

Bioinspired Water Preorganization in Confined Space for Efficient Water Oxidation Catalysis in Metallosupramolecular Ruthenium Architectures

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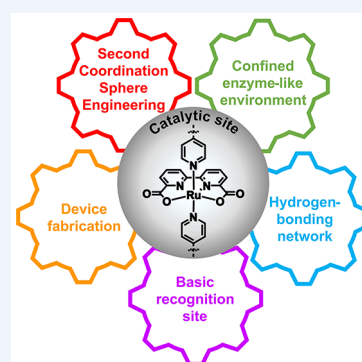
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CONSPECTUS: Nature has established a sustainable way to maintain aerobic life on earth by inventing one of the most sophisticated biological processes, namely, natural photosynthesis, which delivers us with organic matter and molecular oxygen derived from the two abundant resources sunlight and water. The thermodynamically demanding photosynthetic water splitting is catalyzed by the oxygen-evolving complex in photosystem II (OEC-PSII), which comprises a distorted tetramanganese–calcium cluster (CaMn_4O_5) as catalytic core. As an ubiquitous concept for fine-tuning and regulating the reactivity of the active site of metalloenzymes, the surrounding protein domain creates a sophisticated environment that promotes substrate preorganization through secondary, noncovalent interactions such as hydrogen bonding or electrostatic interactions. Based on the high-resolution X-ray structure of PSII, several water channels were identified near the active site, which are filled with extensive hydrogen-bonding networks of preorganized water molecules, connecting the OEC with the protein surface. As an integral part of the outer coordination sphere of natural metalloenzymes, these channels control the substrate and product delivery, carefully regulate the proton flow by promoting pivotal proton-coupled electron transfer processes, and simultaneously stabilize short-lived oxidized intermediates, thus highlighting the importance of an ordered water network for the remarkable efficiency of the natural OEC.

Transferring this concept from nature to the engineering of artificial metal catalysts for fuel production has fostered the fascinating field of metallosupramolecular chemistry by generating defined cavities that conceptually mimic enzymatic pockets. However, the application of supramolecular approaches to generate artificial water oxidation catalysts remained scarce prior to our initial reports, since such molecular design strategies for efficient activation of substrate water molecules in confined nanoenvironments were lacking. In this Account, we describe our research efforts on combining the state-of-the-art $\text{Ru}(\text{bda})$ catalytic framework with structurally programmed ditopic ligands to guide the water oxidation process in defined metallosupramolecular assemblies in spatial proximity. We will elucidate the governing factors that control the quality of hydrogen-bonding water networks in multinuclear cavities of varying sizes and geometries to obtain high-performance, state-of-the-art water oxidation catalysts. Pushing the boundaries of artificial catalyst design, embedding a single catalytic Ru center into a well-defined molecular pocket enabled sophisticated water preorganization in front of the active site through an encoded basic recognition site, resulting in high catalytic rates comparable to those of the natural counterpart OEC-PSII.

To fully explore their potential for solar fuel devices, the suitability of our metallosupramolecular assemblies was demonstrated under (electro)chemical and photocatalytic water oxidation conditions. In addition, testing the limits of structural diversity allowed the fabrication of self-assembled linear coordination oligomers as novel photocatalytic materials and long-range ordered covalent organic framework (COF) materials as recyclable and long-term stable solid-state materials for future applications.



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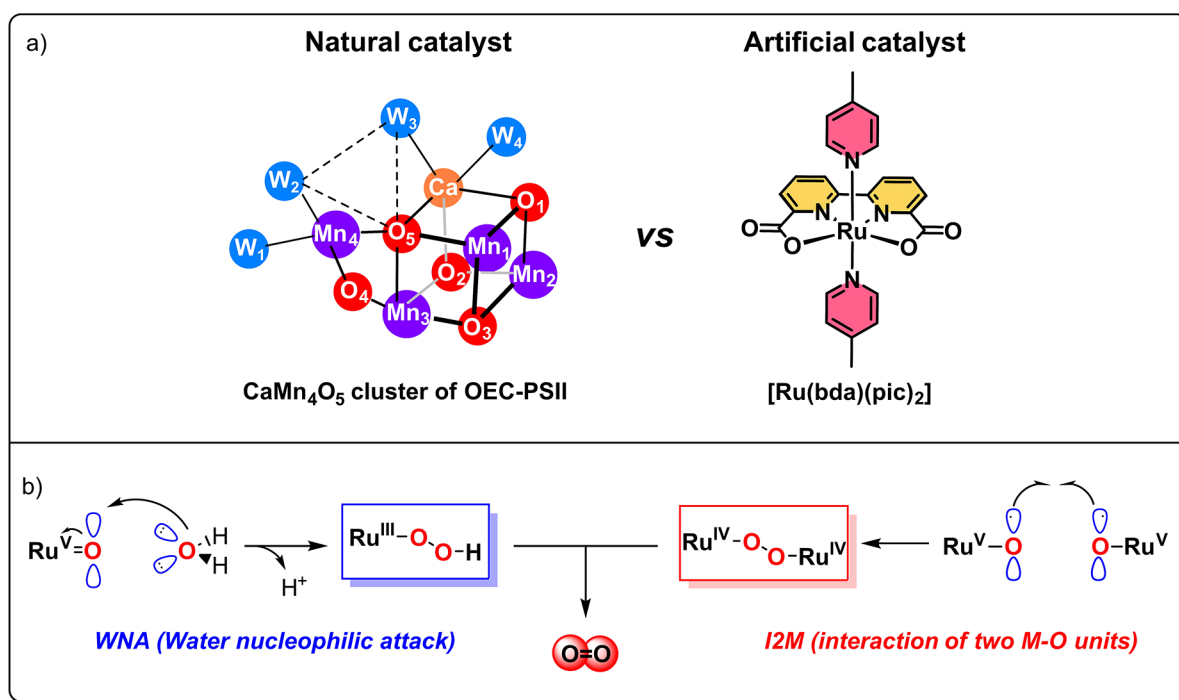


Figure 1. (a) Schematic representation of the natural oxygen-evolving complex in PSII with bound water (blue spheres) in comparison to the molecular structure of the artificial water oxidation catalyst $[\text{Ru}(\text{bda})\text{pic}_2]$. (b) O–O bond formation pathways for Ru-based WOCs: single-site water nucleophilic attack (WNA) and bimolecular interaction of two metal-oxo units (I2M).

differently sized trinuclear $\text{Ru}(\text{bda})$ macrocycles revealed the importance of intracavity hydrogen-bonding networks for the catalytic performance.

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- Noll, N.; Krause, A.-M.; Beuerle, F.; Würthner, F. Enzyme-like water preorganization in a synthetic molecular cleft for homogeneous water oxidation catalysis. *Nat. Catal.* **2022**, *5*, 867–877.⁴ In this article, preorganization of substrate water molecules in front of the active site of a single-site $\text{Ru}(\text{bda})$ unit was accomplished by a tailored enzyme-like pocket, resulting in high water oxidation activity.

