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COMMUNICATION

Synthesis and assembling properties of bioorganometallic cyclometalated Au(III) alkynyls bearing guanosine moieties†

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A guanosine-based Au(III) compound was demonstrated to serve as a versatile bioorganometallic conjugate, which could form a variety of aggregates in the absence and presence of KPF_6 *via* self-assembly of the guanosine moiety.

Bioorganometallic chemistry is a rapidly growing research field at the interface of various disciplines.[1] Conjugation of organometallic compounds with biomolecules such as DNA, amino acids, and peptides is envisioned to provide novel systems depending on the properties of both components. Nucleobases of DNA possess acceptors and donors for hydrogen bonding, which permits self-association into various nano-architectures. A variety of modified nucleobases with fluorescent, electrical, magnetic, and metal ion binding properties have been reported to expand the scope of their applications.[2] A typical example is the assembly of guanosines and their derivatives to octameric or polymeric species in the presence and absence of a cation (Fig. 1).[3] For example, Rivera *et al*. developed a series of 8-aryl-2′-deoxyguanosine derivatives which expand the Hoogsteen edge of dG and stabilize G-quadruplexes.[4] Attachment of oligo(*p*-phenylene-vinylene) (OPV) to yield 8-OPV-G is demonstrated to form π-conjugated organic nanoparticles *via* G-quadruplex self-assembling.[5] Moreover, 8-(pyren-1-yl)-dG represents an optical label for DNA analytical and electron transfer studies.[6] On the other hand, there has been a growing interest in luminescent transition metal complexes owing to their application to organic light-emitting devices.[7] Luminescent Au(III) compounds have not been investigated so much in contrast to isoelectronic platinum(II) compounds.[8] To the best of our knowledge, the synthesis and study of the assembling properties of bioorganometallic Au(III) alkynyl complexes bearing guanosine moieties have not been reported so far. Herein, we report the synthesis of two Au(III) complexes **1** and **2** possessing guanosine moieties to study their assembling properties.

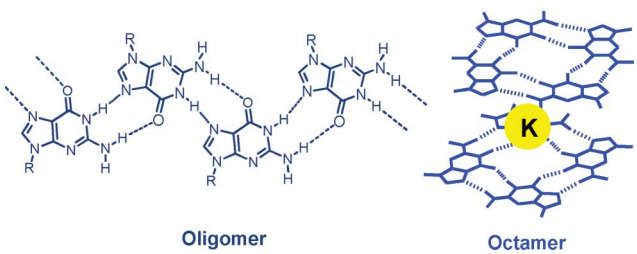

Fig. 1 Assembly types of guanosine derivatives.

The synthetic routes to **1** and **2** are outlined in Scheme 1. The Stille cross-coupling reaction of the 8-bromoguanosine **3** with the tin compound **4** afforded the protected guanosine **5**,[9] which was followed by deprotection with K_2CO_3 to give the 8-ethynylguanosine **6**. The structure of **5** was confirmed by single-crystal X-ray analysis.† An intramolecular hydrogen bond was found between N(1) and O(6) (N(1)–O(6), 2.651(7) Å; N(1)–H–O(6), 129 (3)°). In the crystal packing structure, an intermolecular hydrogen bonding network was observed (Fig. 2).[10] As the final key step, the coupling of **6** or **7** with the cyclometallic Au(III) complex **8**, was carried out using the copper-catalyzed Sonogashira procedure under an argon atmosphere to give the expected Au(III) compound **2** or **1**, respectively. Interestingly, the solubility of both Au(III) complexes is different. Bioorganometallic compound **1** is soluble in chlorinated solvents at room temperature, and very easily soluble in THF even at a low temperature. However, bioorganometallic compound **2** shows poor solubility, being slightly soluble in chlorinated solvents and soluble in THF at room temperature. Therefore, in this communication, we only study the assembling properties of **1**. Additionally, bioorganometallic compound **1** was fully characterized by ^1H, ^{13}C, 2D NMR, IR, and HRMS techniques (ESI†).

