Organic LETTERS

Letter

pubs.acs.org/OrgLett

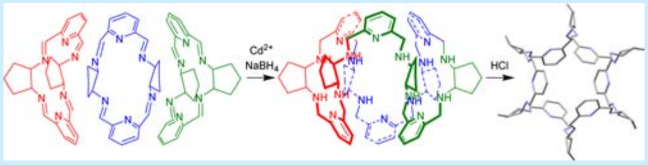
Expansion of a 2 + 2 Macrocycle into a 6 + 6 Macrocycle: Template Effect of Cadmium(II)

Janusz Gregoliński,* Katarzyna Ślepokura, Tomasz Paćkowski, and Jerzy Lisowski*

Department of Chemistry, University of Wrocław, 14 F. Joliot-Curie, 50-383 Wrocław, Poland

S *Supporting Information*

ABSTRACT: The reaction of *trans*-1,2-diaminocyclopentane with 2,6-diformylpyridine results in formation of 2 + 2, 3 + 3, and 4 + 4 Schiff base macrocycles as well as trace amounts of 6 + 6 and 8 + 8 macrocycles. In contrast, the 6 + 6 Schiff base macrocycle is a dominant product of the reaction of the isolated 2 + 2 macrocycle with excess of cadmium(II) chloride. The X-ray crystal structure of the protonated amine derivative of the 6 + 6 macrocycle reveals an unusual container-like conformation with the S_6 axis.



Macrocycles constitute a versatile and important class of compounds that find application in selective binding of metal ions or organic guests, sensing, catalysis, mimicking biological systems, and engineering new materials. New fascinating macrocycles, sometimes possessing a considerable size and unusual topology, are being constantly discovered. Apart from classical types of macrocycles, such as crown ethers, calixarenes, resoricinarenes, and porphyrins, other types of macrocycles also attract continuing attention.[1,2] For instance, large macrocyclic imines and amines derived from chiral diamines and dicarbonyl compounds have been studied in the context of metal binding, chiral properties, DNA interactions, organic guest binding, catalysis, and formation of porous materials.[3−6]

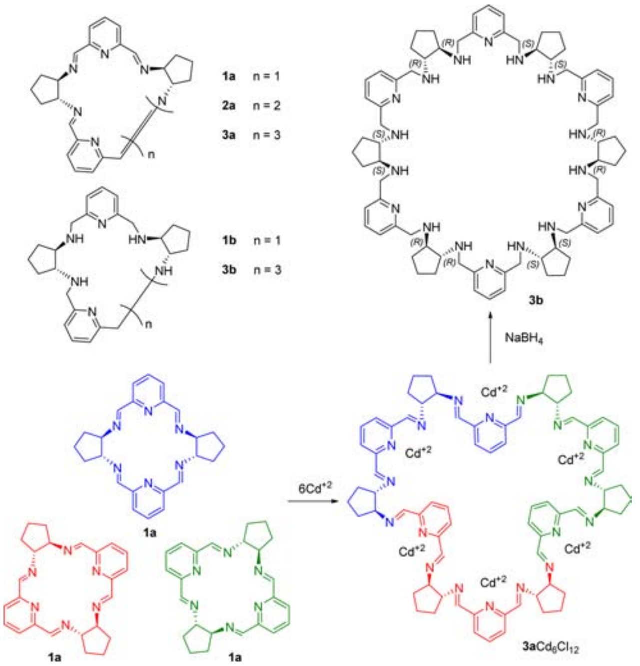
Since the formation of the imine bond is reversible, the condensation of diamine and dicarbonyl substrates can lead to a dynamic combinatorial library of compounds,[7] including various macrocyclic products, while the library's composition can be influenced by the selection of an appropriate template or reaction conditions. For instance, the 2 + 2, 3 + 3, and 4 + 4 macrocycles can be selectively obtained in the reaction of *trans*-1,2-diaminocyclohexane (DACH) and 2,6-diformylpyridine (DFP), depending on the reaction conditions.[3,8,9] It should be mentioned that imine and amine macrocycles based on DACH are interesting chiral molecular receptors.[10] In the case of crude Schiff base, reaction products derived from DACH and DFP traces of large 5 + 5, 6 + 6, and even larger macrocycles have been additionally observed in the mass spectra.[9,11] Analogous large amine macrocycles have also been observed in trace amounts after the reduction of the members of the library with sodium borohydride. Similarly, we have observed traces of 4 + 4 and larger macrocycles in the case of analogous reaction of *trans*-1,2-diaminocyclopentane (DACP). The latter chiral diamine is much less frequently used in syntheses in comparison with its more common diaminocyclohexane analogue. The subtle change of geometric requirements of DACP in comparison with those of DACH may lead to a somewhat different structure of the respective products, resulting, e.g., in improved enantioselective catalysts.[12] In order to check such an influence on the formation of macrocyclic products, we have undertaken a systematic investigation of the reaction of both racemic and enantiopure DACP with DFP.

