Ladderanes

Supramolecular Construction of Molecular Ladders in the Solid State[**]

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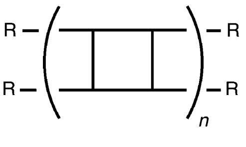
In memory of Xiuchun Gao

An [*n*]ladderane is a molecule that consists of *n* edge-sharing cyclobutane rings (where $n \geq 2$) that define a molecular equivalent of a macroscopic ladder.[1] Ladderanes are considered promising building blocks in optoelectronics[2] and, very recently, have been identified in biological systems ($n = 3$ and 5), in the form of ladderane lipids,[3,4] which are integral components in the microbiological conversion of ammonium and nitrite ions to dinitrogen gas.[3,4] In the simplest case, a *cis*-fused [*n*]ladderane ($n = 3, 5, 7\ldots$) can be constructed by photochemical dimerization of two all-*trans*-poly-*m*-enes ($m = 2, 3, 4\ldots$). Despite the apparent simplicity of this intermolecular process, however, such a transformation generally fails.[1] This can be attributed to the lack of a method that overcomes the energetic cost, due to solvent[5] and entropy[1,5] effects, of organizing two polyene molecules in a suitable geometry in the liquid phase for photoreaction, although a covalent linker that holds two polyene chains in a parallel orientation for a high-yield, intramolecular photoaddition to give a [*n*]ladderane ($n = 3$ and 5) has been reported.[6]



[*n*]ladderane

We believe that a supramolecular approach to covalent synthesis[7,8] in the organized, solvent-free environment of the solid state[8] can provide a solution to the problem of organizing two polyenes for an intermolecular reaction to give a ladderane. Specifically, by taking an approach to control reactivity in solids[9] by using molecules that serve as linear templates,[10–13] we have anticipated that the cocrystallization of resorcinol (1,3-benzenediol), or a derivative, with an all-*trans*-bis(4-pyridyl)poly-*m*-ene (4-pyr-poly-*m*-ene) would produce a four-component molecular assembly, 2(resorcinol)·2(4-pyr-poly-*m*-ene), in which each resorcinol preorganizes, through two $O{-}H\cdots N$ hydrogen-bonding interactions, two poly-*m*-enes for [2+2] photoaddition.[14] In this design, the two polyenes (Scheme 1) would be positioned by

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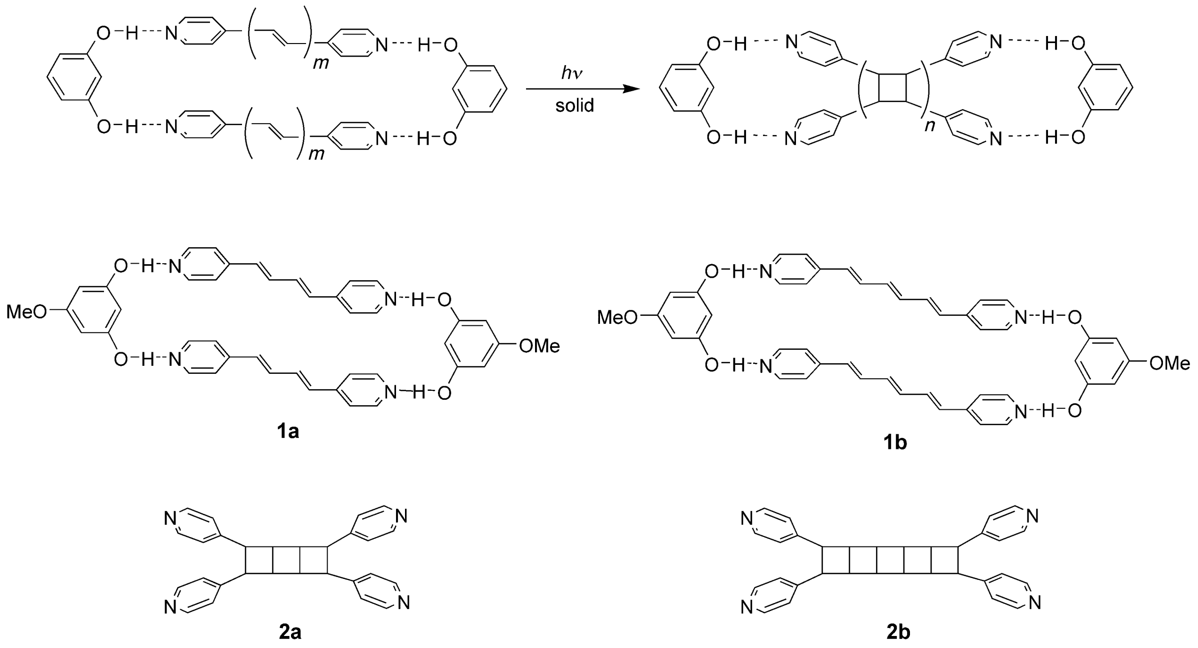

