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Cyclic Tetramer of a Metalloporphyrin Based on a Quadruple Hydrogen Bond

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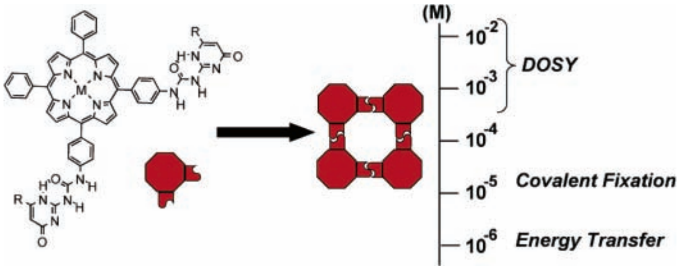
ABSTRACT



This paper describes the selective formation of a cyclic tetramer from a readily synthesized metalloporphyrin with two self-complementary quadruple hydrogen-bonding units. The extremely strong quadruple hydrogen-bonding unit, 2-ureido-4[1*H*]-pyrimidinone, enabled the formation of a stable cyclic tetramer based on a tetraphenylporphyrin derivative over a wide concentration range. This hydrogen-bonded tetramer is a new functional unit for use in a higher-ordered architecture of a supramolecular porphyrin assembly.

Much attention has been paid to the covalent architecture of a porphyrin array, motivated by its functions of biological importance such as a light-harvesting antenna.[1] Unfortunately, a covalent approach[2,3] intrinsically involves difficult synthetic efforts due to the tetrapyrrolic heterocyclic structure of a porphyrin ring. Therefore, it is quite reasonable to assume that the noncovalent architecture of a porphyrin array might be more advantageous because of a preorganized structure of the rigid porphyrin ring and its capability to be a molecular junction. Up to now, indeed, a variety of porphyrin arrays based on a noncovalent strategy mainly via axial coordination bonds have been extensively studied.[4] Compared to a coordination bond, the use of a hydrogen bond to fabricate a porphyrin array[5,6] is, nevertheless, limiting except for several synthetic porphyrins that are challenging to make. In general, the elegance of a supramolecule should be partially ensured by simple building blocks having good

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(1) (a) McDermott, G.; Prince, S. M.; Freer, A. A.; Hawthornthwalte-Lawless, A. M.; Papiz, M. Z.; Cogdell, R. J.; Isaacs, N. W. *Nature* **1995**, *374*, 517. (b) Roszak, A. W.; Howard, T. D.; Southall, J.; Gardiner, A. T.; Law, C. J.; Isaacs, N. W.; Cogdell, R. J. *Science* **2003**, *302*, 1969.

(2) Selected reviews about porphyrin arrays: (a) Lindsey, J. S. *New. J. Chem.* **1991**, *15*, 153. (b) Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435. (c) Satake, A.; Kobuke, Y. *Tetrahedron* **2005**, *61*, 13.

(3) Selected examples for a porphyrin array fabricated by a covalent bond: (a) Wagner, R. W.; Seth, J.; Yang, S. I.; Kim, D.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **1998**, *63*, 5042. (b) Peng, X.-B.; Aratani, N.; Takagi, A.; Matsumoto, T.; Kawai, T.; Hwang, I.-W.; Ahn, T.-K.; Kim, D.-H.; Osuka, A. *J. Am. Chem. Soc.* **2004**, *126*, 4468. (c) Tsuda, A.; Osuka, A. *Science* **2001**, *293*, 79. (d) Nakano, A.; Osuka, A.; Yamazaki, T. *Chem.−Eur. J.* **2001**, *7*, 3134.

