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Bioorganic Chemistry of Rigid-Rod Molecules: Adventures with *p*-Oligophenyls

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Abstract: Studies on the usefulness of rigid-rod molecules to address pertinent questions of biological relevance are summarized. Emphasis is placed on (a) the supramolecular functional plasticity of *p*-octiphenyl β-barrels expressed in molecular recognition (adaptable synthetic hosts), molecular translocation (adaptable synthetic ion channels) and molecular transformation (esterases, RNases), (b) molecular recognition of polarized membranes by rigid push-pull rods, as well as (c) the synthetic organic chemistry of rigid-rod molecules.

Keywords: Antibiotics · β-Barrels · Enzyme mimics · Ion channels · Molecular recognition · Sensors

The research theme of *the Matile group* is to explore the usefulness of rigid-rod molecules in bioorganic chemistry. *p*-Oligophenyls were selected as model rods to initially limit the overwhelming scope of this novel theme in bioorganic chemistry. These *p*-oligophenyls were synthesized to verify, in many variations, the captivating promise of bioorganic chemistry of rigid-rod molecules, *i.e.* that minimized molar entropy with regard to axial deflection and compression will maximize the preorganization of supramolecular architecture in complex systems. Several aspects of bioorganic chemistry of rigid-rod molecules have been reviewed previously [1–4].

Rigid-rod β-barrels have evolved as an important research topic from early studies on one-dimensional hydrogen-bonded chains [5] and cation-π 'slides' [6] established along *p*-oligophenyl scaffolds to selectively transport protons and potassium cations across bilayer membranes [1][7]. The general structure **1** of these barrel-stave supramolecules [2] is shown in Fig. 1.

Rigid-rod β-barrels **1** are synthesized by conventional coupling of the N-terminus of short peptides with lateral carboxylates placed along the rigid scaffold in *p*-octiphenyl **2**. The yield of this reaction varies as the physical properties of the *p*-octiphenyl octapeptides **3** vary with each peptide sequence. Intermolecular interdigitation of the peptide strands in monomers **3** to form antiparallel β-sheets and cylindrical self-assembly directed by the non-planar arene-arene torsions in the *p*-oligophenyl 'stave' yields rigid-rod β-barrels **1**.

The discovery of this versatile synthetic route to the otherwise poorly accessible β-barrel tertiary structure was the starting point to exploit the inherent *functional plasticity* [2] of this motif beyond pure peptide chemistry [8–23] (Fig. 2). The *structural plasticity* of rigid-rod β-barrels with regard to both barrel length and barrel diameter has been reviewed in an earlier special issue of CHIMIA [3].

The functional plasticity of rigid-rod β-barrels **1** is designed based on a very simple, general and reliable correlation between the chemical nature of barrel interior and exterior on the one hand and peptide primary structure *ABCDEF* on the other. Namely, the formation of antiparallel β-sheets firmly orients the amino acid side chains *BDF* and *CE* in opposite directions. The graphical illustration of this rigid topology in Fig. 2 exemplifies the HL-repeat in rigid-rod β-barrel **1c**. Preferential peripheral crowding during cylindrical self-assembly of β-sheets into *p*-oligophenyl β-barrels finally places residues *BDF* at the outer and residues *CE* at the inner barrel surface.

All functions of rigid-rod β-barrels known today have been designed according to this binary correlation between primary and tertiary structure. In general, water-sol-