Scheme 1.

the templates such that the C=C bonds of the olefins lie parallel and separated by <4.2 Å, a position suitable for the photoreaction. UV irradiation of the solid would produce the targeted [*n*]ladderane, with the C=C bonds reacting to form the fused cyclobutane framework. Herein, we report the application of 2(5-OMe-res)·2(4-pyr-poly-*m*-ene) (where: $m=2$ (**1a**) and 3 (**1b**); 5-OMe-res = 5-methoxyresorcinol) to construct [*n*]ladderanes (where $n=3$ (**2a**) and 5 (**2b**)) in the solid state. The remarkable efficiency of this intermolecular process is exemplified by the fact that the polyenes are converted to the ladderanes stereospecifically, in gram quantities, and in 100% yield.[11]

In a typical experiment, one equivalent of 5-OMe-res[11] was cocrystallized with an equimolar amount of a 4-pyr-poly-*m*-ene[15] in methanol. Single crystals of **1a** and **1b** suitable for X-ray analysis formed in the methanolic solution within a period of approximately one day.

Single-crystal X-ray structure analyses of **1a** and **1b** reveal that the linear templates preorganize each polyene into a position for intermolecular photoaddition that is favorable for ladderane formation.[6]

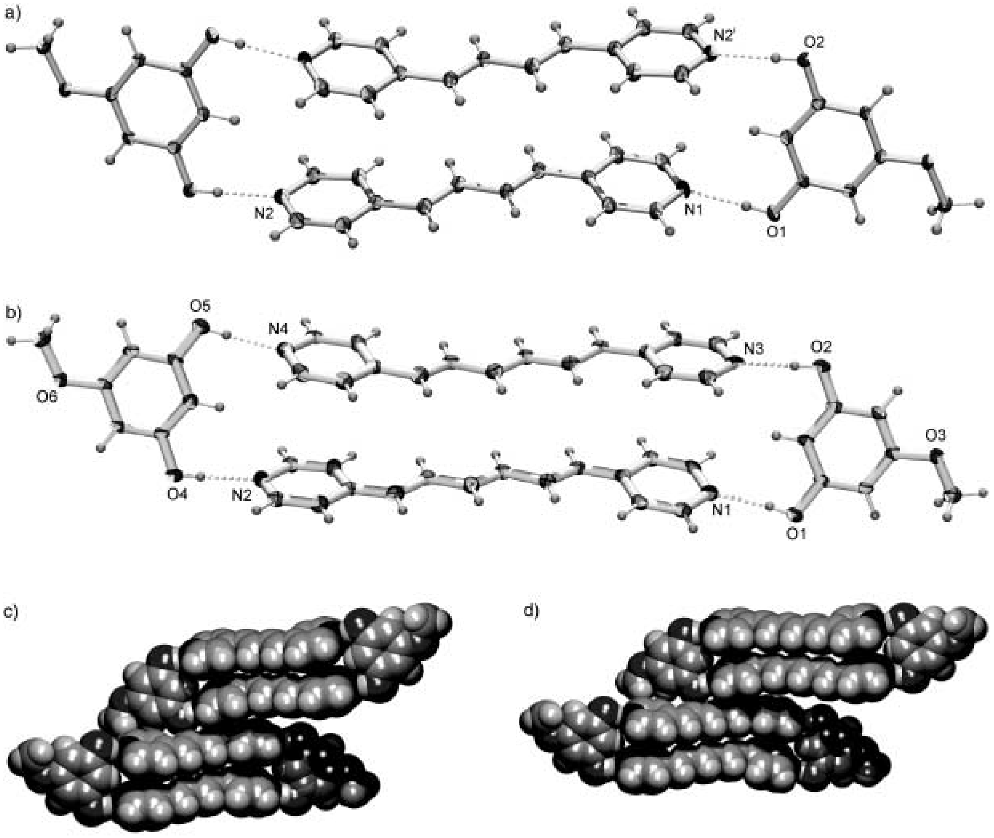

Figure 1. X-ray crystal structures of **1a** and **1b**: a) ORTEP view of **1a**, b) ORTEP view of **1b**, c) space-filling view of the packing of **1a**, and d) space-filling view of the packing of **1b**. Selected interatomic distances [Å] and angles [°]: a) O1···N1 2.761(3), O2···N2^{i} 2.736(3), O1-H1O···N1 175.5(2), O2-H2O···N2^{i} 171.4(2); b) O1···N1 2.792(5), O2···N3 2.777(6), O4···N2 2.782(6), O5···N4 2.756(6), O1-H1O···N1 173.6(3), O2-H2O···N3 173.4(3), O4-H4O···N2 176.6(3), O5-H5O···N4 175.1(3). Symmetry operator i: $-x+1$, $-y$, $-z+2$. The asymmetric unit of 2(5-OMe-res)·2(4-pyr-poly-2-ene) consists of one half assembly, which resides around a crystallographic center of inversion, whereas that of 2(5-OMe-res)·2(4-pyr-poly-3-ene) involves two full assemblies, which are virtually identical.

