Ribose-protected thioguanosine-based $^1$H NMR spectroscopic probe for the detection of cesium from solid cesium-containing sources in acetonitrile

Qun Luo $^{a,c}$, Daihua Tang $^{a,*}$, Gang Wu $^{b,*}$

$^a$Key Laboratory of Photochemical Conversion and Optoelectronic Materials, Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, PR China
$^b$Department of Chemistry, Queen’s University, Kingston, Ontario, Canada K7L 3N6
$^c$The Graduate School of Chinese Academy of Sciences, Beijing 100049, PR China

A R T I C L E   I N F O

Article history:
Received 22 June 2008
Accepted 2 September 2008
Available online 11 September 2008

Keywords:
Cesium
Selectivity
Sensitivity
Ribose-protected thioguanosine
NMR probe

A B S T R A C T

Ribose-protected thioguanosine (TG) exhibited remarkable preference for cesium over other alkali metal (Na$^+$, K$^+$, Rb$^+$) and alkaline earth metal ions (Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$, Ba$^{2+}$) in acetonitrile by $^1$H NMR measurements. Furthermore, TG displayed excellent sensitivity for cesium even under 500/1 NaCl/CsCl and KCl/CsCl environments. The most distinct feature is that only in a cesium environment, the thioamide $\delta$NH peak becomes highly broadened and finally disappeared, and the amino NH$_2$ peak shows a downfield shift, suggesting that TG-based $^1$H NMR spectroscopic probe is factually useful for the detection of cesium from solid cesium-containing sources in organic solvents.

Cs-selectivity is of interest not only for fundamental research but also for realistic applications. $^{137}$Cs is a dangerous radionuclide ($t_{1/2} = 30$yr, $\beta$-emission) that is a major product of uranium and plutonium fission [1], and $^{137}$Cs irradiation can induce interstrand cross-links (ISCs), which are particularly deleterious to cell [2]; the source containing radioactive $^{137}$CsCl may cause serious social, economic and medical consequences [3], and nonradioactive CsCl may also induce some diseases [4–6] due to its selective interactions with specific peptides [7]; the toxicity of cesium ions is due to its ability to replace potassium in muscles and red cells [8], affecting the functions of potassium channels [9]. Thus, the development of ionophores with high cesium-selectivity is of real significance in many applications including environmental and security monitoring, nuclear waste management, nutrition, clinical toxicology, and biotechnology [10–12].

The detection methods for cesium mainly include electron absorption spectrum, fluorescence spectrum and electrochemical techniques [10,12–16]. Recently NMR probe techniques have received considerable attention due to its ability to provide clear structural information for these selective interactions [17–19]. In this regard, traditional detection methods for cesium usually are based on solution samples, for a more convenient and practical purpose, it is of interest whether cesium can be directly detected from solid cesium-containing samples in organic solvents. As for the ionophores, besides the traditional calixarencrowns [10,16,20], other types of ionophores have been developed to meet various requirements, for example, inorganic clay materials exhibit remarkable Cs$^+$/Na$^+$ (CsCl/NaCl) selectivity [21]; inorganic–organic hybrid materials display preferable affinity to cesium over other alkali and alkaline earth metal ions except magnesium [22].

Since both radioactive $^{137}$Cs [2,3,8] and nonradioactive $^{133}$Cs [4–9] are deleterious to environment and human health, biologically important small molecules with high cesium-selectivity may be of particular interest due to their biocompatibility. The sulfur analogs of the current nucleic acids constitute a most important type of non-natural nucleic acids (modified nucleic acids). Of these sulfur-containing analogs, thioguanine and thioguanosine have been used to treat a variety of diseases [23–28]. Here we present a ribose-protected thioguanosine-based $^1$H NMR spectroscopic probe for cesium detection, where cesium can be directly detected from solid cesium-containing sources in acetonitrile. To the best of our knowledge, this is the first example of a biologically important small molecule exhibiting remarkable preference for cesium over other alkali metal (Na$^+$, K$^+$, Rb$^+$) and alkaline earth metal ions (Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$, Ba$^{2+}$). Synthesis of ribose-protected thioguanosine (Fig. 1, TG) was achieved by following a similar approach [29,30] (see Supporting information).

The solubilities of alkali metal chloride salts NaCl, KCl, RbCl and CsCl are 0.00025, 0.0024, 0.0036 and 0.0084 g in 100 g of acetonitrile at 25 °C, respectively [31]. As to the solubilities of alkaline earth metal chloride salts MgCl$_2$, CaCl$_2$, SrCl$_2$ and BaCl$_2$ in acetonitrile, in our experiments, the four salts also were sparingly soluble in this solvent.

