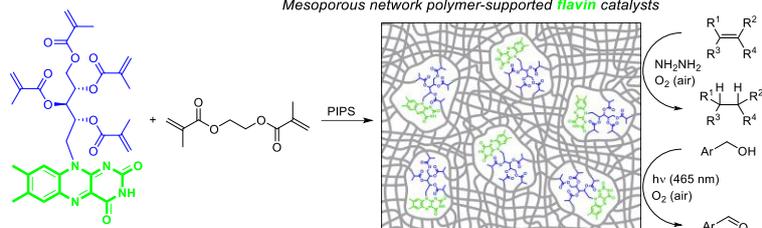# Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Preparation of Flavin-Containing Mesoporous Network Polymers and Their Catalysis

Leave this area blank for abstract info.

Yukihiro Arakawa, Fumiaki Sato, Kenta Ariki, Keiji Minagawa, Yasushi Imada*

Mesoporous network polymer-supported *flavin* catalysts

Preparation of Flavin-Containing Mesoporous Network Polymers and Their Catalysis

Yukihiro Arakawa[a], Fumiaki Sato[a], Kenta Ariki[a], Keiji Minagawa[a,b] and Yasushi Imada[a, *]

[a]Department of Applied Chemistry, Tokushima University, Minamijosanjima, Tokushima 770-8506
[b]Institute of Liberal Arts and Sciences, Tokushima University, Minamijosanjima, Tokushima 770-8502

ARTICLE INFO

ABSTRACT

Riboflavin tetramethacrylate (RFlTMA) was prepared as a flavin monomer and copolymerized with ethylene glycol dimethacrylate (EGDMA) under polymerization-induced phase separation conditions. The resulting flavin-containing mesoporous network polymer, poly(RFlTMA-*co*-EGDMA), was found to be a more effective catalyst than riboflavin tetraacetate (RFlTA), a soluble analogue, for aerobic hydrogenation of olefins despite its heterogeneity, which allowed for its multiple recovery and reuse through simple filtrations and washings without loss in catalytic activity. In addition, the polymeric flavin was demonstrated to be utilized also as an effective photocatalyst in the oxidation of benzyl alcohols.

A variety of natural flavoenzymes catalyses, such as monooxygenase catalysis and DNA photolyase catalysis, have inspired chemists to develop metal-free thermal redox and photoredox reactions catalyzed by simple flavin molecules [1]. For instance, we have so far developed some flavin-catalyzed aerobic oxidation reactions including sulfoxidation [2a,2e], amine oxidation [2e], Baeyer-Villiger reaction [2a,2d,2f], and hydrogenation of olefins with hydrazine [2b,2c] under environmentally friendly conditions. Recently, we extended our attention to the immobilization of flavin catalysts onto a synthetic polymer to improve their practicability and reported highly reusable poly(styrene-*co*-divinylbenzene)-supported flavin catalysts for the aerobic reduction of olefins, which was the first example of immobilizing a flavin catalyst onto insoluble supports via covalent bond [3].