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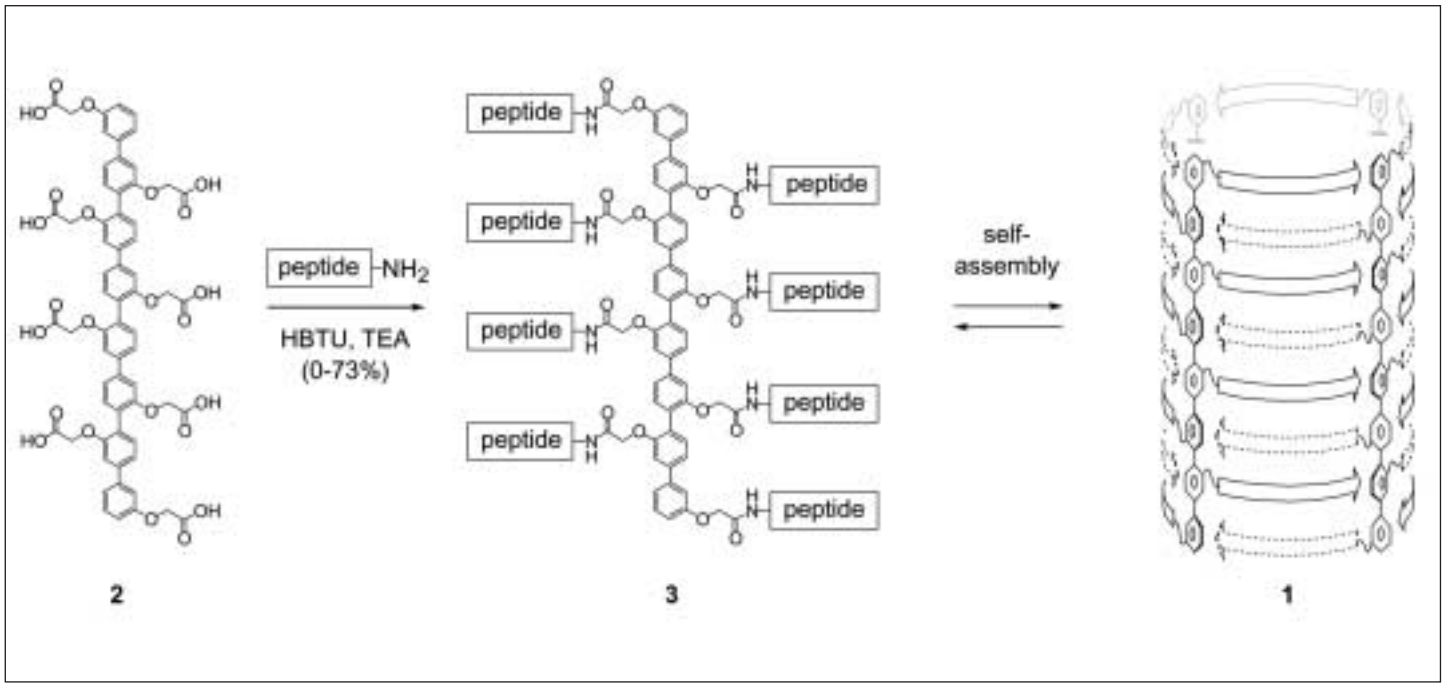


Fig. 1. Synthesis of rigid-rod β-barrels from *p*-octiphenyl rods (peptide synthesis, protection-deprotection steps and other details are omitted for clarity). Details on β-barrel suprastructure are specified in Fig. 2.

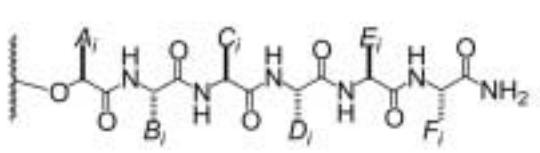
uble barrels with internal hydrophobic channels (**1h**–**j**) require external hydrophilic residues (*BD*) and internal hydrophobic residues (*C*). Reversed amphiphilicity (*BDF* = hydrophobic, *CE* = hydrophilic) gives artificial ion channels (**1a**–**g**) with high, indeed remarkable reliability, also because the length of the *p*-octiphenyl stave matches the thickness of common lipid bilayer membranes very well [5][24].

