Preliminary communication

The first water soluble metal–enediyne complexes: structural characterization of *trans*-[Os(en)₂(η²-L)Br]⁺Br⁻ (en = ethylenediamine, L = *cis*-1,6-bistrimethylsilyl-3-ene-1,5-diyne)

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Abstract

The first water soluble metal–enediyne complexes have been prepared by displacement of the dihydrogen ligand of [Os(II)(en)₂(η²-H₂)(H₂O)](OTf)₂ (en = ethylenediamine, OTf = CF₃SO₃⁻), 1, with an enediyne molecule, *cis*-1,6-bistrimethylsilyl-3-ene-1,5-diyne, 2. Different σ donor ligands can be introduced to the trans position of the enediyne ligand to prepare different metal–enediyne complexes. The single crystal X-ray analysis of *trans*-[Os(en)₂(η²-L)Br]⁺Br⁻ (L = *cis*-1,6-bistrimethylsilyl-3-ene-1,5-diyne), 4, shows that the osmium(II)(en)₂ moiety binds specifically to the double bond of the enediyne molecule. This structure represents a new mode of metal–enediyne coordination. 4 crystallizes in the monoclinic space group $P2_1/a$, with $Z = 4$, $a = 13.150(2)$ Å, $b = 11.384(4)$ Å, $c = 18.413(9)$ Å, and $\beta = 100.74(2)°$. The structure was solved by direct methods and refined to conventional agreement indices $R = 0.054$ and $R_w = 0.048$ with 2880 unique reflections for which $I > 3\sigma(I)$.

Keywords: Metal–enediyne complexes

1. Introduction

The recent discovery of enediyne antibiotics, including neocarzinostatin chromophore, calicheamicins, esperamicins and dynemicins, has generated tremendous interest in the fields of chemical, biological and medical research. This class of compounds is found to have very potent antitumor effects. Studies have shown that the biological function of these molecules is exerted through double stranded DNA cleavage. As exemplified by calicheamicin γ_1^I, all of these enediyne antibiotics are composed of three functional domains: (1) a cyclic enediyne fragment, which cleaves DNA upon activation; (2) a delivery vehicle, such as the polysaccharide portion of calicheamicin γ_1^I, to direct the enediyne fragment to the DNA targets; (3) a device, such as the trisulfide fragment of calicheamicin γ_1^I, to trigger the activation of the enediyne fragment [1,2].

calicheamicin γ₁
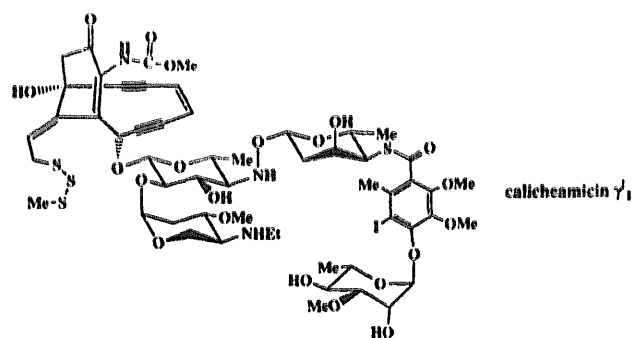
Bergman has shown that, at elevated temperature, acyclic enediyne molecules undergo cyclization to form aromatic products via 1,4-benzenoid diradical intermediates (Scheme 1) [3]. It is found that in biological systems, a nucleophile can trigger the Bergman cyclization of calicheamicin γ_1^I to generate a 1,4-benzenoid diradical intermediate, which can specifically abstract one hydrogen atom from the C5' position of deoxycytidine and another hydrogen atom from an unspecified ribose position of the opposing strand, causing double stranded cleavage of DNA [4].

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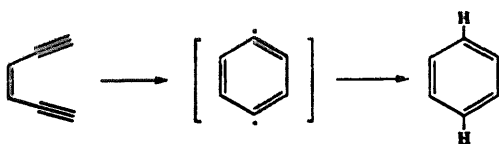
Scheme 1. Enediyne cyclization.

