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Metal–Organic Scaffolds: Heavy-Metal Approaches to Synthetic Ion Channels and Pores**

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Biological ion channels are composed of transmembrane bundles of α helices, whereas the larger pores needed to transport hydrophilic molecules rather than inorganic ions across lipid bilayer membranes are in general β barrels. There are also excellent examples available in the literature of naturally occurring compounds that form ion channels or pores but are not produced by ribosomal peptide synthesis (macrolide antibiotics such as amphotericin B or nystatin, bacterial polyhydroxybutyrates, lantibiotics such as nisin, gramicidin A).[1] The vision to create systems that can function in a similar way as biological ion channels and pores has been around for more than two decades.[1,2] The objective of these endeavors is not to bioengineer, chemically modify, or reproduce existing biological structures. Somewhat in line with Feynman's "we only understand what we can create,"[1] the bold objective is to synthesize ion channels and pores from scratch, using scaffolds that do not occur in biology. Over the years, several research groups have made very important contributions to today's rich collection of functional supramolecular architectures that show more or less pronounced signs of acting as ion channels.[1,2]

The classical approach to synthetic ion channels is based on functional macrocycles such as cyclodextrins, crown ethers, calixarenes, and, more recently, cucurbiturils.[1,2] Linear oligomers have been used in many variations as membrane-spanning scaffolds that fold or self-assemble into uni- or supramolecular ion channels and pores.[1,2] Examples range from simple alkyl and alkoxy chains to polyamines, oligotetrahydrofuran derivatives, β peptides, peptoids, and oligosteroids. The introduction of rigid-rod molecules such as oligophenyls, oligonaphthalenedimides, or oligoperylenediimides as transmembrane scaffolds continues to be productive.[3] This approach has provided access to artificial β-barrel pores that can serve as multianalyte sensors in complex matrices,[4] to the π stacking of architectures with photosynthetic and ion channel activity,[5] and to the selective transport of protons, potassium cations, or chloride anions along transmembrane hydrogen-bonded chains as well as cation–π and anion–π slides.[3] Polymers have been explored successfully over the years to build structurally less-defined but cost-efficient ion channels and pores. These "plastic pores" are of particular interest to exploit powerful multivalency effects.[6]

The rational design of synthetic ion channels and pores is difficult. The challenge is not only to install favorable interactions within the functional architecture itself but also with the surrounding membrane and with the water, ions, and molecules passing across the membrane. Often, the active nanostructures are simply expected to somehow emerge as the result of the most comfortable positioning of facial or cylindrical amphiphiles in an at least biphasic environment. Efforts to introduce recognition modules for more precise assembly of the pores have focused mainly on hydrogen bonding, charge repulsion, and ion pairing. The usefulness of π-stacked architectures has been explored systematically during the last three years.[7] Coordination chemistry, however, has appeared only occasionally in design strategies for synthetic ion channels and pores. Copper(II) ions have been used to accomplish the ligand-gated assembly of cation–π slides.[8] As in the α barrels responsible for terpenoid biosynthesis,[9] the coordination of Mg^{2+} ions to carboxylate clusters at internal pore surfaces has been used to stabilize synthetic pores, modulate their ion selectivity, and enable their use as sensors.[4,10] With the appearance of four milestone reports on the use of coordination chemistry to create synthetic ion channels and pores, this situation has changed dramatically during this year.

The first functional system arises from the recent studies on π-stacked structures.[7] In the presence of potassium cations, guanine residues assemble into G quartets (Scheme 1).[11] The π stacking of these planar supramolecular macrocycles on top of one another gives cylindrical architectures with the potassium cations located between two quartets. The resulting ionophoric π stacks look like perfect ion channels, although biological G quartets belong to "DNA chemistry" and have, as such, nothing to do with biomembranes. The concept of G-quartet ion channels is thus both innovative and counterintuitive from a biological point of

