Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3056–3059
Tetrahedron Letters

A rigid bicyclo[3.3.0]octane (octahydropentalene): a heavily constrained novel aliphatic template for molecular self-assembly

Amol M. Kendhale [a], Rajesh Gonnade [b], P. R. Rajamohanan [c], Gangadhar J. Sanjayan [a,*]

[a] Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India
[b] Centre for Materials Characterization, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India
[c] Central NMR Facility, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

Received 9 January 2008; revised 6 March 2008; accepted 12 March 2008
Available online 15 March 2008

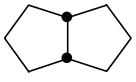
Abstract

This Letter reports the utility of a heavily constrained cis-fused bicyclo[3.3.0]octane (octahydropentalene) aliphatic template for effecting molecular self-assembly. An attractive feature of this system is its heavily constrained alicyclic backbone that would allow for the exploration of self-assembling systems with conformationally ordered features.

1. Introduction

Molecular self-assembly has emerged as a powerful tool for the construction of well-defined supramolecular architectures and nano-scale materials with extensive structural diversity and applications.[1,2] During the past three decades, chemists have made considerable progress in understanding the fundamental rules of self-assembling processes involving weak non-covalent interactions such as Van der Waals, capillary, π–π and hydrogen bonds.[3] Because of their directionality and specificity in recognition processess,[4] hydrogen bonds have been proved to be superior among other non-covalent forces for the programmed self-assembly of smaller molecular components to generate supramolecular ensembles with pre-defined structural features. In order to further enhance the strength, directionality and specificity of hydrogen bonding interactions, there is currently intense research interest in the design and development of novel self-assembling motifs having arrays of hydrogen bond donor (D) and acceptor (A) sites,[5–7] appended on various templates.

This Letter reports the utility of a heavily constrained *cis*-fused bicyclo[3.3.0]octane[8] (octahydropentalene) aliphatic template for effecting molecular self-assembly. Such self-assembling systems, based on heavily constrained aliphatic templates, would be of use for the design and development of novel self-assembling systems devoid of π-stacking interferences commonly observed in their aromatic counterparts.[1a] Bicyclo[3.3.0]octane, the parent compound of polyquinanes,[9] adopts a heavily constrained structural framework with a preference for a cis-fused ring junction, since the trans-fusion of two five-membered rings would involve considerable torsional strain, with a very large enthalpy difference (cis to trans ~29.6 KJ/mole).[10,11]



bicyclo[3.3.0]octane (octahydropentalene)

The possibility of quick access to heavily substituted frameworks such as **3** in as little as three steps would extend the application potential of such systems. Compound **3** represents a simple example of a diverse self-assembling system obtainable from a cis-fused bicyclo[3.3.0]octane template by changing the stereochemistry of the side chains attached to the bicyclo[3.3.0]octane framework. The wide scope of the Weiss reaction to

* Corresponding author. Tel./fax: +91 02025893153.
E-mail address: gj.sanjayan@ncl.res.in (G. J. Sanjayan).

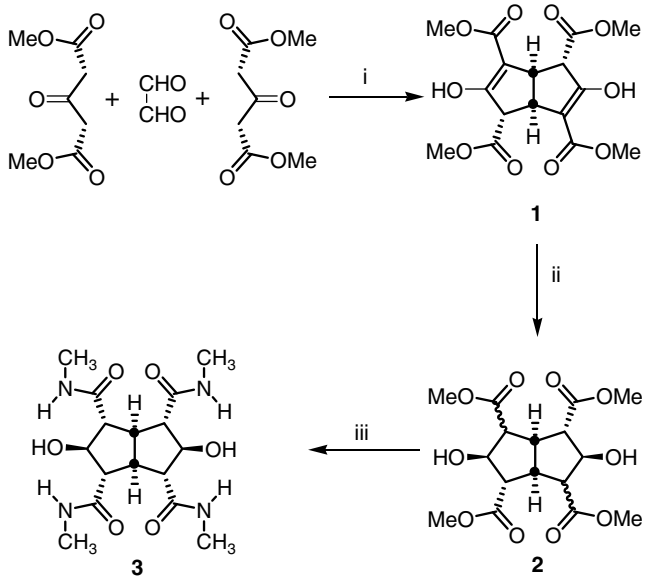
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.03.062

provide bicyclo[3.3.0]octane (octahydropentalene) analogs of diverse architectures, substituents and stereochemistries means that the bicyclo[3.3.0]octane framework may be used as a versatile template on which self-assembling systems of diverse structural architectures can be designed and developed.

