

Converting Sequences of Aromatic Amino Acid Monomers into Functional Three-Dimensional Structures: Second-Generation Helical Capsules**

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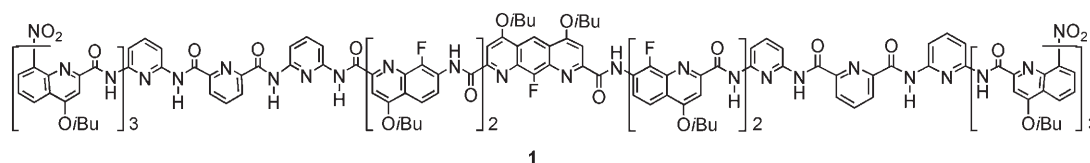
The relationships between primary sequence, folded structure, and function are the basic tenets of nucleic acids and protein machineries. Both comprise a main chain that consists of a constant repeat unit—the sugar–phosphate backbone and the α -peptidic backbone—and variable sequences of side chains—nucleobases

and amino acid residues—that determine their structure and, ultimately, their function. Foldamers are synthetic oligomers that adopt stable

folded conformations.^[1] As biopolymers, many foldamers are based on a constant main chain and variable side chains. However, increasing attention is being paid to sequences in which the main chain also features variable components. Some prime examples include hybrid sequences of α and β peptides^[2] and hybrid sequences of aliphatic and aromatic units.^[3] Here we present our investigation of an oligoamide foldamer sequence containing five different aromatic units. Its folded structure and its function, namely, specific molecular recognition of alkane diols and alkane diamines, are essentially defined by main-chain sequence variations, and the role of side chains is limited to determining solubility. These results represent significant steps towards the elaboration of new, nonnatural codes for sequence–structure–function relationships.

Like other aromatic oligoamide foldamers,^[4] compound **1** was designed to fold into a robust helical structure stabilized by local conformational preferences at each rotatable bond

and by intramolecular aryl–aryl interactions. It is composed of five different units that have all been characterized independently in the context of simpler sequences consisting of only one or two types of units: 8-amino-2-quinolinecarboxylic acid (Q),^[5] 2,6-diaminopyridine and 2,6-pyridinedicarboxylic



acid (P),^[6] 7-amino-8-fluoro-2-quinolinecarboxylic acid (Q^F),^[7] and 1,8-diaza-9-fluoro-2,7-anthracenedicarboxylic acid (A^F).^[8] The sequence of **1** was designed according to two criteria. Firstly, each monomer type should code for an increasing helix diameter from the sequence termini to its center, thus defining a sizeable hollow space inside the helix in which guest molecules can potentially reside. This is ensured by the fact that P, Q^F, and A^F monomers have one, two, and three fused rings, respectively, while all present their amino and/or carboxylic acid functions at a 120° angle. Second, the monomers should display suitable recognition functions towards the hollow so as to establish specific interactions with the guest. In the case of **1**, amide protons, pyridine and quinoline endocyclic nitrogen atoms, and fluorine atoms are expected to converge towards the helix hollow. The quinoline trimers (Q₃) at each end of the sequence are known to form a helix too narrow to accommodate any guest^[9] and should thus cap the cavity of **1**. Three quinoline units were used so as to prevent the hybridization of **1** into double helices, as was observed with a Q₂P₃AP₃Q₂ sequence.^[8c]

Compound **1** represents an extension of prototypical sequences Q₂P_nQ₂ that were shown to host one water molecule ($n=3$ or 5) or small polar guests such as formic acid and methanol ($n=7$).^[9] It is related both to receptors based on helically folded oligomers with open hollows^[10] and to macropolycyclic containers and self-assembled capsules that completely seclude their guests and isolate them from the surrounding medium.^[11] As reported in detail in the Supporting Information, **1** was synthesized following a convergent approach. A Q₃ acid chloride module and a monoprotected P₃ module were first assembled then coupled to a dimer Q^F₂. In a final step, a Q₃P₃Q^F₂ amine was reacted with 0.5 equiv of the diacid chloride of A^F to yield **1**. Speculations as to which guests would be suitable for **1** were made at the time of its

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design so as to define its sequence. Pyridine monomers have been shown to bind to hydroxy functions.^[6,9] Molecular modeling shows that the $Q^F_2A^FQ^F_2$ central module should span over one helical turn and define a hollow large enough to accommodate an alkyl chain. Alkanediols thus appeared to be suitable guests for **1**.