The possibility to install active sites within the ion-conducting pathway by variation of internal residues *C* and *E* is so far unique for synthetic ion channels. It attracted our interest because it made the fundamental shift of attention from biomimickry toward practical applications of 'multifunctional' synthetic ion channels as drugs, sensors and catalysts envisionable, also on the single-molecule level. Realized examples in these directions include binding of 8-X-pyrenyl-1,3,6-trisulfonates by internal (**1c**) or peripheral (**1b**) histidines, α-helical peptides by internal arginine–histidine dyads (**1d**, **1e**), and oligonucleotide duplexes by internal lysines (**1g**) with nanomolar dissociation constants. Ion channels with anionic interior (**1f**) bind inorganic cations, whereas the resulting metallopores with internal Mg^{2+}-aspartate complexes bind organic anions such as ATP, phytate, heparin, thiamine pyrophosphate and poly((4-phosphonophenyl)acetylene). Maximal functional plasticity was so far realized for rigid-rod β-barrel **1c** with ion channel, esterase, RNase, and fibrillogenic activity. The first practical sensing applications will be reported soon [15].

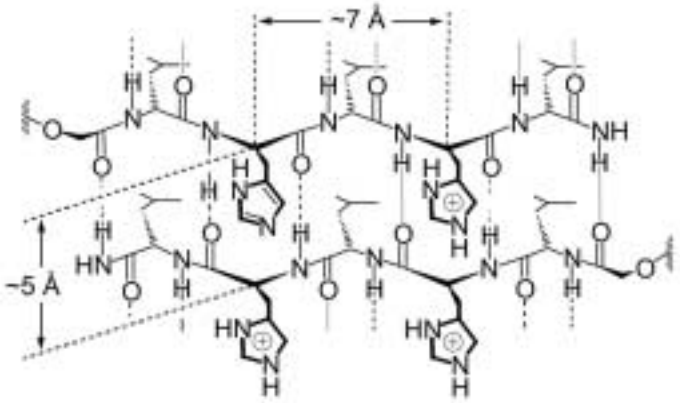
Another important topic within the general theme of the Matile group focuses on the recognition of polarized bilayer membranes by rigid push-pull rods [4]. This is of interest because plasma membranes of Gram-positive and -negative bacteria have unusually high, inside-negative membrane potentials and today's level of antibiotic resistance calls for new antibacterials on the one hand and a better understanding of ion-channel forming natural antibiotics on the other.

Rigid push-pull rods are exceptionally well suited to explore membrane recognition mechanisms (Fig. 3). Their axial dipole, created with terminal π acceptors Y and π donors X, is not subject to conformational changes. Also unlike α-helical dipoles, it can be 'switched-off' without global structural changes. Recognition and depolarization of polarized bilayer membranes by rigid push-pull rods with different combinations of cyano (**4i**) and sulfone (**4iii**, **4v**–**vii**) acceptors and methoxy (**4i**, **4vii**) and sulfide (**4iii**, **4v**, **4vi**) donors demonstrate irrelevance of the chemical nature of the axial rod dipole for operational dipole–potential interactions. Loss in cell membrane recognition with an additional positive charge near the positive (**4v**) but not the negative (**4vi**) dipole terminus shows that a subtle combination of charge translocation plus dipole–potential interaction rather than overall rod asymmetry governs the recognition of weakly polarized membranes. This difference in activity of structural isomers **4v** and **4vi** helps to better understand why melittin (a pore-forming α-helical peptide from bee venom) is a toxin, whereas the very similar magainin 2 (isolated from frog skin) is a natural antibiotic. In the more recent push-pull β-barrel **4vii**, high cell membrane recognition provided by push-pull rods (**4i-4vi**, Fig. 3) is supramolecularly amplified (n = 4) and unified with the high activity of rigid-rod β-barrel ion channel **1g** (Fig. 2).

