ORGANIC LETTERS

2004
Vol. 6, No. 3
309−312

Noncovalent Self-Assembly of Bicyclo[4.2.2]diketopiperazines: Influence of Saturation in the Bridging Carbacyclic Ring

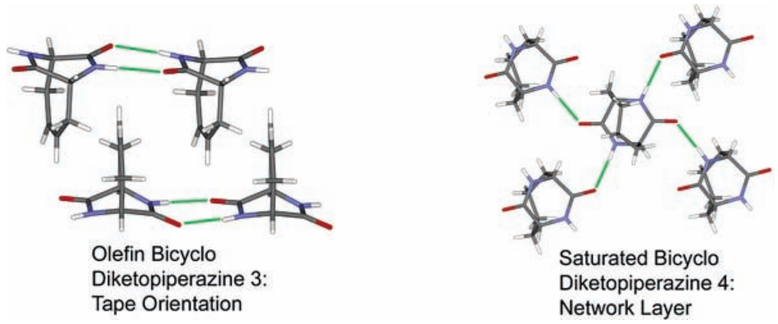
Yanming Du, Christopher J. Creighton, Brett A. Tounge, and Allen B. Reitz*

Drug Discovery Division, Johnson & Johnson Pharmaceutical Research and Development, Spring House, Pennsylvania 19477

areitz@prdus.jnj.com

Received October 28, 2003

ABSTRACT



Olefin Bicyclo Diketopiperazine 3: Tape Orientation

Saturated Bicyclo Diketopiperazine 4: Network Layer

We have prepared 7,9-diazabicyclo[4.2.2]dec-3-ene-8,10-dione (3) and 7,9-diazabicyclo[4.2.2]decane-8,10-dione (4), which differ by virtue of the degree of unsaturation in the bridging carbacyclic tether on a 2,5-diketopiperazine. Remarkably different self-assembly patterns were observed in the solid state for the two compounds, attributed to subtle variations in the conformational constraints imposed by the tether.

Understanding the factors involved in the solid-state orientation of organic crystals has potential application to the design of materials with nonlinear optical properties, electrical superconductivity, or unexpected, enhanced reactivity.[1] 2,5-Diketopiperazines (DKP) have been extensively studied both because they are useful synthons in organic chemistry[2] and due to their propensity to form large macromolecular arrays in the solid state.[3] The formation of sequential intermolecular amide-amide hydrogen bonds between adjacent DKPs enables the growth of molecular assemblies that can be studied and characterized using X-ray crystallography and NMR techniques.[4]

The X-ray structure of the parent, unsubstituted DKP itself was determined in 1938 and was the first structure determined that contained an amide bond.[2a] In this work, DKP was found to be planar and to form linear tape structures in which the association between two neighboring DKPs formed a cyclic eight-membered ring involving two intermolecular hydrogen bonds (Figure 1a).

The vast majority of substituted DKPs adopt the linear tape orientation in the solid state.[5] Only three DKPs, cyclo(L-his-D-his),[6] cyclo(D-ala-L-ala),[7] and a chiral 2,5-diazabicyclo-

---

(1) Gavezzotti, A. *Crystallogr. Rev.* **1998**, *7*, 5−121.

(2) For a recent review, see: Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297−3312.

(3) (a) Corey, R. B. *J. Am. Chem. Soc.* **1938**, *60*, 1598−1604. (b) Palacin, S.; Chin, D. N.; Simanek, E. E.; MacDonald, J. C.; Whitesides, G. M.; McBride, M. T.; Palmore, G. T. R. *J. Am. Chem. Soc.* **1997**, *119*, 11807−11816. (c) Chin, D. N.; Palmore, G. T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 2115−2122. (d) Luo, T. J. M.; Palmore, G. T. R. *J. Phys. Org. Chem.* **2000**, *13*, 870−879. (e) Bergeron, R. J.; Phanstiel, O. IV; Yao, G.; Milstein, S.; Weimar, R. *J. Am. Chem. Soc.* **1994**, *116*, 8479−8484.