The ability of **1** to bind various guests was assessed by titrations in anhydrous $CDCl_3$ monitored by 1H NMR spectroscopy. For all guests except water, guest binding and release was found to be slow on the NMR timescale at 298 K; the full and empty hosts give rise to distinct and well-resolved NMR signals. Spectra from a typical titration experiment are shown in Figure 1. Binding constants, within the 500–5000 $L\ mol^{-1}$ range, were calculated for a series of guests by integrating NMR spectra (Table 1). All titrations were performed twice and the standard deviation was estimated to be less than 20%. As expected, several linear alkanediols (entries 1–3, Table 1) as well as an unsaturated diol (entry 5, Table 1) bind to **1**. The size difference between ethylene

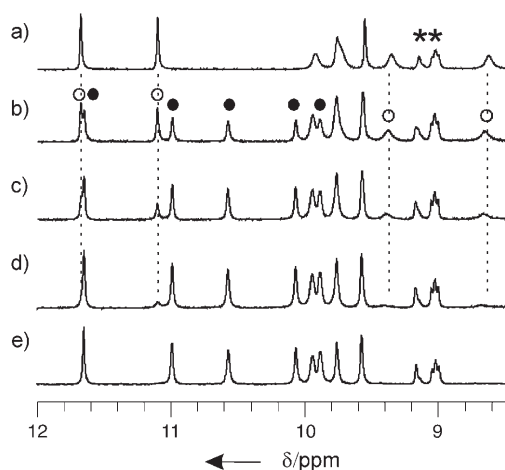


Figure 1. Representative 300 MHz NMR spectra of **1** in $CDCl_3$ (2 mM) at 25 °C titrated with 1,4-butanediol: a) 0 equiv, b) 0.5 equiv, c) 1 equiv, d) 2 equiv, and e) 4.5 equiv. The selected window mostly shows amide resonances. A few aromatic resonances are marked with stars. Some signals of the empty host and of the host–guest complex are marked with white and black circles, respectively.

Table 1: Binding constants between **1** and various guests in $CDCl_3$ at 25 °C.

Entry	Guest	K [$L\ mol^{-1}$]
1	ethylene glycol	0.64×10^3
2	1,3-propanediol	2.5×10^3
3	1,4-butanediol	3.3×10^3
4	1,3-butanediol	— ^[a]
5	<i>cis</i> -2-butene-1,4-diol	5.2×10^3
6	1,5-pentanediol	— ^[a]
7	<i>n</i> -butanol	— ^[a]
8	<i>n</i> -hexane	— ^[a]
9	1,4-butanedithiol	— ^[a]
10	4-amino-1-butanol	3.0×10^3
11	1,4-butanediamine	4.2×10^3

[a] No binding was detected by NMR spectroscopy in the presence of over 20 equiv of guest.

glycol and 1,4-butanediol results in a moderate discrimination by the host: a factor of five in favor of the latter. However, complete selectivity was observed against guests that are presumably too large to be accommodated in the capsule: no binding was detected with 1,3-butanediol, a branched isomer of 1,4-butanediol, and with 1,5-pentanediol, which is only one CH_2 unit longer than 1,4-butanediol (entries 4 and 6, Table 1). No binding is also observed when terminal hydroxy groups are replaced by either methyl groups or thiols. For instance, *n*-butanol, an isostere of 1,3-propanediol, and *n*-hexane and 1,4-butanedithiol, two isosteres of 1,4-butanediol, do not bind to **1** (entries 4 and 6, Table 1). On the other hand, amine functions appear to show affinity for **1** comparable—within experimental error—to that of hydroxy functions (entries 10–11, Table 1). Another two guests, 2-butyne-1,4-diol and 2,2,3,3-tetrafluoro-1,4-butanediol, were tested inconclusively because they are insoluble in chloroform: cooling a hot solution resulted in precipitation of the guest with no observable binding.

