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Oligobisvelcraplex: Self-Assembled Linear Oligomer by Solvophobic π−π Stacking Interaction of Bisvelcrands Based on Resorcin[4]arene

Hyejae Ihm,[†] Jae-Suk Ahn,[†] Myoung Soo Lah,[‡,§] Young Ho Ko,[‖] and Kyungsoo Paek*,[†,‡]

CAMDRC and Department of Chemistry, Soongsil University, Seoul 156-743, Korea, Department of Chemistry and Applied Chemistry, Hanyang University, Ansan 426-791, Korea, Center for Bioactive Molecular Hybrids, Yonsei University, Seoul 120-749, Korea, and Center for Smart Supramolecules, Pohang University of Science and Technology, Pohang 790-784, Korea

kpaek@ssu.ac.kr

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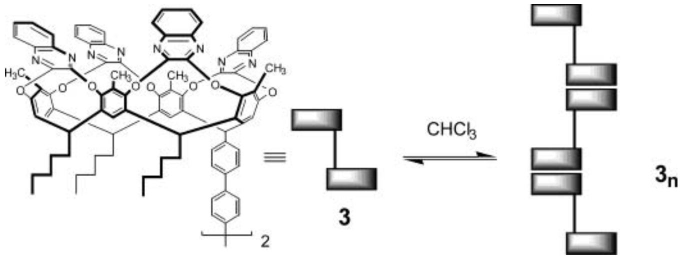
ABSTRACT



Bisvelcrand 3 based on resorcin[4]arene was obtained by a stepwise route, and the formation of oligobisvelcraplex 3_n by solvophobic π−π stacking interaction was observed. ^{1}H NMR spectroscopic studies revealed that $\Delta G^{\ddagger}_{\text{pseudorotation}}$ of oligobisvelcraplex 3_n is 16.7 kcal mol^{-1} in $C_6D_5NO_2$ solution. The pulsed field gradient spin−echo (PGSE) NMR experiment and VPO experiment showed that the number of aggregation (*n*) ranges from 7 to 10 in $CHCl_3$ solution at 298 K. In high concentration, bisvelcrand 3 tends to form gels or fiber.

The self-assembly of low-molecular-weight building blocks into polymeric nanostructures has attracted considerable interests for application in nanotechnology.[1] Multiple interactions between self-organizing building blocks promote the construction of well-defined supramolecular polymeric structures comparable to covalent polymers. These self-assembled systems are held together by reversible noncovalent forces such as hydrogen bonds,[2] metal−ion coordination,[3] or solvophobic π−π stacking interactions. Among these, the

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[†] Soongsil University.

[‡] Yonsei University.

[§] Hanyang University.

[‖] Pohang University of Science and Technology.

(1) (a) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071. (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382. (c) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988. (d) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348. (e) Lehn, J. M. *Chem. Eur. J.* **2000**, *6*, 2097. (f) Whitesides, G. M.; Boncheva, M. *Proc. Natl. Acad. Sci. USA.* **2002**, *99*, 4769. (g) Clark, T. D.; Tien, J.; Duffy, D. C.; Paul, K. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **2001**, *123*, 7677. (h) Pease, A. R.; Jeppesen, J. O.; Stoddart, J. F.; Luo, Y.; Collier, C. P.; Heath, J. R. *Acc. Chem. Res.* **2001**, *34*, 433.

(2) Self-assembled polymeric structures using hydrogen bonding: (a) Ashton, P. R.; Collins, A. N.;. Fyfe, M. C. T.; Menzer, S.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 735. (b) Castellano, R. K.; Nuckolls, C.; Eichhorn, S. H.; Wood, M. R.; Lovinger, A. J.; Rebek J. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2603. (c) Yamaguchi, N.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 143. (d) Klok, H.-A.; Jolliffe, K. A.; Schauer, C. L.; Prins, L. J.; Spatz, J. P.; Möller, M.; Timmerman, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1999**, *121*, 7154. (e) Fenniri, H.; Mathivanan, P.; Vidale, K. L.; Sherman, D. M.; Hallenga, K.; Wood, K. V.; Stowell, J. G. *J. Am. Chem. Soc.* **2001**, *123*, 3854. (f) Schenning, A. P. H. J.; v. Herrikhuyzen, J.; Jonkheijm, P.; Chen, Z.; Würthner, F.; Meijer, E. W. *J. Am. Chem. Soc.* **2002**, *124*, 10252.

