Lipophilic thioguanosine: An anion receptor for cesium fluoride

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ABSTRACT

A lipophilic thioguanosine ([5'-tert-butyl-dimethylsilyl]-2',3'-O-isopropylidene thioguanosine, TG) behaves as an anion receptor for CsF, and both deprotonation reaction and supramolecular interactions involved.

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1. Introduction

Nucleic acids are an important class of bioorganic molecules and their interactions with (metallic) cations have been well studied [1–3]. However, relatively fewer studies have reported on their utility as ion-pair [4,5] or anion receptors, partially because of the fact that oligonucleotides such as DNA and RNA are polyanions [6]. On the other hand, because nucleic acids contain N–H and C–H groups as well as π–electron base moieties, it is possible to use them as anion receptors or sensors [7–10]. For example, Davis and coworkers reported that a calix[4]arene–guanosine conjugate can be used as an ion-pair receptor for NaCl, KCl, NaBr, and KBr [4]. In comparison, thioguanosine may exhibit significantly different recognition ability for certain ionic species because the acidity of the (C=S)NH proton (pK a = 11–13) is much higher than that of an oxo amide (pK a = 17) [11]. Indeed, sulfur-containing nucleic acid analogs are the most important type of non-natural (modified) nucleic acids [12–20]. Of these sulfur-containing analogs, thioguanine and thioguanosine have been used to treat a variety of diseases such as tumor and HIV [12–16]. Recently we reported that a ribose-protected thioguanosine ([5'-tert-butyl-dimethylsilyl]-2',3'-O-isopropylidene thioguanosine, TG) could behave as an ion-pair receptor for CsCl in acetonitrile [5]. Here we use NMR, ESI–MS, electronic absorption and emission spectroscopic measurements to show that this lipophilic thioguanosine (TG, Fig. 1) exhibits remarkable affinity for CsF over other cesium salts (chloride, bromide, iodide, nitrate, perchlorate, picrate and sulphate) in acetonitrile. These results suggest that TG is also an efficient fluoride receptor or sensor. To date, the investigations for fluoride receptors or sensors are mainly based on organic ammonium fluorides such as tetra-n-butyl ammonium fluoride (TBAF) as fluoride sources [11,21–24]. However, fluoride sources from metal fluorides such as CsF are of interest not only for fundamental research but also for realistic applications [25,26].

2. Results and discussion

The interaction behaviors of TG toward CsF could be observed by 1H NMR measurements. To obtain comparable results, seven other cesium salts were utilized (CsCl, CsBr, CsI, CsNO 3 , CsClO 4 , cesium picrate and Cs 2 SO 4 ). The influences of 8 cesium salts on TG were depicted in Fig. 2. The results could be described in five situations: (1) No obvious changes for 1H NMR spectra of TG in the presence of CsNO 3 and CsClO 4 . (2) Only broadening for the thioamide NH peak in the presence of cesium picrate and Cs 2 SO 4 . (3) Broadening for the thioamide NH peak and downfield shift and broadening for the amino NH 2 peak in the presence of CsBr and CsI. (4) In a cesium chloride environment, the thioamide NH peak became highly broadened and finally disappeared, and the disappearance of thioamide NH peak was attributed to
N–H...Cl– (CsCl) hydrogen bonding. The amino NH2 peak showed a downfield shift from 5.70 to 6.0 ppm [5]. It was obvious that the situations (2)–(4) only involved the changes for the active thioamide NH and/or amino NH2 peaks. Broadening and/or disappearance of thioamide NH peak were probably attributed to N–H...anion hydrogen bonding. Nonactive C–H signals did not change. (5) The most significant changes were observed in the spectrum of TG–CsF. The thioamide NH peak disappeared and the amino NH2 peak showed an upfield shift from 5.70 to 4.75 ppm. The upfield shift of the amino NH2 peak might be attributed to electronic effect of TG base induced by CsF. Furthermore, the H8 peak on the thioguanine base shows an upfield shift from 7.85 to 7.56 ppm and the peaks for other protons on the ribose show different downfield or upfield shifts (Figs. S1 and S2 in the Supporting Information).

Fig. 1. Lipophilic thioguanosine (TG) as an anion receptor for CsF.

