Dynamic Hosts

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A Molecular Claw: A Dynamic Cavitand Host**

*Keith Hermann, Mina Nakhla, Judith Gallucci, Erdin Dalkilic, Arif Dastan, and Jovica D. Badjić**

The design, synthesis, and study of concave molecules with enforced cavities[1] have, in the last four decades, revealed some benefits of molecular encapsulation.[2] Cavitands can be used to promote chemical reactions,[3] stabilize reactive intermediates,[4] investigate new forms of stereoisomerism,[5] detect important analytes[6] and even resolve the solid-state structure of compounds of interest.[7] The strategy for obtaining a synthetic host consists of employing methods of computational chemistry to design a desired receptor followed by experimental optimization of its synthesis including kinetic/thermodynamic templation,[8] dynamic combinatorial approach,[9] self-assembly[10] or transition-metal catalyzed macrocyclization.[11] Despite many advances, creating a supramolecular receptor/catalyst remains a challenging task requiring time-consuming optimization of both the synthesis and operation. Furthermore, placing functional groups on the inner side of cavitand's concave surface is difficult but essential for improving its function.[12] Indeed, self-assembled cages with functionalized inner face have been investigated while covalent hosts with such topology remain elusive.[12] The folding of oligomers into three-dimensional globular or rod-like structures[13] presents an elegant solution to the problem yet there remains uncertainty about the nature of the chemical information embedded in functional oligomers to ensure folding into desired secondary/tertiary structure.[14]

The action of biological molecules epitomizes the synchronized and cooperative motion of molecules and/or their parts to implement the function.[15] In line with natural systems,[16] synthetic hosts could benefit from dynamic elements of design[17] yet incorporating such components into artificial structures[18] is far from trivial and at the forefront of supramolecular chemistry.[19] We have investigated the action of gated molecular baskets[20] while self-assembled,[21] self-folding[22] as well as switchable cavitands[23] were studied by others to add to the milieu of hosts with intriguing dynamic characteristics.[24]

[*] K. Hermann, M. Nakhla, J. Gallucci, Prof. J. D. Badjić
Department of Chemistry and Biochemistry
The Ohio State University
100 West 18th Avenue (USA)
E-mail: badjic@chemistry.ohio-state.edu
E. Dalkilic, Prof. A. Dastan
Ataturk University Faculty of Sciences, Erzurum (Turkey)

