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Gas-phase formation and reactions of radical cations of guanosine, deoxyguanosine and their homodimers and heterodimers☆

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ABSTRACT

Electrospray ionisation of methanolic solutions containing a mixture of the nucleoside deoxyguanosine, dG, incubated with $Cu(NO_3)_2$ resulted in the formation of a range of ions, including doubly charged copper nucleoside complexes $[Cu^{II}dG_n]^{2+}$, with n ranging from 2 to 10. Collision-induced dissociation of these complexes proceeds via a number of different pathways that depend on the size of the cluster, *n*. When $n = 3$, monomeric radical cations are formed via redox processes. When $n = 4$, dimeric radical cations are formed. Related complexes are formed for the nucleoside guanosine, Gs, and these $[Cu^{II}Gs_n]^{2+}$ complexes fragment in similar fashions to their $[Cu^{II}dG_n]^{2+}$ counterparts. A key finding is that the radical cations of dG and Gs have fragmentation patterns that depend on the way they are formed. Thus radical cations, $dG^{\bullet+}$ and $Gs^{\bullet+}$, formed directly in the electrospray ionisation source or via collision-induced dissociation of $[Cu^{II}dG_3]^{2+}$ and $[Cu^{II}Gs_3]^{2+}$ complexes fragment in the same way, giving the radical cation of the guanine base at *m/z* 151 via cleavage of the *N*-glycosidic bond. In contrast, the collision-induced dissociation spectra of radical cations formed via the sequences $[Cu^{II}dG_4]^{2+} \rightarrow dG_2^{\bullet+} \rightarrow dG^{\bullet+}$ and $[Cu^{II}Gs_4]^{2+} \rightarrow Gs_2^{\bullet+} \rightarrow Gs^{\bullet+}$ are dominated by the loss of CH_2O and further loss of $C_2H_3O_2$ from the sugar moiety. These different fragmentation reactions are attributed to different tautomeric structures of the radical cations. Quantum chemical calculations were carried out on possible structures of the radical cation dimer of the model 9-methylguanine. Three low energy structures were found. Two of these represent base pairs of the kind found in supramolecular motifs of guanine derivatives, and one of these possesses a novel tautomeric structure that may have important biological implications.

1. Introduction

Metal ions and metal complexes bind to nucleic acids at a range of different sites [1–8], and can also promote supramolecular complex formation *via* hydrogen bonding and/or base stacking interactions [9–17]. Electrospray ionisation (ESI) mass spectrometry of mixtures of metal ions/metal complexes and nucleic acids has proven to be a useful way of uncovering such supramolecular complexes (for a recent review on ESI/MS of metal ion-nucleic acid complexes, see [18]). For example, ESI of solutions of silver(I) and the nucleobase adenine resulted in the formation of polymeric silver adenine clusters of the type $[Ad_x + Ag_y - zH]^{(y-z)+}$ [19,20]. Guanine (G) and its derivatives exhibit a diverse range of supramolecular architectures in the condensed phase, including alkali earth metal templated tetramers, **A**, and "ribbon" structures, **B** [9–11]. ESI mass spectrometry studies of guanine and its derivatives have also revealed a range of complexes, some of which exhibit "magic numbers" [21–26]. An example of such a magic number is the well-known guanosine quartet, which has been observed to assemble around various cations including NH_4^+ and alkali metal cations [12–17]. ESI of mixtures of either deoxyguanosine (dG, **C1**) or guanosine (Gs, **C2**) and transition metals often yields a range of complexes of different stoichiometry, and the gas-phase chemistry of mass-selected complexes can be dependant on the size and nature of the complex. For example, the collision-induced dissociation (CID) spectra of $[Pt^{II}LdG_n]^{2+}$ complexes (where L = 2,2′:6′,2″ terpyridine, terpy, or diethyltriamine, dien) give primary fragmentation channels arising from loss of dG and protonated dG to

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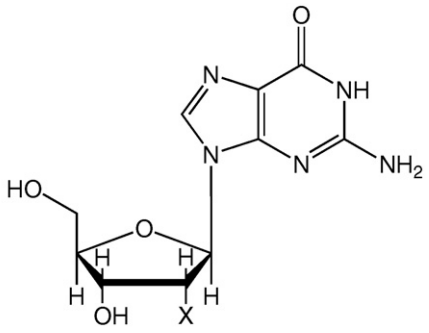
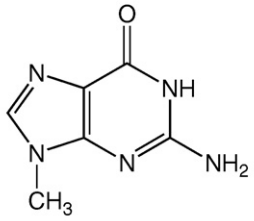
yield the fragment ions $[Pt^{II}LdG_{n-x}]^{2+}$ and $[Pt^{II}LdG_{n-x}\text{-}H]^{+}$, respectively [26]. The relative abundances of the $[Pt^{II}LdG_{n-x}]^{2+}$ fragments depend on the nature of the ligand, L, with the most abundant peaks being observed for $n-x=5$ when L = terpy and $n-x=4$ when L = dien. When a redox active metal such as Cu(II) is used, Cheng and Bohme have shown that monomeric and dimeric radical cations of guanosine, Gs, can be formed via CID of $[Cu^{II}Gs_n]^{2+}$ complexes [25]. This contrasts with previous studies on the fragmentation of copper ternary complexes, $[Cu^{II}LdG]^{2+}$ (L = 2,2′:6′,2″ terpyridine, terpy, or diethyltriamine, dien), where cleavage of the *N*-glycosidic bond occurred in preference to loss of the radical cation [24]. Cheng and Bohme found that the fragmentation of the $[Cu^{II}Gs_n]^{2+}$ complexes is size dependant [25]. When $n=2$, loss of the protonated nucleoside (Eq. (4)) and cleavage of *N*-glycosidic bond (Eqs. (6) and (7)) occurs. With $n=3$, the complexes undergo only charge separation with formation of the monomeric radical cation (Eq. (1)). And with $n=4$, the fragmentation entails the loss of the neutral nucleoside (Eq. (3)) and formation of the dimeric radical cation (Eq. (2)).

