A Systematic Study of the Relationship between Molecular and Crystal Structure among 3,5-Diazabicyclo[2.2.2]octane-2,6-diones

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ABSTRACT: A simple, convergent synthesis of 3,5-diazabicyclo[2.2.2]octane-2,6-diones (bicyclic *N,N*-diacylaminals) has been developed, providing access to a large series of compounds differing only in their substituents at the bridgehead positions. These compounds crystallize in several different forms, but always in such a way that each molecule forms four hydrogen bonds. The sheer number of bicyclic amidals that can be synthesized and crystallized provides an opportunity to elucidate crystal-engineering structure−structure relationship (SSR) principles.

Introduction

Interest in molecules that self-assemble by hydrogen bonds in solution and in the solid state has blossomed recently,[1] partly because of the potential applications to nanotechnology.[2] Despite many years of effort, it remains largely impossible to predict crystal structures from molecular structures. An approach that might lead to progress in this area is to synthesize a whole series of homologous compounds and study their "structure−structure relationships" (SSRs). However, many compounds with interesting self-assembly properties are not easy to prepare, so it can be difficult to obtain sufficient numbers of analogues to discern SSRs.

We recently reported a new supramolecular synthon, the bicyclic *N,N*-diacylaminal ("amidal"), and the unique self-assembly and solid-state host−guest behavior of two representatives of this class, **1a** and **1b** (Figure 1).[3] Although **1a** and **1b** could be prepared convergently and in only four steps from commercially available starting materials, further studies of the self-assembly of bicyclic amidals would benefit from even shorter and simpler synthetic routes. We considered **2**, which possessed a "stripped-down" bicyclic amidal structure, with the two amide planes rigidly held at a dihedral angle of 120°, close to the 112−118° of **1a**.[3] We noted the resemblance of **2** to **3**, a compound whose self-assembly was studied by Lehn.[4] However, diamide **3** was chiral, which complicated the study of its self-assembly, and its linear synthesis and resolution did not lend itself to the preparation of a large number of analogues.

Results and Discussion

The synthesis of **2** was convergent and incredibly simple (Table 1). A diethyl alkylmalonate was allowed to undergo a NaOEt- or HMPT-catalyzed[5] Michael reaction with a vinyl ketone, and the adduct was
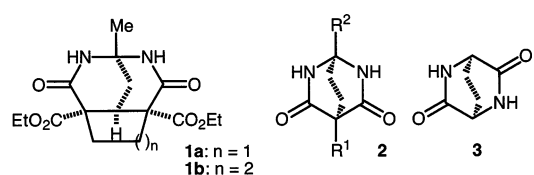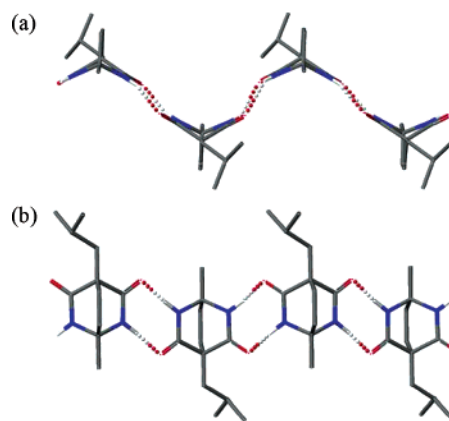

Figure 1. Self-assembling bis(amides).

Figure 2. (a, b) Two views of a four-monomer unit of the pleated tape formed by **2b**. The one-dimensional tapes formed by **2a**, **2c**, **2d**, **2e**, and **2f** look very similar.

Ⓦ 3D rotatable structures of Ⓦ **2a**, Ⓦ **2b**, Ⓦ **2c**, Ⓦ **2e**, and Ⓦ **2f** in MOL format are available.

dissolved in 7 M NH₃ in MeOH. Thirteen amidals, **2a**−**m**, were prepared in this way in variable yields. (See the Supporting Information for experimental details.) In several cases, crystals suitable for X-ray analysis precipitated directly from the reaction mixture. In the others, the reaction mixture was concentrated, and the residue was recrystallized, usually from EtOH or MeOH. Most of the amidals were insoluble in less polar solvents.

We have solved the structures of 11 amidals **2** by X-ray crystallography; the two other amidals have not yielded crystals of sufficient quality for X-ray analysis. A majority of the amidals, **2a**−**f**, self-assemble by the familiar $\mathbf{R}_2^2(8)$ amide dimer[6] into a pleated tape (Figure

* To whom correspondence should be addressed. Robert B. Grossman, Department of Chemistry, University of Kentucky, Lexington, KY 40506-0055. Tel.: (859) 257-1285. Fax: (859) 323-1069. E-mail: robert.grossman@uky.edu. Web: http://www.chem.uky.edu/research/grossman.