A dicobalt octacarbonyl complex has been used in a number of enediyne syntheses because of its ability to stabilize cyclic enediynes by coordination to the triple bonds [5]. However, no report has appeared on the influence of metal complexes on enediyne cyclization in biological systems, despite enormous research efforts in the area of enediyne antibiotics (recently, there has been a report on metal-accelerated enediyne cyclization [6]). We are interested in the preparation of water soluble metal–enediyne complexes in order to develop metal–enediyne-based new DNA cleavage agents. The use of metals to stabilize cyclic enediynes and the attachment of DNA recognition agents such as oligonucleotides to the metal–enediyne complexes may be able to deliver these highly reactive molecules to DNA with controllable specificity. These coordinated cyclic enediynes might then be released upon photolysis, oxidation or reduction at the vicinity of DNA to conduct the double stranded cleavage. Herein, we report our work on the synthesis and characterization of the first water soluble metal–enediyne complexes.

2. Results and discussion

An osmium dihydrogen complex, $[Os(II)(en)_2(\eta^2\text{-}H_2)(H_2O)](OTf)_2$ (en = ethylenediamine, OTf = $CF_3SO_3^-$), 1, [7] is chosen as the starting material to prepare metal–enediyne complexes for the following reasons: (1) this complex is soluble both in water and in organic solvents; (2) it contains a labile π acid ligand, $\eta^2\text{-}H_2$, and a labile σ donor ligand, H_2O. It has been demonstrated that a stronger π acid, such as an alkene, can displace the $\eta^2\text{-}H_2$ and a stronger σ donor, such as an amine, can displace the water ligand [7,8].

When an acetone solution of 1 (167 mg, 0.29 mmol, 14.6 mM) and cis-1,6-bistrimethylsilyl-3-ene-1,5-diyne, 2, [9] (175 mg, 0.79 mmol) was heated under N_2 at 45 °C for 16 h, the ^1H NMR spectrum of the reaction

mixture after removal of solvent and 2 shows the formation of 3 (Scheme 2). 3 is soluble in water. In its ^1H NMR spectrum, two broad peaks at δ 4.76 and 5.21 are observed, each corresponding to four amine protons of the two ethylenediamine ligands. This pattern indicates a plane of symmetry in the new complex and the retention of the original trans configuration of 1. The NMR signal of the two vinyl protons of the enediyne is shifted upfield from δ 5.76 in 2 to δ 4.18 in 3, consistent with the coordination of the enediyne double bond to the osmium(II) center. A dramatic change in the ^{13}C NMR signal of the olefin carbons from the uncoordinated to the osmium(II)-coordinated enediyne is observed. In the free enediyne, the ^{13}C signal of the olefin carbons is observed at δ 122. In 3, the ^{13}C signal of the coordinated enediyne olefin carbon is shifted to δ 27.9. However, there is no significant change in the C–H coupling constant of the olefin carbon signal ($J_{C-H} \approx$ 164–169 Hz). This suggests that there is strong π back-bonding from the electron-rich osmium(II) center to the olefin double bond in 3, but no significant rehybridization of the enediyne olefin carbons after coordination. The bonding between the metal center and the double bond is therefore more like a π complex rather than a metalla-cyclopropane. 3 was converted to 4 and purified. Lithium bromide (70 mg, 0.81 mmol) was added to the crude acetone solution of 3 and the resulting brown slurry was filtered. An orange solution was obtained and concentrated under vacuum. Addition of ether to the solution produced 4 as an orange solid (99 mg, 49%).

Characterization of 4: ^1H NMR (acetone-d_6, 270 MHz) δ 5.30 (br, 4H), 4.87 (br, 4H), 4.26 (s, 2H), 2.80 (m, 4H), 2.26 (m, 4H), 0.17 (s, 18H). MS(FAB) m/e calc. for $C_{16}H_{36}N_4Si_2BrOs$: 611.1277; obsd: 611.1278. Anal. Found: C, 27.32; H, 4.99; N, 8.11%. $C_{16}H_{36}Br_2N_4OsSi_2$. Calc.: C, 27.82; H, 5.25; N, 8.11%. NMR data for 3: ^1H NMR (acetone-d_6, 400 MHz) δ 5.21 (br, 4H), 4.76 (br, 4H), 4.18 (s, 2H), 2.67 (m, 4H), 2.44 (m, 4H), 0.15 (s, 18H) and ^{13}C NMR (acetone-d_6, 100 MHz) δ 121.7 (q, $J_{CF} =$ 320 Hz), 111.5, 92.0, 47.0, 27.9, 0.39.

