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Attachment of a Ru^{II} complex to a self-folding hexaamide deep cavitand.

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ABSTRACT: We report the design, synthesis and characterization of a new Ru^{II} metallocavitand that is catalytically active in alkene epoxidation reactions. The elaboration of the resorcin[4]arene's aromatic cavity produced a self-folding, deep hexaamide cavitand featuring a single diverging terpyridine (tpy) group installed at its upper rim. The construction of the metallocavitand involved the initial chelation of a Ru^{III} chloride complex by the tpy ligand followed by the incorporation of 2-(phenylazo)pyridine (azpy) as an ancillary ligand. The resulting Ru^{II} chloro complex was converted into the catalytically active aqua counterpart by a ligand exchange process.

The concept of merging molecular recognition with catalysis constitutes an area of growing interest in chemical research.¹ The synthetic availability of resorcin[4]arene cavitands that are not symmetrically substituted² allows the incorporation of functional groups at their upper rims that coordinate to catalytic metal centers. Examples of these structural modifications include oxazoline³ porphyrin,^{4,5} salphen,^{6,7} and pyridine⁸ substituted resorcin[4]arene cavitands. All these molecular constructs feature a selective binding site in close proximity to an organometallic catalytic site. They constitute a viable strategy to achieve new selectivity and activity in transition metal catalysis.9

Inspired by the wide range of oxidative transformations catalyzed by the polypyridyl $Ru^{IV}=O$ species,¹⁰ we decided to investigate the feasibility of covalently attaching a heteroleptic terpyridine (tpy) Ru^{II} aqua complex at the upper rim of a resorcin[4]arene cavitand, trans-1•Ru^{II}•(azpy)•OH₂ (Figure 1). It is well known that Ru is a redox metal capable of $d\pi$ -p π back-bonding, in addition to the conventional σ -bonding.¹¹In polypyridyl complexes, the Ru^{IV}=O high oxidation state can be achieved from the initial Ru^{II}-OH₂ derivative through two successive proton-coupled electron transfer (PCET) processes.¹² A sacrificial chemical oxidant, i.e. iodosobenzene diacetate, can be used to mediate the electron transfer processes.

In Ru^{IV}=O complexes, the ligand selection plays a key role in tuning the redox potential, based on electronic effects. Catalysis performance and control of the oxygen transfer mechanisms in epoxidation reactions (radical or concerted)^{13,14} can be optimized by the choice of ancillary ligand. Owing to its strong electron-withdrawing properties and redox-active nature,¹⁵ 2-(phenylazo)pyridine (azpy) was selected as the ancillary ligand. Llobet et al. reported that 4•Ru^{II}•(azpy)•(OH₂) complexes (7 = tpy) display a single two-electron wave for the Ru^{II}/Ru^{IV} couple that is shifted to high positive potentials.¹⁶ That is, azpy destabilizes the Ru(III) oxidation state and ren-ACS Paragon Plus Environment

ders the Ru^{IV}=O species suitable for stereoselective epoxidation reactions.¹⁴



Figure 1. Structures of 2-(phenylazo)pyridine (azpy), metalloresorcin[4]arene cavitand *trans*-1•Ru^{II}•(azpy)•OH₂ and olefins 2, 3 and 4 used in the epoxidation assays.

We synthesized hexaamide cavitand 1 with a 2,2':6',2" terpyridine ligand at its upper rim by condensation of the known diamine cavitand 5^{17} and the terpyridine aldehyde 6^{18} in dioxane solution and using air as oxidant (Scheme 1). Hexaamide cavitands aka. self-folding cavitands closely related to 1 were previously described by Rebek et al.¹⁹ The seam of up to seven intramolecular hydrogen bonds at the upper rim of hexaamide cavitands stabilizes the "vase" conformation. These sizable hosts feature an electron rich aromatic cavity suitable for the inclusion of neutral and cationic organic/organometallic guests.

Scheme 1. Synthesis of the hexaamide cavitand 1, the metallocavitands and the reference complex.



