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Synthesis and characterisation of macromolecules containing multiple tetrazole functionalities

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ABSTRACT

The synthesis of tetra-tetrazole macromolecules, containing various aromatic cores including benzene, pyridine and pyrazine directly attached to the tetrazole moieties, is described. This variation allowed for the generation of ligands with greater potential for metal ion complexation. Metal ion complexation reactions of the tetra-tetrazole macromolecules with the chelating pyridyl-tetrazole arms result in the formation of metal complexes where the metal ion was bound at the pendant arms rather than at the central core.

1. Introduction

The development of 'click' chemistry, as described by Sharpless and co-workers,[1,2] has resulted in an increase in the number of publications involving tetrazoles.[3–7] There are also several reviews on tetrazoles in the literature, including their use as carboxylic acid bioisosteres in drug discovery and as functional ligands in co-ordination chemistry.[8–10] Our interest in tetrazoles stems from their use 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 several tetra-tetrazole macrocycles from 1,2-, 1,3- and 1,4-dicyanobenzene and 2,6-pyridinedicarbonitrile derivatives, as well as the first example of a host–guest interaction between a tetra-tetrazole macrocycle and a solvent molecule.[10–14] In order to increase the flexibility of tetra-tetrazole ligands, we have removed some of the rigidity of the system by synthesising macromolecules to include flexible pendant arms, thus allowing the pendant arms to adapt their conformation for complexation to a metal ion more easily than analogous macrocycles. Macromolecules containing several tetrazole groups have been previously reported.[15–17] This paper focuses on the synthesis and characterisation of tetra-tetrazole macromolecules using the bis-tetrazoles 1,3-bis(tetrazol-5-yl) benzene[14] (**1**), 2,6-bis(2*H*-tetrazol-5-yl)pyridine[13] (**2**) and 2,3-bis(1*H*-tetrazol-5-yl)pyrazine (**3**) as the starting building blocks (see Schemes 1 and 2). Preliminary studies on the complexation reactions of these macromolecules with several metal salts have also been conducted.

2. Results and discussion

The bis-tetrazole compounds (**1**, **2** and **3**) were synthesised following reported procedures from 1,3-dicyanobenzene, 2,6-pyridinedicarbonitrile and 2,3-pyrazinedicarbonitrile, respectively.[13,14,18] The ^{13}C NMR spectra of the three compounds showed a signal at ~158 ppm for **1**, at ~155 ppm for **2** and at ~150 ppm, confirming the formation of the tetrazole systems.[11–16] The synthesis of 2-(6′-bromohexyl)-5-phenyl-2*H*-tetrazole (**4**) and 2-(6″-bromohexyl)-(2-tetrazol-5-yl)pyrazine (**6**) was carried out using a similar procedure to that previously reported for the synthesis of 2-(6″-bromohexyl)-(2-tetrazol-5-yl)pyridine (**5**).[19] In the ^{1}H NMR spectra of **4** and **6**, two triplet signals, at ~4.9 ppm and at ~3.4 ppm, corresponding to the expected shift for the side-chain $N-CH_2$ and CH_2-Br signals were observed. The ^{13}C NMR spectra of **4** and **6** showed that the tetrazole carbon signal resonated at ~162 ppm indicative of N2 alkylation.

The phenyl macromolecules **7** and **8** were synthesised by reacting 2-(6′-bromohexyl)-5-phenyl-2*H*-tetrazole (**4**) with 1,3-bis(tetrazol-5-yl)benzene (**1**) in acetonitrile with triethylamine as base to afford the tetra-tetrazole macromolecules, as in Scheme 1.

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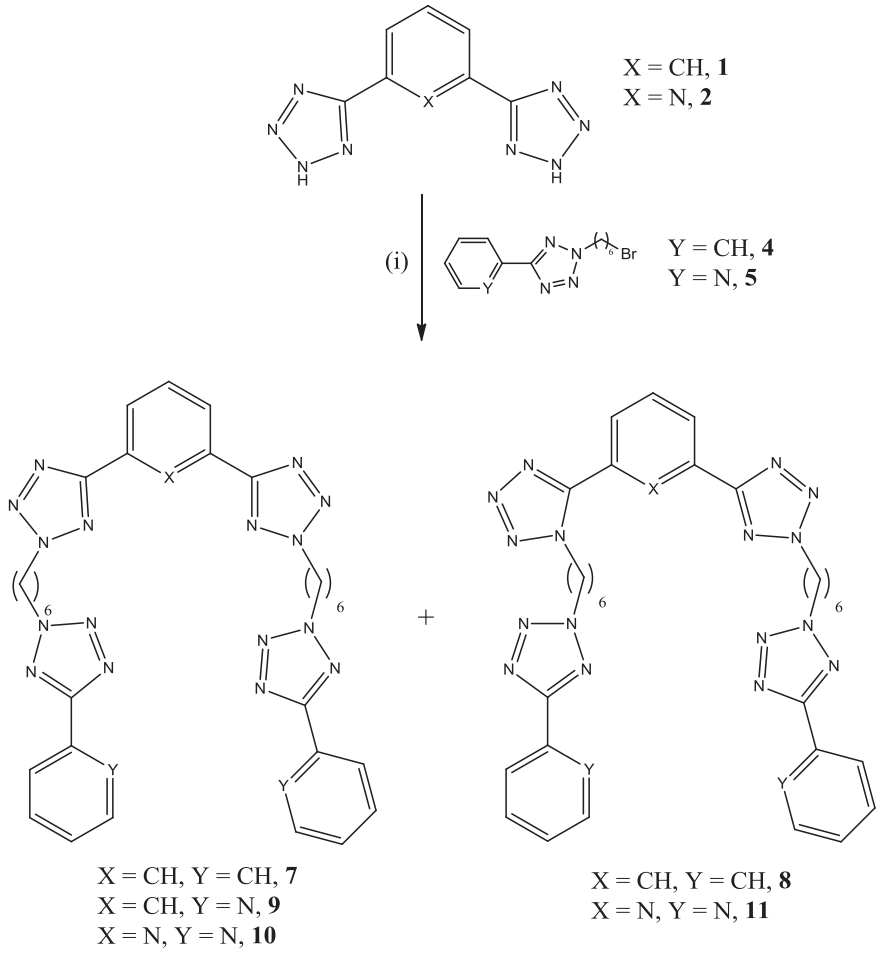