$^*$ Corresponding authors. Tel.: +86 10 8254 3772; fax: +86 10 6255 4670 (D. Tang), Tel.: +1 613 533 2644; fax: +1 613 533 6669 (G. Wu).
E-mail addresses: dhtang@mail.ipc.ac.cn (D. Tang), gangwu@chem.queensu.ca (G. Wu).
Figs. 2 and 3 present the $^1$H NMR spectra of TG with NaCl, KCl, RbCl, CsCl, MgCl$_2$, CaCl$_2$, SrCl$_2$, and BaCl$_2$. No obvious changes for the $^1$H NMR spectra of TG were observed in the presence of NaCl, KCl, RbCl, CsCl, MgCl$_2$, CaCl$_2$, SrCl$_2$, and BaCl$_2$. The most distinct feature is that only in a cesium chloride environment, as seen in Fig. 2e, the thioamide NH peak became highly broadened and finally disappeared, and the amino NH$_2$ peak showed a downfield shift from 5.66 to 6.0 ppm (see Figs. S1 and S2 in Supporting information). Low temperature NMR revealed us that two amino NH$_2$ protons are equivalent. These results suggested that Cs$^+$ ions interact with TG through multipoint recognition, including the sites of thioamide NH and amino NH$_2$ of TG molecules.

$^{13}$C NMR measurements could provide further understanding of the supramolecular interactions between TG and Cs$^+$ ions. The changes for $^{13}$C NMR signals mainly occurred on the five carbon atoms of thioamine base, but no any obvious changes for the carbon atoms of ribose skeleton. Among the five carbon atoms on the thionguanine base, the $^{13}$C NMR peak for C-2 covalently linked to NH$_2$ group showed a small downfield shift from 153.6 to 154.1 ppm. Although H-8 on the thionguanine base did not show an obvious shift from $^1$H NMR measurements, a distinct feature did occur with the $^{13}$C NMR spectra: C-8 peak became highly weakened (and/or broadened) (see Figs. S3 and S4).

The supramolecular interactions between TG and Cs$^+$ ions could also be observed from mass spectrometric and infrared spectroscopic measurements. In the MALDI/TOF mass spectrum of complex of TG with cesium ions, an intense peak at $m/z$ 586.13 corresponded to [TG+Cs$^+$] (calculated value, 586.09) (see Fig. S5). In the infrared spectra of TG and TG–CsCl, the absorption of thioamide NH and amino NH$_2$ groups at the range 3100–3500 cm$^{-1}$ became weakened and broadened due to the formation of TG–Cs$^+$ complex (see Fig. S6).

The $^{133}$Cs NMR spectra for both CsCl and CsCl–TG samples in CD$_3$CN are shown in Fig. 4. A single resonance was observed for both solutions with chemical shifts of 0.003 and 7.291 ppm (relative values), respectively. The small chemical shift difference suggested that weak interactions occur between Cs$^+$ ions and TG in CD$_3$CN, because strong interactions between cesium ions and ligands will cause $^{133}$Cs NMR resonance a large downfield shift [32].

To further investigate the selective interactions between TG and cesium ions, four samples 1–4 with different NaCl/CsCl molar ratios and four samples 5–8 with different KCl/CsCl molar ratios were
prepared by routine procedure (see Supporting information). Figs. S7 and S8 present 1H NMR measurements showing the influence of NaCl, KCl and CsCl with different NaCl/CsCl and KCl/CsCl molar ratios on TG in CD$_2$CN at 298 K. In particular, as seen in Figs. S7c and S8c, even under 500/1 NaCl/CsCl and KCl/CsCl environments containing TG (0.00276 mmol) and CsCl (0.0034 mmol) for 500/1 NaCl/CsCl sample and CsCl (0.00267 mmol) for 500/1 KCl/CsCl sample, the most distinct feature that the thioamide NH peak becomes highly broadened and finally disappeared, and that the amino NH$_2$ peak shows a downfield shift could be observed, indicating that TG exhibits excellent selectivity and sensitivity for Cs$^+$ ions and that the interaction behavior between TG and Cs$^+$ ions may follow an equimolar stoichiometry, because a large excess of CsCl did not cause any further change for TG. As such, cesium-selectivity and sensitivity could also be observed relative to Rb$^+$, Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$ and Ba$^{2+}$ ions (spectra not shown).

These results strongly suggested that the crucial factor whether the distinct interactions occur between TG and alkali and alkaline earth metal chloride salts is the nature of those metal salts rather than their different solubilities in acetonitrile. Indeed, all the alkali and alkaline earth metal chloride salts used are sparingly soluble in acetonitrile [31]. Nevertheless, TG could display excellent recognition selectivity and sensitivity [19] for Cs$^+$ ions. The rate constant obtained for the binding of cesium ions to TG was approximately 800 s$^{-1}$ according to the downfield shift of $^{133}$Cs NMR resonance of CsCl by TG [18,32] (see Fig. 4).