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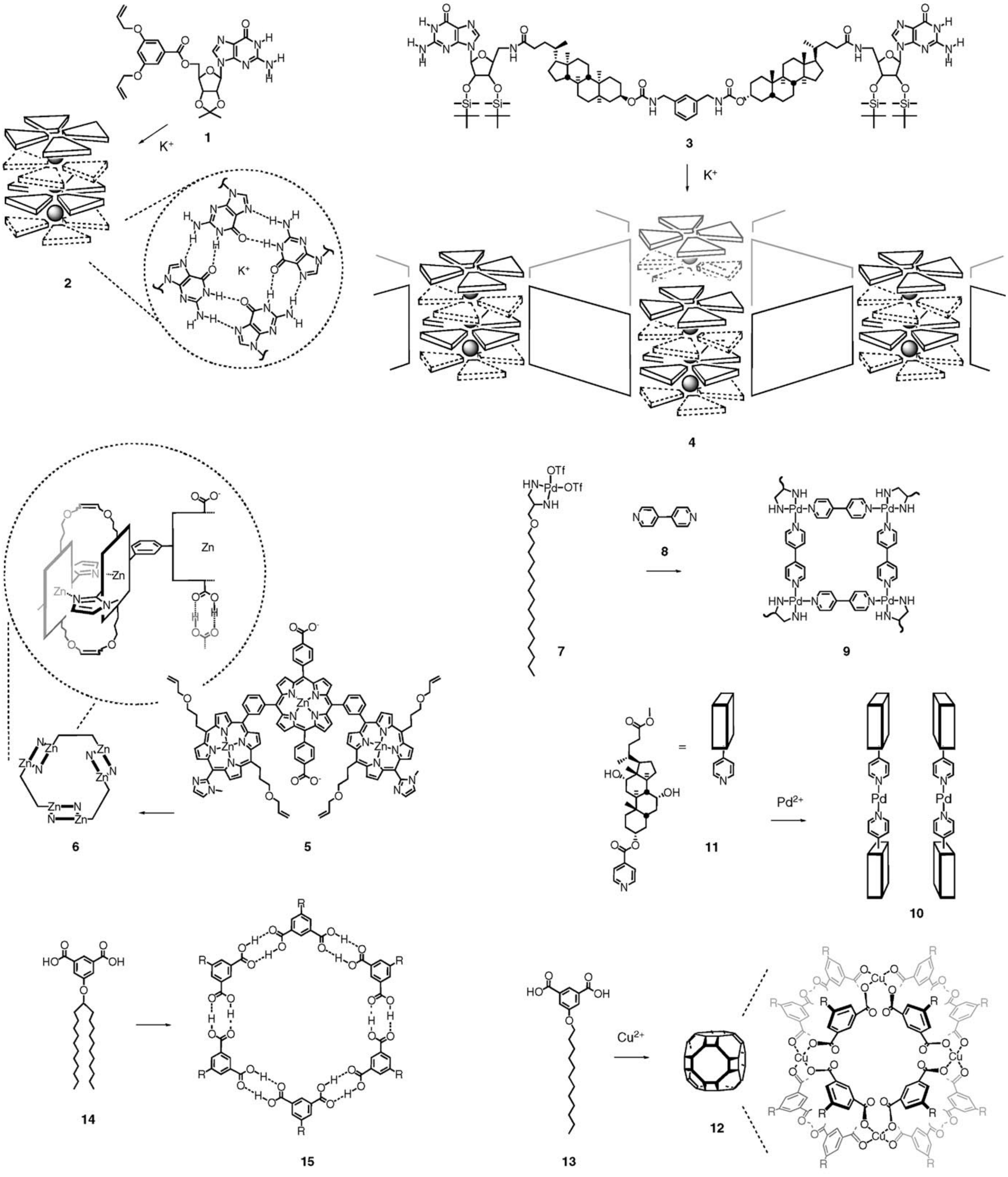

Scheme 1. Metal–organic scaffolds that form ion channels and pores. The G-quartet π-stacking unit **4**, the cyclic oligo(zinc porphyrins) **6**, the metal–organic "barrel staves" **10**, and the metal–organic polyhedrons **12** are thought to act as ion channels or pores, whereas the eventual assembly of coordination squares **9** and the metal-free rosettes **15** is thought to be irrelevant for function.

