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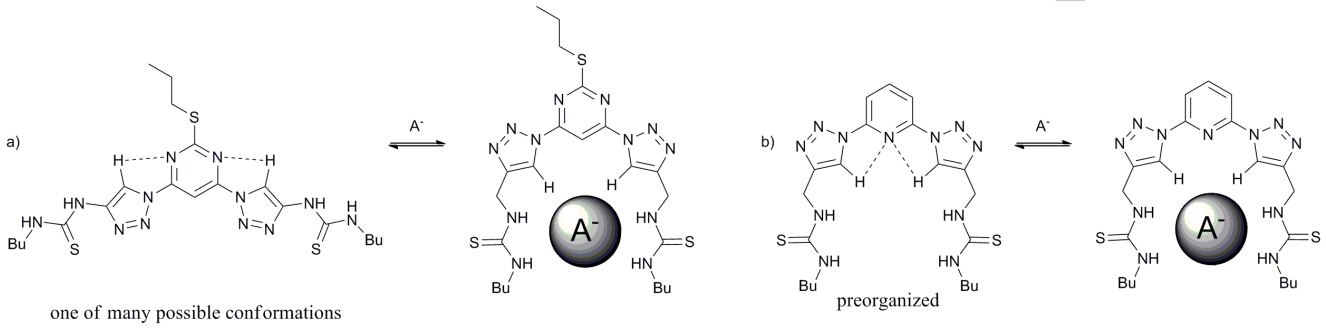

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Preorganisation in bistriazolyl anion receptors

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ABSTRACT

A series of 4,6-bis-(1,2,3-triazolyl)-pyrimidine and 4,6-bis-(1,2,3-triazolyl)-pyridine anion receptors were synthesized and the effect of the pyrimidine and pyridine moieties on their binding properties was examined. We found that intramolecular interactions preorganize the 4,6-bis-(1,2,3-triazolyl)-pyridine receptors resulting in higher anion binding constants in comparison with the non-preorganized 4,6-bis-(1,2,3-triazolyl)-pyrimidine receptor.

Anions play an important role in chemical and biological processes[1]. In the last two decades, increasing attention has been devoted to the synthesis of receptors for these anions[2]. The majority of anion binding motifs make use of strong hydrogen bond donor groups like NH and OH. Only a few years ago it has been discovered that CH hydrogen bonds can also play a determining role in receptor-anion binding[3]. Recently, the use of 1,4-disubstituted-1,2,3-triazoles in anion recognition gained interest because of their large polarity (dipole moment ~5D) with the positive end of the dipole situated at the CH group[4]. This reduces the electron density in the CH bond, making it suitable for hydrogen bonding. The practical utility of 1,4-disubstituted 1,2,3-triazoles as functional species in intra- and intermolecular interactions is enhanced by the fact that they are readily accessible through the Cu(I)-catalyzed coupling of azides and alkynes[5]. Triazolophanes for example have unexpectedly large halide binding constants, which take advantage of macrocyclic preorganisation to direct four triazole CH donors and four phenylene CH donors into the central cavity[6]. Moreover, preorganized aryl-triazole pentads are shown to be good receptors for chloride anions.[7]

In the design of a receptor, preorganizing the conformation is crucial to obtain high binging affinities. Intramolecular hydrogen bonds have already been used to preorganize acyclic receptors[7,8]. Herein we demonstrate the effect of pyridine and pyrimidine moieties on the preorganisation of 4,6-bis-(1,2,3-triazolyl)-pyrimidine and 4,6-bis-(1,2,3-triazolyl)-pyridine anion.

The 4,6-bis-(1,2,3-triazolyl)-pyrimidine receptor **1** was synthesized from thiobarbituric acid as shown in fig 1.