Compound 1 lacks symmetry and shows different signals for each proton in its ¹H NMR spectrum in CD₂Cl₂ solution. The benzimidazole NH signal is a sharp singlet at $\delta = 12.36$ ppm (H², Figure 2a), indicating its involvement in strong hydrogen bonding. The six amide NH protons resonate as separate singlets in the downfield region of the spectrum (\bullet , Figure 2a). The unidirectional orientation of amide groups at the upper rim of 1 renders the entire molecule chiral. It exists in solution as a mixture of two conformational cycloenantiomers whose interconversion requires the tautomerization of the imidazole unit and concomitant rotation of the amide groups.¹⁹ The racemization process is fast on the human timescale but slow on the EXSY timescale resulting in a pattern of exchange crosspeaks between related NH signals. We calculated an energy barrier of 16 kcal/mol for the cycloenantiomerization process. A total of 16 singlets are observed for the aromatic protons of the resorcin[4] arene core and the bridging walls (\bullet and H^{1,8}, Figure 2). The terpyridine substituent has five distinct proton signals owing to its free rotation through the connecting C-C bond (H^{3-7} , Figure 2). Because CD₂Cl₂ is a suitable guest for the aromatic cavity of 1, the vase conformation is adopted in this solvent. This is shown by the appearance of signals centered at $\delta = 5.63$ ppm (•, Figure 2a) that represent different triplets for the methyne protons.^{20,21}

Single crystals suitable for X-Ray diffraction were grown from a methylene chloride solution of 1. In the solid state, cavitand 1 also adopts the vase conformation and assembles into dimerlike capsules including six methylene chloride molecules (Figure 2b). The two monomers of 1 involved in the dimer assembly are cycloenantiomers (M/P).^{19,22} The seam of seven hydrogen bonds present at the upper rim of 1 that is responsible for the "vase" stabilization is clearly seen in the solid structure (Figure 3a). The average distance between nitrogen and oxygen in the five C=O···HN hydrogen bonds is 2.862 Å. Two of the three intra-ring hydrogen bonds are 0.1 Å shorter than the two inter-ring counterparts. The two hydrogen bonds involving the imidazole units have distances of 2.746 Å (ImNH··O=C) and 3.114 Å (NH···NIm) between donor/acceptor atoms. Ruthenium was coordinated to cavitand 1 with RuCl₃ in ethanol solution at reflux for 12 h (Scheme 1). The octahedral 1-RuCl₃ was isolated as a brown solid in 83% yield and characterized by a high-resolution spectra and X-ray crystallography. The ¹H NMR spectrum of **1**•Ru^{III}Cl₃ in CD₂Cl₂ displayed complex and broad signals. Of special interest was the observation of four signals resonating at very high field, in the range of $\delta = -3$ to -8 ppm (SI).



Figure 2. a) Downfield regions of the ¹H NMR spectrum of cavitand 1 in CD_2Cl_2 solution. See Scheme 1 for proton assignments; b) solid state structure of the dimer of the terpyridine substituted cavitand 1; the six included CH_2Cl_2 molecules are shown as space filling models.

We assigned these signals to the protons of the tpy unit coordinated to Ru^{III}. A six coordinate Ru^{III} complex should be in the S = 2 spin state and thus paramagnetic.²³ However, other dynamic processes occurring in solution like aggregation (*vide infra*) or conformational exchange cannot be excluded as additional sources of the observed signal broadening. The solid-state structure of $1 \cdot Ru^{III} \cdot Cl_3$ showed the tendency to dimerize by filling the cavity of one monomer with the tpy•Ru^{III}•Cl₃ moiety of another (**Figure 3b**). This type of arrangement induces a conformational change in two bridging aryl walls having vicinal diamides, which become equatorially oriented. The two adjacent remaining bridging aryl walls, one equipped with tpy•Ru^{III}•Cl₃ moiety and the other with a vicinal diamide, maintain an axial orientation.