Table 1.
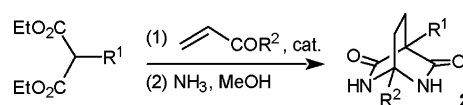
2	R^1, R^2	space group	description of hydrogen-bond network	H···O distances[a] (Å)	N−H···O angles[a] (°)	H···O=C angles[a] (°)	N−C=O···H geometry and deviation from planarity[a] (°)
a	Et, Me	$P\bar{1}$	pleated tape, $R_2^{(2)}8$ dimers	2.064, 2.028	152.1, 158.1	122.5, 118.8	syn 25.2, syn 18.4
b	*i*-Bu, Me	$P\bar{1}$	pleated tape, $R_2^{(2)}8$ dimers	2.002, 2.057	163.1, 147.3	115.3, 116.9	syn 15.7, syn 29.8
c	H, Ph	$P\bar{1}$	pleated tape, $R_2^{(2)}8$ dimers	1.949, 1.969	169.4, 163.8	122.8, 125.2	syn 3.7, syn 8.5
d	Et, Ph	$P\bar{1}$	pleated tape, $R_2^{(2)}8$ dimers[b]				
e	*i*-Pr, Me	$P2_1/m$	pleated tape, $R_2^{(2)}8$ dimers	2.055	155.1	121.3	syn 17.8
f	Bn, Ph	$P2_1$	pleated tape, $R_2^{(2)}8$ dimers	2.011, 2.057	145.9, 162.9	120.5, 122.8	syn 27.5, syn 14.3
g	H, Me	$P2_1/c$	pleated sheet, $R_4^{(4)}18$ tetramers	2.078, 1.906	147.1, 177.1	166.6, 127.8	anti 29.0, anti 22.6
h	Me, Me	$Pnma$	pleated sheet, $R_4^{(4)}18$ tetramers	2.196	146.4	137.3	anti 8.4
i	Me, Ph	$Pnma$	pleated sheet, $R_4^{(4)}18$ tetramers	2.112	154.7	125.5	anti 49.3
j	Bn, Me	$P2_1/c$	pleated sheet, $R_2^{(2)}8$ dimers & $R_4^{(6)}24$ hexamers	2.033, 2.012	160.5, 168.9	120.9, 138.0	syn 22.9, anti 22.9
k	Ph, Et	$P\bar{1}$	rectangular column, $R_4^{(4)}18$ tetramers	1.997, 2.151, 1.998, 1.981	175.0, 135.0, 161.4, 167.1	124.7, 158.4, 142.9, 141.2	syn 29.0, syn 0.6, anti 86.0, syn 40.4
l	*i*-Bu, Et	c	c				
m	Ph, Me	c	c				

[a] The positions of the H atoms were calculated. [b] This structure could not be refined in a satisfactory manner (see text). [c] Crystals of these compounds that were suitable for X-ray crystallographic analysis could not be grown.

2), analogous to the structure of racemic **3**.[4] As in the structure of *rac*-**3** but unlike in the structures of **1a** and **1b**, the eight atoms involved in the $R_2^{(2)}8$ dimer in the solid-state structures of **2a**−**f** are very close to coplanar. The structure of **2f** also features edge-to-face interactions between the Ph groups of one tape and the Bn groups of the next. Such aromatic interactions are absent from the other arene-containing structures, but **2f** is the only amidal whose crystal structure is available in which both R^1 and R^2 are aromatic. No intermolecular interactions other than hydrogen bonds and van der Waals contacts can be discerned in the structures of **2a**−**e**. Amidal **2d** crystallizes as a modulated superstructure with seven molecules in the asymmetric unit, but, owing to the weakness of supercell reflections, its structure cannot be refined in a satisfactory manner.

The second most common supramolecular form is assumed by the three amidals, **2g**−**i**. They self-assemble by $R_4^{(4)}18$ tetramers[6] into a pleated sheet (Figure 3), analogous to the structure of enantiopure **3**.[4] Some differences among the three structures are evident; for example, in **2h** and **2i**, the plane containing the two R−C bonds in one amidal overlaps with the same plane in the facing amidal in the tetramer, whereas in **2g**, it does not. Also, in **2i**, the R−C−C−R line is much more tilted with respect to the plane of the 2D sheet than in **2h**, and the N−C=O···H dihedral angle is distorted to 130.7° (optimally 180°). All of these differences likely reflect the different steric demands of the R groups in the three amidals. Again, no intermolecular interactions other than hydrogen bonds and van der Waals contacts can be discerned in the structures of **2g**−**i**.

