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Enhanced catalytic decomposition of a phosphate triester by modularly accessible bimetallic porphyrin dyads and dimers†

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A series of metalloporphyrin dimers were modularly prepared and shown to catalyze the methanolysis of a phosphate triester, yielding rates that are large compared to the rate of the uncatalyzed reaction. Up to 1300-fold rate acceleration can be achieved *via* a combination of cavity-localized Lewis-acid activation and methoxide-induced methanolysis.

Cofacial porphyrin assemblies[1] have attracted great attention over the past several decades due to their unusual photophysical properties,[2] a coordination environment that can accommodate two or more metal centers,[3] and structural rigidity.[4] Of particular interest to us is the design of assemblies suitable for applications involving molecular recognition[5] and catalysis.[1] In such cases, manipulating the distance between two or more porphyrin entities can afford cavities with differing shapes and sizes that are capable of recognizing and transforming small-molecule substrates.[6] In deploying cofacial multiporphyrin architectures, two metal centers can be exploited in a cooperative fashion to increase the rate of bimolecular reaction,[1,6] as is often observed in biological systems. Additionally, careful cavity design can yield bio-inspired structures with catalytic behavior and potency reminiscent of enzymes, without being constrained by biological operating conditions.

Many porphyrin-based supramolecular catalysts have taken advantage of the axial ligation ability of metalloporphyrins to position reactive moieties in close proximity within a cavity, thereby reducing the entropic barrier for the ensuing reaction.[7] Surprisingly, non-directive interactions such as van der Waals forces and solvophobic effects, which are highly prevalent in biological systems, have rarely been explored.[8] Given the broad range of substituents available in the synthetic chemistry of porphyrins, the periphery of assemblies can readily be tuned to provide attractive environments for both hydrophobic and hydrophilic reactants. Thus, we set out to explore the use of these non-covalent interactions for the solvolysis of phosphate triesters, a process that has important implications in the decomposition of biologically relevant phosphate diesters[9] as well as the degradation of toxic organophosphate-based nerve agents.[10] As a model, we selected a cyclic cofacial porphyrin dimer that would allow us to approximate the action of phosphotriesterases (PTEs), whose active sites comprise two zinc ions: one coordinates the substrate and the other delivers a coordinated hydroxide to induce hydrolysis (Fig. 1, left).[11] We reasoned that related bis-porphyrin assemblies could, in principle, bind and activate an organophosphate substrate at one metal site, while simultaneously delivering a methoxide nucleophile from the second in a cooperative fashion (Fig. 1, right). In polar media, a hydrophobic organophosphate substrate could also be driven to interact favorably with the highly hydrophobic porphyrinic cavity, further enhancing substrate binding. Together, these interactions could serve to bring an organophosphate sufficiently close to a nucleophilic methoxide ion to catalyze substrate solvolysis within the cavity.

In designing cyclic porphyrin dyads and dimers, we wanted to explore, *via* the incorporation of different bimetallic arrangements into the hydrophobic porphyrinic cavity, how the local reaction environment—and especially its propensity for catalysis—could be tuned. While phosphotriesterases employ Zn^{II} ions to deliver a nucleophilic hydroxide to the substrate,[11] the dianionic environment of the porphyrin ligand does not permit such a feature in our design. As such, we incorporated Al^{III}, which can accommodate an anionic methoxide ligand as the nucleophile. By manipulating the porphyrin

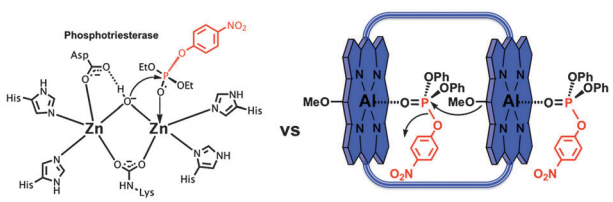

Fig. 1 Degradation of a phosphate triester in the active site of a phosphotriesterase enzyme[11] (left) and proposed catalytic methanolysis of a phosphate triester in an Al porphyrin dimer.

