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Flavinium and Alkali Metal Assembly on Sulfated Chitin: A Heterogeneous Supramolecular Catalyst for H₂O₂-Mediated Oxidation

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Dedication ((optional))

Abstract: Heterogeneous multiple catalyst assemblies were developed in which the flavinium cation and Na or Li cations were easily immobilized on a chitin-derived anionic polymeric scaffold via noncovalent ionic interactions. The supramolecular flavinium catalysts were successfully employed for the environment-friendly heterogeneous Baeyer-Villiger oxidation and sulfoxidation by H₂O₂. Owing to the cooperative catalytic effect of flavinium, alkali metal, and sulfated chitin, the supramolecular flavinium assembly showed relatively superior catalytic activity for Baeyer-Villiger oxidation of cyclic ketones in comparison with the corresponding homogeneous flavinium catalyst. Since the ionic assembly was stable under the reaction conditions, the catalyst could be readily recovered by simple filtration and reused.

Immobilization of homogeneous catalysts on polymeric solid supports is a topic of great interest in organic and polymer chemistry since the obtained heterogeneous catalysts offer advantages such as easy separation of the products and catalyst reusability, making a major contribution to green and sustainable chemistry.^[1] However, a frequently observed drawback of the solid-immobilized catalysts is that their catalytic activity is generally lower than that of the corresponding homogeneous system because of the mass transfer limitations. The contribution of homogeneous organocatalysts has increased significantly in past two decades because they can be used for metal-free selective transformations^[2] and for the construction of organo/metal combined catalysts.^[3] However, there are only a limited number of successful examples of immobilized organocatalysts in contrast to similarly immobilized transition metal catalysts.^[4] In general, the organocatalyst is covalently linked to the polymeric support, which requires multiple, time-consuming, expensive synthetic manipulations. An alternative approach involves noncovalent anchoring of the organocatalysts to polymeric supports by utilizing intermolecular ionic interactions,

which allows facile immobilization and thus helps overcome the synthetic drawbacks.^[5] However, very few attempts have been made toward noncovalent immobilization,^[5,6] and it is still a challenge to develop a facile strategy for immobilizing organocatalysts onto polymeric support and enhancing the inherent catalytic activity of the immobilized catalyst.

Supramolecular catalysis, which involves an assembly of multiple catalyst species through weak intermolecular interactions, has recently generated considerable interest as it aims to create enzyme-inspired artificial catalysts with high activity and selectivity.^[7] Taking inspiration from the concept of supramolecular multicomponent catalysis, a novel design strategy for a heterogeneous polymer-immobilized organocatalyst that shows an enhanced catalytic activity owing to the cooperative catalytic effect of three closely situated components has been described in this study. Herein, cationic flavinium and alkali metal assemblies were prepared on anionic sulfated chitin (**sc-1-M**, M = Na or Li, Figure 1) with the aid of noncovalent ionic interactions. The flavinium containing assemblies were employed as a reusable heterogeneous supramolecular catalyst for the Baeyer-Villiger (BV) oxidation of ketones. This catalyst proved to be more efficient than the homogeneous counterpart because of the combination of flavinium, alkali metal, and sulfated chitin.

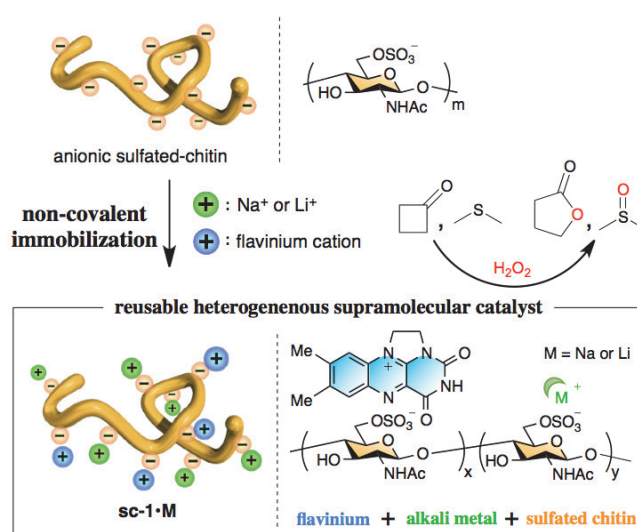


Figure 1. Schematic illustration of the synthesis of supramolecular flavinium catalysts based on sulfated chitin by the non-covalent immobilization method.

