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Switching the activity of a photoredox catalyst through reversible encapsulation and release†

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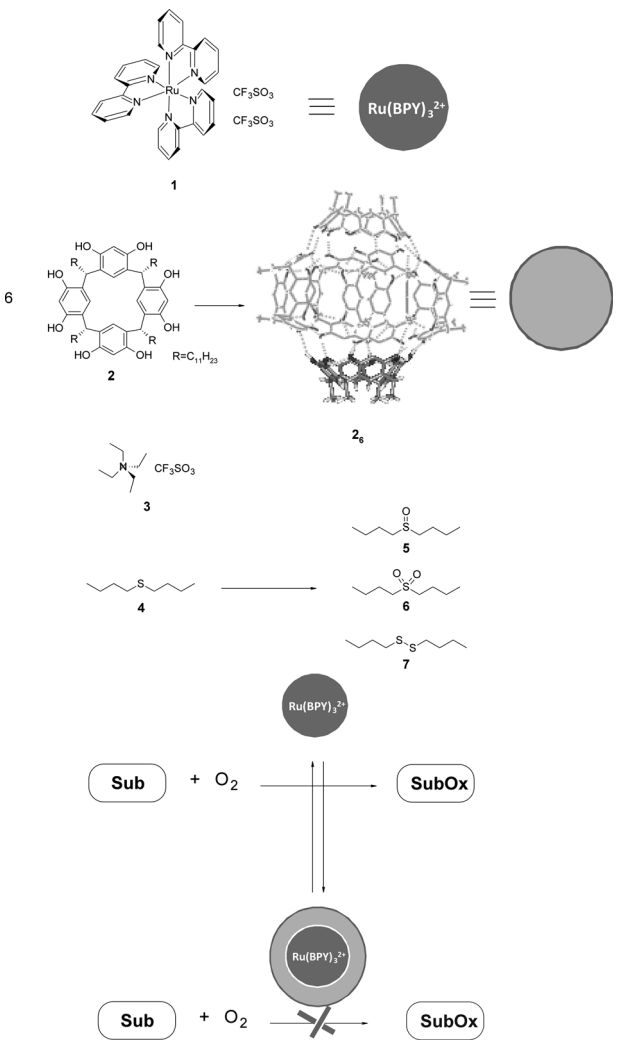
Reversible encapsulation of $[Ru(bpy)_3]^{2+}$ within a self-assembled hexameric resorcin[4]arene capsule turns off the photocatalytic aerobic oxidation of an aliphatic sulfide. Upon addition of a competitive cationic guest, the Ru(II) catalyst is released into solution where its catalytic activity is restored.

In Nature, enzymes catalyze chemical transformations and their activity is finely regulated. Frequently, a series of allosteric effectors are involved that turn on or off the catalytic activity depending on the requirements of the entire organism. In abiotic catalytic systems, allosteric regulation remains a little explored application.[1,2] Regulation has been achieved through precisely defined molecular scaffolds whose conformation and geometry can be controlled by the addition of orthogonal chemical entities.[3] Light of proper wavelength can be used as an alternative effector that enables the function of reversible allosteric synthetic catalytic systems.[4,5]

Here, we present an alternative approach to the modulation of the catalytic activity based on reversible encapsulation. The catalyst is sequestered within a self-assembled host to turn off its action; subsequent release by addition of a competitive guest re-activates the catalyst in the bulk solvent. In order to reduce the concept to practice, several requirements need to be fulfilled: (i) a high binding affinity must exist between the catalyst and the host, (ii) encapsulation must cause the rapid and effective separation of the catalyst from the substrate and (iii) the system must be reversible.