In this article, we present a new type of flavin catalyst supported on a mesoporous network polymer. Mesoporous network polymers are attractive supports to immobilize low-molecular-weight catalysts because of their robustness, insolubility, and high surface area, which can be prepared using well-established polymerization-induced phase separation (PIPS) technique [4]. We have prepared a flavin-containing mesoporous network polymer by copolymerization of ethylene glycol dimethacylate (EGDMA) and riboflavin tetramethacrylate (RFlTMA) under PIPS conditions and explored its thermal redox and photoredox catalytic activities.
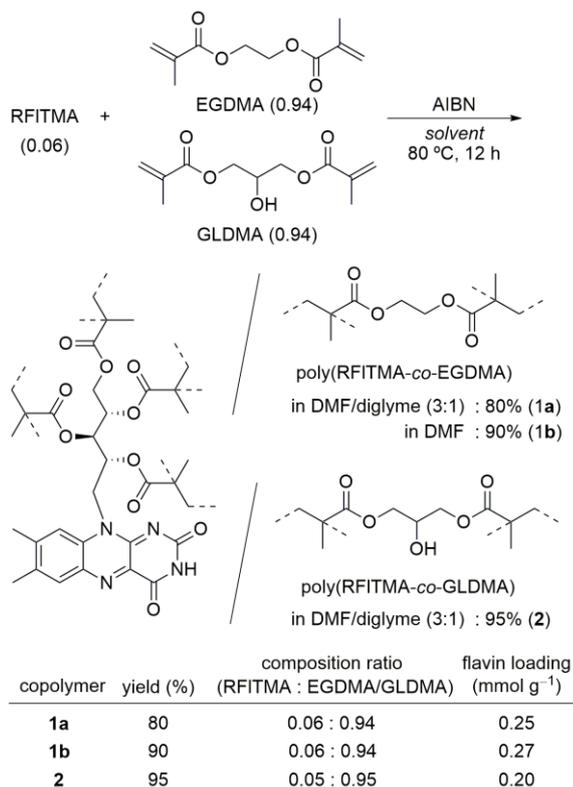
Riboflavin (Vitamin B$_2$) is readily available in commerce and its tetraacylated derivatives, such as riboflavin tetraacetate (RFlTA), can be readily synthesized in a single step [2b,5].

* Corresponding author. e-mail: imada@tokushima-u.ac.jp
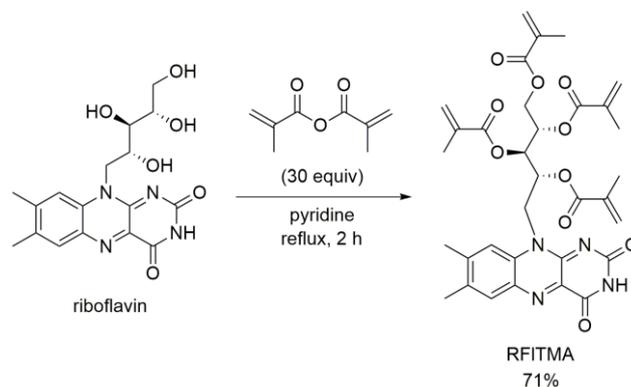
Figure 1. Preparation of RFlTMA.

Thereupon we designed RFlTMA as a new flavin-containing monomer, which was successfully prepared by the reaction of riboflavin with methacrylic anhydride in pyridine under reflux conditions (Figure 1). According to the PIPS technique reported previously [4], RFlTMA was then copolymerized with EGDMA (RFlTMA : EGDMA = 0.06 : 0.94) using 2,2'-azobis(isobutyronitrile) (AIBN) as an initiator in DMF/diglyme (3:1) under heating and inert conditions (Figure 2). The copolymerization proceeded smoothly and the resulting gel was crushed and washed well with THF, methanol, and diethyl ether and dried *in vacuo* to give a bright yellow copolymer, poly(RFlTMA-*co*-EGDMA) (**1a**), in 80% yield. The flavin loading of poly(RFlTMA-*co*-EGDMA) was estimated to be 0.25 mmol g^{-1} from its nitrogen content determined by elemental
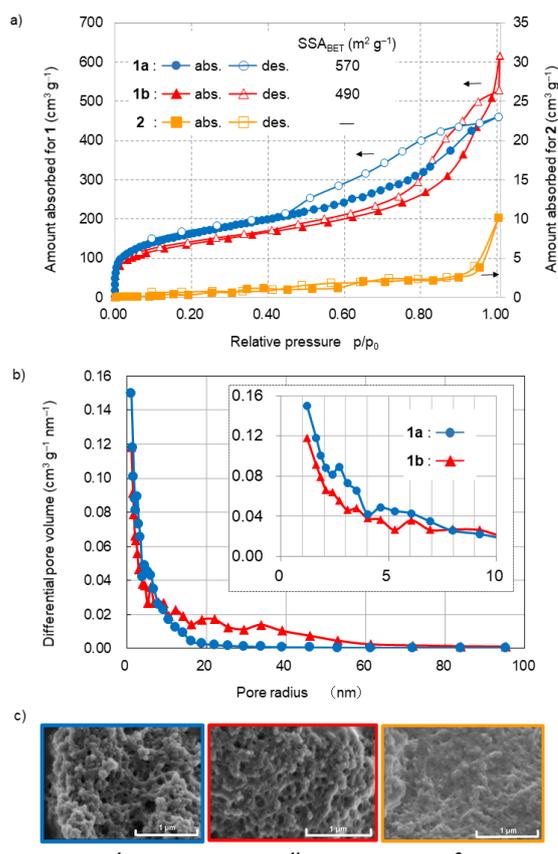
Figure 2. Synthesis of poly(RFlTMA-*co*-EGDMA) and poly(RFlTMA-*co*-GLDMA).