In this paper, we present the formation of a 4 + 4 macrocycle based on DACP and DFP with a bound benzene guest molecule held by CH−π interactions as well the formation of an unusual large, container-shaped 6 + 6 macrocycle possessing S_6 improper axis (Scheme 1). The latter macrocycle has been obtained in a selective manner by fusing together three molecules of 2 + 2 macrocycles templated by the excess of Cd(II) ions. In this respect, the DACP amine differs from DACH, where very selective, cooperative templation effect of two Cd(II) ions leads to 3 + 3 macrocycles.[9]

Depending on the reaction conditions, we have observed formation of various macrocyclic products in the reactions of DFP with both enantiopure and racemic DACP. In the case of enantiopure DACP, a chiral 2 + 2 macrocycle is formed in lanthanide(III) templated condensation, while a chiral 3 + 3 macrocycle can be obtained in good yields without a metal template in methanol. In the case of the reaction of racemic DACP in methanol, a meso-type 2 + 2 Schiff base macrocycle **1a** can be obtained in almost quantitative yield (96%) after 24 h reflux (see the Supporting Information for experimental details and spectroscopic characterization). This macrocycle can be converted to a 2 + 2 amine macrocycle **1b** by the reduction with sodium borohydride in methanol/chloroform mixture (76% yield). The meso-type 2 + 2 Schiff base macrocycle **1a** adopts a stepped Z-shaped conformation, similar to that observed for the related DACH derivative (Figure 1, see the Supporting Information for details of structure determination and description).[8] In the case of **1a**, the amplification of a particular library member is driven by its very poor solubility in methanol and acetonitrile. This selectivity is not observed in solvents such

Received: June 4, 2014
Published: August 21, 2014

Scheme 1. Macrocycles 1a–3a and 1b–3b and the Transformation of 1a to $3a(Cd)_6^{12+}$



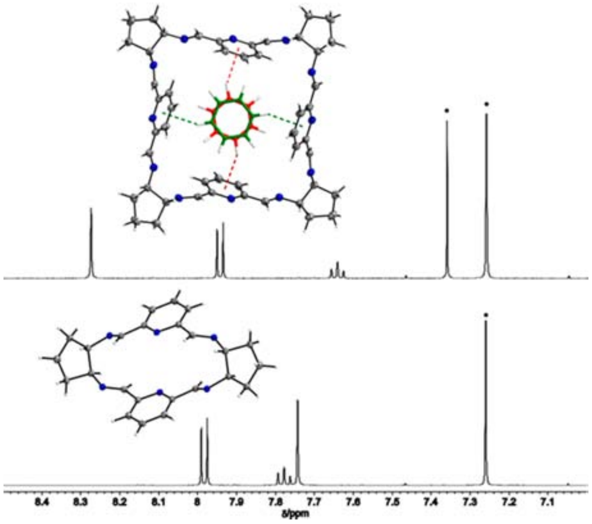


Figure 1. Molecular structures and fragments of ^1H NMR spectra (500 MHz, $CDCl_3$) of **1a** (bottom) and **2a** (top); asterisks denote chloroform and benzene signals.

as chloroform, ethyl acetate, and benzene. For instance, the condensation of DFP and racemic DACP in methanol/benzene mixture results in the dynamic library and formation of a mixture of heterochiral 2 + 2, 3 + 3, and 4 + 4 Schiff base macrocycles (Figure S23, Supporting Information). On the other hand, the homochiral macrocycles are not observed in this mixture, which may indicate a somewhat lower strain of heterochiral meso-type macrocyles derived from DACP. Recrystallization of the above mixture from benzene allowed isolation of a small amount of pure **2a** (2% total yield) as well as growing single crystals.