view. The first G-quartet ion channels were prepared by Davis and co-workers through a potassium-templated assembly of hydrophobic guanine molecules **1** followed by a Grubbs ring-closing metathesis to stabilize the π-stacked G-quartet **2**.[12] The more recent use of nucleoside–sterol conjugate **3** to form large pores is more than a simple variation of the theme.[13] In this system, the G-quartet π stacks are envisioned not to act as small ion channels but to serve as transmembrane "metal–organic" scaffolds. The connection of these scaffolds with the rigid lithocholate spacers could then produce porous "metal–organic frameworks"[14] (MOFs) **4** in the lipid bilayer membrane. Experimental data available in support of active suprastructure **4** include CD spectra with the characteristic signals of π stacks of G quartets. Small single-channel conductance levels (<0.1 nS) found in planar bilayer conductance experiments could conceivably originate from currents flowing through the π-stacked G quartets. The frequent occurrence of cation-selective ($P_K/P_{Cl}=6.4$; $P=$ permeability) pores with very large conductance levels (1–5 and >20 nS) supports the formation of giant metallopores between the transmembrane π stacks.

The second approach toward metal–organic synthetic ion channels and pores is the result of work from Kobuke and co-workers.[15] The self-assembly of oligoporphyrins such as **5** into cylindrical supramolecules such as **6** has been studied in-depth to build light-harvesting systems for artificial photosynthesis. The design, which focuses on coordination chemistry, is subtle. Three zinc porphyrin molecules are linked together with *meta*-substituted aromatic rings. Interdigitating two-point coordination of the terminal methylimidazole rings to the adjacent zinc porphyrin rings connects the monomers in a highly directional manner to produce a cylindrical trimer. This supramolecular macrocycle can be transformed into unimolecular macrocycle **6** by ring-closing metathesis. The carboxylate groups at the central zinc porphyrin unit are essential to possibly assist dimerization in the bilayer and to assure that the ends of the transmembrane metallopore are hydrophilic. The resulting metallopores show the expected stable ion current, respectable homogeneity, large conductance (≤ 2 nS), ohmic behavior, and the negative reversal potential expected for moderate cation selectivity ($V_r=-28$ mV). Moreover, they are permeable to cations as large as tetrabutylammonium ions and can be blocked reversibly by fourth generation poly(amidoamine) (PAMAM) dendrimers (diameter = 2.7 nm).

A revolutionary approach toward the use of coordination chemistry in the design of synthetic ion channels and pores has been proposed by Fyles and Tong.[16] The palladium-amphiphile **7** was expected to bind to bilayer membranes, with the alkyl chain aligned to the lipid tails of one leaflet and the palladium–diamine complex residing at the membrane–water interface. Addition of bipyridine (**8**) should then produce the shape-persistent coordination squares **9**. The use of this classical, so-called "Fujita–Stang", motif in porous metal–organic systems[14] could act as the selectivity filter of an ion channel. Several different channel-like products were obtained by mixing **7** and **8** in the planar bilayer. One product seems to possess some of the expected characteristics of coordination square **9** such as short lifetime, rare occurrence (because of the structure, lability, and complexity of the envisioned supramolecule), and a slightly too small radius according to Hille analysis (known to give increasing underestimates with decreasing radii). The palladium-amphiphile **7** alone also formed large and stable ion channels of unknown suprastructure.

The preparation of palladium-gated ion channel **10** is the first approach toward smart channels with functional metal–organic scaffolds.[17] Facially amphiphilic cholates such as **11** have been reported previously to self-assemble into bundles that span one leaflet of a lipid bilayer membrane and have a hydrophilic interior to mediate ion transport.[1,2,17] In channel **10**, coordination chemistry is used to bring the cholate bundles in the two leaflets together. Namely, the pyridine ring attached to the cholate is thought to end up in the middle of the bilayer membrane. The addition of Pd^{2+} ions results in their coordination to the pyridine rings of both leaflets of the bilayer and produce an active channel, whereas removal of the Pd^{2+} ions with hexathia[18]crown-6 closes the metallochannel. The validity of this approach to palladium-gated channels was confirmed with an elegant series of ion-transport experiments in vesicles with an internal fluorescent probe. Such a characterization of readily accessible fluorogenic vesicles is a fully appropriate and sometimes preferable method to study multifunctional transport systems such as **10**. The complementary single-channel currents have been recorded previously for bundles of monomeric, dimeric, and tetrameric cholate analogues.[1,17] The use of metal–organic scaffolds for reversible ligand gating is particularly important because the design of ligand-gated synthetic ion channels and pores is traditionally one of the most challenging topics in the field.[1,5,7]