The binding into the capsule hollow does not lead to considerable variations in the CH_2 NMR signals of the guest ($\Delta\delta < 0.25$ ppm). This contrasts with numerous binding studies within macrocyclic or self-assembled containers whose walls also consist of aromatic units.^[11] Unlike in most of these hosts, the aryl groups of **1** are expected to expose their edges and not their faces to the guest; thus, ring current effects do not come into play. Nevertheless, the chiral environment of **1** leads to diastereotopic patterns in the guest signals ($\Delta\delta$ up to 0.4 ppm, see the Supporting Information). The multiplicity of the NMR signals of the capsule indicates that, for all symmetrical guests, the complex also is symmetrical on average. Even though smaller guests such as ethylene glycol may find several suitable positions within the capsule hollow, these structures rapidly equilibrate. On the other hand, 4-amino-1-butanol, a dissymmetrical guest, breaks the symmetry of the helix whose signals split into two when the complex forms (see the Supporting Information). This indicates that the amine and hydroxy functions create different environments in the host cavity and that any flip-flop motion of the guest is slow, if at all possible.

In the absence of any specific guest, some amide resonance chemical shift values were shown to increase with the water content of the sample. As was previously characterized with $Q_2P_nQ_2$ sequences ($n=3, 5, 7$), this finding indicates that water is also bound in the capsule but that its binding and release is fast on the NMR timescale, as could be expected for a smaller guest.^[9] The binding constant of water could not be accurately measured because it is difficult to assess the amount of guest in the sample. An estimate based on previous studies of smaller helical capsules gives a binding constant of the order of $100\ L\ mol^{-1}$ in $CDCl_3$.^[9] When the titrations of Table 1 are performed in chloroform “from the bottle”, that is, containing residual water, apparent binding drops by about 50% because water competes with the guest. Although accurate binding constants cannot be calculated in this case, competition experiments clearly show that the overall trend in guest preferences is unchanged.

Detailed information about host–guest interactions were obtained through crystallographic studies. Single crystals of **1**

containing 1,3-propanediol, 1,4-butanediol, and 1-amino-4-butanol suitable for X-ray analysis were all obtained by diffusion of hexane into chloroform solutions (see the Supporting Information). The three structures possess almost identical unit cells and are essentially superimposable (Figure 2). The polar hydroxy or amine groups of the guests are hydrogen bonded to the NH functions of a 2,6-pyridinedicarboxamide ($d_{\text{N-O/N}}$: 2.91–3.11 Å, N-H/O/N: 143–160°).

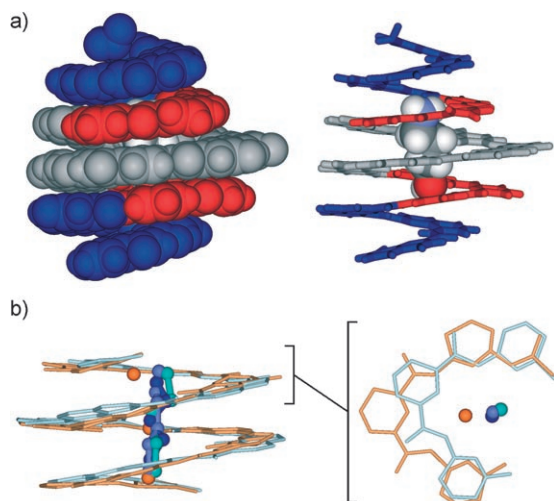


Figure 2. Solid-state structures of host-guest complexes of **1**. a) Side views of CPK and stick representations of **1** containing 4-amino-1-butanol. Q and P monomers are shown in blue and red, respectively. Q^F and A^F monomers are shown in gray. Isobutyl side chains and included solvent molecules have been removed for clarity. b) Overlay of the solid-state structures of **1** containing 4-amino-1-butanol, 1,4-butanediol, 1,3-propanediol, and three water molecules. The latter complex is shown in orange while the three former complexes are depicted using dark and light blue. The blue helix backbone represents the backbones of the three former complexes which are essentially superimposable. All six terminal Q units, isobutyl side chains, hydrogen atoms, and included solvent molecules have been removed for clarity. The structure on the right depicts a top view of the upper three P units and the nearby guest heteroatoms (N or O) using the same color code. This structure clearly shows that one water molecule (orange sphere) occupies an offset position with respect to hydroxy and amine functions in other complexes.