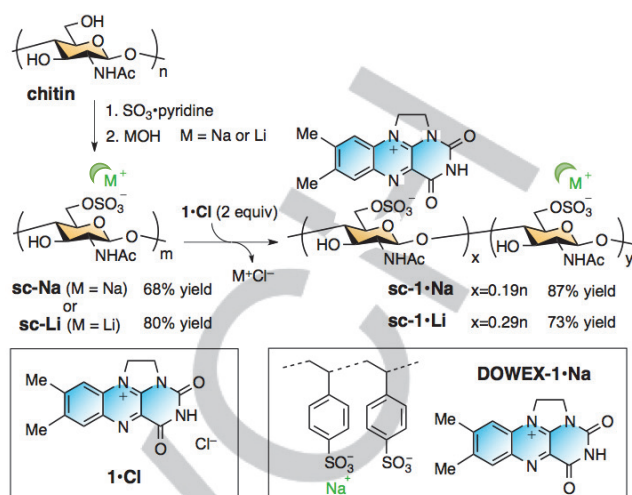
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By mimicking the function of flavin-dependent monooxygenases, a series of cationic flavinium catalysts have been developed, and they now occupy a unique place as organocatalysts for chemoselective oxidation reactions performed under mild conditions using H_2O_2 , which is one of the most inexpensive, non-hazardous, and minimally polluting oxidants.^[8] Therefore, the flavinium catalysts are recognized as an intriguing tool for conducting environmentally benign oxidative transformations such as BV oxidation^[9] and sulfoxidation,^[10] although an example of a reusable polymer-immobilized flavinium catalyst has never been demonstrated. Owing to its easy availability and environmental advantages, a 1,10-bridged-flavinium catalyst (**1•Cl**), which is derived from commercially prepared riboflavin (vitamin B₂), was deemed to be suitable for immobilization.^[11] The 6-O-sulfated chitin, which functioned as a polymeric scaffold for the catalysts, was synthesized by the previously reported selective sulfation of chitin with $\text{SO}_3\cdot\text{pyridine}$,^[12] and subsequent neutralization with NaOH or LiOH afforded the corresponding Na- or Li-assembled sulfated chitin (**sc-Na** or **sc-Li**, Scheme 1). The desired supramolecular catalysts (**sc-1•Na** and **sc-1•Li**) were prepared by an ion exchange reaction of **1•Cl** with **sc-Na** and **sc-Li**, respectively, which were lyophilized from H_2O before use. The ion exchange reaction was carried out under heterogeneous conditions by soaking the lyophilized **sc-Na** or **sc-Li** in a methanol solution of **1•Cl** (3.5 mM, 2 equiv) for 15 min. After collection by filtration and washing with Et_2O , the initial white color of the sulfated chitin turned yellow, indicating complexation with yellow **1** (Figure 2A (a-c)). The obtained supramolecules, **sc-1•Na** and **sc-1•Li**, were insoluble in common organic solvents such as MeOH, EtOH, DMSO, CH_3CN , 1,4-dioxane, THF, EtOAc, Et_2O , hexane, CH_2Cl_2 , and CHCl_3 , but showed moderate solubility in H_2O . This made it possible to estimate the amount of immobilized **1** (degree of immobilization, D.I.) using the solution NMR technique. The NMR spectrum revealed that **sc-1•Na** and **sc-1•Li** had 19% and 29% D.I., respectively. The NMR spectra of **1•Cl**, **sc-Na**, and **sc-1•Na** in D_2O revealed that the immobilization had occurred without any decomposition of the flavinium cation and sulfated chitin (Figure 2B (f-h)). The SEM images of **sc-Na** and **sc-1•Na** revealed that the original three-dimensional sponge-like scaffold of sulfated chitin was unchanged after the immobilization of **1** (Figure 2C).