copolymer	yield (%)	composition ratio (RFITMA : EGDMA/GLDMA)	flavin loading (mmol g^{-1})
1a	80	0.06 : 0.94	0.25
1b	90	0.06 : 0.94	0.27
2	95	0.05 : 0.95	0.20

Figure 3. Characterization of **1a**, **1b**, and **2**: (a) nitrogen absorption isotherms at 77 K and the resulting specific surface area determined by the BET method (SSA$_{BET}$), (b) pore size distributions calculated by the DH method, (c) SEM images.

Figure 4. Flavin-catalyzed aerobic reduction of **3a** to **4a**: (a) comparison of yields between catalytic reactions and a blank reaction, (b) catalyst recovery and reuse protocol (left) and reusability of **1a** (right).

analysis. The actual CHN content of poly(RFlTMA-*co*-EGDMA) was in good agreement with the theoretical value, indicating that the present copolymerization took place according to the feed molar ratio. A strong fluorescence emission peak at around 540 nm was observed in solid state of **1a** ($\Phi = 0.124$), indicating that flavin units could be dispersed to the polymer network rather homogeneously, while RFlTMA showed little emission in its solid state ($\Phi = 0.007$) due to concentration quenching (see supporting information). For comparison, the same copolymerization was carried out in DMF in the absence of diglyme that is known to assist PIPS, which afforded another poly(RFlTMA-*co*-EGDMA) (**1b**, 0.27 mmol g^{-1}) in 90% yield through the same work up (Figure 2). Furthermore, we were also interested in using glycerol dimethacrylate (GLDMA) instead of EGDMA because of the additional hydroxyl functionality, so that the corresponding copolymerization was performed according to the procedure that was used for preparing **1a**, providing an orange copolymer, poly(RFlTMA-*co*-GLDMA) (**2**, 0.20 mmol g^{-1}), in 95% yield (Figure 2).