In each case, the linear templates and polyenes form discrete, four-component molecular assemblies that are held together by four O−H⋅⋅⋅N hydrogen bonds (Figure 1 a,b), wherein the templates orient the polyenes in a parallel arrangement. The separation between the stacked C=C bonds ranges from 3.78 to 3.82 Å and 3.69 to 3.97 Å in **1a** and **1b**, respectively. Nearest-neighbor assemblies of each solid pack in an antiparallel fashion so that the olefins of the hydrogen-bonded assemblies are the sole C=C bonds organized to undergo reaction (Figure 1 c,d).

To evaluate the reactivity of the solid-state molecular assemblies, powdered crystalline samples of **1a** and **1b** were subjected to UV irradiation (broadband Hg lamp) for periods of approximately 120 and 72 h, respectively. As evidenced by ^{1}H NMR spectroscopy (in [D$_6$]DMSO), **2a** and **2b** formed stereospecifically and in 100 % yield (Figure 2). Each ladderane is characterized by the complete disappearance of the olefinic protons and the emergence of cyclobutane protons in the $\delta = 3.0$–4.3 ppm range.[6,16] The three fused cyclobutane rings of **2a** produced two broad signals at $\delta = 3.49$ and 4.30 ppm (1:1 ratio), while the five fused cyclobutane rings of **2b** produced three broad signals at $\delta = 3.12$, 3.27, and 4.27 ppm (1:1:1 ratio).

To confirm the structures of the ladderanes, the reactions were repeated in gram quantities. The linear templates were then separated from each photoproduct by solvent extraction. Single-crystals of **2a** and **2b**·2(benzene) were grown, over a period of approximately three days, by way of slow solvent evaporation from ethanol and benzene, respectively.