1. INTRODUCTION

Anthropogenic climate change and progressively rising global energy demands due to a rapidly growing population drive the quest for a transition to a carbon-neutral and sustainable energy supply.^{5,6} Over millions of years, natural photosynthesis has produced most of the fossil energy reserves on earth using the abundant feedstocks sunlight and water.^{7,8} Toward a sustainable energy economy, artificial photosynthesis has developed as an emerging technology by exploiting the high energy potential of the sun with the ambitious goal to store solar energy in the chemical bonds of solar fuels such as hydrogen or methanol.^{9,10} To compensate for the diurnal fluctuations of the sun, particularly elemental hydrogen can be

utilized as a long-term and large-scale storage medium due to its very high energy density.¹¹ Similar to the natural blueprint, the abundant resource water constitutes the ideal source for the generation of green hydrogen as a nearly inexhaustible solar fuel by utilizing the process of photocatalytic water splitting into its elements.¹² Regardless of the reductive half reaction, the complex multielectron process of water oxidation ($2\text{H}_2\text{O} \rightarrow 4\text{H}^+ + 4\text{e}^- + \text{O}_2$) with its high overpotential is considered as major bottleneck for the realization of artificial photosynthetic systems.^{13,14}

The natural archetype oxygen-evolving complex in photosystem II (OEC-PSII) provides a perfect blueprint for effective molecular catalyst design (Figure 1a). Several groups tried to replicate the structural features of the native OEC,¹⁵ but typically no catalytic activity and high overpotentials due to the absence of a sophisticated protein matrix were observed.^{16,17} Accordingly, the development of molecular water oxidation catalysts (WOCs) operating at low overpotential has become an intense area of research over the past decades.^{18,19} Redox-active transition metal complexes have emerged as ideal candidates for challenging water oxidation catalysis owing to their versatile redox chemistry and the wide range of accessible oxidation states.²⁰ Since the discovery of the “blue dimer” by Meyer and co-workers in 1982,²¹ ruthenium-based WOCs have evolved as the most efficient and robust catalyst class among the various transition metals, combining high catalytic activities (turnover frequency (TOF)) and stabilities (turnover number (TON)) with low overpotentials.^{22,23} In this context, the $[\text{Ru}(\text{bda})\text{L}_2]$ catalyst family (bda = 2,2'-bipyridine-6,6'-dicarboxylate, L = aromatic *N*-heterocycles) introduced by Sun and co-workers has been established as state-of-the-art WOCs by enabling catalytic activities comparable to the natural OEC.^{24,25} The introduction of the dianionic bda ligand lowers the redox potential of the Ru center and provides access to the

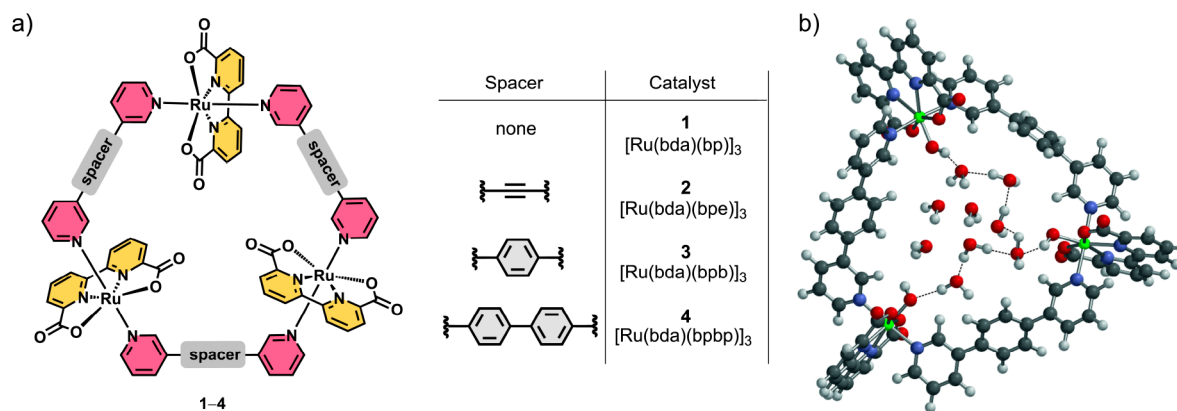


Figure 2. (a) Molecular structures of differently sized trinuclear macrocycles 1–4. (b) DFT-optimized structure of the hydrogen-bonded water network inside the cavity of [Ru^{IV}–OH(bda)(bpb)]₃ (3) (bpb = 1,4-bis(pyridyl-3-yl)benzene). Figure 2b was reproduced with permission from ref 1. Copyright 2016 Nature Publishing Group.

high oxidation states. In addition, the unique structural features of the hexacoordinated Ru complexes with a distorted octahedral coordination geometry and an obtuse O–Ru–O angle of $\sim 124^\circ$ generates a vacant seventh coordination site for substrate water binding without ligand exchange (Figure 1a).²⁵ As a result of multiple concerted proton-coupled electron transfer processes (PCETs) the crucial high-valent Ru(V)-oxo species is generated for subsequent O–O bond formation.²⁶ Similar as discussed for the natural counterpart, O₂ formation can either occur through the interaction of two metal-oxo species (I2M) or through the nucleophilic attack of a substrate water molecule (WNA) (Figure 1b).²⁷ In this context, the class of Ru(bda) catalysts, which generally performs water oxidation via an intrinsic I2M pathway, is one of the most striking examples for mechanistic changes as a result of subtle structural adjustments or lower activation barriers.²⁵ Toward solar fuel devices, the development of highly active WOCs following a unimolecular WNA pathway is particularly interesting for applications under high dilution conditions as in photocatalysis or upon anchoring on electrode surfaces. Conversely, diffusion-limited collision of two catalytic subunits becomes rather unlikely under these conditions, resulting in a mechanistic switch from I2M to a less efficient WNA mechanism.^{28,29}

Catalysts operating under a unimolecular WNA pathway are generally significantly more difficult to optimize due to the rate-limiting interaction of the catalytic site with solvent water molecules in most cases. Prior to our initial reports,^{1,2} WNA-operating Ru catalysts usually showed very inefficient catalytic rates with TOFs in the range of ~ 0.01 – 2 s^{-1} .²⁰ To compete with the catalytic proficiency of natural enzymes, concepts from the emerging field of supramolecular catalysis appeared promising to us for the development of bioinspired molecular catalysts to promote catalyst-substrate interaction in confined space.^{22,23} As preferred hosts in supramolecular chemistry, we envisioned metallosupramolecular macrocycles^{30–32} as ideal three-dimensional coordination environment to promote the preorganization of hydrogen-bonded water molecules close to the active site and facilitate PCETs resulting in a reduced activation barrier for water nucleophilic attack. In 2016, our group demonstrated the first example of a defined cyclic metallosupramolecular architecture comprising multiple Ru(bda) subunits that facilitate a unimolecular water nucleophilic

attack by achieving an outstanding catalytic activity that rivals the natural counterpart.¹