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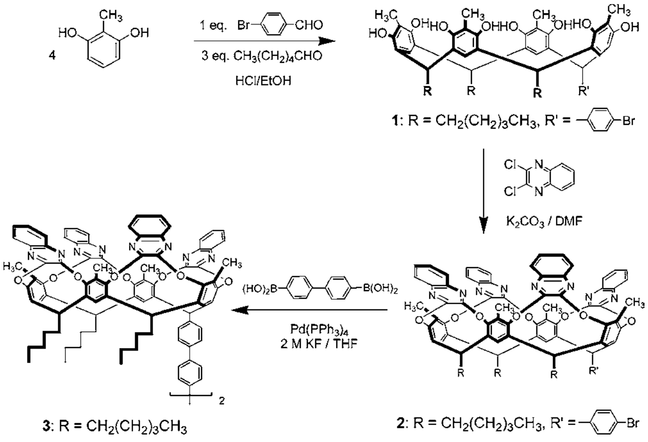
nanostructural systems formed mainly by $\pi-\pi$ stacking interaction are quite limited.[4]

Velcrands self-dimerize to velcraplex by solvophobic $\pi-\pi$ interactions of their large common surfaces in which the 2-methyl groups of a velcrand insert into the aryl cavity of its partner.[5] Recently Dalcanale et al. reported a dynamic polyvelcraplex by solvophobic $\pi-\pi$ stacking interaction and metal coordination.[6] When two velcrands were covalently linked through their feet, an unprecedented polyvelcraplex only by $\pi-\pi$ stacking interaction could be formed. Here we report on the synthesis of bisfunctional velcrand **3** and its characteristics as an oligomeric self-assembly.

Hexadecols, which consists of two octols (resorcin[4]arene or methylresorcin[4]arene) connected through a biphenyl foot in a back-to-back fashion, were synthesized by heterogeneous condensation among resorcinol or 2-methylresorcinol, hexanal, and 4,4′-bisformylbiphenyl.[7] However, when tetramethylhexadecol was condensed with 2,3-dichloroquinoxaline, the corresponding bisvelcrand could not be isolated. Therefore, a stepwise route for bisvelcrand **3** was developed as shown in Scheme 1. Heterocondensation among 2-methyl resorcinol and a 3:1 molar ratio of hexanal and 4-bromobenzaldehyde in a solution of EtOH and HCl at 60 °C gave octol **1** in 35% yield. Octol **1** was reacted with 2,3-dichloroquinoxaline in a mixture of K_2CO_3 and DMF at room temperature to afford a velcrand **2** in 40% yield. Under the Pd(0)-catalyzed Suzuki coupling reaction between velcrand **2** and 4,4′-biphenyldiboronic acid in a mixture of THF and an aqueous KF solution (2 M),[8] bisvelcrand **3** was obtained in 45% yield. Velcrands **2** and **3** were characterized by ^{1}H NMR and MALDI-TOF MS spectra and elemental analyses.

Scheme 1. Synthesis of Bisvelcrand **3**



A high degree of association between the repeating units is a prerequisite for forming a high degree of self-assembly. The stability of oligovelcraplex by **3** could be assumed from that of velcraplex **2**, which has the same aromatic surface as that of bisvelcrand **3**. Since the exchange rate between monomeric and dimeric species of velcrand **2** is slow on the NMR time scale, the association constant (K_a) of velcrand **2** was determined to be 4.9 × 10^4 M^{-1} in $CDCl_3$ at 298 K by the single-point method,[5] which gave free energy ($-\Delta G°$) of 6.4 kcal/mol (Table 1). As the polarity of the solvent increases, the dimerization constants of **2** increase due to the enhanced solvophobic driving forces. In over 20% CD_3OD in $CDCl_3$, velcrand **2** existed exclusively as velcraplex. The MALDI-TOF spectrum of velcrand **2** showed a velcraplex peak of 5% intensity.