A major challenge in catalytic BV oxidation is the development of a greener and chemoselective method for ketones containing other functional groups.^[13] For example, it has been difficult to achieve chemoselective BV oxidation of ketones that have carbon-carbon double bonds as this functional group generally undergo epoxidation under the oxidative conditions.^[14] On the other hand, Baeyer-Villiger monooxygenases (BVMOs), which are flavin-dependent enzymes, have been widely employed as biocatalysts because they perform chemoselective BV oxidation of ketones while tolerating the alkene functionality.^[15] Therefore, the catalytic activity of **sc-1•Na** and **sc-1•Li** was investigated for the BV oxidation of substrate **2a** bearing an alkene functionality, where a diluted solution of **2a** in MeOH (0.1 M) was used in the presence of the catalyst (5 mol%) and H_2O_2 (2 equiv) at 25 °C (Table 1). The initial rates of the BV oxidation with the catalyst (v_{obs}) and without the catalyst (v_0) were measured, and the enhancement in the reaction rate in the presence of the catalyst relative to that for the non-catalyzed process (v_{obs}/v_0) was



Scheme 1. Synthesis of **sc-1•Na** and **sc-1•Li** from chitin.

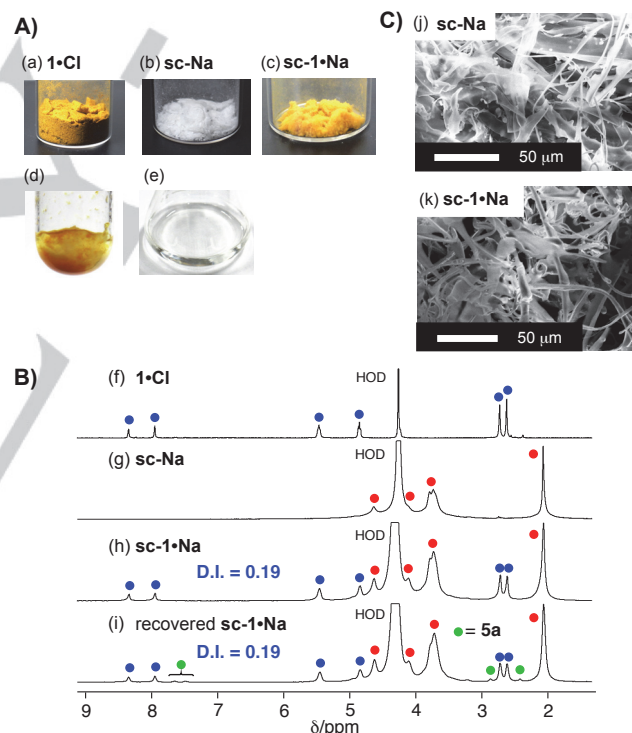


Figure 2. Photographic and SEM images, and ^1H NMR spectra of the prepared catalysts. (A) Photographic images of **1•Cl** (a), **sc-Na** (b), **sc-1•Na** (c), the reaction mixture (d), and filtrate (e) of **sc-1•Na**-catalyzed BV oxidation of **2d** (entry 4 in Table 2). (B) ^1H NMR spectra (500 MHz, D_2O , 80 °C) of **1•Cl** (f), **sc-Na** (g), **sc-1•Na** (h), and **sc-1•Na** recovered after the catalytic sulfoxidation of **4a** (entry 9 in Table 2, i). (C) SEM images of **sc-Na** (j) and **sc-1•Na** (k).

calculated for each catalyst to evaluate their performance. **Sc-1•Na** and **sc-1•Li** successfully catalyzed the chemoselective BV oxidation of **2a** under heterogeneous conditions to give the corresponding lactones (**3a_{major}** and **3a_{minor}**) without the oxidation of the alkene moiety. These supramolecular catalysts apparently