In this Account, we summarize our research efforts since then on differently sized mono- and multinuclear Ru(bda)-based metallosupramolecular architectures targeting the challenging process of water splitting. After introducing our initial results on multinuclear macrocycles, we will discuss the paramount factors that govern the strength of hydrogen-bonded water networks in bioinspired metallosupramolecular cavities of varying size and geometry. As a particular highlight, water oxidation in an enzyme-mimetic molecular cleft equipped with a basic recognition site will be demonstrated as a remarkable model for state-of-the-art WOCs. Toward an artificial device, collaborative achievements by employing our metallosupramolecular architectures in chemical, electro-, and photocatalytic water oxidation catalysis as well as for heterogeneous water oxidation using a sophisticated covalent–organic framework will be discussed.

2. WOC BY [3+3] Ru(bda) MACROCYCLES OF VARYING SIZE

The high proton mobility in water results from proton migration through an ordered hydrogen-bonded water network according to the Grotthuss mechanism.³³ Reminiscent of natural enzymatic pockets, supramolecular preorganization of small molecules can be promoted by the molecular design of confined environments.³⁴ In the field of water oxidation catalysis, initial approaches mainly focused on accelerating the bimolecular intercatalyst coupling of the I2M pathway via encapsulation of mononuclear Ru WOCs into supramolecular nanocages,³⁵ while reports on macrocyclic Ru WOCs were rather scarce prior to our first report.³⁶ For our novel “macrocycle approach”, the catalytically active Ru(bda) subunits are embedded into multinuclear [n_1+n_2] macrocyclic assemblies through self-assembly (n_1 = number of Ru(bda) subunits; n_2 = number of ditopic bridging ligands).³⁷ To control the structural diversity of the metallosupramolecular architectures, the desired geometry and properties can be programmed into the molecular structure of the preorganized ditopic bridging ligands. This allows us to not only control the molecular size of the macrocyclic cavity, but also to structurally modify the ligand framework and to guide and manipulate the preorganized water network for the crucial water nucleophilic attack pathway through the introduction of functional groups

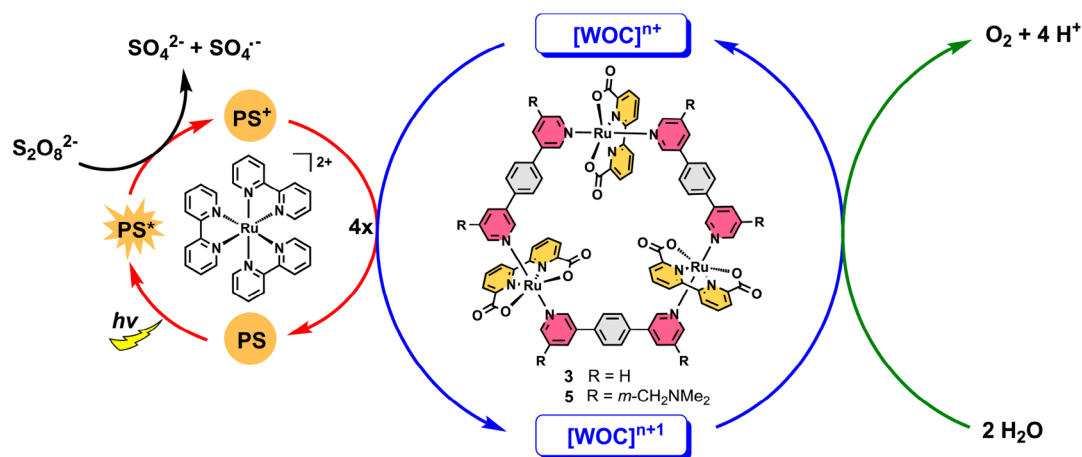


Figure 3. Schematic representation of the catalytic cycle of photocatalytic water oxidation using $[\text{Ru}(\text{bpy})_3]^{2+}$ as PS, $\text{Na}_2\text{S}_2\text{O}_8$ as SEA and macrocycles **3** and **5**, exemplarily, as molecular WOCs.

such as a pendant base.^{4,38} Compared to noncyclic and more flexible complexes, the steric confinement and reduced structural flexibility of such cyclic arrangements facilitate substrate water binding to the Ru site and, thus, efficiently suppress the bimolecular I2M approach as competing mechanistic pathway. A potential side benefit of such multinuclear structures is cooperative effects between the catalytic centers. However, axial ligand dissociation is considered to be one of the main degradation pathways of WOCs under the operating conditions, resulting in limited turnover numbers and reduced catalytic stability. In this regard, cyclic arrangements provide higher catalyst stability due to the chelate effect of the pyridyl bridging ligands and thus extend the catalyst lifetime by reducing critical ligand oxidation.^{22,36}

In 2016, our group presented the first example of the novel “macrocycle approach” with the trigonal $[3 + 3]$ macrocycle $[\text{Ru}(\text{bda})(\text{bpb})_3]$ **3** ($\text{bpb} = 1,4\text{-bis}(\text{pyridyl})\text{-3-yl-benzene}$) as a highly efficient WOC (Figure 2a).¹ A substantial increase in catalytic activity of 50 s^{-1} per Ru center up to an overall TOF of 150 s^{-1} (TON = 7400) for macrocycle **3** was observed in chemical water oxidation at pH 1 using cerium ammonium nitrate (CAN) as a sacrificial oxidant. Kinetic experiments including H/D kinetic isotope effect (KIE) studies and ^{18}O labeling experiments unambiguously confirmed a mechanistic switch to a unimolecular WNA mechanism with the $\text{Ru}^{\text{IV}}\text{-OH}$ to $\text{Ru}^{\text{V}}\text{=O}$ oxidation as the rate-determining step. To gain profound insights into the dynamic proton-coupled oxidation processes within the macrocyclic void of supramolecular WOC **3**, molecular dynamics simulations using the hybrid quantum mechanics/molecular mechanics (QM/MM) approach were performed.^{1,2} Accordingly, an extensive hydrogen-bonded water network was identified within the interior of the macrocycle that is stabilized by cooperative effects between the individual Ru centers. The equatorial bda ligands act as efficient proton relays through the hydrogen-bonded water network, allowing rapid proton abstraction from the reactive centers through concerted proton-coupled electron transfer (PCET) processes, thus resulting in a lower activation barrier for the crucial water nucleophilic attack (Figure 2b).