Following is a figure with structures and chemical symbols:

**Fig. 2.** 1H NMR (400 MHz) measurements showing the influences of 8 Cs-salts on TG in CD3CN at 298 K. Sample TG: TG (1.3 mg) in CD3CN (0.4 mL); TG + CsF: TG (1.3 mg) and CsF (2 mg) in CD3CN (0.4 mL); TG + CsCl: TG (1.3 mg) and CsCl (2 mg) in CD3CN (0.4 mL); TG + CsBr: TG (1.3 mg) and CsBr (2 mg) in CD3CN (0.4 mL); TG + CsI: TG (1.3 mg) and CsI (2 mg) in CD3CN (0.4 mL); TG + CsNO3: TG (1.3 mg) and CsNO3 (2 mg) in CD3CN (0.4 mL); TG + CsClO4: TG (1.3 mg) and CsClO4 (2 mg) in CD3CN (0.4 mL); TG + CsPic: TG (1.3 mg) and cesium picrate (2 mg) in CD3CN (0.4 mL); TG + Cs2SO4: TG (1.3 mg) and Cs2SO4 (2 mg) in CD3CN (0.4 mL).

The bifluoride (FHF–) [11,21–24] was observed in CD3CN at 16.30 ppm in the low temperature 1H NMR spectrum (Fig. S3). These behaviors were solvent-dependent. FHF– proton signal could be observed at 16.16 ppm in DMSO–d6 at room temperature (Figs. S4 and S5). Selective pulse [27] on FHF– proton signal shows correlations with the proton signals of thioguanine base and ribose, indicating the spatial proximity of FHF– proton with these protons on TG molecule (Fig. S6). In this solvent the upfield shifts of the amino NH2 peaks with changing into a 1:1 doublet suggested that the two amino NH2 protons encountered different chemical environments. Especially the methyl proton signals on silicon and tert-butyl were splitted into two unequal groups, respectively, which might be associated with C–H...FHF– interactions (Figs. S5 and S6). These results confirm the supramolecular interactions of FHF– ions with TG molecule. Furthermore, it was found that fluoride anion of CsF would more readily induce Si–O cleavage of TG molecule in DMSO than in acetonitrile.

13C NMR measurements could provide further understanding of the interactions of TG with CsF (Figs. S7 and S8). For TG–CsF in acetonitrile, significant changes were observed from the five carbon atoms on the thioguanine base. A distinct feature is that the 13C NMR signal at 177.2 ppm disappeared (probably highly broadened). Furthermore, slight changes also occurred for the five carbon atoms on the ribose. Thus, it is evident that the thioguanine base was the main interacting site between TG and CsF. The small changes for the ribose skeleton can probably be attributed to supramolecular C–H...F– (and other fluoride-induced anions) interactions.

We also used 133Cs NMR to probe the interactions between TG and the cesium salts in CD3CN and the results are summarized in Table S1 (Figs. S9–S14). In the case of CsCl, a single 133Cs NMR signal was observed for both CsCl and TG–CsCl at chemical shifts of 0.003 and 7.291 ppm, respectively [5]. The observed small chemical shift difference suggested a weak interaction between Cs+ ions and TG in CD3CN [28]. Upon addition of CsF to TG solution in CD3CN, the 133Cs NMR resonance for TG–CsF shows an downfield shift ($\Delta\delta = 40.14$ ppm) relative to CsF (Fig. S9). However, the 19F NMR resonance for TG–CsF shows an upfield shift ($\Delta\delta = -22.8$ ppm) relative to CsF (Fig. S15). The downfield shift
for $^{133}\text{Cs}$ NMR resonance is attributed to the interactions of TG with $\text{F}^-$ (and other fluoride-induced anions) rather than with $\text{Cs}^+$ ions.

