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Stabilizing Two Classical Antiaromatic Frameworks: Demonstration of Photoacoustic Imaging and the Photothermal Effect in Metalla-aromatics**

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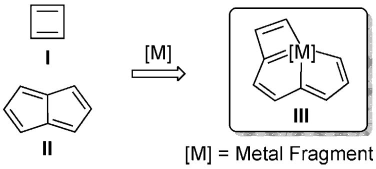
Abstract: *Antiaromatic species are substantially less thermodynamically stable than aromatic moieties. Herein, we report the stabilization of two classical antiaromatic frameworks, cyclobutadiene and pentalene, by introducing one metal fragment through the first [2+2] cycloaddition reaction of a late-transition-metal carbyne with alkynes. Experimental observations and theoretical calculations reveal that the metal fragment decreases the antiaromaticity in cyclobutadiene and pentalene simultaneously, leading to air- and moisture-stable products. These molecules show broad absorption from the UV to the near-IR region, resulting in photoacoustic and photothermal effects for metalla-aromatic compounds for the first time. These results will encourage further efforts into the exploration of organometallic compounds for photoacoustic-imaging-guided photothermal therapy.*

Aromaticity, an old but still fascinating topic in organic chemistry, has attracted continuous attention from both experimental and theoretical chemists for many decades.[1] According to the Hückel aromaticity rule,[2] cyclic species with $4n+2$ π electrons are aromatic and thus more stable than antiaromatic moieties that contain $4n$ π electrons. For instance, cyclobutadiene (CBD; Scheme 1, compound I) and pentalene (Scheme 1, compound II), two typical representatives of antiaromatic compounds for monocyclic and bicyclic systems, are highly unstable.[3,4]



Scheme 1. The stabilization of two antiaromatic frameworks (CBD and pentalene) with a single metal fragment.

CBD, with four π electrons, is highly reactive and antiaromatic and was first captured in 1965.[3] Thereafter, the antiaromaticity and geometry of CBD have continued to intrigue computational and synthetic chemists.[5] Pentalene, the archetypal antiaromatic compound with eight π electrons, is highly unstable and was first observed in 1997 in argon matrices.[4,6] Thus, efforts have been made to stabilize these antiaromatic species. Among various stabilizing approaches, introducing a metal fragment into the carbocycle has been an effective strategy.[7–10] A series of metallapentalenes[8,9] and metallacyclobutadienes[10] have been realized through this strategy. However, the simultaneous stabilization of two antiaromatic systems by one metal fragment has not been reported to date. Herein, we report the stabilization of two typically antiaromatic frameworks, CBD and pentalene, by introducing a metal fragment (III in Scheme 1) through unprecedented [2+2] cycloaddition reactions of alkynes with a late-transition-metal carbyne complex. These novel metalla-aromatics exhibit broad absorption and remarkable photoacoustic and photothermal properties.

The treatment of osmapentalyne **1**[7] with HC≡CCOOH or HC≡COEt in dichloromethane at room temperature afforded complexes **2** or **3**, respectively (Scheme 2), which are air and moisture stable. Specifically, both of them can be stored in air at room temperature for several weeks in the solid state. The driving force for the formal [2+2] cycloaddition reaction of osmapentalyne **1** with the alkynes could be attributed to the release of the large ring strain in the five-membered ring of osmapentalyne, which was reported[7] to be 24.3 kcal mol^{-1} and is significantly larger than that of osmabenzyne (9.6 kcal mol^{-1}).[11] Therefore, our studies show that osmapentalyne **1** can be viewed as a model complex for the mechanistic study of the cycloaddition reaction between alkyne and metal carbyne. **1** is a suitable model complex because of the extreme ring strain which stems from the nonlinear triple bond in the five-membered ring.