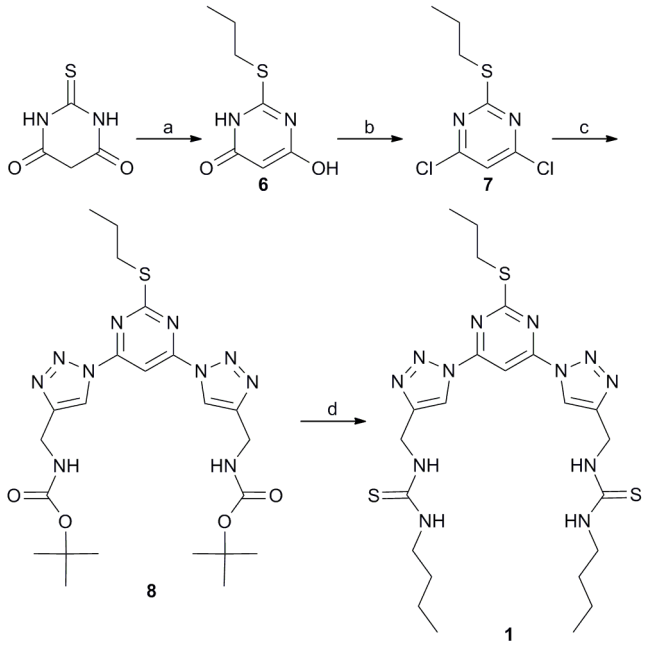

Fig 1: Reagents and conditions: a) 1-bromopropane, Et_3N, MeOH, reflux, 20h, 90%; b) $POCl_3$, reflux, 18h, 58%; c) 1. NaN_3, Bu_4NBr, THF, 50°C, 3h; 2. N-boc-propargylamine, $CuSO_4$, NaAsc, *tert*-butanol/H_2O, 50°C, 2h, 71%; d) 1. HCl in dioxane (4N), rt, 30 min; 2. butylisothiocyanate, Et_3N, CH_2Cl_2, rt, 18h, 67%

Thiobarbituric acid was first alkylated with 1-bromopropane in the presence of triethylamine yielding the desired derivative **6**, which was then chlorinated with $POCl_3$ to afford **7**. Compound **8**

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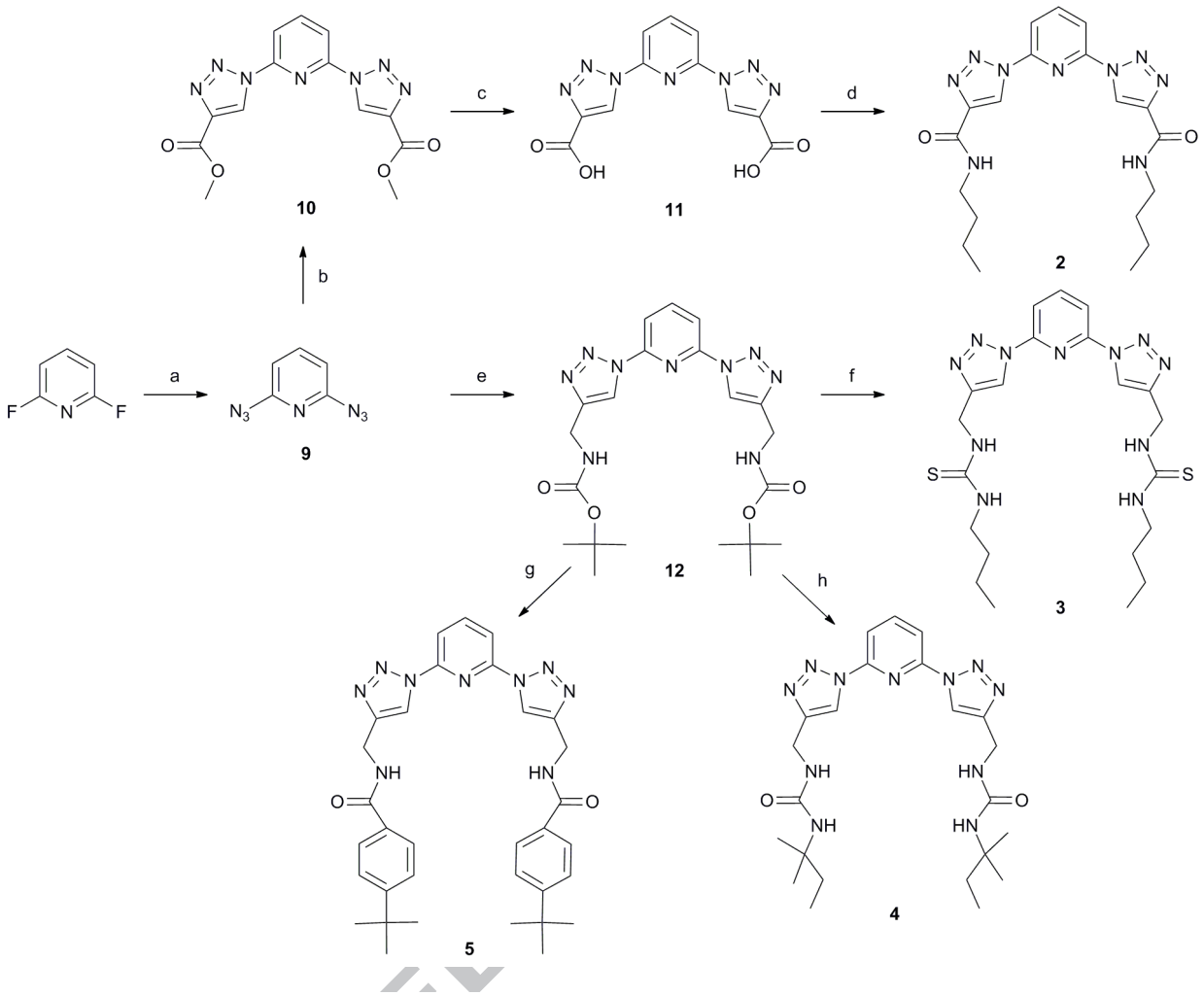