(4) Selected examples for a porphyrin array fabricated by a coordination bond: (a) Drain, C. M.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1994**, 2313. (b) Shoji, O.; Okada, S.; Satake, A.; Kobuke, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2201. (c) Kuramochi, Y.; Satake, A.; Kobuke, Y. *J. Am. Chem. Soc.* **2004**, *126*, 8668. (d) Ikeda, C.; Satake, A.; Kobuke, Y. *Org. Lett.* **2003**, *5*, 4935. (e) Tsuda, A.; Sakamoto, S.; Yamaguchi, K.; Aida, T. *J. Am. Chem. Soc.* **2003**, *125*, 15722. (f) Ambroise, A.; Li, J.; Yu, L.; Lindsey, J. S. *Org. Lett.* **2000**, *2*, 2563.

(5) For hydrogen-bonded porphyrin arrays, see: (a) Drain, C. M.; Shi, X.; Milic, T.; Nifiatis, F. *Chem. Commun.* **2001**, 287. (b) Shi, X.; Barkigia, K. M.; Fajer, J.; Drain, C. M. *J. Org. Chem.* **2001**, *66*, 6513. (c) Drain, C. M.; Fischer, R.; Nolen, E. G.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 243. (d) Ikeda, C.; Nagahara, N.; Motegi, E.; Yoshioka, N.; Inoue, H. *Chem. Commun.* **1999**, 1759. (e) Balaban, T. S.; Eichhoffer, A.; Lehn, J.-M. *Eur. J. Org. Chem.* **2000**, 4047. (f) Sessler, J. L.; Wang, B.; Harriman, A. *J. Am. Chem. Soc.* **1995**, *117*, 704.

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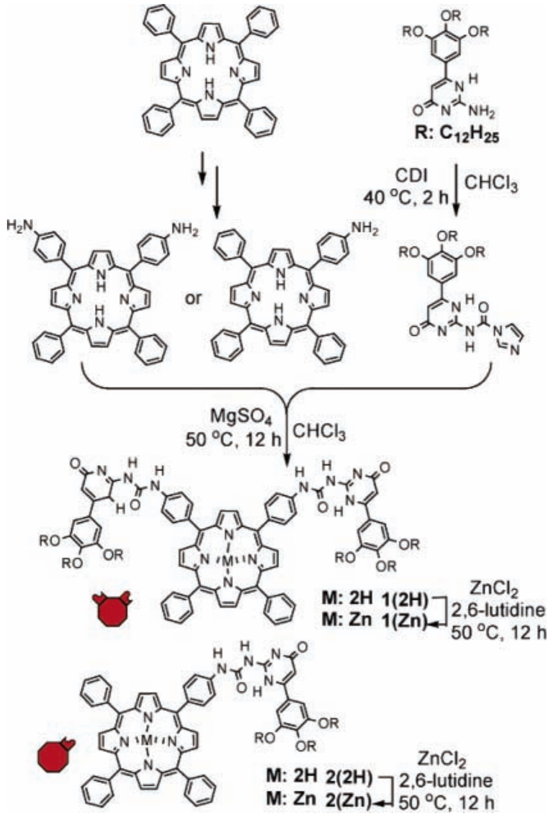
Scheme 1



synthetic accessibility. As the pioneers pointed out, establishing an efficient synthetic method for a porphyrin possessing multivalent hydrogen-bonding units is a key issue.[5b] However, it is inevitable that one would encounter a simple dilemma when one tries to fabricate a hydrogen-bonded porphyrin array of significant stability; for the stronger hydrogen-bonding unit, harder synthetic efforts would be required. As an antidote against such a perplexing situation, applying a strong hydrogen-bonding unit,[7,8] 2-ureido-4[1*H*]-pyrimidinone (UPy), is a favorable approach because it has both the ability to form a strong duplex via a self-complementary quadruple hydrogen bond ($K_{ass} > 10^7\ M^{-1}$)[9] and synthetic accessibility. Herein, we report the straightforward synthesis of a metalloporphyrin **1** bearing two UPy moieties at the 10- and 15-positions (Scheme 1) and its selective and spontaneous cyclization to a tetramer, which is stable over a wide concentration range. Simultaneously, we show the possibility that the present cyclic tetramer can be a new functional unit toward higher-ordered supramolecular porphyrin arrays.