Single-crystal X-ray structure analyses confirm the structures of **2a** and **2b** (Figure 3). Each photoproduct consists of a *cis*-fused cyclobutane framework with ends that are functionalized with four 4-pyridyl groups. The C−C bond lengths and C-C-C bond angles of the fused cyclobutane units compare well to both calculated and experimentally related structures.[6,16]

The ladderanes **2a** and **2b** appear to form within **1a** and **1b** through stepwise [2+2] photodimerizations. ^{1}H NMR spectra obtained 24 and 48 h into each reaction reveal that lower-order [*n*]ladderanes form during the generation of each

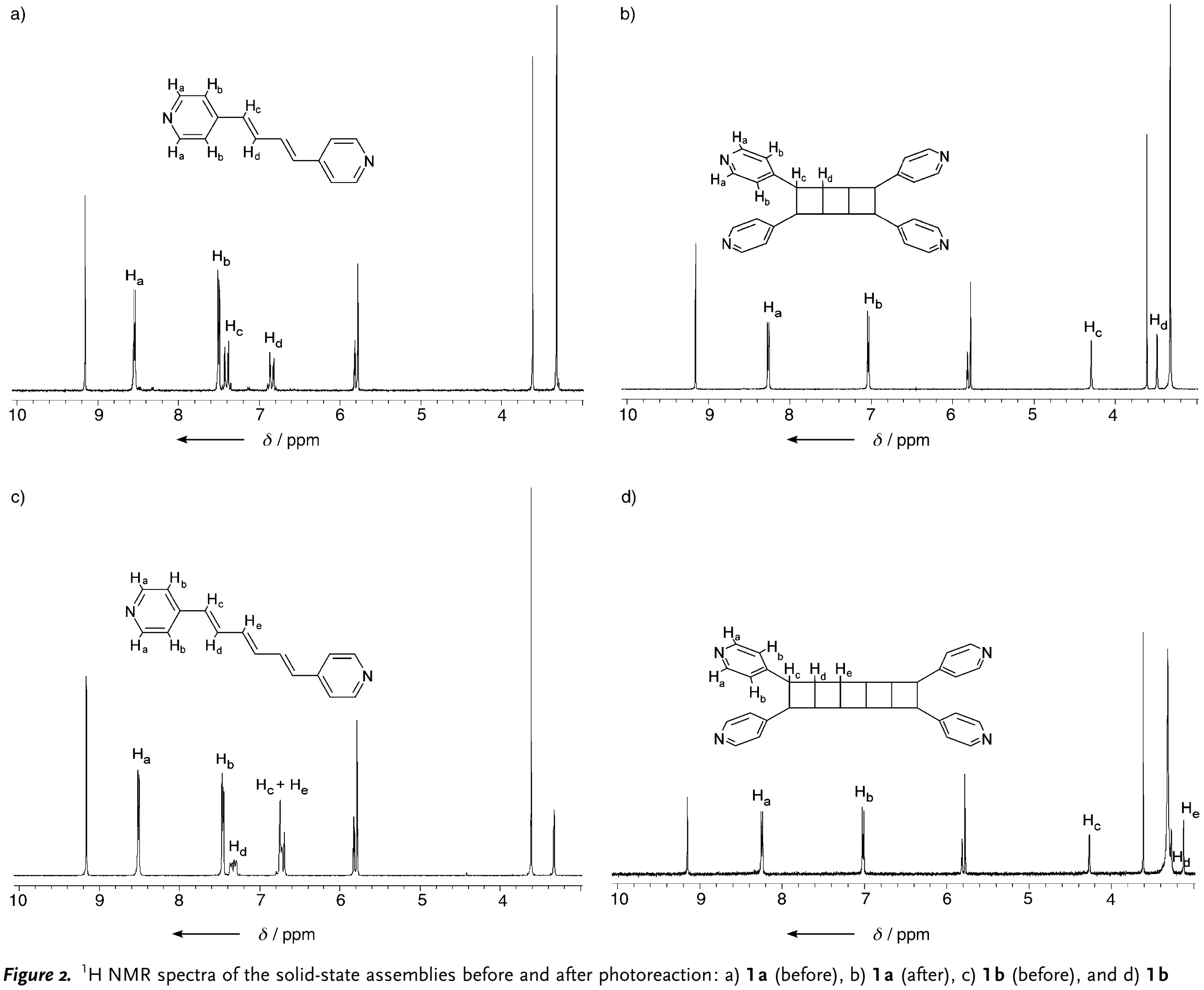

Figure 2. ^{1}H NMR spectra of the solid-state assemblies before and after photoreaction: a) **1a** (before), b) **1a** (after), c) **1b** (before), and d) **1b** (after).

