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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.

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 ($pK_a \approx 11–13$) 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 ^{1}H NMR measurements. To obtain comparable results, seven other cesium salts were utilized (CsCl, CsBr, CsI, $CsNO_3$, $CsClO_4$, cesium picrate and Cs_2SO_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 ^{1}H 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_2SO_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

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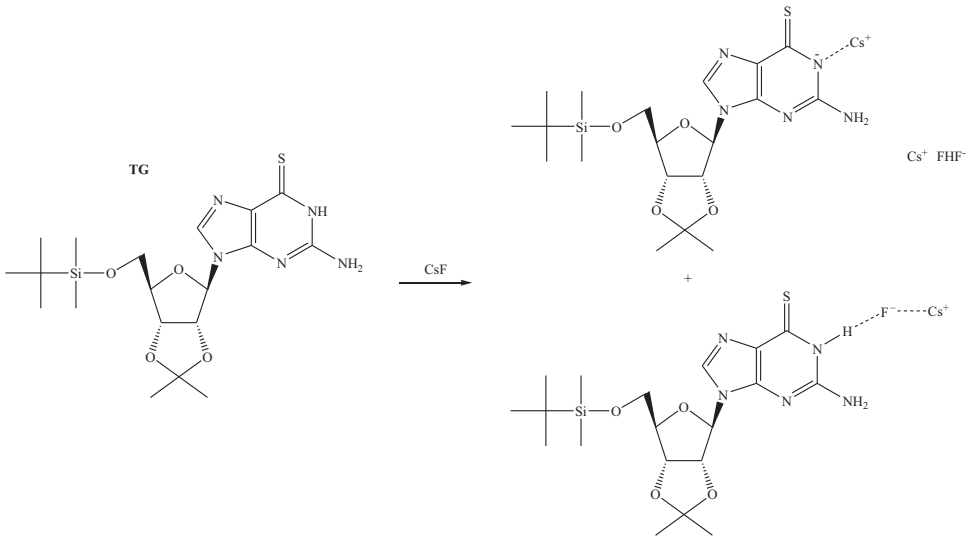

Fig. 1. Lipophilic thioguanosine (TG) as an anion receptor for CsF.

N–H. . .Cl^- (CsCl) hydrogen bonding. The amino NH_2 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 NH_2 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 NH_2 peak showed an upfield shift from 5.70 to 4.75 ppm. The upfield shift of the amino NH_2 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).

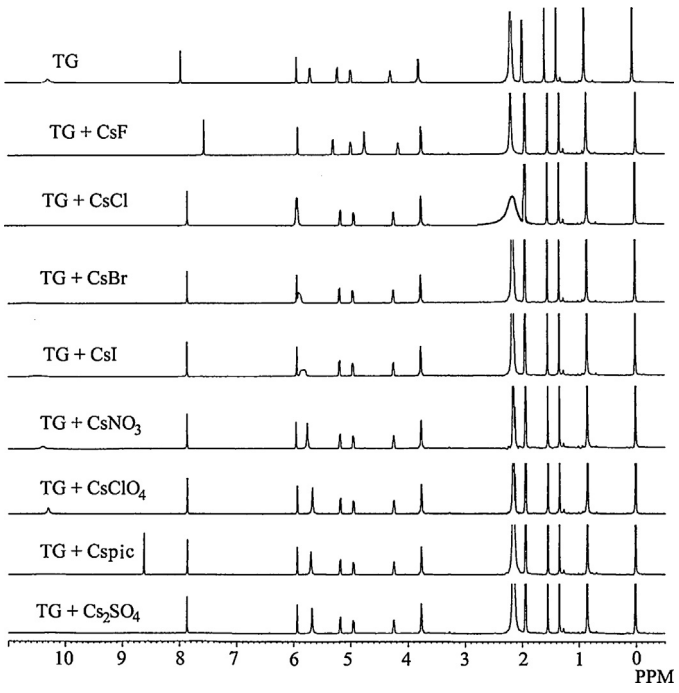

Fig. 2. ^{1}H NMR (400 MHz) measurements showing the influences of 8 Cs-salts on TG in CD_3CN at 298 K. Sample TG: TG (1.3 mg) in CD_3CN (0.4 mL); TG + CsF: TG (1.3 mg) and CsF (2 mg) in CD_3CN (0.4 mL); TG + CsCl: TG (1.3 mg) and CsCl (2 mg) in CD_3CN (0.4 mL); TG + CsBr: TG (1.3 mg) and CsBr (2 mg) in CD_3CN (0.4 mL); TG + CsI: TG (1.3 mg) and CsI (2 mg) in CD_3CN (0.4 mL); TG + $CsNO_3$: TG (1.3 mg) and $CsNO_3$ (2 mg) in CD_3CN (0.4 mL); TG + $CsClO_4$: TG (1.3 mg) and $CsClO_4$ (2 mg) in CD_3CN (0.4 mL); TG + Cspic: TG (1.3 mg) and cesium picrate (2 mg) in CD_3CN (0.4 mL); TG + Cs_2SO_4: TG (1.3 mg) and Cs_2SO_4 (2 mg) in CD_3CN (0.4 mL).

The bifluoride (FHF^-) [11,21–24] was observed in CD_3CN at 16.30 ppm in the low temperature ^{1}H NMR spectrum (Fig. S3). These behaviors were solvent-dependent. FHF^- proton signal could be observed at 16.16 ppm in DMSO-d_6 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 NH_2 peaks with changing into a 1:1 doublet suggested that the two amino NH_2 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.

^{13}C 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 ^{13}C 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 ^{133}Cs NMR to probe the interactions between TG and the cesium salts in CD_3CN and the results are summarized in Table S1 (Figs. S9–S14). In the case of CsCl, a single ^{133}Cs 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 CD_3CN [28]. Upon addition of CsF to TG solution in CD_3CN, the ^{133}Cs NMR resonance for TG–CsF shows an downfield shift ($\Delta\delta$ = 40.14 ppm) relative to CsF (Fig. S9). However, the ^{19}F NMR resonance for TG–CsF shows an upfield shift ($\Delta\delta$ = −22.8 ppm) relative to CsF (Fig. S15). The downfield shift