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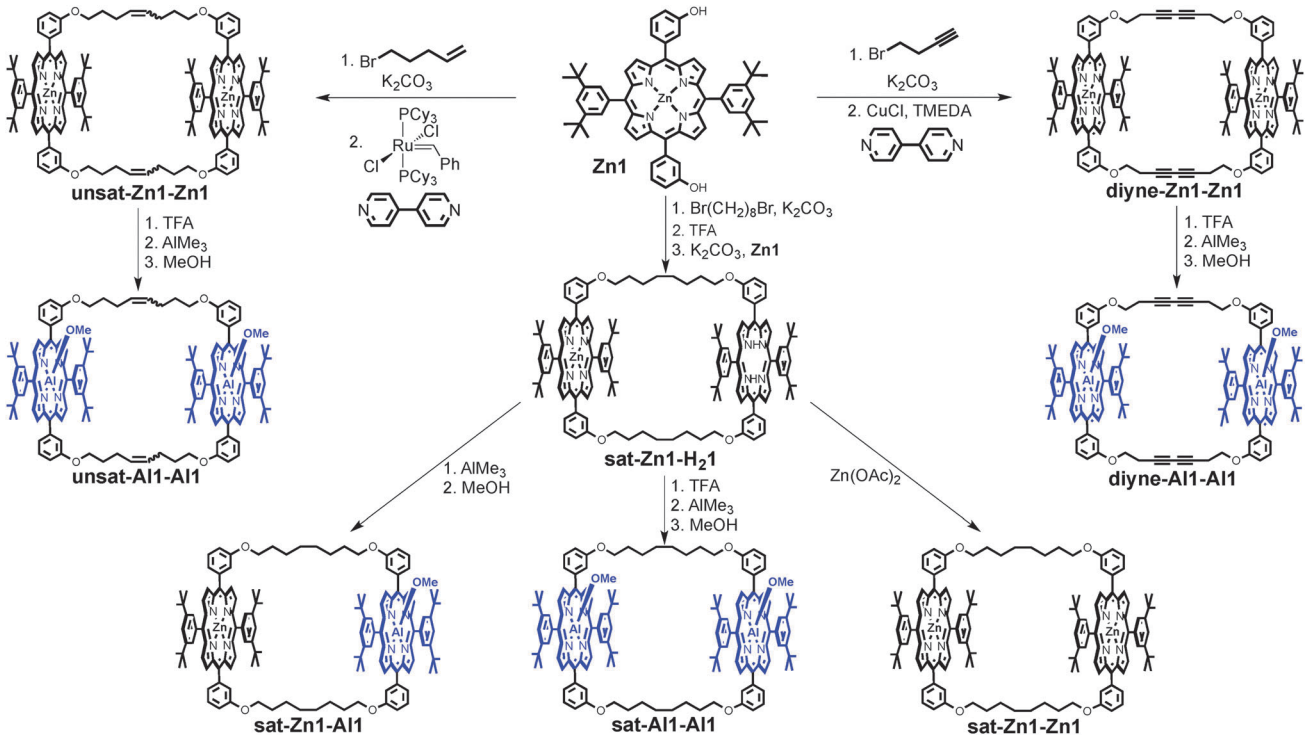


Scheme 1 Modular synthesis of catalytic porphyrin dimers starting from the same starting porphyrin monomer, **Zn1**.

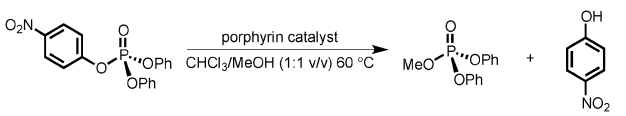
substituents, the electronic environment can be further adjusted to simultaneously enhance the nucleophilicity of this methoxide for catalysis as well as the Lewis acidity of the metal center.