The metal–organic polyhedron (MOP) **12**, a MOP-18 derivative, represents an even more vigorous approach toward the use of coordination chemistry for the synthesis of ion channels and pores.[18] The fast and mild preparation of this stable, three-dimensional metal–organic cage from isophthalate-amphiphile **13** and $Cu(OAc)_2$ was first reported by Yaghi and co-workers.[14] MOP **12** is a neutral cuboctahedron with a hydrophobic outer surface and an outer diameter of up to about 50 Å. The exceptionally stable hydrophilic interior has a diameter of 13.8 Å and can be reached from all sides, mainly through six coordination squares each with a diameter of 6.6 Å.

Metal–organic polyhedron **12** caused the appearance of small, ohmic, long-lived and surprisingly homogenous single-channel conductance levels in lipid bilayer membranes. Their conductance (36 pS) and their ion selectivity ($V_r=-31$ mV, $V_r=$ reversal potential; $P_K/P_{Cl}=5.5$) were consistent with cation flux through the channels of **12**. Although weak, the unusual Eisenmann XI selectivity sequence ($Li^+>Na^+>K^+>Rb^+>Cs^+$) and blockage by the permeating cation ($IC_{50}=220$ mM for potassium) indicated that the cations bind relatively strongly to the MOP channel during translocation. Consistent and complementary insights from ion-transport experiments in fluorogenic vesicles were provided to further validate these results.

With aromatic surfaces exposed to the interior, the large channels in **12** are vaguely reminiscent of the synthetic ion channels formed by amphiphilic calixarenes.[19] Some of their properties are indeed quite similar, and cation–π interactions have been suggested in both cases to contribute to ion selectivity. The larger diameter of **12** may well be reflected by the passage of larger cations such as rubidium. The small ion channels formed by the isophthalate-MOP **12** differ from the even smaller channels obtained previously from isophthalate-amphiphiles **14** in the absence of any metal ions.[20] Amphiphile **14** is the only active compound out of a set of 17 isophthalate analogues: the addition or removal of two methylene groups in the alkyl chain already annihilates ion-channel activity. The channels show ohmic properties and very low conductance (15.4 pS) and are quite stable and cation selective ($Cs^+ > K^+ > Na^+$). The very low conductance is incompatible with the existence of supramolecular rosettes **15**, a classical motif of exceptional beauty, as the active suprastructure.

The use of metal–organic scaffolds to create ion channels and pores promises access to ultrastable "nanospace."[14] Rapid ongoing progress particularly with highly porous MOFs as hydrogen sponges indicate enormous potential in this direction.[14] The only systematic approach that is available today to stabilize confined space within pores relies on internal charge repulsion between residues on inner pore surfaces.[21]

With MOP-type metal–organic scaffolds, however, it appears difficult to introduce favorable interactions with the ions and molecules moving through the pores. These properties are desired to create smart, stimuli-responsive systems that are capable of molecular recognition and transformation for applications in sensing[22] or catalysis.[23] The topological matching between holey spheres and planar bilayers is difficult; the common tubular shape seems preferable.[1,2] Further contraction or even complete elimination of organic components as in porous polyoxometalate spheres[24] would presumably further minimize meaningful perspectives for future development toward multifunctional systems. On the other hand, increasing the size and complexity of the organic part, as in palladium-gated channel **10**, promises access to metal–organic architectures of variable shape and increasing responsiveness to chemical and physical stimulation.[17] For example, expanded metal–organic frameworks already allow the nature of water within confined space to be studied on the molecular level.[25] Moreover, advanced metal–organic architectures with cylindrical shapes and the ability of molecular recognition have been developed.[26]