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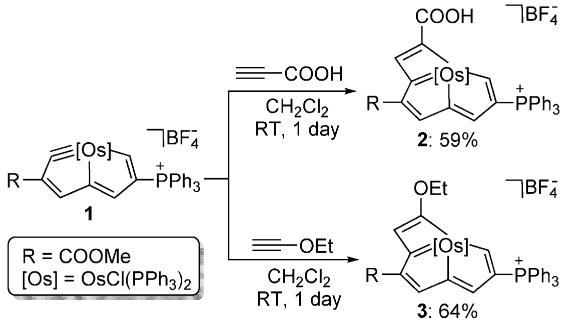


Scheme 2. [2+2] cycloaddition reactions of **1** with alkynes.

The structure of **2** was confirmed by single-crystal X-ray diffraction (Figure 1).[12] The most interesting structural feature is that the metal was shared by the CBD and pentalene rings simultaneously. Note that the geometry can be viewed as a pentagonal bipyramid in which the seven coordination sites are occupied by four carbon atoms (C1, C4, C7, and C9), one chlorine atom, and two phosphorus atoms, leading to a coordinatively saturated metal center with 18 electrons. More interestingly, the nine conjugated carbon atoms in the equatorial plane constitute a chain of carbon atoms (C1–C9) as a tetradentate ligand coordinating to transition-metal center. The X-ray structure indicates that complex **2** has an essentially planar metallatricyclic moiety. The mean deviation from the least-squares plane through the ten atoms (Os1 and C1–C9) is 0.0257 Å, and the sum of angles in the two fused five-membered rings and the four-membered ring are 539.9°, 539.9°, and 359.9°, which are very close to the ideal values of 540° (5-membered ring) and 360° (4-membered ring), respectively. The Os1–C1 (2.053 Å), Os1–C4 (2.096 Å), and Os1–C7 (2.060 Å) distances are within the range of the Os–C bond lengths in osmapentalene (1.926–2.175 Å) reported previously.[8] The C–C bond lengths in these two five-membered rings (1.376–1.410 Å) were between those of single and double C–C bonds and comparable to those of benzene (1.396 Å).

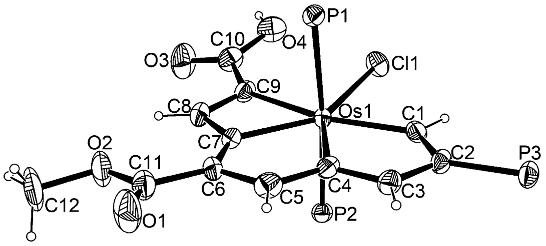


Figure 1. Molecular structure of the cation of **2** (thermal ellipsoids set at 50% probability). The phenyl moieties in PPh_3 have been omitted for clarity.

In the planar metallacyclobutadiene unit of **2**, the transannular distance of C7–C9 (2.128 Å) was at the lower end of those in previously reported metallacyclobutadiene complexes (2.030–2.530 Å).[13] Thus, the metallacyclobutadiene unit in **2** is compressed along the C7–C9 direction, leading to the disappearance of the bonding interaction between Os1 and C8, in sharp contrast to the previous report of 1,3-related metal–carbon bonding.[14] Indeed, the Wiberg bond index of Os1–C8 is calculated to be 0.03, indicating a negligible interaction. Accordingly, compound **2** contains a metallapentalene unit and a metallacyclobutadiene unit, which can be considered as a rare example of a metallacyclobutadiene with a late transition metal. Therefore, we have successfully stabilized two classical antiaromatic systems by using one metal fragment at ambient temperature. This result demonstrates the ability of a metal fragment to stabilize antiaromatic and/or strained systems.[7,15]

Complex **2** was further characterized by NMR spectroscopy, high-resolution mass spectrometry (HRMS), and elemental analysis. In the ^{1}H NMR spectrum, the doublet resonance signal at $\delta = 14.00$ ppm is assigned to the OsC*H* proton, which falls within the range of signals of OsC*H* protons in reported osmapentalynes and osmapentalenes ($\delta =$ 13.25–14.25 ppm).[7,8] The other three proton signals on the metallacycle are detected in the aromatic regions (H3: 8.54, H5: 8.78, and H8: 8.20 ppm).