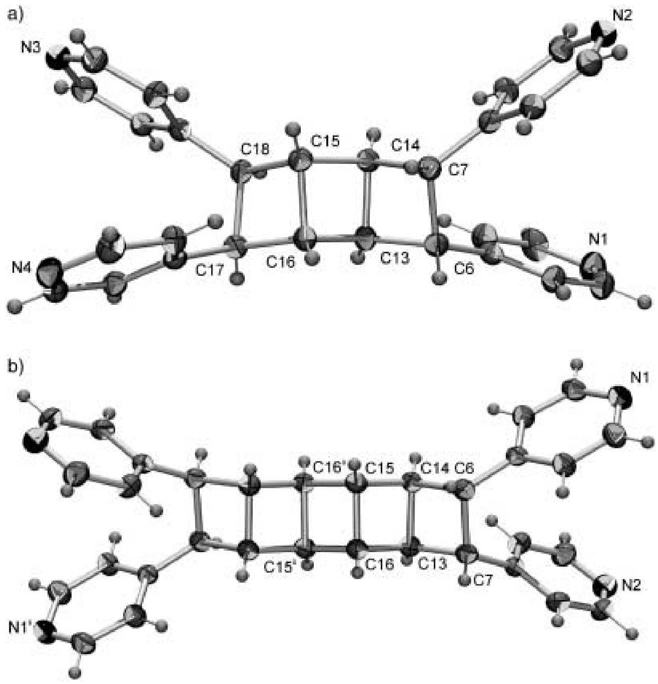

Figure 3. ORTEP perspectives of the ladderanes: a) **2a** and b) **2b**. Selected interatomic distances [Å] and angles [°]: C6-C7 1.593(5), C13-C14 1.566(5), C15-C16 1.575(5); b) C6-C7 1.585(3), C13-C14 1.567(3), C15-C16 1.585(3), C16-C15^{ii} 1.526(3). Symmetry operator ii: $-x+2$, $-y$, $-z+1$. The asymmetric unit of **2a** contains two full ladderanes, which are virtually identical, while that of **2b**·2(benzene) contains one half ladderane, which resides around a crystallographic center of inversion, and an included benzene molecule, respectively.

final product. Thus, a product consistent with a single cycloaddition (i.e., "[1]ladderane") precedes **2a** while products consistent with single and double cycloadditions (e.g., [3]ladderane) precede **2b**. Such observations contrast reactivity experiments involving 1,4-butadienes,[14,17] which exhibit similar packing in the solid state and react, via a single photodimerization, to produce *cis*-vinyl cyclobutanes and rearrange thermally, via a Cope rearrangement,[18] into *cis–cis* cyclooctadienes.[19] Here, the relatively strong O−H···N hydrogen bonds between the templates and reactants may serve to force divinyl groups from a first photoaddition into a conformation suitable for a second and third photoaddition, thus leading to each ladderane product.[20] In the case of **2b**, such stepwise transformations may occur either randomly or by way of a "zipper" process in the solid.[6] Experiments are underway to determine the structures of the lower-order ladderanes and the sequence by which the photocycloadditions occur.[21]

In this report, we have demonstrated that a linear template may be used to position two polyenes for an intermolecular reaction to produce [*n*]ladderanes ($n=3$ or 5). The template preorganizes the polyenes, through hydrogen-bonding interactions, for [2+2] photodimerizations in the solid state. By using the organized, solvent-free environment of the solid state[9] for reaction, the ladderanes can be formed in gram quantities and in 100% yield. We believe that these results illuminate the utility of applying concepts of supramolecular chemistry and self-assembly to address a problem of covalent synthesis[7,8] and we are now exploring whether such template molecules can be used to construct ladderanes of increasing size and complexity in the solid state.[8]

Experimental Section

1a and **1b**: 4-pyr-poly-2-ene and 4-pyr-poly-3-ene were prepared according to a literature procedure.[22] 5-OMe-res was commercially available. Cocrystals of **1a** were obtained by evaporation of a solution of 4-pyr-poly-2-ene (0.058 g, 0.28 mmol) and 5-OMe-res (0.039 g, 0.28 mmol) in hot methanol (3.0 mL). Co-crystals of **1b** were obtained in a similar manner using 4-pyr-poly-3-ene (0.030 g, 0.13 mmol) and 5-OMe-res (0.018 g, 0.13 mmol).