Fig 2: Reagents and conditions: a) NaN_3, DMF, 70°C, 48h, 27%; b) methyl propiolate, $[(CH_3CN)_4Cu]PF_6$, THF, 50°C, 2h, 51%; c) NaOH, MeOH/H_2O, rt, 16h, 88%; d) *n*-butylamine, HOBt, HBTU, DMF, rt, 20h, 49%; e) N-boc propargylamine, $[(CH_3CN)_4Cu]PF_6$, THF, 2h, 50°C, 85%; f) 1. HCl in dioxane (4N), rt, 1h, 2. butyl isothiocyanate, CH_2Cl_2, rt, 16h, 43%; g) 1. HCl in dioxane (4N), rt, 1h, 2. 4-(tert-butyl)benzoyl chloride, CH_2Cl_2, DIPEA, rt, 16h, 59%; h) 1. HCl in dioxane (4N), rt, 1h, 2. *tert*-pentyl isocyanate, Et_3N, CH_2Cl_2, rt, 16h, 54%

was then obtained in an one pot procedure by a substitution reaction with NaN_3, followed by a click reaction with N-Boc-propargylamine[9]. Finally the the desired receptor **1** was obtained after removal of the Boc-group[10] and subsequent treatment of the resulting product with butyl isothiocyanate. The synthetic details and structural analysis data are described in Electronic Supplementary Information (ESI).

The 4,6-bis-(1,2,3-triazolyl)-pyridine receptors **2-5** were synthesized from 2,6-difluoropyridine as shown in fig 2. In a first step, 2,6-diazidopyridine **9** was synthesized by a reaction of 2,6-difluoropyridine with NaN_3 in DMF. Compound **10** was then obtained by a click reaction between molecule **9** and methyl propiolate. A saponification reaction of **10** with NaOH and a subsequent amide coupling reaction with *n*-butylamine yielded the desired receptor **2**. Molecule **12** was synthesized by a click reaction between 2,6-diazidopyridine **9** and N-Boc-propargylamine. Finally, receptors **3-5** were synthesized by a Boc-deprotection reaction of **12** and subsequent reaction of the resulting product with respectively butyl isothiocyanate, *tert*-pentyl isocyanate and 4-tert-butylbenzoyl chloride. The R-groups of the receptors **1-5** were chosen for the purpose of solubility in acetonitrile, which was the solvent chosen for the ^{1}H NMR-titrations.

The binding constants of all the receptors were determined by ^{1}H NMR titrations with the tetra-*n*-butylammonium salts of the anions in acetonitrile. The data was fitted to a 1:1 binding model as confirmed by Job plot analysis (Fig S1 in the ESI) and the anion binding constants were calculated with HypNMR[11]. The binding constants are shown in Table 1 and reveal that, for all the receptors, the binding with the chloride anion is stronger than with bromide. For the 4,6-bis-(1,2,3-triazolyl)-pyridine receptors **2-5**, a downfield shift of the ^{1}H NMR resonances of the triazole CH protons and NH protons was observed upon addition of the tetra-*n*-butylammonium salts of chloride and bromide, clearly indicating the formation of hydrogen bonds to the anion (Fig 3).