Amidals **2j** and **2k** form supramolecular structures unique among the group described in this paper. Like **2g**, amidal **2j** crystallizes in the $P2_1/c$ space group in the form of a two-dimensional corrugated sheet (Figure 4), but in other respects the two structures differ greatly. In crystalline **2j**, one O of each amidal forms two bifurcated hydrogen bonds, whereas the other O forms none, so the total number of hydrogen bonds in the
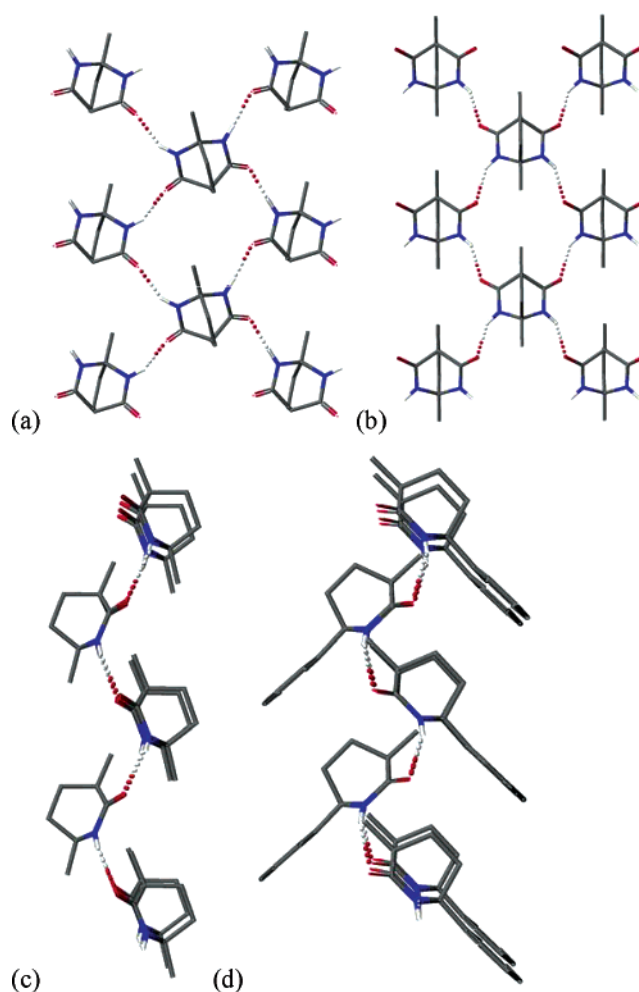

Figure 3. Portions of the pleated sheets formed by (a) **2g**, (b, c) **2h**, and (d) **2i**. Note the unusual N−C=O···H dihedral angle in crystalline **2i**.

Ⓦ 3D rotatable structures of Ⓦ **2g**, Ⓦ **2h**, and Ⓦ **2i** in MOL format are available.
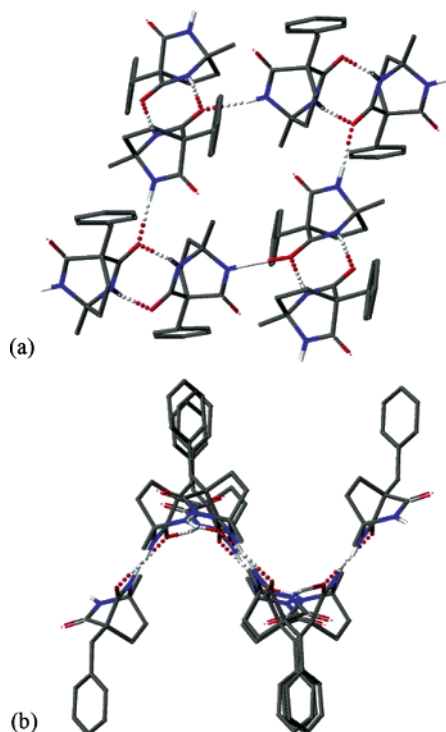
Figure 4. (a, b) Two views of an eight-monomer segment of the two-dimensional pleated sheet formed by **2j**. The tetramer of dimers is clearly visible in panel a.