Based on these initial results, tuning the size of the macrocyclic cavity in a series of trinuclear $\text{Ru}(\text{bda})$ macrocycles **1–4** bearing ditopic bridging ligands of varying length allowed us to elucidate the impact of the ring size on the catalytic performance and the quality of the inner hydrogen-

bonded network (Figure 2b).² Remarkably, the previously reported macrocycle **3** shows the highest catalytic rate under comparable conditions, making **3** one of the most active $\text{Ru}(\text{bda})$ WOCs known to date operating via the WNA pathway. Based on theoretical studies, middle-sized WOC **3** provides the ideal cavity size to allow cooperative proton abstraction through an ordered water network. Such cooperative effects are prevented for the smaller macrocycles **1** and **2** due to steric constraints, which result in a limited accessibility of substrate water molecules to the inner void and force each $\text{Ru}(\text{bda})$ center to catalyze water oxidation independently. The quality of the hydrogen-bonded water network within the individual macrocycles is experimentally reflected in the magnitude of the H/D kinetic isotope effects (KIE) for **1–4**. A clear optimum with a high experimental KIE value was observed for medium-sized macrocycle **3**, indicating a higher degree of proton coupling in the rate-determining oxidation step compared to the other macrocycles, which explains the high catalytic activity of supramolecular WOC **3**. Detailed investigations by single-crystal X-ray analysis in the initial Ru^{II} state of a fluorine-functionalized $[3 + 3]$ macrocyclic derivative of **3** provided experimental evidence for the presence of a hydrogen-bonded water network within such macrocyclic cavities.³⁹

3. LIGHT-DRIVEN WOC BY STRUCTURALLY DIVERSE $[n+n]$ $\text{Ru}(\text{bda})$ MACROCYCLES

Visible light-driven water oxidation under neutral conditions is of pivotal importance to assess the suitability of novel WOCs for application in solar fuel devices.⁴⁰ The photocatalytic activities of WOCs are studied by means of a three-component system comprising photosensitizers (PS) based on a ruthenium tris(bipyridine) $[\text{Ru}(\text{bpy})_3]^{2+}$ and a compatible sacrificial electron acceptor (SEA), i.e., sodium persulfate. Accordingly, similar to natural photosynthesis, activation of the catalyst by a mild oxidant, generated by irradiation of the PS in the presence of SEA, constitutes the key step in light-driven water oxidation (Figure 3).^{41,42} Here, the PS acts as powerful one-electron oxidant with a sufficiently high redox potential to enable catalytic water oxidation under neutral conditions after transfer of four consecutive oxidizing equivalents from PS^+ to the WOC, followed by regeneration of both components.⁴³ Due to the more complex process for the applied three-component system and the limited stability of the sensitizer, lower TOF

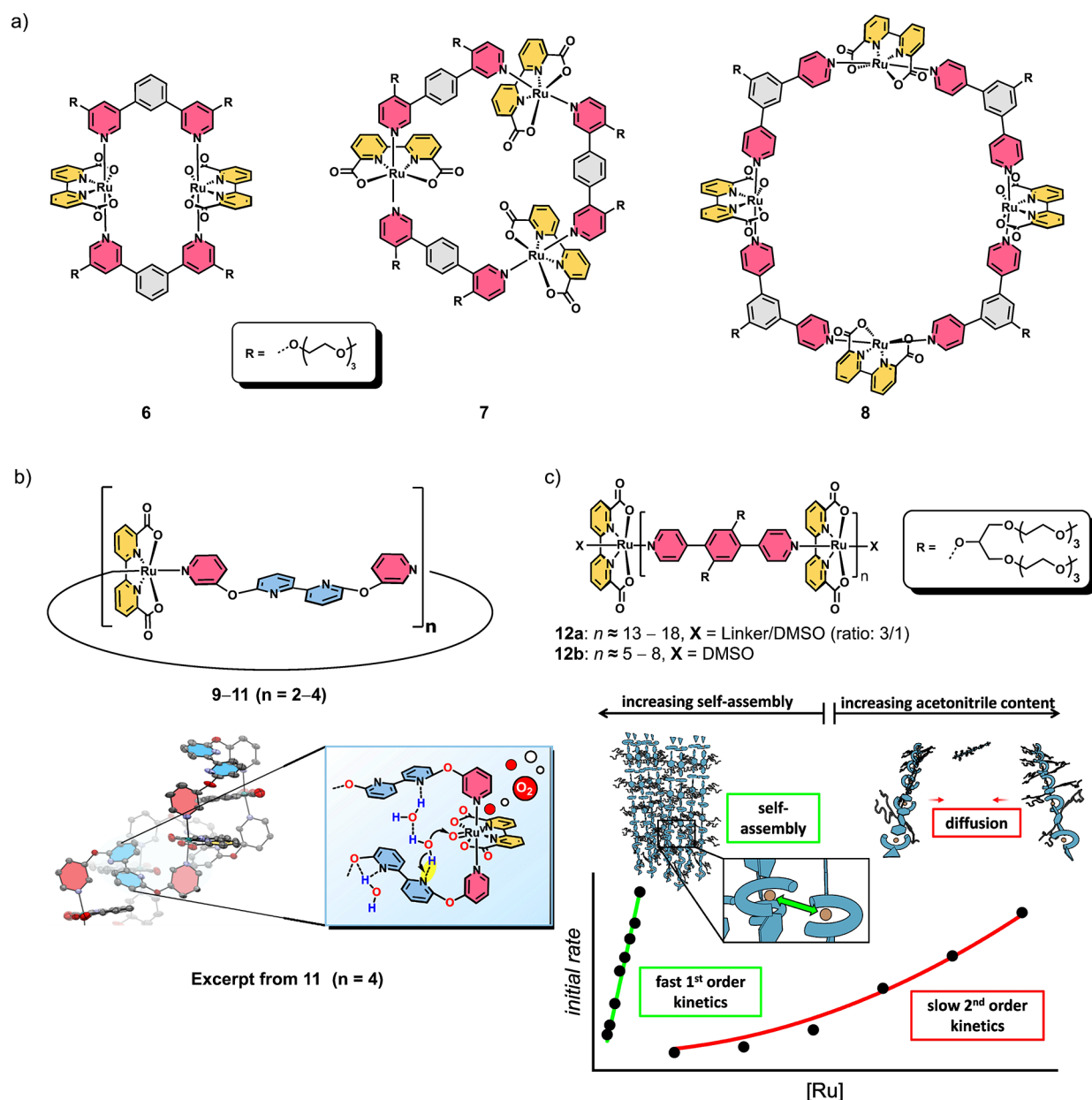


Figure 4. Molecular structure of (a) multinuclear [2 + 2] to [4 + 4] Ru macrocycles 6–8 and of (b) base-functionalized di- to tetranuclear Ru macrocycles 9–11. An excerpt of the single-crystal X-ray structure of the tetramer 11 shows the structural prerequisite for facilitated proton transfer through the pendant base within the multinuclear structure. (c) Structures of differently sized Ru(bda) oligomers 12a, 12b and schematic illustration of varying reaction kinetics for O–O bond formation depending on the amount of cosolvent and respective oligomer size. Panels b and c were adapted with permission from refs 38 and 47. Copyright 2023 and 2022, respectively, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