Solid-state photoreactions and isolation of **2a** and **2b**: UV irradiation of powdered crystalline **1a** (500 W Hg lamp) over a period of 120 h resulted in 100% conversion of poly-2-ene to [3]ladderane. In the case of **1b**, the quantitative formation of the [5]ladderane was achieved after 72 h. In both cases, the irradiation experiments were performed by placing finely ground samples of either **1a** or **1b** between two pyrex plates and turning each sample in eight-hour intervals to ensure uniform irradiation. The irradiated solids were stirred with 1M KOH solution, then extraction with methylene chloride and evaporation of the organic phase yielded the appropriate ladderane as a white solid in 85% yield. All procedures were readily scaled up to give the ladderanes in gram quantities. Single crystals of **2a** were grown from ethanol, while single crystals of **2b** were grown from benzene yielding a 1:2 benzene solvate. ^{1}H NMR of **1a** before irradiation (300 MHz, [D$_6$]DMSO): $\delta=9.15$ (br s, 2H), 8.54 (dd, 4H), 7.50 (dd, 4H), 7.40 (dd, 4H), (dd, 4H), 5.82 (br t, 1H), 5.78 (br d, 2H), 3.61 ppm (s, 3H). ^{1}H NMR of irradiated **1a** (300 MHz, [D$_6$]DMSO): $\delta=9.16$ (br s, 4H), 8.26 (dd, 8H), 7.04 (dd, 8H), (br t, 2H), 5.78 (br d, 4H), 4.30 (br s, 4H), 3.61 (s, 6H), 3.49 ppm (br s, 4H). ^{1}H NMR of **1b** before irradiation (300 MHz, [D$_6$]DMSO): $\delta=9.16$ (br s, 2H), 8.52 (dd, 4H), 7.46 (dd, 4H), 7.33 (m, 2H), 6.72 (m, 4H), 5.82 (br t, 1H), 5.79 (br d, 2H), 3.61 ppm (s, 3H). ^{1}H NMR of irradiated **1b** (300 MHz, [D$_6$]DMSO): $\delta=9.15$ (br s, 4H), 8.25 (dd, 8H), 7.02 (dd, 8H), (br t, 2H), 5.78 (br d, 4H), 4.27 (br s, 4H), 3.61 (s, 6H), 3.27 (br s, 4H), 3.12 ppm (br s, 4H).

Crystal data for **1a**: monoclinic, $P2_1/c$, $a=9.182(5)$, $b=13.381(5)$, $c=15.122(5)$ Å, $\beta=106.712(5)°$, $V=1779.5(13)$ Å^3, $Z=4$, $\rho_{calcd}=1.300$ g cm^{-3}, $R_1=0.0441$ for 2324 reflections with $I>2\sigma(I)$. Crystal data for **1b**: triclinic, $P\bar{1}$, $a=9.081(3)$, $b=21.143(4)$, $c=21.308(18)$ Å, $\alpha=87.92(4)$, $\beta=79.47(6)$, $\gamma=78.91(2)°$, $V=3947(4)$ Å^3, $Z=2$, $\rho_{calcd}=1.260$ g cm^{-3}, $R_1=0.0891$ for 6150 reflections with $I>2\sigma(I)$. Crystal data for the **2a**: triclinic, $P\bar{1}$, $a=12.534(5)$, $b=12.583(5)$, $c=14.787(5)$ Å, $\alpha=100.388(5)$, $\beta=106.555(5)$, $\gamma=89.945(5)°$, $V=2195.7(14)$ Å^3, $Z=2$, $\rho_{calcd}=1.260$ g cm^{-3}, $R_1=0.0647$ for 4018 reflections with $I>2\sigma(I)$. Crystal data for **2b**·2(benzene): monoclinic, $P2_1/c$, $a=9.475(2)$, $b=15.048(3)$, $c=12.235(2)$ Å, $\beta=95.95(3)°$, $V=1735.0(6)$ Å^3, $Z=4$, $\rho_{calcd}=1.196$ g cm^{-3}, $R_1=0.0438$ for 1625 reflections with $I>2\sigma(I)$. All crystal data were measured on a Nonius Kappa CCD single-crystal X-ray diffractometer at 77 K. After anisotropic refinement of all non-hydrogen atoms, aromatic, methine, and hydroxyl hydrogen atoms were placed in idealized positions and allowed to ride on the atom to which they were attached. The structure of **1b** was determined to be a rotational twin, the twinning law being a twofold rotation about the (011) reciprocal lattice direction. All crystallographic calculations were conducted using SHELXL-97.[23] CCDC-218101 (**1a**), CCDC-218102 (**1b**), CCDC-218103 (**2a**), and CCDC-218104 (**2b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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[1] For a recent highlight on ladderanes, see: H. Hopf, *Angew. Chem.* **2003**, *115*, 2928–2931; *Angew. Chem. Int. Ed.* **2003**, *42*, 2822–2825.

