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Coiled Molecules in Spring Loaded Devices

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Straight chain alkanes have linear, extended shapes as their lowest energy conformations in solution but can assume more compact shapes when confined to small spaces. Many bent shapes are observed by crystallography for alkyl chains in naturally occurring protein receptors,[1,2] and in synthetic host molecules.[3] Each bend (gauche conformation) creates steric repulsions and increases the energy by ~0.55 kcal/mol in the liquid state.[4] We show here that an alkane coiled in a self-assembled capsule applies stress to the surrounding container. The system is a spring-loaded device that can operate reversibly in response to acids and bases. The coiled alkane offers an alternative to existing driving forces and models for molecular machinery.

We have encountered compacted alkanes in synthetic receptors. Alkanes such as *n*-decane (C_{10}) are encapsulated in **1.1** (Figure 1)[5] in an extended conformation but the longer tetradecane (C_{14}) adopts a helical conformation.[6] The coiled conformation is shorter but thicker: it allows the alkane to fit and to make attractive CH−π interactions with the aromatic surfaces of the capsule, but induces at least 8 gauche conformations along the backbone. The encapsulated tetradecane is at an uneasy equilibrium, and exerts pressure on the capsule as the alkane tries to uncoil. A newly discovered property of **1.1**, its ability to incorporate spacer elements,[7] suggested its application as a spring-loaded device. Glycoluril structures **2a**−**b** (Figure 2) can insert between the halves of the capsule, much like leaves can be inserted to extend a dining table. The capsule's length increases and allows the accommodation of longer guests.

We prepared **2c**, a glycoluril bearing weakly basic sites that can be protonated by strong acids. Addition of **2c** to the capsule **1.1** containing the coiled guest C_{14} causes changes in the NMR spectrum (Figure 3a,b). *The alkane relaxes to an extended conformation in a new host capsule*. The guest's methylene signals move downfield as the corresponding carbons move away from the anisotropic ends of the capsule. The doubling of the signals indicates the geminal hydrogens of the CH_2 groups at C_2 (and C_{13}) are diastereotopic, and places them near an asymmetric magnetic environment. In sharp contrast, addition of **2c** to the capsule **1.1** containing the extended guest C_{10} shows no changes in the spectrum (Figure 3c).

Addition of HCl gas to the solution of C_{14} in the extended capsule caused the precipitation of **2c** as its hydrochloride salt and regenerated the spectrum of coiled C_{14} in the original capsule **1.1** (Figure 3d). Next, the addition of Et_3N: to the precipitated suspension liberated **2c** into solution and regenerated the spectrum of extended C_{14} in the extended capsule **3**. The coiling/extension cycles were repeated at least six times before the build-up of Et_3-NHCl salt began to interfere with the spectroscopy. These cycles are summarized in Figure 4.

The term "spring-loaded" suggests a range of macroscopic phenomena and has been frequently evoked at the molecular level as well: the behavior of diiron-oxo bisporphyrins,[8] cis/trans isomerization of retinal,[9] interconversion of peptide helices,[10] and

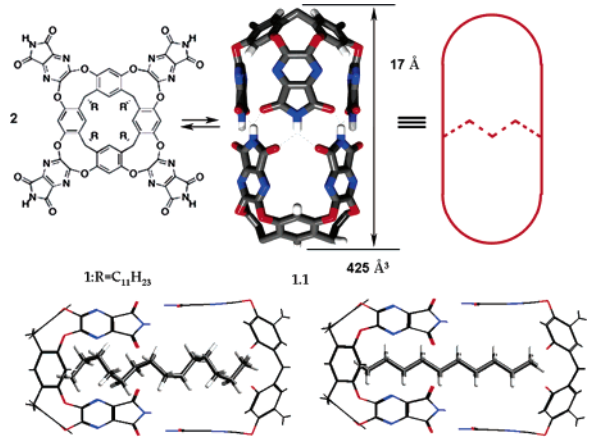

Figure 1. (Top) Tetraimide cavitand **1**, the dimeric capsule **1.1** and its cartoon representation. (Bottom) alkanes inside **1.1**: (left) decane is accommodated in its fully extended, anti conformation; (right) the longer tetradecane coils into a helical conformation. Peripheral alkyl groups and some capsule "walls" have been removed for viewing clarity.