values are generally obtained under photocatalytic conditions which may explain why only a small number of light-driven Ru WOCs have been investigated so far.^{1,43,44} In this regard, the dilute photochemical conditions should be particularly advantageous for our metallosupramolecular architectures, as the diffusion-controlled encounter of 12M-operating catalysts becomes unlikely under these conditions. Indeed, a more than 2 orders of magnitude higher catalytic activity was observed for macrocycle 3 with a TOF of 10.9 s^{-1} ($\text{TOF}_{\text{Ru}} = 3.7 \text{ s}^{-1}$, $\text{TON} = 430$) compared to previously reported mononuclear Ru complexes ($\text{TOF} < 0.5 \text{ s}^{-1}$).^{1,39} In-depth photocatalytic studies with trinuclear Ru macrocycle 3 and its more water-soluble derivative 5 revealed that the photocatalytic performance is not limited by the intrinsic catalytic activities of the WOC in the

respective solvent mixture but rather by the lifetime of the photogenerated oxidant PS^+ and its oxidative efficiency.⁴³

In the following years, we were able to improve the catalytic performance of our supramolecular Ru complexes by second coordination sphere engineering for enhanced interaction with the surrounding water environment.^{38,43,45–48} To adjust the size of the parent [3 + 3] Ru macrocycle, the binding geometries of the ditopic pyridyl ligands were altered, allowing the isolation of a homologous series of [2 + 2] to [4 + 4] Ru macrocycles 6–8 (Figure 4a). The different size of the di- to tetranuclear complexes was confirmed by analytical GPC and diffusion ordered NMR spectroscopy (DOSY).⁴⁶ Oligo-(ethylene glycol) chains (OEG) were introduced into the ligand scaffold to ensure sufficient solubility in aqueous

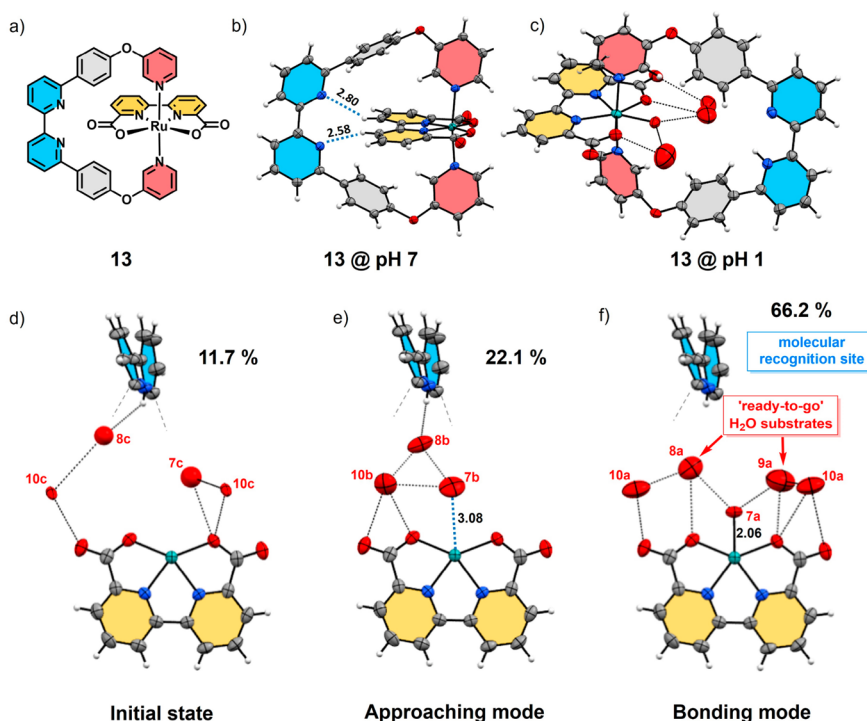


Figure 5. (a) Molecular structure of **13** and single crystal X-ray structures of (b) mononuclear complex **13** at the Ru^{II} state under neutral conditions and (c) **13** at a predominant Ru^{III} state after acidic catalytic water oxidation (pH 1). (d–f) Three different states of the hydrogen-bonded water network inside the enzyme-mimetic molecular cleft of **13** at pH 1: (c) Initial state (11.7% occupancy); (d) approaching mode (22.1% occupancy); and (e) bonding mode (66.2% occupancy). Adapted with permission from ref 4. Copyright 2022 Springer Nature Limited.

mixtures.^{45,48} Subsequent photocatalytic studies revealed an increase in stability and in catalytic activity per Ru center with TOF values of 0.6 s⁻¹, 3.3 s⁻¹, and 5.8 s⁻¹ for **6–8**, respectively, while operating via the unimolecular WNA mechanism. Thus, a clear structure–activity relationship was established showing a trend toward enhanced cooperative water oxidation with increasing ring size and preferred formation of hydrogen-bonded water networks.^{46,49}

So far, we have demonstrated that hydrogen-bonded water networks stabilized by cooperative effects within differently sized Ru(bda) macrocyclic cavities can provide rate-accelerating proton relays.^{1,2,39,46} However, as shown by the groups of Llobet and Concepcion, the incorporation of an auxiliary base into the equatorial ligand framework can also promote the preorganization of substrate water molecules for significant reduction of the activation barrier for the WNA pathway by acting as proton-accepting moiety.^{50,51} Therefore, we introduced pendant bipyridine units into the macrocyclic oxygen-bridged ligand framework of a series of di- to tetranuclear Ru(bda) complexes **9–11** (Figure 4b). Indeed, a notable increase of catalytic activity under neutral photocatalytic conditions was observed with TOF_{Ru} values of 5.5 s⁻¹, 14 s⁻¹, and 15.5 s⁻¹ for **9–11**, respectively, which significantly outperform our previously investigated tri- and tetranuclear macrocycles **7** and **8**. Interestingly, comparative studies under chemical conditions at pH 1 revealed catalytic activities similar to those of our previously investigated trimer **3** with a constant TOF_{Ru} value of ~50 s⁻¹ for **9–11** with no apparent size effect. Based on single crystal X-ray analysis for the whole series, an enhanced tendency for intramolecular folding was observed for the larger macrocycles due to π – π interactions between the bipyridine units under neutral conditions. This leads to a

stronger orientation of the proton-accepting units toward the active sites, which facilitate PCETs by deprotonating incoming water molecules at the rate-determining step of the WNA pathway as experimentally confirmed by an increased H/D kinetic isotope effect (Figure 4b). Under acidic conditions, the proximal functionalities predominate as nonfolded bipyridinium cations and thus can no longer act as proton acceptors, resulting in a constant TOF value for **9–11**.³⁸