Table 1. Association Constants (K_a) and Free Energies ($-\Delta G°$) for Dimerization[a] of the Velcrand **2** in Various Solvents at 25°C

solvent	K_a [M^{-1}]/10^4	$-\Delta G°$ [kcal mol^{-1}]
$CDCl_3$	4.9	6.4
5% CD_3OD[b]	9.5	6.8
10% CD_3OD[b]	176.0	8.5
20% CD_3OD[b]	dimer	dimer

[a] See ref 5. The initial concentration was 10 mM. [b] In $CDCl_3$ solution.

The X-ray crystal structure of velcrand **2** shows its velcraplex structure as shown in Figure 1.[9] Even though the feet are disordered, the $\pi-\pi$ stacking of aromatic surfaces are intact to those of velcraplex.[5]

The ^{1}H NMR spectrum of bisvelcrand **3** in $CDCl_3$ (3.54 mM) at 298 K showed two kinds of methyl peaks (δ 3.17 for out, δ 2.33 for up) and three kinds of methine peaks (δ 3.47, 3.57, 5.14). As this solution is diluted from 3.54 to 0.10 mM, the methyl peaks for monomeric species started to appear at 2.67 (for out methyls) and 2.53 (for up methyls)

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(3) Self-assembled polymeric structures using metal-coordination: (a) Biradha, K.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3392. (b) Noveron, J. C.; Lah, M. S.; Del Sesto, R. E.; Arif, A. M.; Miller, J. S.; Stang, P. J. *J. Am. Chem. Soc*. **2002**, *124*, 6613. (c) Michelsen, U.; Hunter, C. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 764. (d) Velten, U.; Lahn, B.; Rehahn, M. *Macromol. Chem. Phys*. **2003**, *198*, 2789. (e) Andress, P. R.; Schubert, U. S. *Adv. Mater*. **2004**, *16*, 1043.

(4) Self-assembled polymeric structures using $\pi-\pi$ stacking interaction: (a) Lahiri, S.; Thompson, J. L.; Moore, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 11315. (b) Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Soc.* **2002**, *124*, 5350. (c) Höger, S.; Bonrad, K.; Mourran, A.; Beginn, U.; Möller, M. *J. Am. Chem. Soc.* **2001**, *123*, 5651. (d) Saiki, Y.; Sugiura, H.; Nakamura, K.; Yamaguchi, M.; Hoshi, T.; Anzai, J. *J. Am. Chem. Soc*. **2003**, *125*, 9268. (e) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210. (f) Mansikkamäki, H.; Nissinen, M.; Rissanen, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1243.

(5) Cram, D. J.; Choi, H. J.; Bryant, J. A.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7748.

(6) Pirondini, L.; Stendardo, A. G.; Geremia, S.; Campagnolo, M.; Samori, P.; Rabe, J. P.; Fokkens, R.; Dalcanale, E. *Angew. Chem., Int. Ed.* **2003**, *42*, 1384.

(7) (a) Paek, K. *Bull. Korean Chem. Soc.* **1994**, *15*, 706. (b) Paek, K.; Tunstad, L. M. G.; Maverick, E. M.; Knobler, C. B.; Cram, D. J. *J. Incl. Phenom. Macrocycl. Chem.* **2003**, *45*, 203.

