Tetratetrazole Macrocycles

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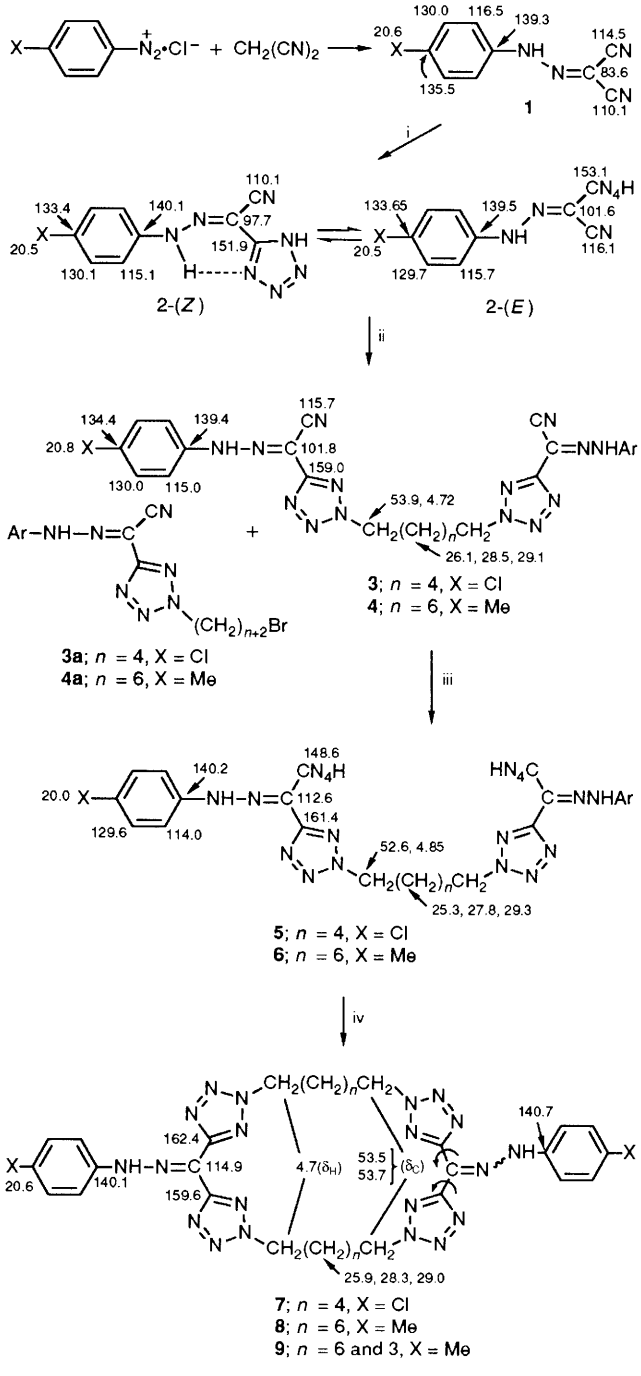
A synthetic route to tetratetrazole macrocycles which allows for variation in cavity size is described.

The wide interest in macrocycles containing subheterocyclic rings[1] has led to a range of polyazole macrocycles which include pyrazole[2,3] and triazole[4] rings as sub-units as well as groupings of these with other five- and six-membered rings.[3,4] Despite the interest in these systems tetratetrazole macrocycles have not been reported and the tetrazole ring has only appeared in macrocycles of the cyclophane type involving *ortho* disubstituted benzene[5] and azine[6] ring systems. We report the first tetratetrazole macrocycles from a synthetic route† that contains the potential for variation in cavity size and further macrocyclic development.