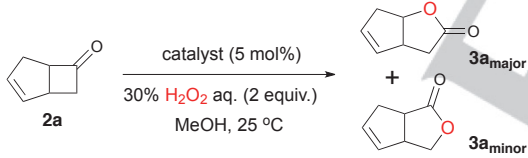
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accelerated the BV oxidation and afforded 39-fold enhancement in v_{obs}/v_0 (entries 1–3, Table 1). These results were a significant improvement as compared to that of the corresponding homogeneous monomeric catalyst **1•Cl** (entries 2–4), even though immobilizing homogeneous catalysts onto solid supports frequently leads to a decrease in the inherent catalytic activity. Thus, the **sc-1•Na**-catalyzed BV oxidation of cyclobutanones (**2a-d**) proceeded smoothly to give the corresponding γ -butyrolactones (**3a-d**) in 72–97% yields (entries 1–4, Table 2).

To explain the enhancement in catalytic activity of **sc-1•Na** and **sc-1•Li**, several comparison experiments were conducted. It was found that **sc-Na** without **1** also accelerated the oxidation reaction by a factor of 3.5 relative to the non-catalyzed process (entry 5), and the v_{obs}/v_0 value increased to 7.9 when Li was used as the counter cation of sulfated chitin (entry 6). A homogeneous system using 1 equiv of NaCl or LiCl complexed with 15-crown 5-ether afforded a weak but apparent catalytic activity ($v_{\text{obs}}/v_0 = 1.8$ or 1.6, entries 7 and 8), probably because the Lewis acid catalysis of the alkali metal cation promoted the electrophilic activation of the carbonyl group. **DOWEX-1•Na**, in which **1** was partially immobilized onto the Na salt of the commercially available cation-exchanging resin (DOWEX, 50Wx8, 100–200 Mesh, Dow Chemical) based on polystyrene sulfonate (Scheme 1, Supporting Information), was also prepared. Using **DOWEX-1•Na** as a catalyst, the v_{obs}/v_0 value was 25, which was worse than the result obtained with **sc-1•Na** (entry 9). This implied a unique positive effect of sulfated chitin on the catalysis of the immobilized **1**. However, the v_{obs}/v_0 value of **DOWEX-1•Na** was better than that

of **1•Cl**, suggesting that a cooperative effect of **1** and Na was operative as these were closely situated on the polymeric scaffold. The importance of the polymeric scaffold fixing **1** and Na was supported by the fact that the homogeneous system of **1•Cl** in the presence of NaCl complexed with 15-crown 5-ether showed 17-fold enhancement as compared to that achieved by using **1•Cl** alone (entry 10). To date, the substrate scope for the conventional artificial flavinium catalysts has been limited to strained cyclobutanones because of their modest oxidizing power,^[9,16] whereas BVMOs can promote the BV oxidation of less-strained five- and six-membered cycloalkanones.^[15] Based on the rationale that the cooperative catalysis of **sc-1•Na** and **sc-1•Li** would enable them to promote the BV oxidation of the relatively less-strained cycloalkanones as well, the oxidation of 2-adamantanone (**2e**) with H_2O_2 was conducted at 70 °C using a series of the catalysts (Table 3). **Sc-1•Na** and **sc-1•Li** successfully catalyzed the BV oxidation of **2e** to afford the corresponding lactone **3e** in good yields, and the former exhibited slightly better activity than the latter (entries 1–3). In contrast, **1•Cl** and **sc-Na** showed hardly any catalytic activity in the BV oxidation (entries 4, 5). The v_{obs}/v_0 value of **sc-1•Na** was ca. 200 times higher than that of the non-catalyzed process and ca. 6 times higher than that of **1•Cl**, clearly indicating the advantage of the present supramolecular immobilization method using sulfated chitin (entries 1, 2, and 4). Thus, the immobilization of **1** on **sc-Na** increased the oxidizing power of **1** and provided the first BVMO-mimicking flavinium catalyst that participated in an efficient BV oxidation of six-membered cycloalkanones (entries 6 and 7 of Table 2). Interestingly, the fine-tuning of the oxidizing power resulted in characteristic selectivity; **sc-1•Na** did not promote the BV oxidation of a less-reactive unsubstituted cyclohexanone (**2g**, entry 8 of Table 2). Contrary to the successful result of chitin-based **sc-1•Na**, polystyrene-based **DOWEX-1•Na** did not exhibit any catalytic potential in the BV oxidation of **2e** (entry 6 of Table 3). The sulfated chitin evidently contributed to the supramolecular catalysis, although its role is not clear at this stage. It is known that the hydroxy group of chitosan is capable of activating the carbonyl groups through the hydrogen bond formation.^[17] As supported by the fact that **sc-Na** showed relatively higher activity than homogeneous Na cation complexed with 15-crown 5-ether (entries 5 and 7, Table 1), the hydroxy and amide pendant groups of the sulfated chitin likely played a role in the activation or trapping of the reagents through hydrogen bonding interactions. Moreover, chitin is known to form a controlled helical structure in the crystalline and solution phases.^[18] Recently, helical polymer-based catalysts have attracted considerable attention because their helical chirality and regularly arrayed structure is useful for designing polymeric catalysts with high enantioselectivity and catalytic activity.^[19] The CD spectrum of **sc-1•Na** film cast on a quartz plate revealed that weak, but apparent induced CD signals at around 400 and 260 nm corresponding to the achiral flavinium cation chromophores (Figure S2, Supporting Information), suggesting that, in **sc-1•Na**, the flavinium and Na cations attached to the side chain are likely ordered along the helical main-chain of the optically active sulfated chitin. Thus, the positive effect of the regularly arrayed **1** and alkali metal cations as well as the hydroxy groups of the sulfated chitin on their cooperative catalysis cannot be ruled out. The catalyst **sc-1•Na** also efficiently performed the chemoselective oxidation of sulfides (**4a-d**) and provided the