Table 1: Stability constants ($\log(K_a)$) determined by ^{1}H NMR titrations with the tetra-*n*-butylammonium salts of the anions in acetonitrile.

Receptor	Cl^-	Br^-
1	2.24±0.07	1.91± 0.01
2	1.36± 0.01	0.95±0.2
3	3.4±0.1	2.62±0.05
4	3.02±0.03	2.69±0.02
5	1.34±0.01	1.01±0.02

The highest binding affinities were obtained for receptor **3** with $\log(K_a)$ of 3.4 for chloride and 2.62 for bromide. Receptor **4** has comparable binding constants with $\log(K_a)$ of 3.02 for chloride and 2.69 for bromide. The binding constants of the two receptors **2** and **5** on the other hand were significantly lower with

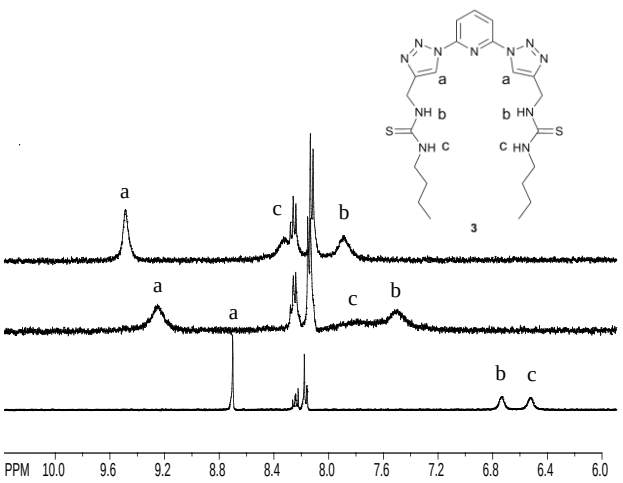

Fig 3: ^{1}H NMR spectra (aromatic region) of **3** upon titration with tetra-*n*-butylammonium chloride

log(K_a) of respectively 1.356 and 1.34 for chloride and 0.95 and 1.01 for bromide.

The anion binding strength of **3** was then compared with **1**. With a log(K_a) of 2.24 for chloride and 1.91 for bromide, the binding constants of receptor **1** are approximately a tenfold lower in comparison with the analogous pyrimidine-based receptor **3**. The stack plot of receptor **1** shows a downfield shift of the ^{1}H NMR resonances of the triazole CH protons and NH protons, indicating the formation of hydrogen bonds to the anion (Fig 4). The pyrimidine CH proton on the other hand show only a small upfield shift up to the addition of approximately one equivalent of tetra-*n*-butylammonium chloride, followed by a small downfield shift upon addition of more tetra-*n*-butylammonium chloride. This might indicate that the pyrimidine CH proton is not involved in the anion binding. Comparing the structure of both receptors reveals that, for the pyrimidine receptor **1**, the triazole CH protons can form electrostatically attractive hydrogen bond-like interactions with the nitrogen atoms of the pyrimidine, yielding a more linear conformation. This implicates that the receptor might need to undergo a flip conformational change upon anion binding (Fig 5). Moreover, repulsive interactions between the nitrogen atoms of the pyrimidine and the triazoles further destabilize the complex. For the pyridine receptor **3** on the other hand, intramolecular hydrogen binding between the triazole CH atoms and the nitrogen atom of the pyridine does preorganize the receptor for anion binding.

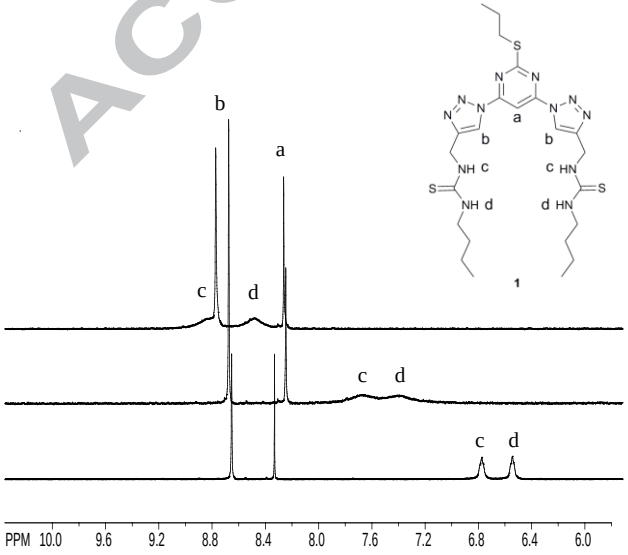

Fig 4: ^{1}H NMR spectra (aromatic region) of **1** upon titration with tetra-*n*-butylammonium chloride