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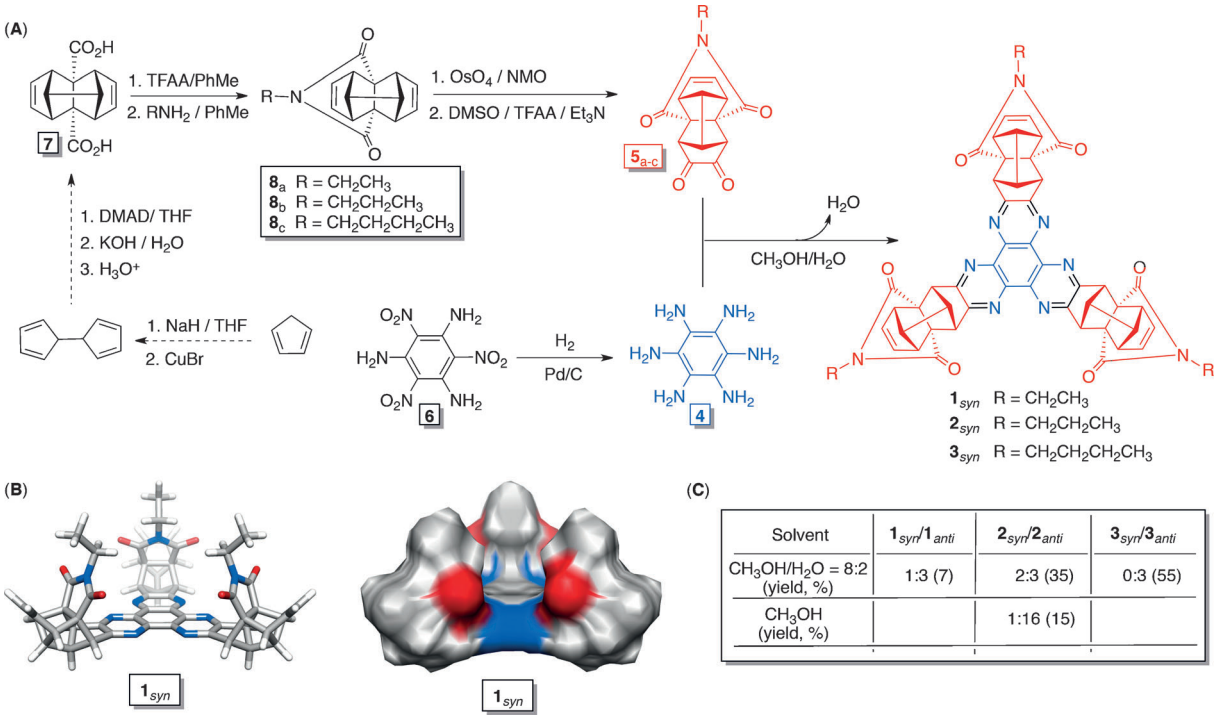
Herein, we describe a synthetic method for obtaining internally functionalized and dynamic cavitands of type **1**–**3** (Figure 1). These hosts are modular, comprising intriguing electronic characteristics, unique topology and remarkable mode of action: there could be interest for using this type of molecules as "claws" for selectively "grabbing" small chemical analytes and reporting on their presence.

The synthesis of C_{3v} symmetric $\mathbf{1}_{syn}$–$\mathbf{2}_{syn}$ was completed following the convergent strategy described in Figure 1 A.[25] In particular, we investigated the condensation of transient hexaaminobenzene **4** and diketones $\mathbf{5}_{a\text{-}c}$ (Figure 1 C). Although hexaaminobenzene **4**[26] decomposes under ambient conditions, this compound can be generated[27] in situ and used in the synthesis of various derivatives of 1,4,5,8,9,12-hexaazatriphenylene (HAT).[28] Furthermore, Paquette and co-workers employed diacid **7**[29] in the synthesis of curved hydrocarbons dodecahedrane[30] and C_{16}-hexaquinacene.[31] This molecule can now be prepared on large scale[31] by a domino Diels–Alder reaction of 9,10-dihydrofulvalene and dimethyl acetylenedicarboxylate (DMAD, Figure 1 A). Importantly, compound **7** can be converted into $\mathbf{5}_{a\text{-}c}$, which is unstable and undergoes decomposition at room temperature.

In the Schiff base condensation of **4** and $\mathbf{5}_{a\text{-}c}$, combined in an approximate 1:3 stoichiometric ratio and at a low temperature, we observed the formation of both *syn* and *anti* diastereomers of **1**–**3** isolated in overall 7–55% yield (Figure 1 C); note that the yield was estimated since the unstable reactants ought to be generated in situ. The proportion of diastereomers was, in these reactions, expected to correlate with solvent polarity[32] and the size of appended alkyl groups in $\mathbf{5}_{a\text{-}c}$. That is to say, more polar solvents ought to facilitate the formation of compact $\mathbf{1}_{syn}$–$\mathbf{3}_{syn}$ stereoisomers, as assisted by the hydrophobic effect,[32] while more sizeable alkyl groups in $\mathbf{5}_{a\text{-}c}$ should favor the formation of $\mathbf{1}_{anti}$–$\mathbf{3}_{anti}$ stereoisomers, as a result of the steric strain. In line with such reasoning, the greatest quantity of desired *syn* compound formed in the case of **2** in $CH_3OH/H_2O = 8{:}2$ (Figure 1 C). We deduce that the propyl chains are in $\mathbf{5}_b$ long enough to permit favorable desolvation of the *syn* transition state and at the same time short enough to avoid adverse interactions, that is, van der Waals strain in the course of forming $\mathbf{2}_{syn}$ versus $\mathbf{2}_{anti}$. When this same reaction was run with neat CH_3OH, we only isolated trace quantities of $\mathbf{2}_{syn}$, suggesting an important role of the hydrophobic effect in controlling the outcome of the condensation.