The assembling properties of **1** were studied by ^1H NMR spectroscopy. As shown in Fig. 3a, the amino protons (NH_2) are equivalent as a sharp singlet at 6.33 ppm in DMSO-d_6 while the amide proton (NH) resonates at 10.78 ppm. These chemical shifts indicate that **1** is mostly present in a monomeric species (Fig. 3b).

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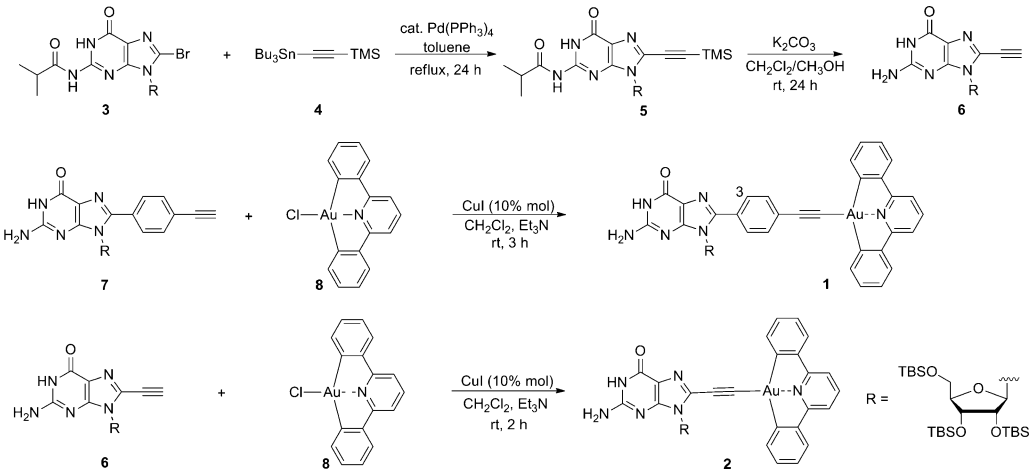

Scheme 1 Synthesis of the bioorganometallic compounds **1** and **2**.

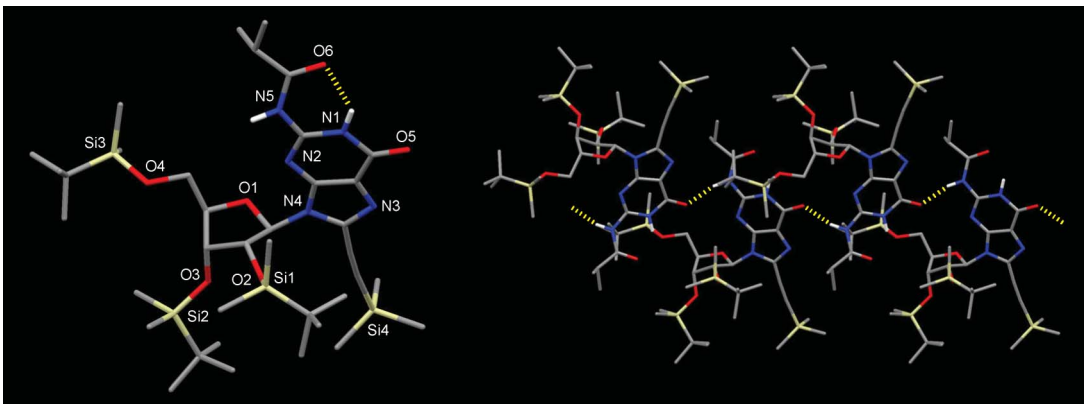

Fig. 2 Crystal structure (left) and packing structure (right) of **5**.