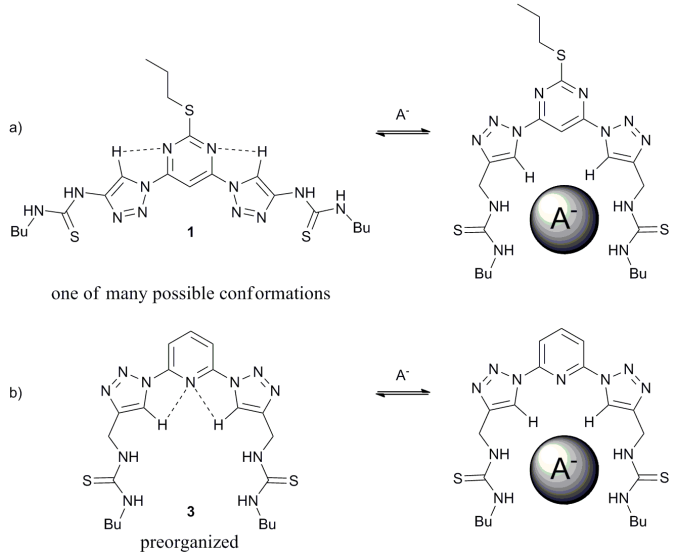

Fig 5: Anion binding of a) 4,6-bis-(1,2,3-triazolyl)-pyrimidine receptor **1** and and b) 4,6-bis-(1,2,3-triazolyl)-pyridine receptors **3**

The amide receptors **2** and **5** possess two less NH binding sites then the (thio)urea receptors **3** and **4**, resulting in lower binding affinities. Moreover, intramoleculair hydrogen bonding of the amide groups to the N^3 nitrogen atom of the triazoles can further disfavour anion binding. This effect apparently does not occur for the less acidic (thio)urea receptors **3** and **4**.

By comparing the receptors **2** and **5**, we could also evaluate the effect of terminal preorganisation. The NH-groups of receptor **2** will most likely prefer to point out of the cavity because of repulsion between the carbonyl group and the N3 nitrogen atom of the triazole, unlike receptor **5** which doesn't suffer from such an effect. However the binding constants of **2** and **5** are almost the same, indicating that the terminal preorganisation doesn't influence much of the binding affinity.

In summary, a series of 4,6-bis-(1,2,3-triazolyl)-pyrimidine and 4,6-bis-(1,2,3-triazolyl)-pyridine anion receptors were synthesized and their binding properties were examined. Intramolecular hydrogen bonding between the triazole CH atoms and the nitrogen of the pyridine preorganize the 4,6-bis-(1,2,3-triazolyl)-pyridine receptors **2-5** for anion binding. This results in higher anion binding constants in comparison with the receptor **1**, where intramolecular CH-N interactions can stabilize a conformation which is less suited for anion binding. On the other hand, terminal preorganisation doesn't have a great influence on the binding affinity.

