



Formation of polynuclear copper complexes of guanine-based nucleobases in the gas phase studied by ESI-MS



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ABSTRACT

Electrospray ionization of water/methanol solutions containing the DNA nucleoside deoxyguanosine and Cu(II) sulphate provide direct experimental evidence for the formation of a series of charged clusters containing up to four Cu(II) ions and up to three sulphate anion plus a variable number of deoxyguanosine ligands, which we refer to as polynuclear copper complexes. The complexes are of the type $[\text{Cu}_m(\text{dGuo})_n(\text{SO}_4)_{m-1}]^{2+}$ with $m=2-4$ and $n=4-11$. Complexes containing two and three Cu(II) ions have relative abundances in the range 1–13%, thus representing a significant fraction of all the Cu-containing ion species. Their chemical composition is determined by high resolution mass measurements and confirmed by comparison of experimental and simulated isotope patterns. Complex stabilities and some structural information are assessed by collision induced fragmentation experiments. In some specific cases ion mobility measurements have been exploited to resolve the contribution of singly and doubly charge ions overlapping in the same m/z region. Some feasible structures are proposed in which two Cu moieties are bridged by a sulphate anion. In addition, singly charged ions formally corresponding to a complex between a protonated ligand and a CuSO_4 moiety $([\text{Cu}(\text{dGuo} + \text{H})(\text{dGuo})_{n-1}\text{SO}_4]^+, n=2-5)$ are observed. Finally, the effect of the counter-anion in the stabilization of the polynuclear Cu complexes is studied in a series of experiments performed using Cu(II) nitrate and chloride salts to replace CuSO_4 , and the latter is found to have the highest propensity for polynuclear copper cluster generation.

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1. Introduction

The self-association of DNA and RNA nucleobases stabilized by the interaction with metal ions and metal complexes has several biological implications and ample literature is available on this topic [1–3]. The presence of metal ions not only determines the three dimensional architecture of nucleic acids, but it influences their physical, chemical and biochemical properties, for instance by aiding catalytic mechanisms or mediating the interaction of DNA (or RNA) with small bioactive molecules. Recently, the effect of metal ions coordination with the base pairing in synthetic DNA has been exploited to modify the electronic properties of DNA and DNA-like materials with profound implications in the development of DNA nanotechnology [4]. A special and more restricted topic in the wide field of metal ions–nucleic acid associations is given by binuclear and multi-nuclear metal complexes with DNA, which are of relevance in biotechnology and medicine considering the twofold role of such complexes in molecular recognition and in catalysis [5]. Several organo-metal complexes engineered to perform enzyme-mediated hydrolysis, oxidation of double-stranded DNA,

and DNA cleavage contain di- and multi-nuclear metal active sites [6–10].

The formation of DNA complexes, their shape in a solvent free environment and the effect of metal ion ligands in the base pairing has been recently addressed using mass spectrometry and ion mobility techniques [11–14]. Ample literature is available on experimental (via ESI-MS) and theoretical gas phase studies of alkali and alkaline-earth metal cationization of nucleobases [15–22], as well as on the interaction of transition metals with nucleobases [1,23–25]. The formation of Cu complexes with biomolecules in the gas phase has been reviewed in [26], while the formation of Cu complexes of guanosine or deoxyguanosine under ESI-MS has been specifically addressed by the groups of Bohme [27] and O'Hair [28]. The authors demonstrated that the ESI ionization of water/methanol solutions containing a mixture of the nucleobase with Cu(II) salts results in the formation of doubly charged copper nucleoside complexes of the type $[\text{Cu}(\text{L})_n]^{2+}$ (with L = guanosine/deoxyguanosine and n ranging from 2 to 10) as well as singly charged complexes such as $[\text{CuL}_2]^+$ and $[\text{Cu}(\text{L}-\text{H})_n]^+$ with $n=2, 3$ deriving from charge reduction processes that are well known to occur under ESI conditions. While the Cu–nucleobase complexes observed in [27,28] contained only one Cu ion, in this work we report on the observation of polynuclear Cu(II) complexes in the ESI-MS of a water/methanol solution of CuSO_4 and

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deoxyguanosine. The polynuclear complexes consist in series of charged clusters containing up to four Cu(II) ions and up to three sulphate anion plus a variable number of ligand molecules. The relative abundances are about 10% for the most intense clusters and have been detected both using a API 3000 (Applied Biosystem) Triple Quadrupole Mass Spectrometer and a Waters Synapt HDRS ion mobility mass spectrometer.