The interactions of TG with CsF could also be confirmed by ESI–MS measurements (Fig. 3). A prominent signal at $m/z$ 454.3 (base peak) in the positive-ion-mode ESI–MS corresponded to $[\text{TG} + \text{H}]^+$ (calculated value: 454.2), but no $[\text{TG} + \text{Cs}]^+$ signal was observed. In the negative-ion-mode ESI–MS, a prominent signal at $m/z$ 452.3 (base peak) corresponded to $[\text{TG} - \text{H}]^-$ (calculated value: 452.2), and many supramolecular species were also observed: $[\text{TG} + \text{OH}^- + \text{H}_2\text{O}] (m/z$ 488.2), $[\text{TG} + \text{F}^- + \text{H}_2\text{O}] (m/z$ 490.3), $[\text{TG} + \text{FHF} + 2\text{HF}] (m/z$ 532.3) and $[\text{TG} + \text{OH}^- + 2\text{CH}_3\text{OH}] (m/z$ 534.3). These observations suggested characteristic supramolecular interactions of TG with $\text{F}^-$ and other fluoride-induced anions, in addition, the signal at $m/z$ 338.0 was attributed to partial Si–O cleavage of TG molecules by CsF. It should be noted that the formation of bifluoride (FHF) was not completely attributed to deprotonation (thioamide NH proton) of TG base by CsF, also, the reaction of CsF with water in solution could be involved as follows:

\begin{align*}
\text{CsF} + \text{H}_2\text{O} & \rightarrow \text{CsOH} + \text{HF} \\
\text{CsF} + \text{HF} & \rightarrow \text{Cs}^+ \text{FHF}^-
\end{align*}

\(\pi-\pi^*(S2 \text{ state})\) and \(n-\pi^*(S1 \text{ state})\) transitions for TG give rise to the main UV absorption band at the range 300–375 nm, only CsF could cause this band blue-shift (Fig. 4). The blue shift of this absorption band might be attributed to a decrease in charge density of thioguanine base induced by CsF [29,30]. A new absorption band at 260 nm is probably attributed to intramolecular charge transfer (ICT) [28–30]. The emission spectra of TG with 8 cesium salts in acetonitrile are displayed in Fig. 5. At the excitation

![Fig. 3. Positive-ion-mode (top) and negative-ion-mode (bottom) ESI–MS of TG–CsF in CH$_3$CN. Sample preparation: TG (1 mg) and CsF (1 mg) were mixed in CH$_3$CN (1 mL) at room temperature. After ultrasonic agitation and standing for 3 days, the solution was used for ESI–MS measurements.](image)

![Fig. 4. The electronic absorption spectral measurements showing the influence of CsF on TG (4 × 10$^{-3}$ M) in CH$_3$CN at room temperature. Sample preparation: TG, TG (1.8 mg) in CH$_3$CN (100 mL), TG–CsF: CsF (1 mg) was added to sample TG (10 mL).](image)
wavelength of 320 nm, only TG–CsF sample revealed a strong emission band at 375 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) [31]. However, alkali metal ions show different affinity to the lone pairs, thus stopping PIET [31]. Furthermore, it was reported that the binding of fluoride ion would significantly enhance the emission intensity of ionophores probably following charge transfer mechanism [32,33]. Generally, fluoride recognition behaviors mainly include deprotonation reaction and supramolecular interactions. In this case, both behaviors involved, thus, the stability constant for the binding of TG with CsF could not be evaluated. The binding constant of TG with CsCl was approximately $4 \times 10^3 \text{M}^{-1}$ [5]. TG exhibited negligible binding with other cesium salts (CsBr, Csl, CsNO3, CsClO4, cesium picate and Cs2SO4) in acetonitrile from $^1\text{H}$ NMR, $^{133}\text{Cs}$ NMR, electronic absorption and emission spectral observations.