The flavin-containing copolymers **1a**, **1b**, and **2** were further characterized to evaluate their meso-porosity. Specific surface area as well as pore size distribution were estimated by nitrogen absorption and desorption isotherm measurement and analysis, which revealed that **1a** and **1b** could have the BET specific surface area (SSA$_{BET}$) of 570 m^2 g^{-1} and 490 m^2 g^{-1}, respectively, while the surface area of **2** was not measurable due to significantly low N$_2$ absorption volumes in the isotherm measurement (Figure 3a). Pore size distributions for **1a** and **1b** were plotted by the DH method [6], which suggested that both have a high mesopore ratio (pore diameters between 2–50 nm) and also that the size of the mesopores could be better controlled in **1a** than **1b** (Figure 3b). Not only the larger SSA$_{BET}$ but also the better control of mesopore size in **1a** may be attributed to the positive effect of diglyme on PIPS in their synthesis (Figure 2). The surfaces of **1a**, **1b**, and **2** were then visualized in scanning
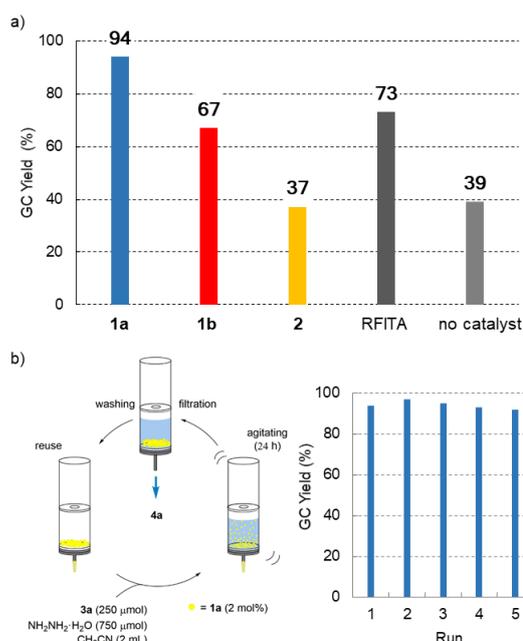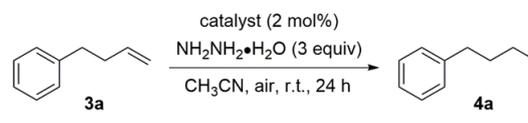
electron microscope (SEM), from which numerous small cavities were clearly observed only in **1a** and **1b** (Figure 3c). In addition, the degrees of swelling of **1a**, **1b**, and **2** in acetonitrile, the solvent used for catalytic reactions mentioned later, were found to be 290%, 250%, and 110%, respectively (see supporting information), which suggested the specific surface area of **1a** would become highest also in acetonitrile.

We then evaluated the catalytic activities of **1a**, **1b**, and **2** in the aerobic hydrogenation of olefins with hydrazine that was previously developed by us as one of the unique flavin-catalyzed thermal reactions [2b,2c]. 4-Phenyl-1-butene (**3a**) was chosen as a test substrate and reactions were carried out with 3 equivalents of hydrazine monohydrate to the substrate in acetonitrile under air at room temperature in the presence of 2 mol% of either **1a**, **1b**, or **2** for 24 hours. For comparison, the reaction in the presence of RFlTA as a soluble catalyst and that in the absence of any catalysts were also conducted under otherwise identical conditions that were previously developed by us for the reaction catalyzed by soluble flavin molecules.[2b] As expected, the best catalytic activity and the highest yield (94%) of butylbenzene (**4a**) were observed in the heterogeneous reaction system with **1a**, which was even better than that observed in the homogeneous system with RFlTA (Figure 4a). The catalytic activity over the homogeneous system may be attributed to the controlled mesoporosity as well as well-dispersed flavin molecules on the support, successfully suppressing self-quenching of redox-active flavin species. Reusability of the catalyst **1a** was tested through the simplified catalyst recycling process using a filter-equipped glass reactor as previously reported.[3,7] which demonstrated that **1a** could be reused without loss in the activity at least 5 times (Figure 4b).

**Table 1.** Aerobic reduction catalyzed by **1a**.[a]

Entry	Substrate	Product	Yield (%)[b]
1	**3b**	**4b**	95
2	**3c**	**4c**	96
3	**3d**	**4d**	74
4	**3e**	**4e**	53
5[c]	**3f**	**4f**	76

[a] Reactions were performed using 250 μmol of the olefin and 750 μmol of hydrazine monohydrate in 2 mL of acetonitrile in the presence of 2 mol% of **1a** under air at room temperature.
[b] Determined by ^{1}H NMR measurement with internal standard.
[c] 1.5 mmol of hydrazine monohydrate was used.