Although the organometallic complexes containing more than one Cu(II) ions and DNA base ligands are well known, as they can be synthesized as solids and structurally characterized by crystallographic methods [29,30], the detection of polynuclear Cu(II) complexes in the gas phase is far less common. The observation of binuclear copper–caffeine complexes of the type $[\text{Cu}_2\text{Caf}_2]^+$ and $[\text{Cu}_2\text{X}_n\text{Caf}_2]^+$ (with Caf = caffeine, when $\text{X} = \text{Cl}^-$ $n = 2, 3$ and when $\text{X} = \text{SO}_4^{2-}$, $n = 1$) and zig-zag or cyclic-tetranuclear isomeric imidazolate-bridged polynuclear copper(II) complexes under ESI conditions are illustrative examples [31,32]. Through a series of seminal papers, Detlef Schroeder and colleagues studied the formation of polynuclear metal ion aggregates under ESI conditions using different solvents and ligands. They drew interesting conclusions about the correlations between gas phase and solution phase structures [33–39]. In particular, in [33] they report on the detection of polynuclear copper anionic and cationic clusters of the type $[\text{Cu}_n(\text{SO}_4)_{n+1}]^{2-}$ and $[\text{Cu}_m(\text{DMF})_p\text{SO}_4]^{2+}$ (with DMF = dimethylformamide, $n = 1–3$, $m = 2–3$ and $p = 2–7$), where the role of the DMF ligand in the stability of the metal cluster is highlighted. The key function played by clusters containing two Cu(II) centres in the mechanism of oxidative coupling reaction of two naphthol molecules is studied in [34], where the effects of bidentate ligands and of different counterions on the efficiency of the coupling reaction are commented. Formation of binuclear complexes with DMF as ligand and Cl^- as counterions have been observed not only with Cu(II) but also with other divalent transition metals such as Co, Ni, and Zn [35]. In the case of Ni(II) the binuclear ions $[\text{Ni}_2(\text{en})_n\text{Cl}_3]^+$ are reported also using ethylenediamine (=en) as ligand [36] and the direct observation of triple ions in aqueous solutions of Ni(II) sulphate is described in [37]. Finally, a pronounced tendency for formation of oligonuclear clusters of palladium containing up to three Pd(II) ions and several solvent molecules have been observed upon ESI-MS from solutions of PdCl_2 in acetonitrile [38,39].

2. Experimental methods

In the ESI mass spectrometric experiments, Cu(II) cations were generated from $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (Merck); 2'-deoxyguanosine¹ and guanosine were purchased from SIGMA-ALDRICH and were used without further purification. HPLC grade methanol and deionized water were used to prepare the solvent mixture. Nucleobases and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ were dissolved in 1:3 water/methanol mixtures at concentrations of 0.5 and 0.2 mM, respectively [40]. ESI mass spectra of the prepared solutions have been performed using an API 3000 (Applied Biosystem) Triple Quadrupole Mass Spectrometer equipped with an ESI source (in the following this instrument will be referred to as TQ-MS). The operating conditions were as follows: ESI in the positive ion mode; ion spray voltage, 5500 V; ring-electrode potential, 300 V; sample flow rate in the range 5–10 $\mu\text{L min}^{-1}$ (via a syringe pump). The ions formed upon

electrospray ionization were sampled at adjustable declustering potentials, thereby allowing control of the extent of fragmentation in the source region. The stabilities of the ionic complexes produced in ESI have been assessed by collision induced fragmentation experiments with N_2 in the middle quadrupole.