The porphyrin **1(2H)** was synthesized by the reaction between the activated isocytosine[10] and 5,10-bis(4-aminophenyl)-15,20-diphenylporphyrin, which can be readily prepared from a commercially available free-base *meso*-tetraphenylporphyrin (TPP).[11] The activated isocytosine substituted by an aromatic ring at the 6-position of the pyrimidinon ring was not as stable as the one with an aliphatic chain. The activated isocytosine was partially deactivated by water during a workup procedure. However, by the simultaneous and immediate addition of aminoporphyrin and magnesium sulfate to an organic layer after quenching an excess carbonyldiimidazole (CDI) by water, deactivation could be minimized; hence, the porphyrin **1(2H)** could be synthesized in good yield.

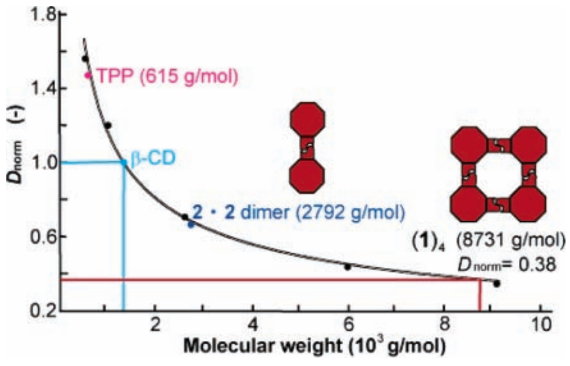


Figure 1. Calibration curve of molecular weight vs the diffusion coefficient of a polystyrene (PDI < 1.05, at 7.2 mg/mL) and determination of the molecular weight of porphyrin **1(2H)** in chloroform.

To estimate the molecular weight of the porphyrin **1(2H)** in solution, DOSY (diffusion ordered spectroscopy) was performed.[12,13] The molecular weight could be successfully calibrated by the normalized diffusion coefficient D_{norm} of a polystyrene with regulated molecular weights (Figure 1), which was defined as the ratio to the diffusion coefficient

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[6] Hydrogen bonds have also been applied for fabricating a hemoprotein mimic. For example: (a) Arai, S.; Ohkawa, H.; Ishihara, S.; Shibue, T.; Takeoka, S.; Nishide, H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 2007. (b) Ohkawa, H.; Arai, S.; Takeoka, S.; Nishide, H. *Chem. Lett*. **2003**, *32*, 1052. (c) Hayashi, T.; Asai, T.; Hokazono, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 12210.

[7] Recent reviews about a multiple hydrogen-bonding unit: (a) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5. (b) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63.

[8] Recent examples about a supramolecular architecture using multiple hydrogen-bonding units: (a) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 810. (b) Park, T.; Todd, E. M.; Nakashima, S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2005**, *127*, 18133. (c) Meyer, M. F.; Nakashima, S.; Zimmerman, S. C. *Org. Lett.* **2005**, *7*, 3005. (d) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128.

[9] (a) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601. (b) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487. (c) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761.

[10] Keizer, H. M.; Sijbesma, R. P.; Meijer, E. W. *Eur. J. Org. Chem.* **2004**, 2553.

[11] Lugaaya, R.; Jaquinood, L.; Fronczek, F. R.; Vicente, M. G. H.; Smith, K. M. *Tetrahedron* **2004**, *60*, 2757.

[12] Mass spectrometry (MALDI-TOF, CSI-TOF) was unsuccessful to detect the molecular ion signal of the assembly of porphyrin **1(2H)**.