In summary, with the introduction of MOP ion channels, metal–organic scaffolds definitely emerge as attractive architectures to create synthetic ion channels and pores. Although difficult to predict at this very early stage, this approach promises to address one of the central challenges in the field—synthetic access to ultrastable nanospace—in a general and original manner. However, what really matters in the end is what can be done with the produced synthetic ion channels and pores. The question of how to functionalize the ultrastable metal–organic space to create smart, stimuli-responsive systems that are capable of sensing membrane potentials, surface potentials, pH values, membrane composition, membrane fluidity, or stress, of selecting ions, and recognizing and eventually transforming molecules remains to be answered. New results from several research groups in the field together with rapid advances in related topics such as porous MOFs and coordination nanotubes justify their high expectations.

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[1] a) S. Matile, A. Som, N. Sordé, *Tetrahedron* **2004**, *60*, 6405–6435; b) A. L. Sisson, M. R. Shah, S. Bhosale, S. Matile, *Chem. Soc. Rev.* **2006**, *35*, 1269–1286.

[2] a) I. Tabushi, Y. Kuroda, K. Yokota, *Tetrahedron Lett.* **1982**, *23*, 4601–4604; b) J.-H. Fuhrhop, U. Liman, V. Koesling, *J. Am. Chem. Soc.* **1988**, *110*, 6840–6845; c) P. Scrimin, P. Tecilla, *Curr. Opin. Chem. Biol.* **1999**, *3*, 730–735; d) G. W. Gokel, A. Mukhopadhyay, *Chem. Soc. Rev.* **2001**, *30*, 274–286; e) U. Koert, L. Al-Momani, J. R. Pfeifer, *Synthesis* **2004**, 1129–1146; f) R. S. Hector, M. S. Gin, *Supramol. Chem.* **2005**, *17*, 129–134; g) P. A. Gale, *Acc. Chem. Res.* **2006**, *39*, 465–475; h) A. P. Davis, D. N. Sheppard, B. D. Smith, *Chem. Soc. Rev.* **2007**, *36*, 348–357; i) P. L. Boudreault, N. Voyer, *Org. Biomol. Chem.* **2007**, *5*, 1459–1465.

[3] a) N. Sakai, J. Mareda, S. Matile, *Acc. Chem. Res.* **2005**, *38*, 79–87; b) V. Gorteau, G. Bollot, J. Mareda, A. Perez-Velasco, S. Matile, *J. Am. Chem. Soc.* **2006**, *128*, 14788–14789; c) A. Perez-Velasco, V. Gorteau, S. Matile, *Angew. Chem.* **2008**, *120*, 935–937; *Angew. Chem. Int. Ed.* **2008**, *47*, 921–923.

[4] a) G. Das, P. Talukdar, S. Matile, *Science* **2002**, *298*, 1600–1602; b) S. Litvinchuk, H. Tanaka, T. Miyatake, D. Pasini, T. Tanaka, G. Bollot, J. Mareda, S. Matile, *Nat. Mater.* **2007**, *6*, 576–580.

[5] S. Bhosale, A. L. Sisson, P. Talukdar, A. Fürstenberg, N. Banerji, E. Vauthey, G. Bollot, J. Mareda, C. Röger, F. Würthner, N. Sakai, S. Matile, *Science* **2006**, *313*, 84–86.

[6] W. H. Binder, *Angew. Chem.* **2008**, *120*, 3136–3139; *Angew. Chem. Int. Ed.* **2008**, *47*, 3092–3095.

[7] S. Bhosale, A. L. Sisson, N. Sakai, S. Matile, *Org. Biomol. Chem.* **2006**, *4*, 3031–3039.

[8] M. M. Tedesco, B. Ghebremariam, N. Sakai, S. Matile, *Angew. Chem.* **1999**, *111*, 523–526; *Angew. Chem. Int. Ed.* **1999**, *38*, 540–543.

[9] L. C. Tarshis, P. J. Proteau, B. A. Kellogg, J. C. Sacchettini, C. D. Poulter, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 15018–15023.