The ^{1}H NMR spectrum of $\mathbf{2}_{syn}$ (400 MHz, 298 K) in CD_2Cl_2 revealed a set of signals corresponding to a C_{3v} symmetric molecule (Figure 2 A); with the assistance of ^{1}H–^{1}H COSY/NOESY spectroscopic methods, we assigned all of the proton resonance signals (Figure S23–24). After plac-



Solvent	$\mathbf{1}_{syn}/\mathbf{1}_{anti}$	$\mathbf{2}_{syn}/\mathbf{2}_{anti}$	$\mathbf{3}_{syn}/\mathbf{3}_{anti}$
CH_3OH/H_2O = 8:2 (yield, %)	1:3 (7)	2:3 (35)	0:3 (55)
CH_3OH (yield, %)		1:16 (15)	

Figure 1. A) The preparation of C_{3v} symmetric $\mathbf{1}_{syn}$–$\mathbf{3}_{syn}$ can be completed on a large scale using simple starting materials and a convergent synthetic strategy. B) Energy-minimized structure of $\mathbf{1}_{syn}$ (MMFFs, Spartan) and van der Waals surface of this molecule showing its cavity ($V = 123$ Å^3); gray C, red O, blue N. C) The condensation of hexaaminobenzene **4** (in CH_3OH/H_2O) and diketone $\mathbf{5}_{a\text{-}c}$ (in CH_2Cl_2) gives *syn* and *anti* diastereomers of **1**–**3** in different ratios (yields are of isolated products).