Complex **3** was also characterized by X-ray diffraction, NMR spectroscopy, HRMS, and elemental analysis. As shown in Figure 2, the structural features of the metallacycle are nearly identical to those of complex **2**. The metallacycle that contains ten atoms (Os1 and C1–C9) is almost coplanar, as reflected by the mean deviation (0.0391 Å) from the least-squares plane and the sum of angles in the fused five-membered rings (540.0° and 539.8°) and four-membered ring (359.9°). The C–C distances (1.367–1.435 Å) in the metallacycle are within the range of typical C–C single- and double-bond lengths. The NMR spectra of complex **3** are also similar to those of **2**. The X-ray diffraction and NMR spectral data suggest that the architectural features of **2** and **3** cations could be attributed to three resonance structures (see the Supporting Information, Scheme S1). Thus, the formation of complexes **2** and **3** represents the first [2+2] cycloaddition reaction of alkynes with a late-transition-metal carbyne complex, although an example of an Os≡Si triple bond was reported recently to undergo [2+2] cycloaddition reaction with an alkyne.[16]

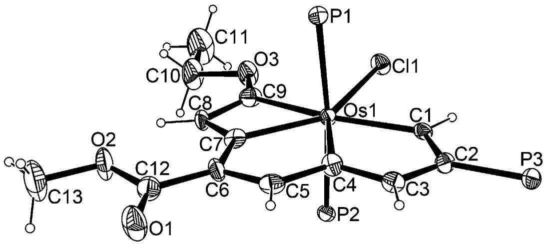
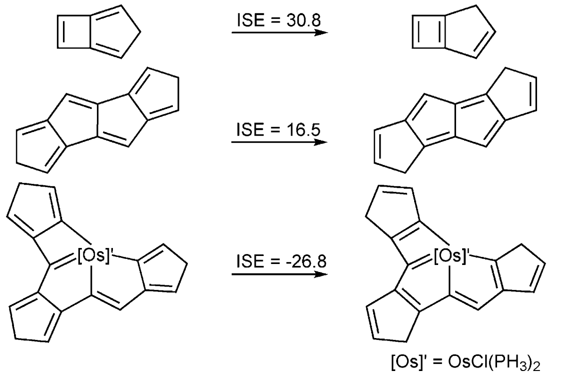


Figure 2. Molecular structure of the cation of **3** (thermal ellipsoids set at 50% probability). The phenyl moieties in PPh_3 have been omitted for clarity.

To probe the aromaticity or antiaromaticity of complexes **2** and **3** by bridging theory and experiment,[17] we performed DFT calculations on an unsubstituted model complex **2′**,



Scheme 3. ISE evaluations of the antiaromaticity of CBD and pentalene and the aromaticity of model complex **2′**.

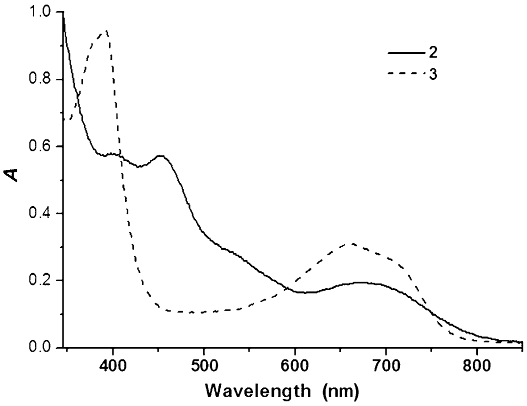


Figure 3. UV/Vis absorption spectra of **2** and **3** measured in CH_2Cl_2 at RT.

where PH_3 was used to replace the PPh_3 ligands. The effective strain-balanced isomerization stabilization energy (ISE) method[18] was used to evaluate the aromaticity. As shown in Scheme 3, the positive ISE values (+30.8 and +16.5 kcal mol^{-1}) of CBD and pentalene confirm the antiaromaticity of these two typical antiaromatic species, whereas the large negative ISE value (−26.8 kcal mol^{-1}) of model complex **2′** reflects its global aromaticity.