Table 2. Photooxidation of 4-methoxybenzyl alcohol.[a]
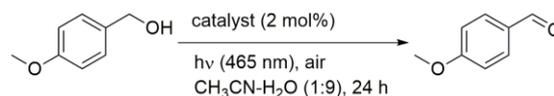
Entry	Catalyst	Yield (%)[b]
1	**1a**	92
2	RFlTMA	51
3	—	0
4[c]	**1a**	0

[a] Reactions were performed with 0.4 mmol of the substrate in a mixture of acetonitrile and water (1:9) in the presence of 2 mol% of a catalyst under air and blue LED light irradiation.
[b] Determined by GC analysis.
[c] Without light irradiation.

We furthermore verified the utility of **1a** in the aerobic hydrogenation of other alkene/alkyne substrates under the above conditions (Table 1). The reduction of 1-decene (**3b**) to 1-decane (**4b**) smoothly proceeded in 95% yield (entry 1). The alkene moiety within 1,2-epoxy-9-decene (**3c**) was selectively hydrogenated to give 1,2-epoxydecane (**4c**) in 96% yield without ring opening of the epoxide moiety (entry 2). Although the catalytic activity was found to somewhat diminish in the presence of coordinating functional groups, the desired reactions still occurred with moderate to high yields. For example, allyl phenyl sulfide (**3d**) was selectively reduced to phenyl *n*-propyl sulfide (**4d**) in 74% yield without oxidation of the sulfide group (entry 3), which is valuable because such a sulfur-containing substrate hardly undergoes hydrogenation under conventional transition metal-based conditions. In addition, 2-allylphenol (**3e**) was converted into 2-propylphenol (**4e**) with a yield of 53% under identical conditions (entry 4), whereas 1-octyn-3-ol (**3f**) underwent hydrogenation twice to 3-octanol (**4f**) in 76% yield when 6 equivalents of hydrazine monohydrate were used (entry 5).

Finally, we preliminarily explored whether the flavin-containing mesoporous polymer **1a** could also work as an effective photocatalyst (Table 2). On the basis of conditions previously reported,[5m,8] a solution of 4-methoxybenzyl alcohol in a mixture of acetonitrile and water (1:9) was shaken and irradiated with blue LED light (465 nm) under air in the presence of 2 mol% of **1a**, which provided 4-methoxybenzaldehyde in 92% yield after 24 hours (entry 1). Under identical conditions, the use of RFlTMA instead of **1a** resulted in a lower yield of the product (51%, entry 2). No reaction was observed without any catalysts or without light irradiation (entries 3 and 4). These results indicate the potential effectiveness of immobilized catalysts with such a high meso-porosity in the photo-induced flavin catalyses [5].

In summary we introduced a flavin-containing mesoporous network polymer, poly(RFlTMA-*co*-EGDMA), that was prepared by copolymerization of RFlTMA, a novel flavin-containing multi-vinyl monomer, with EGDMA under PIPS conditions. Characterizations of poly(RFlTMA-*co*-EGDMA) by elemental analysis, absorption and desorption isotherm analysis, and SEM analysis showed its high meso-porosity. Poly(RFlTMA-*co*-EGDMA) exhibited high catalytic activities comparable with low-molecular-weight flavin catalysts in aerobic hydrogenation of olefins as well as photooxidation of benzyl alcohols, which was readily recovered by filtration and reused without a loss in activity.

References and notes

[1] a) H. Iida, Y. Imada, S.-I. Murahashi, Org. Biomol. Chem. 13 (2015) 7599–7613;
b) R. Cibulka, Eur. J. Org. Chem. 2015 (2015) 915–932;
c) G. de Gonzalo, M. W. Fraaije, ChemCatChem 5 (2013) 403–415;
d) Y. Imada, T. Naota, Chem. Rec. 7 (2007) 354–361.