Acknowledgments

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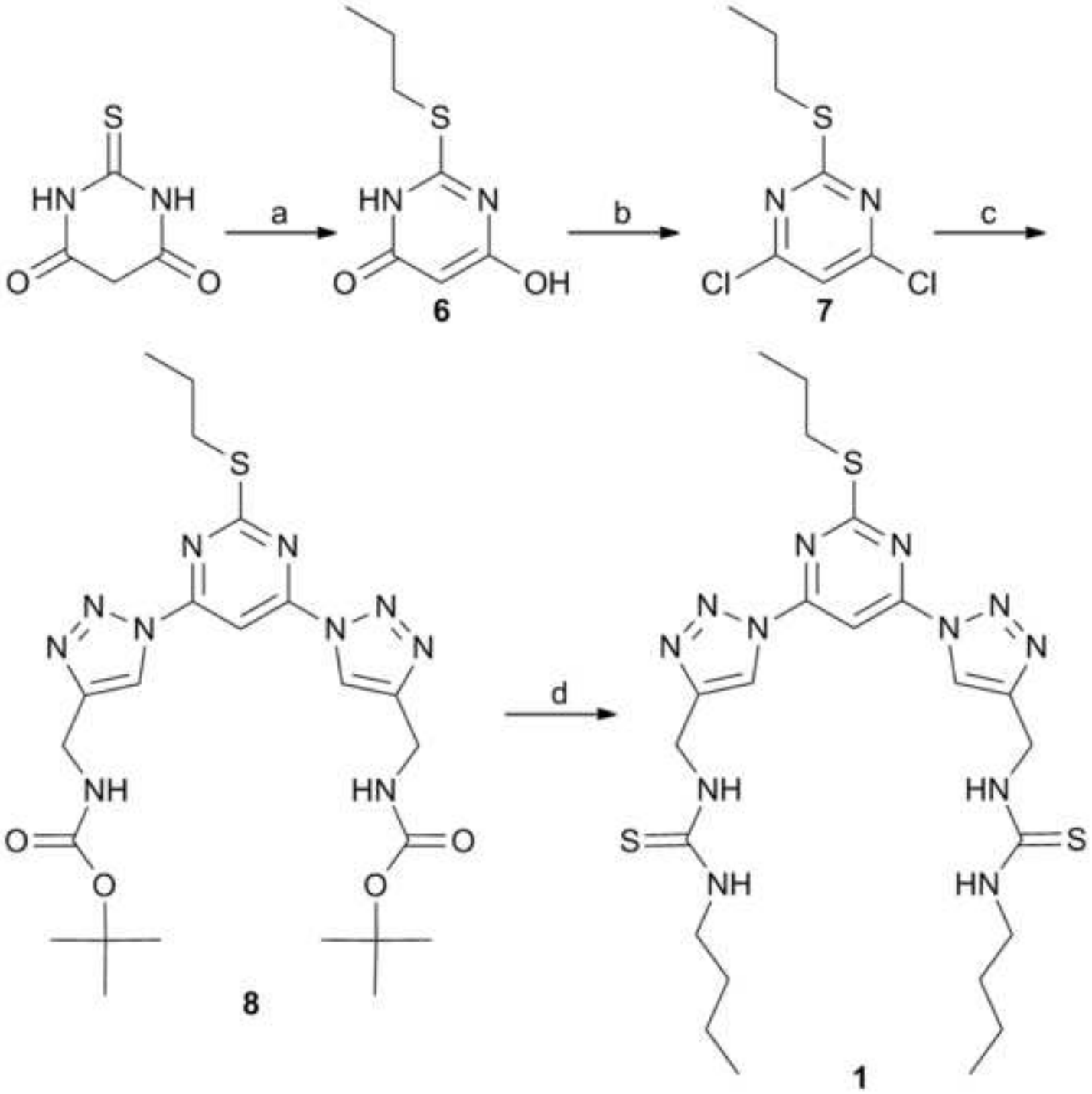