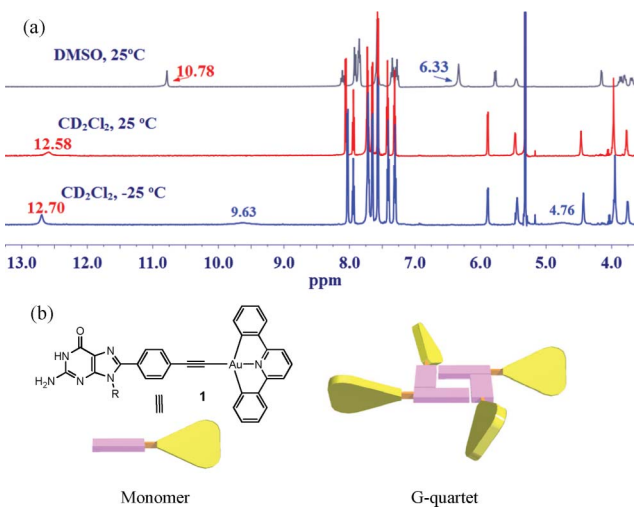

Fig. 3 ^{1}H NMR spectra of **1** in the absence of KPF_6.

In contrast, when CD_2Cl_2 was used as a solvent, the amino signal became unobservably broad at room temperature with a downfield shift of the amide signal to 12.58 ppm. These findings suggest that **1** assembles into a mixture of oligomeric species even in the absence of an alkaline cation.[11] Lowering the temperature to –25 °C, the amide signal became sharper and downfield-shifted (12.70 ppm). Simultaneously, two new signals appeared at 9.63 and 4.76 ppm, which correspond to hydrogen-bonded (NH_{2b}) and non-hydrogen-bonded (NH_{2f}) amino protons, respectively. A 2D NOESY experiment yielded a cross-peak between NH_{2b} and H3 (ESI, Figure S1†). These chemical shifts are in agreement with an empty G-quartet structure even without assistance of a cation (Fig. 3b).[5,12]

When 0.25 equivalents of KPF_6 were added to a THF-d_8 solution of **1**, the ^{1}H NMR spectrum changed, with disappearance of both the amino and amide signals at 25 °C (Fig. 4). Lowering the temperature to –15 °C, a new sharp signal was observed at 12.39 ppm. At a lower temperature, –30 °C, another new set of amide signal gradually appeared at around 12.59 ppm. The ratio of these two signals is 1 : 2. At the same time, two new sets of signals appeared at 9.50 and 6.80 ppm with the same ratio. The downfield signal (9.50 ppm) may be assigned to a hydrogen-bonded amino proton and the other signal (6.80 ppm) can be assigned to a non-hydrogen-bonded amino proton. In order to assign these two sets of signals, the assembling properties of **1** were studied in the presence of 0.125 and 0.5 equivalents of KPF_6 in THF at various temperatures. Addition of 0.125 equivalents of KPF_6 resulted in only one main set of the sharp signal at 12.39 ppm above –30 °C, and the amino signals split into two

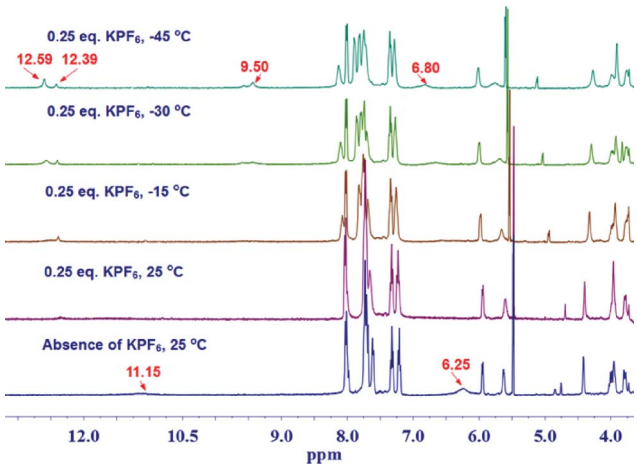

Fig. 4 ^{1}H NMR spectra of **1** in the presence of 0.25 eq. of KPF_6 in THF-d_8 at various temperatures.