We further examined the local aromaticity of these rings in **2′** by dissecting the ISE value of **2′** (Scheme S2). Interestingly, the ISE values for the three local rings were computed to be −3.4, −17.8, and −6.8 kcal mol^{-1}, and the sum of these ISE values (−28.0 kcal mol^{-1}) is close to that (−26.8 kcal mol^{-1}) of model complex **2′**. The ISE value (−17.8 kcal mol^{-1}) of the central five-membered ring suggests its higher aromaticity over the other two rings. The higher aromaticity of the central five-membered rings in **2′** was also essentially supported by nucleus-independent chemical shift (NICS)[19] calculations on **2′**. Specifically, the NICS(1) values of the four-membered ring and the fused five-membered rings in **2′** are +4.5, −5.5, and −0.9 ppm, respectively, which are significantly decreased in comparison with those of the parent CBD (+17.6 ppm) and pentalene (+17.4 ppm),[7] confirming the stabilization of the metal center.

The UV/Vis absorption spectra of complexes **2** and **3** are examined. These complexes exhibit a broad absorption band ranging from the ultraviolet to the visible region and extending into the near-infrared (NIR) region (Figure 3 and Figure S2 in the SI). Considering the low-energy absorption bands, the absorption maximum of **2** occurs at $\lambda = 672$ nm ($\log\varepsilon = 3.30$, where ε is the molar extinction coefficient, measured in $\text{M}^{-1}\text{cm}^{-1}$) and for **3** at $\lambda = 660$ nm ($\log\varepsilon = 3.49$), red-shifted by 248 nm and 236 nm, respectively, compared to that of complex **1** ($\lambda_{max} = 424$ nm).[7] The relatively large bathochromic shift of the absorption maximum suggests the effective conjugation of the metallacyclobutadiene unit and metallapentalene unit in complexes **2** and **3**. To understand the absorption spectra, we performed time-dependent DFT (TD-DFT) calculations on the full model **2** at the TD-B3LYP/6-311++G(d,p) level. As shown in Figure S1, the metallacyclobutadiene unit of complex **2** shows significant contributions to both the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The absorption bands detected at $\lambda = 672$ and 455 nm of complex **2** can be assigned to the electronic transitions HOMO→LUMO and HOMO-4→LUMO with oscillator strengths of 0.61 and 0.59, respectively.

The broad absorption spectra and its extension into the NIR region motivated us to study the photoacoustic (PA) properties of these novel metalla-aromatic compounds. PA imaging is a powerful imaging technology based on optical excitation and ultrasound detection.[20] Compared with the traditional optical imaging methods, PA imaging remarkably enhances the penetration depth and spatial resolution.[21] Recently, an organometallic carbonyl cluster was demonstrated as a reliable photoacoustic contrast agent under an incident wavelength of $\lambda = 410$ nm.[22] However, to our knowledge, the study of PA imaging and the photothermal effect based on metalla-aromatic complexes has never been reported. The PA imaging was performed in vitro using a photoacoustic instrument at $\lambda = 680$ nm. As shown in Figure 4a, the PA signal increased, as expected, with the increasing concentration of **2** and **3**. Note that the slightly stronger photoacoustic signal of complex **3** is consistent with the higher absorptivity compared with complex **2** at $\lambda = 680$ nm. These results demonstrated the potential of these metalla-aromatic compounds in PA imaging.

In addition, the extension of the absorption spectra into NIR region (Figure S2) makes it possible to use **2** and **3** as photothermal agents. With this in mind, the photothermal effect was also examined by monitoring the temperature increase of 1 mL solution of various concentrations of **2** (from 0.25 to 1.00 mg mL^{-1}) under NIR laser irradiation ($\lambda = 808$ nm, 1 W cm^{-2}). As shown in Figure 4b, with various concentrations of **2** clear temperature increases were measured under laser irradiation. The solution containing 1.00 mg mL^{-1} of **2** exhibits significant temperature increase from 32 to 56 °C within 5 min, while the pure solvent (containing none of compound **2**) has a negligible temperature change (less than 4 °C) under the similar conditions. A strong linear correlation ($R^2 = 0.989$) was found between the temperature change and the concentration of **2** (Figure S3).