The methylene units are surrounded by a ring of fluorine atoms of the host. The guests' butyl chains are slightly bent in close to an eclipsed conformation (C-C-C-C torsion: 144° and 115° for 1,4-butanediol and 4-amino-1-butanol, respectively). This conformation may explain the high affinity of **1** for *cis*-2-butene-1,4-diol, which already has a similar shape. In contrast, the propyl chain of 1,3-propanediol adopts an extended, all-*anti* conformation. As a result, although it has one less CH₂ unit, 1,3-propanediol is located in the center of the capsule. It does not shift towards one end and its terminal oxygen atoms occupy positions very near those of the two longer guests.

The structure of a crystal of **1** grown in the absence of any specific guest but in the presence of a large excess of water could also be resolved. The unit cell parameters are slightly but reproducibly different from those of the first three structures. This latter capsule contains exactly three water

molecules, two of which are also bound to the 2,6-pyridinedicarboxamide units. The central part of the capsule contains one water molecule. One of the two peripheral water molecules is found at the same position as the hydroxy groups of the other guests. However, the other water molecule is found at a position offset by over 1.5 Å from the position occupied by hydroxy and amine functions in the other complexes (Figure 2b). A closer look at the structure reveals that this peculiar position in fact results from a significant conformational change in the aryl-amide backbone that in all cases adjust the position of 2,6-pyridinedicarboxamide units within hydrogen-bonding distance of the guest (Figure 2b). This ability of the helical capsule to adjust bending angles at the aryl-amide linkage and adapt its conformation to the presence of one or another guest is a new element in the field of aromatic amide foldamers, which are generally depicted as rather rigid structures. It also represents a new type of induced fit that could be compared to that of a snake around its prey.

The crystal structures of **1** shed light on a number of NMR results including the diastereotopic motifs in the guests' signals, the slow guest binding and release which require considerable conformational changes of the capsule, and the probably impossible flip-flop motion of the guests within the helix cavity. The structures also fully validate the initial design. They show that **1** completely surrounds its guests and confirm the respective role of each aromatic monomer in the sequence. Terminal Q units cap the helix hollow and prevent hybridization of the helix into a duplex.^[6,8c] Pyridine units define a binding site for polar hydroxy or amine moieties, and Q^F and A^F units provide a nonpolar environment in the center of the sequence. On this basis, capsules with a high affinity for 1,5-pentanediol or 1,6-hexanediol might be designed through the incorporation of additional Q^F units.

In conclusion, this study illustrates how sequence-structure-function relationships can be rationally established using codes that are different from those nature uses. In addition to the remarkable binding properties of **1**, it clearly appears that sequences slightly longer than **1** will accommodate more challenging guests and possibly help mediate some chemical transformations. Ultimately, the ability to tune the groups that converge towards the cavity of molecular capsules, as made possible by our design, may become a critical advantage to implement function. Our current efforts concentrate on developing strategies towards the synthesis of even larger helical capsules and at unraveling the recognition modes between the capsule inner wall and guest molecules.

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- [1] *Foldamers: Structure, Properties and Applications* (Eds.: S. Hecht, I. Huc), Wiley-VCH, Weinheim, **2007**; C. M. Goodman, S. Choi, S. Shandler, W. F. DeGrado, *Nat. Chem. Biol.* **2007**, *3*, 252; D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore,