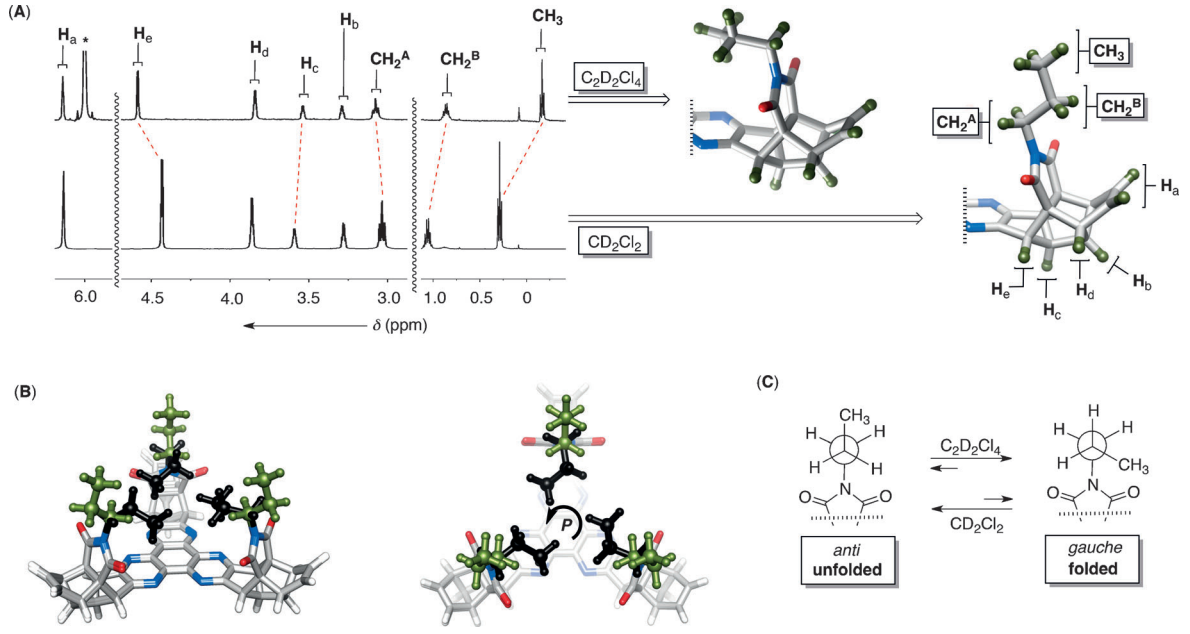


Figure 2. A) ^{1}H NMR spectra (400 MHz, 298.0 K) of $\mathbf{2}_{syn}$ in $C_2D_2Cl_4$ (top) and CD_2Cl_2 (bottom). B) Side and top views of energy-minimized structures of $\mathbf{2}_{syn}$ (MMFFs, Spartan) with propyl chains assuming *anti* (green) and *gauche* (black) conformation about C_1–C_2 sigma bond. C) Newman projections of *anti*/*gauche* conformers of $\mathbf{2}_{syn}$ in dynamic equilibrium.

ing host $\mathbf{2}_{syn}$ in $C_2D_2Cl_4$, the signal corresponding to CH_3 group underwent a considerable upfield shift ($\Delta\delta = -0.39$ ppm, Figure 2A). In addition, the resonances of CH_2^A ($\Delta\delta = +0.28$ ppm), CH_2^B ($\Delta\delta = -0.15$ ppm), H_e ($\Delta\delta = +0.18$ ppm), and H_c ($\Delta\delta = -0.03$ ppm) protons altered as well. To account for the observation, we first realized that changing the nature of bulk solvent caused the perturbation of protons adjacent to the aromatic "floor". While the polarity of dichloromethane ($\varepsilon_\rho = 9.1$) and tetrachloroethane ($\varepsilon_\rho = 8.4$) is comparable, the size difference between these two solvents is considerable.

Presumably, smaller molecules of CD_2Cl_2 (61 Å^3, Spartan) could fill the pocket in $\mathbf{2}_{syn}$ (190 Å^3)[33] and push the propyl chains to extend out and adopt *anti* conformation (Figure 2 B/C). On the contrary, sizeable $C_2D_2Cl_4$ (108 Å^3, Spartan) could not effectively solvate the interior of $\mathbf{2}_{syn}$ to drive the propyl chains to assume less stable *gauche* conformation and thereby coil into the host's cavity (Figure 2 B/C).[34] In line with the mechanistic scenario, CH_3 and $CH_2{}^B$ groups pivot about the cavitand to reside a) on top of the central HAT ring in the shielded region of the magnetic field (Figure 2 A/B, $C_2D_2Cl_4$) or b) further away from the HAT aromatic to experience reduced anisotropic effects (Figure 2 A/B, CD_2Cl_2). Finally, each $CH_2{}^A$ group at the rim is the pivoting point about which the alkyl chain revolves: the position of the $CH_2{}^A$ protons alters to face the inner (CD_2Cl_2, Figure 2 A) or outer side ($C_2D_2Cl_4$, Figure 2 A) of the host's cavity (Figure 2 B), which is reflected in the chemical shift of these protons (Figure 2 A); note that similar spectroscopic changes accompanied compound $\mathbf{1}_{syn}$ (Figure S25) upon the same alteration of solvents.