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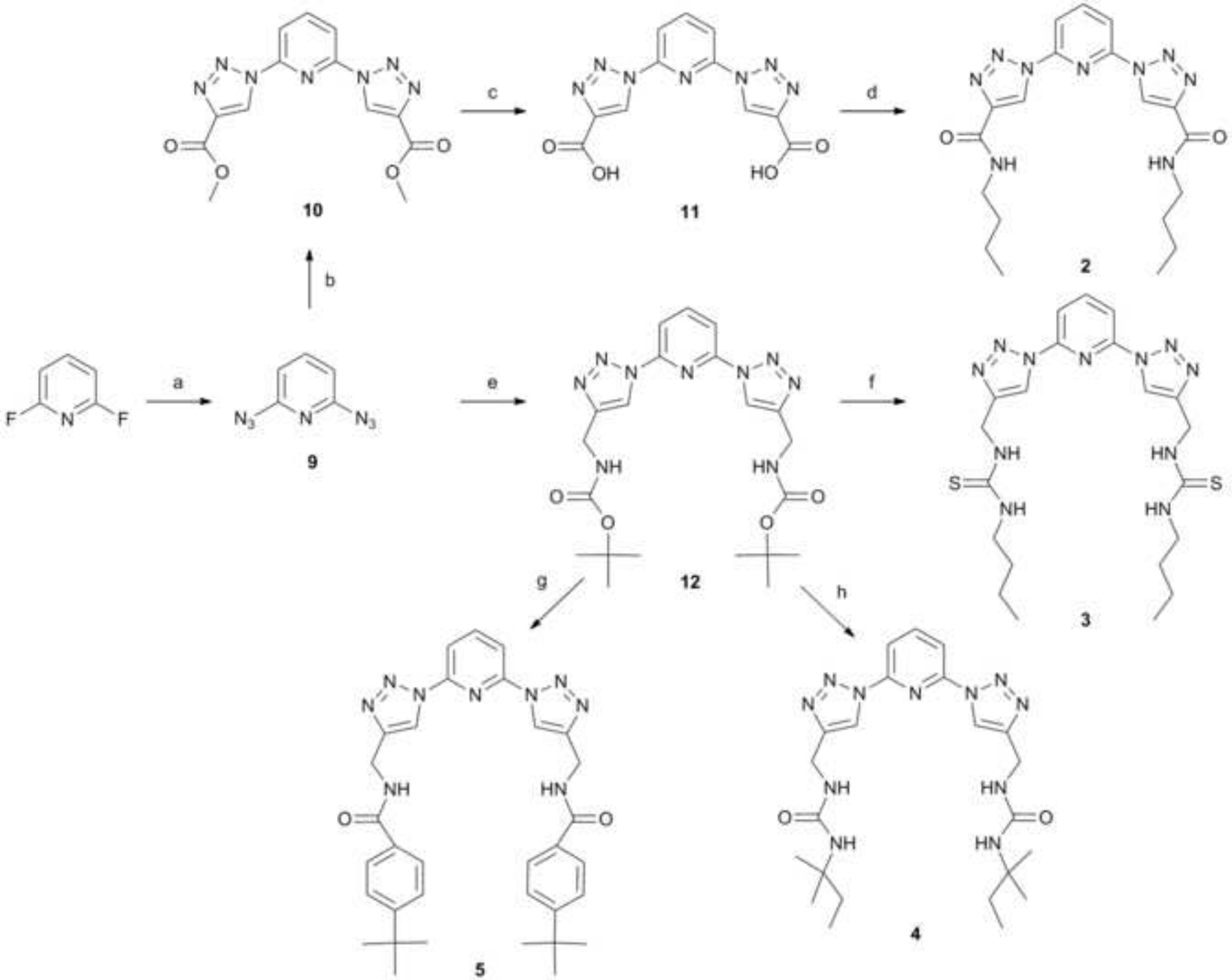

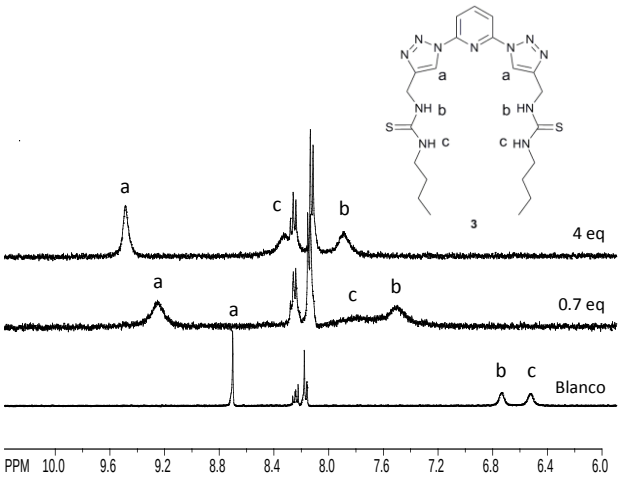

Fig 3: ^{1}H NMR spectra (aromatic region) of **3** upon titration with tetra-*n*-butylammonium chloride

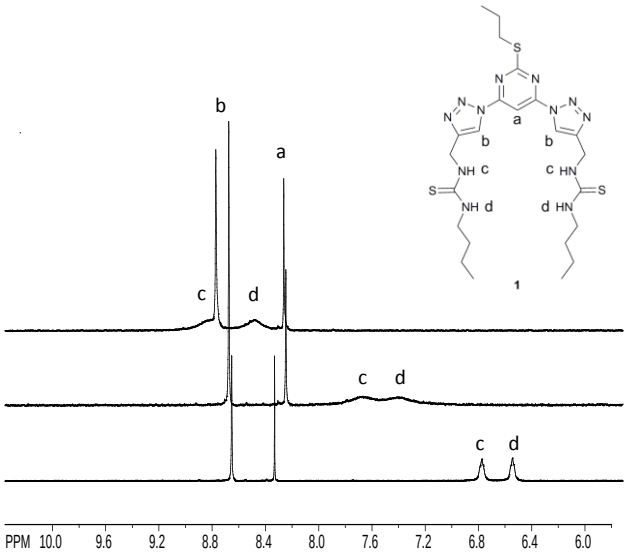

Fig 4: ^{1}H NMR spectra (aromatic region) of **1** upon titration with tetra-*n*-butylammonium chloride