As a comparison, we tested the interactions of TG with cesium picrate by 1H NMR measurements. Although cesium picrate is highly soluble in acetonitrile, the addition of cesium picrate did not have a pronounced effect on the 1H NMR shifts. The only difference is that the thioamide NH peak on TG molecule became slightly weakened and broadened (see Figs. S9 and S9b). The $^{133}$Cs NMR signal for TG–Cs picrate in CD$_2$CN showed a very small downfield shift ($\Delta_{\delta} = 0.767$ ppm) relative to that for Cs picrate in CD$_2$CN (see Fig. S10), suggesting that the interactions between TG and cesium picrate are very weak. Together with the aforementioned result that the $^{133}$Cs NMR signal for TG–CsCl in CD$_2$CN showed a downfield shift ($\Delta_{\delta} = 7.288$ ppm) relative to that for CsCl in CD$_2$CN (Fig. 4), it is evident that TG exhibited remarkable preference for cesium chloride over cesium picrate, suggesting that the selective interactions between TG and cesium ions may be anion-dependent. In the interactions between TG and (n-C$_4$H$_9$)$_4$NCI in CD$_2$CN, the most distinct feature is that the thioamide NH and amino NH$_2$ peaks showed downfield shifts from 10.33 to 12.75 ppm and 5.75 to 7.0 ppm, respectively. Furthermore, C–H8 signal showed a small upfield shift ($\Delta_{\delta} \approx 0.1$ ppm) from 7.86 to 7.77 ppm (see Figs. S9 and S9d). These significant differences indicated that the interaction behaviors of TG with chloride anion may also be cation-dependent.

For the electronic absorption spectrum of TG in acetonitrile, the S2 state, which is due to a $\pi^*\pi$ excitation, gives rise to the main UV absorption band centered at 330 nm, while a weaker shoulder at 345 nm is due to the S1 state $\pi\pi^*$ transition (see Figs. S10 and S11). The emission spectra of TG, TG–NaCl, TG–KCl, TG–RbCl and TG–CsCl samples in acetonitrile are displayed in Fig. 5. At the excitation wavelength of 330 nm, the TG–CsCl sample revealed strong emission band at 380 nm, while the emission intensity at this band corresponding to TG sample was very weak. The quenching mechanism of TG is probably based on photoinduced electron transfer (PIET) [33]. However, alkali metal ions show different affinity to the lone pairs, thus stopping PIET. At this excitation wavelength, no emission enhancement was observed for TG–NaCl, TG–KCl and TG–RbCl samples, indicating that no obvious interactions took place between TG and Na$^+$, K$^+$ and Rb$^+$ ions.

The 1:1 CsCl:TG binding model could be confirmed by ESI-MS measurements (see Fig. S12). The positive-ion-mode ESI-MS gave a prominent signal at $m/z$ 586.3 corresponding to [TG + Cs$^+$] (calculated value: 586.09) and the negative-ion-mode ESI-MS gave a prominent signal at $m/z$ 488.3 corresponding to [TG + Cl$^-$] (calculated value: 488.2), suggesting that TG may bind both cesium cation and chloride anion to form a 1:1 TG:CsCl complex. According to the 1:1 M$^+$:L (M = metal ion, L = nucleobase or nucleotide) binding model for the emission enhancement (Fig. 5) as a function of nucleobase or nucleotide concentration [34], the stability constant for the binding of TG to cesium was approximately $4 \times 10^4$ M$^{-1}$.

The above observations confirmed that TG could simultaneously bind cesium cation and chloride anion to form an ion pair. It is specially noted that the simultaneous binding of cationic and anionic guests as an ion pair by heteroditopic receptors is an expanding area of molecular recognition [35–37].

TG cannot extract CsCl from water phase to chloroform layer, suggesting that cesium cation bonds water molecule more strongly than does TG. TG can probe the existence of cesium ions in CH$_2$CN, suggesting that TG may be a unique and effective ionophore for the detection of both radioactive $^{133}$Cs and nonradioactive $^{133}$Cs from solid cesium-containing sources in organic solvents. It is believed that this complexation process is reversible since there is no change on thin-layer chromatography (TLC) and that TG can be recycled.

In conclusions, ribose-protected thioguanosine (TG) exhibited remarkable preference for cesium over other alkali metal (Na$^+$, K$^+$, Rb$^+$) and alkaline earth metal ions (Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$, Ba$^{2+}$) in acetonitrile by 1H NMR measurements. Furthermore, TG displayed excellent sensitivity for cesium even under 500/1 NaCl/CsCl and KCl/CsCl environments. These results suggested that ribose-protected thioguanosine (TG)-based $^1$H NMR spectroscopic probe is factually useful for the detection of cesium from solid cesium-containing sources in organic solvents. From a practical viewpoint, this research may provide a basis for real-time detection of both radioactive $^{133}$Cs and nonradioactive $^{133}$Cs in the field of environmental and life sciences. Meanwhile, this finding may open a new route to the direct detection of metal ions from solid samples in organic solvents.

**Acknowledgements**

Financial support from the Knowledge Innovation Program of Chinese Academy of Sciences, the National Natural Science
Foundation of China and the Natural Sciences and Engineering Research Council (NSERC) of Canada is gratefully acknowledged.

Appendix A. Supplementary data


References