The revolution of the alkyl groups within $\mathbf{2}_{syn}$ must be fast on the NMR time scale to average the observed proton resonance signals (Figure 2). In fact, the folded state of $\mathbf{2}_{syn}$ is C_3 symmetric with *gauche* alkyl chains forming right (*P*) or left-handed (*M*) stereoisomers and therefore including diastereotopic $CH_2{}^A$/$CH_2{}^B$ protons (Figure 2 B).[35] Variable-temperature NMR study of $\mathbf{2}_{syn}$ in both $C_2D_2Cl_4$ (298–248 K, Figure S26) and CD_2Cl_2 (298–177 K, Figure S27) did not show any decoalescence but a consistent shift of the alkyl resonance signals: in particular, triplet corresponding to CH_3 moved upfield at higher temperatures. Apparently, a low activation barrier must be characterizing the folded/unfolded dynamic equilibrium (Figure 2 C) with the folded state of $\mathbf{2}_{syn}$ being preferred at higher temperatures. We reason that the formation of folded $\mathbf{2}_{syn}$ is, in both solvents, accompanied by a release of solvent molecules ($\Delta S° > 0$) for which the equilibrium free energy is more favorable ($\Delta G° < 0$) at higher temperatures.

Since the solvation of the inner space of $\mathbf{2}_{syn}$ is a form of molecular recognition[36] we decided to titrate CH_2Cl_2 to this host in noncompeting $C_2D_2Cl_4$ and quantify the interaction. As larger quantities of the guest could not saturate $\mathbf{2}_{syn}$ (Figure S28), we tested more sizeable $CHCl_3$ (75 Å^3,) and CCl_4 (89 Å^3, Figure S29). The binding affinity improved, but it was still difficult to quantify the interaction with ^{1}H NMR spectroscopy. Ultimately, we completed an incremental addition of CBr_4 (108 Å^3, Figure 3 B) to $\mathbf{2}_{syn}$: the nonlinear least-square fitting of the experimental data to a 1:1 stoichiometric model ($R^2 = 0.99$, Figure 3 B) gave the association constant of $K_a = 1.77 \pm 0.02\,\text{M}^{-1}$.[37] Evidently, the formation of the 1:1 complex was accompanied with downfield shift of CH_3 (Figure 3 B) resonances, which is in line with the "opening" of the host to accept the guest (Figure 3 A). We reasoned that the small binding energy ($\Delta G°$) for the formation of [$\mathbf{2}_{syn}\subset CBr_4$] is, in part, due to relatively stable ground state of the folded host having its cavity already populated with three alkyl chains. In fact, the affinity of $\mathbf{1}_{syn}$ toward complementary CBr_4 was somewhat greater with $K_a = 3.73 \pm 0.02\,\text{M}^{-1}$ ($R^2 = 0.99$, Figure 3 B): it costs less energy to displace shorter ethyl groups from the interior of $\mathbf{1}_{syn}$ than