The water ligand of 3 can also be displaced by other σ donor ligands, such as acetonitrile and pyridine, as shown by ^1H NMR spectroscopy. While the dicationic osmium(II)–enediyne complexes, such as 3 and the
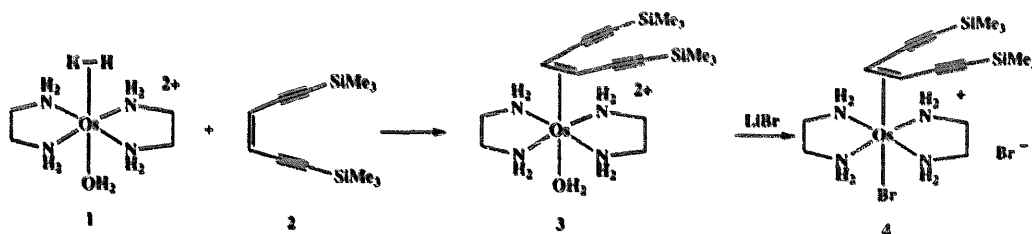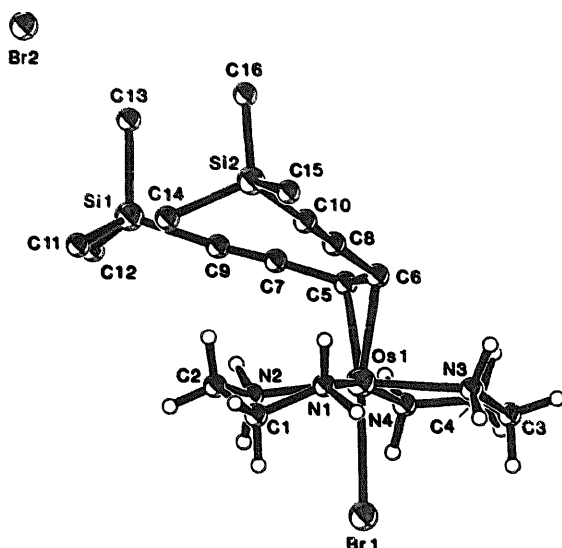

Scheme 2. The synthesis of metal–enediyne complexes

Fig. 1. Structure and labeling scheme for 4: Os–C5 2.13(2), Os–C6 2.18(1), C5–C6 1.44(2), C5–C7 1.49(2), C6–C8 1.45(2), C7–C9 1.19(2), C8–C10 1.20(2), C9–C10 4.26(3) Å; Os–C5–C6 72.1(10), Os–C6–C5 68.8(9), Os–C5–C7 115(1), Os–C6–C8 117(1), C5–C6–C8 121(1), C6–C5–C7 117(1)°.

acetonitrile coordinated compound, are soluble in water, complex 4, though stable in the presence of water, is insoluble in water. In acetonitrile solution, the enediyne ligand of 3 can be released photochemically when exposed to an Hg lamp (450 W, medium pressure). The reaction was carried out in a quartz tube at room temperature. A mixture of *cis* and *trans*-1,6-bistrimethylsilyl-3-ene-1,6-diyne is produced in less than 10% yield.

Single crystals of 4 are obtained from slow diffusion of ether into an acetone solution of the metal–enediyne

complex. The crystal of 4 is air stable and its X-ray analysis confirms the specific binding of the metal center to the double bond of the enediyne ligand.

Crystal data for 4 (298 K): $C_{16}H_{36}N_4Si_2OsBr_2$, FW = 690.67; monoclinic, space group $P2_1/a$, (No. 14), $Z = 4$, $a = 13.150(2)$ Å, $b = 11.384(4)$ Å, $c = 18.413(9)$ Å, $\beta = 100.74(2)°$, $V = 2708(1)$ Å^3, $D_c = 2.541$ g cm^{-3}, $\mu(MoK\alpha) = 77.6$ cm^{-1}, and R (Rw) = 0.054 (0.048) for 2880 independent unique reflections ($I > 3\sigma(I)$).

A distorted octahedral geometry about the osmium center, *trans*-en ligands and *trans*-enediyne–bromine ligands is observed for 4 (Fig. 1). The C5–C6 double bond distance (1.44(2) Å) is almost identical to the single bond distances of C5–C7 (1.49(2) Å) and C6–C8 (1.45(2) Å). This significant lengthening of the double bond distance demonstrates the strong back bonding of the osmium d electrons to the π^* orbital of the coordinated enediyne olefin bond. The distance between the two terminal alkyne carbon is 4.26(3) Å, slightly larger than that calculated for acyclic enediynes (4.1 Å) [2]. The angle between the plane of Os–C6–C5 and the plane of the enediyne ligand (C5–C6–C7–C8) is 110.53°.