Scheme 1. Reagents and conditions: (i) Et_3N, MeCN, Δ, 24 h.

Both the symmetric **7** and asymmetric **8** tetra-tetrazole macromolecules were isolated from the crude reaction mixture. The symmetric compound **7** was the major product of the reaction and was isolated, as a white solid, in 41% yield with a melting point of 107—109 °C. The ^{1}H NMR spectrum of **7** had a small number of signals due to the plane of symmetry within the molecule. The signals associated with bis(tetrazol-5-yl)benzene region were as expected with a singlet, doublet and triplet signal being observed at 8.93, 8.26 and 7.64 ppm, respectively. The signals of the phenyl moiety attached to the *mono*-tetrazole appeared as a multiplet at 7.47 ppm, similar to that observed in the starting material **4**. The symmetry of the molecule was confirmed by a single triplet signal observed for the eight protons of the *N*2 substituted methylene carbons at 4.66 ppm. The other methylene signals were observed at 2.09 and 1.46 ppm. The ^{13}C NMR spectrum confirmed one signal for the four *N*2 substituted tetrazoles at 165.1 ppm. The alkyl region was uncomplicated with three signals observed at 25.7, 29.1 and 52.9 ppm, respectively.

The asymmetric macromolecule **8** was also isolated as a white solid, in 23% yield, with a melting point of 111—114 °C. The ^{1}H NMR spectrum confirmed the asymmetric nature of the compound as most signals were doubled due to the asymmetry. The four signals at 8.83, 8.36, 8.13 and 7.69 ppm for the central phenyl ring were indicative of asymmetric alkylation. A triplet was observed for the methylene attached to the *N*2 substituted tetrazoles at 4.65 ppm and a second triplet was observed at 4.48 ppm for the *N*1 substituted tetrazole. The remaining methylene signals were observed as multiplets. The ^{13}C NMR spectrum confirmed the substitution pattern with the appearance of three peaks for the tetrazoles at 165.5 and 163.6 ppm for the *N*2 substituted tetrazoles and at 153.9 ppm for the *N*1 substituted tetrazole. The signals for the methylene carbons adjacent to the tetrazole moieties were seen at 53.1 and 52.8 ppm for the carbons adjacent to the *N*2 substituted tetrazoles and at 47.9 ppm for the *N*1 substituted tetrazole.

The pyridyl-substituted phenyl macromolecule **9** was synthesised by reacting 2-(6″-bromohexyl)-(2-tetrazol-5-yl)pyridine (**5**) with 1,3-bis(tetrazol-5-yl)benzene (**1**) in acetonitrile with triethylamine as base, as in Scheme 1. The tetra-tetrazole macromolecule **9** was isolated as a white solid in 28% yield. The mass balance of the reaction was unreacted starting materials and intractable side products, which could not be fully separated or characterised. The product **9** was readily identified by ^{1}H NMR and ^{13}C NMR spectroscopy, which showed a simple splitting pattern as a result of the plane of symmetry in the molecule. If asymmetry had been observed, there would have been a doubling of signals in the NMR spectra, as were observed in the case of compound **8**. In the ^{1}H NMR spectrum, the signals associated with bis(tetrazol-5-yl)benzene region were again observed at 8.92, 8.23 and 7.62 ppm, respectively, as a singlet, doublet and triplet signal, as had been previously observed in compound **7**. The formation of the tetra-tetrazole macromolecule **9** was confirmed by the disappearance of the CH_2—Br signal at ca. 3.40 ppm and the retention and doubling of the integration of the *N*2—CH_2 signal. This signal was observed as a double-triplet at 4.69 ppm. The ^{13}C NMR spectrum showed two peaks at 164.8 ppm and at 164.6 ppm, identifying that the compound was *N*2 substituted, with the difference in the