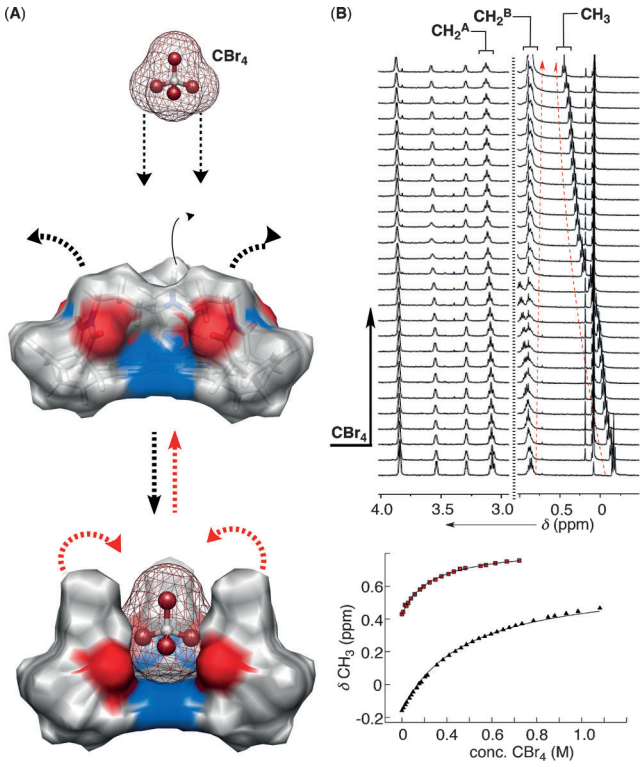


Figure 3. A) Energy-minimized structure of folded and unfolded (MMFFs, Spartan) forms of $\mathbf{2}_{syn}$ trapping CBr_4 guest. B) ^{1}H NMR spectra (400 MHz, 298.0 K) of $\mathbf{2}_{syn}$ (1.0 mM) in $C_2D_2Cl_4$ obtained upon incremental addition of CBr_4 (0–1.1 M) and the nonlinear least-square analysis of the ^{1}H NMR chemical shifts of CH_3 (ppm) in $\mathbf{1}_{syn}$ (1.0 mM, red) and $\mathbf{2}_{syn}$ (1.0 mM, black) as a function of CBr_4 concentration (M). A 1:1 stoichiometric model gave association constants K_a (M^{-1}) at 298.0 K.

longer propyl groups in $\mathbf{2}_{syn}$. Furthermore, it could be argued that less polarizable and shorter ethyl groups are forming less favorable contacts with the HAT "floor";[38] note that changing the nature of bulk solvent might improve the stability of the host–guest complex.

The solid-state structure of $\mathbf{3}_{anti}$ shows a pairwise assembly of these compounds in the unit cell besides multiple and disorganized molecules of $CHCl_3$ (Figure 4). The distance between the two HAT rings is 3.5 Å (middle region, Figure 4 A), with a slipped geometry of such π-stacked aromatics (Figure 4 B).[39] Interestingly, two molecules of $\mathbf{3}_{anti}$ face each other with one imide moiety, while the remaining two imide groups point away. The butyl chain of the facing imides (bottom region, Figure 4 A) assumes the *anti* conformation about the C_1–C_2/C_2–C_3 bonds: with the aromatic ring populating the space next to $\mathbf{3}_{anti}$, the alkyl chain extends out. In contrast, two alkyl groups on the remaining imides (top region, Figure 4 A) are disordered but clearly coiled to fill the space above each HAT ring.

Novel hosts of type $\mathbf{1}_{syn}$–$\mathbf{2}_{syn}$ comprise a unique topology and also employ an intriguing mode of action in trapping guests. Importantly, the organic framework of these compounds can be modified to give functional molecules and materials with tunable electrochemical or optical characteristics.[40] In particular, we are investigating the functionaliza-

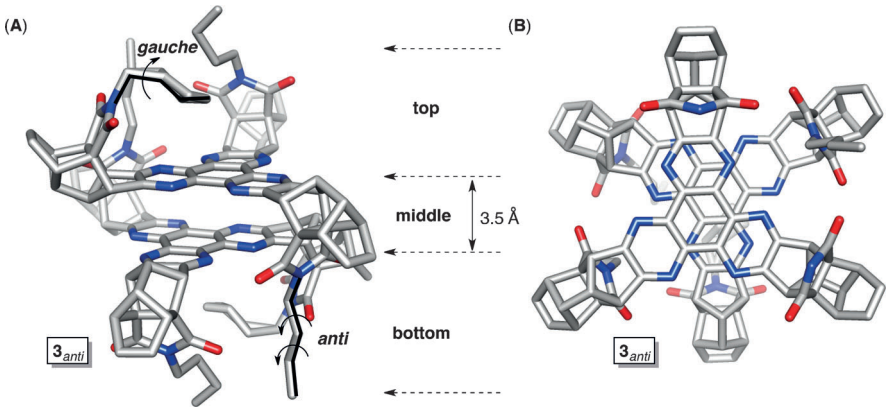


Figure 4. Stick representations of the solid-state structure of $\mathbf{3}_{anti}$ showing the orientation of two molecules within the unit cell. See text for details.

tion of the inner amides as well as an extension of the outer olefins for optimizing the recognition characteristics of molecular claws.