Nucleobases recognise one another by specific patterns of hydrogen bonding. Besides the Watson–Crick pairing observed in DNA, a number of non-Watson–Crick/non-canonical hydrogen-bonding motifs have been found to mediate RNA–RNA interactions and create binding sites for proteins and small molecule ligands [27]. It is not clear, however, what roles hydrogen bonding and tautomerism have on the assembly of metal complexes of guanine and its derivatives via ESI/MS and how these factors might influence their subsequent gas-phase chemistry. Thus, here we examine: (i) the CID reactions of a range of homo ($[Cu^{II}dG_n]^{2+}$ and $[Cu^{II}Gs_n]^{2+}$) and hetero $[Cu^{II}dG_nGs_m]^{2+}$ complexes; (ii) the fragmentation reactions of the monomeric nucleoside radical cations; (iii) the fragmentation reactions of the nucleoside homodimeric and heterodimeric radical cations; (iv) possible structures of the dimer radical cation for the model 9-methylguanine (9-MeG, **C3**). Our results suggest an unusual mode of base pairing that plays a role in the formation and fragmentation chemistry of nucleoside dimeric radical cations.



C1 = deoxyguanosine (dG): X = H
C2 = guanosine (Gs): X = HO



C3 = 9-methylguanine (9-MeG)

$$[Cu^{II}Gs_n]^{2+} \rightarrow [Cu^{II}Gs_{n-1}]^{+} + Gs^{\bullet+} \quad (1)$$

$$[Cu^{II}Gs_n]^{2+} \rightarrow [Cu^{II}Gs_{n-2}]^{+} + Gs_2^{\bullet+} \quad (2)$$

$$[Cu^{II}Gs_n]^{2+} \rightarrow [Cu^{II}Gs_{n-1}]^{2+} + Gs \quad (3)$$

$$[Cu^{II}Gs_n]^{2+} \rightarrow [Cu^{II}Gs_{n-2}(Gs\text{-}H)]^{+} + GsH^{+} \quad (4)$$

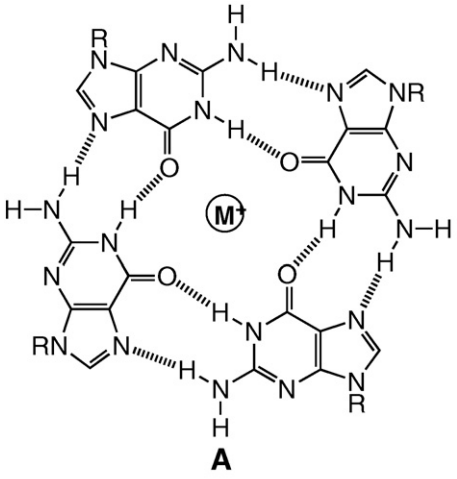
$$[Cu^{II}Gs_n]^{2+} \rightarrow [Cu^{II}Gs_{n-3}(Gs\text{-}H)]^{+} + Gs_2H^{+} \quad (5)$$

$$[Cu^{II}Gs_n]^{2+} \rightarrow [Cu^{II}Gs_{n-1}G]^{2+} + R\text{-}H \quad (6)$$

$$[Cu^{II}Gs_n]^{2+} \rightarrow [Cu^{II}(Gs_{n-1}G)\text{-}H]^{+} + R^{+} \quad (7)$$

2. Experimental

All reagents were used as supplied: $Cu(NO_3)_2$ (Ajax chemicals, 99%), guanosine hydrate (Aldrich, 98%) and deoxyguanosine (Sigma, 99%). Complexes were prepared by mixing 2:1 mM solutions of the nucleosides:$Cu(NO_3)_2$, dissolved in 3:1 methanol:water, right before infusing the reaction mixture into the mass spectrometer.



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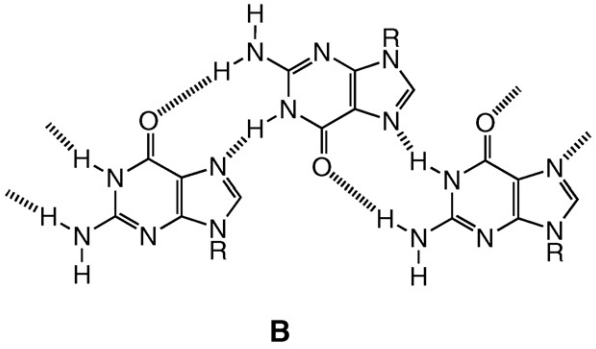

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