In addition, we applied our metallocupramolecular approach to the generation of self-assembled linear Ru(bda) coordination oligomers **12** as novel materials for photocatalytic water oxidation. Due to their diverse synthetic modularity, the accumulation of individual Ru(bda) catalysts into metallocupramolecular coordination oligomers is advantageous for application in water oxidation catalysis, which has been relatively unexplored thus far.^{52,53} The size of the linear oligomeric [Ru(bda)L]_n catalysts was controlled by adjusting the ratio between the two molecular building blocks using bifunctional OEG-functionalized bipyridine derivatives as linker units **L**. Based on several complementary techniques such as ¹H NMR end group analysis, DOSY NMR spectroscopy, atomic force microscopy (AFM), vapor pressure osmometry (VPO) and elemental analysis, combined experimental data revealed an average size distribution of $n = 13–18$ for **12a** and $n = 5–8$ repeating units for **12b** with a high level of accuracy (Figure 4c). The extended oligomers allowed visible light-driven water oxidation in pure water, which resulted in high catalytic efficiencies of up to 14.9 s⁻¹ and TONs of more than 1000 turnovers per Ru center independent of the chain length. In addition, detailed H/D kinetic isotope effect experiments revealed a change from second to first order kinetics with decreasing acetonitrile content while maintaining

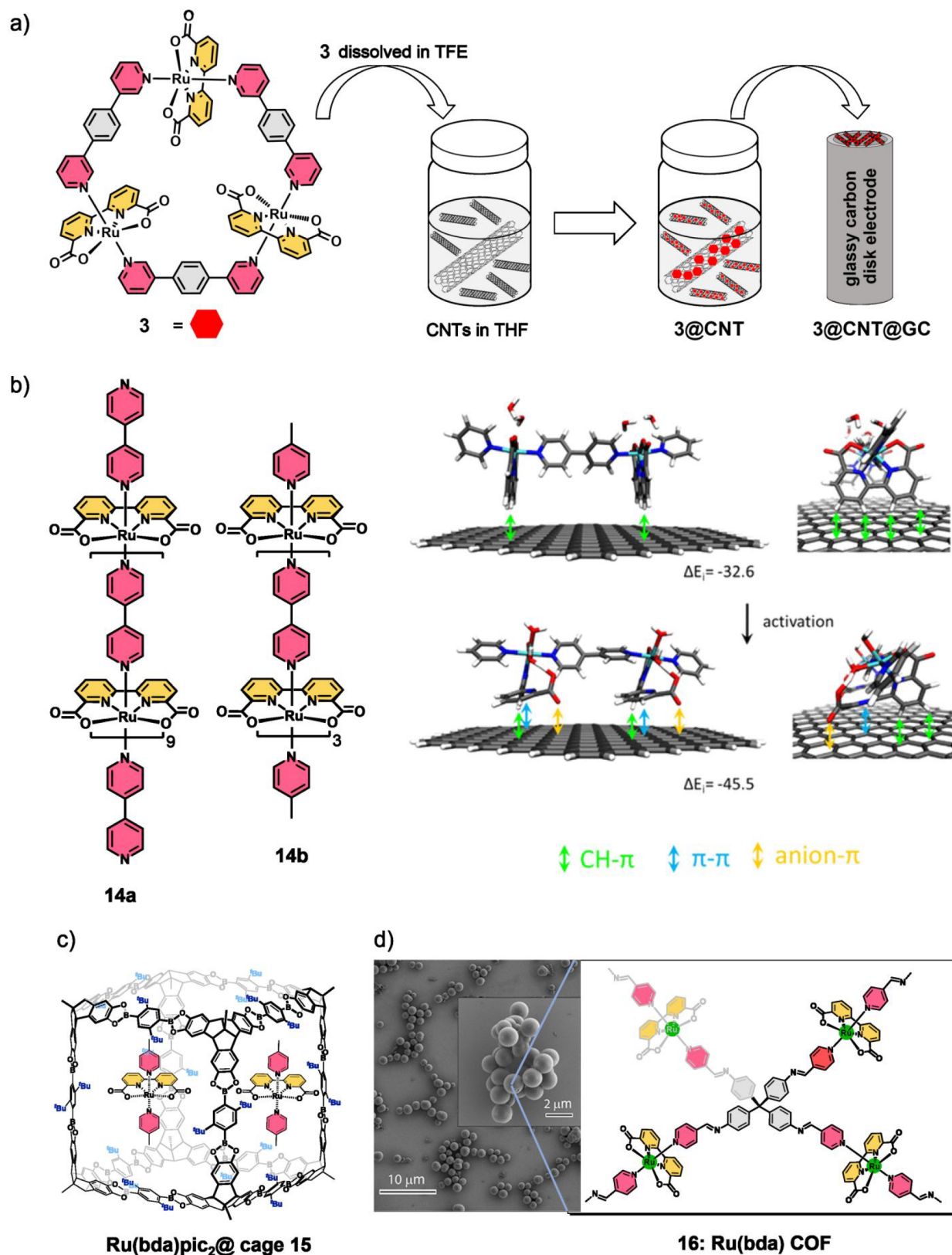


Figure 6. (a) Schematic illustration of the fabrication of molecular hybrid electrodes via immobilization of, e.g., WOC 3 on CNTs and subsequent deposition onto glassy carbon disc. (b) Molecular (left) and calculated (right) structure of Ru(bda) oligomers **14a,b** before (top) and after (bottom) activation upon immobilization on MWCNTs electrodes after repetitive voltammetry cycles based on semiempirical calculations. (c) Crystalline materials based on boronate ester cages filled with Ru(bda)(pic)₂ WOCs and (d) an interpenetrated 3D COF network with Ru(bda) centers (green) applied in heterogeneous water oxidation catalysis. Adapted with permission from refs 3, 61, 67, and 68. Copyright 2020, John Wiley and Sons and 2021, 2024, and 2022, American Chemical Society, respectively.

the I2M mechanistic pathway. This high catalytic performance was attributed to the formation of self-assembled aggregated superstructures with a high local concentration of individual Ru centers in pure water, which promotes intra-assembly oxygen evolution (Figure 4c).⁴⁷