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[1] a) D. J. Cram, *Science* **1983**, *219*, 1177 – 1183; b) D. J. Cram, *Science* **1988**, *240*, 760 – 767.
[2] a) *Molecular Encapsulation: Organic Reactions in Constrained Systems* (Eds.: U. H. Brinker, J.-L. Mieusset), J. Wiley & Sons LTD, Chichester, UK, **2010**; b) F. Hof, S. L. Craig, C. Nuckolls, J. Rebek, Jr., *Angew. Chem.* **2002**, *114*, 1556 – 1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488 – 1508.
[3] a) Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100 – 103; b) *Supramolecular Catalysis* (Ed.: P. W. N. van Leeuwen), Wiley-VCH, Weinheim, **2008**.
[4] Z. Lin, J. Sun, B. Efremovska, R. Warmuth, *Chem. Eur. J.* **2012**, *18*, 12864 – 12872.
[5] J. Rebek, *Acc. Chem. Res.* **2009**, *42*, 1660 – 1668.
[6] A. P. Umali, E. V. Anslyn, *Curr. Opin. Chem. Biol.* **2010**, *14*, 685 – 692.
[7] Y. Inokuma, S. Yoshioka, J. Ariyoshi, T. Arai, Y. Hitora, K. Takada, S. Matsunaga, K. Rissanen, M. Fujita, *Nature* **2013**, *495*, 461 – 466.
[8] J. D. Badjić, S. Stojanović, Y. Ruan, *Adv. Phys. Org. Chem.* **2011**, *45*, 1 – 37.
[9] S. R. Beeren, J. K. M. Sanders, *Dyn. Comb. Chem.* **2010**, 1 – 22.
[10] D. Ajami, J. Rebek, *J. Org. Chem.* **2009**, *74*, 6584 – 6591.
[11] F. Fabris, C. Zonta, G. Borsato, O. De Lucchi, *Acc. Chem. Res.* **2011**, *44*, 416 – 423.
[12] S. Kubik, *Top. Curr. Chem.* **2012**, *319*, 1 – 34.
[13] a) G. Guichard, I. Huc, *Chem. Commun.* **2011**, *47*, 5933 – 5941; b) Y. Zhao, J. S. Moore, *Foldamers* **2007**, 75 – 108.
[14] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173 – 180.
[15] J. Huang Tony, K. Juluri Bala, *Nanomedicine* **2008**, *3*, 107 – 124.
[16] C. Fahrenbach Albert, J. Bruns Carson, D. Cao, J. F. Stoddart, *Acc. Chem. Res.* **2012**, *45*, 1581 – 1592.
[17] H.-J. Schneider, *Angew. Chem.* **2009**, *121*, 3982 – 4036; *Angew. Chem. Int. Ed.* **2009**, *48*, 3924 – 3977.
[18] C. R. Benson, A. I. Share, A. H. Flood, *Bioinspiration Biomimicry Chem.* **2012**, 71 – 119.
[19] L. C. Palmer, J. Rebek, Jr., *Org. Biomol. Chem.* **2004**, *2*, 3051 – 3059.
[20] S. Rieth, K. Hermann, B.-Y. Wang, J. D. Badjic, *Chem. Soc. Rev.* **2011**, *40*, 1609 – 1622.
[21] a) J. L. Atwood, L. J. Barbour, A. Jerga, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4837 – 4841; b) P. Ballester, G. Gil-Ramirez, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 10455 – 10459.
[22] U. Lücking, F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **2000**, *122*, 8880 – 8889.
[23] I. Pochorovski, M.-O. Ebert, J.-P. Gisselbrecht, C. Boudon, W. B. Schweizer, F. Diederich, *J. Am. Chem. Soc.* **2012**, *134*, 14702 – 14705.