(8) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(9) Crystal structure of **2**: $C_{89}H_{81}BrN_8O_9$, M = 1486.53, colorless crystal 0.80 × 0.50 × 0.45 mm, monoclinic C2/*c*, $a = 36.820(3)$, $b = 29.693(3)$, $c = 38.200(3)$ Å; $\alpha = 90°$, $\beta = 113.646(2)°$, $\gamma = 90°$; $V = 38257(6)$ Å^3, $Z = 16$, $\rho_{calcd} = 1.032$ mg/m^3(including solvent), μ(Mo Kα, $\lambda = 0.71073$ Å) = 0.482 mm^{-1}, $2\theta_{max} = 56.64°$; 120 558 measured reflections, 45 568 unique of which 10 057 were observables [$I > 2\sigma(I)$]. The structure was solved by direct methods and refined by full-matrix least squares calculations with SHELXTL. The final $R_1 = 0.2233$, w$R_2 = 0.5004$ for 10 057 reflections of $I > 2\sigma(I)$; measurements: Brukers SMART CCD equipped with a graphite crystal incident-beam monochromator.

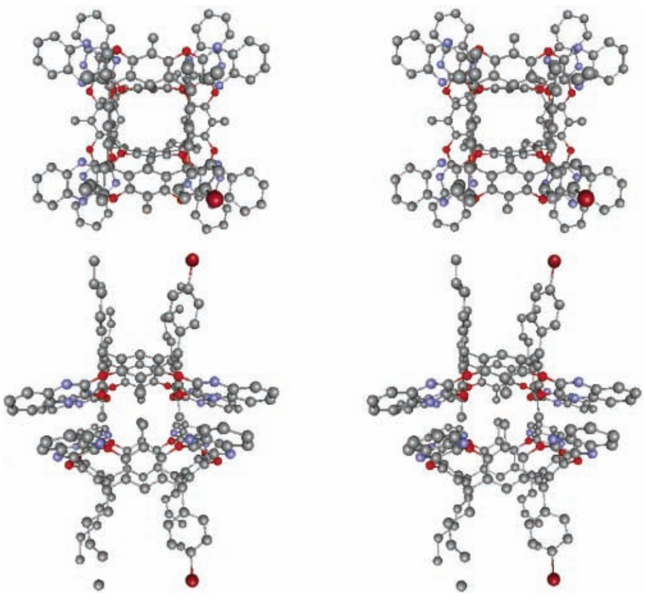

Figure 1. Stereoviews of X-ray crystal structure of velcraplex **2**: top-view (upper) and side-view (lower). The feet are disordered. Hydrogens and solvents are omitted for clarity.

ppm. These chemical shifts at high concentration (0.5 ppm downfield shift for out methyl, 0.2 ppm upfield shift for up methyls) prove the oligovelcraplex formation of **3** in solution.

The energy barrier for pseudorotation between the so-called kite conformers of oligobisvelcraplex $\mathbf{3}_{\boldsymbol{n}}$ was observed by ^{1}H NMR VT experiment.[10] As the temperature was increased from 25 to 100 °C, the chemical shifts of methyls of oligovelcraplex $\mathbf{3}_{\boldsymbol{n}}$ in $C_6D_5NO_2$ were observed as shown in Figure 2. As the temperature increases, the two kinds of methyl proton peaks (centered at 3.08, 3.88 ppm) broadened and coalesced as a doublet at about 90 °C to provide $\Delta G^{\ddagger}$ of 16.7 kcal mol^{-1}. When velcrand **2** was studied in the same conditions, $\Delta G^{\ddagger}$ of 15.7 kcal mol^{-1} was observed. The higher $\Delta G^{\ddagger}$ of oligovelcraplex **3** in solution than velcraplex **2** also supports that bisvelcrand **3** exists as oligobisvelcraplex $\mathbf{3}_{\boldsymbol{n}}$ in solution, imposing a larger hindrance to fast equilibrium between kite structures on the ^{1}H NMR time scale.