The self-assembling system **3** can be readily obtained in good yield starting from glyoxal using the Weiss protocol.[12] Reaction of glyoxal with diacetyl acetone in the presence of a base affords the bicyclo[3.3.0]octane-derived bis-β-keto ester **1**, which was subjected to reduction using $NaBH_4$ in methanol to afford the dihydroxy bicyclic ester **2**. The self-assembling system **3** was obtained in excellent yield by amidation of **2** with saturated methylamine solution in methanol at room temperature (Scheme 1).

Self-assembling system **3** crystallized in the monoclinic space group *C2/c* from hot water. The hydrogen bonding interactions in **3** according to crystal structure studies are shown in Figure 1.

The analysis of the crystal structure showed that the D/A self-complementary hydrogen bonding codes (D = donor, A = acceptor) in **3** are clearly projected for intermolecular hydrogen bonding interactions, a pre-requisite for efficient self-assembling.[1] The self-complementary individual strands undergo self-assembly through intermolecular N–H···O=C hydrogen bonding interactions. The hydrogen-bonds in **3** are fairly strong with D–H···A distances [*d*(N–H···O)] in the range 1.99–2.0 Å. The *N*-methyl groups of the adjacent self-assembling strands of **3** are uniformly separated by 4.88 Å, an observation that could provide insight for developing such templates into potential protein-β-sheet nucleators.[13] It is noteworthy that the extended sheet structures have been disclosed recently



Scheme 1. Synthesis of **3**. Reagents and conditions: (i) (a) NaOH, MeOH, reflux; (b) de-ionized H_2O, 1 M HCl (89%); (ii) $NaBH_4$, MeOH, rt, 4 h (62%); (iii) MeOH, $MeNH_2$, rt, 24 h (96%).

