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Haoxiang Gao[a]; Liping Cai[b]; Yanxing Qi[a]; Hanqing Wang[a]
[a] Chinese Academy of Sciences, Lanzhou Institute of Chemical Physics, Lanzhou, People's Republic of China [b] National Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou, People's Republic of China

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Synthesis of 1,3-{Di-[*N*-bis(dimethylamino)methane]}-benzyl-diamide and its Molecular Recognition of Nucleotides in Aqueous Solution

HAOXIANG GAO[a], LIPING CAI[b], YANXING QI[a] and HANQING WANG[a,*]

[a]*Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, People's Republic of China;* [b]*National Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China*

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1,3-Di-{*N*-[bis(dimethylamino)methane]}benzyl-diamide 1 was synthesized by the reaction of isophthaloyl dichloride with 1,1,3,3-tetramethylguanidine (TMG). Its structure was confirmed by IR, ^{1}H NMR, EI-MS and elemental analysis. ^{1}H NMR results of the interaction of 1 with phosphate-containing biomolecules showed it has the ability of selective molecular recognition for nucleotides.

Keywords: Guanidine derivative; Nucleotides; Molecular recognition; ^{1}H NMR

INTRODUCTION

Molecular recognition plays a major role in biological systems and is achieved through combined non-covalent interactions such as hydrogen bonding, electrostatic interactions and hydrophobic interactions [1]. Molecular recognition of relevant biological targets constitutes a dynamic branch of organic chemistry. The selective recognition of nucleotides by synthetic host compounds has been the subject of a large number of studies in the last ten years [2–6]. These studies make essential contributions to the understanding of the mechanisms of noncovalent interactions involving nucleic acids, as well as for future applications of supramolecular chemistry in the fields of analytical, biological and medicinal chemistry. Substantial progress has been made towards understanding the fundamental principles responsible for the sequence-selective recognition of duplex DNA by small organic molecules.

The guanidine functional group is an important structural component in many biologically active compounds. The hydrogen-bond mediated interaction of guanidinium ions with phosphate and carboxylate-containing biomolecules is of considerable interest in bioorganic chemistry [7–11]. Not least of these are the key interactions of guanidine-containing side chains of arginine residues involved in substrate recognition at enzyme active sites [12,13]. In addition, the guanidinium motif has also been utilized in synthetic host receptors for phosphate- and carboxylate-containing guest molecules, which are of considerable current interest [14–16]. Although fully substituted guanidines are not common, their presence can facilitate binding to complex receptors and therefore can be of key importance for the development of bioactive molecules. Thus, new methods for the synthesis of penta-substituted guanidines have been reported recently [17–20]. The present paper reports the synthesis of a bis(arylguanidine) molecular tweezers and the study of its nucleotide molecular recognition properties using ^{1}H NMR.

EXPERIMENTAL

FT-IR spectra were recorded on a Nicolet 10 DX spectrometer (KBr). ^{1}H NMR spectra were obtained on a Bruker AC-P 200M NMR instrument in $CDCl_3$ or DMSO-d_6 solution with TMS as internal reference. EI-MS spectra were obtained with a VG AB-HS instrument. HRMS(ESI) spectra were obtained with

*Corresponding author.

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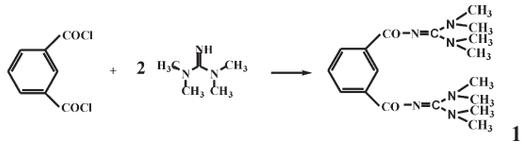

SCHEME 1

a Bruker Daltonics APEX II 47e FTICR-HRMS instrument.

Synthesis

1,1,3,3-Tetramethylguanidine (TMG) (20 mmol) and THF (20 ml) were added to a flame-dried round-bottomed flask. The mixture was cooled to 9°C by an ice–water bath. To this stirred solution 10 mmol of isophthaloyl dichloride in THF (15 ml) were added dropwise over 1 h. A white precipitate ($[TMGH]^+ \cdot Cl^-$) was formed immediately. During the addition the reaction temperature was maintained at 9–18°C. The ice–water bath was then removed and the resulting white slurry was allowed to stir for two additional hours at room temperature, filtered and the precipitate was washed with chloroform. The solvent was removed by rotary evaporation to yield a yellow oil. The crude product was dissolved in benzene, and the white precipitate ($[TMGH]^+ \cdot Cl^-$) was removed by filtration. Removal of the solvent *in vacuo* left a residue, which was recrystallized from cyclohexane–chloroform (Scheme 1). Yield, 90%; mp 146–148°C; ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H), 7.89 (d, 2H), 7.40 (t, 1H), 2.85 (s, 24H); ^{13}C NMR δ 172.9, 167.9, 137.8, 131.3, 129.8, 127.2, 40.1; EI/MS (m/z): 360 (M^+), 302, 246, 219(100), 174, 142, 104,71; IR (KBr) 3029, 3009, 1590, 1522 (C=N), 1359, 1226, 1160, 869 cm^{-1}. Anal. calcd for $C_{18}H_{28}N_6O_2$: C, 59.96; H, 7.83; N, 23.32. Found: C, 59.86; H, 7.94; N, 23.21.