(4) (a) Palmore, G. T. R.; MacDonald, J. C. *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Material Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; John Wiley & Sons, Inc.: New York, 2000; pp 291−336. (b) Archer, E. A.; Gong, H. G.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139−1159.

10.1021/ol036101u CCC: $27.50

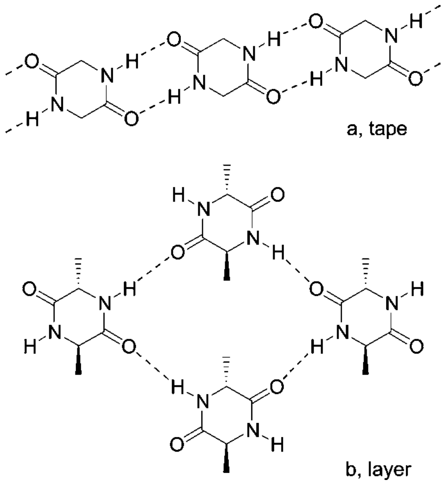


Figure 1. Schematic view of hydrogen binding patterns observed for 2,5-diketopiperazines in the solid state.[5]

[2.2.2]octane-3,5-dione,[8] form a layer-type structure (Figure 1b) in which each of the two DKP amides forms hydrogen bonds with two adjacent neighbors.[9,10] Analysis of the previously reported DKP crystal structures reveals that the choice of substitution can have a dramatic influence upon the preferred packing form. For example, DKPs bearing carboxylic acid groups on the 2- and 6-positions formed layers,[11] whereas bulky spirocyclic substitution promoted the tape orientation.[3b] We here report that the preference for the tape or layer DKP orientation in the solid state can be controlled by the degree of unsaturation in a bridging carbacyclic tether in bicyclo[4.2.2]-2,5-diketopiperazines.

We prepared eight-membered lactam **1** via a synthetic sequence using ring-closing metathesis (RCM) of an *N*-(2,4-dimethoxybenzyl) (DMB)-protected bis(allylglycine) as the key step.[12] Compound **1** was converted to protected DKP **2** in formic acid followed by refluxing in *s*-BuOH/toluene.[13] Initial attempts to remove the DMB group using ceric ammonium nitrate (CAN) in a 2:1 mixture of CH_3CN/water were problematic, so an efficient nonaqueous procedure was developed in which **2** was treated with thioanisole in TFA[14] and the concentrated residue was treated with diethyl ether. The precipitate of DKP **3** that formed was then isolated and recrystallized (MeOH). To study the effects of saturation of the olefin in **3** upon macromolecular self-assembly, DKP **4** was prepared by hydrogenation of **3** using Pd/C (Figure 2).

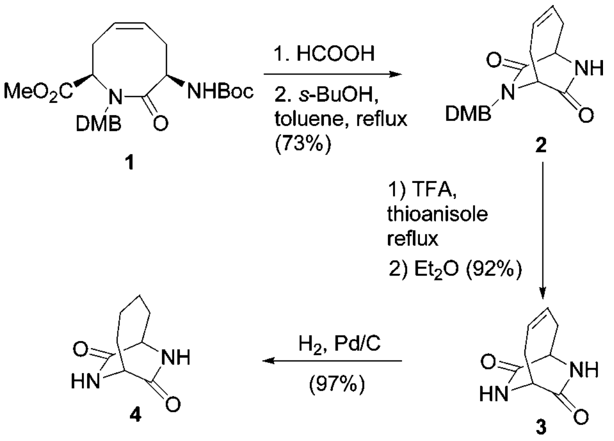


Figure 2. Synthesis of bicyclo[4,2,2]-2,5-diketopiperazines **3** and **4**.