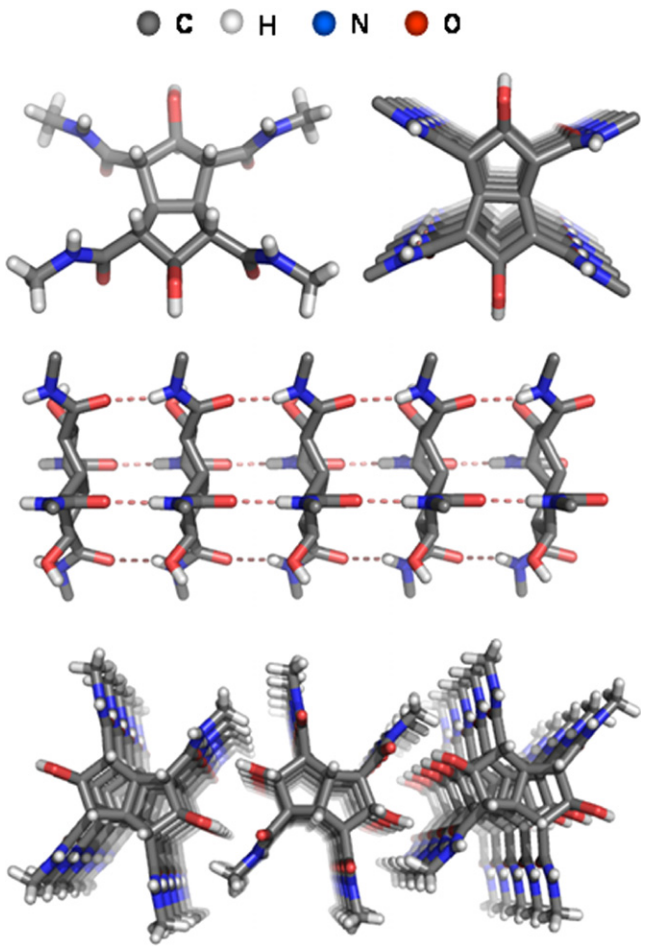


Fig. 1. Crystal structure of the bicyclo[3.3.0]octane-derived self-assembling system **3** showing intermolecular hydrogen bonding interactions. Crystal structure and intermolecular arrangement (top), side view of the intermolecular hydrogen bonding interactions (middle), and supramolecular structure formation involving the amide and hydroxyl groups (bottom).

in certain cyclopropane. γ-Peptides stabilized by C–H...O hydrogen bonds,[14] and also in isotactic acrylamide oligomers.[15] The individual strands in protein β-sheets are in close proximity, involving extensive intermolecular hydrogen bonding interactions; an observation that has been explored in the design of novel synthetic β-sheet nucleators/scaffolds. It should be emphasized that synthetic β-sheet scaffolds have considerable relevance in the understanding and development of potential therapies for Alzheimer's disease, a leading cause of dementia in the elderly, which is pathologically defined by the occurrence of amyloid plaques, composed of the amyloid β-protein, and neurofibrillary tangles.[16] Closer inspection of the crystal structure further reveals that **3** undergoes yet another mode of self-assembly via the hydroxyl groups, appended on the periphery of the octahydropentalene framework (Fig. 1, bottom) leading to the formation of a supramolecular structural architecture. The hydroxyl groups participate in intermolecular O...H...O=C hydrogen bonding patterns with D–H···A distance [*d*(O–H···O=C)] of 2.0 Å.

In summary, we have demonstrated the utility of a cis-fused rigid bicyclo[3.3.0]octane (octahydropentalene) template for effecting molecular self-assembly. The striking feature of this system is its heavily constrained alicyclic backbone coupled with the possibility of stereochemical alterations on the pentalene periphery that would allow for the exploration of self-assembling systems with diverse structural architectures. We are currently exploring the possibility of stereochemical alterations on the bicyclo-[3.3.0]octane template to investigate their self-assembling propensity, and will report the results in due course.

2. Experimental

2.1. Tetramethyl 3,7-dihydroxy-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (2)

To an ice cooled solution of tetramethyl bicyclo[3.3.0]-octane-3,7-dione-2,4,6,8-tetracarboxylate **1**[12] (2 g, 5.405 mmol) in methanol (10 ml), sodium borohydride (0.408 g, 10.81 mmol) was added at 0 °C and the resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate (10 ml) and quenched via dropwise addition of 1 N HCl (20 ml). The product was extracted with ethyl acetate (3×250 ml). The organic layer was washed with $NaHCO_3$, followed by water and brine, then dried over anhydrous Na_2SO_4, concentrated and the product was purified by column chromatography providing **2** as a low melting white semi-solid 1.27 g (yield: 62.6%) $R_f = 0.25$, 50% EtOAc/pet. ether; mp 82–84 °C; ^{1}H NMR (200 MHz, $CDCl_3$, ppm) δ 4.65 (1H, m) 4.38 (1H, t, $J = 13$ Hz) 3.72 (3H, s) 3.71 (3H, s) 3.66 (3H, s) 3.65 (3H, s) 3.25–2.92 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 173.9–172.5, 77.6, 77.1, 56.0, 55.2, 54.0, 51.9–50.0, 44.9, 42.7; IR ($CHCl_3$), ν (cm^{-1}): 3508, 3020, 2954, 2360, 1731, 1436, 1267, 1215, 1176, 757, 667; LCMS: 375.07 (M+1), 397.04 (M+Na); Anal. Calcd for $C_{16}H_{22}O_{10}$: C, 51.34; H, 5.92; Found: C, 51.58; H, 5.62.