[13] The evaluation of molecular weight by DOSY has also been reported in the literature: (a) Viel, S.; Capitani, D.; Mannina, L.; Segre, A. *Biomacromolecules* **2003**, *4*, 1843. (b) Zhao, T.; Beckham, H. W. *Macromolecules* **2003**, *36*, 9859. (c) Zhao, T.; Beckham, H. W.; Gibson, H. W. *Macromolecules* **2003**, *36*, 4833. (d) Michelsen, U.; Hunter, C. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 764.

of an internal standard, heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (β-CD). The data plots for the mono-UPy-substituted porphyrin **2(2H)** (which should exist as a dimer) and TPP were well fitted to the calibration curve. This result indicated reliability of the calibration curve. The estimated molecular weight of 8600 g/mol for **1(2H)** ($D_{\mathrm{norm}} = 0.38$), given experimental error, was virtually identical to that calculated as a tetramer (8731 g/mol). It is also noteworthy that the D_{norm} values of **1(Zn)** were almost comparable to those of **1(2H)**, indicating the selective formation of the cyclic tetramer of the metalloporphyrin (Table 1).[14]

Table 1. Diffusion Coefficients of Metalloporphyrins **1** Relative to Methylated β-Cyclodextrin in $CDCl_3$ at Room Temperature

	D_{norm} (−)	estimated M_{w} (g/mol)	M_{w} (calcd) (g/mol)
TPP	1.48	630	615
2(2H)	0.65	3000	2792[a]
β-CD	1.00		1430
1(2H)	0.38	8600	8731[b]
1(Zn)	0.37[c]	8900	8992

[a] Calculated as a dimer. [b] Calculated as a tetramer. [c] Measured with the addition of 10 equiv of 1-(4,4′-dimethoxytrityl)-1*H*-imidazole to prevent aggregation.

The concentration dependency of the diffusion coefficients of the porphyrin **1** was investigated to reveal the ring-chain equilibrium of the porphyrins (Figure 2).[15,16] The D_{norm} value of **1(2H)** was concentration independent up to a certain concentration, which is a characteristic behavior of ring formation. An increase in the concentration should induce a significant decrease in D_{norm} due to the polymerization, as seen in the typical supramolecular polymer **3**,[17,18] whereas the D_{norm} values of the porphyrin **1(2H)** showed a slightly gradual decrease that is considered to be due to the aggregation via the $\pi-\pi$ stacking rather than to the ring-opening polymerization.[19] All these results suggested that a cyclic tetramer of a porphyrin **1(2H)** was quite stable in a wide concentration range up to at least 20 mM.[20]

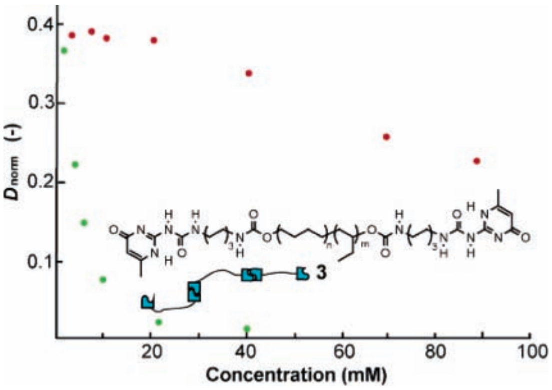

Figure 2. Concentration dependency of the D_{norm} value of porphyrin **1** (red circles) and typical supramolecular polymer **3** (green cirlces) in $CDCl_3$.

To support the tetramer formation by a conventional analysis, an analogue of **1(2H)** was synthesized, which possesses double bonds for the covalent fixation by an olefin metathesis (Figure 3a). After treating **4** with the Grubbs catalyst in a diluted condition (24 μM), the partially cross-linked porphyrin **5a** and fully cross-linked porphyrin **5b** were obtained.[21] Porphyrin **5b** could be successfully analyzed by