4. WATER PREORGANIZATION IN ENZYME-LIKE POCKET OF SINGLE-SITE [1+1] Ru(bda) MACROCYCLE

A major goal of supramolecular chemistry is to mimic and to accomplish the catalytic proficiency of natural enzymes by tailored design of the active site.^{54,55} As shown by our macrocycle approach, the design of confined environments leads to improved catalytic activity for challenging oxidative water splitting. Because our previous results suggested that only one Ru(bda) unit is needed as WOC while the others only support the proton relay functionality, the next step toward synthetic enzyme mimics was to encode a recognition site into the confined nanoenvironment around a single catalytic site to enable selective substrate preorganization, as has been reported for selected examples of catalytic transformations^{56,57} but not for water oxidation catalysis. Therefore, we have developed a molecular design strategy by embedding the catalytic Ru(bda) framework into the well-defined macrocyclic nanostructure of mononuclear complex **13** that is equipped with a proximal bipyridine site to promote precise substrate water preorganization in the vicinity of the active site through noncovalent interactions (Figure 5). A thorough analysis by pH-dependent H/D kinetic isotope effect studies and NMR experiments revealed a change in reaction kinetics for base-containing **13** upon a transition from acidic to neutral conditions. While complex **13** operates via a very inefficient bimolecular I2M mechanism with a strongly reduced catalytic performance under neutral photocatalytic conditions, a mechanistic switch to a very effective unimolecular WNA mechanism was observed at pH 1, accelerating chemically driven water oxidation with a remarkable TOF of 140 s⁻¹ per Ru unit. Detailed single crystal X-ray analysis of **13** in the Ru^{II} state under neutral conditions and at a predominant Ru^{III} resting state after chemical water oxidation provided conformational insights into the relative spatial orientation of the axial ligand depending on the pH value and into the initial states of O–O bond formation. At pH 7, the conformation is dominated by weak hydrogen bonding interactions between the equatorial bda scaffold and the free bipyridine base, resulting in a fixation of the bda unit inside the macrocyclic cavity that sterically hinders the bimolecular I2M approach and, thereby, limits the activity (Figure 5b). However, protonation of the bipyridine moiety under acidic conditions results in a ligand rotation due to electrostatic repulsion, which confines the active site in an enzyme-like binding pocket (Figure 5c). Three different occupancies of the crystal structure, i.e., initial, approaching, and bonding mode, were observed within the confined cavity at the Ru^{III} state of **13**. Thus, direct structural evidence for a well-defined intracavity water network stabilized by hydrogen bonding interactions to the protonated bipyridine site was provided. Supramolecular preorganization of water molecules close to the seven-coordinated Ru^{III}–OH₂ active site significantly reduces the kinetic barrier for water oxidation and prepares the catalytic system for the subsequent water nucleophilic attack by positioning “ready-to-go” water molecules (Figure 5d–f). These results unequivocally justify our strategy for water

oxidation catalysis by conceptually mimicking the catalytic pocket design of enzymes to promote the preorganization of water molecules in front of the active site, resulting in accelerated O₂ evolution rates that even outperform our previously reported macrocycle **3** (TOF_{Ru} = 50 s⁻¹) and rival the natural archetype OEC-PSII.⁴

5. COVALENT ORGANIC FRAMEWORKS AND HETEROGENEOUS WATER SPLITTING

Splitting water into hydrogen and oxygen provides a very attractive solution for the replacement of harmful fossil fuels with a clean and renewable one. Here, as the most advanced technology, photoelectrochemical cells can directly convert solar energy into electrical energy.⁵⁸ Toward this goal, heterogenization of highly active and robust homogeneous WOCs onto conducting surfaces under formation of molecular hybrid anodes is highly desirable, since their performance is only limited by the total amount of deposited catalyst. In addition to the commonly applied covalent attachment of molecular catalysts onto electrodes,⁵⁹ immobilization of WOCs on graphitic surfaces such as multiwalled carbon nanotubes (MWCNTs) through noncovalent catalyst-surface interactions has emerged as novel supramolecular anchoring strategy.^{40,60} To promote heterogeneous water oxidation catalysis, Ru-based WOCs functioning via a unimolecular WNA mechanism are the preferred candidates as they circumvent any adverse effects associated with restricted mobility.^{1,2}

In a collaborative research project with Llobet and co-workers, linear Ru(bda) oligomer **14a** and trinuclear macrocycle **3** were investigated as molecular catalysts for heterogeneous electrocatalytic water oxidation.^{3,61} Benefiting from noncovalent π – π and CH– π interactions, each catalyst was successfully anchored on MWCNTs and subsequently immobilized as monolayer on glassy carbon electrodes, as evidenced by AFM and electrochemical techniques (Figure 6a,b). The new molecular hybrid anode materials displayed high maximum turnover frequencies of 23 s⁻¹ for macrocycle **3** and 2.3 s⁻¹ for oligomer **14a**, respectively,^{3,61} according to the analysis described by Savéant.^{62,63} Additionally, the foot of the wave analysis (FOWA) revealed TOF_{max} values (maximum turnover frequencies in the limit of an infinite potential) of 3200 s⁻¹ for **3** and 3700 s⁻¹ for **14a**, respectively. Furthermore, there is a high catalytic stability of 1.8 million turnovers for macrocycle **3** without degradation, which is 2 orders of magnitude larger compared to the linear oligomeric material (TON(**14a**) = 94000) and is among the highest values reported so far for Ru WOCs. Detailed electrochemical measurements revealed the generation of catalytically active species for both WOCs after catalyst activation on anodes by repetitive cyclic voltammetry (CV) scans, resulting in exceptionally high current density in the range of 200 mA cm⁻² at a potential of 1.45 V vs NHE. Semiempirical calculations on graphene-like surfaces revealed a Ru-diaqua species as the activated structure for WOCs **3** and **14a**, respectively, that feature a partially de coordinated bda ligand providing additional stabilizing π – π interactions upon surface immobilization. Moreover, the acidic proton environment of the generated Ru-diaqua species facilitates consecutive oxidation to pivotal Ru^V state without additional charge buildup.³ Most recently, based on a straightforward synthesis of tetramer **14b** being end-capped with picoline units an even better WOC performance could be achieved with a TON of 2.0 × 10⁷ and

TOF of 133 s^{-1} ($\text{TOF}_{\text{max}} = 6500 \text{ s}^{-1}$), thereby rivalling the activity of PSII and breaking the ground for a novel structural modification concept to enhance the stability of heterogeneous Ru-WOCs.⁶⁴

To achieve full water splitting in a single nanosystem, the simultaneous H_2 and O_2 evolution could be demonstrated by semiconductor nanocrystals in another collaborative work.⁶⁵ CdS nanorods decorated with Pt nanoparticles for the reductive half-reaction and a molecular Ru water oxidation catalyst anchored onto the nanorods for the oxidative half-reaction provided an efficient nanodevice for visible light-driven photocatalytic water splitting in the absence of any sacrificial reagent.

