DNA Double Strand Breaks via Reductive O_2-Activation by Dicopper Complex: large acceleration by introducing an intercalator as DNA Binding Site

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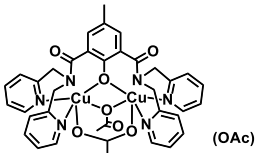
DNA double-strand breaks (dsb) are important reactions for gene editing and therapeutic applications. Bleomycin is an anticancer drug, and its iron complex, Fe-BLM is the strongest DNA cutter and catalyzes single- and double-strand breaks, ratio of which is reported to be in the range 1:3 to 1:20.[1] Burst of dsb by Fe-BLM via reductive O_2-activation with dithiothreitol (DTT) was reported, but the mechanism has not been clarified yet.[2] Metal complexes able to reproduce burst of DNA dsb may be useful to gain some insight into the mechanism. Various metal complexes have been developed to mimic oxidative DNA cleavage by Fe-BLM. Roelfes reported that a N4Py iron(II) complex $[Fe(MeCN)(N4Py)](ClO_4)_2$ (**3**) shows high activity in the oxidative DNA cleavage as a model compound of Fe-BLM.

Recently, we reported that a dicopper complex of *p*-cresol-2,6-bis(amide-tether-dpa) ligand (HL1) $[Cu_2(\mu\text{-}OAc)_2(L1)](OAc)$ (**1**) oxidatively cleaves DNA double-strand in the presence of AscNa.[3] **1** (30 μM) converted 26% of supercoiled plasmid DNA to linear form in 1 min via reductive O_2-activation with AscNa (150 μM), being much more active than **3**. The kinetic and spectroscopic studies showed that **1** is rapidly reduced to Cu(I)Cu(II) and Cu(I)Cu(I) species, both of which are involved in the rate-limiting three electron reduction of O_2 to HO• responsible for DNA cleavage. Moreover, measurement of the DNA binding revealed that rigid DNA binding within the 16 base pair intervals is essential for DNA dsb.

In this study, we synthesized a new dinucleating ligand (HL2) having a DNA binding site to improve DNA binding. HL2 forms a dicopper complex $[Cu_2(\mu\text{-}OAc)_2(L2)](OAc)$ (**2**), which largely accelerated DNA dsb, much faster than **1**.



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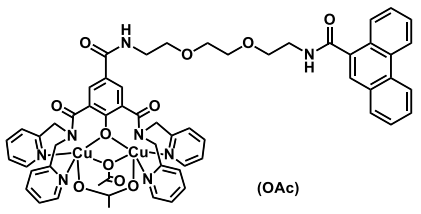

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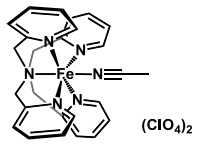

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