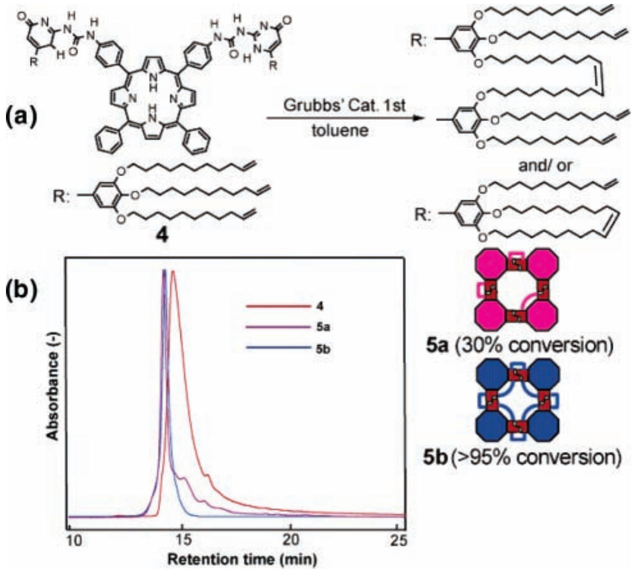

Figure 3. (a) Covalent fixation of porphyrin **4** via olefin metathesis. Reaction conditions for **5a**: 24 μM, 25 mol % cat., 3 h. For **5b**: 24 μM, 100 mol % cat., 5 h. (b) Elution curves in the size exclusion chromatography of porphyrin **4** (red line), **5a** (purple), and **5b** (blue). Chloroform was used as an eluent.

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[14] The lifetime of the quadruple hydrogen-bonded dimer **2(Zn)·2(Zn)** was determined by EXSY (exchange spectroscopy) as 130 ms, which was comparable to that of **2(2H)·2(2H)** as well as to the reported value. (See ref 9b.) The quadruple hydrogen bond could resist a 10 equiv addition of imidazole, although the lifetime was somewhat shorter (80 ms). A full investigation about a lifetime in various conditions will be reported elsewhere.

[15] Keizer, H. M.; Gonzalez, J. J.; Segura, M.; Prados, P.; Sijbesma, R. P.; Meijer, E. W.; de Mendoza, J. *Chem.−Eur. J.* **2005**, *11*, 4602.

[16] (a) Folmer, B. J. B.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2001**, *123*, 2093. (b) Jacobson, H.; Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 1600.

[17] Folmer, B. J. B.; Sijbesma, R. P.; Versteegen, G. M.; van der Rijt, J. A. J.; Meijer, E. W. *Adv. Mater.* **2000**, *12*, 874.

[18] A porphyrin bearing two UPy moieties at the 5- and 15-positions was also synthesized as a reference, which should tend to form a linear structure rather than a cyclic structure. However, the porphyrin was insoluble in any apolar solvents at room temperature, probably because of the polymerization. This insolubility also supports the ring formation of the porphyrin **1**.

[19] The concentration dependency of porphyrins **5a** and **5b** can also be seen in the Supporting Information.

[20] Templated porphyrin **5b** was able to exist as a tetramer in the solid phase. The stability of the nontemplated porphyrin tetramer in the solid phase is under investigation. To our best knowledge, the cooperative quadruple hydrogen bond was observed in a competition experiment, intimating its possibility to exist as a tetramer in the solid phase.

