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Unprecedented folding in linker based flexible tripodal molecule and their conformational analysis

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ABSTRACT

Here, we first time report the flexible tripodal molecules, contained propylene as a linker, thiocyanuric acid as central core and, *p*-nitro phenol **1** and pyridazinone **2** as terminal for conformational studies. The conformational studies of these tripodal molecules have been carried by X-ray crystallography, 2D-NOESY spectra and computational studies. Both the molecules have shown folded conformations in solid and solution state however solid state conformation is not stable in gaseous state.

1. Introduction

The conformation of tripodal molecule allows the rational control of binding properties such as complex stability and selectivity. Compared to a rigid cyclic system, they can show rapid complexation/decomplexation kinetics and may undergo significant conformational changes upon binding [1]. Further the tripodal molecule can act as receptors for different chemical species: transition metal ions [2], lanthanide ions [3], actinide ions [4], anions [5], or cations [6]. The tripodal molecules are also increasingly applied in the fields of catalysis [7], molecular recognition [8] and biomimetics [9]. These all applications are driven by presence of functional groups [10] as well as heteroaromatic moieties [11] of tripodal molecule. The presence of functional group on tripodal molecules have prone to shown pH sensor [12], metal-binding site [13], and hydrogen bond donors/acceptors [14] which is oriented towards a central cavity enables selective substrate for recognition. The tripodal molecule contained heteroaromatic moieties also causes weak interactions [15], metal coordination [16], ionic interactions [17], and hydrophobic interactions [18]. In addition to this, other non-covalent forces, i.e. π-stacking of aromatic units, can be used as a strategic design highly sensitive for solvent employed by π···π and C–H···π interactions regarding for understanding the host–host and host–guest interactions [19].

In this article we report the synthesis of two new flexible tripodal molecules (**1** and **2**) appended with *p*-nitro phenol and pyridazinone moieties for their conformational studies. These tripodal molecule contained small molecule like thiocyanuric acid as central core, propylene as spacer in middle and, *p*-nitro phenol **1** and pyridazinone **2** moieties in terminal (Scheme 1). The selection of terminal *p*-nitro phenol and pyridazinone system have been taken for synthesis of tripodal molecules because these systems are electron deficient systems due to presence of electron withdrawing substituent like nitro, nitrile and amide function in the ring. Electron deficient systems are prone for folding [20]. Conformational studies have been carried out, in solid state by crystal structure, in solution state by 2D-NOESY spectra and in gaseous state by DFT calculations.

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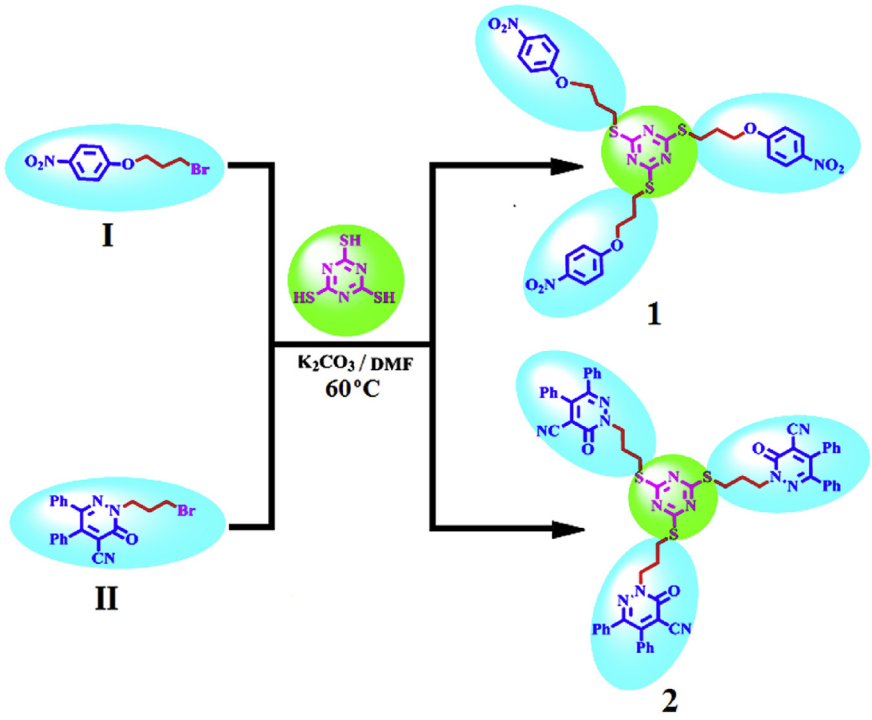

Scheme 1. Synthesis of flexible tripodal molecule.