2.2. Tetramethyl 3,7-dihydroxy-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxamide (3)

A saturated solution of methyl amine in methanol (30 ml) was added to tetramethyl 3,7-hydroxy-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate **2** (1 g, 2.673 mmol) at 0 °C. After 2 h, the ice bath was removed and the reaction mixture was sealed and stirred at room temperature for 24 h. The white solid precipitate that formed was filtered and the residue was washed with methanol (20 ml) and dried in a vacuum desiccator. The dried white solid **3** weighed 0.95 g (Yield: 96%); mp >285 °C; ^{1}H NMR (400 MHz, D_2O, ppm) δ 4.36 (2H, t, $J = 10.07$ Hz) 2.84–2.79 (2H, m) 2.76 (12H, s) 2.67–2.63 (4H, m); ^{13}C NMR (100 MHz, D_2O, ppm) δ 174.3, 77.9, 58.5, 42.5, 25.9; IR (nujol), ν(cm^{-1}): 3442, 3296, 3107, 2948, 2921, 2852, 2362, 1643, 1623, 1573, 1461, 1415, 1377, 1323, 1253, 1159, 1091, 1051, 954; MALDI-TOF MS: 371.42 (M+1), 393.38 (M+Na), 409.34 (M+K); Anal. Calcd for $C_{16}H_{26}N_4O_6$: C, 51.88; H, 7.08; N, 15.13. Found: C, 51.63; H, 6.81; N, 15.37.

2.3. Crystallographic data for 3

($C_{16}H_{26}N_4O_6$): $M = 370.41$, crystal dimensions $0.78 \times 0.04 \times 0.04$ mm^3, monoclinic, space group $C2/c$, $a = 21.191(8)$, $b = 4.8840(19)$, $c = 17.271(7)$ Å, $\beta = 93.389(6)°$; $V = 1784.4(12)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.379$ g cm^{-3}, μ (Mo-K$_\alpha$) $= 0.106$ mm^{-1}, $F(000) = 792$, $2\theta_{max} = 50.00°$, 7770 reflections collected, 1559 unique, 1039 observed ($I > 2\sigma(I)$) reflections, 121 refined parameters, R value 0.0820, $wR_2 = 0.2117$ (all data $R = 0.1195$, $wR_2 = 0.2370$), $S = 1.041$, minimum and maximum transmissions 0.9218 and 0.9963, respectively, maximum and minimum residual electron densities +0.743 and −0.341 e Å^{-3}. Crystallographic data of **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 656550.

Acknowledgements

AMK thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for a research fellowship. This work was funded partly by the International Foundation for Science (IFS), Sweden; Grant No. F/4193-1, and the Department of Science and Technology (DST), New Delhi.

References and notes

1. (a) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH Publishers: Weinheim, Germany, 1995; (b) Fredericks, J. R.; Hamilton, A. D. In *Comprehensive Supramolecular Chemistry*; Sauvage, J.-P., Hosseini, M. W., Eds.; Pergamon Press: Oxford, 1996; (c) Steed, J. W.; Atwood, J. L. In *Supramolecular Chemistry*; Wiley: New York, 2000; Vol. 9, Chapter 16.
2. For selected review articles on the application potential of molecular self-assembly, see: (a) Ajayaghosh, A.; Praveen, V. K. *Acc. Chem. Res.* **2007**, *40*, 644–656; (b) Lu, Y.; Liu, J. *Acc. Chem. Res.* **2007**, *40*, 315–323; (c) Wu, J.; Pisula, W.; Müllen, K. *Chem. Rev.* **2007**, *107*, 718–747.
3. For selected review articles on molecular self-assembly, see: (a) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290–296; (b) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071–4098; (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4012; (d) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426; (e) Sessler, J. L.; Jayawickramarajah, J. *Chem. Commun.* **2005**, 1939–1949; (f) Pollino, J. M.; Weck, M. *Chem. Soc. Rev.* **2005**, *34*, 193–207.
4. (a) Schuster, P.; Zundel, G.; Sandorfy, C. In *The Hydrogen Bond: Recent Developments in Theory and Experiments*; North-Holland: Amsterdam, The Netherlands, 1976; Vols. 1–3; (b) Kollman, P. A.; Allen, L. A. *Chem. Rev.* **1972**, *72*, 283–303.
5. (a) Ma, Y.; Kolotuchin, S. V.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2002**, *124*, 13757–13769; (b) Arduini, M.; Crego-Calama, M.; Timmerman, P.; Reinhoudt, D. N. *J. Org. Chem.* **2003**, *68*, 1097–1106; (c) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5–16;

