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Catalytic Rigid-Rod β-Barrels with Hydrazide Cofactors to Convert Poor Substrates as Hydrazone Conjugates

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Abstract: The usefulness of pyrene-1,3,6-trisulfonates as cofactors for *p*-octiphenyl β-barrel ion channels to mediate recognition and conversion of otherwise inaccessible benzaldehyde substrates is described.

Keywords: β-Barrels · Bioorganic chemistry · Enzyme mimics · Ion channels · Molecular recognition

The fact that supramolecule **1** catalyzes the hydrolysis of amide **2** rather than ester **3** may deserve some comments (Fig. 1) [1]. In traditional enzyme mimics that operate with hydrophobic binding pockets in water, hydrophobic substrates like **3** should be preferred over hydrophilic substrates like **2** in the same way that the hydrolysis of an ester is preferred over that of an amide. Barrel-stave supramolecule **1**, however, is not a traditional enzyme mimic. It is a rigid-rod β-barrel with a hydrophobic outer surface (provided by leucine residues) and a hydrophilic inner surface (provided by partially protonated histidine residues) [2]. In water, rigid-rod β-barrel **1** exists – like certain biogenic β-barrel pores – as a slightly soluble prepore that inserts spontaneously into bilayer membranes to form active pores. In contrast to biogenic (pre)pores, however, the central channel of synthetic β-barrel **1** is decorated with catalytic histidine residues. Hydrophilic, preferably anionic substrates like amide **2** are, therefore, recognized and converted within this water-filled, cationic, catalytic channel. Hydrophobic substrates like *p*-acetoxybenzaldehyde **3**, however, may bind nonspecifically either to the outer barrel surface or, if present, to the bilayer membrane, in any case far from the internal active sites of catalyst **1**.

Molecular recognition of neighboring, protonated histidines on one face of an antiparallel β-sheet by pyrene-1,3,6-trisulfonates (as in **2**) turned out to be a particularly powerful strategy to initiate catalysis within barrel **1**. We speculated, therefore, that temporary attachment of pyrene-1,3,6-trisulfonate 'cofactors' would drag unwilling substrates like **3** into the catalytic interior of barrel **1** as well.

To test this hypothesis, 'cascade blue' hydrazide **4** was selected as cofactor of choice (Fig. 2). Reaction with aldehydes like **3** gives hydrazones like **5** as substrate-

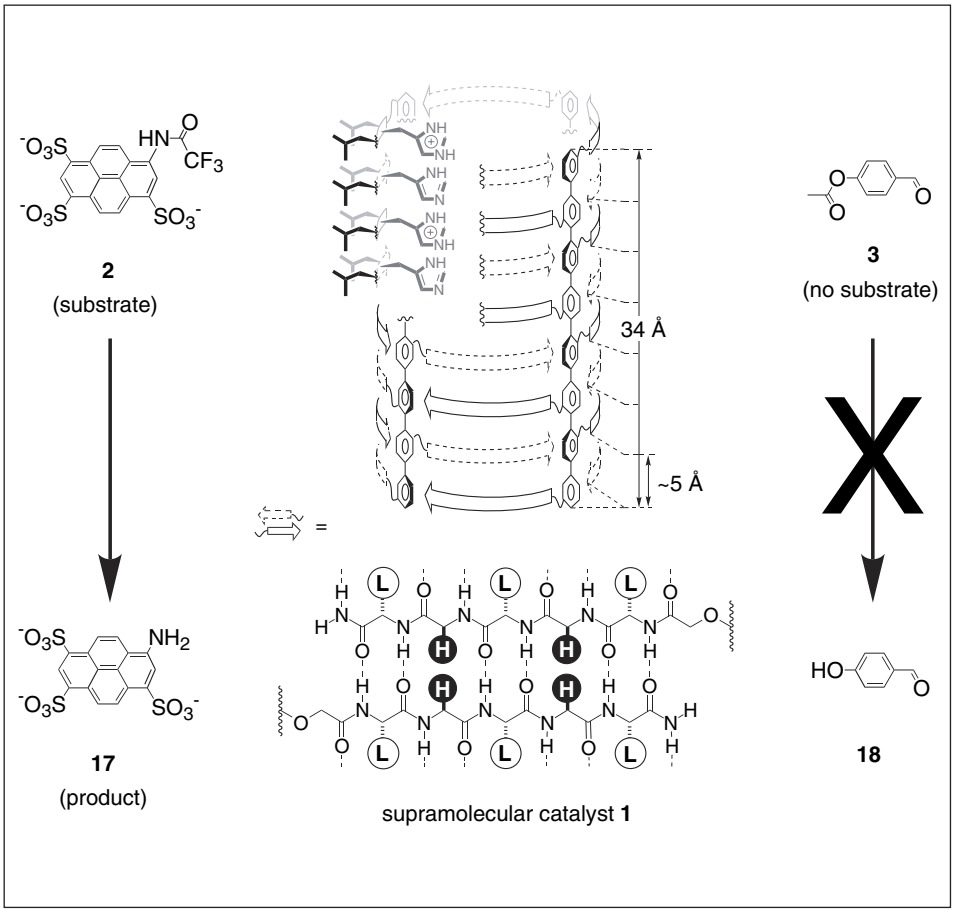

Fig. 1. Why does rigid-rod β-barrel **1** catalyze the hydrolysis of amide **2** but not that of ester **3**?