The full synthetic sequence is shown in Scheme 1, beginning with 1,1-dicyanohydrazones **1** which provide for a planar sp^2 carbon between adjacent pairs of tetrazole rings. The sequence of steps shown is necessary and for example it was not possible to introduce two unsubstituted tetrazole rings at the hydrazone methine carbon. The monotetrazole derivatives **2** showed complicated NMR spectra due to an *E–Z* isomerization, details of which will be reported elsewhere. The compounds **2** were joined into the dimeric structures **3**



Scheme 1 Full ^{13}C NMR shown for series with X = Me, shifts for **4** and **8** in $CDCl_3$ and for **1**, **2** and **6** in $(CD_3)_2SO$; some ^1H shifts also shown. *Reagents*: i and iii, NaN_3, NH_4Cl, LiCl, Me_2NCHO; ii, Et_3N, $Br(CH_2)_8Br$, CH_2Cl_2; iv, K_2CO_3, MeCN, $Br(CH_2)_{n+2}Br$.

† The following is a typical procedure and was applied to the series with X = Me. [For ^{13}C NMR data for compounds **1–9** (X = Me) see Scheme 1 (JEOL 270 MHz, JNH-270 machine)]. A solution of *p*-toluidine (5.45 g, 51 mmol) in water (75 cm^3) was treated with 36% aqueous HCl (10.9 cm^3), stirred at 2 °C and treated with sodium nitrite (4.563 g) in water (15 cm^3); the whole mixture was added quickly to a solution of malononitrile (4.37 g, 66 mmol) in a mixture of MeOH (12 cm^3) and water (25 cm^3) containing sodium acetate trihydrate (13.85 g). Yellow compound **1** (X = Me), m.p. 170–171 °C (from EtOH), (93% yield separated).

(*ii*) A mixture of **1** (X = Me) (6.0 g, 32 mmol), NaN_3 (2.33 g, 36 mmol), NH_4Cl, (1.91 g, 36 mmol) and LiCl (0.2 g) in dry dimethylformamide (40 cm^3) was stirred at 120 °C for 24 h, cooled, the insoluble salts removed and the solvent evaporated under reduced pressure. A solution of the residue in water (150 cm^3) was brought to pH 2 with conc. HCl to give **2** (X = Me), m.p. 207–209 °C (from EtOH) (94%). ^1H and ^{13}C NMR spectra showed mixtures of isomers; a full series with X = MeO, Me, H, Br, Cl, NO_2 has been prepared and studied.

(*iii*) A suspension of **2** (X = Me) (0.75 g, 3.3 mmol) in CH_2Cl_2 (5 cm^3) was treated dropwise with Et_3N (0.46 cm^3, 3.3 mmol) in CH_2Cl_2 (2 cm^3) and heated under reflux till it went clear when 1,8-dibromooctane (0.303 ml, 1.65 mmol) in CH_2Cl_2 2 cm^3 was added and the whole mixture stirred at 40 °C for 72 h. The solution was evaporated and the residue chromatographed on a flash column of silica gel (230–400 mesh ASTM) with CH_2Cl_2 as eluant. Early fractions contained compound **4a**, (m.p. 59 °C) (14%) (which could be converted into **4** by futher treatment with **2** as described) followed by compound **4**, m.p. 157–8 °C (from CH_2Cl_2–light petroleum, b.p. 40–60 °C) (57% yield) (*M*, found: 580; requires 564). δ_H ($CDCl_3$), 1.38–2.08 [m, 12H, $(CH_2)_6$], 2.33 (s, 3H, Me), 4.72 (m, 4H, CH_2–N), 7.15, 7.20 (pairs ds, J_{AB}, 8.8 Hz, AA^1BB^1, *p*-tolyl), 12.12 (br, 2H, NH).

(*iv*) The cyano groups of **4** were converted to tetrazoles as described giving **6**, m.p. 226–228 °C (from dimethyl sulfoxide–H_2O) (97%). NMR showed all expected ^1H and ^{13}C signals.