The solid-state structures of **3** and **4** were determined by X-ray crystallography. The piperazine rings in both compounds were determined to be in boat conformations, as was observed for a bicyclo[2.2.2]-DKP previously.[8] Unexpectedly, dramatic differences were observed between **3** and **4** related to the orientation of the tether and the overall crystal packing orientation. The bridging ring of **3** was planar (Figure 3), and each molecule was aligned with two neighboring molecules via hydrogen bonds to form an infinite tape. Adjacent tapes were associated by interdigitation of their cyclic side chains in an antiparallel orientation.

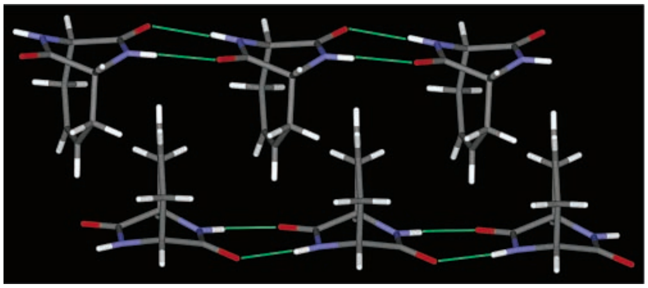


Figure 3. Crystal packing pattern of DKP **3** showing the tape orientation and interdigitating antiparallel strands.

In contrast, the crystal formed by **4** had a twisted bridging side chain (Figure 4) and each molecule formed a hydrogen bond with four neighboring molecules to form an infinite layer. The layers were packed together by interdigitation of cyclic side chains in a parallel orientation.

---

(5) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383−2420.

(6) Benedetti, E.; Bavoso, A.; Di Blasio, B.; Pavone, V.; Pedone, C.; Paolillo, L.; D'Alagni, M. *Int. J. Pept. Protein Res.* **1988**, *31*, 220−224.

(7) Benedetti, E.; Corradini, P.; Pedone, C. *J. Phys. Chem.* **1969**, *73*, 2891−2895.

(8) Brienne, M.-J.; Gabard, J.; Leclercq, M.; Lehn, J.-M.; Cesario, M.; Pascard, C.; Chevé, M.; Dutruc-Rosset, G. *Tetrahedron Lett.* **1994**, *35*, 8157−8160.

(9) 2,5-Diketopiperazines can form well-defined two-dimensional layers when cocrystallized with other molecules; for example: Palmore, G. T. R.; McBride, M. T. *J. Chem. Soc., Chem. Commun.* **1998**, 145−146.

(10) 2,5-Diketopiperazines bearing pendant groups that can directly participate in hydrogen bonding arrays have been discussed in ref 5.

(11) Lyssenko, K. A.; Lenev, D. A.; Kostyanovsky, R. G. *Tetrahedron* **2002**, *58*, 8525−8537.

(12) Creighton, C. J.; Reitz, A. B. *Org. Lett.* **2001**, *3*, 893−895.

(13) Halpern, B.; Nitecki, D. E. *Tetrahedron Lett.* **1967**, *8*, 3031−3033.

(14) (a) Kiso, Y.; Ukawa, K.; Nakamura, S.; Ito, K.; Akita, T. *Chem. Pharm. Bull.* **1980**, *28*, 673−676. (b) Weygand, F.; Steglich, W.; Bjarnason, J.; Akhtar, R.; Chytil, N. *Chem. Ber.* **1968**, *101*, 3623−3641.