To accommodate the aforementioned criteria, we designed a series of porphyrin dyads and dimers that we envisioned would be readily attainable from a single zinc–porphyrin monomer, **Zn1**, in a highly modular fashion. After quantitative olefin functionalization, **Zn1** can be converted to the unsaturated dimer **unsat-Zn1–Zn1** in good yield (84%) through a one-step templated ring-closing metathesis reaction (tRCM), a strategy previously employed by our group[12] and others[13] (Scheme 1, left path). Demetallation of **unsat-Zn1–Zn1** with trifluoroacetic acid (TFA) gives the free-base dimer, which is readily remetallated with $AlMe_3$ to provide **unsat-Al1–Al1** in quantitative yield.

The fully saturated monozincated porphyrin dyad **sat-Zn1–$H_2$1** can also be readily obtained from **Zn1** in good yield in 3 steps (Scheme 1, middle path). This mixed porphyrin synthetic strategy allows ready access to heterobimetallic porphyrin dyads containing various **Zn1–M1** combinations. As above, the free-base porphyrin component can be metallated with $AlMe_3$ to afford **sat-Zn1–Al1** in quantitative yield without transmetallation. Alternatively, **sat-Zn1–$H_2$1** can be demetallated with TFA and remetallated to give the homobimetallic **sat-Zn1–Zn1** or **sat-Al1–Al1** species. Finally, the more rigid diacetylene-linked dimer, **diyne–Zn1–Zn1**, can be obtained from **Zn1** through a templated Glaser–Hay coupling and can be readily modified to provide **diyne–Al1–Al1**. Our design allows for the modular synthesis of *eight* distinct robust cyclic multiporphyrin assemblies from a single porphyrin in *five or fewer steps*. The result is a series of hollow supramolecular metalloporphyrin assemblies with tunable metal environments and degrees of rigidity that can be employed for the catalytic solvolysis of phosphate triesters.

The methanolysis of *p*-nitrophenyl diphenyl phosphate (PNPDPP), a common simulant for toxic nerve agents,[14] is enhanced by all of the bimetallic porphyrin assemblies (Table 1). As expected, significantly enhanced rates were observed when the porphyrin catalysts contained Al–OMe centers as compared to the Zn-containing catalysts. The most active catalyst, **diyne–Al1–Al1**, enhances the rate of methanolysis by ~225-fold rate relative to the uncatalyzed process, and by ~14-fold relative to **sat-Zn1–Zn1**, the least potent of the six bimetallic catalysts. The rigidity of the linker has a moderate, but noticeable, effect on the catalysis rate, with the most rigid dimer, **diyne–Al1–Al1**, showing a 2.2-fold enhancement over the flexible **sat-Al1–Al1** dimer. That the Zn dimers show ~3-fold enhanced catalysis rates compared to the Zn

Table 1 Observed initial rates (through 10% conversion) for the methanolysis of PNPDPP (25 mM) with 3 mol% porphyrin catalyst



Entry	Catalyst	Observed rate/M s^{-1}	Relative rate *vs.* uncat. reaction
1	**sat-Zn1–Zn1**	1.47×10^{-8}	16
2	**unsat-Zn1–Zn1**	1.53×10^{-8}	17
3	**sat-Zn1–Al1**	6.03×10^{-8}	66
4	**sat-Al1–Al1**	9.51×10^{-8}	104
5	**unsat-Al1–Al1**	1.69×10^{-7}	184
6	**diyne–Al1–Al1**	2.05×10^{-7}	224