The macrocycle **2a** is of S_4 symmetry, and it is achiral. Apart from the S_4 axis there are no other symmetry elements. This 4 + 4 macrocycle binds in its center the benzene molecule (Figure 2). The characteristic feature of this binding is positioning of the aromatic benzene ring in the "mean plane of the macrocycle", rather than perpendicularly. The latter orientation was actually expected, as it would correspond to a parallel arrangement of the benzene ring in respect to pyridine rings of the macrocyclic host, resulting from $\pi-\pi$ interactions. The geometry of the 4 + 4 macrocycle–benzene assembly may suggest the presence of C–H⋯π interactions (the respective benzene C–pyridine N distance equal to 3.915(4) Å, benzene H–pyridine N distance equal to 3.00 Å, benzene C–π distance equal to 3.646(4) Å and benzene H–π distance equal to 2.84 Å).[13] The C–H bond of benzene is clearly not perpendicular to the plane of the pyridine ring and points to the nitrogen atom; thus, this interaction can also be regarded as a kind of hydrogen bond involving the π-electron density at the nitrogen atom. Alternatively, the unusual positioning of the benzene molecule in the center of **2a** can be explained by some degree of mechanical locking; the opposite pairs of pyridine rings are somewhat slanted and act as a kind of tweezers holding the benzene ring. One pair of tweezers blocks the benzene ring from the top and the other pair blocks it from the bottom, so the combined effect is partial locking of the benzene molecule in the macrocyclic cavity (Figure 2, right).

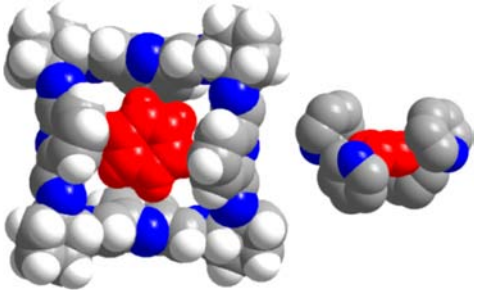


Figure 2. (Left) Top view of **2a** together with the benzene molecule bound in the center. Only one position of disordered benzene is shown. (Right) Side view of four pyridine fragments surrounding the benzene ring.

We have also investigated the influence of templating metal ions on the dynamic library originating from the condensation of DFP and DACP. In particular, the reaction of the 2 + 2 product with the excess of Cd(II) ions in methanol/chloroform mixture results in the formation of very poorly soluble crude cadmium complex of **3a**. The mass spectrum of the isolated cadmium derivative of **3a** indicates the presence of a hexanuclear Cd(II) complex of the 6 + 6 Schiff base macrocycle (Figure 3, Scheme 1). The ^1H NMR spectrum of this product confirms the presence of a single compound of high effective symmetry (Figure S24, Supporting Information). Moreover, the filtrate obtained after filtration of cadmium derivative of **3a** indicates substantial amounts of even larger 8 + 8 macrocycle, as indicated by mass spectra (Figure S25, Supporting Information).

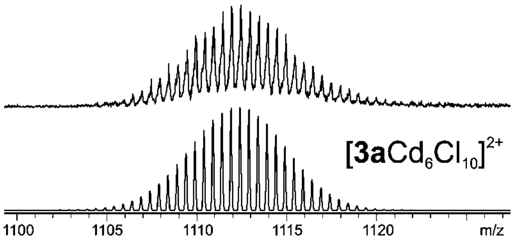


Figure 3. Experimental (top) and simulated (bottom) mass spectrum of the hexanuclear Cd(II) derivative of **3a**.

Reduction of cadmium complex of the Schiff base macrocycle 6 + 6 **3a** with sodium borohydride in methanol containing 3% of water (water was added in order to increase solubility of inorganic materials), followed by removal of Cd(II) as cadmium sulfide, resulted in the formation of analogous 6 + 6 macrocyclic amine **3b** (the synthesis was repeated several times, total yield 20−30%). The ^{1}H and ^{13}C NMR spectra of **3b** are different to those of **1b** and indicate the presence of a symmetric macrocyclic product (Figure 4). The neutral macrocyclic amine **3b** has been converted into the protonated form **3c** in the reaction with HCl (53% yield). The X-ray crystal structures (Figures 5 and 6, and Figures S31−S32, Supporting Information) of single crystals of the dodecahydrochloride derivative **3c** grown from water/acetonitrile mixture (denoted as **3c**^{a}) or from methanol/acetonitrile mixture (denoted as **3c**^{b}) confirm the presence of a 6 + 6 macrocycle.