broad bands at 9.50 and 6.80 ppm (Fig. 5a). From the ratio of the guanosine : KPF_6 (8 : 1), this species might be assigned to an octamer (Fig. 5b). In addition, analysis of the sample by CSI-TOF MS resulted in a spectra showing a peak $m/z = 4626$ which matches the mass $[\mathbf{1}_8+2Na]^{2+}$ in THF (ESI, Figure S2†). This is because the alkali metal-mediated gas-phase binding of the G-quadruplex occurs in the order $Na^+ > K^+$, in contrast to the stabilizing order in solution.[13] After adding 0.5 equivalents of KPF_6 at −30 °C, the amide proton was mainly observed as a broad signal around 12.59 ppm (Fig. 5a). Lowering the temperature to −60 °C made the amide proton signal sharper and the more major signal (Fig. 5a). This set of signals was not assigned to a hexadecamer because amide protons of the hexadecamer display at least two sharp signals. With the increased amount of potassium ion and at the lower temperature, the species with the broad signal (12.59 ppm) became the major one. These findings suggest that this set of signals might be assigned to a polymeric columnar aggregate (Fig. 5b).[14]

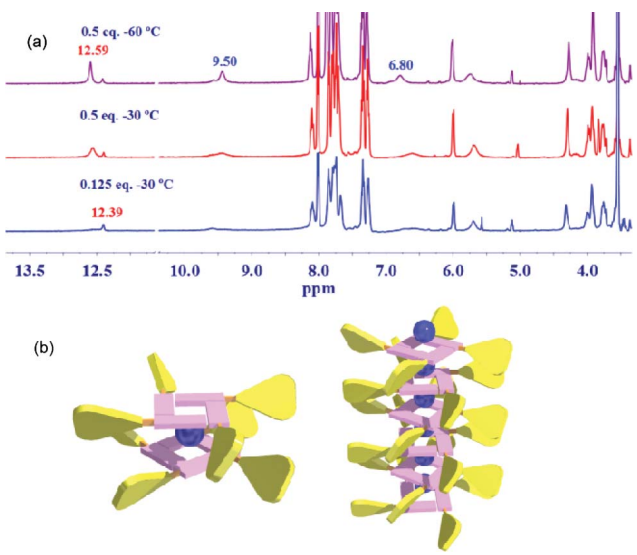

Fig. 5 ^{1}H NMR spectra of **1** in the presence of different amounts of KPF_6 in THF-d_8.

The assembling properties were also studied by CD, absorption, and emission techniques. As shown in Fig. 6a, upon addition of KPF_6 a drop in intensity was observed with the absorption band at 248–326 nm, accompanied by the concomitant growth of a new low-energy shoulder in the region of 380–450 nm. Moreover, as shown in Fig. 6b, the CD spectrum changed dramatically after addition of KPF_6. These observations indicate a change in the confirmation and/or secondary structure of **1**, namely, from oligomers to an octamer or polymeric columnar aggregate.

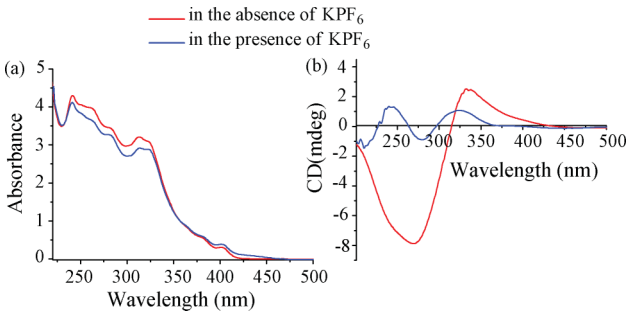

Fig. 6 (a) UV–vis spectra and (b) CD spectra of **1** in the absence (red line) and presence (blue line) of KPF_6 (0.25 eq.) in CH_2Cl_2 (1.0×10^{-4} M).