[2] a) Y. Arakawa, K. Yamanomoto, H. Kita, K. Minagawa, M. Tanaka, N. Haraguchi, S. Itsuno, Y. Imada, Chem. Sci. 8 (2017) 5468–5475;
b) Y. Imada, T. Kitagawa, T. Ohno, H. Iida, T. Naota, Org. Lett. 12 (2010) 32–35;
c) Y. Imada, H. Iida, T. Naota, J. Am. Chem. Soc. 127 (2005) 14544–14545;
d) Y. Imada, H. Iida, S.-I. Murahashi, T. Naota, Angew. Chem. Int. Ed. 44 (2005) 1704–1706;
e) Y. Imada, H. Iida, S. Ono, S.-I. Murahashi, J. Am. Chem. Soc. 125 (2003) 2868–2869;
f) S.-I. Murahashi, S. Ono, Y. Imada, Angew. Chem. Int. Ed. 41 (2002) 2366–2368.

[3] Y. Arakawa, R. Kawachi, Y. Tezuka, K. Minagawa, Y. Imada, J. Polym. Sci. Part A: Polym. Chem. 55 (2017) 1706–1713.

[4] S. Ogasawara, S. Kato, J. Am. Chem. Soc. 132 (2010) 4608–4613.

[5] For selected studies that utilize riboflavin or RFlTA as a catalyst, see:
a) N. P. Ramirez, B. König, J. C. Gonzalez-Gomez, Org. Lett. 21 (2019) 1368–1373;
b) G. Tang, Z. Gong, W. Han, X. Sun, Tetrahedron Lett. 59 (2018) 658–662;
c) T. Morack, J. B. Metternich, R. Gilmour, Org. Lett. 20 (2018) 1316–1319;
d) M. März, M. Kohout, T. Neveselý, J. Chudoba, D. Prukała, S. Niziński, M. Sikorski, G. Burdziński, R. Cibulka, Org. Biomol. Chem. 16 (2018) 6809–6817;
e) J. B. Metternich, D. G. Artiukhin, M. C. Holland, M. von Bremen-Kühne, J. Neugebauer, R. Gilmour, J. Org. Chem. 82 (2017) 9955–9977;
f) R. Martinez-Haya, M. A. Miranda, M. L. Marin, Eur. J. Org. Chem. 2017 (2017) 2164–2169;
g) B. Muhldorf, R. Wolf, ChemCatChem 9 (2017) 920–923;
h) J. B. Metternich, R. Gilmour, J. Am. Chem. Soc. 138 (2016) 1040–1045;
i) T. Neveselý, E. Svobodová, J. Chudoba, M. Sikorski, R. Cibulka, Adv. Synth. Catal. 358 (2016) 1654–1663;
j) T. Hering, B. Mühldorf, R. Wolf, B. König, Angew. Chem. Int. Ed. 55 (2016) 5342–5345;
k) B. Mühldorf, R. Wolf, Angew. Chem. Int. Ed. 55 (2016) 427–430;
l) J. B. Metternich, R. Gilmour, J. Am. Chem. Soc. 137 (2015) 11254–11257;
m) C. Feldmeier, H. Bartling, K. Magerl, R. M. Gschwind, Angew. Chem. Int. Ed. 54 (2015) 1347–1351;
n) J. Dad'ová, E. Svobodová, M. Sikorski, B. König, R. Cibulka, ChemCatChem 4 (2012) 620–623.

[6] D. Dollimore, G. R. Heal, J. Appl. Chem. 109 (1964) 109–114.

[7] Y. Arakawa, M. Wiesner, H. Wennemers, Adv. Synth. Catal. 353 (2011) 1201–1206.

[8] a) J. Svoboda, H. Schmaderer, B. König, Chem. Eur. J. 14 (2008) 1854–1865;
b) H. Schmaderer, P. Hilgers, R. Lechner, B. König, Adv. Synth. Catal. 351 (2009) 163–174.

Appendix A. Summlementary data

Supplementary data to this article can be found online at https://....