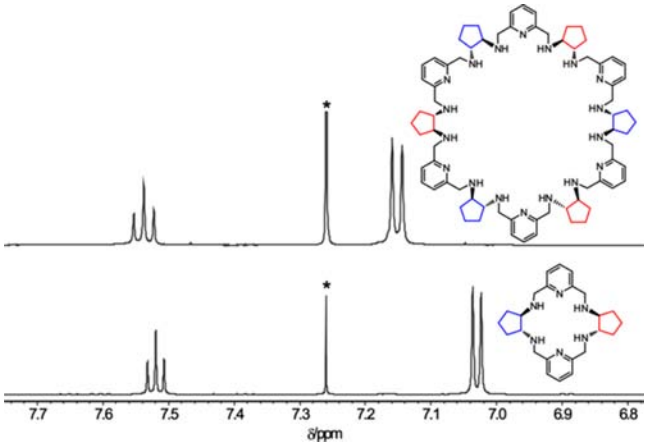


Figure 4. Comparison of the aromatic region of ^{1}H NMR spectra (500 MHz, $CDCl_3$) of **1b** and **3b**. * denote residual solvent signals.

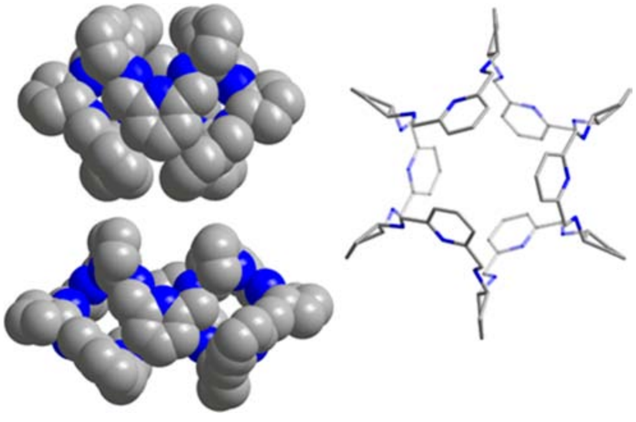


Figure 5. (Left bottom) Side view of **3c**^{a} (perpendicular to the noncrystallographic C_2 symmetry axis of the molecular structure). (Left top and right) Side and top views, respectively, of the molecular structure of **3c**^{b} (hydrogen atoms, chloride anions, and solvent molecules omitted for clarity).

In **3c**^{b} the dodecahydrochloride derivative of the 6 + 6 macrocyclic amine adopts an interesting folded conformation, which effectively results in a formation of a centrosymmetric container like molecule. (Figure 6 and Figure S32, Supporting Information). The macrocycle possesses a noncrystallographic S_6 symmetry axis and is of approximate D_{3d} symmetry. The S_6 axis is related to the presence of six compartments of the macrocycle. Each of these compartments contains a set of three nitrogen atoms belonging to the pyridine fragment and the two adjacent cyclopentane diamine fragments. In the protonated form **3c**^{b}, these compartments accommodate chloride anions via hydrogen bonds (Figure S32, Supporting Information); a similar situation is observed in the case of crystal form **3c**^{a} (**3c**^{a} of C_2 symmetry corresponds to a slightly elongated version of **3c**^{b}). In the neutral macrocycle **3b**, these compartments would be preorganized for the binding of metal ions. The Schiff base 6 + 6 precursor of **3b** has likely a similar geometry where each compartment is fitted with Cd(II) ion, resulting in the hexanuclear cadmium complex of **3a** indicated by the mass spectrum. One can hypothesize that the tendency of Cd(II) to coordinate to the pyridine nitrogen and the two neighboring nitrogen atoms of DACP in each loop compartment is the origin of the unusual templation effect and formation of large macrocycles. Thus, the [6 + 6] macrocycle may be the smallest symmetric cycle that permits such coordination pattern, and this could be the driving force for its formation. On the other hand, the structures of **1a** and **2a** indicate that the relative dispositions of the imine and pyridine nitrogen atoms are not preferable for the formation of Cd(II) complexes where all of these atoms would be engaged in metal coordination.