To investigate the photothermal stability of complex **2**, we compare the absorption spectra and the HRMS of **2** (1.00 mg mL^{-1}) before and after $\lambda = 808$ nm laser irradiation

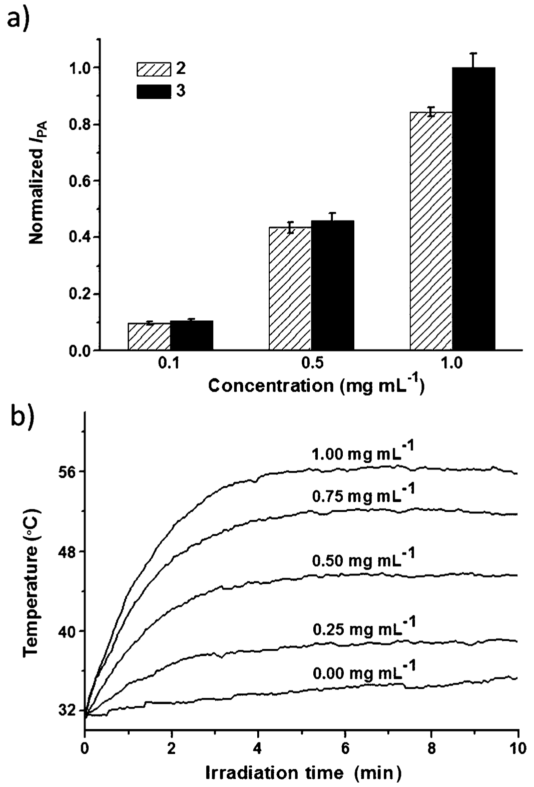


Figure 4. Photoacoustic and photothermal properties of metalla-aromatics **2** and **3**. a) Normalized PA intensity (I_{PA}) of **2** and **3** with different concentrations (0.1, 0.5, and 1.0 mg mL^{-1}) in water–ethanol solution (90% *v*/*v*) monitored at $\lambda = 680$ nm. Error bars show the standard deviation. b) Photothermal effect of DMSO solutions of complex **2** at different concentrations (0.25, 0.50, 0.75, and 1.00 mg mL^{-1}) and of the pure solvent alone upon laser irradiation ($\lambda = 808$ nm, 1 W cm^{-2}).

(1 W cm^{-2}) for an hour. Interestingly, there was no significant discrepancies between the absorption spectra and the HRMS before and after irradiation (Figure S4), which suggest that complex **2** has good stability under the photothermal conditions. The photothermal effect of complex **3** also has been demonstrated and was found to be similar to that of complex **2** (Figure S5). It has been reported that irreversible thermal ablation of cancer cells can be caused by keeping the temperature over 50 °C for approximately 4–6 minutes.[23] Therefore, these results indicate that these novel metalla-aromatic species could be promising theranostic agents for PA-imaging-guided photothermal cancer therapy. However, the biocompatibility of these compounds remains to be investigated for in vitro and in vivo applications.

In this work, the stabilization of two typical antiaromatic systems, CBD and pentalene, was achieved by the introduction of only one metal fragment. The products were formed by the first [2+2] cycloaddition reactions of late-transition-metal carbyne complexes with alkynes. Theoretical calculations confirmed the stabilization of the incorporated metal fragment by the significant decrease of antiaromaticity simultaneously in both CBD and pentalene. Additionally, the unique structure of these systems leads to novel properties. As a result, significant photoacoustic and photothermal effects for metalla-aromatic compounds have been demonstrated for the first time. Our findings not only highlight the ability of transition-metal fragments to stabilize multiple antiaromatic systems, but also encourage further explorations of organometallics for photoacoustic-imaging-guided photothermal therapy, especially in cancer theranostics.

Keywords: antiaromaticity · cycloaddition · density functional calculations · metallacycles · osmium

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