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Non-covalently dendronized flavins as organocatalysts for aerobic reduction of olefins

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ABSTRACT

A variety of association complexes of synthetic flavin with diaminopyridine and melamine receptors are described in terms of synthesis, association properties, and catalytic activities for aerobic hydrogenation of olefins. The 1:1 association complex of lumiflavin **1** with 2,6-bis(acylamino)pyridine receptor bearing 3,4,5-trialkoxybenzyl ether dendron unit **2** acts as an efficient supramolecular organocatalyst for the aerobic reduction of styrene at ambient temperature under atmospheric air pressure.

1. Introduction

Flavin is a model compound of various flavin-containing oxidases[1] and monooxygenases[2] that has attracted much attention as an environmentally benign organocatalyst for aerobic oxidative organic transformations.[3,4] Fig. 1 shows a common catalytic cycle for aerobic oxidative transformation with flavoenzymes and synthetic flavins. Reduction of oxidized flavin (Fl_{ox}) to the reduced flavin (Fl_{red}) and subsequent O_2 incorporation affords 4a-hydrodioxyflavin (FlOOH). This species undergoes dissociation of H_2O_2 or oxygen transfer to substrates (S) to regenerate Fl_{ox}. Oxidases employ the first dehydrogenation process as a crucial step for oxidative transformation.[1] Simulation of these enzymatic functions with neutral[5] and cationic[6] flavin catalysts provides the dehydrogenative transformation of alcohols,[5a,b,e] amines,[5e,6a] hydrazines,[6b] thiols,[5c,d] NADH model compounds,[5d] and nitroalkanes.[5c] Monooxygenases promote oxygen transfer to the substrate with FlOOH.[2] The aerobic oxygenation of various heteroatom compounds including amines,[7a,c] sulfides,[7a,c] and ketones[7b] can be also performed using this catalytic process with the synthetic flavin catalysts under O_2 atmospheric pressure.

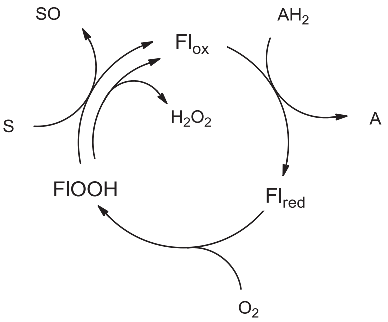

Fig. 1. Catalytic cycle for oxidative transformations with flavoenzymes and synthetic flavins.

In 2005, we reported that a series of synthetic flavins act as efficient catalysts for generation of the reducing agent diimide NH=NH,[8] using these aerobic and anaerobic processes for the oxidation of hydrazine. This principle can be applied to provide a convenient method for the aerobic reduction of olefins that proceeds under mild conditions of 1 atm of molecular oxygen or air (Eq. 1).[9] The catalytic hydrogenation of olefins can be performed with a small amount of hydrazine, 1 atm of O_2 or air, and an organocatalyst, to produce water and nitrogen gas as the sole waste products. This is a useful alternative to transition-metal catalysts and H_2 gas[10] with

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respect to atom efficiency and safety. As part of our program, which is aimed at the formation of new organic functional materials, we have investigated the development of efficient organocatalysts enhanced by molecular association and aggregation. Association complexes of neutral flavins with 2,6-bis(acylamino)pyridines bearing poly(benzyl ether) dendron units act as efficient supramolecular organocatalysts for aerobic reduction.[9c]

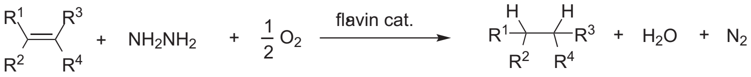
In an attempt to produce novel enzyme-like catalytic functions, we have been investigating the association properties and catalytic activities of new supramolecular flavin complexes with a variety of 2,6-bis(acylamino)pyridine and melamine (1,3,5-triazine-2,4,6-triamine) receptors. This has lead to association complexes of lumiflavin (**1**) with 2,6-bis(acylamino)pyridine doubly-linked to a poly(3,4,5-trisubstituted benzyl ether)dendron unit bearing long alkoxy chains as terminal groups (**2**), which are efficient supramolecular organocatalysts for the aerobic oxidation of olefins. The catalytic activity is much higher than those of non-associated **1** or its association complexes with non-dendronized receptors **3**–**5** (Scheme 1). This is a rare example of an organocatalyst that is enhanced by the hydrogen-bonding association of organic molecules, although a variety of metallic[11] and non-metallic dendrimers[12] have been widely used as catalysts for organic transformation. Rotello and colleagues reported that neutral flavins covalently linked to a benzyl ether dendron unit at the 3-position exhibit high catalytic activity for the aerobic oxidation of 1-benzyl-1,4-dihydronicotinamide in water.[13] The present strategy is an alternative, unique supramolecular approach to the development of next-generation artificial flavoenzymes. In this paper, we describe the full details of the synthesis and characterization of the supramolecular flavin complexes, with focus on the dynamic association behavior and catalytic activity for the aerobic reduction of olefins in air under mild conditions.