(*v*) A mixture of **6** (102 mg, 0.157 mmol) and potassium carbonate (220 mg, 1.57 mmol) was stirred under reflux in MeCN (50 cm^3) under an atmosphere of N_2, treated with 1,8-dibromooctane (0.029 cm^3, 0.157 mmol) and heated under reflux for 48 h. The solid potassium carbonate was removed (filtrate A) and washed with EtOAc; the combined washings and filtrate A were evaporated under reduced pressure and the oily residue chromatographed on a silica gel column (230–400 mesh ASTM) using a gradient of CH_2Cl_2 to EtOAc to give **8**, (containing ½EtOAc of crystallisation) m.p. 77–79 °C (from $CHCl_3$–light petroleum, b.p. 40–60 °C) (28%). Removal of the EtOAc of crystallisation gave a waxy solid (*M*, found: 745; requires 760); δ_H($CDCl_3$), 1.14–2.01 [m, 24H, two $(CH_2)_6$], 2.28 (s, 6H, 2 *p*-Me), 4.69 (m, 8H, 4 CH_2–N), 7.14–7.22 two overlapping AA^1BB^1 sets (8H, 2 *p*-MeC_6H_4-N), 12.0–12.2 (br, 2H, NH). Similarly prepared were **3**, (m.p. 205 °C, 62%), **5** (m.p. 246–7 °C, 81%), **7** [½EtOAc m.p. 233–4 °C, 31% (*M*, found: 725; requires 745)] and **9** (½EtOAc) (m.p. 89–90 °C, 35%).

and **4** by treating their anions with dibromoalkanes. The remaining cyano groups were then converted to tetrazole rings which were bridged again with further dibromoalkane molecules to give the macrocycles **7–9**. The macrocyclic structures were confirmed by ^1H and ^{13}C NMR spectra. Molecular weight measurements were made on a Perkin Elmer 115 Molecular Weight Machine by the isopiestic method to eliminate the possibility of polymeric products. Each of the synthetic steps was first modelled using a Me group in place of the $(CH_2)_n$ group. The methyl compounds also provided models for the assignments of the NMR spectra of the macrocycles. The 2,5-substituted tetrazole-substitution pattern is inferred from these assignments by comparison with the trends[7,8] which we have reported for the C-5 shift and for 2-*N*-alkyl shifts of tetrazole systems where 2-*N*-alkyl substituents are more deshielded than 1-*N*-alkyl groups and where the tetrazole 5-C shift moves downfield by 8–12 ppm on 2-*N*-alkylation. Macrocycles with methylene chains of equal length showed half the number of C-CH_2-C carbons in the ^{13}C NMR spectra but two CH_2–N carbons could just be distinguished. Significantly when the methylene chains had very different lengths, as for compound **9**, all of the CH_2 signals could be seen. The different 5-C chemical shifts of the two tetrazole rings in the macrocycles could be due to the *E* and *Z* allignments of the exocyclic hydrazone moiety. Alternatively these shifts also could arise if one of the tetrazole rings (5-C shift, 162.4 ppm) were planar and conjugated with the exocyclic hydrazone moiety while the other (5-C shift, 159.6 ppm) was twisted out of the conjugation plane. Such an effect arises with 5-aryltetrazoles[8] where for example conjugated 2-methyl-5-(*p*-chlorophenyl)tetrazole shows a 5-C shift of 163.3 ppm while ring twisted 2-methyl-5-(*o*,*o*-dichlorophenyl)-tetrazole has 5-C shift 159.9 ppm (the 1-methyl isomer having a 5-C shift of 150.6 ppm). It proved difficult to fully purify the macrocycles but microanalytically pure samples containing some EtOAc of solvation were obtained. The presence and quantity of the EtOAc was readily confirmed by 270 MHz ^1H NMR spectra. Samples obtained from EtOH solution also retained EtOH of solvation.

There is considerable conformational flexibility in these macrocycles due to rotation of the bonds from the tetrazole C-5 and N-2 atoms. A form with all of the tetrazole azo –N=N– units facing inwards allows for the possibility of complexation of two cations in the macrocycle where each could be held in a square planar arrangement between two such –N=N– moieties. Stoichiometric 1 : 1 complexes, which separated as powders, have been obtained by stirring compound **8** separately with $Ni(NCS)_2$ and $Zn(NCS)_2$ in methanol. These complexes and other possibilities are being explored.

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