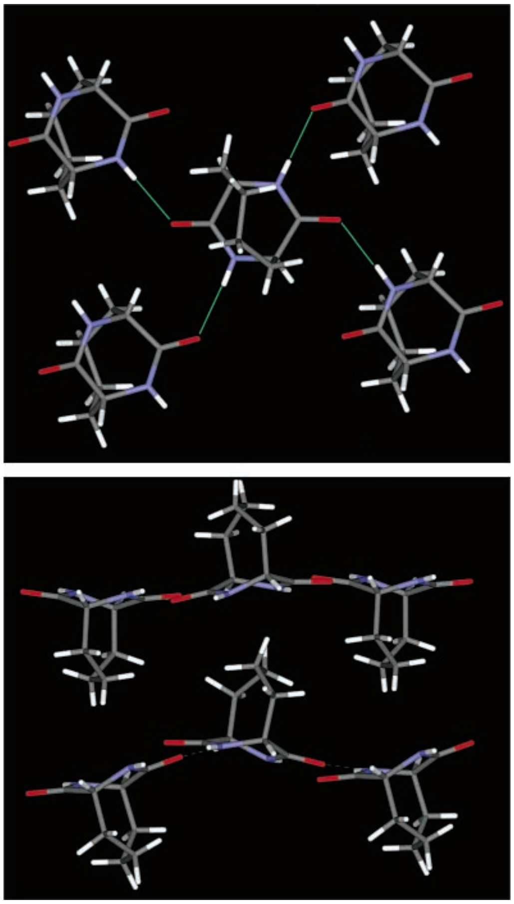


Figure 4. Crystal packing pattern of DKP **4** showing the layer orientation and interdigitating parallel strands.

As a result of the twist in the side chains for **4**, the density in the crystal packing was less than that for **3**. Therefore, the shift between tape and layer macromolecular self-assembly for the bicyclic DKPs **3** and **4** is dependent upon the extent of saturation in the bridging tether, with full saturation producing the layer form.

Analysis of DKPs 3 and 4 in the Gas Phase. Examination of the X-ray structure of **3** revealed that many of the bonds were distorted and the bond angles were atypical. For example, the $=C-CH_2-C$ angle in **3** was 120°, much larger than the typical 109° sp^3 bond angle. In addition, the vinylic carbon had a $C-C-C$ bond angle of 136° $(CH=CH-CH_2)$, considerably different than the expected 120°. These abnormal bond angles indicate a high level of ring strain for **3**. We wondered whether this conformation was found only in the solid state promoted by the favorable energetics associated with crystal packing or was inherently the most stable conformation in the gas phase as well.

A manual conformational search on **3** was performed by varying the out-of-plane bend for the HCCC dihedral atoms in the cyclic side chain in 10° increments (Table 1). HCCC-1 was the dihedral angle defined by the hydrogen on one of the bridgehead carbons of the diketopiperazine ring, the bridgehead carbon, the allylic methylene in the bridging side chain, and the adjacent vinyl carbon. HCCC-2 was the analogous angle on the other side of the bicyclic structure, and HCCC-1 and HCCC-2 were allowed to vary independently. An energy minimization was performed for each angle using the Polak-Ribier conjugate gradient method (OPLS-AA force field, HCCC-1 constrained). The resulting structures are shown in Figure 5. The planar conformation (HCCC-1, 180°; HCCC-2, −180°) was the most stable in the gas phase and overlapped extremely well with the solid-state structure of **3** (Supporting Information). This confirmed that the conformation of **3** in the X-ray structure was indeed the most stable one in the gas phase, even though the bond angles are characteristic of a highly strained structure. For DKP **4**, a conformation search was performed using the Monte Carlo Multiple Minimum (MMCM, 1000 steps) method in Maestro.[15] After each step, the resulting conformer was minimized using the PRCG method (gas phase, OPLS-AA force field). The most stable conformation of **4** in which the tether has adopted a twist structure to avoid ring strain

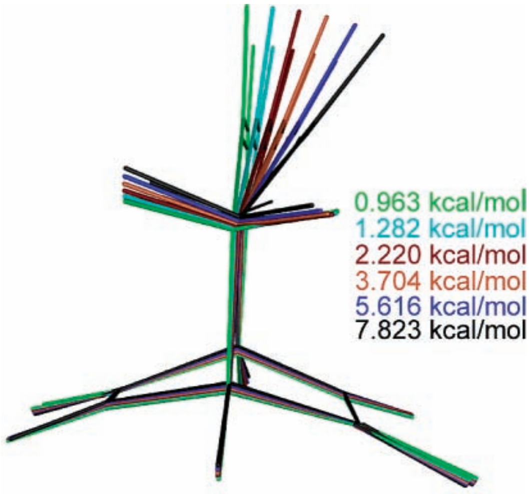


Figure 5. Variation of the calculated energies for **3** as a function of incrementally bending the olefin-containing tether (HCCC-1 and HCCC-2).