2. Results and discussion

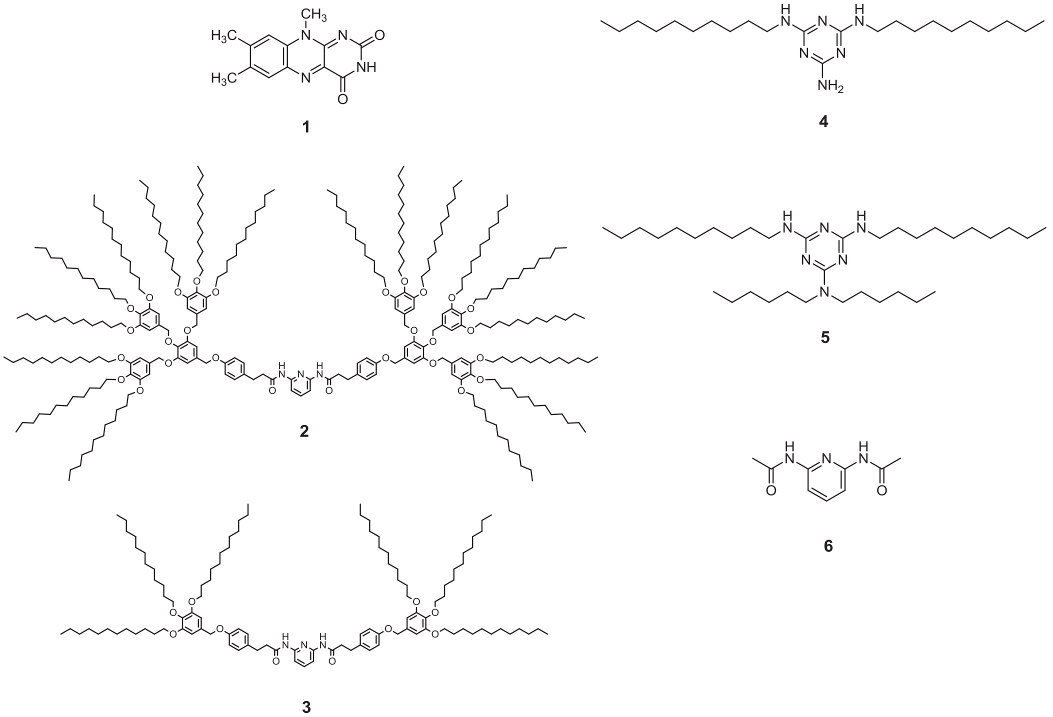
2.1. Synthesis and characterization of association complexes of lumiflavin

The synthetic routes to 2,6-diaminopyridines **2** and **3**, and to melamine derivatives **4** and **5** are shown in Fig. 2. Dendronized bis(acylamino)pyridine **2** and its non-dendronized analogue **3** were prepared by the reaction of 2,6-bis[3-(4-hydroxyphenyl)propanoylamino]pyridine (**9**) with the corresponding dendritic and nondendritic 3,4,5-trisubstituted benzyl halides (**8** and **7**), respectively, in the presence of K_2CO_3 in acetone. *N*^{2},*N*^{4}-Didecyl-1,3,5-triazine-2,4,6-triamine (**4**) was prepared by the reaction of 2,4,6-trichloro-1,3,5-triazine (**10**) with decylamine and subsequent amination of the resulting 6-chloro-*N*^{2},*N*^{4}-didecyl-1,3,5-triazine-2,4-diamine (**11**) with ammonium hydroxide in aqueous solution. *N*^{2},*N*^{4}-Didecyl-*N*^{6},*N*^{6}-dihexyl-1,3,5-triazine-2,4,6-triamine (**5**) was prepared by amination of **11** with dihexylamine.

The association properties of lumiflavin **1** with receptors **2**–**5** and 2,6-bis(acetylamino)pyridine (**6**) were examined in $CDCl_3$ using ^1H NMR (270 MHz) analysis. Job's plots for the association of **1** with **4** indicated that flavin **1** forms a 1:1 complex with 2,6-diaminopyridine receptors (Fig. 3). The association constants K_a for complexes **1**·**2**, **1**·**3**, **1**·**4**, and **1**·**5** in $CDCl_3$ at 303 K were determined to be 306, 341, and 387, and 30 M^{-1}, respectively, on the basis of the concentration dependence of the ^1H NMR chemical shift of the N(3)H proton signal (Fig. 4). The K_a values for receptors **2**–**4** are in the range of 306–387 M^{-1}, which are similar to that with less bulky receptor **6** (437 M^{-1}).[9c] This result strongly suggests that lumiflavin **1** is sufficiently associated with these receptors via typical 3-point hydrogen bonding, as shown in Scheme 2. It is reasonable to assume that asymmetrical didodecylaminotriazine **4**



$$\underset{R^2\ \ R^4}{\overset{R^1\ \ R^3}{C{=}C}} + NH_2NH_2 + \frac{1}{2}O_2 \xrightarrow{\text{flavin cat.}} R^1R^2CH{-}CHR^3R^4 + H_2O + N_2 \tag{1}$$



Scheme 1. Lumiflavin **1** and receptors **2**–**6**.