- Chem. Rev.* **2001**, *101*, 3893; S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173.
- [2] W. S. Horne, J. L. Price, J. L. Keck, S. H. Gellman, *J. Am. Chem. Soc.* **2007**, *129*, 4178; A. Hayen, M. A. Schmitt, F. N. Ngassa, K. A. Thomasson, S. H. Gellman, *Angew. Chem.* **2004**, *116*, 511; *Angew. Chem. Int. Ed.* **2004**, *43*, 505; S. De Pol, C. Zorn, C. D. Klein, O. Zerbe, *Angew. Chem.* **2004**, *116*, 517; *Angew. Chem. Int. Ed.* **2004**, *43*, 511; C. Baldauf, R. Gunther, H.-J. Hofmann, *J. Org. Chem.* **2006**, *71*, 1200; M. A. Schmitt, S. H. Choi, I. A. Guzei, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 4538; G. V. M. Sharma, V. B. Jadhav, K. V. S. Ramakrishna, P. Jayaprakash, K. Narsimulu, V. Subash, A. C. Kunwar, *J. Am. Chem. Soc.* **2006**, *128*, 14657; K. Ananda, P. G. Vasudev, A. Sengupta, K. M. P. Raja, N. Shamala, P. Balaram, *J. Am. Chem. Soc.* **2005**, *127*, 16668.
- [3] N. Raynal, M.-C. Averlant-Petit, G. Bergé, C. Didierjean, M. Marraud, D. Duru, J. Martinez, M. Amblard, *Tetrahedron Lett.* **2007**, *48*, 1787; P. K. Baruah, N. K. Sreedevi, R. Gonnade, S. Ravindranathan, K. Damodaran, H.-J. Hofmann, G. J. Sanjayan, *J. Org. Chem.* **2007**, *72*, 636; N. Delsuc, F. Godde, B. Kauffmann, J.-M. Léger, I. Huc, *J. Am. Chem. Soc.* **2007**, *129*, 11348; D. Srinivas, R. Gonnade, S. Ravindranathan, G. J. Sanjayan, *J. Org. Chem.* **2007**, *72*, 7022; D. Srinivas, R. Gonnade, S. Ravindranathan, G. J. Sanjayan, *Tetrahedron* **2006**, *62*, 10141.
- [4] For reviews, see: L. Cuccia, I. Huc in *Foldamers: Structure, Properties and Applications* (Eds.: S. Hecht, I. Huc), Wiley-VCH, Weinheim, **2007**, pp. 3–33; Z.-T. Li, J.-L. Hou, C. Li, H.-P. Yi, *Chem. Asian J.* **2006**, *1*, 766; I. Huc, *Eur. J. Org. Chem.* **2004**, *17*, B. Gong, *Chem. Eur. J.* **2001**, *7*, 4336.
- [5] H. Jiang, J.-M. Léger, I. Huc, *J. Am. Chem. Soc.* **2003**, *125*, 3448; H. Jiang, J.-M. Léger, C. Dolain, P. Guionneau, I. Huc, *Tetrahedron* **2003**, *59*, 8365; C. Dolain, H. Jiang, J.-M. Léger, P. Guionneau, I. Huc, *J. Am. Chem. Soc.* **2005**, *127*, 12943; C. Dolain, A. Grélard, M. Laguerre, H. Jiang, V. Maurizot, I. Huc, *Chem. Eur. J.* **2005**, *11*, 6135.
- [6] V. Berl, I. Huc, R. G. Khoury, M. J. Krische, J.-M. Lehn, *Nature* **2000**, *407*, 720; V. Berl, I. Huc, R. G. Khoury, J.-M. Lehn, *Chem. Eur. J.* **2001**, *7*, 2810; H. Jiang, V. Maurizot, I. Huc, *Tetrahedron* **2004**, *60*, 10029–10038; A. Acocella, A. Venturini, F. J. Zerbetto, *J. Am. Chem. Soc.* **2004**, *126*, 2362; C. Dolain, C. Zhan, J.-M. Léger, I. Huc, *J. Am. Chem. Soc.* **2005**, *127*, 2400–2401; D. Haldar, H. Jiang, J.-M. Léger, I. Huc, *Angew. Chem.* **2006**, *118*, 5609; *Angew. Chem. Int. Ed.* **2006**, *45*, 5483; C. Zhan, J.-M. Léger, I. Huc, *Angew. Chem.* **2006**, *118*, 4741; *Angew. Chem. Int. Ed.* **2006**, *45*, 4625; D. Haldar, H. Jiang, J.-M. Léger, I. Huc, *Tetrahedron* **2007**, *63*, 6322.
- [7] Q. Gan, C. Bao, B. Kauffmann, A. Grélard, J. Xiang, S. Liu, I. Huc, H. Jiang, *Angew. Chem. Int. Ed.* **2008**, *47*, 1715; *Angew. Chem.* **2008**, *120*, 1739.