Recently, Zen *et al.*[6] reported the visible light photoredox[7] oxidation of thioethers mediated by the catalytic complex $[Ru(bpy)_3]^{2+}$ **1** through conversion of O_2 into H_2O_2. We envisioned that sequestering the catalyst within a host might lead to controlling its catalytic activity. In contrast to other synthetic allosteric systems, the capsular effector employed acts only as a host, through supramolecular interactions without formation of new covalent bonds. Upon encapsulation of the catalyst, the catalytic activity is switched off but can be reversibly restored by displacement of the catalyst through addition of a competitive guest. Resorcin[4]arene **2** with long alkyl chains is an easily prepared scaffold that spontaneously self-assembles in apolar, water saturated solvents like chloroform and benzene. The assembly is a spherical hexameric capsule $\mathbf{2_6}\cdot(H_2O)_8$ held together by 60 hydrogen bonds (Scheme 1).[8]



Scheme 1 Structure of catalyst **1** $[Ru(bpy)_3]^{2+}(OTf)_2$, resorcin[4]arene **2** and capsule $\mathbf{2_6}\cdot(H_2O)_8$, competitive guest $(NEt_4)(OTf)$ **3**, substrate dibutyl sulfide **4** and oxidation products **5**, **6** and **7**. Schematic representation of the reversible encapsulation of catalyst **1**.

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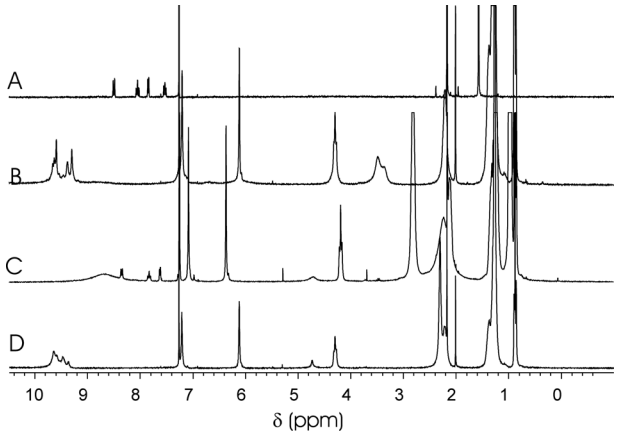

Fig. 1 ^{1}H NMR spectra in chloroform-d: (A) **1** (2.3 mM); (B) **1** (2.3 mM) and **2** (13.8 mM); (C) **1** (2.3 mM), **2** (13.8 mM) and **3** (22.9 mM); (D) **2** (13.8 mM).

The assembly is observed above micromolar concentration and presents a cavity of about 1375 Å^3 that can accommodate six to eight chloroform or benzene solvent molecules[9] or other suitable neutral[10] or cationic species.[11] $[Ru(bpy)_3]^{2+}$ **1** is a pseudo-spherical cationic complex that, if balanced with weakly coordinating anions like triflate, is soluble at low concentration in apolar solvents and can be quantitatively encapsulated within the hexameric capsule $\mathbf{2_6}\cdot(H_2O)_8$.[12] This was shown by ^{1}H NMR as reported in Fig. 1A, where catalyst **1** in chloroform-d presents four resonances in the aromatic region of the spectrum. Upon addition of 6 equivalents of **2** the resonances of the Ru(II) complex completely disappear as a consequence of encapsulation of the metal species (Fig. 1B), while new, extremely weak broad resonances emerge upfield at 6.6 ppm. The encapsulation slightly changes the visible spectrum of **1**. The maximum at 455 nm is shifted by about 8 nm to shorter wavelengths upon addition of the capsule but maintains comparable intensity (see ESI†). This suggests that the encapsulation does not drastically alter the absorption properties of **1**. The catalyst can be released into solution by addition of an excess of a competitive cationic guest[11] such as $(NEt_4)(OTf)$ **3**. As reported in Fig. 1C and D new, downfield resonances appear for the encapsulated tetraethylammonium cation **3**. Concomitantly, free **1** is observed in the aromatic region of the NMR spectrum. The typical resonances and coupling constants are present but at slightly lower chemical shifts than reported in Fig. 1A. This could be due to either weak cation–π interactions between **1** and the external surface of the aromatic capsule $\mathbf{2_6}$ or caused by the increased concentration of ions present in solution. As a confirmation of the release of **1** into solution, the absorption maximum in the UV-VIS spectrum was restored to 453 nm (see ESI†).