Fascinating classes of metallosupramolecular architectures constitute three-dimensional (3D) materials such as covalent organic frameworks (COF) and cages, which combine the key advantages of long-range ordered molecular frameworks, namely recyclability, durability and an inherent porosity with the structural accuracy of homogeneous molecular catalysts.⁶⁶ In this regard, we explored two strategies so far. The first one illustrated in Figure 6c is based on water-stable boronate ester cages **15** with high porosity that can embed $\text{Ru}(\text{bda})(\text{pic})_2$ WOCs to afford improved stability and better light-driven water oxidation performance by generating a pseudoheterogeneous environment while retaining their I2M mechanism.⁶⁷ The second illustration depicted in Figure 6d is based on the covalent implementation of molecular $\text{Ru}(\text{bda})$ units into extended 3D COF **16**. Here, a $\text{Ru}(\text{bda})$ -based dialdehyde was utilized as molecular building block to ensure covalent connectivity via reversible imine bonding throughout the interpenetrated network. The cooperative interplay between multiple catalytic sites within the crystalline $\text{Ru}(\text{bda})$ -COF framework enabled the highest catalytic performance for organometallic solid-state materials reported to date with $\text{TON}_{\text{max}} = 11.4$ and $\text{TOF}_{\text{max}} = 0.12 \text{ s}^{-1}$ (recalculated from a monomeric unit for better comparability with the homogeneous systems discussed before). Furthermore, the outstanding catalytic stability and recyclability of the heterogeneous system was showcased by an almost unaltered catalytic performance after several cycles under acidic and neutral conditions.⁶⁸

6. CONCLUDING REMARKS AND OUTLOOK

For a future carbon-neutral and sustainable energy economy based on water-derived green hydrogen, the sluggish oxygen-generating half reaction is considered the main obstacle for the development of artificial photosynthetic devices. In this Account, we have outlined our research efforts on the design of bioinspired metallosupramolecular Ru architectures that promote crucial catalyst-substrate interactions in confined space, resulting in a significant number of state-of-the-art WOCs.

By fine-tuning the second coordination sphere of multi-nuclear assemblies, well-defined hydrogen-bonded water networks can be accommodated in the catalyst's interior of $\text{Ru}(\text{bda})$ macrocycles by cooperative effects between properly arranged multiple catalytic sites, which lowers the activation barrier of proton-coupled electron transfer processes and accelerates catalytic water oxidation via WNA pathway. As a next step, enhanced catalyst-substrate interaction through a preorganized water network was achieved within a designed catalytic binding pocket equipped with a basic recognition site that substantially accelerates the water nucleophilic attack. Moreover, such an internal base can also act as a proton

acceptor to tune the catalytic activity of PCET reactions under neutral conditions. Second coordination sphere engineering also gave rise to novel ligands such as tda (2,2':6',2''-terpyridine-6,6''-dicarboxylate), which afford high performance Ru WOCs due to a dangling proton-accepting carboxylate group, but this highly active state is only attainable in electrocatalysis at neutral or higher pH.⁶⁹

Making use of secondary, noncovalent interactions, our initial endeavors have demonstrated the successful heterogenization of metallosupramolecular macrocycles and oligomers under formation of efficient molecular hybrid materials for electrochemically driven heterogeneous water oxidation. As long-term catalytic stability under highly oxidizing conditions remains critical for future applications, our results on the successful implementation of catalytic Ru units into the interpenetrating network of covalent organic frameworks (COF) and cages have provided recyclable catalytic materials.

While a large variety of WOCs are meanwhile available, their comparison is challenging because their catalytic performance is highly dependent on the environment (solvent composition, pH, concentration, temperature, additives, etc.) and the respective method utilized for the generation of the active state for water oxidation, i.e. chemical, photo- or electrocatalysis which also includes parameters coming from the respective experimental setup. This issue is illustrated by the fact that many catalysts perform well under some conditions but poorly for others. Particularly difficult is the comparison of homogeneous and heterogeneous catalysts. Additionally, the blatant lack of mutual standard procedures for the measurement of catalytic performance in any of the three methods (chemical, photo-, and electrocatalysis) further aggravates this issue. Problems in comparability range from differences in the provided energy, e.g., irradiation of monochromatic light from a laser source or from a solar simulator in photocatalytic experiments or the applied (over)potential in electrocatalysis over the selection of auxiliary components (solvents/electrolytes, sacrificial reagents, photosensitizers, ...) to the calculation methods during data evaluation (e.g., the difference between TOF and TOF_{max} calculated by FOWA in electrocatalysis).⁶⁴ Despite these limitations, the values obtained with the same method can often be compared reasonably. For instance, the activity of several Ru WOCs in chemical catalysis at pH 1 or photocatalysis has been assessed in a recent perspective article.⁷¹ In our own studies described in this Account, we always ensured comparability by using the same setups and comparable conditions. By comparing our Ru WOCs with those reported by other groups we see particular advantages by the fact that our second coordination sphere engineering afforded mostly catalysts operating via the WNA mechanism. This affords high TOFs already at low concentrations, an advantage that becomes immediately apparent under (dilute) photocatalytic conditions, where macrocycle **11** together with a $\text{Ru}(\text{tda})$ catalyst currently perform best.^{38,72} Likewise, among Ru WOCs applied for electrocatalysis linear or cyclic oligomers of $\text{Ru}(\text{tda})$ and $\text{Ru}(\text{bda})$, e.g., **14b**, perform best with regard to TOF, TON, and required overpotential.^{3,60,61,64}

In conclusion, this Account provides guidelines for the rational design of metallosupramolecular architectures to guide the formation of well-defined water networks for the promotion of challenging oxidative water splitting. We envision that the insights into mechanistic pathways for proton-coupled

electron transfer steps outlined in this Account can be extended to other transition metals and various types of catalytic transformations and might be efficiently implemented in solar fuel devices in the future.

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CRedit: **Niklas Noll** conceptualization, writing-original draft; **Frank Würthner** conceptualization, funding acquisition, supervision, writing-review & editing.

Notes

The authors declare no competing financial interest.

Biographies

Niklas Noll studied chemistry at the University of Würzburg and the University of South Carolina (Columbia, SC) funded by the Promos stipend of the German Academic Exchange Service (DAAD). He received his Ph.D. degree at the University of Würzburg under the supervision of Prof. Frank Würthner in 2023. His Ph.D. project was focused on Second Coordination Sphere Engineering in Macrocyclic Ruthenium Water Oxidation Catalysts.

Frank Würthner studied chemistry at the University of Stuttgart and carried out postdoctoral research at MIT (Cambridge, MA) and at the BASF central research laboratories in Ludwigshafen, followed by a habilitation at the University of Ulm (2001). Since 2002, he is a professor at the University of Würzburg. His work encompasses the synthesis of functional dyes, their application in organic electronics, photonics, and photovoltaics, the construction of complex supramolecular architectures composed of π -scaffolds, the mechanistic elucidation of self-assembly pathways, and the investigation of light-induced processes in dye-based nanosystems and photocatalytic water splitting.

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