(d) Schmuck, C.; Geiger, L. *J. Am. Chem. Soc.* **2004**, *126*, 8898–8899; (e) Yang, X.; Gong, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 1352–1356; (f) Baruah, P. K.; Gonnade, R.; Phalgune, U. D.; Sanjayan, G. J. *J. Org. Chem.* **2005**, *70*, 6461–6467; (g) Prabhakaran, P.; Puranik, V. G.; Sanjayan, G. J. *J. Org. Chem.* **2005**, *70*, 10067–10072; (h) Sun, H.; Steeb, J.; Kaifer, A. E. *J. Am. Chem. Soc.* **2006**, *128*, 2820–2821; (i) Ohkawa, H.; Ligthart, G. B. W. L.; Sijbesma, R. P.; Meijer, E. W. *Macromolecules* **2007**, *40*, 1453–1459.

6. H-bond-mediated self-sorting in designed self-assembling systems has been described recently, see: (a) Jolliffe, K. A.; Timmerman, P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 933–937; (b) Wu, A.; Isaacs, L. *J. Am. Chem. Soc.* **2003**, *125*, 4831–4835.
7. For columnar/tubular assemblies of cyclic structures, see: (a) Horne, W. S.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 9372–9376; (b) Jagannadh, B.; Reddy, M. S.; Rao, C. L.; Prabhakar, A.; Jagadeesh, B.; Chandrasekhar, S. *Chem. Commun.* **2006**, 4847–4849; (c) Fujimura, F.; Fukuda, M.; Sugiyama, J.; Morita, T.; Kimura, S. *Org. Biomol. Chem.* **2006**, *4*, 1896–1901.
8. (a) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647–3692; (b) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293–4296; (c) Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9282–9283.
9. (a) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer: Berlin, 1987; (b) Little, R. D. *Chem. Rev.* **1996**, *96*, 93–114; (c) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671–720.
10. Chang, S.-j.; McNally, D.; Shary-Tehrany, S.; Hickey, S. M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109–3118.
11. In terms of stability, *cis*-Bicyclo[3.3.0]octane is about 6 kcal/mol more stable than its *trans* isomer. See: Barrett, J. W.; Linstead, R. P. *J. Chem. Soc.* **1936**, 611.
12. (a) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, *9*, 4885–4887; (b) Bertz, S. H.; Rihs, G.; Woodward, R. B. *Tetrahedron* **1982**, *38*, 63–70. Reduction of 1 gives inseparable stereomixture of 2, see:; (c) Yates, P.; Smakula, E.; French, G. B. *J. Am. Chem. Soc.* **1960**, *82*, 6347–6353.
13. (a) Schneider, J. P.; Kelly, J. W. *Chem. Rev.* **1995**, *95*, 2169–2187; (b) Gellman, S. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 717–725; (c) Kemp, D. S.; Bowen, B. R. *Tetrahedron Lett.* **1988**, *29*, 5077–5080; (d) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152; (e) Khakshoor, O.; Demeler, B.; Nowick, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 5558–5569.
14. Qureshi, M. K. N.; Smith, M. D. *Chem. Commun.* **2006**, 5006–5008.
15. Kendhale, A.; Gonnade, R.; Rajamohanan, P. R.; Sanjayan, G. J. *Chem. Commun.* **2006**, 2756–2758.
16. Ryu, E. K.; Choe, Y. S.; Lee, K.-H.; Choi, Y.; Kim, B.-T. *J. Med. Chem.* **2006**, *49*, 6111–6119.