Table 1. Energy Minimization of DKP 3 in Gas Phase

HCCC-1 starting (deg)	HCCC-1 minimized structure (deg)	HCCC-2 minimized structure (deg)	energy (kcal/mol)
180	180.0	−180.0	0.963
170	175.4	−171.7	1.282
160	170.6	−163.4	2.220
150	165.4	−154.7	3.704
140	159.6	−145.7	5.616
130	153.7	−136.4	7.823

---

[15] *Maestro 5.1*; Schrödinger, Inc.: Portland, OR, 2001.

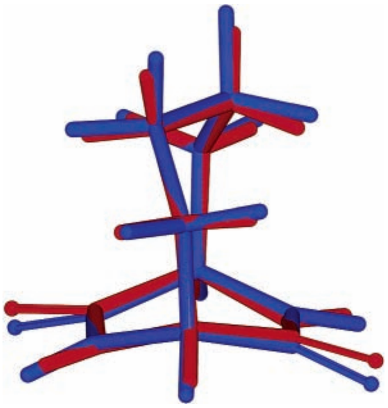


Figure 6. Minimum energy structure for **4**, from the computational analysis (blue) and the crystal structure (red) superimposed on each other.

overlapped very well with the structure determined by X-ray crystallography (Figure 6). The bond angles in **4** were not atypical, and the bonds were not distorted to any significant degree.

The ability to control noncovalent self-assembly is essential for the development of new materials with defined and tunable physical properties. Hydrogen bonding has proved to be a primary means for instituting such noncovalent arrays, due to relative strength and predictable orientation.[16] Furthermore, the combination of hydrogen bonding and hydrophobic interactions determine the overall final orientation.[17]

In summary, we have prepared 7,9-diazabicyclo[4.2.2]-dec-3-ene-8,10-dione (**3**) and 7,9-diazabicyclo[4.2.2]decane-8,10-dione (**4**), two novel bicyclo[4.2.2]-2,5-diketopiperazines, and studied their conformational preferences in both the solid state and gas phase. The orientation of the macromolecular self-assembly of these DPKs was controlled by variation of the extent of saturation of the bridging tether. Remarkably, the X-ray crystal structure of olefin **3** revealed an extended tape orientation in the solid state, whereas saturated derivative **4** was found to be of the network layer type. There have been only a few layer 2,5-diketopiperazines that have been reported to date. The highly strained solid-state structure of **3** was also found to be preferred in the gas phase. This study may provide additional insight into the factors that control DKP self-assembly.

Acknowledgment. We acknowledge the assistance and advice of Gregory Leo. We also thank Dr. Reza Ghadiri of the Scripps Research Institute and Dr. Xinjian Lei of Air Products for helpful suggestions.

Supporting Information Available: Full experimental procedures for the preparation of **2**−**4**, crystallographic details for **3** and **4** (cif files), and comparison of calculated conformations of compounds **3** and **4** in gas phase with those obtained from the solid state. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036101U

---

[16] Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed*. **2001**, *40*, 2382−2426.

[17] (a) Reinhoudt, D. N.; Crego-Calama, M. *Science* **2002**, *295*, 2403−2407. (b) Xing, B.; Yu, C. W.; Chow, K. H.; Ho, P. L.; Fu, D.; Xu, B. *J. Am. Chem. Soc*. **2002**, *124*, 14846−14847. (c) Schnarr, N. A.; Kennan, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 667−671.