Table 1. Observed initial rates and rate enhancement for catalytic BV oxidation of **2a** with H_2O_2 in diluted condition^[a]



Entry	Catalyst	Yield [%] ^[b,c]	v_{obs} [$\mu\text{mol/h}$] ^[c]	v_{obs}/v_0 [^[c,d]]
1	none	0.3	0.80 (= v_0)	—
2	sc-1•Na	15	31	39
3	sc-1•Li	17	31	39
4	1•Cl	10	13	16
5	sc-Na ^[e]	1.1	2.8	3.5
6	sc-Li ^[e]	3.3	6.5	7.9
7	NaCl and 15-crown-5 ^[f]	0.5	1.4	1.8
8	LiCl and 15-crown-5 ^[f]	1.1	1.3	1.6
9	DOWEX-1•Na	11	20	25
10	1•Cl , NaCl, and 15-crown-5	6.2	13	17

[a] Conditions: **2a** (0.1 M), catalyst (5 mol%, based on the flavinium cation), 30% H_2O_2 aq. (2.0 equiv), 1,1,2,2-tetrachloroethane (internal standard, 0.5 equiv), MeOH, 25 °C. Reaction progress was monitored by GC. [b] Total yield of **3a_{major}** and **3a_{minor}** after 1 h. [c] Average of two runs. [d] Reaction rate relative to the non-catalyzed reaction (entry 1). [e] On the basis of the monomer units of the polymer, 0.26 equiv of **sc-Na** or **sc-Li** was used as a catalyst, which is an equimolar amount of **sc-1•Na** (entry 2). [f] NaCl or LiCl (1 equiv) was used along with 15-crown 5-ether (1 equiv).

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Table 2. BV oxidation and sulfoxidation of **2** and **4** catalyzed by **sc-1•Na** in the presence of H₂O₂

BV oxidation ^a					Sulfoxidation ^b				
Entry	Substrate	Product	Time (h)	Yield (%)	Entry	Substrate	Product	Time (h)	Yield (%)
1			3	80 ^c (major : minor = 8 : 1)	9			2	82
2			6	97 (major : minor = 4 : 1)	10			4	80
3			18 (40 °C)	72	11			11	89
4			5	97 ^d	12			9	77
5 (1st reuse)			5	95 ^d	13			2	86 ^{d,f}
6			24	84 ^e	14 (1st reuse)			2	89 ^{d,f}
7			24	88 ^e	15 (2nd reuse)			2	84 ^{d,f}
8			24	<5 ^{d,e}	16 (3rd reuse)			2	88 ^{d,f}
					17 (4th reuse)			2	88 ^{d,f}
					18 (5th reuse)			2	85 ^{d,f}
					19 (6th reuse)			2	80 ^{d,f}
					20 (7th reuse)			2	87 ^{d,f}