Ⓦ A 3D rotatable structure of **2j** in MOL format is available.

structure of **2j** is the same as in the others. Each amidal makes one $\mathbf{R}_2^2 8$ dimer, and each dimer is connected to four others through four single hydrogen bonds, so the entire structure can be considered to be made up of tetramers of dimers. An $\mathbf{R}_4^6 24$ hexamer can also be discerned in the tetramer of dimers; in each $\mathbf{R}_4^6 24$ hexamer, one molecule contributes two N−H bonds to the hydrogen-bonding network, one contributes an N−H bond and an O atom, and one contributes only an O atom (the latter makes bifurcated hydrogen bonds). The Bn groups of **2j** point perpendicular with respect to the plane of the 2D network, giving it the appearance of "hairy corrugated cardboard". On the other hand, amidal **2k** forms a "rectangular column" made up of $\mathbf{R}_4^4 18$ tetramers. There are two molecules in the asymmetric unit; they differ in the orientation of the CH_2−CH_3 bond with respect to the bicyclic system. In the column, pairs of amidals are oriented 90° to one another as one descends down the column. Each amidal is singly hydrogen bonded to four others. Two of the N−C=O···H dihedral angles are distorted to greater than 30°, with one nearly perpendicular (94.0°). The rectangular columns stack closely against one another. The discovery of these two unique self-assembly patterns is testament to the power of "analoguing" to uncover the diverse ways by which similar molecules can self-assemble in the solid state.

No relationship between the supramolecular structures and the geometric parameters of the hydrogen-bonding arrays can be discerned. For example, structures **2h** and **2i** both form pleated sheets, and both crystallize in the *Pnma* space group, yet the N−C=O···H array in **2h** is nearly planar, whereas in

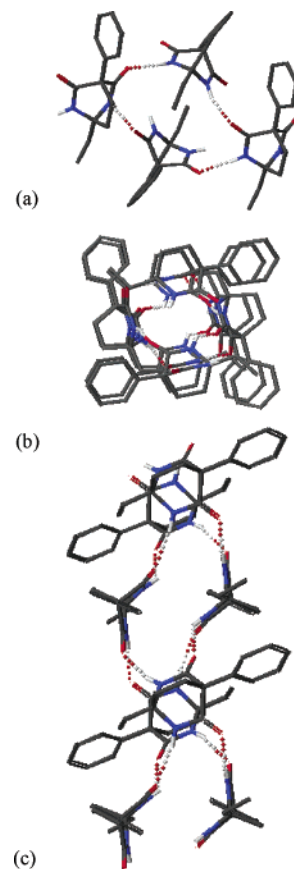**Figure 5.** (a) The $\mathbf{R}_4^4 18$ tetramer in the structure of crystalline **2k**, and (b, c) two views of an eight-monomer unit of the one-dimensional tape formed by **2k**.

Ⓦ A 3D rotatable structure of **2k** in MOL format is available.

2i, it is twisted 49° from planarity, the second largest twist in this set of crystals. The results confirm that the energy of the hydrogen bond can be maintained in a wide range of geometries, and, as a result, the hydrogen bond geometry is able to relax so that other favorable interactions in the crystal are maximized.

Amidal **1a** forms cyclic, chair-shaped hexamers with a cavity occupied by two solvent molecules when it is crystallized from toluene, chlorobenzene, or benzotrifluoride, and it forms pleated tapes interspersed with columns of solvent when it is crystallized from benzene, nitrobenzene, or heptane−CH_2Cl_2.[3] Unfortunately, a systematic search for similar solvent-dependent behavior of **2** has been precluded by the general insolubility of **2** in nonpolar solvents, which are unable to disrupt the hydrogen-bonding networks of **2**. (We are able to crystallize **2h** from mesitylene, but the crystals are identical to those from MeOH.) We conclude that the compact structures of amidals **2** make them pack too snugly to behave similarly to **1a**. Their snug packing into pleated sheets and tapes is also apparently more favorable than their self-assembly into hexagonal hoops.[4]

Conclusion

We have prepared a series of 13 bicyclic amidals that differ from one another by small degrees. The crystal structures of 11 of these compounds reveal two main motifs, the pleated tape and the pleated sheet. The

energetic difference between these two motifs appears to be rather small, with small changes in the structure of the monomers (cf. **2a** to **2h**, and **2d** to **2i**) causing a change from one motif to the other. Two amidals crystallize into unique motifs that nevertheless preserve the total number of hydrogen bonds. Unlike **1a**, none of the amidals **2a**−**k** incorporate solvent into their crystals. Future work will explore other aspects of the self-assembly of bicyclic amidals.

Supporting Information Available: Experimental details for the preparation and full characterization of compounds **2a**−**m**, and tables of X-ray crystallographic data for **2a**−**c**,**e**− **k**; the X-ray data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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