From the $^1\text{H}$ NMR spectra of TG showing the influences of LiF, NaF, KF, RbF and CsF on TG in acetonitrile (Fig. 6), significant cation size effects could be observed (lithium through cesium). The changes for the $^1\text{H}$ NMR spectra of TG mainly occurred on the thioguanine base. The thioamide NH peak was gradually broadened and finally disappeared from lithium to cesium. The amino NH2 peak showed a small downfield shift in the presence of Li+, Na+ and K+ ions, however, Rb+ and Cs+ ions induced a large upfield shift from 5.70 to 5.39 and to 4.75 ppm, respectively. As an only nonactive hydrogen on the thioguanine base, H8 peak showed an upfield shift from 7.85 to 7.65 ppm in Rb+ and to 7.56 ppm in Cs+ ions, respectively. These results demonstrate that remarkable interactions of TG with RbF and CsF took place rather than with LiF, NaF and KF. Furthermore, as above mentioned, the CH peaks on the ribose showed downfield or upfield shifts in the presence of CsF. Thus, it is evident that the most significant interactions occur between TG and CsF in the series of alkali metal fluoride salts. These significant differences could be attributed to gradually decreasing Coulombic influences on F$^-$ through Li$^+$ to Cs$^+$ [26], so that F$^-$ ions of CsF could exhibit strong accepting N–H and/or C–H hydrogen bonding capacity [26]. Thus, the interaction behaviors of TG toward fluoride ions may also be cation-dependent.

A competition experiment involving CsF/CsCl was performed by $^1\text{H}$ NMR measurement. In a mixture of TG and equimolar amounts of CsF/CsCl in CD3CN, the $^1\text{H}$ NMR spectroscopic behavior of TG was completely dominated by CsF, suggesting that TG exhibited remarkable preference for CsF over CsCl.

The response of TG to CsF could be observed in a D2O/CD3CN mixed solvent (1:99, v/v) [34]. The most distinct feature is that H8 peak on the thioguanine base showed an upfield shift from 7.86 to 7.68 ppm (Figs. S16 and S17). Note that the molar concentration of D2O in the mixed solvent is about 0.125 M, more than 60 times the concentration of TG. Nevertheless, water could reverse these supramolecular interactions, thus, this process is reversible and TG can be recycled. It should be mentioned that fluoride has the highest hydration enthalpy of all water anions due to its small size and high polarizing ability [35], so that many receptors could not recognize fluoride [33] and fluoride salt (CsF) [25] in water-containing media. Thus, TG may also be an efficient sensor for direct detection of CsF in organic solvents and water-containing media.
3. Conclusion

TG exhibits remarkable sensitivity toward CsF over other cesium salts (chloride, bromide, iodide, nitrate, perchlorate, picate and sulphate) in acetonitrile. NMR, ESI–MS, electronic absorption and emission spectroscopic results suggest both depletion of TG by CsF and supramolecular interactions of TG with CsF, where characteristic thioamide N–H...F− (and other fluoride-induced anions) involved. Thus, TG behaves as an anion receptor for CsF. More importantly, the response of TG to CsF could be observed in a H2O/CH3CN mixed solvent. This finding will extend our understanding of the influences of anions on the structures and functions of nucleosides, nucleotides and nucleic acids, because it is well known that the sulfur (or oxygen) and NH protons of (thio)amide on DNA and RNA bases act as hydrogen-bond acceptors and donors in base pairing, respectively.

4. Experimental

4.1. General procedures

All reagents for syntheses were used as received without further purification. Synthesis of TG was achieved previously [5]. CsF was chosen as the fluoride source due to its high fluoride activity (or basicity) among alkali metal fluorides [26]. Typically, excessive CsF and other cesium salts were used to react with TG. Electronic absorption spectra were recorded on a Perkin-Elmer Lambda 35 UV/Vis Spectrophotometer with a quartz cuvette (1 cm path length). Fluorescence spectra were recorded with a JASCO FP-6500 spectrometer. ESI mass spectra were obtained in both positive- and negative-ion modes on a Shimadzu LC-MS 2010 mass spectrometer with the scanned mass ranges set between 0 and 1000 amu.

4.2. NMR measurements

1H NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz. Each measurement in CD3CN (D2O/CD3CN mixed solvent) and in [D8]DMSO was performed at room temperature. Low temperature 1H NMR measurements were done for both TG and TG–CsF samples in CD3CN. All 1H chemical shifts were referred to the signal of TMS. 133Cs NMR spectra were recorded on a Bruker Avance 400 spectrometer at 52 MHz and the 133Cs chemical shifts were referenced using cesium salts in CD3CN as external standards. 19F NMR spectra were recorded on a Bruker Avance 400 spectrometer at 376 MHz, and the 19F chemical shifts were referenced by setting the signal of CsF in CD3CN at −148.0 ppm.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.02.020.

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