Ion mobility and MS^2 experiments were performed using a Waters Synapt HDRS ion mobility mass spectrometer. This instrument, already described in details elsewhere [41,42], has a hybrid quadrupole/ion mobility/orthogonal acceleration time-of-flight (OA-ToF) geometry. It is equipped with an ESI source from which ions are extracted towards a quadrupole mass filter for parent ion mass selection. In the ion-mobility mode, mass-selected ions are accumulated in an argon-filled linear ion trap and periodically released into the mobility T-wave cell (filled with nitrogen at ~ 2 mbar), where they separate according to their mobility by action of a continuous train of transient voltage pulses (travelling waves). After extraction from the mobility cell, ions enter the acceleration region of a reflectron time-of-flight (TOF) mass analyzer having a mass resolution ($m/\Delta m$) of about 16,000. Accurate masses were determined via internal calibration with reference compounds having known mass-to-charge ratios. In the following this instrument will be referred to as QTOF-MS. For the fragmentation experiments (MS^2), the desired ions produced via ESI were mass selected using the quadrupole mass analyzer. Different ions with the same m/z value were subsequently separated in the T-wave cell and, finally, they were fragmented in an He filled collision cell. In this way, fragmentation spectra of the different ion species were registered.

3. Results and discussion

A typical ESI mass spectrum of Cu(II)/dGuo solutions recorded at low declustering potential (30 V) using the TQ-MS is reported in Fig. 1, where assignments of the most relevant peaks in the m/z range 100–1600 are also reported. In good agreement with previous experimental determinations [27,28] it shows a series of Cu-containing doubly charged ions corresponding to $[\text{Cu}(\text{dGuo})_n]^{2+}$ ($n = 2–9$) as well as the corresponding singly charged complexes $[\text{Cu}(\text{dGuo})_n]^+$. Under ESI conditions [43] the latter derive from particularly efficient charge reduction processes due to the high second ionization energy of Cu (20.292 eV) that reduces the stability in the gas-phase of monoligated copper dications $\text{Cu}(\text{L})^{2+}$ [21,44,45]. Hence, in the low mass range m/z 100–600 our ESI-MS spectrum closely resembles that already reported [28]. We note in passing that Cu clusters containing solvent molecules (either CH_3OH or H_2O) are only barely visible under the ESI conditions used in our experiments. This can be easily explained taking into account that, during droplet shrinking in the ESI process, dGuo molecules tend to replace solvent molecules in the solvation sheath of Cu^{2+} due to the higher preference of Cu^{2+} ions for coordination with dGuo compared to water and methanol. At the higher masses, however, in addition to ions formed by the clustering of ligands and solvent molecules around a single metal ion centre, the mass spectrum reveals the presence of ionic clusters containing two or more Cu ions that we refer here as polynuclear complexes. Complexes containing two and three Cu(II) ions have relative abundances in the range 1–13%, thus representing a significant fraction of all the Cu-containing ion species in the spectrum. Complexes containing three or more Cu(II) ions have much lower abundances and in some cases their detection was impossible using the TQ-MS instrument, but they have been detected using the QTOF-MS. The chemical composition of all the complexes have been determined by high resolution mass measurements and confirmed by comparison of experimental and simulated isotope patterns [46].

¹ Abbreviations used throughout the paper are the followings: dGuo: 2'-deoxyguanosine ($\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_4$, monoisotopic mass = 267.10); dR: deoxyribose group ($\text{C}_5\text{H}_9\text{O}_3$ monoisotopic mass = 117.06); Me: methanol (CH_3OH monoisotopic mass = 32.03); Guo: guanosine ($\text{C}_{10}\text{H}_{13}\text{N}_5\text{O}_5$, monoisotopic mass = 283.09); G: guanine ($\text{C}_5\text{H}_5\text{N}_5\text{O}$ monoisotopic mass = 151.05); R: ribose group ($\text{C}_5\text{H}_9\text{O}_4$ monoisotopic mass = 133.05). For the atom numbering in 2'-deoxyguanosine see Scheme S1 in the Supplementary Material.

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