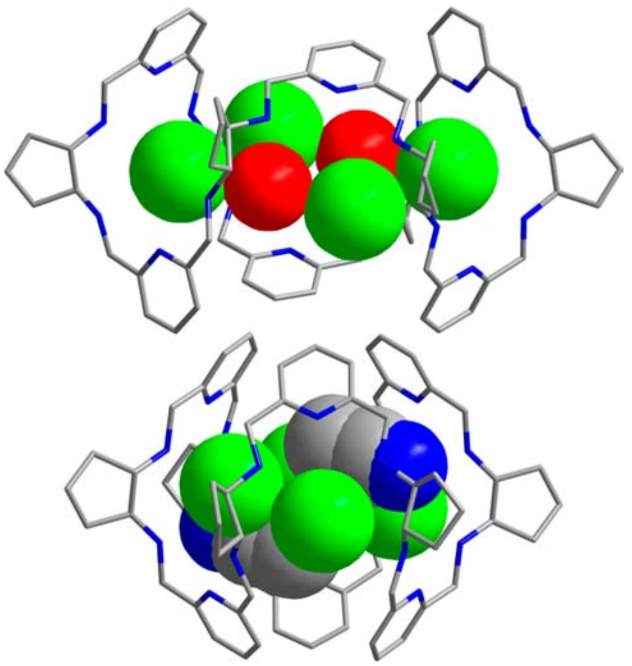


Figure 6. Protonated 6 + 6 macrocyclic amine surrounding four chloride anions and two water molecules in **3c**^{a} (top) or four chloride anions and two acetonitrile molecules in **3c**^{b} (bottom), hydrogen atoms omitted for clarity.

The interior of the protonated container-shaped amine molecule **3c**^{b} is occupied by four chloride anions and two acetonitrile solvent molecules (Figure 6). Similarly, in **3c**^{a} the macrocycle embraces four chloride anions and two water solvent molecules (Figure 6).

In contrast to the Cd(II) ion, the application of the smaller Zn(II) ion in the reaction with the 2 + 2 Schiff base **1a** under analogous conditions led to very unselective products, as indicated by spectroscopic data. In this case, the reduction of the mixture of Schiff base products by sodium borohydride results in a mixture containing the reduced unreacted macrocycle

2 + 2, a small amount of 6 + 6 macrocycle, as well as 4 + 4, 5 + 5, and 8 + 8 macrocycles and oligomeric 3 + 2, 5 + 4, 6 + 5, and 7 + 6 derivatives (Figures S26−S28, Supporting Information), yet a different result is observed with lanthanide(III) ions, which tend to prefer formation of racemic form of a chiral 2 + 2 macrocycle.

While the reactions of enantiopure DACP with DFP are very similar to those of enantiopure DACH, the same reactions of racemic DACP differ from the reactions of racemic DACH. In the latter case, the condensation in methanol results in the mixture meso-type 2 + 2 and 4 + 4 macrocycles,[8] and the application of Cd(II) template leads to highly diastereoselective amplification of a 3 + 3 heterochiral macrocycle from this dynamic combinatorial library.[9]

In summary, we have demonstrated an unprecedented template effect leading to a selective formation of 6 + 6 macrocycle **3**. Both the amine derivative **3b** and its precursor Schiff base macrocycle **3a** seem to be predisposed to bind six metal ions; thus, they may constitute a new platform for the formation of multinuclear complexes. It is also likely that bridging the structure of **3b** by further functionalization of amine nitrogen atoms will "freeze" the conformation of this macrocycle observed in the crystals **3c**^{b}, resulting in a new type of organic container molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details for the macrocycle synthesis and characterization (^{13}C and ^{1}H NMR spectra, views of molecular structures) as well as X-ray crystallographic information (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: janusz.gregolinski@chem.uni.wroc.pl.
*E-mail: jerzy.lisowski@chem.uni.wroc.pl.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by NCN Grant No. 2011/01/D/ST5/02816.