[a] Conditions: **2** (0.5 M), **sc-1•Na** (3 mol%, based on the flavinium cation), 30% H₂O₂ aq. (2.0 equiv.), *t*-BuOH, 25 °C. [b] Conditions: **4** (1.0 M), **sc-1•Na** (3 mol%, based on the flavinium cation), 30% H₂O₂ aq. (1.5 equiv.), EtOH, 25 °C. [c] Determined by ¹H NMR. [d] Determined by GC. [e] Conditions: **2** (0.15 M), **sc-1•Na** (10 mol%, based on the flavinium cation), 30% H₂O₂ aq. (2.0 equiv.), *t*-BuOH, 70 °C.

corresponding sulfoxides (**5a-d**) without overoxidation to sulfones (entries 9–12, Table 2, also see Table S1 of Supporting Information).^[20] Owing to the characteristic chemoselectivity of the flavinium catalyst, the carbon-carbon double and triple bonds of **4c** and **4d** were well-tolerated under the present oxidation condition (entries 11 and 12).

The catalytic cycle of **1** under the optimized reaction conditions is shown in Scheme 2A.^[8b,c,21] The flavinium cation **1** is transformed into the oxidatively active hydroperoxyflavin (**1_{OOH}**) species by the nucleophilic addition of H₂O₂, which participates in the monooxygenation of the substrate (S) to give the oxidized product (SO) and hydroxyflavin (**1_{OH}**). This is followed by the transformation of **1_{OH}** into **1** via a dehydration/hydration equilibrium to complete the catalytic cycle. In the catalytic cycle, the environmentally benign H₂O molecule is generated as a solo by-product. While flavinium catalysis is responsible for the oxidative activation of H₂O₂, Lewis acid catalysis of the Na cation

and hydrogen bond catalysis of sulfated chitin play a role in the activation and/or trapping of the ketone (Scheme 2B). Therefore, the closely situated three components of **sc-1•Na** display a unique cooperative catalytic effect that enables an efficient BV oxidation of ketones. It is anticipated that the rate-limiting step in the catalytic cycle of **1** is the addition of H₂O₂ to **1** (Scheme 2A) as the electrophilicity of the 1,10-bridged flavinium cations such as **1** is not high.^[8b,21] Accordingly, it is the cationic form **1** that predominantly exists under the present reaction conditions, whereas the neutral catalytic intermediates such as **1_{OOH}** and **1_{OH}**, that may lead to the dissociation of the flavin catalyst from the anionic polymeric scaffold, are scarcely exited. Indeed, the supramolecular catalysts **sc-1•Na** and **sc-1•Li** were easily separated by simple filtration of the reaction mixture after the reaction without any contamination. The yellow color attributed to dissociated flavin was not observed in the filtrate (Figure 2A(d,e)) and the ¹H NMR spectrum of the recovered **sc-1•Na** revealed no

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decrease in the quantity of immobilized **1** (Figure 2B(i)). Thus, the supramolecular complex **sc-1•Na** functioned without the dissociation of **1** under the present reaction conditions, where cationic **1** was tightly attached to the surface of the anionic sulfated chitin through ionic interactions. The recovered **sc-1•Na** could be reused as a catalyst in the oxidation of **2d** and **4a** without apparent loss of the activity (entries 5 and 13–20, Table 2).