[10] N. Sakai, N. Sordé, G. Das, P. Perrottet, D. Gerard, S. Matile, *Org. Biomol. Chem.* **2003**, *1*, 1226–1231.

[11] J. T. Davis, *Angew. Chem.* **2004**, *116*, 684–716; *Angew. Chem. Int. Ed.* **2004**, *43*, 668–698.

[12] M. S. Kaucher, W. A. Harrell, Jr, J. T. Davis, *J. Am. Chem. Soc.* **2006**, *128*, 38–39.

[13] L. Ma, M. Melegari, M. Colombini, J. T. Davis, *J. Am. Chem. Soc.* **2008**, *130*, 2938–2939.

[14] a) D. J. Tranchemontagne, Z. Ni, M. O'Keeffe, O. M. Yaghi, *Angew. Chem.* **2008**, *120*, 5214–5225; *Angew. Chem. Int. Ed.* **2008**, *47*, 5136–5147; b) R. Banerjee, A. Phan, B. Wang, C. Knobler, H. Furukawa, M. O'Keeffe, O. M. Yaghi, *Science* **2008**, *319*, 939–943; c) M. Fujita, M. Tominaga, A. Hori, B. Therrien, *Acc. Chem. Res.* **2005**, *38*, 369–380; d) S. T. Seidel, P. J. Stang, *Acc. Chem. Res.* **2002**, *35*, 972–983.

[15] A. Satake, M. Yamamura, M. Oda, Y. Kobuke, *J. Am. Chem. Soc.* **2008**, *130*, 6314–6315.

[16] T. M. Fyles, C. Tong, *New J. Chem.* **2007**, *31*, 655–661.

[17] C. P. Wilson, S. J. Webb, *Chem. Commun.* **2008**, 4007–4009.

[18] M. Jung, H. Kim, K. Baek, K. Kim, *Angew. Chem.* **2008**, *120*, 5839–5841; *Angew. Chem. Int. Ed.* **2008**, *47*, 5755–5757.

[19] Y. Tanaka, Y. Kobuke, M. Sokabe, *Angew. Chem.* **1995**, *107*, 717–719; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 693–694.

[20] T. M. Fyles, R. Knoy, K. Müllen, M. Sieffert, *Langmuir* **2001**, *17*, 6669–6674.

[21] a) B. Baumeister, A. Som, G. Das, N. Sakai, F. Vilbois, D. Gerard, S. P. Shahi, S. Matile, *Helv. Chim. Acta* **2002**, *85*, 2740–2753; b) V. Gorteau, G. Bollot, J. Mareda, D. Pasini, D.-H. Tran, A. N. Lazar, A. W. Coleman, N. Sakai, S. Matile, *Bioorg. Med. Chem.* **2005**, *13*, 5171–5180.

[22] S. Matile, H. Tanaka, S. Litvinchuk, *Top. Curr. Chem.* **2007**, *277*, 219–250.

[23] a) N. Sakai, N. Sordé, S. Matile, *J. Am. Chem. Soc.* **2003**, *125*, 7776–7777; b) B. Baumeister, N. Sakai, S. Matile, *Org. Lett.* **2001**, *3*, 4229–4232.

[24] A. Müller, D. Rehder, E. T. K. Haupt, A. Merca, H. Bögge, M. Schmidtmann, G. Heinze-Brückner, *Angew. Chem.* **2004**, *116*, 4566–4570; *Angew. Chem. Int. Ed.* **2004**, *43*, 4466–4470.

[25] M. L. Wei, C. He, W. J. Hua, C. Y. Duan, S. H. Li, Q. J. Meng, *J. Am. Chem. Soc.* **2006**, *128*, 13318–13319.

[26] a) T. Yamaguchi, S. Tashiro, M. Tominaga, M. Kawano, T. Ozeki, M. Fujita, *Chem. Asian J.* **2007**, *2*, 468–476; b) T. Yamaguchi, S. Tashiro, M. Tominaga, M. Kawano, T. Ozeki, M. Fujita, *J. Am. Chem. Soc.* **2004**, *126*, 10818–10819.