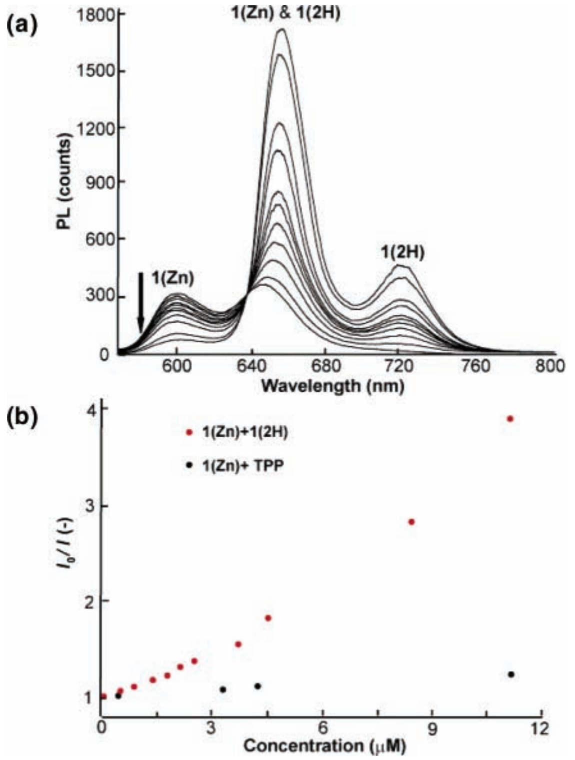

Figure 4. (a) Fluorescence spectra from a titration of **1(2H)** to **1(Zn)** measured in chloroform at room temperature upon illumination at $\lambda_{exc} = 550$ nm, with the constant concentration of **1(Zn)** at 3.2 μM. Each spectrum was recorded using separate solutions containing a different ratio of **1(Zn)** to **1(2H)**, prepared 12 h in advance of the measurement. (b) Stern−Volmer plots of energy-transfer (from **1(Zn)** to **1(2H)**) titrations at [**1(Zn)**] = 3.2 μM.

size-exclusion chromatography (SEC) without any dissociation by a continuous dilution during the elution (Figure 3b). The molecular weight determined from the peak top of the elution curve was approximately 7000 g/mol for **5b**. Because the hydrodynamic volume of a cyclic molecule is smaller than that of a linear molecule,[4b] this result strongly supported the fact that the porphyrin **1(2H)** and **4** formed a tetramer at 24 μM.

We have performed energy-transfer experiments using **1(Zn)** and **1(2H)** as a donor and an acceptor, respectively, to demonstrate both the formation of the cyclic tetramer under very dilute conditions and its potential functions. It is known that the immediate exchange and equilibration can take place when two kinds of UPy derivatives are mixed. For example, in a mixed solution of UPy bound to a donor and UPy bound to an acceptor, the statistical mixture of the donor−donor, donor−acceptor, and acceptor−acceptor duplex is quickly formed, and hence the energy transfer is induced.[22] On the other hand, very interestingly, upon a simple titration of **1(2H)** to **1(Zn)**, no energy transfer was indicated. At least 12 h was required before the energy transfer was successfully observed (Figure 4). This extremely slow equilibration strongly indicated the slow exchange due to the cooperative hydrogen bond in **1(Zn)** and **1(2H)**,[20] namely, the ring formation of **1(Zn)** and **1(2H)**. Despite the relatively low efficiency of the energy transfer in the ring,[23] probably due to the long distance between the adjacent chromophores and the uncompleted exchange, the cyclic tetramer consisting of **1(Zn)** and/or **1(2H)** did act as a functional unit for applications in light-harvesting modules.

In summary, the strong, self-complementary quadruple hydrogen-bonding unit, UPy, enabled the formation of a cyclic tetramer from a readily synthesized metalloporphyrin over a wide concentration range. According to the energy-transfer measurements, this tetramer would act as a new functional unit in a higher-ordered metalloporphyrin assembly. The noncovalent architecture using the hydrogen-bonded cyclic tetramer as a building block is currently in progress.

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Supporting Information Available: Synthetic details of all porphyrin derivatives and 2D-NMR experiments, as well as the additional supporting data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Precipitation during olefin metathesis caused by the intercyclic tetramer cross-linking was not observed. Deactivation of the catalyst was confirmed by the addition of 2-norbornene to the portion of the reaction mixture in advance of the evaporation step in the purification procedure.

(22) (a) Neuteboom, E. E.; Beckers, E. H. A.; Meskers, S. C. J.; Meijer, E. W.; Janssen, R. A. J. *Org. Biomol. Chem.* **2003**, *1*, 198. (b) Dudek, S. P.; Pouderoijen, M.; Abbel, R.; Schenning, A. P. H. J.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 11763.

(23) Van Patten, P. G.; Shreve, A. P.; Lindsey, J. S.; Donohoe, R. J. *J. Phys. Chem. B* **1998**, *102*, 4209.