[2] W. Li, M. A. Fox, *J. Am. Chem. Soc.* **1996**, *118*, 11752–11758.

[3] a) J. S. S. Damste, M. Strous, W. I. C. Rijpstra, E. C. Hopmans, J. A. J. Geenevasen, A. C. T. van Duin, L. A. van Niftrik, M. S. M. Jetten, *Nature* **2002**, *419*, 708–712; b) E. F. DeLong, *Nature* **2002**, *419*, 676–677.

[4] M. M. M. Kuypers, A. O. Sliekers, G. Lavik, M. Schmidt, B. B. Jørgensen, J. G. Kuenen, J. S. S. Damste, M. Strous, M. S. M. Jetten, *Nature* **2003**, *422*, 608–611.

[5] For discussions on organizing molecules in solution, see: a) D. H. Williams, E. Stephens, M. Zhou, *Chem. Commun.* **2003**, 1973–1976; b) M. Rekharsky, Y. Inoue, S. L. Tobey, A. Metzger, E. V. Anslyn, *J. Am. Chem. Soc.* **2002**, *124*, 14959–14967.

[6] H. Hopf, H. Greiving, P. G. Jones, P. Bubenitschek, *Angew. Chem.* **1995**, *107*, 742–744; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 685–687.

[7] M. C. T. Fyfe, J. F. Stoddart, *Acc. Chem. Res.* **1997**, *30*, 393–401.

[8] a) J. Xiao, M. Yang, J. W. Lauher, F. W. Fowler, *Angew. Chem.* **2000**, *112*, 2216–2219; *Angew. Chem. Int. Ed.* **2000**, *39*, 2132–2135; b) J. J. Kane, R.-F. Liao, J. W. Lauher, F. W. Fowler, *J. Am. Chem. Soc.* **1995**, *117*, 12003–12005.

[9] a) K. Tanaka, F. Toda, *Chem. Rev.* **2000**, *100*, 1025–1074; b) V. Ramamurthy, K. Venkatesan, *Chem. Rev.* **1987**, *87*, 433–481.

[10] a) L. R. MacGillivray, *CrystEngComm* **2002**, *4*, 37–42; b) D. B. Varshney, G. S. Papaefstathiou, L. R. MacGillivray, *Chem. Commun.* **2002**, 1964–1965; c) L. R. MacGillivray, J. L. Reid, J. A. Ripmeester, G. S. Papaefstathiou, *Ind. Eng. Chem. Res.* **2002**, *41*, 4494–4497; d) G. S. Papaefstathiou, A. J. Kipp, L. R. MacGillivray, *Chem. Commun.* **2001**, 2432–2433; e) L. R. MacGillivray, J. L. Reid, J. A. Ripmeester, *J. Am. Chem. Soc.* **2000**, *122*, 7817–7818.