[24] T. Ishi-i, M. Crego-Calama, P. Timmerman, D. N. Reinhoudt, S. Shinkai, *J. Am. Chem. Soc.* **2002**, *124*, 14631 – 14641.
[25] S. M. Grayson, J. M. J. Frechet, *Chem. Rev.* **2001**, *101*, 3819 – 3867.
[26] D. A. Dixon, J. C. Calabrese, J. S. Miller, *Angew. Chem.* **1989**, *101*, 79 – 81; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 90 – 92.
[27] J. Mahmood, D. Kim, I.-Y. Jeon, M. S. Lah, J.-B. Baek, *Synlett* **2013**, 246 – 248.
[28] a) J. J. Wolff, A. Zietsch, B. Nuber, F. Gredel, B. Speiser, M. Wuerde, *J. Org. Chem.* **2001**, *66*, 2769 – 2777; b) R. Juárez, M. M. Oliva, M. Ramos, J. L. Segura, C. Aleman, F. Rodriguez-Ropero, D. Curco, F. Montilla, V. Coropceanu, J. L. Bredas, Y. Qi, A. Kahn, M. C. Ruiz Delgado, J. Casado, J. T. Lopez Navarrete, *Chem. Eur. J.* **2011**, *17*, 10312 – 10322.
[29] M. J. Wyvratt, L. A. Paquette, *Tetrahedron Lett.* **1974**, *15*, 2433 – 2436.
[30] L. A. Paquette, *Chem. Rev.* **1989**, *89*, 1051 – 1065.
[31] R. T. Taylor, M. W. Pelter, L. A. Paquette, *Org. Synth.* **1990**, *68*, 198 – 205.
[32] R. Breslow, K. Groves, M. U. Mayer, *Pure Appl. Chem.* **1998**, *70*, 1933 – 1938.
[33] N. R. Voss, M. Gerstein, *Nucleic Acids Res.* **2010**, *38*, W555 – W562.
[34] J. W. Park, S. Y. Lee, H. J. Song, K. K. Park, *J. Org. Chem.* **2005**, *70*, 9505 – 9513.
[35] A. Scarso, L. Trembleau, J. Rebek, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 13512 – 13518.
[36] A. Shivanyuk, J. Rebek, *Chem. Commun.* **2002**, 2326 – 2327.
[37] *Frontiers in Supramolecular Organic Chemistry and Photochemistry* (Eds.: H. J. Schneider, H. Duerr), Wiley-VCH, Weinheim, **1991**.
[38] a) C. Zhao, R. M. Parrish, M. D. Smith, P. J. Pellechia, C. D. Sherrill, K. D. Shimizu, *J. Am. Chem. Soc.* **2012**, *134*, 14306 – 14309; b) N. J. Zondlo, *Acc. Chem. Res.* **2013**, *46*, 1039 – 1049.
[39] a) C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525 – 5534; b) S. E. Wheeler, *Acc. Chem. Res.* **2013**, *46*, 1029 – 1038.
[40] a) J.-M. Herrera, S. J. A. Pope, A. J. H. M. Meijer, T. L. Easun, H. Adams, W. Z. Alsindi, X.-Z. Sun, M. W. George, S. Faulkner, M. D. Ward, *J. Am. Chem. Soc.* **2007**, *129*, 11491 – 11504; b) S. Furukawa, T. Okubo, S. Masaoka, D. Tanaka, H.-C. Chang, S. Kitagawa, *Angew. Chem.* **2005**, *117*, 2760 – 2764; *Angew. Chem. Int. Ed.* **2005**, *44*, 2700 – 2704; c) D. Hanifi, D. Cao, L. M. Klivansky, Y. Liu, *Chem. Commun.* **2011**, *47*, 3454 – 3456; d) Y. Zhang, D. Hanifi, S. Alvarez, F. Antonio, A. Pun, L. M. Klivansky, A. Hexemer, B. Ma, Y. Liu, *Org. Lett.* **2011**, *13*, 6528 – 6531.