RESULTS AND DISCUSSION

^{1}H NMR Studies of Molecular Recognition Ability of 1

^{1}H NMR spectroscopy has been widely used to investigate receptor–substrate interactions. In this investigation the ^{1}H NMR spectra of six nucleotides (2′-deoxyadenosine 5′-monophosphoric acid hydrate **2**, adenosine 5′-monophosphate **3**, cytidic acid **4**, uridine-5′-monophosphate **5**, guanosine 5′-triphosphate **6** and 2′-deoxycytidine-5-monophosphoric acid monohydrate **7**) were recorded in the absence and presence (of 1 equiv) of the host receptor **1**. It was found that upon the addition of the receptor to D_2O solutions of (**4**–**7**), no appreciable changes in the chemical shifts of the latter species (less than 0.02 ppm) were observed. However, significant changes in the chemical shifts of **2** and **3** were observed upon the addition of 1 equiv of **1** indicating that compound **1** is interacting selectively with these species. Major changes in the spectra of **2** and **3**, (Fig. 1) upon addition of 1 equiv of **1** in D_2O at room temperature are shown in Table I.

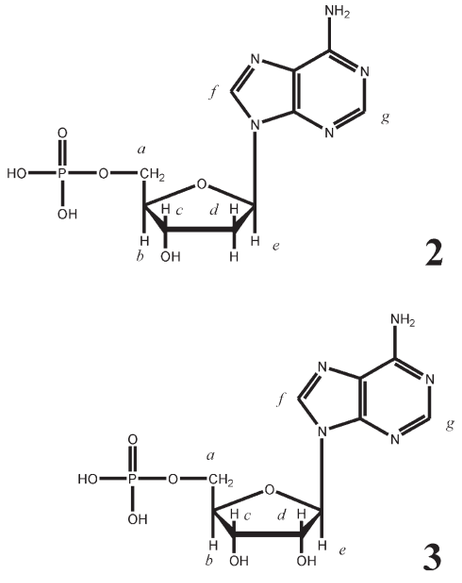

FIGURE 1

The association constants (K_a) for these new host–guest systems were determined by ^{1}H NMR titration [21], in conjunction with the nonlinear least-squares fit of the data to 1:1 models. The experiment consisted of holding one component (usually the guest) at constant concentration and varying the concentration of the second component. Titration curves obtained in D_2O are shown in Fig. 2. For the guests **2** and **3** the plot of chemical shift *versus* the guest:host ratio gives a curve with a well-defined break at 1 equiv of **1**.

The values of K_a (molecular complex formation constant) were calculated by using Microcal Origin

TABLE I Chemical shifts of **2** and **3** in the absence and presence of receptor **1**

Entry	δa	δb	δc	δd	δe	δf	δg
2 (0.010 M)	2.730	2.566	3.979	4.192	6.471	8.269	8.500
2 (0.010 M) + **1** (0.010 M)	2.718	2.456	3.816	4.137	6.382	8.118	8.439
3 (0.010 M)	3.994	4.583	4.435	4.318	6.125	8.347	8.546
3 (0.0118 M) + **1** (0.0118 M)	3.889	4.575	4.316	4.258	6.033	8.143	8.507

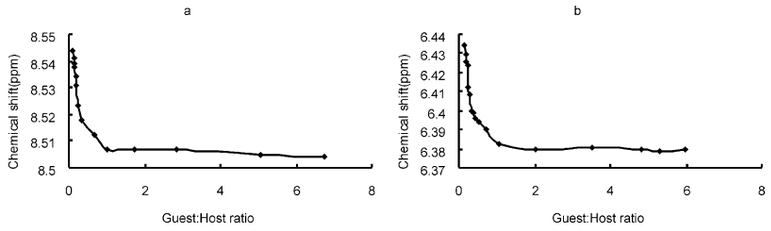

FIGURE 2 Plot of observed (◆) chemical shift of the proton of nucleotide upon titration with **1**. (a) nucleotide **2** in D_2O (0.01 M) (b) nucleotide **3** in D_2O (0.0118 M).

TABLE II Association constants K_a determined from the titration of guests **2** and **3** with **1** in D_2O at room temperature using ^1H NMR

Guest	K_a (M^{-1})
2	2.3×10^4
3	7.2×10^4

5.0 (Microcal software, Inc.). The results from the ^1H NMR titrations of **2** and **3** with receptor **1** are summarized in Table II.

In summary, we synthesized a new guanidine derivative host **1** in high yield under mild conditions. Inspection of Table I provides an insight into the nature of complexation of **1** with the nucleotide. By ^1H NMR titration methods, we have studied the association of **1** with various nucleotides. The association constants for formation of the 1:1 complex range from 2.3×10^4 to 7.2×10^4. These results illustrate the potential of **1** as a new host molecule for the complexation of nucleotides in host–guest chemistry.

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