■ REFERENCES

(1) Selected recent examples of large macrocycles: (a) Kaitz, J. A.; Diesendruck, C. E.; Moore, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 12755−12761. (b) Kawai, H.; Utamura, T.; Motoi, E.; Takahashi, T.; Sugino, H.; Tamura, M.; Ohkita, M.; Fujiwara, K.; Saito, T.; Tsuji, T.; Suzuki, T. *Chem.—Eur. J.* **2013**, *19*, 4513−4524. (c) Li, M.; Klärner, F.-G.; Sakamoto, J.; Schlüter, A. D. *Chem.—Eur. J.* **2013**, *19*, 13348−13354. (d) Lee, S.; Chen, C.-H.; Flood, A. H. *Nat. Chem.* **2013**, *5*, 704−710. (e) Scully, C. C. G.; Rai, V.; Poda, G.; Zaretsky, S.; Burns, D. C.; Houliston, R. S.; Lou, T.; Yudin, A. K. *Chem.—Eur. J.* **2012**, *18*, 15612−15617. (f) Matsui, K.; Segawa, Y.; Itami, K. *Org. Lett.* **2012**, *14*, 1888−1891. (g) Fritzsche, M.; Bohle, A.; Dudenko, D.; Baumeister, U.; Sebastiani, D.; Richardt, G.; Spiess, H. W.; Hansen, M. R.; Höger, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3030−3033. (h) Jester, S.-S.; Shabelina, N.; Le Blanc, S. M.; Höger, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 6101−6105. (i) Feng, W.; Yamato, K.; Yang, L.; Ferguson, J. S.; Zhong, L.; Zou, S.; Yuan, L.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2009**, *131*, 2629−2637. (j) Tian, L.; Wang, C.; Dawn, S.; Smith, M. D.; Krause, J. A.; Shimizu, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 17620−17629.

(2) Selected examples of large Schiff base macrocycles: (a) Stadler, A.-M.; Jiang, J.-J.; Wang, H.-P.; Bailly, C. *Chem. Commun.* **2013**, *49*, 3784−3786. (b) Kim, M. J.; Choi, Y. R.; Jeon, H.-G.; Kang, P.; Choi, M.-G.; Jeong, K.-S. *Chem. Commun.* **2013**, *49*, 11412−11414. (c) Okochi, K. D.; Han, G. S.; Aldridge, I. M.; Liu, Y.; Zhang, W. *Org. Lett.* **2013**, *15*, 4296−4299. (d) Leeland, J. W.; White, F. J.; Love, J. B. *J. Am. Chem. Soc.* **2011**, *133*, 7320−7323. (e) Guieu, S.; Crane, A. K.; MacLachlan, M. J. *Chem. Commun.* **2011**, *47*, 1169−1171. (f) Jiang, J.; MacLachlan, M. J. *Org. Lett.* **2010**, *12*, 1020−1023. (g) Hui, J. K.-H.; MacLachlan, M. J. *Chem. Commun.* **2006**, 2480−2482. (h) Bru, M.; Alfonso, I.; Burguete, M. I.; Luis, S. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 6155−6159.

(3) (a) Zhao, C.; Ren, J.; Gregolinski, J.; Lisowski, J.; Qu, X. *Nucleic Acids Res.* **2012**, *40*, 8186−8196. (b) Krężel, A.; Lisowski, J. *J. Inorg. Biochem.* **2012**, *107*, 1−5. (c) Lisowski, J. *Inorg. Chem.* **2011**, *50*, 5567−5576. (d) González-Alvarez, A.; Alfonso, I.; Cano, J.; Díaz, P.; Gotor, V.; Gotor-Fernández, V.; García-España, E.; Garcia-Granda, S.; Jiménez, H. R.; Lloret, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 6055−6058. (e) Gregoliński, J.; Starynowicz, P.; Hua, K. T.; Lunkley, J. L.; Muller, G.; Lisowski, J. *J. Am. Chem. Soc.* **2008**, *130*, 17761−17773. (f) Gregoliński, J.; Lis, T.; Cyganik, M.; Lisowski, J. *Inorg. Chem.* **2008**, *47*, 11527−11534. (g) Gregoliński, J.; Lisowski, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6122−6126.