In conclusion, it was found that anionic sulfated chitin could be employed as an effective scaffold for the noncovalent immobilization of multiple catalysts, and the constructed reusable supramolecular catalyst showed superior catalytic activity for BV oxidation with H₂O₂ because of the cooperative catalytic effect of flavinium, alkali metal, and sulfated chitin. The sulfated chitin was readily derived from chitin, which represents the world's second most abundant biopolymer,^[18c-e] and the immobilization of the catalysts onto the scaffold was performed by the facile soaking method. The present methodology presents new avenues to

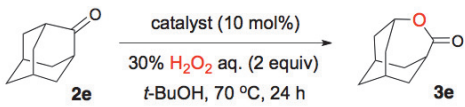
develop a series of heterogeneous supramolecular catalysts for greener and more sustainable processes in organic synthesis.

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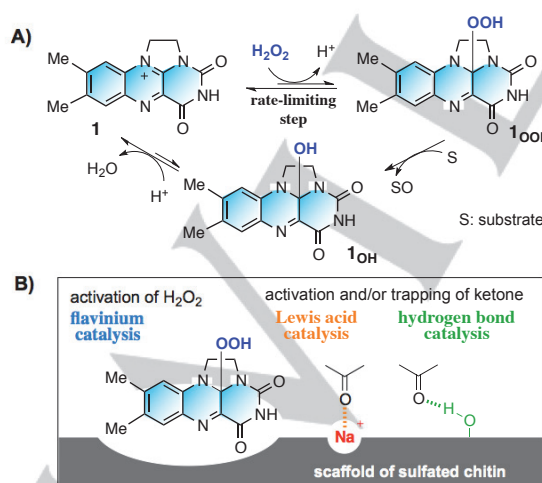
Keywords: flavin • green chemistry • heterogeneous catalysis • oxidation • supramolecular chemistry

Table 3. Catalytic BV oxidation of **2e** with H₂O₂^[a]



Entry	Catalyst	Yield (%) ^[b]	<i>v</i> _{obs} [μmol/h] ^[c]	<i>v</i> _{obs} / <i>v</i> ₀ ^[c,d]
1	none	2.9	0.080	—
2	sc-1•Na	93	16	2.0 × 10 ²
3	sc-1•Li	82		
4	1•Cl	5.0	2.5	31
5	sc-Na ^[e]	5.8		
6	DOWEX-1•Na	9.1		

[a] Conditions: **2e** (0.15 M), catalyst (10 mol%, based on the flavinium cation), 30% H₂O₂ aq. (2.0 equiv), 1,1,2,2-tetrachloroethane (internal standard, 1.7 equiv), *t*-BuOH, 70 °C, 24 h. [b] Yield was determined by ¹H NMR. [c] Average of two runs. [d] Rate relative to the non-catalyzed reaction (entry 1). [e] On the basis of the monomer units of the polymer, 0.59 equiv of **sc-Na** was used as a catalyst, which is an equimolar amount of **sc-1•Na** used in entry 2.



Scheme 2. (A) Proposed mechanism of flavinium catalysis and (B) schematic illustration of cooperative catalysis.

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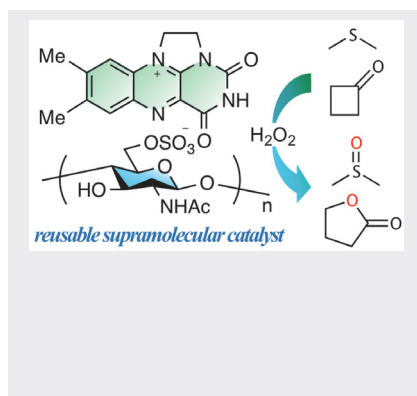
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Heterogeneous multiple catalyst assemblies were developed in which the flavinium cation and Na or Li cations were easily immobilized on a chitin-derived anionic polymeric scaffold via noncovalent ionic interactions. Owing to the cooperative catalysis of flavinium, alkali metal, and sulfated chitin, the supramolecular flavinium assembly showed relatively superior catalytic activity for heterogeneous Baeyer-Villiger oxidation of cyclic ketones in comparison with the corresponding homogeneous flavinium catalyst.



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Flavinium and Alkali Metal Assembly on Sulfated Chitin: A Heterogeneous Supramolecular Catalyst for H₂O₂-Mediated Oxidation