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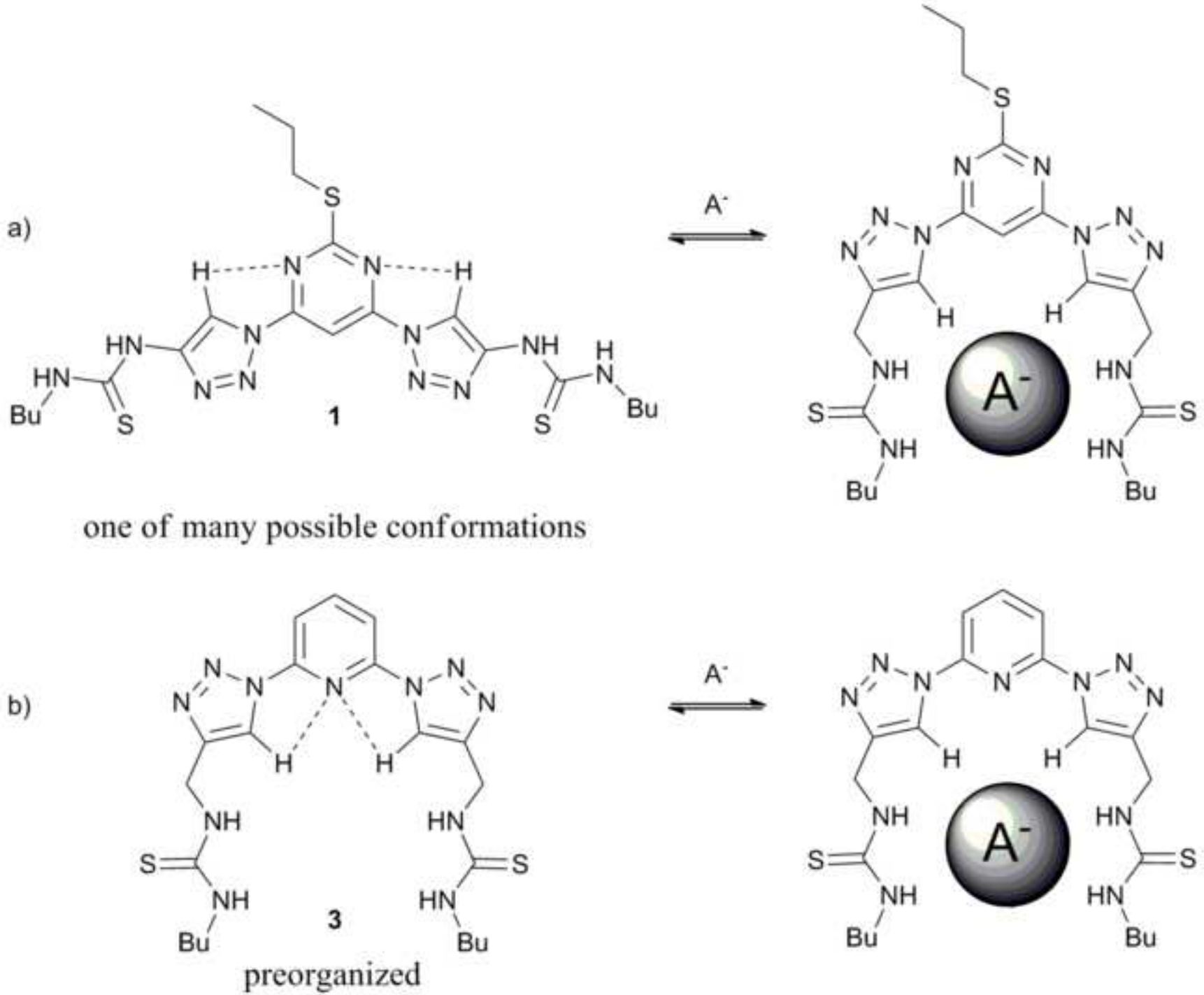

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