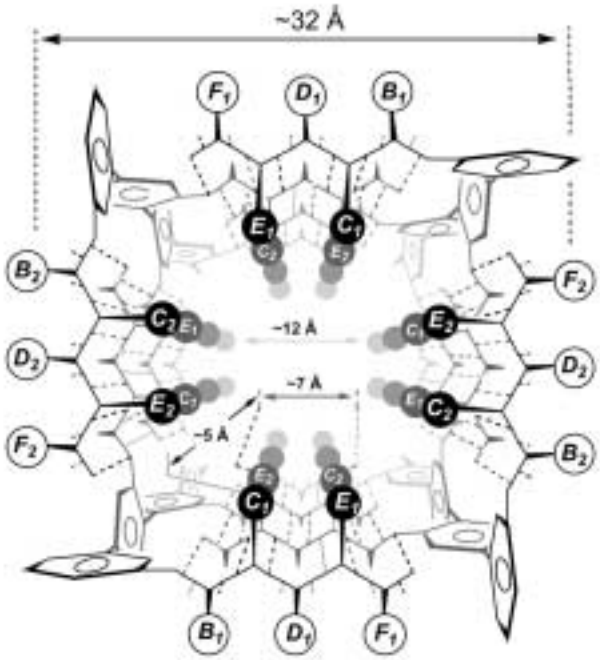
Another important topic in the Matile group is synthetic organic chemistry of rigid-rod molecules. To exemplify these studies, the general route to asymmetric *p*-octiphenyl rods **4** (Fig. 3) developed in the Geneva labs is shown in the Scheme. The synthesis begins with biphenyl **4a**, a versatile (and therefore cheap) stain known as 'Fast Blue B salt'. Key steps in the synthesis of asymmetric rods **4** are a 'Suzuki-oligomerization' of biphenyls **4b** and **4c** to 'jump' directly to the diiodinated *p*-sexiphenyl **4d**, and more Suzuki-couplings with acceptor **4f** and donor **4g** to reach an *p*-octiphenyl level with quite complex substitution pattern. Attachment of the lateral side chains in the last step of the multistep *p*-oc-



primary structure
(general; i = 1, 2)



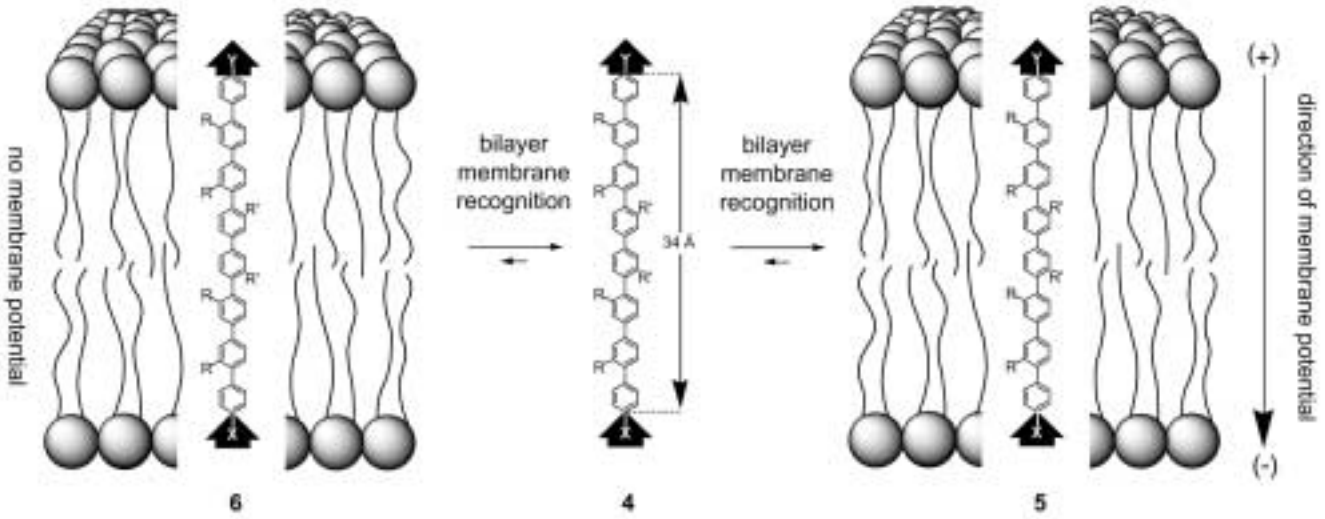
secondary structure
(example **1c***)*



tertiary structure
(general)