[11] We used "template switching" to identify a template that affords each [*n*]ladderane in 100% yield. See: T. Friščić, L. R. MacGillivray, *Chem. Commun.* **2003**, 1306–1307.

[12] For use of linear templates in the solid state, see also: a) Y. Ito, B. Borecka, J. Trotter, J. R. Scheffer *Tetrahedron Lett.* **1995**, *36*, 6083–6086; b) D. G. Amirakis, M. A. Garcia-Garibay, S. J. Rowan, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2001**, *113*, 4386–4391; *Angew. Chem. Int. Ed.* **2001**, *40*, 4256–4261; c) S. Phba, H. Hosomi, Y. Ito *J. Am. Chem. Soc.* **2001**, *123*, 6349–6352; d) D. G. Amirsakis, A. M. Elizarov, M. A. Garcia-Garibay, P. T. Glink, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2003**, *115*, 1158–1164; *Angew. Chem. Int. Ed.* **2003**, *42*, 1126–1132; e) N. Shan, W. Jones, *Tetrahedron Lett.* **2003**, *44*, 3687–3689.

[13] For use of linear templates in the liquid phase, see: a) T. R. Kelly, C. Zhao, G. J. Bridger, *J. Am. Chem. Soc.* **1989**, *111*, 3744–3745; b) R. J. Pieters, I. Huc, J. Rebek *Tetrahedron* **1995**, *51*, 485–498; c) D. M. Bassani, V. Darcos, S. Mahony, J.-P. Desvergne, *J. Am. Chem. Soc.* **2000**, *122*, 8795–8796; c) D. M. Bassani, X. Sallenave, V. Darcos, J.-P. Desvergne, *Chem. Commun.* **2001**, 1446–1447; d) H. Zitt, I. Dix, H. Hopf, P. G. Jones, *Eur. J. Org. Chem.* **2002**, 2298–2307.

[14] G. M. J. Schmidt, *Pure Appl. Chem.* **1971**, *27*, 647–678.

[15] S. Woitellier, J. P. Launay, C. W. Spangler, *Inorg. Chem.* **1989**, *28*, 758–762.

[16] a) G. Mehta, M. B. Viswanath, A. C. Kunwar, *J. Org. Chem.* **1994**, *59*, 6131–6132; b) R. N. Warrener, G. Abbenante, C. H. L. Kennard, *J. Am. Chem. Soc.* **1994**, *116*, 3645–3646; c) M. A. Miller, J. M. Schulman, *J. Mol. Struct.* **1988**, *163*, 133–141.

[17] a) A. Elgavi, B. S. Green, G. M. J. Schmidt, **1973**, *95*, 2058–2059; b) M. D. Cohen, A. Elgavi, B. S. Green, Z. Ludmer, G. M. J. Schmidt, *J. Am. Chem. Soc.* **1972**, *94*, 6776–6779.

[18] For a theoretical treatment of the Cope rearrangement in ladderanes, see: D. J. Tantillo, R. Hoffmann, *Angew. Chem.* **2002**, *114*, 1075–1078; *Angew. Chem. Int. Ed.* **2002**, *41*, 1033–1036.

[19] For oligomerizations and polymerizations of cyclobutanes in the solid state, see: a) L. Addadi, M Lahav, *J. Am. Chem. Soc.* **1978**, *100*, 2838–2844; b) M. Hasegawa, *Chem. Rev.* **1983**, *83*, 507–518.

[20] For movement in crystals, see: a) G. R. Desiraju, *Nature* **2003**, *423*, 485; b) I. C. Paul, D. Y. Curtin, *Acc. Chem. Res.* **1973**, *6*, 217–225.

[21] V. Enkelmann, G. Wegner, K. Novak, K. B. Wagener, *J. Am. Chem. Soc.* **1993**, *115*, 10390–10391.

[22] P. Carsky, S. Hünig, I. Stemmler, D. Scheutzow, *Liebigs Ann. Chem.* **1980**, 291–304.

[23] G. M. Sheldrick, SHELXL-97, Program for Refinement of Crystal Structure, University of Göttingen, Göttingen (Germany), **1997**.