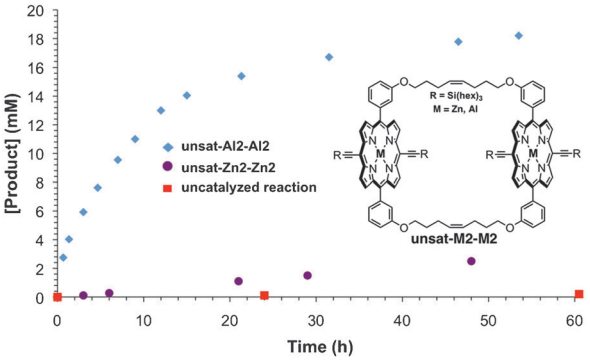


Fig. 2 Reaction profiles for the methanolysis of PNPDPP carried out in the absence or presence of 3 mol% of **unsat-Al2–Al2** or **unsat-Zn2–Zn2**.

monomer, which in turn is 5 times faster than the uncatalyzed reaction, points to the advantage of having Lewis acid activation and cavity encapsulation operating in concert. Lewis acid activation is clearly essential for catalysis, as the free base dimer, **unsat-$H_2$1–$H_2$1**, only elicits a reaction rate similar to that for the uncatalyzed reaction.

The importance of having cavity-localized methoxide nucleophiles is clearly demonstrated by the increased reaction rates observed when the Zn centers in **sat-Zn1–Zn1** are successively replaced with Al–OMe groups (Table 1, *cf*. entries 1, 3, and 4). Thus, we were intrigued about the possibility of tuning the electronic properties of the metalloporphyrin to further enhance the nucleophilicity of the methoxide ions and catalysis. To accomplish this, we replaced the 3,5-di-^{t}butyl aryl substituents on **unsat-Al1–Al1** with Si(hex)$_3$-protected alkynyl groups (Fig. 2). We reasoned that the delocalization of the porphyrin electron density into a silyl-protected acetylene would better stabilize partial positive charge on the Al center, making it more Lewis acidic and the $^-$OMe anion more nucleophilic,[15] both of which would enhance catalysis. Indeed, CHELPG calculations show that the partial charge separation between Al and OMe is greater for a porphyrin bearing 10,20-(C$\equiv$CSi(hex)$_3$) groups ($^-$OMe: -0.653 e, Al: 1.248 e) compared to an analogous porphyrin with 3,5-di-^{t}butyl aryl substituents ($^-$OMe: -0.645 e, Al: 1.189 e).

As shown in Fig. 2, **unsat-Al2–Al2** is highly active for the methanolysis of PNPDPP, engendering a rate that is over 1300 times the uncatalyzed rate and $\sim$7 times faster than **unsat-Al1–Al1**. Along with a stronger $^-$OMe nucleophile, the highly Lewis acidic Al–OMe centers in **unsat-Al2–Al2** bind PNPDPP more effectively, as observed from the 2-fold binding constant increase of PNPDPP in **unsat-Al2–Al2** (49 M^{-1}) over **unsat-Al1–Al1** (25 M^{-1}). Moreover, the presence of a solvophobic encapsulation effect for PNPDPP is clearly demonstrated by both Zn and Al dimers, which bind PNPDPP in 1 : 1 v/v $CHCl_3$/MeOH at concentrations 15–50 times higher than expected statistically (Section XII in ESI†).

In summary, we have demonstrated that covalently linked hollow metalloporphyrin dimers possessing tunable Lewis acidic metal sites can significantly increase the rate of methanolysis of the nerve agent simulant PNPDPP. While the absolute turnover numbers are still quite modest when directly compared to the k_{cat}'s reported for PTEs,[11] the advantage of our highly modular synthetic approach is its facile scope for tuning the many design parameters available, thus influencing the catalytic rate in a single synthetic enzyme cavity. For our small dimers, where a 1 : 1 substrate/cavity binding stoichiometry was observed (Section XII in ESI†),[16] the most critical factors for enhanced catalysis are Lewis acid activation and the presence of Al–OMe centers (Sections IX and XII in ESI†). This combination of supramolecular encapsulation and activation resembles the molecular organization features in some enzymes and points to the vast potential that mimicking biological designs can bring to supramolecular catalysis, without being limited by the narrow activity range defined by biological pHs.[10]

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