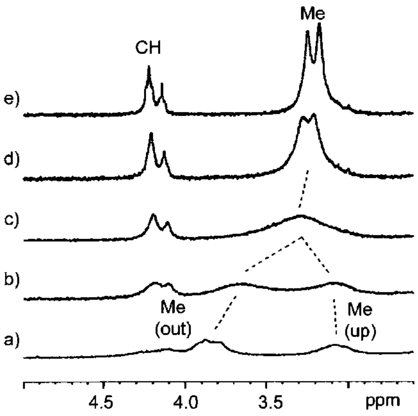

Figure 2. Partial variable-temperature ^{1}H NMR spectra (400 MHz) of bisvelcrand **3** in $C_6D_5NO_2$ (3.5 mM) at (a) 25, (b) 60, (c) 75, (d) 90, and (e) 100 °C.

The pulsed-field gradient spin−echo (PGSE) NMR technique[11] was used to measure the diffusion coefficients of $CDCl_3$ solution of **2** or **3** at 298 K. As the solution of **2** is concentrated from 0.2 to 4 mM, the diffusion coefficient of **2** decreases from $5.7 \pm 0.2 \times 10^{-10}$ to $4.9 \pm 0.2 \times 10^{-10}$ m^2 s^{-1}, respectively, which means that the overall average size of **2** increases, supporting the dimerization of **2**. In the case of bisvelcrand **3**, the measured diffusion coefficient shows a noticeable change at concentrations from 0.1 to 0.3 mM as shown in Figure 3. The concentration dependence of the diffusion coefficients indicates that bisvelcrand **3** oligomerizes as its concentration increases. And then, from the concentration of 0.4 mM, the diffusion coefficient decreases slightly. The overall volume estimated from the diffusion coefficient at 1.5 mM is approximately 10 times larger than that obtained at 0.1 mM. Such an oligomerization of bisvelcrand **3** was disrupted by adding velcrand **2**. The diffusion coefficient of **3** at 2.0 mM $CDCl_3$ increased remarkably from $1.4 \pm 0.1 \times 10^{-10}$ m^2 s^{-1} to $3.4 \pm 0.1 \times 10^{-10}$ m^2 s^{-1} upon addition of 2 equiv of **2**.

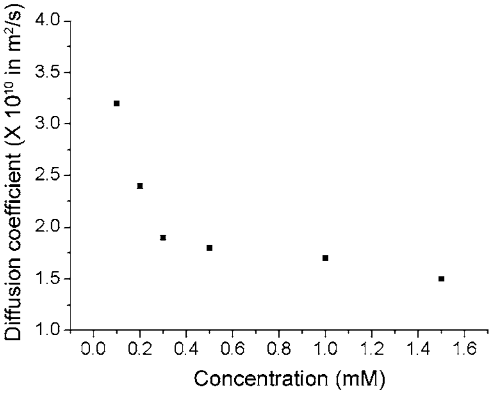

Figure 3. Concentration dependence of diffusion coefficient of polyvelcraplex **3** in $CDCl_3$ at 298 K.

The size of oligobisvelcraplex $\mathbf{3}_{\boldsymbol{n}}$ in $CHCl_3$ at 40 °C was also observed by vapor pressure osmometry (VPO).[12] As the stoichiometric concentration of **3** increases from 7 to 20 g/kg (solute/solvent), the mean molecular weight was gradually increased from 5600 to 20 000 Da (2821 Da for **3**) and saturated at 20 000 Da. This implies that bisvelcrand **3** exists as averaged heptameric oligovelcraplex $\mathbf{3}_{\boldsymbol{n}}$ ($n = 7$) in $CHCl_3$ at 40 °C.

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(10) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707.

(11) (a) Stejskal, E. O.; Tanner, J. E. *J. Chem. Phys.* **1965**, *1*, 159. (b) Stilbs, P. *Prog. Nucl. Magn. Reson. Spectrosc.* **1987**, *19*, 1. (c) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148.