A suspension of **1**•Ru^{III}•Cl₃ in an ethanol/water (4:1) mixture was refluxed for 12 h with azpy²⁴ in the presence of Et₃N and LiCl. This reaction is known to produce the exchange of two chloro ligands by the bidentate azpy ligand with concomitant reduction of Ru^{III} to Ru^{III}. After the exchange of the noncoordinated chloride anion by the more lipophilic PF₆⁻ counterpart, the crude reaction mixture was purified by column chromatography. The mono-chloro metallocavitand $[1 \cdot Ru^{II} \cdot (azpy) \cdot Cl]^+ PF_6$ was isolated in 88% yield as a pink solid and characterized by a set of high resolution spectra (UV-Vis, HRMS, ¹H, ¹⁹F and ³¹P NMR) and differential pulse voltammetry (DPV). Most likely, the isolated solid is composed of a mixture of the cis- and trans- isomers (relative orientation of the pyridyl N atom with respect to the central N of the tpy) owing to the non-symmetric nature of the bidentate ligand. Treatment of $[1 \cdot Ru^{II} \cdot (azpy) \cdot Cl]^+ PF_6$ with excess AgPF₆ in an acetone/water mixture (3 mL : 10 drops) at 60°C for 12 h produced a precipitate of AgCl. Addition of water to the filtered acetone solution afforded a brown solid of the aqua complex $[1 \cdot \text{Ru}^{\text{II}} \cdot (\text{azpy}) \cdot \text{OH}_2]^{2+}$ (PF₆)₂, probably a mixture of isomers deriving from the staring material.²⁵

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Figure 3. a) Top view of the *M*-cycloenantiomer of **1** in the solid state. Included CH₂Cl₂ molecules are not shown. The distances (Å) between heteroatoms involved in hydrogen bonds are reported; b) X-ray structure of the dimer aggregate assembled by **1**•Ru^{III}•Cl₃. Non-polar hydrogen atoms are omitted for clarity.

Six-coordinated Ru^{II} should be in the S = 1 spin state resulting in a diamagnetic complex, which is expected to produce wellresolved NMR spectra. However, the ¹H NMR spectra in CD₂Cl₂ solution of both the aqua complex [1•Ru^{II}•(azpy)•OH₂]²⁺ (PF₆⁻)₂ and the parent mono-chloro metallocavitand [1•Ru^{II}•(azpy)•Cl]⁺ PF₆⁻ displayed broad and ill-defined signals. Remarkably, neither spectra showed the upfield-shifted signals observed in the paramagnetic precursor 1•Ru^{III}•Cl₃. This result provides support to the diamagnetic nature of Ru^{II} in the two heteroleptic complexes.

The 'H NMR spectra of the two heteroleptic complexes featured signals in the region of 4 ppm. These signals are assigned to methine protons that experience a shielding effect owing to the equatorial orientation of the bridging aryl walls in resorcinarene cavitand. Both 2D NOESY and ROESY spectra revealed the existence of cross peaks due to chemical exchange between the signals of the methine protons resonating at $\delta = 4$ ppm and those at $\delta = 5.6$ ppm (SI). These results hint to the existence of a fluxional chemical exchange process in solution that is slow/intermediate in the chemical shift time scale and involves multiple conformers of the chloro and aqua metallocavitands featuring a partial-kite structure and producing the broadening of some their proton signals. A significant difference between the two ¹H NMR spectra of the heteroleptic metallocavitands is the presence of a broad singlet resonating at $\delta \approx 1.7$ ppm in the case of the aqua derivative. We assign this signal to the hydrogen atoms of the water molecule coordinated to the Ru^{II} metal center. Unfortunately, all our attempts to grow single crystals of $[1 \cdot Ru^{II} \cdot (azpy) \cdot Cl]^+ PF_6^$ and $[1 \cdot Ru^{II} \cdot (azpy) \cdot OH_2]^{2+}$ (PF₆)₂ were unsuccessful. Nevertheless, the high resolution MALDI-MS (+) spectra of the two complexes showed ion peaks for their corresponding monocationic species $[M - PF_6]^+$ and $[M - 2PF_6 - H]^+$, respectively, with isotopic patterns that nicely coincide with the theoretical ones (SI).