Several catalytic tests were performed to show the effect of the encapsulation on the catalytic activity of **1**. Dibutyl sulfide **4** was added (50 eq.) to a solution of **1** (2.3 mM) in chloroform-d at 50 °C under visible light provided by a 120 W lamp under 1 atm. of O_2. The formation of the corresponding dibutyl sulfoxide **5**, sulfone **6** and dibutyl disulfide **7** was monitored over time as reported (Table 1, entry 1). The small amounts of disulfide **7** observed might reasonably derive from a partial CH deprotonation of the intermediate sulfide radical cation, a well-known reaction of these species.[13] After 3 h the sulfoxide **5** was obtained in 32% yield, together with **6** and **7** at 2% and 5% yields, respectively. A catalytic test was repeated with the addition of 6 eq. of **2** (13.8 mM) under identical experimental conditions. Complete inactivity of the catalyst was observed (Table 1, entry 2). Control experiments were carried out under other various experimental conditions (Table 1, entries 3–6) confirming that no oxidation occurred if any one of the species – catalyst, light or O_2 – was missing. Addition of a competitive guest for the capsule like $(NEt_4)(OTf)$ **3** (10 eq. compared to **1**) in the aerobic oxidation by **1** and capsule $\mathbf{2_6}\cdot(H_2O)_8$ led to complete restoration of the catalytic activity (Table 1, entry 7). This was due to displacement of **1** from the cavity of $\mathbf{2_6}\cdot(H_2O)_8$ into solution. Lower amounts of competitive ammonium guest **3** with respect to the catalyst led to incomplete displacement of **1** from the capsule as confirmed by a gradual decrease of the amount of all oxidation products (Table 1, entries 8 and 9). A larger ammonium competitive species such as $(NPr_4)(OTf)$ proved to be a poor competitive guest for the capsule since it did not completely restore the catalytic activity of the catalyst **1** (Table 1, entry 10). The oxidation reaction can be further accelerated by simply decreasing the amount of substrate employed (Table 1, entries 11 and 12). With 4% or 8% mol of the catalyst the reaction was complete within 200 or 100 min, respectively.

Table 1 Catalytic tests for the aerobic oxidation of **4** mediated by **1** and regulated by addition of **2** and competitive guest **3**

#	1	$\mathbf{2_6}$	O_2	$h\nu$	3	**5**^{a} (%)	**6**^{a} (%)	**7**^{a}(%)
1	+	–	+	+	–	32	2	5
2	+	+	+	+	–	0	0	0
3	–	–	+	+	–	0	0	0
4	+	–	–	+	–	0	0	0
5	+	–	+	–	–	0	0	0
6	+	–	+	+	+	36	7	4
7	+	+	+	+	+^{b}	29	1	1
8	+	+	+	+	+^{c}	10	1	1
9	+	+	+	+	+^{d}	5	0	0
10	+	+	+	+	+^{e}	10	1	1
11	+^{f}	–	+	+	–	63	13	8
12	+^{g}	–	+	+	–	79	10	11

Experimental conditions: [**1**] = 2.3 mM, [**2**] = 13.8 mM, [**4**] = 115 mM, chloroform-d 0.5 mL, T = 50 °C, 3 h. +: presence, –: absence. A 120 W halogen lamp was used.^{a} Determined with GC. ^{b} [**3**] = 23 mM (10 eq. with respect to $\mathbf{2_6}$). ^{c} [**3**] = 11.5 mM (5 eq. with respect to $\mathbf{2_6}$). ^{d} [**3**] = 4.6 mM (2 eq. with respect to $\mathbf{2_6}$). ^{e} $[(NPr_4)(OTf)]$ = 23 mM (10 eq. with respect to $\mathbf{2_6}$) was used instead of **3**. ^{f} [**4**] = 57.5 mM. ^{g} [**4**] = 28.8 mM.