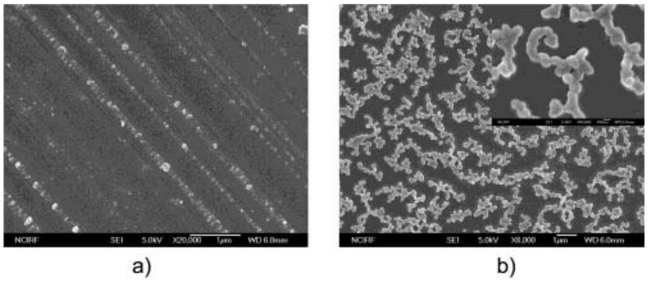
(12) (a) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1330. (b) Shetty, A. S.; Zhang, J.; Moore, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 1019. (c) Issacs, L.; Witt, D.; Lagona, J. *Org. Lett.* **2001**, *3*, 3221.

When bisvelcrand **3** was dissolved in chloroform or THF under the high concentration, the solution became turbid, showing polymerlike viscoelastic behavior. Since the presence of elongated stacks is a possibility in formation of macroscopic organogels, the minimal gel concentration (wt %) of **3** was determined to be 11 wt % in chloroform and 13 wt % in THF. Although the bisvelcrand **3** generally needs a higher minimal concentration than the typical organogels (<5 wt %), macroscopic gelation seems to be due to the fiber-forming property of bisvelcrand **3** in concentrated solution.

When the more concentrated polybisvelcraplex $\mathbf{3}_n$ was viewed between crossed polarizers with an optical microscope, it was birefringent and produced the polymeric optical textures. The ability to pull fibrous structures from the polymer is similar to the characteristic of other hydrogen-bonded polymers.[2] This indicates a high degree of the linear chain extension of polybisvelcraplex $\mathbf{3}_n$.

Scanning electron microscopy was used to study the microscopic structure of polybisvelcraplex $\mathbf{3}_n$. The electron micrographs of the sample formed by bisvelcrand **3** in $CHCl_3$ revealed nicely aligned linear strands in a concentration range of 0.03−0.4 mM (Figure 4a).

The diameter of the strands is about 60 nm. Each strand is composed of densely packed small dots whose diameter corresponds to that of the strands. Under the lower concentration (<0.01 mM), numerous dots were observed. Formation of the polymeric structure depends on the concentration of solute as well as the polarity of solvents.[1a] In THF, its structure appeared to be different from that in chloroform. Although the structure is not aligned linearly, it shows interesting figures in which long and linear bundles with the diameter of about 110−120 nm are twisted as shown in Figure 4b.

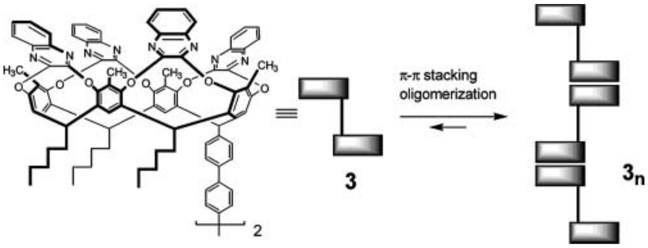


a) b)

Figure 4. Scanning electron microscopy images of aggregate of polybisvelcraplex **3**; (a) 0.14 mM in chloroform (scale bar = 1 μm); (b) 0.11 mM in THF, scale bar = 1 μm (scale bar = 100 nm) (inset: magnified image).

In conclusion, bisvelcrand **3** was obtained by a stepwise route and the unprecedented oligobisvelcraplex $\mathbf{3}_n$ was observed. Oligobisvelcraplex $\mathbf{3}_n$ in solution was formed only by solvophobic $\pi-\pi$ stacking interaction. In high concentration, bisvelcrand **3** showed a high tendency to form gels or fiber. In solid, the morphology of polybisvelcraplex $\mathbf{3}_n$ was affected by the solubility and polarity of solvent.

Scheme 2. Illustration of Oligovelcraplex $\mathbf{3}_n$ Formation of Bisvelcrand **3**



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Supporting Information Available: Experimental procedure of **2**, **3**, and PGSE NMR and crystallographic data (CIF format) of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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