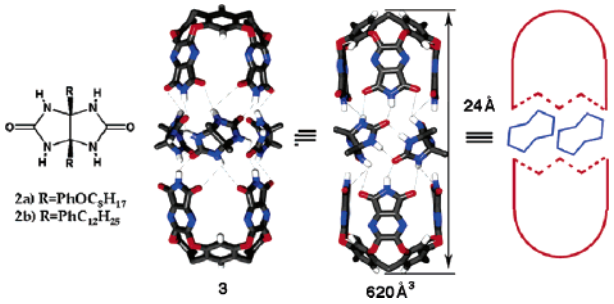

Figure 2. Proposed structure for the expanded capsule **3**: it is composed of two molecules of **1** and four molecules of **2a** or **2b**. Perpheral functional groups have been removed and the cartoon representation is also shown.

inclusion compounds in the solid state.[11] But to what extent is a coiled alkane the driving force—the compressed spring—in the reversibly formed assemblies at hand?

The formation of new hydrogen bonds helps drive the molecular device from the coiled to extended states. The glycolurils can make the maximum number of hydrogen bonds as shown in Figure 2 and pair their best acceptors with the cavitand's superior donors. The capsule **1.1** is an *organized solvent sphere*, fixed by synthesis. This space cannot be empty and the C_{14} must contort itself and assume the size, shape, and chemical surface that are optimal to fill it. In bulk solution the alkane has the same C−H/π interactions on offer, but must organize many solvent molecules (mesitylene) to experience them. Release of these molecules to the bulk solvent, solvophobic forces, should also drive encapsulation. The coiling of C_{14} within **1.1** provides the spring-loading in the form of guest strain, and the reversible lengthening of the space to **3** provides the relief. The encapsulated C_{10} has no driving force for change;

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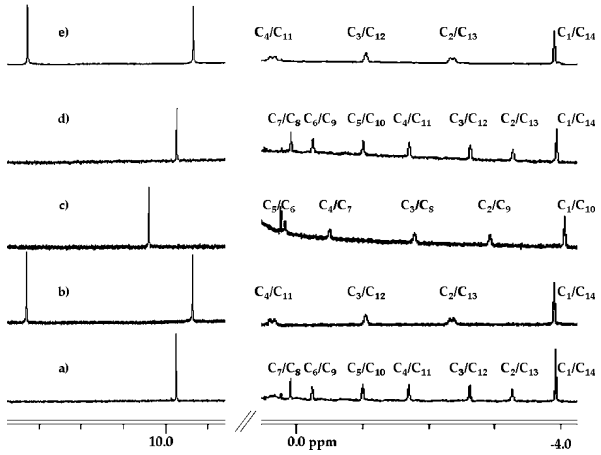

Figure 3. Proton NMR spectra of the encapsulation complexes (600 MHz, in mesitylene-d_{12} solvent). Furthest upfield resonances are guest hydrogens nearest the ends of the capsule: (a) C_{14} in **1.1**; (b) C_{14} in **1.1** with **2c** added. The methylene resonances of the alkane move downfield as it relaxes to an extended conformation. (c) C_{10} in **1.1** with or without **3**. The methylene resonances indicate an extended conformation.[6] (d) The solution b treated with HCl gas. The C_{14} returns to its compressed state in **1.1**. (e) The suspension obtained from solution d with added Et_3N. The spacers insert to give capsule **3** with extended guest as in solution b.

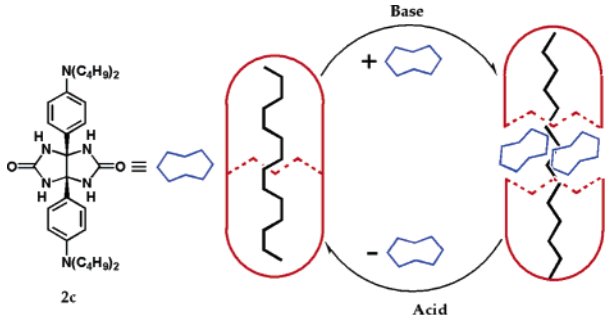

Figure 4. Schematic representation of the coiling/uncoiling cycles of tetradecane, $C_{14}H_{30}$. The C_{14} is encapsulated as a helical coil in **1.1**. Addition of spacer **2c** to the solution generates the longer assembly **3** and the C_{14} guest relaxes to an extended conformation. Addition of HCl to **3** protonates the aniline sites of the spacer and causes precipitation of **2c** as its dihydrochloride salt; the system reverts to coiled C_{14} in the original capsule **1.1**. Addition of triethyl amine to the mixture releases the spacer into solution where it inserts and generates the longer assembly with extended C_{14} inside.

the spacers can add hydrogen bonds but the longer capsule leads to a poorer fit with additional empty space—vacuum—in the complex.