The spectroscopic properties of the two metallocavitands were compared to the reference counterparts, $[7 \cdot Ru^{II} \cdot (azpy) \cdot Cl]^+$ ClO_4^- and $[7 \cdot Ru^{II} \cdot (azpy) \cdot OH_2]^{2+} (ClO_4^-)_2$. The latter complexes were prepared following a reported procedure and using a similar manifold of reactions as for the former.¹⁴ The UV-Vis spectra of the heteroleptic metallo cavitands displayed a characteristic MLCT (Metal to Ligand Charge Transfer) band, centered at 529 nm for $[1 \cdot Ru^{II} \cdot (azpy) \cdot Cl]^+ PF_6^-$ and blueshifted (502 nm) in the case of the aqua derivative (SI). This behavior is in total agreement with the reported spectra for the reference complexes. The IR spectra registered for $[1 \cdot Ru^{II} \cdot (azpy) \cdot OH_2]^{2+} [PF_6^-]_2$ and its reference showed a broad band centered at $\approx 3390~{\rm cm}^{-1}$ that was assigned to the OH vibration in the $Ru^{II}{\cdot}OH_2$. This band was absent in the two parent chloro complexes. The chloro and aqua metallocavitands displayed an additional broad band at $\approx 3240~{\rm cm}^{-1}$ assigned to the vibration of NHs in hydrogen-bonded amides.⁸ The N=N stretching frequency of the coordinated ancillary ligand was appreciably lower than for the free azpy ligand. This is consistent with back-bonding donation from the metal.¹¹

We performed preliminary epoxidation assays using $[1 \cdot Ru^{\hat{1}} \cdot (azpy) \cdot OH_2]^{2+}$ (PF₆)₂ as catalyst and styrene 2 or *trans*- β -methyl styrene **3** as test substrates. The reactions were performed at 298 K in NMR tubes with a solution of CD₂Cl₂ (550 µL) containing 3 µmol of substrate, 6 µmol of iodosobenzene diacetate, 150 µmol of water to ensure the generation of the sacrificial oxidant iodosylbenzene from the diacetate iodobenzene precursor and 5 mol-% of the catalyst.²⁶ The progress of the reaction was monitored using ¹H NMR spectroscopy by acquiring a series of spectra of the reaction mixture at regular time intervals. After 70 min, the analysis of the reaction mixtures revealed that ~20% of the alkenes were converted and the vield of the epoxides was ~15 %. At this point, the sacrificial oxidant was consumed in a larger amount than required for the $\sim 20\%$ conversion of the substrate and the reactions slowed down significantly. Most likely, after two to three turnovers the catalyst for the epoxidation reaction is partially destroyed. We obtained similar results using the reference aqua complex $[7 \cdot Ru^{II} \cdot (azpy) \cdot OH_2]^{2+}$ $(ClO_4)_2$ as catalyst. Increasing the amount of the cavitand catalyst to 10 mol-% led to an increase in the yield of the epoxide to ~ 50 % after 50 min of reaction. Encouraged by these findings, we investigated the epoxidation of the cis- β -alkyl styrene olefin 4 equipped with a terminal trimethyl ammonium function.²⁷ Substrates bearing a trimethylammonium "knob" engage in 1:1 inclusion complexes with Zn-salphen monofunctionalized cavitands that can accelerate the reaction of the bound guests. ^{6,7} Unfortunately, the amount of the epoxide produced from 4 using the metallocavitand as catalysts was almost identical to that obtained using the neutral olefins. Taken together, these results indicate that the covalent attachment of the tpy• Ru^{II} •(azpy)• OH_2 moiety to a self-folding hexamine cavitand preserves the catalytic properties of the metal center but it does not show signs of supramolecular catalysis.²⁸ The small reduction in catalytic efficiency observed for the cavitand catalyst in the epoxidation of the cationic olefin 4 compared to the neutral counterparts, 2 and 3, is assigned to putative complexes displaying binding geometries not suitable for intramolecular oxygen transfer.

In conclusion, we report the synthesis and characterization of the terpyridine functionalized self-folding cavitand **1**. We metallated the terpyridine moiety with ruthenium and customized the metal center for two-electron oxygen transfer reactions by preparing the corresponding Ru^{II} aqua derivative with 2-(phenylazo)pyridine as ancillary ligand. A limited catalytic activity of the aqua metallocavitand was demonstrated through the epoxidation reaction of simple olefins. The proximity between the catalytic center and the cavitand binding site in **1** did not produce a supramolecular catalyst for the epoxidation of **4**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data for new compounds. 1D and 2D NMR, MS, IR, UV/Vis spectra, DPV and HPLC data of compounds and complexes.

X-ray crystallography data for 1

X-ray crystallography data for 1•Ru^{III}•Cl₃

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 22 *P/M* indicates the stereochemical designation of the axial chirality defined by the unidirectional sense of rotation of the amide groups viewed from above the cavity. See Figure 3a.

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²⁸ The aqua metallocavitand also failed to act as supramolecular catalysts in the oxidation of primary alcohols.





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