2. Experimental section

2.1. General methods

All reactions were performed according to the condition as under at ambient temperature, and reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL300 and AL500 FT-NMR spectrometer (300 and 500 MHz). TMS was used as internal reference, and chemical shift values were expressed in δ ppm units.

2.2. Synthesis

Pyridazinone molecules were synthesized according to literature procedure [21].

2.2.1. Synthesis of compounds (*I* and *II*)

In a 100 ml round- bottom flask, aromatic and hetero-aromatic compounds (3.4 mmol) were dissolved in minimum amount of dry DMF and to that anhydrous potassium carbonate (3.4 mmol) was added and reaction mixture was stirred for 30 min. Subsequently, 1, 3 dibromopropane (20.4 mmol) was added to the reaction mixture and stirring was continued for next 15–20 h. Completions of the reaction was monitored with TLC (15% Ethyl Acetate and Hexane). After completion of reactions DMF was removed in vacuo and extracted with chloroform and washed with water. The organic layer was dried over sodium sulphate and solvent was evaporated through rotaevaporator after that we obtained crude product. The obtained crude products were purified by column chromatography with mixture of 15% Ethyl Acetate and Hexane as eluent.

*2.2.1.1. 1-(3-bromopropoxy)-4-nitrobenzene (**I**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34–2.39 (quint- 2H, $-CH_2$), 3.60–3.62 (t, 2H, $-CH_2$), 4.20–4.23 (t, 2H,$-CH_2$), 6.95–6.99 (m, 2H, Ar–H), 8.19–8.22 (m, 2H, Ar–H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 29.47, 31.99, 66.18, 114.54, 126.03, 141.76, 163.75; FAB MS: m/258.98 (M+H); Elemental analysis for $C_9H_{10}BrNO_3$: Calcd: C, 41.56; H, 3.88; Br, 30.72; N, 5.39; O, 18.45; Found: C, 41.45; H, 3.98; Br, 30.62; N, 5.49; O, 18.46.

*2.2.1.2. 2-(3-bromopropyl)-3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carbonitrile (**II**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.47–2.53 (quint-, 2H, $-CH_2$), 3.50–3.53 (t, 2H, $-CH_2$), 4.46–4.49 (t, 2H, $-CH_2$), 7.08–7.45 (m, 12H, Ar–H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.66, 31.13, 51.71, 113.25, 113.89, 120.33, 128.92, 129.01, 129.25, 130.62, 132.52, 134.18, 145.97, 151.14, 156.79; FAB MS: m/714.12 (M+H); Elemental analysis for $C_{20}H_{16}BrN_3O$: Calcd: C, 60.93; H, 4.09; N, 10.66; O, 4.06; Br, 20.27; Found: C, 60.60; H, 4.33; N, 10.45; O, 4.25; Br, 20.37.

2.2.2. Synthesis of compounds (*1* and *2*)

In a 100 ml round- bottom flask, thiocyanuric acid (845.46 μmol) was dissolved in minimum amount of dry DMF and to that anhydrous potassium carbonate (2.54 mmol) was added and reaction mixture was stirred for 30 min. Subsequently, compound **I** and **II** (2.54 mmol) was added to the reaction mixture and stirring was continued for next 10–12 h at 60 °C. Completions of the reaction were monitored with TLC (25% Ethyl Acetate and Hexane). After completion of reactions DMF was removed in vacuo and extracted with chloroform and washed with water. The organic layer was dried over sodium sulphate and solvent was evaporated through rotaevaporator after that we obtained crude product. The obtained crude products were purified by column chromatography with mixture of 25% Ethyl Acetate and Hexane.

*2.2.2.1. 2,4,6-tris((3-(4-nitrophenoxy)propyl)thio)-1,3,5-triazine (**1**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23–2.28 (quint-, 6H, $-CH_2$), 3.28–3.31 (t, 6H, $-CH_2$), 4.16–4.19 (t, 6H, $-CH_2$), 6.93–6.95 (m, 6H, Ar–H), 8.17–8.20 (m, 6H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.85, 28.75, 66.88, 114.49, 126.03, 141.72, 163.72, 179.39; FAB MS: m/393.04 (M+H); Elemental analysis for $C_{30}H_{30}N_6O_9S_3$: Calcd: C,