Normal alkanes assume strained conformations in several synthetic capsule hosts such as self-assembled hexameric pyrogallolarene cubes[12] and vase-shaped, water-soluble cavitands.[13] Reversible spring loading is, to our knowledge, unprecedented in synthetic assemblies, but in biology most DNA exists in supercoiled and compacted forms.[14] The pressure of compaction can be relieved in bacterial viruses by enlargement of their capsids through addition of protein subunit spacers[15] and when their genetic materials are injected into hosts.[16]

Numerous chemically driven molecular-level devices and machines exist[17] including rotors,[18] motors,[19,20] shuttles,[21] and muscles.[22] These devices involve components that are mechanically interlocked or constrained by covalent bonds; their functional sites respond to external stimuli and cause movement. Here, the system forms and dissipates through the manipulated rules of self-assembly. The compression is controlled by acid/base chemistry that determines the space available to the spring. Harnessing this device to do work is an ongoing effort.

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References

(1) Zanotti, G.; Scapin, G.; Spadon, P.; Veerkamp, J. H.; Sacchettini, J. C. *J. Biol. Chem.* **1992**, *267*, 18541−18550.
(2) Han, G. W.; Lee, J. Y.; Song, H. K.; Chang, C.; Min, K.; Moon, J.; Shin, D. H.; Kopka, M. L.; Sawaya, M. R.; Yuan, H. S. *J. Mol. Biol.* **2001**, *308*, 263−278.
(3) Séneque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183−6189. Hayashida, O.; Sebo, L.; Rebek, J. Jr. *J. Org. Chem.* **2002**, *67*, 8291−8298.
(4) Eliel, E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 10.
(5) Scarso, A.; Trembleau, L.; Rebek, Jr. J. *Angew. Chem., Intl. Ed.* **2003**, *42*, 5499−5502.
(6) Scarso, A.; Trembleau L.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13512−13518. For the correlation of chemical shifts and positions in the capsule see Ajami, D.; Rebek, J., Jr. *Proc. Nat. Acad. U.S.A.* **2006**, *103*, 8934−8936.
(7) Ajami, D.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 5314−5315.
(8) Hodgkiss, J. M.; Chang, C. J.; Pistorio, B. J.; Nocera, D. G. *Inorg. Chem.* **2003**, *42*, 8270−8277.
(9) Roehrig, U. F.; Guidoni, L.; Laio, A.; Frank, I.; Rothlisberger, U. *J. Am. Chem. Soc.* **2004**, *126*, 15328−15329.
(10) Pengo, P.; Pasquato, L.; Moro, S.; Brigo, A.; Fogolari, F.; Broxterman, Q. B.; Kaptein, B.; Scrimin, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3388−3392.
(11) Hollingsworth, M. D.; Werner-Zwanziger, U.; Brown, M. E.; Chaney, J. D.; Huffman, J. C.; Harris, K. D. M.; Smart, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9732−9733.
(12) Palmer, L. C.; Rebek, J., Jr. *Org. Lett.* **2005**, *7*, 787−789.
(13) Trembleau, L.; Rebek, J., Jr. *Science* **2003**, *301*, 1219−1220.
(14) Watson, J. D.; Hopkins, N. H.; Roberts, J. W.; Steitz, A. A.; Weiner, A. M. *Molecular Biology of the Gene*; The Benjamin/Cummings Publishing Company: Menlo Park, CA, 1987; Chapter 9.
(15) Verduin, B. J. M.; Bancroft, J. B. *Virology* **1965**, *37*, 501.
(16) Tzlil, S.; Kindt, J. T.; Gelbart, W. M.; Ben-Shaul, A. *Biophys. J.* **2003**, *84*, 1616−1627.
(17) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines—A Journey into the Nano World;* Wiley-VCH: Weinheim, Germany, 2003.
(18) Rebek, J.; Trend, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 4315. Rebek, J.; Wattley, R. V.; Chakravorti, S.; Trend, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 4333. Rebek, J.; Wattley, R. V. *J. Am. Chem. Soc.* **1980**, *102*, 4853−4854. Rebek, J., Jr.; Costello, T.; Wattley, R. V. *Tetrahedron Lett.* **1980**, 2379−2380. Scarso, A.; Onagi, H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 12728−12729. For a recent review see Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. *Chem. Rev.* **2005**, *105*, 1281−1376.
(19) Kelly, T. R.; Harshani De Silva, H.; Silva, R. A. *Nature* **1999**, *401*, 150−152. Vicario, J.; Walko, M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 5127−5135.
(20) Leigh, D. A.; Wong, J. K. Y.; ois Dehez, F.; Zerbetto, F. *Nature* **2003**, *424*, 174−179.
(21) Ashton, P. R.; Ballardini, R.; Balzani, V.; Baxter, I.; Credi, A.; Fyfe, M. C. T.; Gandolfi, M. T.; Gomez-Lopez, M.; Martinez-Diaz, M.-V.; Piersanti, A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 11932−11942.
(22) Jiménez, M. C.; Dietrich-Buchecker, C.; Sauvage, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3388−3392.

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