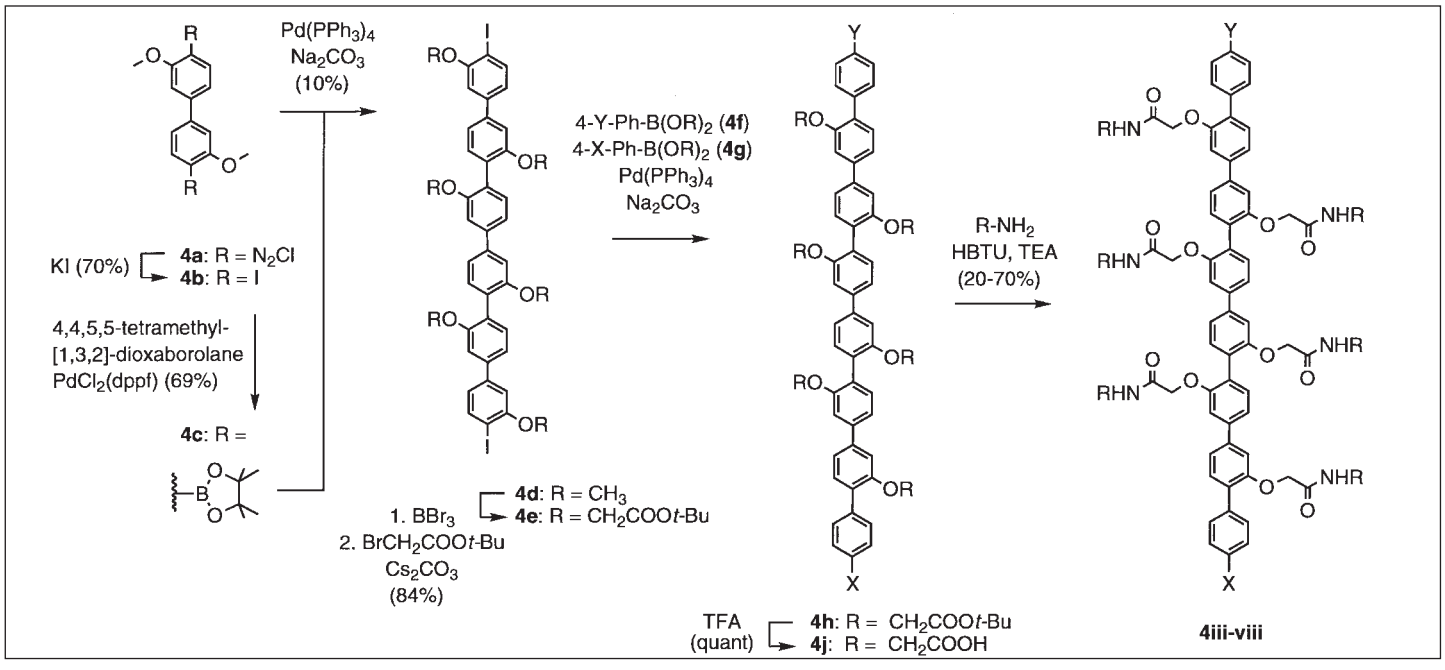
barrel	A_1 B_1 C_1 D_1 E_1 F_1	A_2 B_2 C_2 D_2 E_2 F_2	*n*	functions
1a	*G* L - - - -	same	2	ion channel [7], self-assembled ionophore [7]
1b	*G* L H L - -	same	4	ion channel [8][9], anion recognition, esterase [9]
1c	*G* L H L H L	same	4	ion channel [8][10], anion recognition [10][11][12] esterase [8][10][11], amide hydrolysis [11], RNase [12], fibrillogenesis [13]
1d	*G* L R L H L	same	4	ion channel, anion recognition (α-helices) [14]
1e	*G* L R W H V	same	4	ion channel, anion recognition [15], esterase [16]
1f	*G* L D L D L	same	4	ion channel [8][17][18], metallopore [17][18], anion and cation sensor [15][17][18]
1g	*G* L K L - -	same	6	ion channel [8][19], anion recognition (B-DNA) [20]
1h	*G* E L E - -	*G* K L K - -	4	carotenoid binding in water [21]
1i	*G* E L E - -	*G* K W K - -	6	n.d. [22]
1j	*G* E L E - -	*G* K H K - -	6	binding of hydrophobic organics [23]