- [8] For studies of oligomers composed of an analogue of A^F having a methyl instead of a fluorine in position 9, see: a) E. Berni, B. Kauffmann, C. Bao, J. Lefeuvre, D. M. Bassani, I. Huc, *Chem. Eur. J.* **2007**, *13*, 8463; b) E. Berni, C. Dolain, B. Kauffmann, J.-M. Léger, C. Zhan, I. Huc, *J. Org. Chem.* **2008**, *73*, 2687; c) E. Berni, J. Garric, C. Lamit, B. Kauffmann, J.-M. Léger, I. Huc, *Chem. Commun.* **2008**, DOI: 10.1039/b719712h.
- [9] J. Garric, J.-M. Léger, I. Huc, *Angew. Chem.* **2005**, *117*, 1990; *Angew. Chem. Int. Ed.* **2005**, *44*, 1954; J. Garric, J.-M. Léger, I. Huc, *Chem. Eur. J.* **2007**, *13*, 8454.
- [10] For selected examples, see: R. B. Prince, S. A. Barnes, J. S. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 2758; H. Abe, N. Masuda, M. Waki, M. Inouye, *J. Am. Chem. Soc.* **2005**, *127*, 16189; J.-L. Hou, X.-B. Shao, G.-J. Chen, X.-Y. Zhou, X.-K. Jiang, Z.-T. Li, *J. Am. Chem. Soc.* **2004**, *126*, 12386; M. Waki, H. Abe, M. Inouye, *Angew. Chem.* **2007**, *119*, 3119; *Angew. Chem. Int. Ed.* **2007**, *46*, 3059; C. Li, G.-T. Wang, H.-P. Yi, X.-K. Jiang, Z.-T. Li, R.-X. Wang, *Org. Lett.* **2007**, *9*, 1797; For a review, see: J. Becerril, J. M. Rodriguez, I. Saraogi, A. D. Hamilton in *Foldamers: Structure, Properties and Applications* (Eds.: S. Hecht, I. Huc), Wiley-VCH, Weinheim, **2007**, pp. 195–228.
- [11] For recent examples, see: S. Shimizu, T. Kiuchi, N. Pan, *Angew. Chem.* **2007**, *119*, 6562; *Angew. Chem. Int. Ed.* **2007**, *46*, 6442; A. Scarso, L. Pellizzaro, O. De Lucchi, A. Linden, F. Fabris, *Angew. Chem.* **2007**, *119*, 5060; *Angew. Chem. Int. Ed.* **2007**, *46*, 4972; D. Ajami, M. P. Schramm, A. Volonterio, J. Rebek, Jr., *Angew. Chem.* **2007**, *119*, 246; *Angew. Chem. Int. Ed.* **2007**, *46*, 242; D. Ajami, J. Rebek, Jr., *Angew. Chem.* **2007**, *119*, 9443; *Angew. Chem. Int. Ed.* **2007**, *46*, 9283; F. C. Tucci, A. R. Renslo, D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **2007**, *119*, 1118; *Angew. Chem. Int. Ed.* **2007**, *46*, 1076; S. M. Biro, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2007**, *129*, 12094; K. Harano, S. Hiraoka, M. Shionoya, *J. Am. Chem. Soc.* **2007**, *129*, 5300; M. Yoshizawa, M. Tamura, M. Fujita, *Angew. Chem.* **2007**, *119*, 3948; *Angew. Chem. Int. Ed.* **2007**, *46*, 3874; K. Ono, M. Yoshizawa, T. Kato, K. Watanabe, M. Fujita, *Angew. Chem.* **2007**, *119*, 1835; *Angew. Chem. Int. Ed.* **2007**, *46*, 1803; Y. Nishioka, T. Yamaguchi, M. Yoshizawa, M. Fujita, *J. Am. Chem. Soc.* **2007**, *129*, 7000; T. Murase, S. Sato, M. Fujita, *Angew. Chem.* **2007**, *119*, 5225; *Angew. Chem. Int. Ed.* **2007**, *46*, 5133; M. Mascal, I. Yakovlev, E. B. Nikitin, J. C. Fetting, *Angew. Chem.* **2007**, *119*, 8938; *Angew. Chem. Int. Ed.* **2007**, *46*, 8782; E. Botana, E. Da Silva, J. Benet-Buchholz, P. Ballester, J. de Mendoza, *Angew. Chem.* **2007**, *119*, 202; *Angew. Chem. Int. Ed.* **2007**, *46*, 198; E. Huerta, G. A. Metselaar, A. Fragos, E. Santos, C. Bo, J. de Mendoza, *Angew. Chem.* **2007**, *119*, 206; *Angew. Chem. Int. Ed.* **2007**, *46*, 202; R. Warmuth, S. Makowiec, *J. Am. Chem. Soc.* **2007**, *129*, 1233.