The chloro precursor [Au(C^N^C)Cl] has been reported to be emissive only at a low temperature, but not at room temperature.[15] However, bioorganometallic compound **1** showed luminescence at 400–700 nm in solution at room temperature because the strong δ-donating alkynyl ligand is considered to enhance the luminescence properties by increasing the d-d splitting. This emission band might have originated from a metal-perturbed $IL^3[\pi–\pi]$ state of the tridentate C^N^C ligand. An increased intensity was observed after addition of KPF_6 at room temperature (Fig. 7a), probably due to the rigidity after the formation of the G-quadruplex. No π–π interaction between C^N^C ligands was observed at room temperature. However, lowering the temperature to a freezing point, a new intense band appeared at 540 nm (Fig. 7b), which is probably due to a π–π interaction between the C^N^C ligands. The ^{1}H NMR also suggests a π–π interaction between the C^N^C ligands. After addition of KPF_6, at the low temperature, the ^{1}H NMR chemical shift of the C^N^C group was changed (*ca.* $\Delta\delta \approx 0.1$ ppm) (Fig. 8). These changes also suggest a tighter assembling aggregate at the lower temperature. A similar π–π interaction was also observed in the absence of KPF_6 at the lower temperature, because **1** forms an empty G-quartet at a low temperature. The empty G-quartet was able to stack with each other as indicated

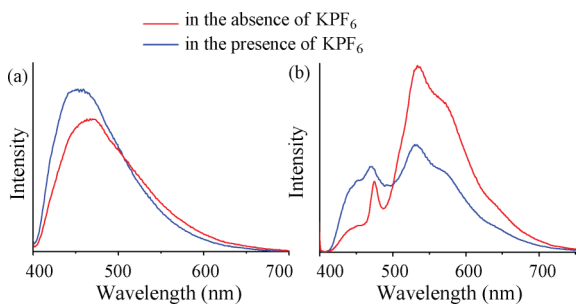

Fig. 7 Emission spectra of **1** ($\lambda_{ex} = 390$) in the presence (blue line)/absence (red line) of KPF_6 (0.25 eq.) in CH_2Cl_2 (1.0×10^{-4} M) at (a) 25 °C and (b) frozen.

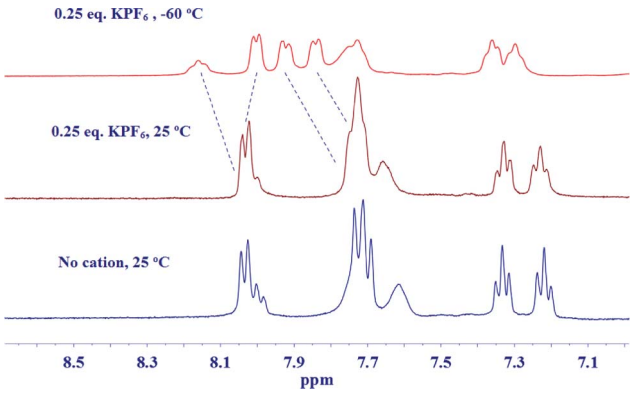

Fig. 8 The aromatic part of the ^{1}H NMR spectrum of **1** in THF-d_8.

by ^{1}H NMR, although the arrangement and distance might be different in the presence of KPF_6. A small change (*ca.* $\Delta\delta \approx 0.03$ ppm) in the chemical shift was observed for the C^N^C group at the lower temperature (ESI, Figure S3†).

In conclusion, new type of bioorganometallic conjugates, **1** and **2**, consisting of the guanosine and cyclometalated Au(III) moieties were synthesized. The bioorganometallic conjugate **1** was demonstrated to form the empty quartet, octamer, and polymeric columnar aggregate depending on the presence of KPF_6. Furthermore, the formation of the G-quadruplex *via* self-assembly was found to induce a π–π interaction. Studies on the application of the G-quadruplex induced metal ion aggregates to functional materials and catalysts are now in progress.

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