The cyclic voltammograms of 4 and 2 are shown in Fig. 2. Two irreversible oxidation waves are observed for 4. The first oxidation at ca. 1.0 V (NHE) is assigned to the oxidation of osmium(II) to osmium(III), which is similar to the recorded $E_{1/2}$ (0.69 V vs. SHE, 0.93 V vs. NHE) of [Os(NH$_3$)$_4$(η^2-CH$_2$=CHCO$_2$H)(H$_2$O)](OTf)$_2$ [10]. The second wave at 1.4 V (NHE) is assigned to the oxidation of the bromide counter ion (we observed a similar oxidation potential for alkaline bromide salts in acetonitrile solution). The uncoordinated enediyne molecule 2 is stable towards oxidation or reduction in

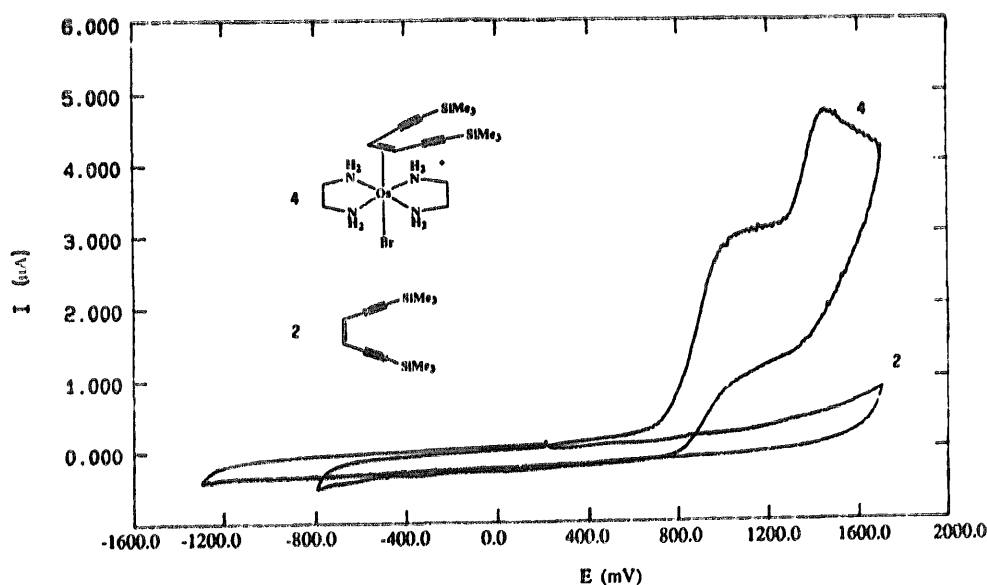Fig. 2. Cyclic voltammograms of 4 and 2 in CH$_3$CN (0.1 M tetrabutylammonium hydroxide. $v = 100$ mV s^{-1}).

the range of -1.2 to $+1.8$ V (NHE). When treated with $(NH_4)_2Ce(NO_3)_6$ at room temperature, 4 is immediately oxidized and the formation of the free enediyne molecule 2 is observed in less than 10% yield.

In summary, the first water soluble metal–enediyne complexes have been prepared. It is found that in the osmium(II)–enediyne complexes the osmium(II)(en)$_2$ moiety binds specifically to the double bond of the enediyne molecule, representing a new mode of metal–enediyne coordination. Different σ donor ligands can be introduced to the trans position of the enediyne ligand in these novel metal–enediyne complexes. In addition to the bis(trimethylsilyl)-substituted enediyne molecule 2, we have used other enediyne molecules that contain alkyl or phenyl substituents on the terminal alkyne carbons to prepare osmium(II)–enediyne complexes. In these complexes, the osmium atoms are also found to bond specifically to the double bonds of the enediyne ligands. Work on the synthesis of osmium(II)(en)$_2$–cyclic enediyne complexes and their interaction with DNA will be carried out.

3. Supplementary material

Tables of atomic coordinates and equivalent isotropic displacement coefficients, bond lengths, bond angles, anisotropic displacement coefficients, hydrogen atom coordinates, isotropic displacement coefficients, torsion angles, non-bonded contacts out to 3.60 Å, and least squares planes (71 pages) and tables of observed and calculated structure factors (20 pages) are available from the authors upon request.

Acknowledgements

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