Additional experiments were undertaken in order to ascertain the real oxidant species. Addition of 2,6-di-*t*-butylphenol did not suppress catalytic oxidation of **4** by free **1**, thus excluding singlet oxygen formation in solution. The reaction in the absence of **1** and in the presence of 1 equivalent of H_2O_2 with respect to the substrate **4** showed a kinetic profile comparable to that observed with free O_2 and **1** under irradiation, suggesting that H_2O_2 is likely photo-catalytically formed from O_2 by visible light activation of **1**. Iodometric determination of the presence of H_2O_2 of an irradiated solution of **1** with O_2 unfortunately did not provide a clear color change because of interference by the intrinsic UV-Vis absorption of **1**. Overall, in agreement with the mechanism proposed by Zen *et al.*,[6] it is

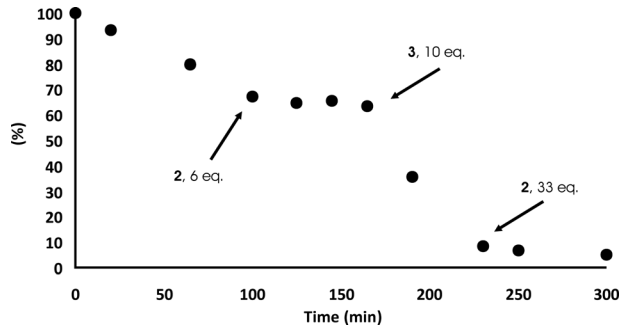

Fig. 2 Variation of the residual sulfide **4** during reversible switching of the photoredox catalytic activity of **1** through sequential additions of **2** (6 eq., 100 min), competitive guest **3** (10 eq., 165 min) and **2** (33 eq., 230 min).

likely that visible light with **1** as a photosensitizer transforms O_2 in the wet solvent employed into H_2O_2 that directly oxidizes the electron rich substrate **4**.

The catalytic system is sensitive to the electron density of the thioether. In fact, after 3 h with methyl phenyl sulfide the reaction provides the corresponding sulfoxide in only 5% yield. This again supports the formation of H_2O_2 as a true oxidant without participation of **1** in the oxygen transfer step.

The reversible control of the catalytic activity of **1** was demonstrated by performing the sulfoxidation experiment described in Fig. 2. The reaction was started following the oxidation of **4** with **1** under visible light with O_2. After 100 minutes 6 eq. of **2** were added to the system leading to the encapsulation of $\mathbf{1}@\mathbf{2_6}\cdot(H_2O)_8$ thus causing a halt of the sulfide consumption and formation of oxidation products. The concentration of the former species remained unchanged until when, after 165 minutes from the beginning of the reaction, 10 eq. of **3** were added leading to release of catalyst **1** into solution, formation of $\mathbf{3}@\mathbf{2_6}$ and consequent restoration of the catalytic activity (Fig. 2). The increased rate of the reaction observed in this second part seems to be related to the presence of an excess of **3** in solution that, as observed in Table 1, entries 1 and 6, slightly promotes oxidation of **4**. A second stopping of the reaction was achieved by addition of a second amount of **2** (33 eq.) after 230 min from the beginning of the reaction. Confinement of the photocatalyst **1** within the supramolecular host $\mathbf{2_6}$ does not alter its absorption properties, therefore the lack of catalytic activity in the presence of the capsule is likely due to the interrupted energy transfer from the Ru(II) center to O_2, the latter probably not being a suitable co-guest for the cavity of $\mathbf{2_6}$, or due to the lack of water within the cavity.[14]

In conclusion, herein we described a new supramolecular method for the reversible modulation of the catalytic activity of a photoredox complex through its reversible encapsulation and release. The photocatalyst is in the on-state as long as it operates free in solution, while it is switched off when sequestered in the self-assembled, hydrogen-bonded capsule. The reversibility of the process is achieved through addition of a suitable competitive guest at proper concentrations.

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