(4) (a) Kobyłka, M. J.; Ślepokura, K.; Acebrón Rodicio, M.; Paluch, M.; Lisowski, J. *Inorg. Chem.* **2013**, *52*, 12893−12903. (b) Sarnicka, A.; Starynowicz, P.; Lisowski, J. *Chem. Commun.* **2012**, *48*, 2237−2239. (c) Lin, S.-Y.; Guo, Y.-N.; Guo, Y.; Zhao, L.; Zhang, P.; Ke, H.; Tang, J. *Chem. Commun.* **2012**, *48*, 6924−6926. (d) Gao, J.; Zingaro, R. A.; Reibenspies, J. H.; Martell, A. E. *Org. Lett.* **2004**, *6*, 2453−2455.

(5) (a) Tashiro, S.; Kubota, R.; Shionoya, M. *J. Am. Chem. Soc.* **2012**, *134*, 2461−2464. (b) Bru, M.; Alfonso, I.; Bolte, M.; Burguete, M. I.; Luis, S. V. *Chem. Commun.* **2011**, *47*, 283−285. (c) López-Periago, A. M.; García-Gonzáles, C. A.; Domingo, C. *Chem. Commun.* **2010**, *46*, 4315−4317.

(6) (a) Kwit, M.; Plutecka, A.; Rychlewska, U.; Gawroński, J.; Khlebnikow, A. F.; Kozhushkov, S. I.; Rauch, K.; de Meijere, A. *Chem.—Eur. J.* **2007**, *13*, 8688−8695. (b) Kaik, M.; Gawroński, J. *Org. Lett.* **2006**, *8*, 2921−2924. (c) Gawroński, J.; Gawrońska, K.; Grajewski, J.; Kwit, M.; Plutecka, A.; Rychlewska, U. *Chem.—Eur. J.* **2006**, *12*, 1807−1817.

(7) (a) Fischmann, S.; Lüning, U. *Isr. J. Chem.* **2013**, *53*, 87−96. (b) Belovich, M. E.; Stoddart, J. F. *Chem. Soc. Rev.* **2012**, *41*, 2003−2024. (c) Klein, J. M.; Saggiomo, V.; Reck, L.; Lüning, U.; Sanders, J. K. M. *Org. Biomol. Chem.* **2012**, *10*, 60−66. (d) Klein, J. M.; Saggiomo, V.; Reck, L.; McPartlin, M.; Pantos, G. D.; Lüning, U.; Sanders, J. K. M. *Chem. Commun.* **2011**, *47*, 3371−3373. (e) Ulrich, S.; Lehn, J.-M. *J. Am. Chem. Soc.* **2009**, *131*, 5546−5559. (f) Herrmann, A. *Org. Biomol. Chem.* **2009**, *7*, 3195−3204. (g) Wessjohann, L. A.; Rivera, D. G.; Leon, F. *Org. Lett.* **2007**, *9*, 4733−4736. (h) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652−3711. (i) Storm, O.; Lüning, U. *Chem.—Eur. J.* **2002**, *8*, 793−798.

(8) Gregoliński, J.; Lisowski, J.; Lis, T. *Org. Biomol. Chem.* **2005**, *3*, 3161−3166.

(9) (a) Gonzalez-Alvarez, A.; Alfonso, I.; Gotor, V. *Chem. Commun.* **2006**, 2224−2226. (b) Gonzalez-Alvarez, A.; Alfonso, I.; Lopez-Oritz, F.; Aguirre, A.; Garcia-Granda, S.; Gotor, V. *Eur. J. Org. Chem.* **2004**, 1117−1127.

(10) Alfonso, I. *Curr. Org. Synth.* **2010**, *7*, 1−23.

(11) Gregoliński, J.; Lisowski, J. Unpublished results.

(12) (a) Gonzalez-Sabin, J.; Rebolledo, F.; Gotor, V. *Chem. Soc. Rev.* **2009**, *38*, 1916−1925. (b) Xu, Q.; Appella, D. H. *J. Org. Chem.* **2006**, *71*, 8655−8657.

(13) Takahashi, H.; Tsuboyama, S.; Umezawa, Y.; Honda, K.; Nishio, M. *Tetrahedron* **2000**, *56*, 6185−6191.