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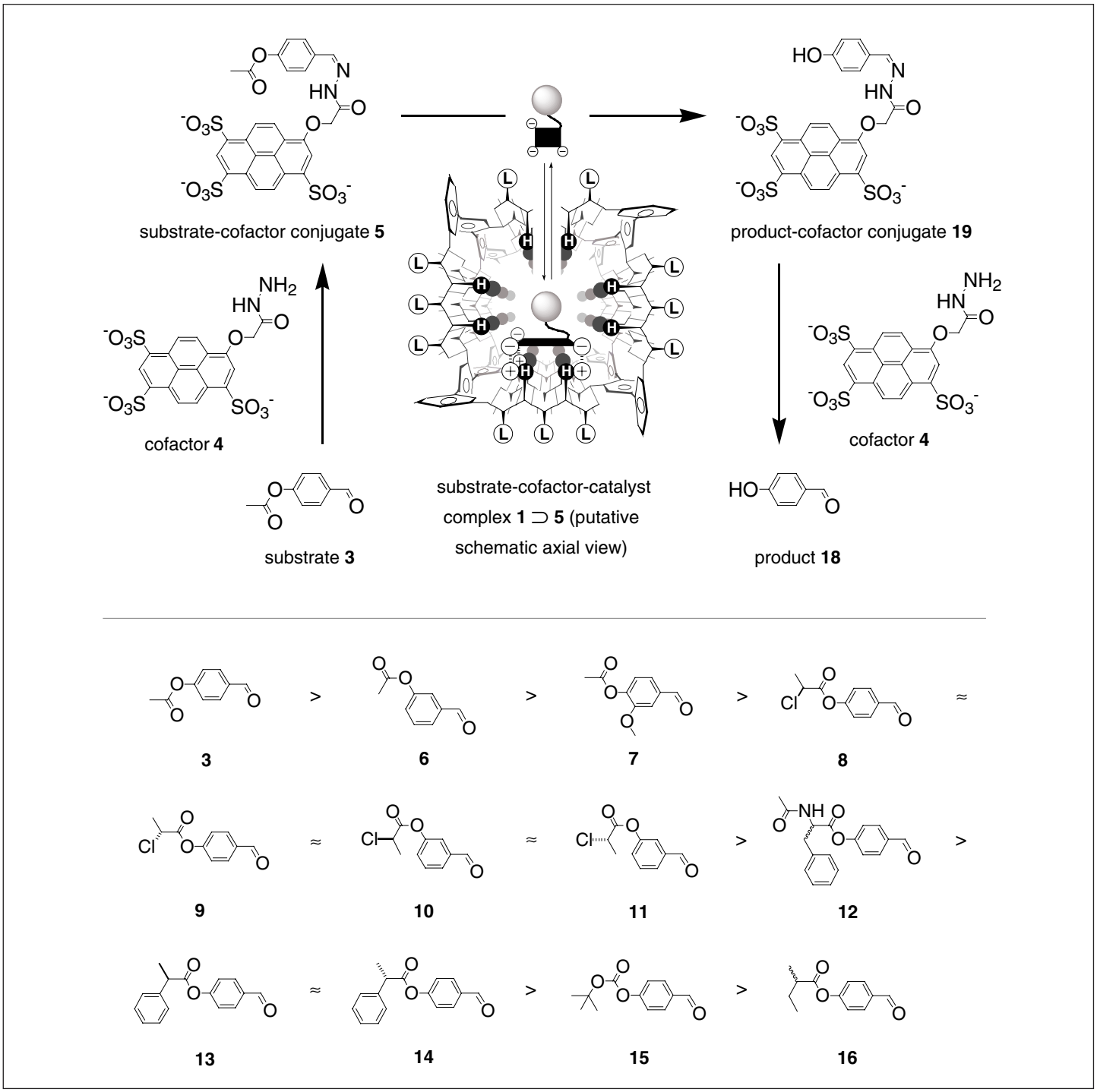

Fig. 2. Top: No problem in catalyzing the esterolysis of substrate **3** as substrate-cofactor conjugate **5** within β-barrel **1** (compare Fig. 1); Bottom: Substrates for β-barrel **1** accessible with cofactor **4.**

cofactor conjugates that are stable under acidic conditions (like pH 5.5 which is optimal for catalysis within barrel **1**) but instable in basic water. In the presence of barrel **1**, the esterolysis of hydrazone **5** was indeed more than 100'000-fold accelerated. Esterolysis of substrates **6**–**16** as substrate-cofactor conjugates demonstrated general applicability of cofactor **4**. Not surprisingly limitations emerged with increasing substrate hydrophobicity (because of external rather than internal binding and micellization of overly amphiphilic substrate-cofactor conjugates), increasing substrate size (because of hindered access to the confined interior), and with regard to negligible enantioselectivity (because of high internal symmetry). Preliminary results indicate that – consistent with the expected mode of action – replacement of every second histidine within barrel **1** by an arginine does not substantially influence catalytic efficiency. The introduction of versatile cofactors as well as insights on active site modification and substrate diversity are expected to facilitate ongoing efforts to couple ion channel and catalytic activity of synthetic multifunctional pores.

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[1] A. Som, S. Matile, *Eur. J. Org. Chem.* **2002**, 3874–3883.
[2] Y. Baudry, B. Baumeister, G. Das, D. Gerard, S. Matile, N. Sakai, A. Som, N. Sordé, P. Talukdar, *Chimia* **2002**, *56,* 667–671.