Fig. 2**.** Functional plasticity of rigid-rod β-barrels. Rational design is based on translation of peptide primary structures (or sequences) *ABCDEF* into antiparallel β-sheet secondary structures (exemplified with *ABCDEF* = *G*LHLHL) and *p*-octiphenyl β-barrel tertiary structures. The β-barrel structure shown is an axial view of the side view in Fig. 1 with distances as in molecular models. *n* = number of *p*-octiphenyls per barrel [3]. One-letter abbreviations are used for amino acids; *G* = -OCH_2CO-.



rod	Y	X	R	R'	*n*	activity	recognition	reference
4i	-CN	-OCH_3	-*G*-azacrown	-H	1	+	+	[25]
4ii	-CN	-CN	-*G*-azacrown	-H	1	+	-	[25]
4iii	-SO_2CH_3	-SCH_3	-*G*-azacrown	-*G*-azacrown	1	+	+	[26]
4iv	-SCH_3	-SCH_3	-*G*-azacrown	-*G*-azacrown	1	+	-	[26]
4v	-SO_2CH_3	-$SCH_2CH_2NH_3^+$	-*G*-azacrown	-*G*-azacrown	1	+	-	[26]
4vi	-$SO_2CH_2CH_2NH_3^+$	-SCH_3	-*G*-azacrown	-*G*-azacrown	1	+	+	[26]
4vii	-SO_2CH_3	-OCH_3	-GLKL-NH_2	-GLKL-NH_2	4	+++	+++	[27]
4viii	-OCH_3	-OCH_3	-GLKL-NH_2	-GLKL-NH_2	4	+++	-	[27]

Fig. 3**.** Molecular recognition of polarized (host-guest complex **5**) compared to unpolarized (host-guest complex **6**) by rigid push-pull rods **4** but not their symmetric analogs together with their respective ion channel activity. *n* = number of *p*-octiphenyls per ion channel. *G* and LKL as in Fig. 2.



Scheme. Synthesis of push-pull *p*-octiphenyls **4** from commercial biphenyl **4a**. The step *p*-sexiphenyl **4e** to *p*-octiphenyl **4h** is a simplifying generalization of several different approaches specified in the corresponding references; some protection-deprotection steps are omitted for clarity.

tiphenyl synthesis [**4j**→(**4iii**–**viii**)] is the most important advantage of the employed strategy because it secures full flexibility for bioorganic studies.

p-Octiphenyl **2** (Fig. 1) is another example for the synthesis of rigid-rod molecules developed and refined in the Matile group [10]. These examples may (re)confirm that it is the ability to make, *in principle*, any desired molecule from scratch that will always be the distinguishing characteristics of bioorganic chemists compared to life scientists relying on biotechnological means. In other words, the purpose of bioorganic chemistry is to strengthen, expand, and enrich (rather than weaken or even change) the field of organic chemistry. This 'mini-account' was, in part, written with the specific aim to illustrate our commitment to and enthusiasm for such integrating educational philosophy. Namely, that undergraduate students, graduate students, and postdoctoral fellows in bioorganic chemistry have the chance to gain expertise *to make and to study* new molecules (here: rods) and supramolecules (here: barrels) of biological relevance.

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