Cambridge Crystallographic Data Centre, CCDC Nos. 633941–633943. Copies of this information may be obtained free of charge from deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

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